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CHROMIUM AND IRON ORGANOMETALLICS IN ORGANIC SYNTHESIS: SYNTHETIC STUDIES TOWARD TOTAL SYNTHESIS OF TAXOL AND CHROMIUM TO IRON TRANSFER PROCESSES

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By

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ABSTRACT

CHROMIUM AND IRON ORGANOMETALLICS IN ORGANIC SYNTHESIS: SYNTHETIC STUDIES TOWARD TOTAL SYNTHESIS OF TAXOL AND CHROMIUM TO IRON TRANSFER PROCESSES

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The Wulff–Kaesler reaction – a chromium-mediated intramolecular [2 + 2] cycloaddition – of Fischer carbene complexes and the dienyne **94** has been demonstrated to be a suitable method for the preparation of the bicyclo[3.1.1]heptanone intermediates as A-ring synthons of taxol and taxane derivatives. A diastereoselective synthesis of taxol A-ring synthons has also been achieved from the reaction with the chiral dienyne **110a,** which results in good syn/anti ratios in favor of the desired bicycloheptanone isomers. The proposed mechanism suggests that asymmetric induction may originate from chelation of the oxygen to the chromium during the reaction.

It has also been revealed that closure of the B-ring of taxol via an aldol condensation/Grob fragmentation does not proceed as anticipated and instead results in undesired fragmentation. A modified strategy has been designed on the basis of careful mechanistic considerations which represents an attractive route to the ABC tricyclic core of taxol and deserves further investigation.

The first examples of both inter- and intramolecular cyclopropanation reactions of dienyl chromium carbene complexes under a non-CO atmosphere have also been demonstrated. The dienyl carbene complexes can react with an electron-deficient olefin to give dienylcyclopropanes as a mixture of *trans*- and *cis*-isomers in an intermolecular fashion. The intramolecular cyclopropanation reaction of alkenyloxy dienyl carbene

complexes with a terminal double bond tethered to the oxygen can occur if the tether length is appropriate. In all cases, the Diels-Alder reaction that was thought to be a possible competitive reaction did not appear to occur.

The serendipitous finding and the subsequent development of a novel iron-mediated thermal *ortho*-benzannulation of Fischer carbene complexes are also described. It is the first time that *trans,trans*-α,β,γ,δ-unsaturated Fischer carbene complexes have been employed successfully for the *ortho*-benzannulation reaction. The first examples of the "*ortho*-cyclohexadienone annulation" with δ,δ-disubstituted dienyl carbene complexes have also been illustrated. This reaction also worked with a few dienyl carbene complexes having a *cis*-α,β-double bond, although the scope for the *cis*-α,β-dienyl substrates has not been established.

Mechanistic studies suggest that two pathways are possible to form the dienone iron tricarbonyl complex and the phenol product. One involves direct transfer of the carbene ligand from Cr to Fe, and the other involves initial coordination of the iron to the diene fragment. A tentative mechanism has been proposed for the chromium to iron transfer processes.

Some new aspects of the *ortho*-benzannulation reaction under thermal conditions in the absence of an iron source have also been illustrated under both argon and CO atmospheres. It was surprising to find that photons were not necessary for a few *cis*-α,β-dienyl carbene complexes of particular structure types, and the unusual reactivity is believed to result from the ring strain in the substrates rather than the possible extra coordination site in the carbene complexes.

To my wife: Xiuni, and our daughter: Angela Weike

my parents: Bogui and Suying, and my sister: Danbo

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Many current colleagues of course deserve special thanks. Cory Newman has been my labmate for four years and we certainly have had a lot of excitement (as well as frustrations) together in the lab. In addition to chemistry, we often talked about sports both in and outside the lab. The trip to Washington, D.C., for the ACS meeting with Cory and his wife Janelle and my wife Xiuni was fun and memorable. It has also been a pleasure to work with Keith Korthals, another wonderful down-to-earth-type Midwesterner, in the same lab for the past five years. Zhensheng Ding, a talented person who has a lot of interests in addition to chemistry, has provided a lot of fun in the lab. I also wish to thank Chunrui Wu, Gang Hu, Victor Prutyanov, Kostos Rampalakos, Alex Predeus and Aman Desai for their help and friendship. In addition, I have had the pleasure to work with Kelsie Betsch, an undergraduate student from Augustana College in Sioux Falls, South Dakota, during the summer of 2004.

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Finally, I would like to thank my parents, Bogui and Suying, who live far away from this country but are always there to support me wherever I go and whatever I do. My sister, a brilliant law school graduate, along with my parents, always has confidence in me and encourages me to fulfill my goals. Of course, the biggest non-academic

achievement at MSU was meeting the lovely girl, Xiuni, who later became my wife. Without her company during the often difficult times, I cannot imagine what my life would have been like. I probably cannot say enough for her about her unwavering support, understanding and love throughout these years. Our daughter Angie Weike certainly has been our great joy, it is such a wonderful thing watching her grow each day. This dissertation is dedicated to these important family members in my life.

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KEY TO ABBREVIATIONS AND SYMBOLS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Bz	Benzoyl
CAN	Ceric Ammonium Nitrate
*m*CPBA	*meta*-Chloroperoxybenzoic Acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIBAL	Diisobutylaluminum Hydride
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
HMPA	Hexamethylphosphoramide
hv	Irradiation with Light
LAH	Lithium Aluminum Hydride
LDA	Lithium Diisopropylamide
L-Selectride	Lithium Tri-*sec*-butylborohydride
MOM	Methoxymethyl
MsCl	Methanesulfonyl Chloride
NMO	*N*-Methylmorpholine N-Oxide
Red-Al	Sodium Dihydrobis(2-methoxyethoxy)-aluminate
TBAF	Tetra-*n*-butylammonium Fluoroborate
TBS	*Tert*-butyldimethylsilyl (TBDMS)
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Troc	β,β,β-Trichloroethoxycarbonyl (Tcec)
EDS	Energy Dispersive Spectrometer
SEM	Scanning Electron Microscopy

CHAPTER ONE

TAXOL: ITS BIOLOGY AND CHEMISTRY

Taxol has created a great impact in the areas of clinical oncology and biomedical research in the past few decades.[1] As Goodman and Walsh wrote in their book entitled *The Story of Taxol*: "Taxol is arguably the most celebrated, talked about, and controversial natural product in recent years: Celebrated because of its efficacy as an anti-cancer drug and because its discovery has provided powerful support for policies concerned with biodiversity. Talked about because in the late 1980s and early 1990s, the American public was bombarded with news reports about the molecule and its host, the slow-growing Pacific yew. Controversial because the drug and the tree became embroiled in several sensitive political issues with broad public policy implications."[2] As a result, it has become one of the few organic compounds, which, like benzene, aspirin and Viagra, is recognizable by name to the average citizen.[3]

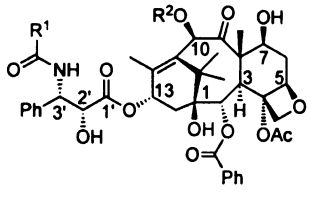
The approval of taxol for use as an anti-cancer drug in 1992 was the culmination of 30 years of work, and many areas of research pertinent to taxol continued very actively and enthusiastically around the world after that. Therefore, the discovery and development of taxol is a complex story with many fronts,[4] and a comprehensive review of taxol is not possible here. The following description is intended to serve as a brief

overview of taxol, and to highlight some most important aspects of the discovery and development, the biological studies and clinical applications as well as the chemistry, especially the synthesis of taxol.

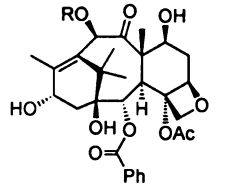
1.1 INTRODUCTION TO THE TAXANE DITERPENES

The taxane family of diterpenoids is a group of substances isolated from various yew (*Taxus*) species.[5] More than 350 taxane diterpenes, or taxoids, have been isolated and characterized, with the majority being reported over the last 15 years or so. The search for derivatives was driven in part by the proven extraordinary anticancer activity of taxol. Some representative examples of taxanes are illustrated in Figure 1.1, all of which are naturally occurring compounds except Taxotere[6] (**2**) – the semisynthetic analog of taxol (**1**).

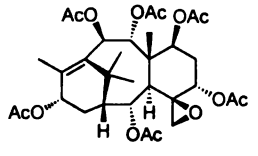
Figure 1.1. Some Examples of the Taxane Family of Diterpenoids.



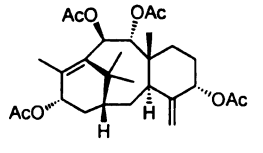
1: Taxol, R^1 = Ph, R^2 = Ac
2: Taxotere, R^1 = *t*-BuO, R^2 = H



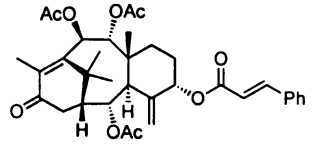
3: 10-Deacetylbaccatin III (10-DAB), R = H
4: Baccatin III, R =Ac



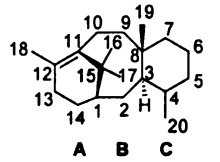
5: Baccatin I



6: Taxusin



7: Taxinine



8: Taxane ABC Skeleton and Numbering

The taxane diterpenes share the ABC tricylic carbon skeleton (**8**) with few exceptions, and the numbering of the 6-8-6 membered ring system is also shown. These compounds bear different degrees of oxygenation and some structural subgroups may be discerned. For example, the C-ring functionality can have an elaborate 3-oxygenated oxetane in taxol (**1**), a less complicated epoxide in baccatin I (**5**), or a simple allylic ester in taxinine (**7**). Among all of the known taxanes, taxol (**1**) is one of the most functionally and stereochemically complex molecules.

The taxanes are a new class of anticancer drug of which taxol is the first clinically effective representative,[7] and some members of its family exhibit multidrug resistance reversing activity.[8]

1.2 THE DISCOVERY OF TAXOL

The story about the discovery of taxol begins with the state of cancer treatment research in the mid 20th century. The successful use of penicillin in World War II ushered in the "antibiotic era", and many drugs such as erythromycins and tetracyclines became available in addition to penicillins and sulfa drugs, which resulted in a significant decease in deaths from infectious diseases of all types, including a major killer – pneumonias.[4a] This changed the mortality patterns drastically such that heart disease and cancer were then becoming the major killers. From late 1940s to early 1950s, the reports of the first few chemotherapeutic agents used for human cancer treatment, especially nitrogen mustards as well as aminopterin and 6-mercaptopurine,[9] led to heightened

interest and belief in chemical agents rather than in radiotherapy and surgery as the techniques of choice in cancer treatment.

However, there were few major cancer research centers at that time. The Sloan-Kettering Institute was the largest private cancer research institute, which evaluated about 3,000 compounds (synthetic and natural) for anticancer effects every year, representing more than 75% of the total American chemotherapy screening capacity.[10] This was certainly inadequate and too slow. Furthermore, there were only a few largely non-coordinated small research groups working on various subjects such as carcinogenesis, etiology and treatment. These situations indicated the necessity and urgency of the formation of a national cancer drug screening program, and in 1953 the Congress directed the National Cancer Institute (NCI) to organize such a program, which led to the creation of the Cancer Chemotherapy National Service Center (CCNSC) within NCI in 1955.[11] Its early strategy was to act as a public screening facility for compounds submitted voluntarily by institutions and companies, and all of them were synthetic compounds and fermentation products with known structures. In 1960, the CCNSC screened more than 30,000 compounds annually – ten times of the volume of the Sloan-Kettering Institute. In the same year, the program was extended to include natural products, from both plants and animals, whose structures were unknown,[10,12] and it was transformed from a service into a "targeted drug development program".[11a]

To get plants assessed as part of the CCNSC screening program was a challenge since the investigation of the bioactivity of plants was essentially a new area at that time. Although for more than a century, it was known that many plant alkaloids – nitrogen-containing secondary metabolites – were bioactive, yet by 1952, only two percent of the

world's plant species had been screened for their alkaloid content.[13] Even less was known about the cytotoxic and anti-tumor possibilities of plant products.

The initial selection of plant extracts to be screened was based on rapid availability. To obtain enough specimens and to get the botanical information correct, collaborations with the U.S. Department of Agriculture (USDA) would be important because one of the most important functions of the USDA was in collecting, identifying, storing and cultivating plant materials as their task of introducing beneficial plants into American agriculture. When the joint NCI–USDA plant screening program was started in 1960, it was decided that random selection of plants for screening was the best way to uncover compounds of hitherto unknown types of activity.[2] Although selective searching – targeting a specific family or genus – would lead to a higher number of hits, but by the same token, it would not uncover substances possessing entirely new structures and mechanisms of activity. The main concept lies in that diversity in morphological characteristics would likely be mirrored by diversity in the types of chemicals that these plants produced, which gives the best chance of finding chemical variety and with that perhaps antitumor activity.

The plant collection agreement between the NCI and USDA resulted in many collecting trips by USDA botanists to a variety of locations in the United States. In 1962, as part of their sweep in the west coast, a team led by Arthur Barclay collected samples of the bark of the Pacific yew, *Taxus brevifolia*, in the Gifford Pinchot National Forest in the state of Washington.[2] Initial studies from a crude extract of the bark showed cytotoxicity against KB cells,[14] and in late 1964, thirty pounds of bark samples were sent by NCI to Wani and Wall, chemists at the Research Triangle Institute in North Carolina

who had been contracted by NCI for fractionation studies.[4a] Subsequently, fractions from this extract showed cytotoxic activity against leukemia cells and inhibitory action against a variety of tumors.

In October 1966, Wall and Wani isolated some pure crystalline needles and named the compound "taxol" (*tax-* for *taxus* and *-ol* for alcohol due to the evidence for the presence of hydroxyl group(s)).[15] It took about two years for them to isolate 0.5 g of pure compound from 12 kg of dried bark in a yield of 0.004%! The isolation of taxol was first presented at the annual meeting of the American Chemical Society in Miami Beach, Florida, in 1967,[16] with little being said about its structure. In 1971, Wall and Wani and their coworkers published the structure of taxol (**1**) including its absolute stereochemistry (Figure 1.1),[17] along with the studies of its antileukemic and antitumor activity. Taxol was the first compound possessing the taxane ring system that had been demonstrated to have such activity.[18] The first structure-activity data were also presented showing that both the taxol core structure and the side chain were essential for activity.[17]

Despite the fact that taxol was the most interesting of the more than 114,000 compounds obtained from about 35,000 samples of roughly 15,000 plant species that were tested during the existence of the NCI–USDA plant program between 1960 and 1981,[19] further investigation of taxol languished for almost a decade due, primarily, to difficulty of extraction from the natural source, problems with the murine screening system, and a belief that taxol was simply another microtubule-destabilizing agent like colchicines and the vinca alkaloids.[20] However, the situation changed dramatically in 1979 when Susan Horwitz and coworkers at the Albert Einstein College of Medicine reported a breakthrough discovery of the unique mechanism of action of taxol.[21] It was

found that taxol stabilizes microtubules instead of destabilizing them like all other known agents, and this mode of action breaks down cellular replication and eventually leads to cell death.[22]

1.3 Biological Study and Clinical Applications of Taxol

1.3.1 The Biological Role of Taxol

As mentioned above, taxol does indeed act on microtubules, but with a completely different mechanism of action.[21] Microtubules are protein structures found within cells, one of the components of the cytoskeleton. A normal microtubule has a diameter of about 24 nm and varying length from several micrometers to possibly millimeters. Microtubules serve as structural components within cells and are involved in many important cellular processes including mitosis, cytokinesis, and vesicular transport. Due to their versatility, usage and importance in the growth of cells, microtubules have been called "the most strategic subcellular targets of anticancer chemotherapeutics."[23]

Microtubules are polymers of α- and β-tubulin dimers. During polymerization, the tubulin dimer binds two molecules of guanosine 5'-triphosphate (GTP), and these GTP-bound dimers join in a head-to-tail fashion to form protofilaments in the presence of magnesium ions. The protofilaments then bundle in a hollow cylindrical filament. Typically, the protofilaments arrange themselves in an imperfect helix with one turn of the helix containing 13 tubulin dimers. From this point, the growth occurs only at the ends of the tubule. Typically, equilibria are set up at both ends of the microtubule with

constant loss and gain of tubulin subunits, the rate of which is often different at the two ends and results in a growing polarity. Worthy of mention is that the tubulin dimer is the binding target of a number of drugs, such as colchicine and nocodazol, which inhibit the polymerization of tubulin,.[24]

In general, microtubules are not static structures. After a certain period of time, the growth and disassembly reaches equilibrium at relative concentrations of the microtubule and free tubulin, and this concentration of tubulin is called the critical concentration.[25] It was proposed that GTP hydrolysis was an ongoing background process and once the hydrolysis catches up to the tip of the microtubule, it begins a rapid depolymerization and shrinkage.

Horwitz and coworkers in 1979 reported the unique mechanism of action of taxol,[21] and they discovered that taxol affects the tubulin-microtubule equilibrium by decreasing both the critical concentration of tubulin (to almost zero mg/mL) and the induction time for polymerization, even in the absence of GTP, MAPs (microtubule-associated proteins) and magnesium ions, which are normally required for polymerization. The extremely stable microtubules formed by taxol showed a shorter average length and resistance both to cooling and to ionic calcium, which usually depolymerize microtubules. They also found that taxol binds much more strongly, though still reversibly, to the intact microtubule than to the tubulin dimer, and the binding site appears to be distinct from that of other anti-microtubule agents and common MAPs.[26] It was later demonstrated that the maximum stabilization effects of taxol occur at a 1:1 ratio of taxol/tubulin dimer.[27] It was of interest to note that Heidemann and Gallas of Michigan

State University showed in 1980 that taxol's microtubule activity *in vitro* was similar *in vivo*.[28]

Studies have shown that taxol affects microtubules in all different phases of the cell life cycle, and it can also disturb many cellular phenomena that are not directly related to cell division but involved with microtubules.[29] Although the molecular mechanisms are not yet completely understood, it has been hypothesized that the programmed cell death or apoptosis results from conflicting growth regulatory signals, for example, from extended mitotic block, which ultimately lead to an unsuccessful attempt to traverse the cell cycle.[30]

1.3.2 Clinical Applications[31]

After the paper on the mechanism of action by Horwitz and coworkers appreared, publications dealing with taxol and microtubules mushroomed. Yet as far as the NCI was concerned, the compound must be highly active in at least one tumor model, otherwise it had little chance of progressing, whatever its mechanism of action. Preclinical studies demonstrated that taxol was active against murine B16, L1210, P388, and P1534 leukemias – cancers characterized by overproduction of white blood cells.[4a] It was also efficacious against a number of leukemias and solid tumors in xenografts (tissues transferred from one species to another), including those in breast, ovary, brain, colon and lung.[32] Taxol also had a proven effect upon Walker 256 carcinoma, sarcoma 180, and Lewis lung tumor cell lines.[33] However, the formulation was problematic during the study because the solubility of taxol in water (less than 0.01 mg/mL) and other aqueous based systems is very low. So many attempts were made using mixed solvent approaches,

emulsions, and liposomes,[34] before the Cremophor-ethanol surfactant formulation was decided by the NCI for further development of taxol. After acceptable animal toxicology studies were completed in 1982, an Investigational New Drug Application (INDA) was submitted to the Food and Drug Administration (FDA) in the following year.[4a] In April 1984, the FDA gave approval to initiate clinical trials of taxol.

Until the filing of an INDA, a compound is tested on cell lines and animals only. The granting of an INDA allows the NCI to begin testing a compound on humans. These tests, called clinical trials, are sequenced into phases, each of which evaluates specific criteria of the compound. Phase I evaluates for safety, to establish that a compound is safe, with respect to dosage for human consumption (to determine a maximum tolerated dose (MTD)); phase II focuses on effectiveness; and phase III aims at comparison against standard therapies. In general the time needed to complete and the number of patients enrolled in clinical trials increases as the phases progress.

Phase I clinical trials for taxol began in April 1984 and were conducted at seven clinical sites.[35] The trials were initially hampered by acute hypersensitivity reactions that were believed to be caused by the use of Cremophor – a polyethoxylated castor oil – in the formulation but the problem was later solved by effective protocols such as prophylactic pretreatment with antihistamines and longer infusion times.[36] The main organ toxicities, such as myelosuppresion, peripheral neuropathy and mucositis in leukemia patients, are dose related and largely reversible. The recommended dose from Phase I studies was generally in the range of 200-250 mg/m^2 (of body surface area), administered in about 3 L of isotonic solution over a period of 6–24 hours.[37] Worthy of

mention is that several trials involving the co-administration of taxol and other drugs, such as cisplatin,[38] were also performed and gave favorable results.

In April 1985, Phase II clinical trials started with use of 24-hour continuous infusion and premedication regimen. Throughout the Phase I and the early Phase II clinical trials, taxol was in short supply and the number of studies was quite limited, so the clinical trials (especially for Phase II) were slowed down. The discovery by the Johns Hopkins group[39] in early 1989 that taxol had important activity in refractory ovarian cancer provided an impetus for the NCI to seriously consider the large-scale production of taxol.[40] In August 1989, the NCI issued a request for applications for a Cooperative Research and Development Agreement (CRADA) to expand supply and clinical trials leading to marketing of taxol. The CRADA competition was won by the Bristol-Meyers Company (soon to become Bristol-Myers Squibb Company) who, with its only contractor – Hauser Chemical Research and in cooperation with the NCI, did an outstanding job of making supplies of taxol available so that broad trials in major types of cancers were able to be conducted. For advanced ovarian cancer, taxol had a response rate of 30–35%, which was significant since these refractory cases had not responded to standard treatment;[39,41] for metastatic breast cancer, it gave a 56% response rate with manageable side effects;[42] for non-small-cell lung cancer, the response rate was 20-50%.[43] The proven efficacy of treating these cancers eventually led to successful marketing of taxol.

The New Drug Application (NDA) for refractory ovarian cancer was approved by the FDA in December 1992 and the Bristol-Myers Squibb Company (BMS) trademarked Taxol® and launched it to the public in 1993. The FDA approved in April 1994 the Supplemental NDA (SNDA) for the treatment of metastatic breast cancer and of breast

cancer that recurred within 6 months of initial chemotherapy treatment. It was also approved for a 3-hour infusion option in the treatment of metastatic ovarian and breast cancers. Then in 1997, the FDA approved Taxol for the second-line treatment of AIDS related Kaposi's sarcoma, and one year later for use in combination with cisplatin for the first-line treatment of non-small cell lung cancer in patients who are not candidates for surgery or radiation therapy. The clinical uses of Taxol are still being expanded as various combination therapies are being explored, for example, recent studies of Taxol have shown promise in Alzheimer's therapy.[44] After its launching on the market in 1993, Taxol quickly became a huge commercial success as the billion-dollar-per-year all time best-selling cancer treatment drug, with annual sales peaking at nearly $1.6 billion in 2000, the same year generic paclitaxel entered market.[45,46]

1.4 The Supply Issue and the Semisynthesis of Taxol

Even during the first years after taxol was launched in the market for the treatment of ovarian and breast cancers, the only method for large-scale production of taxol was the extraction from the bark of the Pacific yew, *Taxus brevifolia*, under good manufacturing practice (GMP) guidelines. But the limited availability of the bark, the low concentrations in the bark and the difficulty in large-scale production were still problems affecting the supply of taxol. The Pacific yew, *Taxus brevifolia*, is a very slow-growing conifer found principally in the understory of old-growth forests in the Pacific Northwest from northern California to Alaska, as well as the Cascade Range in Washington and Oregon, the western slopes of the Rockies, and the Lewis Range in

Montana. About 3,000 trees would need to be killed in order to obtain one kilogram of taxol for the treatment of only about 500 patients. The killing of the slow-growing trees, which may take 125 years to grow 9 meters high and 22 cm in diameter and yield only 3–5 pounds of bark from each tree (giving <0.5 g of taxol), caused ecological and environmental concerns and led to the legislation of the Pacific Yew Act (H.R. 3836) by Congress in 1992.[2]

Alternative ways, such as biosynthesis[47] and semisynthesis[48], for large-scale production of taxol were pursued. Significant work has been carried out both on the scientific study of the biosynthetic pathways to taxol and on the important practical application of plant tissue culture methods to its commercial production.[49] It has been recently reported by BMS and a Korean company called Samyang Genex that the commercial production of taxol by cell culture methods has been achieved but the details of the process have not been released.[47g]

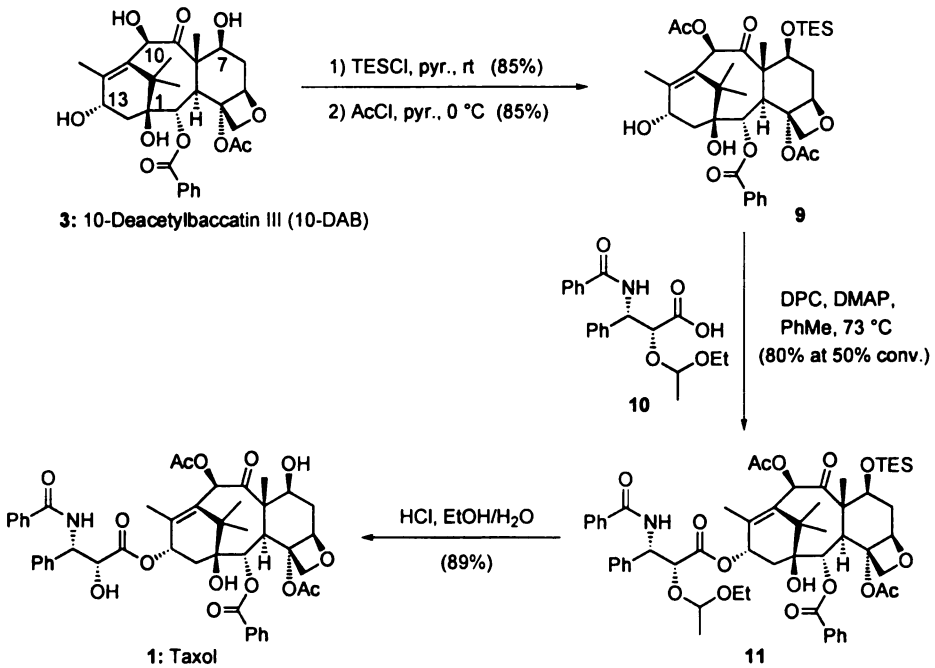
When discussing the supply issue and semisynthesis of taxol, one must also consider the taxol analog – Taxotere (**2**)[6] – the only other taxoid drug currently in clinical use. Taxotere, whose generic name is docetaxel, only differs in two functional groups from taxol (Figure 1.1), and it was first synthesized by French scientists Potier and coworkers.[50] This compound has the same mechanism of action as that of taxol but its potency is approximately twice that of taxol.[51] While most of the effects of Taxotere mirror those of taxol, it appears that the microtubules formed by Taxotere induction are structurally different from those formed by taxol induction.[52] An attractive feature of Taxotere is its increased solubility in water.[53]

The semisynthetic routes to taxol and/or Taxotere start from 10-deacetyl-baccatin III (10-DAB) **3**, which was isolated in 1981 by Potier and coworkers from the needles of the English yew, *Taxus baccata*.[54] This discovery was very significant for a number of reasons. First, 10-DBA is present in substantial concentration and its yield was much higher (~10 times) than that of taxol: about 1.0 g of 10-DAB per kilogram of fresh needles, compared with the yield of 100–150 mg of taxol from a kilogram of dried bark.[55] Secondly, it could be isolated easily and on a much larger scale from a very common English yew. Thirdly, perhaps most importantly, the needles are renewable, and there is no need to kill the trees, although the renewability of needles was not viewed as important until late 1980s, when growing requirements of the clinical trials increased the demand for bark and concerns about saving *Taxus brevifolia* began to surface. Thus, in order to synthesize taxol, the main goal is to attach the side chain at the C-13 position, which was proved to be essential for the anticancer activity from Wall and Wani's original work.[17]

After several preliminary attempts,[50] Potier, Greene and coworkers achieved the first successful semisynthesis of taxol with an intact side chain in 1988 (Scheme 1.1).[56] Since 10-DAB has four hydroxy groups, regioselectivity could be a problem when the side chain is installed. Of the three secondary hydroxyl groups, it was found that the two –OH groups on C-7 and C-10 were more reactive than that on C-13.[50] This is because the –OH group on C-13 is tucked underneath the concave face of the cup- or dome-shaped 10-DAB, which makes it sterically disfavored. The different reactivities were utilized by sequential protection of the two alcohols with TES- and acetyl groups before the –OH group at C-13 was reacted with the acid **10** under the influence of DPC-DMP to attach

the side chain. The yield was only 80% at 50% conversion, perhaps a reflection of the hindered nature of this hydroxyl group, thus leaving much room for improvement before this method could be considered commercially attractive. Acidic treatment of **11** provided taxol in 89% yield. This semisynthesis of taxol from 10-DAB (**3**) has served as the standard protocol for other modified procedures developed later.

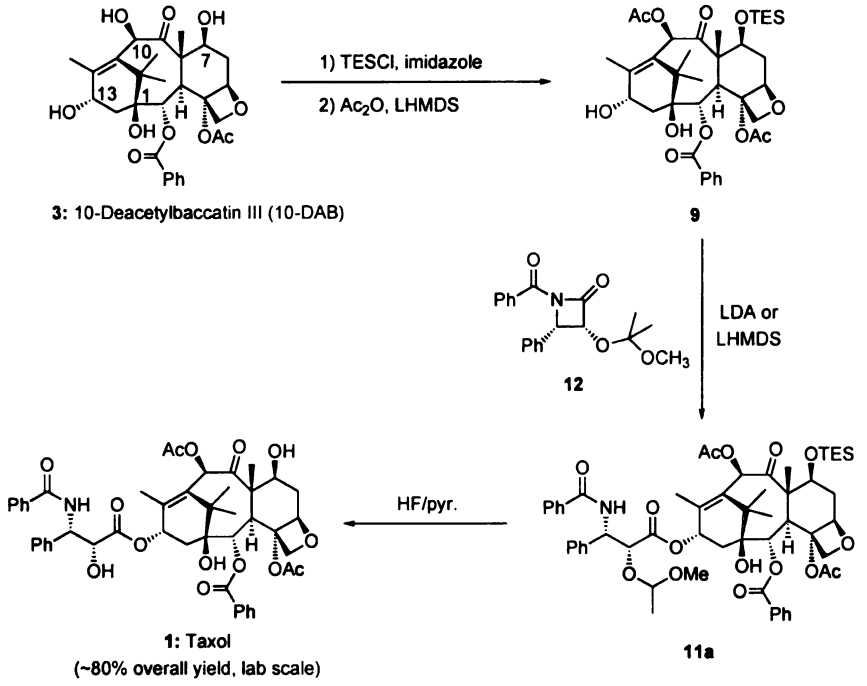
Scheme 1.1. Potier and Greene's Semisynthesis of Taxol.



Holton improved the synthesis by using a more compact β-lactam **12** in the esterification step, which proved to be more effective and efficient and proceeded in nearly quantitative yield.[57] The lactam **12** was initially prepared by chiral resolution of racemic material, however, Ojima subsequently reported a practical asymmetric synthesis of this β-lactam.[58] Deprotection of the C-2' hydroxyl group in **11a** could be carried out using HF/pyridine to give taxol in >98% yield. Holton had patents issued in 1991 and 1992 that were later licensed to BMS. In 1995, BMS started the large-scale production of

taxol by semisynthesis following Holton's approach, which is still the method currently used by BMS for the commercial synthesis of taxol.[47g]

Scheme 1.2. Holton's Semisynthesis of Taxol.



1.5 TOTAL SYNTHESIS OF TAXOL

The total synthesis of taxol represents one of the greatest challenges to synthetic chemistry. Taxol contains an unusual and distorted ABCD ring system with a large number of stereocenters to be controlled; the central B-ring is an eight-membered carbocycle which is notoriously difficult to form because of both entropic and enthalpic factors; the A-ring includes a somewhat problematic bridgehead double bond formally forbidden in a six-membered ring by Bredt's rule;[59] the C-ring is *trans*-fused with its angular methyl group. Moreover, the high degree of oxygenation in the molecule requires

that each oxygen is introduced in a manner such that they can be differentially protected. Additionally, the oxetane ring can open under acidic or nucleophilic conditions, and the –OH group at C-7 may epimerize under basic conditions if left unprotected. All of these considerations taken together constitute a formidable challenge to the synthesis of taxol, but on the other hand, it should not be surprising to find that it is precisely these challenges that have attracted the attention of some of the world's best synthetic chemists and that there are many hundreds of papers in the literature describing approaches to the synthesis of taxol. Synthetic chemists like to challenge their chemical ingenuity and like to conquer "a molecular Mount Everest".[60]

An added incentive was the fear in the early 1990's that natural supplies of taxol would be inadequate to meet the demand for the drug, which gave hope that a synthetic approach could overcome the problem. This concern was alleviated by the development of semisynthetic approaches described above. Furthermore, a total synthesis would likely take 40–50 steps and give low overall yield making it essentially impossible to be considered for a practical process for commercialization. Nonetheless, the promise of the preparation of new analogs and the challenge of developing new synthetic methods continues to provide a rationale for new synthetic approaches. Studies to date have culminated in six completed total syntheses of taxol.

1.5.1 Completed Total Syntheses and Their Strategies

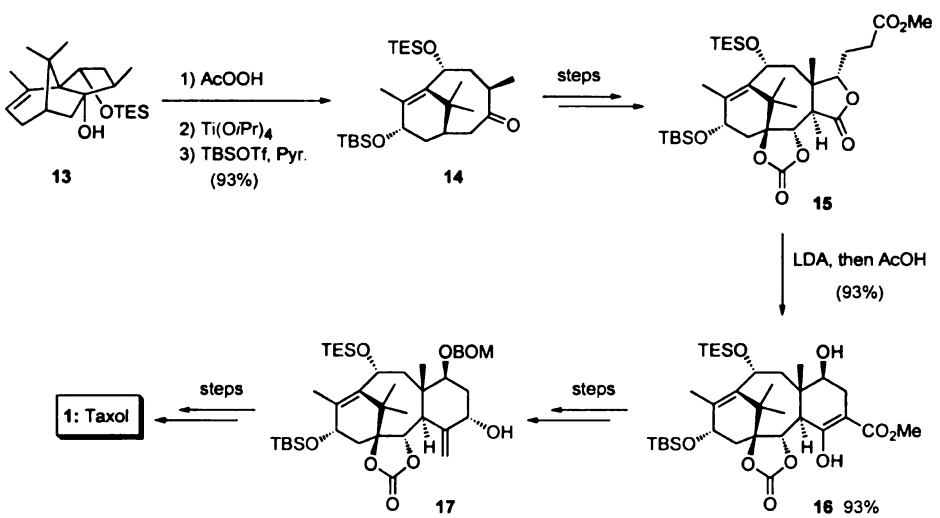
The first two total syntheses of taxol were completed in 1994 by Holton[61] and Nicolaou[62], respectively and essentially simultaneously. Holton actually submitted his synthesis for publication more than a month earlier than Nicolaou, but it appeared a week

later. The journal of *Chemistry and Industry* described the two events as a "photo-finish in the race to artificial taxol".[63] After that, four other groups reported their successful syntheses. The following description will only highlight each of the six elegant completed total syntheses, focusing on their strategies and key steps.

The Holton Synthesis[61]

Holton's synthesis is a linear approach and in the form of AB → ABC → ABCD, which was built on his earlier synthetic studies on taxusin[64] and his discovery of the "epoxy alcohol fragmentation" to install the AB ring system. As shown in Scheme 1.3, this fragmentation worked well to give **14** in 93% yield from **13**, which was readily prepared from commercial available Patchino (β-patchoulene oxide). The AB-ring synthon **14** was then converted to lactone **15**, which underwent the Dieckmann cyclization to form the C-ring. The elaboration of the oxetane D-ring was achieved through the key intermediate **17**. Holton's total thesis of taxol was completed in 41 steps in ca. 2% overall yield.

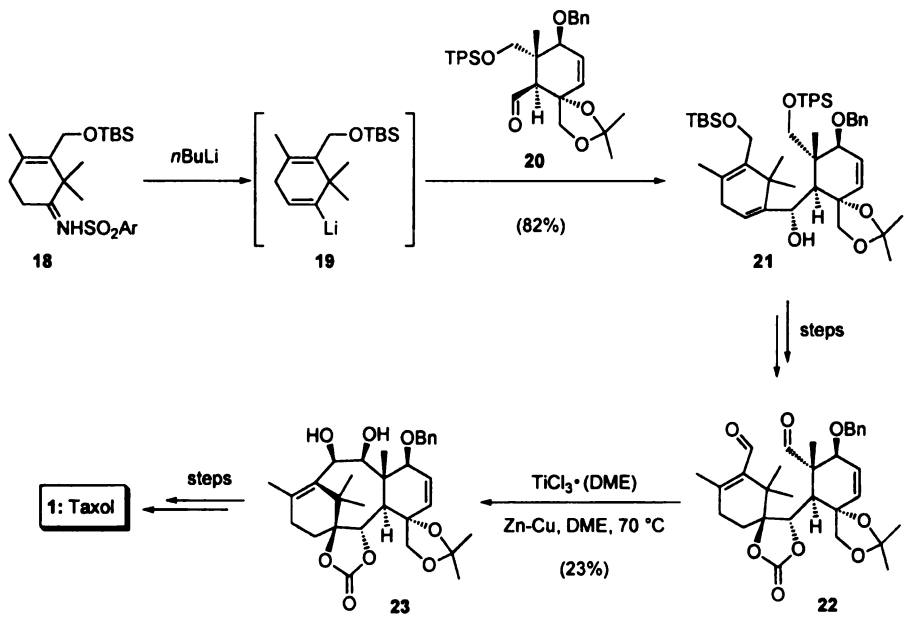
Scheme 1.3. Holton's Approach to the Taxol Skeleton



The Nicolaou Synthesis[62]

Nicolaou adopted a late 8-membered ring formation with a convergent A- and C-ring union, and the synthesis is of the form A + C → A–C → ABC → ABCD. Both A- and C-ring precursors **18** and **20** were prepared by the Diels-Alder reaction with different dienes and dienophiles followed by functional group manipulations. One of the key coupling reactions was to link **18** and **20** using a Shapiro reaction via the in-situ generated lithium species **19** (from sulfonylhydrazone **18**) to form the alcohol **21** with correct stereochemistry at C-2 (taxol skeleton numbering). The second key step was the McMurry coupling of the bis-aldehyde **22** which proved to be troublesome, and even after careful experimentation the best yield of **23** obtained was only 23–25%, with side products being formed in significant amounts. The total synthesis of taxol by Nicolaou and coworkers takes 51 steps and the overall yield is only ca. 0.03%.

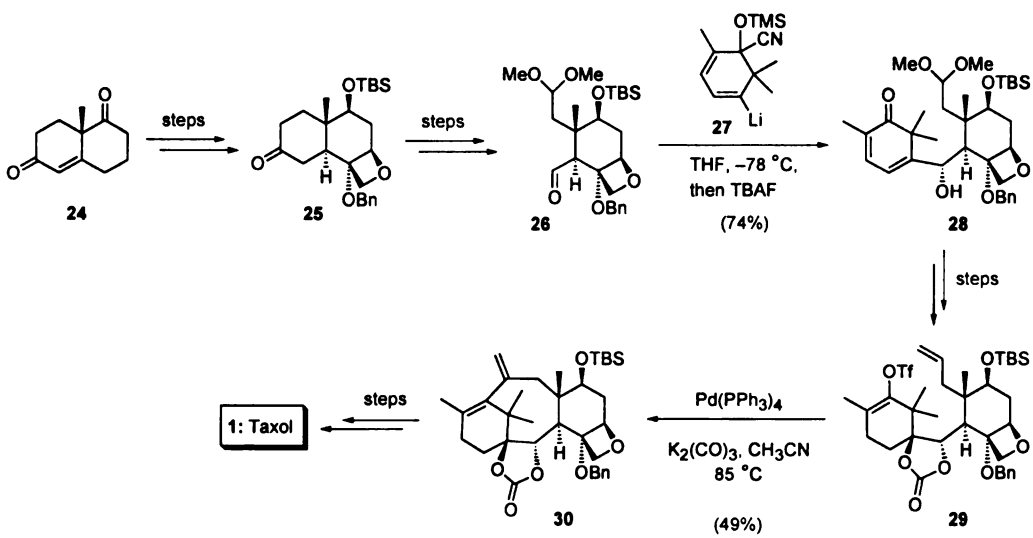
Scheme 1.4. Nicholaou's Approach to the Taxol Skeleton



The Danishefsky Synthesis[65]

The Danishefsky synthesis is of the form C → CD → A–CD → ABCD, and it is the only synthesis to date in which the oxetane D-ring is incorporated early and maintained throughout the synthesis. A key to this strategy was the protection of the C-4 hydroxyl group as its benzyl ether (e.g. in **25**) rather than an acetate to avoid the neighboring group participation by acetate which is a large part of the reason for the oxetane ring's lability in taxol.[66] This synthesis makes effective use of the enantiomerically pure Wieland-Miescher ketone **24** and all the stereochemistry of the ABCD system derives from the chiral center of this ketone. Coupling of the aldehyde **26** with the in-situ generated lithium species **27** (from the corresponding iodide), after treatment of TBAF, gave **28** as a single diastereomer, perhaps analogous to Nicolaou's similar precedent. The key cyclization to give the ABCD system was achieved by an impressive Heck reaction of **29**. Further functionalization of **30** and the completion of the synthesis rely on a few known methods. The Danishefsky's synthesis requires 47 steps from the Wieland-Miescher ketone and the overall yield is ca. 0.2%.

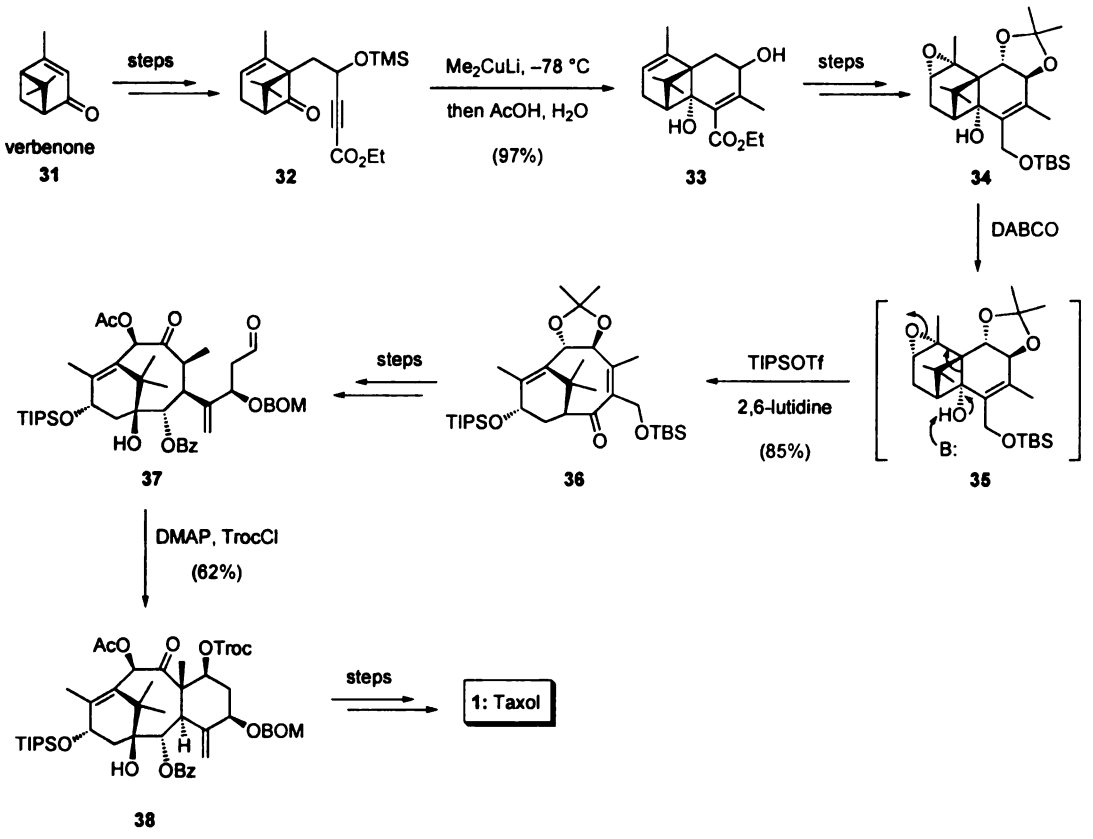
Scheme 1.5. Danishefsky's Approach to the Taxol Skeleton



The Wender Synthesis[67]

Wender utilized a linear approach in the form A → AB → ABC → ABCD, but it is very different from the formally similar Holton synthesis. The synthesis relies on a key rearrangement reaction of intermediate **34** derived from verbenone **31**, the oxidation product of the abundant natural product pinene. The tricyclic intermediate **33** was readily prepared from **31** in five steps, and was then converted to epoxide **34** which set up the base catalyzed fragmentation to give the AB synthon **36** in 85% yield. The C-ring was installed via an aldol condensation (**37** → **38**). This synthesis, which took 37 steps from verbenone in an overall yield of ca. 0.2%, was claimed to be the shortest reported synthesis of taxol.

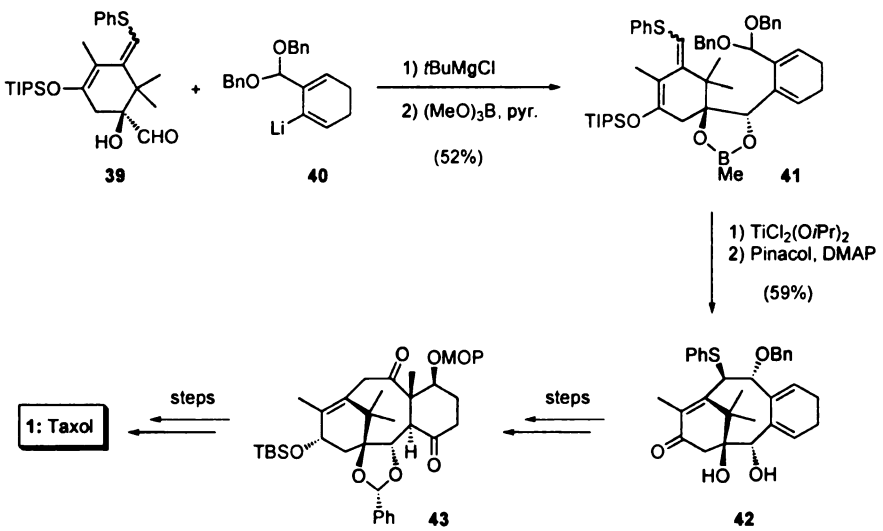
Scheme 1.6. Wender's Approach to the Taxol Skeleton



The Kuwajima Synthesis[68]

The Kuwajima synthesis uses an A + C → A–C → ABC → ABCD approach. A highly functionalized A-ring synthon **39** was brought together with the C-ring precursor **40** to form **41**, which then underwent Lewis acid-catalyzed cyclization to give the ABC tricyclic system **42**. One difference of this synthesis with previous approaches is the protection of the C-1 and C-2 hydroxyl groups late into the synthesis as a cyclic benzylidene acetal (e.g. in **43**) rather than a cyclic carbonate. Another feature of interest was that all the stereochemistry was derived from the C-1 position of the aldehyde **39**.

Scheme 1.7. Kuwajima's Approach to the Taxol Skeleton

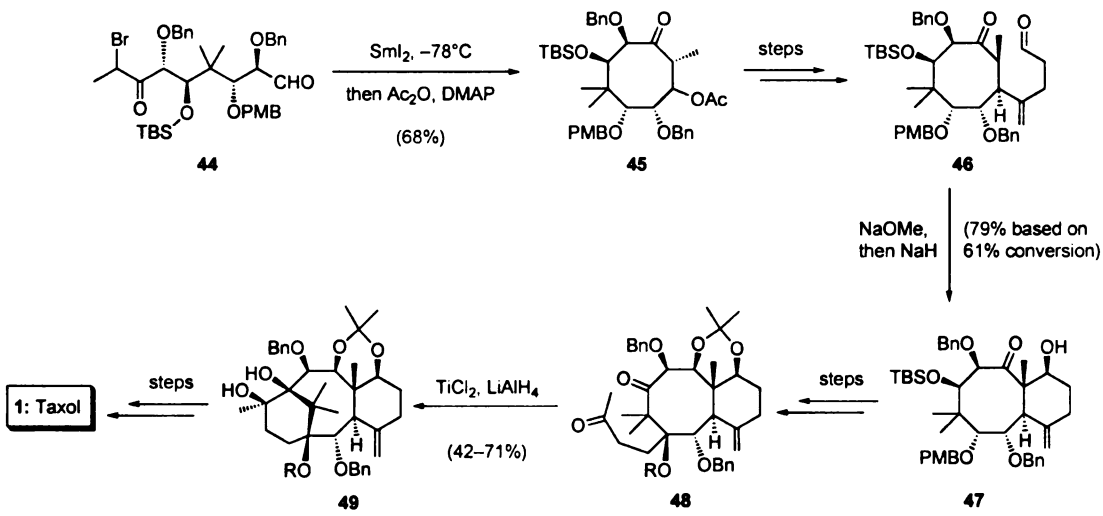


The Mukaiyama Synthesis[69]

The Mukaiyama synthesis is unique in that the B-ring was formed first, leading to a B → BC → ABC → ABCD approach. Cyclization of the bromoaldehyde **44** in the presence of SmI_2 gave the B-ring synthon **45** in 68% yield. The intramolecular aldol condensation of **46** installed the C-ring, followed a few steps later by a pinacol reduction

(McMurry coupling) of **48** to give the ABC tricyclic system **49** in yields ranging from 42–71%, depending on which silyl protecting group was used for the C-1 hydroxyl group.

Scheme 1.8. Mukaiyama's Approach to the Taxol Skeleton



As mentioned earlier, the total synthesis of taxol is unlikely to be used for its commercial production, but the rich and diverse chemistry that was developed during the process was incredibly enormous, as has been demonstrated in the six completed total syntheses.

1.5.2 Some Other Strategies to Access the ABC Tricyclic System

Besides the completed syntheses by the six labs cited above, more than fifty groups world-wide have published articles on their synthetic approaches.[70] When searching the literature, one has to be amazed by so many fascinating constructions and proposed constructions that have been adumbrated and disclosed. Some of the approaches to access the ABC tricylic core are:[71] Swindell's amide fragmentation,[72] Blechert's[73] and Winkler's[74] retroaldol condensations, Shea's[75], Jenkin's[76] and Winkler's[77] intramolecular

Diels-Alder approaches, Blechert's oxidative ring expansion,[78] Trost's fragmentation,[79] Kishi's Nozaki reaction,[80] Paquette's oxy-Cope approach,[81] Funk's intramolecular Claisen rearrangement,[82] Yadav's Wittig rearrangement (ring contraction),[83] Patteden's radical cyclization,[84] Wang's sequential anionic condensation,[85] etc. Many of these may not carry realistic prospects for maturing into comprehensive total synthesis, but the chemistry that was developed for the various approaches to taxol is still remarkable and enormous.

1.6 Studies on Taxol Analogs and Structure–Activity Relations (SARs)

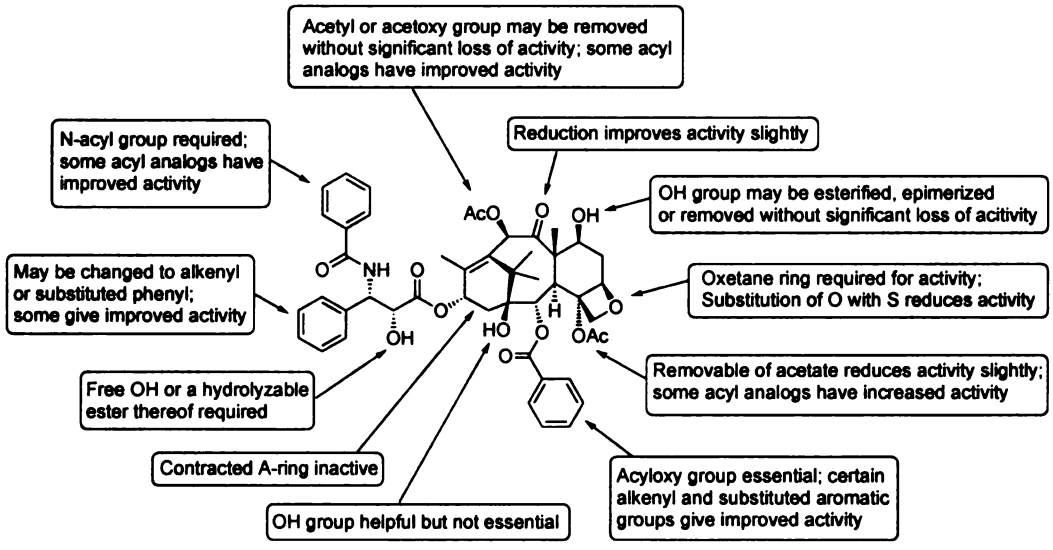
The studies on taxol derivatives and other analogs, in addition to Taxotere, have been very active, with the main purpose of better understanding the structure-activity relationships (SARs) and searching for a new generation of taxol-based antitumor agents with improved physical, chemical and biological profiles. As an example of the latter, it would be most important to have the drug delivered more selectively to the tumor cells. Among the numerous taxol analogs, about two dozen have entered preclinical development, four are currently in phase I clinical trials and six additional analogs are in phase II clinical trials.[47g]

The limited water-solubility of taxol and its initial clinical use requiring a 24-hour infusion prompted great interest in developing more water soluble prodrugs.[86] However, clinicians found later that the infusion times could be reduced to 3 hours, and this removed much of the initial impetus for prodrug development. At this time, therefore, no

prodrugs have entered the market place, but the prodrug approach continues to be of interest as a mechanism for targeting taxol to its site of action.[87]

As mentioned earlier, much of the chemical work on taxol derivatives and analogs has been carried out with a view to determining structure-activity relationships for these compounds and defining the key pharmacophore of taxol.[88] Some of the work is summarized in Figure 1.2, where the key structure-activity relationships of taxol are shown.

Figure 1.2. The Structure-Activity Relationships (SARs) of Taxol.



It is of interest to mention that some bridged analogs of taxol were also prepared and studied, with some showing interesting results and others proving to be inactive.[89] Recent studies by the Horwitz and Kingston groups have shown that the side chain of taxol may be not as essential for activity as was previously thought.[90]

Before concluding this chapter on the biology and chemistry of taxol, it should be mentioned that although taxol was for many years unique in terms of its mechanism of

action, in recent years a number of other natural products have been found to promote the assembly of tubulin into microtubules in the same way as taxol does. The most important and familiar compounds in this class are epothilones A and B,[91] discodermolide[92] and eleutherobin.[93] Efforts were also directed to prepare compounds including both taxol fragment and fragments of these compounds, such as epothilone A, to examine whether improved activity would be achieved.[94]

Taxol has revolutionized the treatment options for patients with advanced forms of breast and ovarian cancers as well as some other types of cancers. As discussed in the previous sections, much fascinating chemistry has also been developed following synthetic explorations pertinent to taxol, and it continues to grow.

All of the work in this thesis was either the result of efforts directly aimed at the synthesis of taxol or the result of serendipitous findings on the way to taxol that led to completely unanticipated areas of chemistry that were of sufficient significance to demand investigation on their own merits.

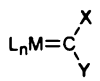
CHAPTER TWO

SYNTHETIC STUDIES TOWARD TAXOL: UTILIZING THE WULFF–KAESLER REACTION OF FISCHER CARBENE COMPLEXES AND 1,6-ENYNES

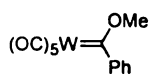
2.1 FISCHER CARBENE COMPLEXES AND THE WULFF–KAESLER REACTION

Transition metal carbene complexes, which have a trigonal planar carbon connected to the metal, contain a formal double bond between the metal and the carbon. The general structure of a metal-carbene complex is shown in **50** (Figure 2.1), where X and Y can be alkyl, alkenyl, alkynyl, aryl, H, or heteroatom-containing (O, N, S, halogens) groups.

Figure 2.1. Metal-Carbene Complexes **50** (General Structure) and **51**



50



51

The tungsten complex **51** was the first characterized stable transition metal carbene complex that was reported by Fischer and Massböl in 1964.[95] This report ushered in the important, dynamic and exciting area of chemistry in metal carbene complexes, which has attracted literally hundreds of chemists to explore the chemistry in this

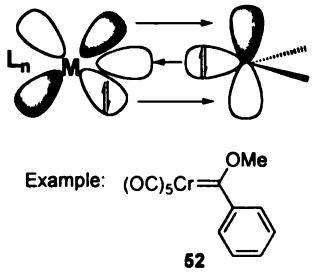
field.[96,97] The investigations have led to the discovery of numerous new complexes, novel reactions and have resulted in a great number of applications to organic synthesis.[97]

2.1.1 Fischer Carbene Complexes: The Background

There are two types of metal-carbene complexes: the Fischer type[95,96] and the Schrock type.[98] Each represents a different formulation of the bonding of the CXY group to the metal (a general structure shown in **50**), and therefore they differ in several ways.[99]

The Fischer carbene complexes contain middle to late transition metals, such as chromium, tungsten and iron, which are in low oxidation states (Figure 2.2). Due to the electron richness of the metal, the ancillary ligands are usually good π acceptors, which are most commonly CO and PPh_3. The carbene carbon is normally stablized by an electronegative heteroatom, for example, nitrogen, oxygen or sulfur. Fischer carbene complexes are considered to have a singlet ground state if removed from the metal. Consequently, the carbene ligand is regarded as a 2-electron σ donor through its filled sp^2 orbital and as a weak π acceptor via back donation of electrons from a filled metal *d* orbital to the empty *2p* orbital of the free carbene. As a result, the carbene carbon of a Fischer-type complex is typically electrophilic.

Figure 2.2. Fischer-type Carbene Complexes



Example: $(OC)_5Cr$=C(OMe)(Ph)

52

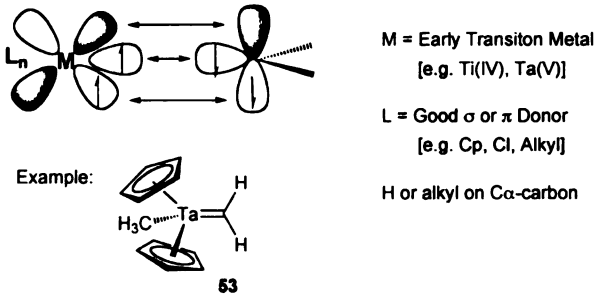
M = Middle to Late Transiton Metal
[e.g. Cr(0), W(0), Mo(0), Fe(0)]

L = Good π Acceptor
[e.g. CO, PPh_3]

Heteroatom on Cα-carbon
[e.g. O, N, S]

On the other hand, Shrock-type carbene complexes contain early transition metals in high oxidation states, such as titanium(IV) and tantalum(V) (Figure 2.3), therefore, good σ or π donor ligands are required (e.g. cyclopentadienyl ligand (Cp), alkyl groups and chlorine). The substituents on the carbene carbon are usually alkyl groups and/or hydrogen. Since Schrock carbene complexes are considered to have a triplet ground state if removed from the metal, the carbene ligand is regarded as a dianionic ligand in its formal oxidation state to form two covalent bonds, and as a result, the carbene carbon is often nucleophilic.

Figure 2.3. Schrock-type Carbene Complexes



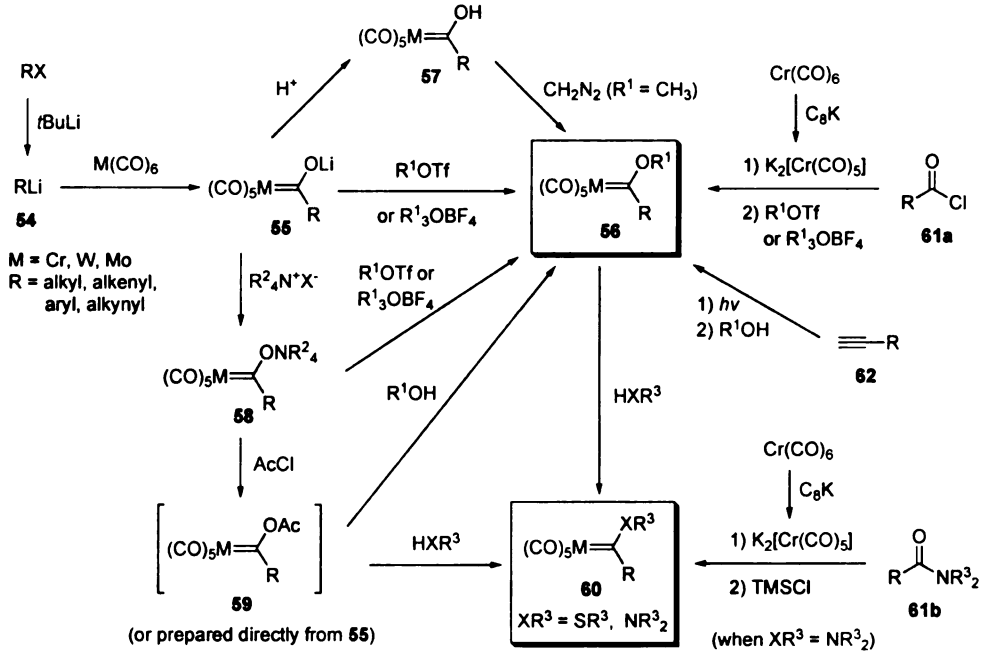
The Wulff research group has been interested in Fischer carbene complexes for more than two decades, mainly focusing on their applications to organic synthesis. Thus, the following discussion will be largely limited to the Fischer carbene complexes.

The Preparation of Fischer Carbene Complexes.

The most commonly used methods for the preparation of Fischer-type carbene complexes are summarized in Scheme 2.1. The most extensively studied Fischer carbene complexes are group 6 complexes with chromium and tungsten complexes as the more common ones. Many of the alkoxy carbene complexes **56** can be conveniently prepared from the corresponding organolithium reagent **54**, where R can be an alkyl, aryl, alkenyl

or alkynyl group. Addition of the organolithium to a group 6 hexacarbonyl gives the lithium metal acylate **55** which is then followed by alkylation with a trialkyloxonium tetraflouroborate[100] or an alkyl trifluoromethane sulfonate[101]. This procedure is normally referred to as the standard Fischer protocol. The yields of carbene complexes by this method are usually good to excellent and most complexes are solids that can be purified by crystallization. Alternatively, since most Fischer carbene complexes can be handled in the presence of air, their purification can be accomplished by silica gel column chromatography. The sensitivity of the complexes to air increases with temperature and an inert atmosphere is normally employed for reactions carried out above room temperature.

Scheme 2.1. The Preparation of Fischer Carbene Complexes



The lithium acylate **55** can also undergo cation exchange with tetraalkylammonium halide to give a stable tetraalkylammonium acylate **58** which can be easily isolated and is more reactive to a given electrophile than the corresponding lithium

acylate. The reaction of **58** with an acyl halide such as acetyl chloride produces an acyloxy carbene complex of the type **59** that is often too unstable for isolation under ambient conditions but its reactivity can be utilized in the preparation of a variety of heteroatom stabilized complexes (e.g. **56** and **60**) by substitution reactions with alcohols, amines and thiols.[102] Acyl complexes of the type **59** can also be generated by reacting the lithium acylate **55** directly with an acyl halide; however, the yield is usually much lower than that from the reaction from **58**. Alternatively, the amino and thiol complexes of the type **60** may be prepared by the direct treatment of the alkoxy complexes **56** with amines and thiols.[103]

Perhaps the most important non-Fischer synthesis of carbene complexes of the types **56** and **60** is by the reactions of the pentacarbonyl chromate dianion with acid halides **61a** and amides **61b**, respectively.[104] This approach is especially useful for the preparation of complexes with a quaternary carbon center next to the carbene carbon, which usually cannot be efficiently made by the standard Fischer protocol.

In addition to these thermal methods discussed above, another approach for the preparation of alkoxy carbene complexes **56** uses metal carbonyl and an alkyne **62** under photochemical conditions.[105] It involves the rearrangement of a metal alkyne complex to a metal alkylidene complex which is then trapped by an alcohol. An advantage of this method is that highly reactive anionic reagents need not be employed; however, the reaction works well only in specific systems and has yet to be optimized for general use.

Reactions with Fischer Carbene Complexes.

The growth in the number of useful reactions and their applications has been exponential with time since the discovery of the first Fischer carbene complex in 1964.[95] The reactions involving Fischer carbene complexes can be divided in two main categories: reactions at the metal center and those at the carbene-carbon substituent.[97] There have been a number of comprehensive reviews of this rich chemistry over the past decades,[97] and some of the major reactions are summarized below.

The two most extensively studied reactions of Fischer carbene complexes at the metal center are cyclopropanation and benzannulation reactions.[97] The cyclopropanation reaction, a formal [2 + 1] cycloaddition, is one of the first reactions of carbene complexes to be investigated, which has been driven not only by potential synthetic applications, but also due to the relationship of this reaction to olefin metathesis.[106] A brief background of the cyclopropanation will be discussed in Chapter 3.

The benzannulation reaction (Dötz-Wulff reaction) of α,β-unsaturated Fischer carbene complexes with alkynes generates new benzene rings that have 1,4-dioxygen substitution. This process occurs in the coordination sphere of the metal under neutral conditions at or near ambient temperature. This reaction has evolved as a very valuable method for the preparation of *p*-alkoxy phenols and quinones and is the most extensively applied reaction of Fischer carbene complexes in organic synthesis.[97] An overview of this reaction, including its mechanistic considerations, the scope and limitations of the reaction and its synthetic applications, will appear in Chapter 4.

In addition to the cyclopropanation and benzannulation reactions, there are many other cycloadditions that take place at the metal center in the coordination sphere of the

metal. Among those is the formation of four-membered and five-membered rings through the coupling of the carbene ligand with alkynes.[97c,d,107]

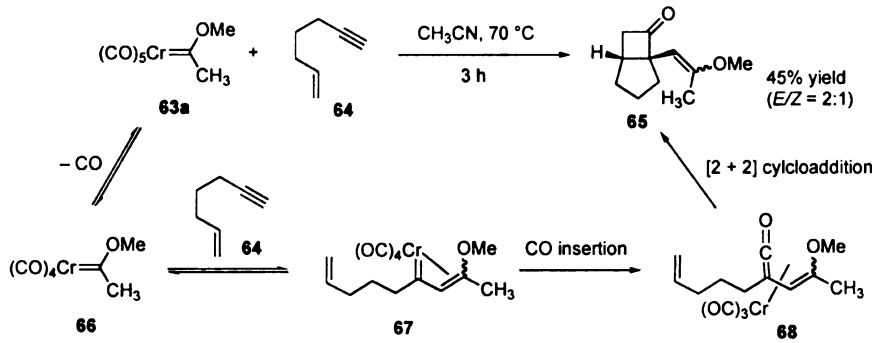
Reactions of Fischer carbene complexes can also occur at the carbene-carbon substituent, where the metal plays the role of reactivity and selectivity auxiliary.[97c,d] For example, α,β-unsaturated alkenyl or alkynyl carbene complexes can act as dienophiles in the Diels-Alder reaction with significant rate enhancement and better regioselectivity over their corresponding ester analogs.[108] These carbene complexes can also undergo [2 + 2] cycloadditions with olefins (mainly for alkynyl complexes),[109] or react with nucleophiles in Michael additions.[110] In addition, the α-carbon of Fischer carbene complexes can be easily deprotonated[111] and the resulting 'metallo-enolate' can participate in aldol condensations with aldehydes and ketones.[112]

2.1.2 The Wulff–Kaesler Reaction of Fischer Carbene Complexes and 1,6-Enynes

The Wulff–Kaesler reaction, a chromium-mediated intramolecular [2 + 2] cycloaddition, was first reported in 1985 for the reaction of Fischer carbene complex **63a** with 1,6-enyne **64** which gave the bicyclo[3.2.0]heptanone **65** in 45% yield (Scheme 2.2).[113] The mechanistic pathway is believed to involve an alkyne insertion in the 16-electron species **66** to generate the η^1,η^3-vinyl carbene complexed intermediate **67**, which then undergoes the insertion of a CO ligand to give vinyl-ketene complex **68** that is trapped intramolecularly by the olefin via a [2 + 2] cycloaddition to afford the bicyclo[3.2.0]heptanone **65**. This was the first example of the chromium-mediated intramolecular [2 + 2] cycloaddition, although similar intramolecular cycloadditions involving metal-free ketenes with tethered olefins are well documented.[114]

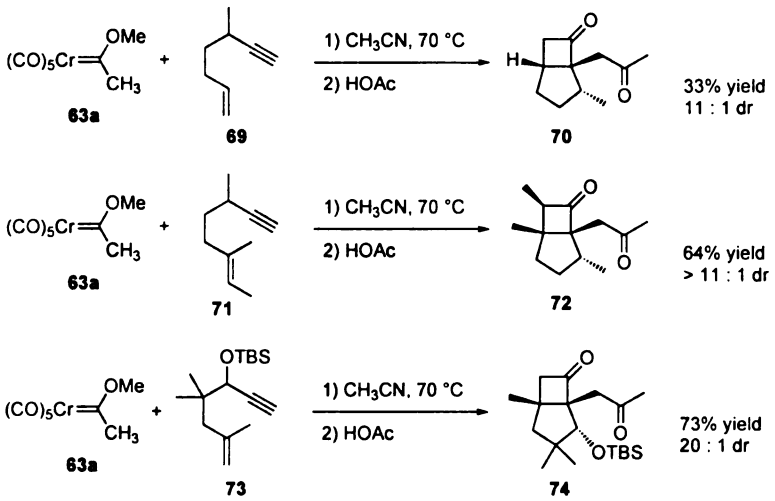
Cyclobutanones have been proven to be versatile synthetic intermediates of great value in organic synthesis.[115]

Scheme 2.2. The Wulff-Kaesler Reaction and Its Mechanism



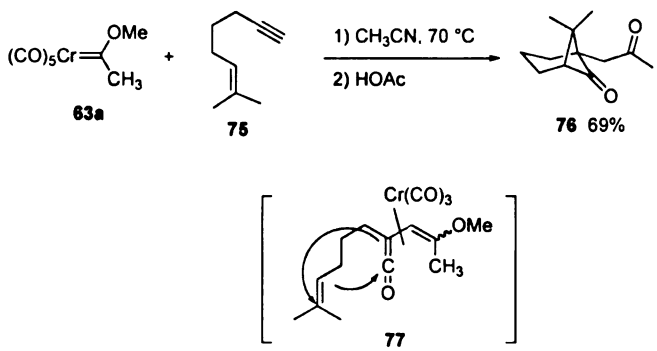
Wulff and Kim further reported in 1993 that this reaction could be carried out with 1,6-enynes having different substitution patterns,[116] and some examples are shown in Scheme 2.3. It was observed that the solvents could have a big effect on the product distribution. Bicycloheptanone products were formed exclusively in a polar and coordinating solvent such as acetonitrile, while in a non-polar and non-coordinating solvent, such as hexane, furans and cyclopentenones were formed.[117] It was also found that metal-mediated reactions showed faster rates and improved stereoselectivities in comparison with the corresponding metal-free cycloadditions of ketenes and alkenes.

Scheme 2.3. Stereoselection in the Wulff-Kaesler Reaction



One of the interesting findings was that, when the olefin in the enyne (as in **75**) was disubstituted at the remote end from the alkyne, bicyclo[3.1.1]heptanone **76** was obtained via a crossed [2 + 2] cyclization of the ketene intermediate **77**.[118] The product **76** has geminal dimethyl groups on the six-membered ring which resembles the taxol A-ring. Further functionalization, such as the incorporation of the C-ring, seemed possible, thus plans began to be considered for the utilization of bicyclo[3.1.1]heptanones of the type **76** as A-ring synthons of taxol and taxane derivatives (refer to Fig. 1.1).

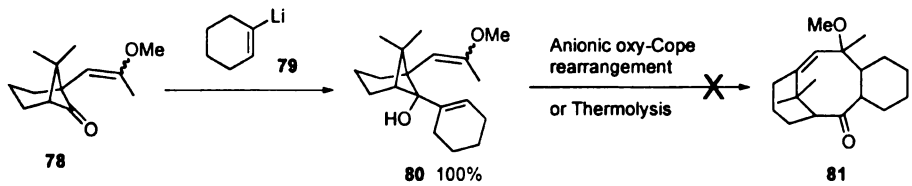
Scheme 2.4. Bicyclo[3.1.1]heptanone **76** from a Crossed [2 + 2] Cycloaddition



2.2 THE RETROSYNTHETIC STRATEGY TOWARD THE TAXOL SKELETON AND PREVIOUS EFFORTS

As mentioned in Section 2.1.2, a plan was initiated to apply the Wulff–Kaesler reaction of Fischer carbene complexes and 1,6-enynes to the construction of synthons for the A-ring of taxol and other taxane derivatives. Dr. Kim first looked at the possibility of using an oxy-cope rearrangement to synthesize the ABC tricyclic skeleton. As shown in Scheme 2.5, the alcohol **80** was prepared quantitatively from the bicyclo[3.1.1]heptanone **78**, but attempts to install the B-ring through anionic oxy-Cope rearrangement or thermolysis (refluxing in xylene) did not afford the desired tricyclic compound **81**.[117] In related studies on the metal-free [2 + 2] cycloaddition, Snider reported that anionic Cope rearrangements of molecules of the type **80** were only successful for unsubstituted allylic alcohols generated by the addition of vinyllithium to a ketone. More highly substituted alkenyllithium adducts (e.g. an analog of the type **80)** failed to react, thus the introduction of the C-ring could not be realized.[114c] Based on these literature results as well as Kim's unsuccessful attempts, the strategy of using anionic oxy-Cope rearrangements to construct the ABC tricyclic core was abandoned.

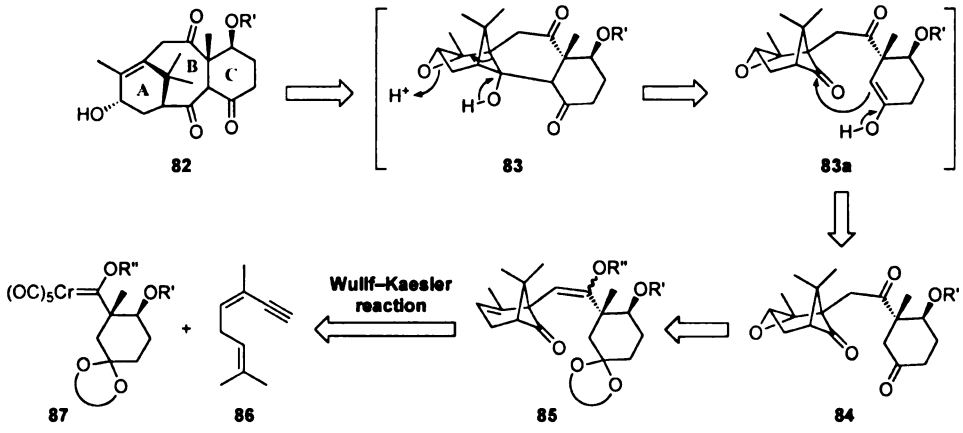
Scheme 2.5. Kim's Initial Attempts on the ABC-Tricyclic Skeleton



A completely different strategy was then devised as shown in Scheme 2.6. It was envisioned that rapid entry into the ABC tricyclic core of taxol be achieved by utilizing the Wulff–Kaesler reaction of carbene complex **87** and enyne **86** which should give the

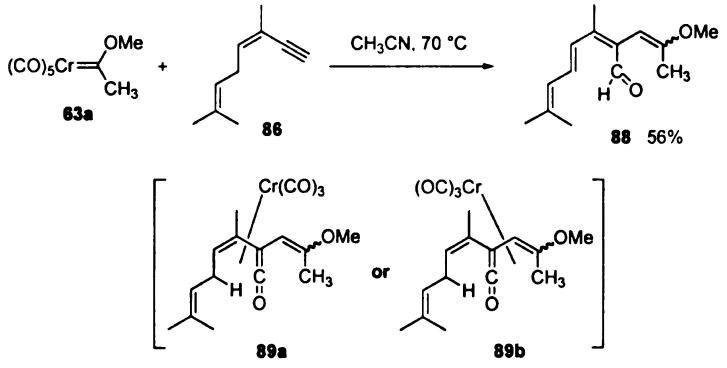
bicyclo[3.1.1]heptanone **85** as a suitable A–C synthon. It was considered that **85** could be further manipulated for subsequent condensation and fragmentation into the ABC skeleton, for example, via acid induced epoxide-ring cleavage of **83**.

Scheme 2.6. Second Generation of Retrosynthetic Strategy



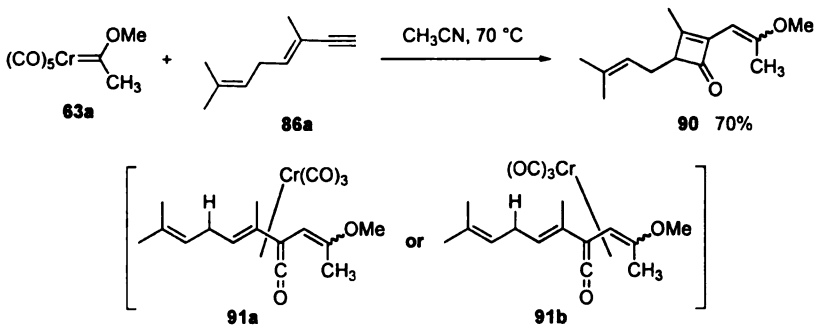
The feasibility of the strategy outlined in Scheme 2.6 was then investigated. Unfortunately, the reaction of carbene complex **63a** with the *cis*-dienyne **86** did not give the [2 + 2] cycloaddition product, instead, a 56% yield of the aldehyde **88** was isolated (Scheme 2.7).[119] This result was rationalized by suggesting that either the vinyl ketene complex **89a** or **89b** was generated during the reaction and underwent a [1,5] sigmatropic hydrogen shift to form **88** rather than an intramolecular [2 + 2] cycloaddition.

Scheme 2.7. Attempted Wulff-Kaesler Reaction with Dienyne **86**



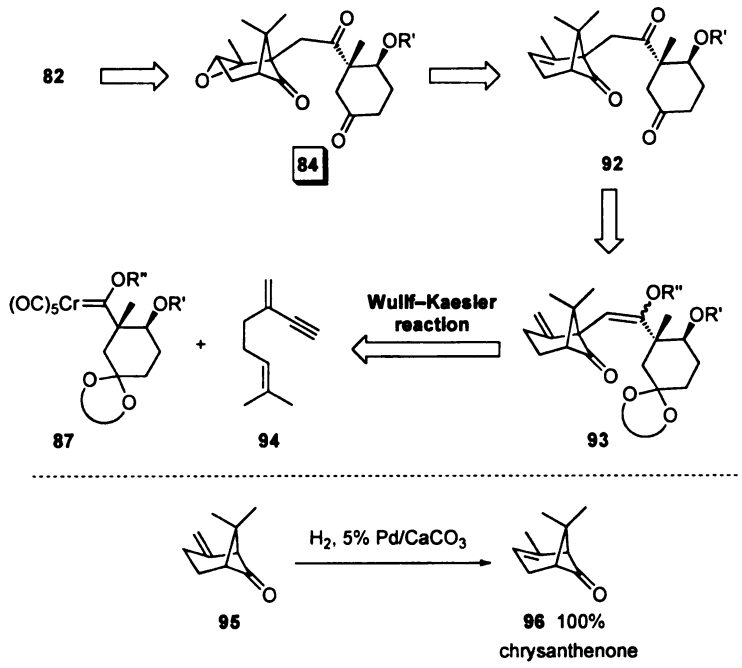
In an effort to prevent the proposed [1,5] sigmatropic shift that gave rise to **88**, the *trans*-dienyne **86a** was then prepared. Presumably, the formation of an aldehyde via [1,5]-H shift would be geometrically prevented by the *E*-configuration of the alkene, as shown in **91a/b** in Scheme 2.8. However, an intramolecular [2 + 2] cycloaddition of **91a/b** would also not be possible because it would otherwise result in the generation of a six membered ring with a *trans*-double-bond. Interestingly, the cyclobutenone **90** was isolated in 70% yield, probably resulting from the electrocyclic ring closure of the vinyl ketene complex **91a.**

Scheme 2.8. The Reaction of Complex **63a** with Dienyne **86a**.



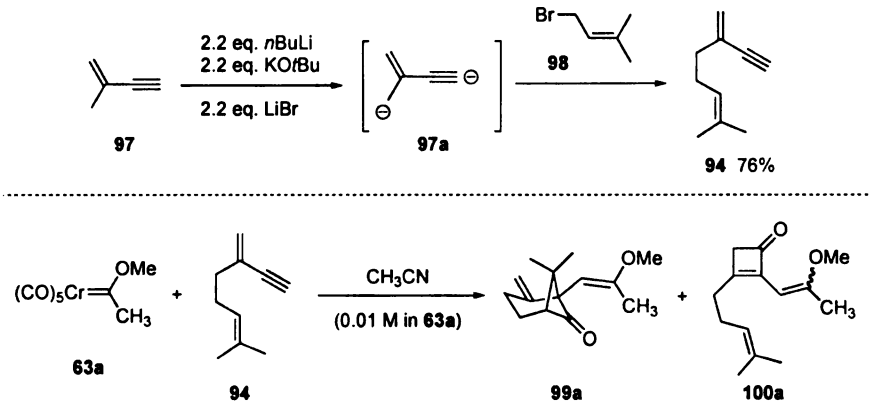
The failure of dienyne **86** to form bicyclo[3.1.1]heptanone products upon reaction with the chromium carbene complex **63a** indicated that the strategy for the synthesis of taxol outlined in Scheme 2.6 was not viable. A slight modification of the strategy was suggested by the known isomerization of the bicyclo[3.1.1]heptanone **95** to chrysanthenone **96**, as shown in Scheme 2.9.[120] If the same isomerization could be effected on intermediate **93** then the original strategy could be saved since epoxidation of **92** would intersect with intermediate **84** (cf. Scheme 2.6) and the new (third generation) retrosynthesis would descend to the isomeric exo-methylene dienyne **94** and the carbene complex **87**.

Scheme 2.9. Third Generation of Retrosynthetic Strategy



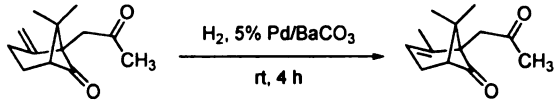
The dienyne **94** could be conveniently synthesized in 76% yield in one pot from the commercially available isopropenyl acetylene **97** by utilizing Brandsma's method,[121] presumably via the dipotassio derivative after treatment with the Lochmann-Schlosser reagent (*n*BuLi–KO*t*Bu)[122] and subsequent transformation into the lithiated dianion by the cation exchange with anhydrous lithium bromide (Scheme 2.10). The reaction of dienyne **94** and carbene complex **63a** afforded the desired bicyclo[3.1.1]heptanone **99a**, along with a substantial amount of the cyclobutenone **100a** being formed as the side product. The product distribution is a function of temperature with the ratio reversing from a predominance of the cyclobutenone **100a** at higher temperatures (e.g. 100 °C) to a distribution in favor of the bicylco[3.1.1]heptanone **99a** at lower temperatures (e.g. 45 °C). Further studies showed that electronic tuning of the alkoxy substituent of the carbene moiety could control the product ratio and a more electron withdrawing group on the oxygen led to a greater proportion of the bicycloheptanone product.[119]

Scheme 2.10. Preparation of **94** and Its Reaction with Complex **63a**



Jiang and Fuertes also examined the *exo* to *endo* isomerization and found that the desired *endo*-isomer **102** could be achieved in 70% yield upon treatment of **101** with 5% $Pd/BaCO_3$ under an atmosphere of hydrogen.[119] Thus, it appeared that the third generation strategy outlined in Scheme 2.9 which incorporated dienyne **94** for providing the *endo*-cyclic double bond required for epoxidation and subsequent fragmentation offered a viable approach to the synthesis of taxol and other taxane derivatives.

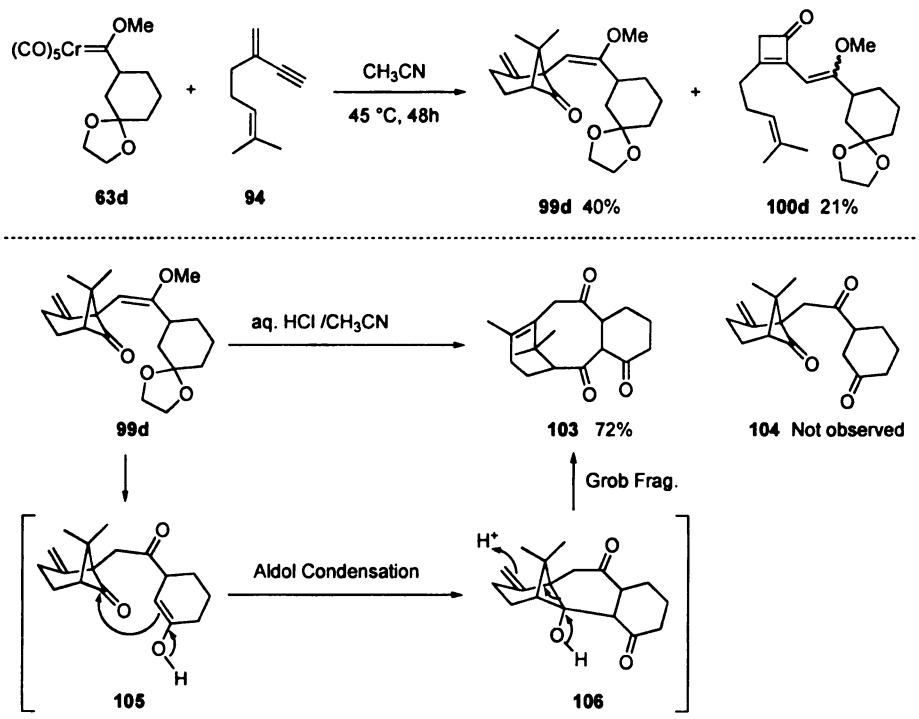
Scheme 2.11. Isomerization of the Double Bond in Bicycloheptanone **101**.



When the more substituted carbene complex **63d** was reacted with dienyne **94**, the bicyclo[3.1.1]heptanone **99d** was obtained as anticipated (Scheme 2.12). However, very surprisingly, after **99d** was subjected to strong acidic conditions, the expected triketone **104** was not observed. Instead, an unknown compound was isolated at that time and was later assigned to be the tricyclic compound **103**.[123] The spectral data appeared to support the structure where one of the two carbonyls in the β-diketone was in the enol form. This assignment was tentative and awaited further confirmation.[124] The proposed mechanism

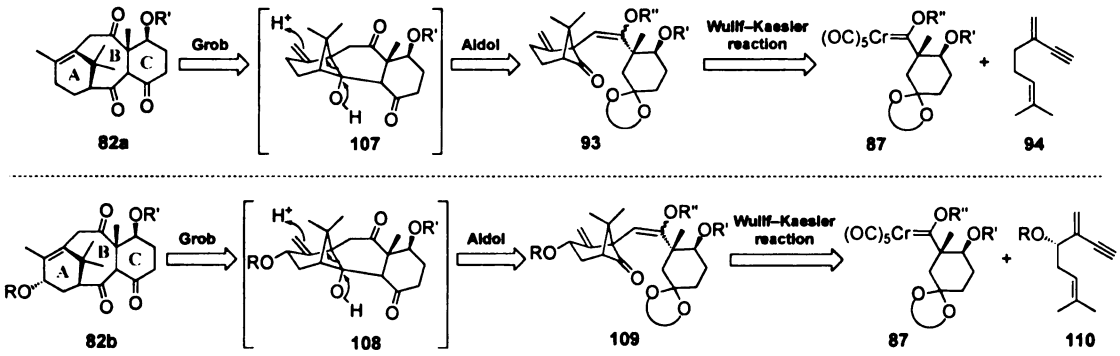
involving intermediate **106** via an aldol condensation and subsequent Grob-type fragmentation[125] seemed to be reasonable.

Scheme 2.12. The Formation of **99d** and Its Subsequent Reaction with an Acid



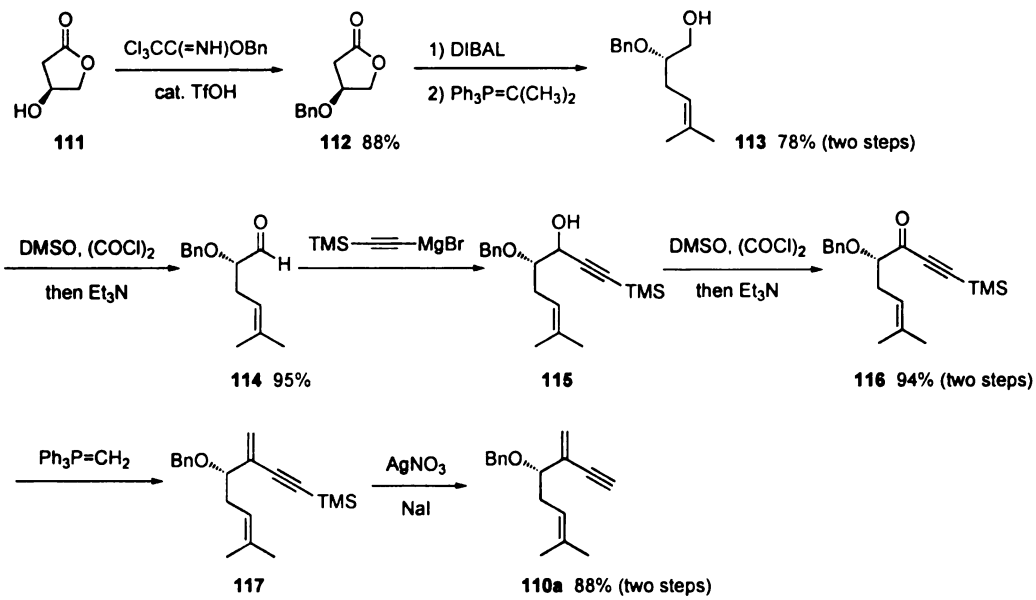
If the structure of **103** were correct, this would be significant for the strategy for the synthesis of taxol and taxanes derivatives because the tricyclic core could then be prepared directly from bicycloheptanones of the type **93**, without the need for performing the isomerization and epoxidation steps (refer to Scheme 2.9)! Therefore, the retrosynthetic strategy was modified such that the B-ring (e.g. in **82a**) is installed by direct aldol condensation and Grob-type fragmentation, as outlined in Scheme 2.13. Since epoxidation would not be involved in the strategy, the oxygen functionality on the A-ring of the ABC tricyclic core **82b** could be introduced in the form of a dienyne of the type **110**.

Scheme 2.13. Fourth Generation of Retrosynthetic Strategy



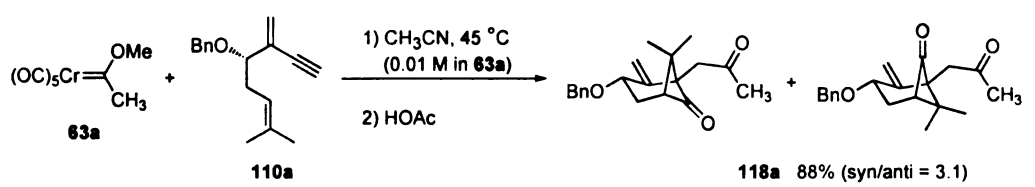
Fuertes developed an efficient way to synthesize the chiral dienynes **110** from commercially available (S)-β-hydroxy-γ-butyrolactone **111**.[126] Scheme 2.14 shows the synthesis of the dienyne **110a** whose alcohol is protected as a benzyl ether. Starting from the chiral lactone **111**, protection of the free alcohol with benzyl trichloroacetimidate in the presence of catalytic amount of triflic acid gives **112** in 88% yield. Then reduction with DIBAL followed by a Wittig reaction affords the alcohol **113** in 78% over two steps. Swern oxidation and subsequent nucleophilic addition of TMS-ethynyl magnesium bromide furnishes the propargylic alcohol **115**, which is then subjected to another Swern oxidation followed by Wittig methylation and removal of the TMS group to furnish the final product **110a**. The synthesis consists of 8 steps and the overall yield is 54%. Thus, a variety of dienynes of the type **110** that differ in the O-protecting group can be prepared using the same sequence with different protecting groups or simply by protecting group exchange (for example, with the TIPS-analog of **110a**, which can be easily deprotected).

Scheme 2.14. The Preparation of Chiral Dienyne **110a**.



The reaction of dienyne **110a** with carbene complex **63a** worked well and gave **118a** in 88% yield as a mixture of syn/anti isomers (Scheme 2.15). The cyclobutenone product was not observed and the syn to anti ratio (3.1 : 1) was good with the major isomer being the desired one that was needed for our proposed fourth generation strategy for the synthesis of the taxol skeleton. Fuertes then went on to make more functionalized bicyclo[3.1.1]heptanones with substituted carbene complexes, but his attempts at closure of the B-ring using Jiang's conditions were unsuccessful.[126]

Scheme 2.15. Synthesis of Bicyclo[3.1.1]heptanone **118a** with Chiral **110a**.



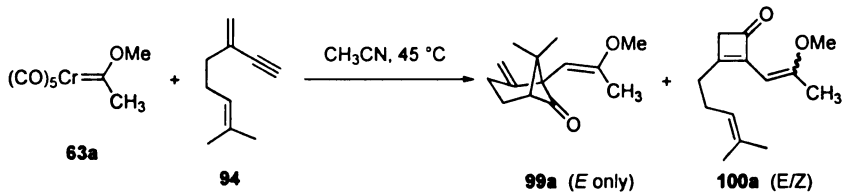
Based on these previous efforts, it was decided to carry out more systematic studies on the Wulff–Kaesler reaction and, of course, to continue the progress toward the total synthesis of taxol.

2.3 FURTHER STUDIES ON THE WULFF–KAESLER REACTION

2.3.1 Bicylo[3.1.1]heptanone Intermediates for the Synthesis of the A-Ring Synthons of Taxol and Taxane Derivatives

This work begins with a look at the Wulff–Kaesler reaction of the chromium carbene complex **63a** with dienyne **94**. This reaction was initially studied by Jiang and it was found that the formation of the desired bicycloheptanone **99a** was favored at a lower temperature with an optimal temperature of 45 °C for a reaction performed at 0.01 M concentration in **63a** for 48 hours.[119,123] It was deemed necessary to determine if a higher concentration of **63a** could be employed and whether the reaction was complete in a shorter time. As shown in Table 2.1, both the overall yields and the ratios of **99a/100a** are essentially the same for reactions performed at both 0.01 and 0.1 M concentrations in complex **63a**. This is significant since it means that the reaction is amenable to scale-up and that large-scale reactions can be carried out without the use of a large amount of solvent. Furthermore, both reactions were complete in 24 hours. The assignment of *E/Z* isomers of **100a** was made by the difference in chemical shift of the enol ether carbons according to Strobel's empirical rule.[127] Since **99a** was obtained as a single isomer, it could not be assigned by Strobel's rule and was assumed to be in the *E* configuration according to studies on related compounds.[119]

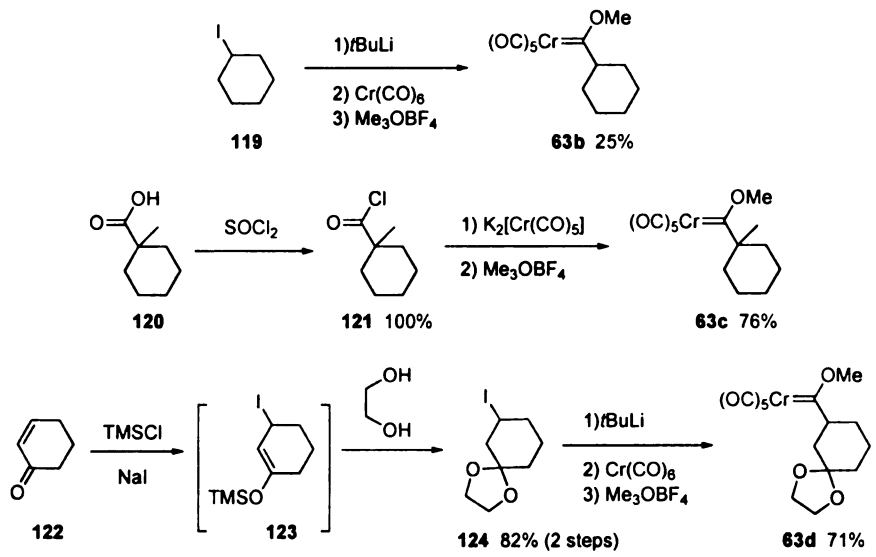
Table 2.1. The Wulff–Kaesler Reaction of Complex **63a** and Dienyne **94**



Entry	[63a], M	Time, h	Yield, %				99a: 100a
			99a	100a*E*	100a*Z*	Total	
1	0.01	48	46	24	12	82	1.3
2	0.1	48	44	23	10	77	1.3
3	0.01	24	46	20	11	77	1.5
4	0.1	24	47	22	12	81	1.4

A few substituted carbene complexes **63b-d** were then prepared to examine the scope of the reaction with dienyne **94** (Scheme 2.16). The complex **63b** was prepared from cyclohexyl iodide **119** in 25% yield using the standard Fischer protocol, and the low yield in this reaction was presumably due to a competing elimination of the 2°-halide **119** under the reaction conditions.

Scheme 2.16. Preparations of Substituted Carbene Complexes **63b-d**.

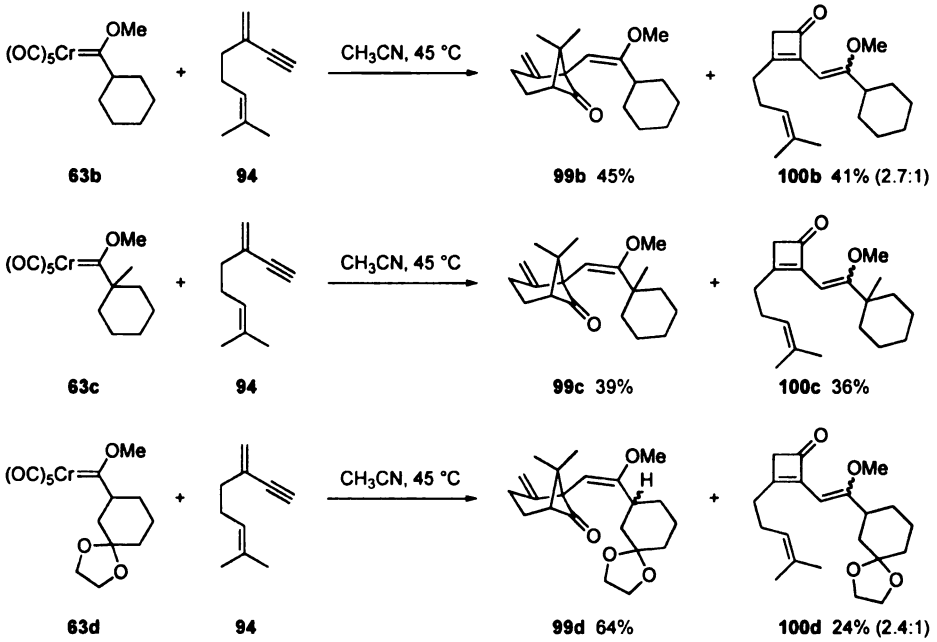


For the tertiary alkyl carbene complex **63c**, the chromate dianion method was used to prepare it.[104] This method was first reported by Semmelhack in the synthesis of alkoxy carbene complexes from acid chlorides with disodium or dilithium pentacarbonylchromate ($Na_2[Cr(CO)_5]$ or $Li_2[Cr(CO)_5]$) that was prepared from sodium naphthalide and trimethylaminopentacarbonyl chromium(0).[104a] Hegedus later developed a similar method to prepare amino carbene complexes from amides using dipotassium pentacarbonylchromate ($K_2[Cr(CO)_5]$) which was generated from the reduction of $Cr(CO)_6$ with potassium graphite (C_8K).[104c] This potassium chromate dianion reagent has also been applied to the synthesis of alkoxy carbene complexes from acid chlorides as well,[104d] and the advantage of using potassium chromate dianion is that the only by-product in principal is graphite which can be filtered off at the end of the reaction. The sodium or lithium chromate dianion approach has naphthalene as the by-product which can be problematic during the purification of the product carbene complex. Thus, the potassium chromate dianion approach was employed in the preparation of complex **63c**. It was pleasing to find that when acid chloride **121** was treated with the in situ generated dipotassium pentacarbonylchromate for three hours followed by methylation with Meerwein's salt, the carbene complex **63c** was obtained in 76% yield.

The synthesis of complex **63d** was originally developed by Jiang[123] and the overall yield was later improved (Scheme 2.16). The precursor iodide **124**, was made from cyclohexenone **122** in 82% yield over two steps. With careful handling of the light sensitive iodide **124** during the preparation of the carbene complex and with the use of Meerwein's salt in the methylation step, the complex **63d** was obtained in 71% yield, which was a significant improvement over the original report (54% yield).[123]

The Wulff-Kaesler reactions of complexes **63b-d** with dienyne **94** were then carried out (Scheme 2.17). In each case, the reaction worked well to give the desired bicyclo[3.1.1]heptanone **99** as the major product, but a significant amount of the cyclobutenone **100** was obtained as a side product. The cyclobutenones were isolated as a mixture of E and Z isomers, except for **100c** which has a quaternary center next to the enol ether. Cyclobutanone **100c** was obtained as a single isomer and its stereochemistry was not determined. It is interesting to note that most of the peaks in the ^{13}C NMR spectra of all three bicycloheptanones **99b-d** are fairly broad, especially for those more downfield, and as a result, it took a long time to obtain the spectra. This unusual peak broadening is probably due to a dynamic process which is slow on the NMR scale, presumably the result of a conformational change in the bicyclic system.

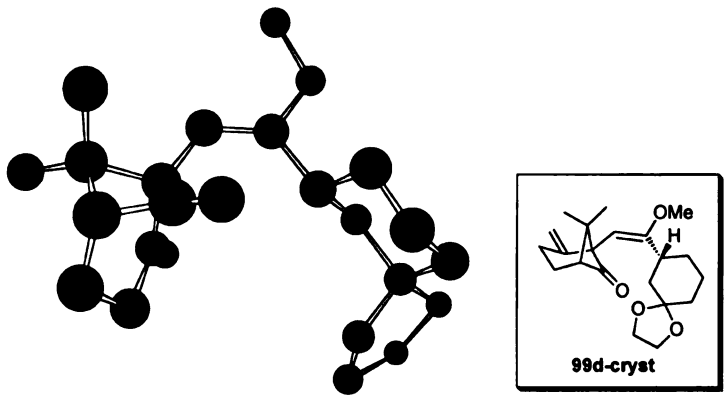
Scheme 2.17. The Wulff–Kaesler Reactions of **63b-d** with Dienyne **94**



It was also pleasing to find that the reaction of complex **63d** gave a higher overall yield (88%) than that was reported by Jiang (61%) and that the product selectivity of **99d**

over **100d** was good. The bicycloheptanone **99d** has a ketone functionality (protected as an acetal) which was necessary for the proposed subsequent B-ring closure in the synthesis of the ABC tricyclic skeleton of taxanes (Scheme 2.13). Very careful NMR studies showed that the bicyclo[3.1.1]heptanone **99d** actually existed as a mixture of two isomers (~1:1 ratio), which were tentatively assigned as the two epimers shown in Scheme 2.17. The mixture of isomers showed nearly a single set of peaks in the ^{1}H NMR spectrum, with the only three peaks of the vinyl protons being partially overlapped and all others showing complete overlap. Fortunately, one of the epimers, **99d-cryst**, could be recrystallized in pure form from EtOAc/hexanes and its X-ray structure clearly shows the relative stereochemistry in this diastereomer (Figure 2.4).

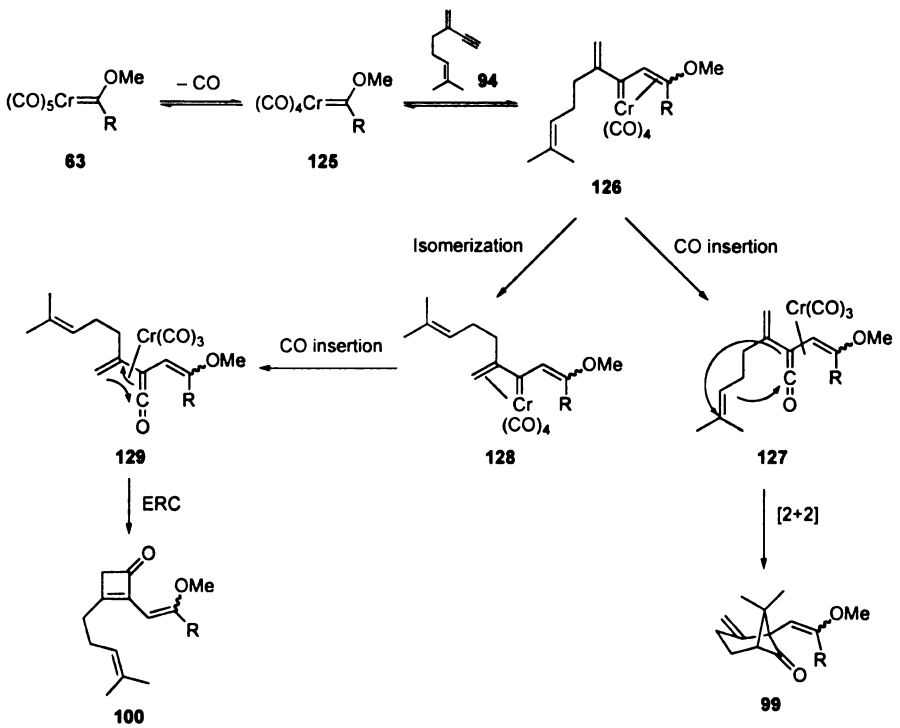
Figure 2.4. X-ray Structure of the Bicyclo[3.1.1]heptanone **99d-cryst**.



A mechanistic proposal to account for the formation of bicycloheptanone product **99** and the cyclobutanone product **100** is presented in Scheme 2.18. The branch point in the mechanism is the η^1,η^3-vinyl carbene complex intermediate **126** which is thought to result from alkyne insertion into the 16-electron species **125**. A CO insertion in intermediate **126** generates the vinyl ketene complex **127** which then gives the desired

bicycloheptanone **99** via a [2 + 2] cycloaddition. Alternatively, complex **126** may form the isomeric η^1,η^3-vinyl carbene complex **128** where the chromium is coordinated to the more electron poor double bond, and after insertion of a CO ligand the intermediate **129** is generated. The formation of the cyclobutanone side product **100** in these reactions is believed to result from the electrocyclic ring closure of intermediate **129** (Scheme 2.18).[119]

Scheme 2.18. The Proposed Mechanism for the Wulff–Kaesler Reaction of Complex **63** with Dienyne **94**



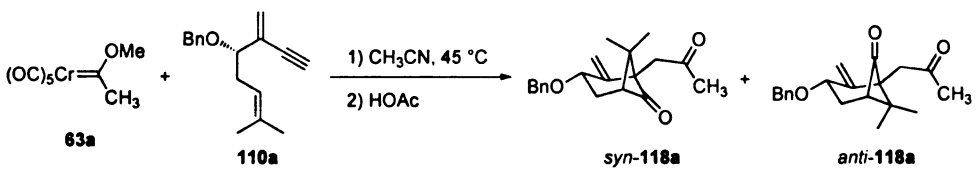
In summary, the successful examples of the reaction of carbene complexes **63a-d** with dienyne **94** have further shown that the Wulff–Kaesler reaction is a feasible way to prepare bicyclo[3.1.1]heptanones as suitable A-ring synthons for the synthesis of taxol and taxane derivatives.

2.3.2 Asymmetric Induction in the Wulff–Kaesler Reaction: Diastereoselective Formation of Taxol A-ring Synthons

As mentioned in Section 2.2, Fuertes extensively studied the Wulff–Kaesler reaction of complex **63a** with a variety of chiral dienynes of the type **110**.[126] In the present work, it was decided to take a closer look at the reactions of dienyne **110a** with different carbene complexes and to determine the diastereoselectivity of these reactions.

The reaction of carbene complex **63a** and the dienyne **110a** was initially carried out at both 0.01 M and 0.1 M in **63a**. After hydrolysis of the enol ether primary product with aqueous acetic acid, it was found that the overall yield of **118a** was only slightly lower when the reaction was performed at 0.1 M than that at 0.01 M in **63a** (Table 2.2). However, the desired isomer *syn*-**118a** was obtained in essentially same yields (63% vs. 66%) since the diastereomeric ratio of syn to anti actually increased a little (3.7 vs. 3.1) when a higher concentration of **63a** was used. These results show that the reaction can be carried out at 0.1 M in **63a** without any significant effect on the yield of *syn*-**118a**. The assignment of the syn/anti isomers was based on their 1D NOESY spectra and on an X-ray structure of the TROC-protected analog of *syn*-**118a** that had been previously determined.[126]

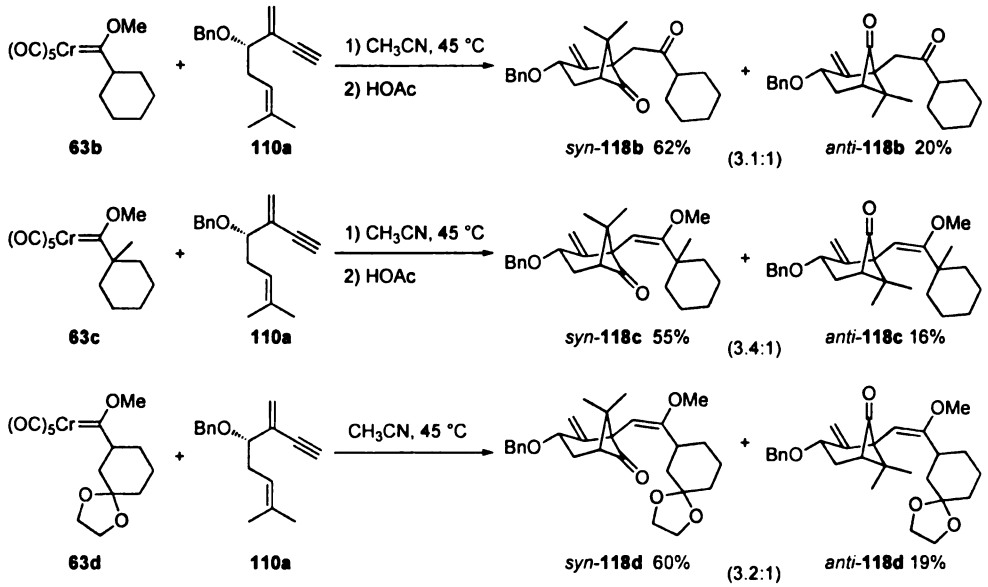
Table 2.2. The Wulff–Kaesler Reaction with Chiral Dienyne **110a**.



Entry	[**63a**], M	Time, h	Yield, %			syn/anti
			syn-**118a**	*anti*-**118a**	Total	
1	0.01	24	66	21	87	3.1
2	0.1	24	63	17	80	3.7

When the chiral dienyne **110a** was reacted with the more substituted carbene complexes **63b-c**, the reactions worked very well (Scheme 2.19).[128] As in the reaction with complex **63a**, the formation of cyclobutenones was basically completely shut down,[129] which is mechanistically interesting and synthetically important. Furthermore, the diastereomeric ratio of syn to anti was greater than 3:1 in all three cases. The *syn*-isomer was the major diastereomer which has the correct stereochemistry required for the proposed synthesis for taxol (Scheme 2.13). Worthy of note is that for the bicycloheptanone **118c**, which has a quaternary carbon next to the enol ether, the hydrolysis with aqueous acetic acid did not lead to a diketone product. Instead, the enol ether form of the product was isolated where each was a single isomer of the enol ether. The problems with the hydrolysis of such compounds will be discussed in detail in Section 2.4. Gratifyingly, complex **63d**, which has a protected ketone group, also reacted with **110a** to efficiently give *syn*-**118d** as the major product (the hydrolysis of **118d** was not carried out).

Scheme 2.19. Diastereoselective Synthesis of Bicyclo[3.1.1]heptanones **118**.



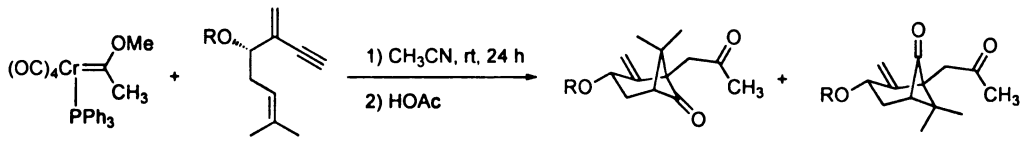
It has been demonstrated in the above reactions that bicycloheptanones of the type *syn*-**118** can be efficiently synthesized from the chiral dienyne **110a** with different carbene complexes containing the C-ring of taxol via the Wulff–Kaesler reaction in a diastereoselective manner. These bicycloheptanones can be used as A-ring synthons of taxol in the proposed total synthesis of this natural product.

2.3.3 Mechanistic Considerations for the Asymmetric Induction

Perhaps the most interesting mechanistic question about the reactions of dienyne **110a** is what is the source of preference for the syn isomer. Fuertes investigated the reactions of the triphenylphosphine carbene complex **130** and dienynes of the type **110** with different protecting groups on the oxygen,[126] and a few examples are shown in Scheme 2.20. The triphenylphosphine ligand in complex **130** is more labile than a CO ligand with the result that the reactions of complex **130** and dienynes **110** can be performed at room temperature. However, the selectivity and yield for the reaction of dienyne **110a** are nearly unaffected by the lower temperature. The reaction of the triphenylphosphine complex **130** (0.1 M) with dienyne **110a** at room temperature gives a syn/anti ratio of 3.2 : 1 (Scheme 2.20), whereas the pentacarbonyl complex **63a** (0.1 M) at 45 °C gives a ratio of 3.7 : 1 (Table 2.2). As can also be seen from Scheme 2.20, when the size of the protecting group R is smaller (methyl vs. benzyl) the diastereomeric ratio increases (4.8 vs. 3.2); when the protecting group is quite large, the selectivity is reversed to give a ratio of 1 : 6.7 in favor of the formation of the anti isomer in the case of R = *t*-butyl. Although these results were obtained when the triphenylphosphine complex **130**

was employed, similar observations would be expected from the reactions with the pentacarbonyl complex **63a**.

Scheme 2.20. The Effect of the Protecting Groups on the Diastereoselectivity



130 **110** *syn*-**118** *anti*-**118**

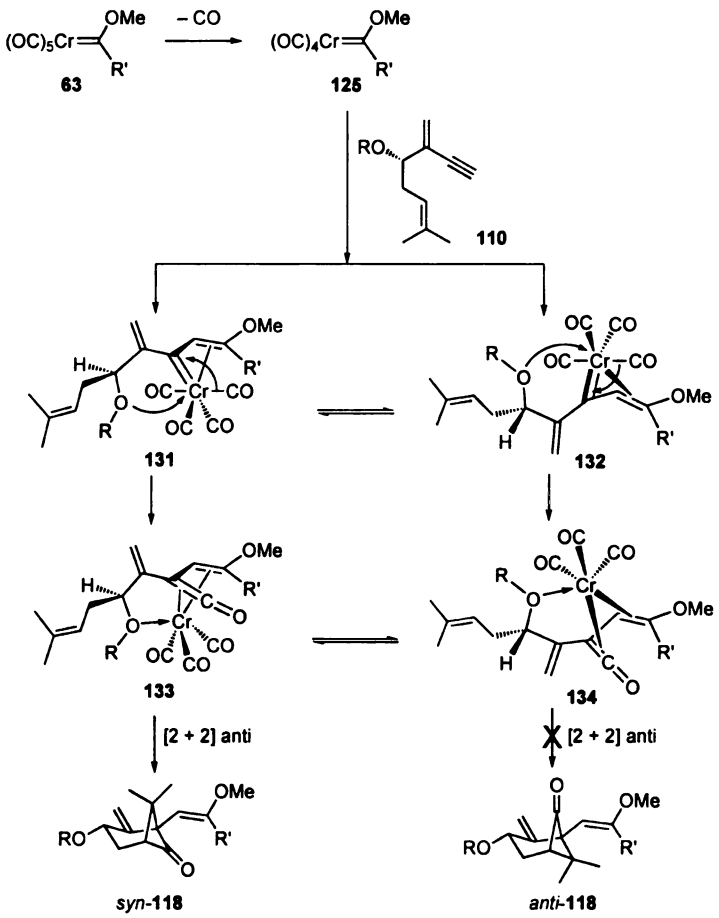
[130], M	dienyne	R	product	overall yield, %	syn/anti
0.1	**110e**	Me	**118e**	89	4.8 : 1
0.1	**110a**	Bn	**118a**	88	3.2 : 1
0.01	**110a**	Bn	**118a**	89	3.2 : 1
0.1	**110f**	*t*-Bu	**118f**	88	1 : 6.7

Based on the above results and the observations of the diastereoselectivity in the reactions of **110a** with different carbene complexes, it is reasonable to believe that the oxygen in **110** plays a special role in the course of the reaction. Specially, the data in Scheme 2.20 suggests that a chelation of the oxygen to the chromium could occur, which leads to the syn isomer. Furthermore, when chelation of the oxygen to the chromium cannot take place (R = *t*-butyl), the anti isomer is formed.

A mechanistic scenario involving coordination of the oxygen to the chromium is shown in Scheme 2.21. Alkyne insertion into the tetra-coordinated complex **125** can give the two different vinyl carbene complexes **131** and **132** which have the chromium carbonyl group bound in an η^1,η^3-fashion to the bottom and the top of the molecule, respectively. In the case of the chromium sitting on the bottom as in **131**, when the oxygen becomes coordinated to chromium, it may facilitate the insertion of CO to generate the vinyl ketene complex **133** which leads to the formation of *syn*-bicyclo[3.1.1]heptanone **118** via a [2 + 2] cycloaddition which occurs on the face of the

ketene that is opposite to the chromium unit (anti to chromium, thus the name "[2 + 2] anti" in Scheme 2.21). However, when the chromium carbonyl group is on the top as in **132**, after the chelation of oxygen to chromium and the generation of the vinyl ketene complex **134**, the alkene side chain is held in a position where it cannot reach the ketene unit and thus the [2 + 2] cycloaddition will not proceed. Therefore, *anti*-**118** cannot be formed in this case.

Scheme 2.21. Chelation of Oxygen to Chromium in the Wulff–Kaesler Reaction

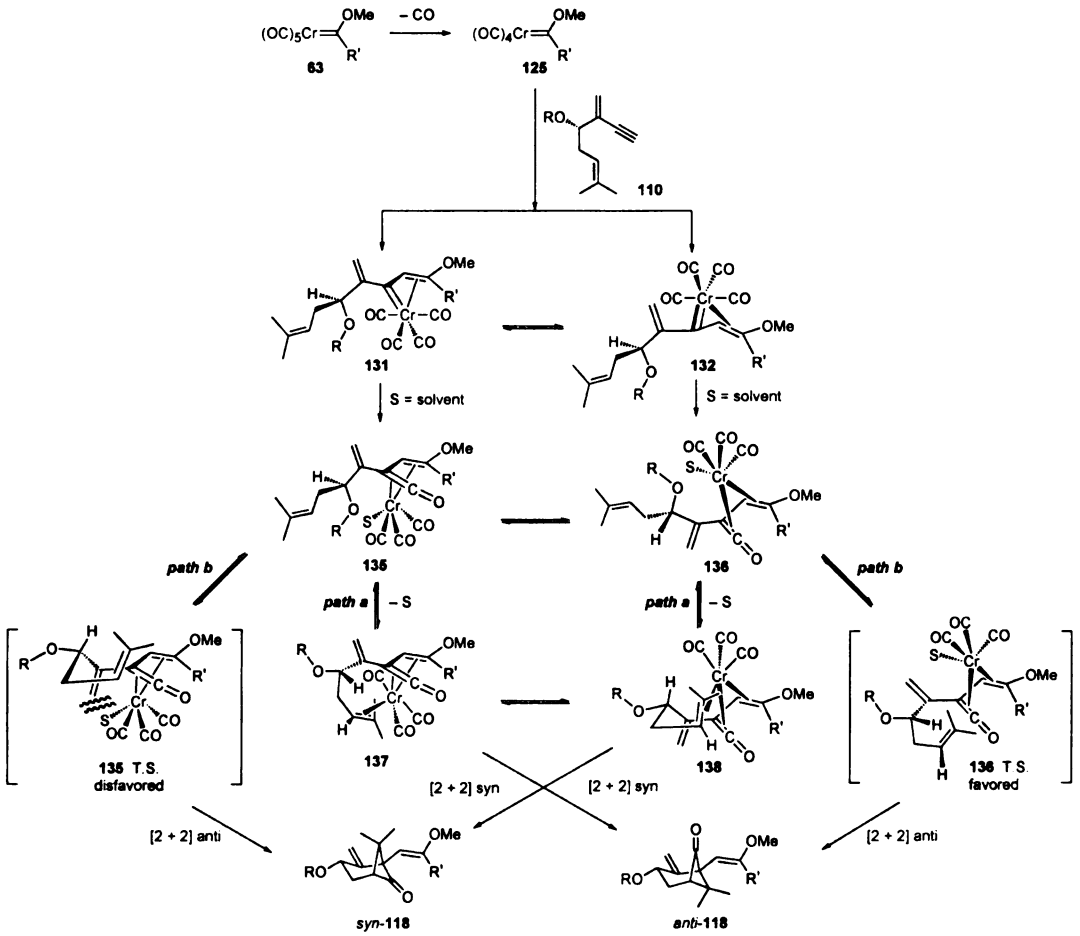


The possibility of oxygen chelation may also explain why cyclobutenones are seen in the reactions of dienyne **94** (Scheme 2.17) but not in the reactions of dienyne **110a** (Scheme 2.19). Chelation of the oxygen to chromium in **133/134** would prevent the

free rotation about the bond between the ketene terminal carbon and its α-carbons. This may prevent the migration of the chromium to the 1,1-disubstituted double bond: **126** to **128** in Scheme 2.18, which in turn could prevent the formation of the cyclobutenone product. As mentioned earlier, it would be expected that chelation of the oxygen may also facilitate the CO insertion which should affect the branch point at intermediate **126** in Scheme 2.18 in a manner that would disfavor cyclobutenone formation.[119]

However, in these experiments, *syn*-**118** was obtained as the major isomer, not the exclusive one. One could argue that there must be some pathway(s) where the product can be formed without chelation. Such a mehanism is proposed in Scheme 2.22.

Scheme 2.22. Proposed Solvent Coordination in the Wulff–Kaesler Reaction



If the oxygen on the dienyne is not coordinating to the chromium during the reaction when intermediates are being generated that are unsaturated at chromium, then it is certainly possible that the solvent may be coordinating to the chromium. In fact, previous work has shown that acetonitrile can coordinate to the chromium and facilitate CO insertion to give a vinyl ketene intermediate much more effectively than other solvents.[130] The solvent assisted vinyl ketene complex formation in the case of the chiral dienyne **110** would lead to the two diastereomeric complexes **135** and **136** as shown in Scheme 2.22. In the absence of oxygen chelation to the chromium, the situation becomes more complex because the [2 + 2] cycloaddition can occur either syn to the metal or anti to the metal (Scheme 2.22). Wulff and Kim suggested in an early publication that the syn approach involving pre-coordination of the olefin to the metal was occuring in a related metal-mediated intramolecular [2 + 2] cycloaddition due to the rate acceleration compared with the corresponding metal free reaction.[116] Nonetheless, both syn and anti [2 + 2] cycloadditions will be considered here.

An analysis of intermediates **137** and **138** by mechanical models does not indicate obvious close contacts that would favor one over the other. However, similar considerations of the transition states **135** and **136** for the anti [2 + 2] cycloaddition lead to the prediction that **135** would be disfavored by the fact that the 1,1-disubstituted alkene is projected directly towards the ligands on the metal. Thus, if the [2 + 2] cycloaddition occurs anti to the metal, then the anti product would be predicted to be the major product in the absence of chelation of the oxygen substituent. If the [2 + 2] cycloaddition occurs syn to the metal, then it is not clear whether syn or anti would be favored.

Taken together, the mechanisms proposed in Schemes 2.21 and 2.22 can explain why both *syn*-**118** and *anti*-**118** are formed and why the *syn*-isomer is predominant when a less bulky group (e.g. benzyl or methyl group) is on the oxygen of the dienyne **110**. Here the syn product results when the oxygen coordinates to the chromium and the anti product results when the solvent competes with the oxygen for coordination. However, when the oxygen in **110** is protected with the bulky *t*-butyl group, the chelation of oxygen to the chromium will be unlikely and instead the coordination of the solvent should be the dominant process. Since all the ketene complexes in Scheme 2.22 would be expected to be in equilibrium, *anti*-**118** should be formed predominantly when pathway (b) is involved and the "[2 + 2] anti" cycloaddition of **136** would be favored, which is consistent with what Fuertes has observed for the reaction with **118f** (Scheme 2.20).

2.4 Revision of the Previously Incorrectly Assigned Tricyclic Intermediate

As discussed above, it has been established that the Wulff–Kaesler reaction of chromium carbene complexes of the type **63** with dienyne **94** worked well to provide bicyclo[3.1.1]hepatones **99** as the desired major products (Scheme 2.17), and that the reactions with the chiral dienyne **110a** resulted in a good stereoselectivity in favor of the syn isomer of **118** for the diastereoselective synthesis of taxol A-ring synthons (Scheme 2.19). The bicycloheptanone *syn*-**118d** actually has the required A–C ring system, thus the next task would be to determine whether the B-ring could be closed to effect the construction of the ABC tricyclic skeleton of taxol.

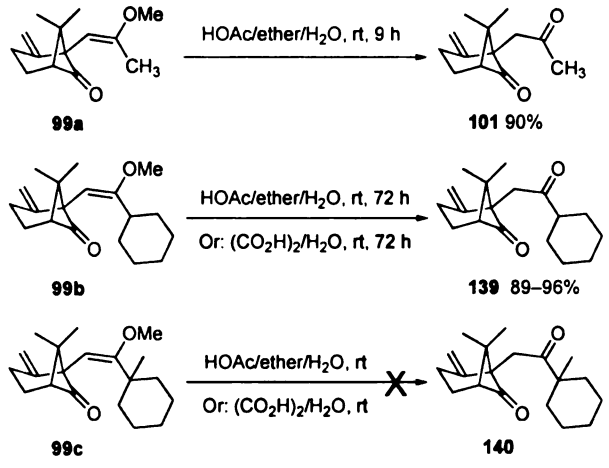
Before moving on to carry out this important task, it was decided to gain further evidence in support of the proposed tricyclic compound **103** (refer to Scheme 2.12). Ideally, it would be great if a crystalline derivative could be prepared so that an X-ray diffraction analysis could be carried out to confirm the structure. Since this compound is an oil, considerable time was spent making a variety of derivatives, including acetals, esters, enamines, alcohols, a ternary imminium salt, hydrazones and a carbazone. For most of these attempts, crystalline products were not observed, while in a couple of cases, solid compounds were isolated, but none gave crystals suitable for an X-ray analysis. Thus, it was very disappointing at the time since the structure still could not be confirmed.

2.4.1 Investigations on the Hydrolysis of Enol Ethers 99 and the Discovery of the Unexpected Fragmentation

At the same time that crystalline derivatives of **103** were sought, investigations were also conducted to explore the unexpected reluctance of the enol ether **118c** to undergo hydrolysis (Scheme 2.19). As demonstrated in Sections 2.2 and 2.3, the hydrolysis of a number of the enol ethers can be conveniently achieved with aqueous acetic acid at room temperature. For examples shown in Scheme 2.23, bicycloheptanones **99a** and **99b**, with either a methyl or cyclohexyl group next to the enol ether, were both easily hydrolyzed with weak acids to form diketone **101** and **139**, respectively, although the reaction rate decreased significantly (72 h vs. 9 h) as the size of the group increased (from methyl to cyclohexyl).[131] It was surprising to find that the hydrolysis of **99c** with weak acids failed, giving only the recovery of the starting material **99c** after stirring with

aqueous acetic acid or oxalic acid for several days. It may be expected that the increased steric bulk near the enol ether may slow the hydrolysis; however, the dramatic effect seen on the rate of hydrolysis was surprising.

Scheme 2.23. Hydrolysis of the Enol Ethers with Weak Acids



Next a strong acid (4 N aq. HCl in CH_3CN) was employed to attempt to convert the enol ether **99c** to diketone **140** at room temperature. As expected, the enol ether in **99c** had reacted, but to our disappointment, the desired diketone **140** was not observed. Instead, two unexpected new compounds were isolated in significant amounts, but their structures were not determined at that time. When **99c** was treated with *p*-tolyl sulfonic acid (PTSA) in wet acetone at room temperature or with oxalic acid in THF/H_2O at 45 °C, similar results were observed.

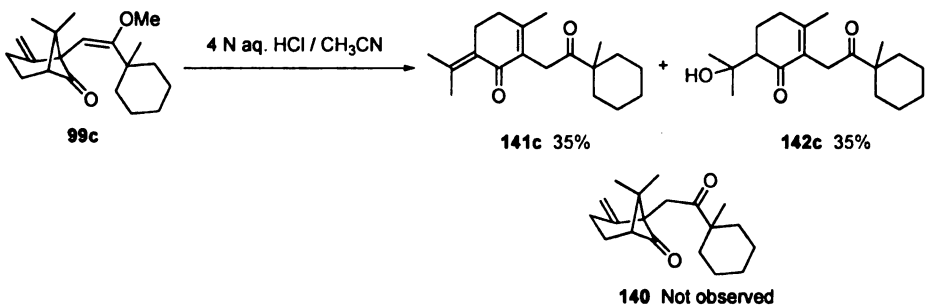
The unsuccessful conversion of **99c** to the corresponding diketone **140** prompted a search for other methods for the conversion of enol ethers to ketones that do not use strong Brønsted acids. During this time, Tsuji and coworkers reported that the palladium complex, $PdCl_2(CH_3CN)_2$, could effectively hydrolyze enol ethers.[132] When the same reaction conditions were applied to **99a**, clean conversion to **101** was observed, however,

enol ether **99c** was unreactive to these conditions. This failure is presumably due to the sterics surrounding the double bond that prevents the coordination of the palladium species. Meanwhile, a search was conducted to find groups other than methyl that could be introduced on the heteroatom of the carbene complex, in the hope that the hydrolysis problem could be solved for dienynes of the type **99c**. A number of substituents were investigated, including MOM, TMS, TIPS, SEM, Troc, chloroethyl, bromoethyl, TMS-ethyl, however none led to satisfactory results. In some cases, the corresponding carbene complexes could not be formed, and in others the Wulff–Kaesler reaction was unsuccessful, and still in others the hydrolysis of analogs of **99c** failed under a variety of methods.

After the attempts to change the oxygen substitutuent of the enol ether proved to be fruitless, attention was then directed to the elucidation of the two structures from the reaction of **99c** under strong acidic conditions. Extensive studies by NMR and mass spectroscopy were undertaken. One of the most striking features of the two compounds is that neither of them has a vinyl proton peak in the ^{1}H NMR spectrum, however, there are peaks in the olefin region in both ^{13}C NMR spectra, which indicates that the exocyclic double bond has been rearranged to a tetrasubstituted olefin. It was initially thought that the quaternary center on the cyclohexane ring might have undergone a rearrangement, but this was proved not to be the case after careful analysis of the spectral data and the finding of a literature example of a successful hydrolysis of an enol ether with a quaternary center next to it.[133] Finally after extensive analysis of several NMR experiments, the identitities of the hydrolysis products of **99c** were determined to the rearranged diketone **141c** and its hydrated form **142c**, as shown in Scheme 2.24.[134] Thus,

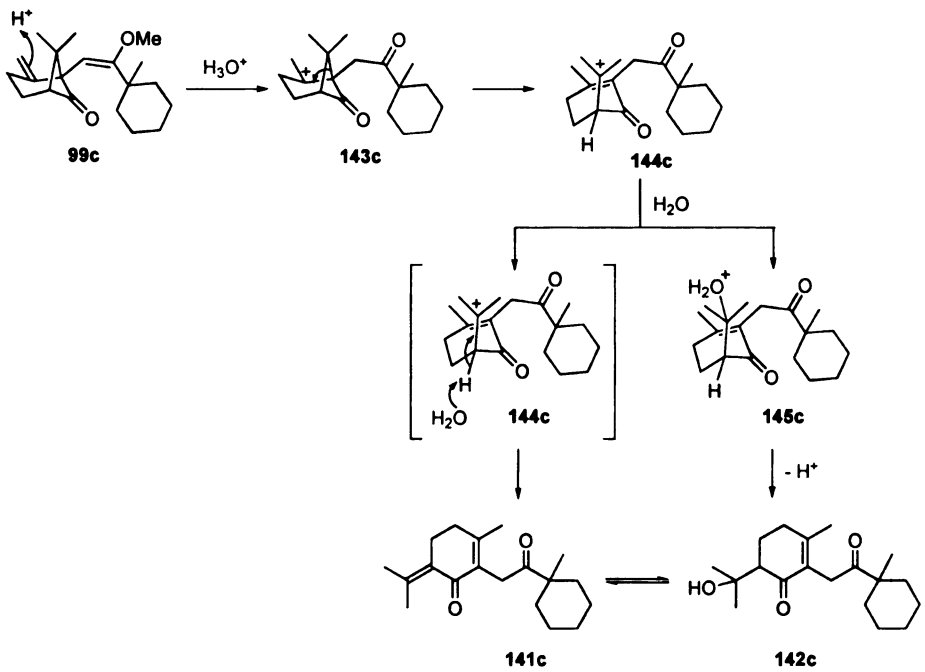
the methylcyclohexyl part of **99c** remained untouched in the reaction, while the bicyclic system underwent fragmentation. Worthy of mention is that the mass spectra were misleading for **142c** which has a molecular weight of 306. The GC–MS results indicated a molecular ion (M^+) of 288, resulting from a favorable loss of H_2O probably in the GC column. Even the FAB–MS, a soft ionization method that usually gives the MH^+ ion as the base peak, had a base peak of 289 with a much lower peak of 307 (about 20% of the intensity of 289). This is probably an unusual case for a FAB–MS spectrum, nonetheless, it dramatically increased the difficulty in the elucidation of the structure of **142c**.

Scheme 2.24. The Unexpected Fragmentation of **99c** under Acidic Conditions



How did this acid catalyzed fragmentation occur? It is believed that the rearrangement is initiated by the protonation of the reactive exocyclic double bond to generate cation **143c**, and then the bond between the two quaternary carbons breaks to relieve the strain in the four-membered ring and form the cation **144c** (Scheme 2.25). Subsequently, cation **144c** can either undergo an elimination to form **141c** or it can be trapped by H_2O to form **142c** – the hydrated form of **141c**. It is also believed that **141c** and **142c** are in equilibrium under reaction conditions.

Scheme 2.25. The Proposed Mechanism for the Fragmentation of **99c**



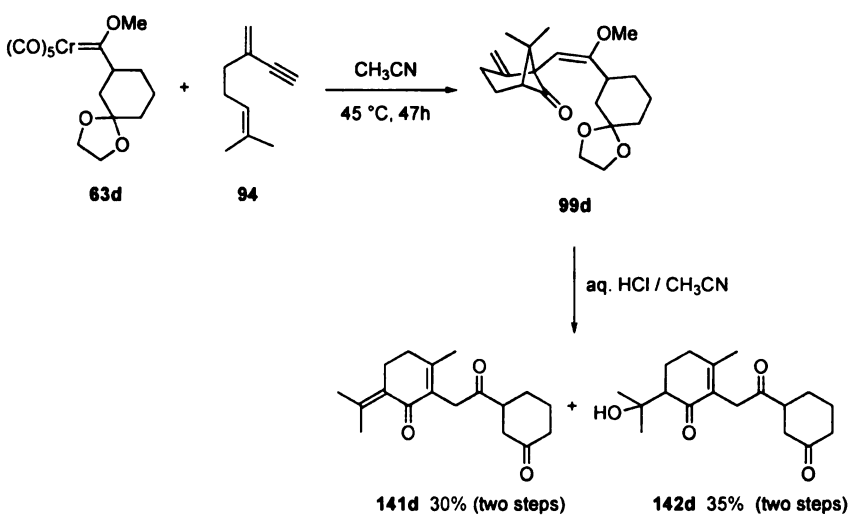
2.4.2 Correction of the Previously Misinterpreted Tricyclic Structure

After the two structures **141c** and **142c** were determined, a re-examination of the structure **103** (Scheme 2.12) was undertaken in light of this new information. As discussed earlier, most of the data fit well with this structure, but there existed some inconsistencies that could not be accounted for.[124] Although the original structure assignment of **103** was tentative, it seemed to be reasonable based on the data available at that time and no better candidate had been brought forward since then.

Fortunately, by carefully comparing the data of **103** with those of the elucidated structures **141c** and **142c**, it became possible to assign the structure of the compound previously identified as **103** as the triketone **142d** (Scheme 2.26). This was an astonishing finding: the ABC tricyclic core of taxol had actually never been formed!! The molecular

weight of **103** is 288 which is 18 less than that of the structure **142d**. As was seen with **142c**, the GC–MS of **142d** also gave a predominant peak for loss of H_2O at m/z = 288 and only a tiny peak for the molecular ion at m/z = 306. The triketone **142d** presumably exists as a mixture of two inseparable diastereomers, and the ^{13}C NMR spectrum showed that some peaks were twinned while others were single peaks. HPLC analysis (using chiral-AD column) showed that there were two sets of enantiomers in a 1:1:1:1 ratio, which is consistent with the fact that product **142d** exists as a mixture of two diastereomers (1:1). In addition, another compound that had not been recorded before was obtained from the reaction of **63d** and **94**. This compound was identified as **141d** and was also isolated in a significant amount (30% yield). The same mechanism is believed to be operating in this case as that shown in Scheme 2.25. It was shown that the two compounds were in equilibrium under reaction conditions because when pure **141d** or **142d** was treated with aqueous HCl/CH_3CN for 10 hours, a mixture of **141d** and **142d** was obtained in each case, slightly in favor of the hydrated form **142d**.

Scheme 2.26. Revision of a Previously Incorrectly Assigned Intermediate and Identification of a New Structure from Reaction of **99d** with HCl



63d **94** **99d**

141d 30% (two steps) **142d** 35% (two steps)

While it is good to finally correct the wrong structure, at the same time, it was bad news because the structure **103** contains the ABC ring system of taxol and as a result inspired continued efforts on the taxol project in the wrong direction. Nevertheless, the Wulff–Kaesler reaction is still a good approach for the construction of bicyclo[3.1.1]heptanones that can serve as A-ring synthons of taxol and taxane derivatives. Thus, a modification of the strategy is needed which employs a different tactic for the closure of the B-ring.

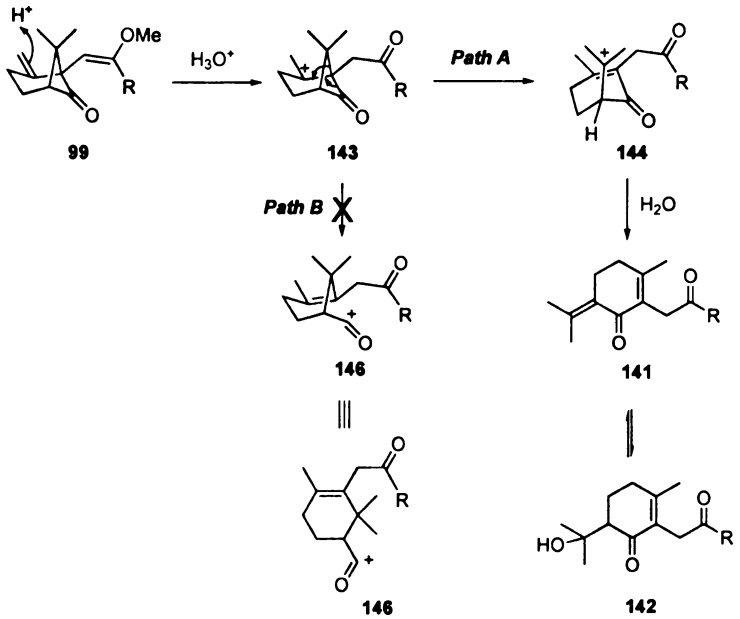
2.5 A Modified Strategy for the Total Synthesis of Taxol

As a direct consequence of the elucidation of the two structures from the reaction of **99d** under strong acidic conditions (Scheme 2.26), the retrosynthetic strategy had to be changed. Clearly, the acid catalyzed rearrangement of the bicyclic system occurs before the aldol reaction can take place, thus the anticipated aldol condensation of **105** and the fragmentation of **106** actually will not be possible as formulated in Scheme 2.12. Careful mechanistic considerations suggested that slight modifications could possibly change the fragmentation pathway of the four-membered ring in favor of the direction that retains the A-ring of taxol.

Under acidic conditions, there are two possible fragmentation pathways (Scheme 2.27). Upon protonation of the exo-cyclic double bond to form the carbocation **143**, either one of the two bonds can be broken to release the strain in the four-membered ring and these are indicated as path (A) or (B). The reason why path (A) is favored in this case is because it generates cation **144** which should be more stable than the acylium ion **146**

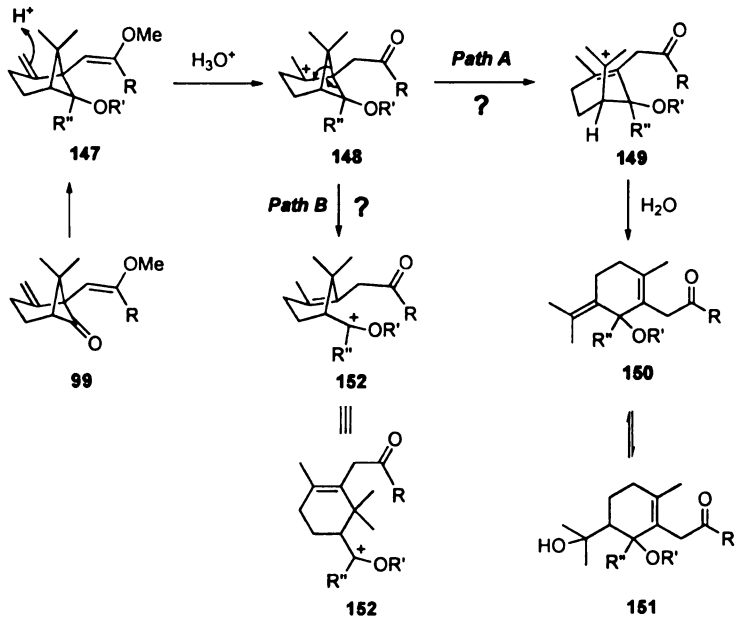
formed via path (B). The cation **144** leads to the formation of the rearranged products **141/142**. However, bond breaking through pathway (B) is required for taxol synthesis since the A-ring of taxol is maintained, thus, a method is needed to reverse the direction of fragmentation such that path (B) would be favored and/or that path (A) would be shut down.

Scheme 2.27. Mechanistic Considerations for the Acid-Catalyzed Fragmentation



According to the above mechanistic analysis, it was anticipitated that if a functional group was introduced to stabilize cation **146**, the fragmentation could be reversed. As shown in Scheme 2.28, a solution was envisioned converting the ketone **99** to its corresponding alcohol or a protected alcohol derivative of the type **147**. Protonation of **147** will give cation **148**, for which fragmentation to **152** may be favored through path (B) because now a much more stable oxonium ion would be formed.

Scheme 2.28. Modified Strategy to Achieve the Desired Fragmentation

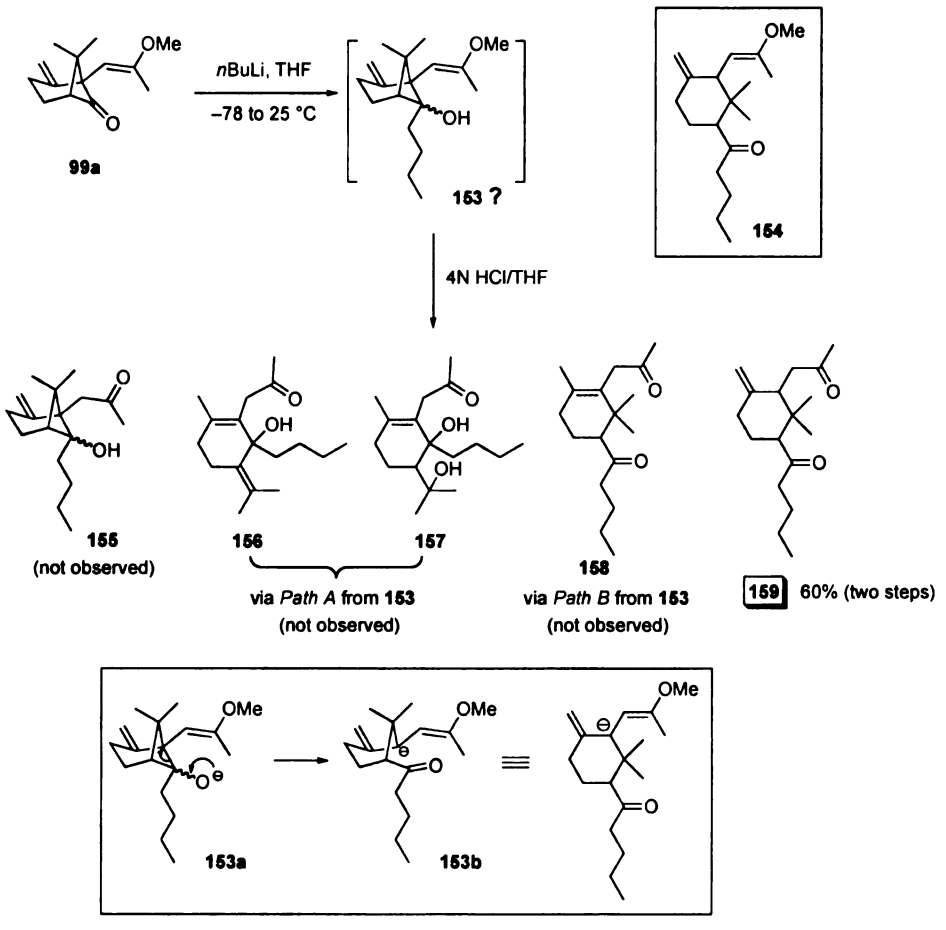


2.6 Studies on Closure of the B-Ring for Entry into the ABC Tricyclic Core of Taxol

The simple bicyclo[3.1.1]heptanone **99a** was chosen to test the idea outlined in Scheme 2.28. Addition of *n*BuLi to **99a** was expected to give **153**, however, after the reaction mixture was warmed to room temperature from –78 °C, a mixture of at least two inseparable isomers were isolated that did not appear to contain an –OH group as determined by its IR spectrum. Since it was difficult to identify the compounds while they were part of a mixture, the mixture was carried on to the next step by treatment with 4 N aqueous HCl in THF. Among the expected products were those with structures such as **156/157** and **158** which would have been formed via the paths (A) and (B), respectively. Alternatively, the ketone **155** would have been also possible as it would

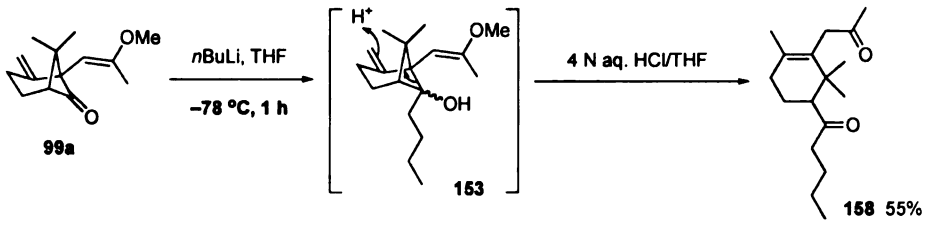
have simply resulted from hydrolysis of **153** (Scheme 2.29). However, none of these compounds was observed, instead, diketone **159** was isolated in 60% yield over the two steps. The formation of **159** with an exo-cyclic double bond was unexpected and presumably resulted from the hydrolysis of **154** which had been generated in the first step. An explanation for formation of **159** is shown in Scheme 2.29. Addition of *n*-butyllithium to **99a** would initially give the alkoxide **153a**, which could fragment to give the intermediate **153b** to relieve the strain in the four-membered ring and give a carbanion that is doubly stabilized by two olefins. The diketone **154** could thus be accounted for by a proton quench of the central position of the pentadienyl anion **153b**.

Scheme 2.29. A Test of New Strategy for the Desired Fragmentation



During the addition of *n*-butyllithium to **99a**, an observation was made that was first ignored but was then reinvestigated. In the course of slow warming of the reaction mixture to room temperature, the TLC was checked when the temperature was around –10 °C. The spot seen on the TLC had a different R_f value (R_f = 0.27, 10% EtOAc) from that of the mixture isolated after warming to room temperature (presumably isomers of **154**, R_f = 0.15, 10% EtOAc). This suggested that a different compound was present prior warming to room temperature and if so this compound could be the alcohol **153**. If this was true, anion **153b** must have been formed at temperatures above –10 °C. With this in mind, it was decided to quench the reaction at a lower temperature. As shown in Scheme 2.30, the reaction was quenched at –78 °C after stirring for an hour at this temperature to give a mixture presumably containing the alcohol **153**. The major product had the same R_f value as the intermediate(s) that was observed at –10 °C. Attempts to isolate this product by chromatography were unsuccessful due to partial decomposition on the silica gel column. Instead, the mixture was treated with aqueous HCl for 3 hours and the diketone **158** was obtained in 55% yield over two steps via the desired fragmentation pathway presumably from **153**.

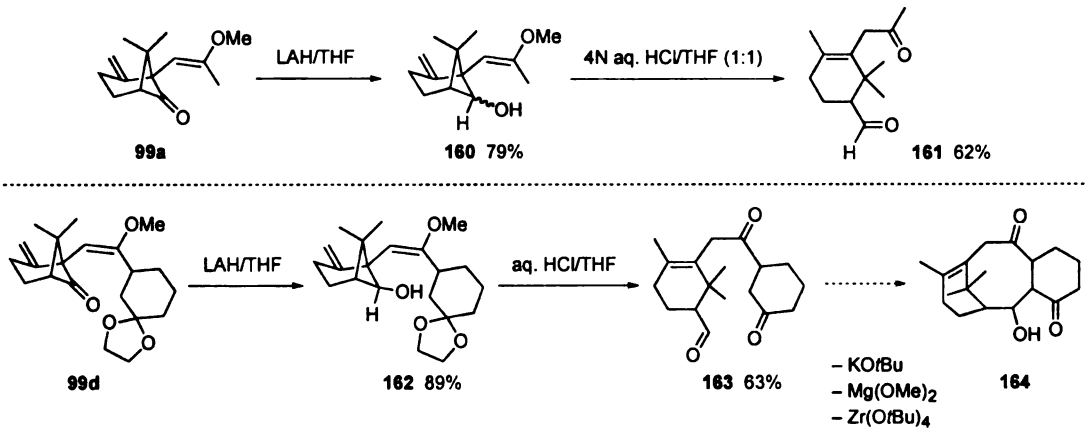
Scheme 2.30. Realization of the Desired Fragmentation!



It was later found that simply treating the ketone **99a** with LAH gave the alcohol **160** in 79% yield, which was then rearranged upon treatment with aqueous HCl to give the aldehyde **161** in 62% yield via the desired fragmentation pathway (Scheme 2.31).

Similarly, the bicyclo[3.1.1]heptanone **99d** was efficiently converted to the alcohol **162** and subsequently to the desired aldehyde **163**, which sets the stage for the B-ring closure. Obviously, B-ring formation could not be achieved under acidic conditions because the aldehyde **163** was obtained under these conditions. Thus an effort was made to effect a base mediated aldol closure. The first base examined was KO*t*Bu, but it gave a complex mixture that did not appear to contain any of the tricyclic compound **164**. An attempt to favor the intramolecular aldol reaction by a base involving a counterion capable of chelation was then examined. However, when **163** was treated with $Mg(OMe)_2$, a Meerwein-Pondorf-Verley (MPV) reaction occurred which reduced the aldehyde to the corresponding alcohol.[135] To avoid the MPV reaction, $Zr(OtBu)_4$ was employed, but only a complex mixture was obtained from the reaction while all the starting material was consumed. It may be that the formation of an eight-membered ring from an aldol condensation could be disfavored in this system. Nonetheless, the conversion of **163** to **164** would represent a very attractive route to the ABC ring system of taxol and thus deserves further consideration.

Scheme 2.31. The Formation of Aldehydes and Attempted B-ring Closure



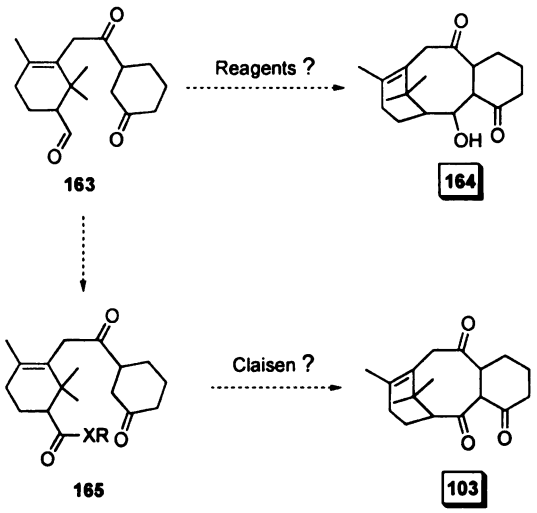
2.7 CONCLUSIONS AND FUTURE DIRECTIONS

The Wulff–Kaesler reaction of Fischer carbene complexes and dienyne **94** has been demonstrated as a suitable method for the preparation of the bicyclo[3.1.1]heptanone intermediates as A-ring synthons of taxol and taxane derivatives. The chiral dienyne **110a** has also been employed in the reaction and results in good syn/anti ratios in favor of the desired bicycloheptanone isomers, thus providing a diastereoselective synthesis of taxol A-ring synthons. The asymmetric induction is believed to originate from chelation of oxygen to chromium during the reaction and a mechanism based on this has been proposed.

It has also been revealed that the closure of the B-ring of taxol via an aldol condensation/Grob fragmentation does not proceed as anticipated and instead results in undesired fragmentation. Extensive analysis of the NMR and mass spectra of the rearranged products led to the correction of a previously misinterpreted structure of a key triketone intermediate. A modified strategy has been designed on the basis of careful mechanistic considerations which represents an attractive route to the ABC tricyclic core of taxol and deserves further investigation.

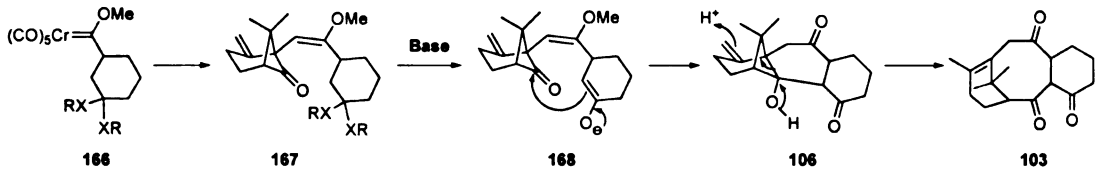
Efforts in the future will certainly be directed to the construction of the ABC tricyclic core as the utmost important task. By no means have the approaches for the aldol condensation in the B-ring closure for **163** been exhausted. Other reagents, including different bases, will be worth examining. In a slight modification, it might be possible to convert the aldehyde functionality to an activated functional group, such as a reactive carboxylic acid derivative **165** (e.g. N-acylamidazoles[136]) to examine Claisen-type condensation, as shown in Scheme 2.32.

Scheme 2.32. Proposed Manipulations of the Aldehyde Functionality for Closure of the B-ring



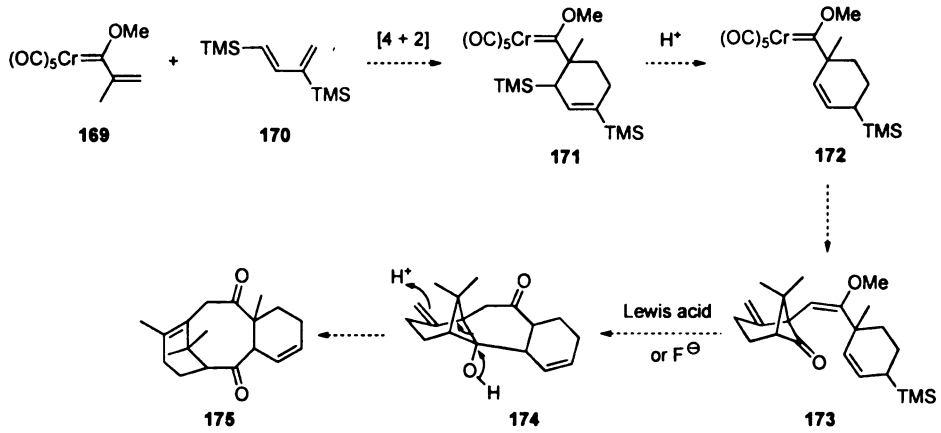
Based on the fragmentation studies described in Section 2.4, if a strong Brønsted acid is not involved in the removal of the protecting group of the ketone on the C-ring, the undesired fragmentation may be avoided. Thus, if the carbonyl group in the carbene complex can be protected as a base-cleavable group in **166**, the bicycloheptanone **167** can be converted to **168** under basic conditions. The aldol condensation of **168** to give **106** might not be a problem in this case because a six-membered ring is formed (Scheme 2.33). The subsequent fragmentation of **106** would be expected to occur via the desired pathway to give the tricyclic compound **103**. The difficulty in this stategy, of course, is to find an appropriate protecting group which can be cleaved by a base (or at least without using strong Brønsted acids) to give a carbonyl group or its equivalent. Dithianes may be an option since there have been a couple of rare examples that they are removed with a base.[137]

Scheme 2.33. A Possible Approach for the Formation of the ABC Tricyclic Core



An alternative strategy to avoid the use of strong Brønsted acids is to synthesize a bicycloheptanone of the type **173** (Scheme 2.34). Carbene complex **171** can be prepared by a Diels–Alder reaction of **169** with **170**. If the adduct **171** can be converted to intermediate **172**, it would provide an interesting substrate for the Wulff–Kaeslser reaction, thus the conversion of intermediate **173** to **174** would be realized without using a strong Brønsted acid (Scheme 2.34).

Scheme 2.34. Another Strategy for the Construction of the Taxol Skeleton



All of the above strategies for the construction of the ABC tricyclic core of taxol rely on nucleophilic additions for closure of the B-ring. Other strategies, for example, utilizing ring closing metathesis (RCM) or the carbon–carbon coupling reactions, can certainly be pursued as well. Accordingly, the structures of the carbene complexes will need to be carefully designed and the viability of their preparations must be taken into considerations.

CHAPTER THREE

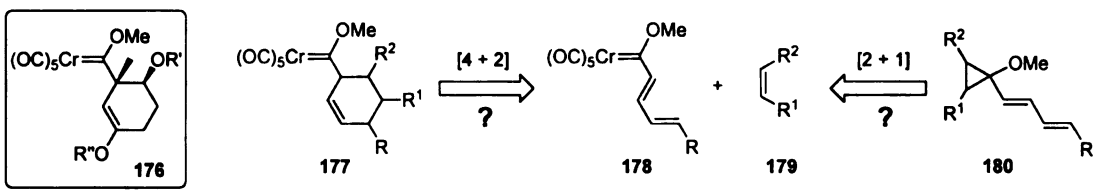
AN INVESTIGATION OF THE CYCLOPROPANATION REACTION OF DIENYL FISCHER CARBENE COMPLEXES

3.1 BACKGROUND ON THE CYCLOPROPANATION REACTION OF FISCHER CARBENE COMPLEXES

During the studies toward the total synthesis of taxol discussed in Chapter 2, at one point it was decided to investigate if carbene complexes of the type **176** (Fig. 3.1), which have a double bond at the β and γ positions to the carbene carbon, could be prepared. These carbene complexes can be interesting substrates in the Wulff–Kaesler reaction for the construction of bicyclo[3.1.1]heptanone intermediates for the synthesis of taxol since the functional group(s) on the C-ring may be further utilized for closure of the B-ring. Because complexes **176** consist of a cyclohexenyl ring, it is reasonable to consider that a [4 + 2] reaction could be employed in their preparation. It has been well established that α,β-Unsaturated Fischer carbene complexes can act as potent dienophiles in Diels–Alder reactions with 1,3-dienes, however, this reaction will give a cyclohexenyl ring with the resultant double bond being at the undesired γ and δ positions.[108] A possible alternative approach to install the double bond in the right position in **176** would be using a dienyl carbene complex as the electron deficient diene source in an inverse electron

demand Diels–Alder reaction. This type of reaction has not been reported.[138] The reactions of simple dienyl carbene complexes of the type **178** with olefins **179** should serve as a model system to test whether this approach to cyclohexenyl carbene complexes of the type **177** is viable (Figure 3.1).

Figure 3.1. Possible Products from the Reactions Involving Dienyl Complexes **178** and Olefins **179**

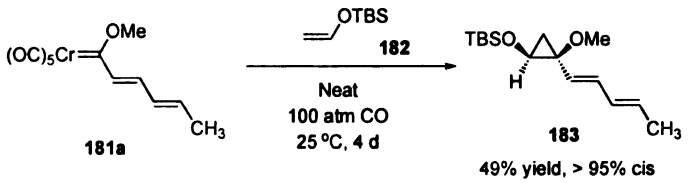


This work was undertaken with full knowledge that the reaction of Fischer carbene complexes with alkenes can also give cyclopropanes. Thus, as shown in Figure 3.1, it was envisioned that both [4 + 2] and [2 + 1] adducts could be possibly formed from the reactions of **178** and **179**.

The cyclopropanation reaction of Fischer carbene complexes, a formal [2 + 1] cycloaddition, is one of the first and longest studied reactions of the heteroatom-stabilized group 6 metal carbene complexes.[106,139] It is well known that Fischer carbene complexes can react with olefins under the proper conditions to produce cyclopropanes, for example, alkoxycarbene complexes readily undergo cyclopropanation under thermal conditions with olefins bearing electron-withdrawing group(s),[140] but a high pressure of carbon monoxide is needed for alkenes with electron-donating substituent(s).[141] Barluenga has recently reported a diastereoselective intermolecular cyclopropanation with unactivated simple alkyl-substituted (electronically neutral) olefins,[142] which has further extended the scope of the reaction.

However, in terms of the Fischer carbene complexes being studied in this reaction, dienyl alkoxy complexes have received little attention.[143] To the best of our knowledge, there is only one known example in the literature which was reported by the Wulff group in 1990 and involves the reaction of the pentadienyl methoxy chromium carbene complex **181a** with the silyl enol ether **182** to give the dienylcyclopropane **183** under a high pressure of carbon monoxide (Scheme 3.1).[144,145]

Scheme 3.1. The Cyclopropanation Reaction of Dienyl Complex **181a** with **182**

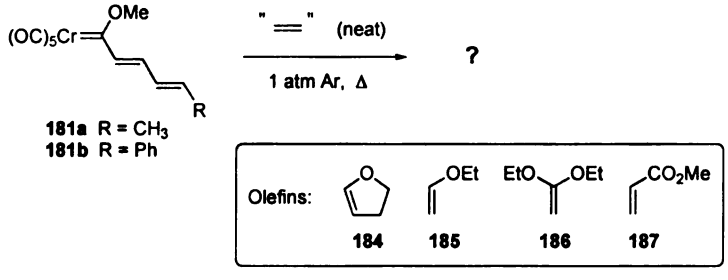


Therefore, a more extensive study of the reactions of this type of doubly unsaturated carbene complexes with olefins was deemed to be necessary. Based on published results of the study of cyclopropanation reactions of Fischer carbene complexes,[106] it was expected that the reactions of **178** and **179** (Fig. 3.1) would be favored to give cyclopropanes **180**, nonetheless, the importance of easy access to complexes of the type **177** made the further search for Diels–Alder reactions of this type worthwhile. By all means, it was considered to be an interesting "one stone, two birds" project that was well worth the anticipated effort. Thus, the reactions of dienyl carbene complexes with olefins were carried out in both inter- and intramolecular fashions.

3.2 INTERMOLECULAR CYCLOPROPANATION REACTIONS OF DIENYL FISCHER CARBENE COMPLEXES

Simple *trans,trans*-dienyl carbene complexes **181a** and **181b** were prepared for the examination of the intermolecular reactions with both electron-rich and electron-deficient olefins **184-187** (Figure 3.2). It would be interesting to see if and how the electronic properties of the olefins would affect their reactions. Complexes **181a** and **181b** were readily prepared by an aldol condensation of the methyl methoxy carbene complex with crotonaldehyde and cinnamaldehyde, respectively, by a procedure developed in the Wulff lab.[112a] Alternatively, complex **181b** could be prepared using Aumman's approach for aldol reactions with non-enolizable aldehydes.[112b,c]

Figure 3.2. The Carbene Complexes and Olefins Designed for Intermolecular Reactions

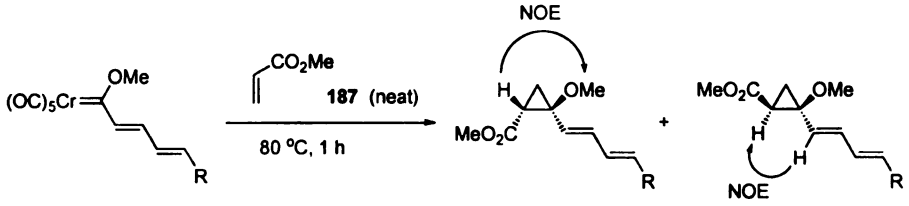


All the reactions were performed under an atmosphere of argon in a glass vessel. When either carbene complex **181a** or **181b** was heated in dihydrofuran **184** at 80 °C, a complex mixture was obtained in each case which did not seem to contain cyclopropanes or Diels–Alder adducts or any of the starting carbene complex. Further attempts with complex **181b** and ethyl vinyl ether **185** or the more electron-rich ketene diethyl acetal **186**[146] also failed to give any cyclopropane products or Diels–Ader products.[147] The failure of the formation of cyclopropanes was not really surprising because there have

been reports in the literature that the cyclopropanation reaction with electron-rich olefins will not take place unless a pressure of carbon monoxide is employed.[141] However, it is not clear why the Diels–Alder reaction also failed with the three electron-rich olefins since the diene unit in the dienyl complexes is expected to be electron deficient.

The reaction of both **181a** and **181b** with methyl acrylate **187**, an electron-deficient olefin, gave cylcopropane products in high yields (Scheme 3.2). Both *trans*- and *cis*-isomers of the cyclopropanes **188** and **189** were obtained and their stereochemistry was determined by 1D NOESY studies. While both reactions gave a moderate 1.9 : 1 diastereomeric ratio in favor of the *trans*-isomer, the phenyl dienyl complex **181b** afforded higher overall yield than that of the pentadienyl complex **181a** (95% vs. 82%). The more stable nature of **181b** under the reaction conditions may be one of reasons that can be attributed to the higher yield in the cyclopropanation reaction. Worthy of mention is that no [4 + 2] adducts were observed in these two reactions.

Scheme 3.2. The Cyclopropanation Reactions of Dienyl Carbene Complexes with Methyl Acrylate



181a R = CH_3
181b R = Ph

188-*trans* R = CH_3 54%
189-*trans* R = Ph 62%

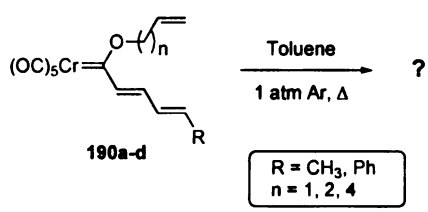
188-*cis* 28%
189-*cis* 33%

The above results have shown that *trans,trans*-dienyl chromium carbene complexes can undergo the cyclopropanation reaction with an electron deficient olefin under an inert atmosphere, but the reaction fails with electron rich olefins. In all cases, no Diels–Alder adducts were observed.

3.3 INTRAMOLECULAR CYCLOPROPANATION REACTIONS OF DIENYL FISCHER CARBENE COMPLEXES

Efforts were then directed to the reactions in an intramolecular fashion. The olefin was incorporated at the end of the alkenyloxy group with different carbon tether lengths to the oxygen (Figure 3.3). Similarly, in addition to the cyclopropanes that were anticipated to be produced, particular attention would be directed to the possibility of the formation of Diels–Alder adducts. The carbene complexes **190a-d** were prepared using either Wulff's aldol condensation protocol[112a] or Aumman's aldol reaction for non-enolizable aldehyde[112b,c] from the corresponding methyl alkenyloxy chromium carbene complexes.[148]

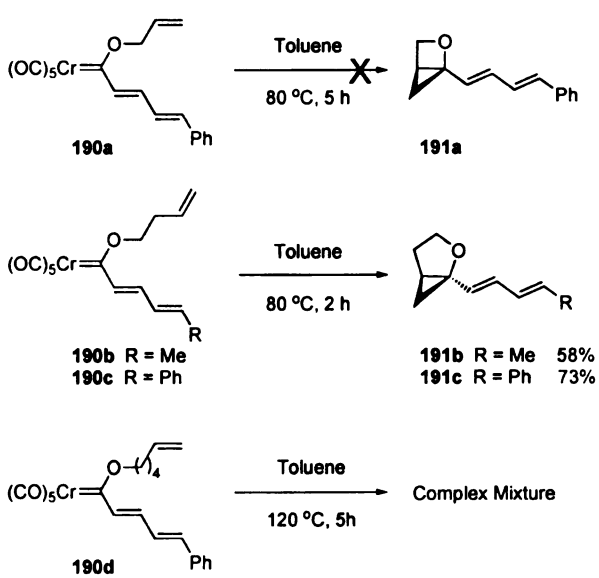
Figure 3.3. Carbene Complexes Designed for Intramolecular Reactions.



As shown in Scheme 3.3, complex **190a** (R = Ph, n = 1) was heated in toluene at 80 °C under an argon atmosphere for 5 hours until all of the starting material was consumed. It was not surprising to find that the reaction did not give any of the cyclopropane **191a**, presumably due to the short tether that would otherwise lead to a structure suffering from the unfavorable ring strain. When the tether length was extended to two carbons between the pendent double bond and the oxygen as in **190b** (R = Me, n = 2) and **190c** (R = Ph, n = 2), both reactions proceeded smoothly. Cyclopropane **191b** (when R = Me) was obtained in a moderate 58% yield and **191c** (when R = Ph) was afforded in 73% yield, which was consistent with the observation that the pentadienyl

complex **181a** gave a little lower yield than that of the phenyl dienyl complex **181b** in intermolecular cyclopropanations (refer to Scheme 3.2). The longer chain alkenyloxy carbene complex **190d** (R = Ph, n = 4) was relatively unreactive and the reaction required heating at 120 °C for 5 hours to go to completion which produced a complex mixture of compounds. Previous studies on the intramolecular cyclopropanation of (non-dienyl) alkoxycarbenes showed that the optimal tether length between the carbene carbon and the olefin was three atoms,[149] and our results supported these observations. Worthy of mention is that the intramolecular Diels–Alder adducts from the reactions of these dienyl alkenyloxy carbene complexes **190a-d** were not observed, although Dötz reported that a dienyl diallylamino tungsten carbene complex was able to produce the [4 + 2] adducts in a low yield[150] and Barluenga reported two successful examples when the allyloxy dienyl complexes have the α,β-double bond embedded in a four-membered ring.[151]

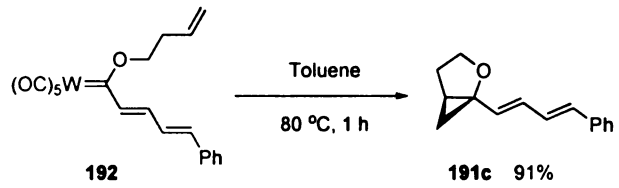
Scheme 3.3. Intramolecular Cyclopropanation Reaction of Dienyl Complexes



There has been one report that the reaction of a Fischer carbene complex and a diene can be fine-tuned to give either the cyclopropanation product or the Diels–Alder

adducts by judicious choice of the metal (chromium vs. tungsten) in the carbene complex.[152] Thus, the tungsten carbene complex **192** was prepared to examine its thermolysis. A little surprisingly, after the tungsten complex **192** was heated at 80 °C for an hour, only cyclopropane **191c** was obtained in 91% yield (Scheme 3.4), with no detectable amount of [4 + 2] adducts being observed. Apparently, the chemospecificity of different metal complexes was not applicable in this case.

Scheme 3.4. The Cyclopropanation Reaction of Tungsten Complex **192**



192 **191c** 91%

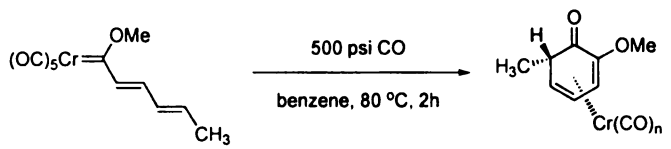
These intramolecular examples have indicated that, even though both the potential 1,3-diene unit and the dienophile are present in the dienyl complexes, the cyclopropanation reaction products, are the only products observed.[153]

3.4 CONTROL REACTIONS UNDER 500 PSI OF CO

In order to test if the presence of CO would affect the reactions of dienyl carbene complexes, complex **190b** was heated in benzene at 80 °C under 500 psi of CO in a Monel Parr reactor. Unfortunately no detectable amount of either the [4 + 2] or [2 + 1] cycloaddition product was obtained. However, a new organometallic compound was observed whose structure was not determined at that time. This compound appeared to be stable in air and the NMR spectra suggested that it still has the intact pendent terminal olefin. In order to confirm that the oxygen tethered olefin was not involved in the

formation of this unexpected product, it was decided to examine the thermolysis of the methoxy carbene complex **181a** in the presence of CO. Complex **181a** was treated to the same conditions as those for **190b**, and as expected, a similar unknown compound was isolated. The compound was initially assigned as the chromium carbonyl cyclohexadienyl complex **193** (n = 3 or 4) based on its NMR and IR spectra. Its unusal stability in air suggests that a chromium tetracarbonyl complex **193b** (n = 4) would be a better candidate because it would be an 18-electron species and thus would be expected to be stable. The molecular weights of the two possible structures **193a** and **193b** are 274 and 302, respectively; however, the mass spectrum shows a molecular ion peak of 278, with no peaks of 274 or 302. This was the big discrepancy in the assignment of the structure of the unexpected metalcarbonyl complexed product. The successful elucidation of the structure led to the serendipitous discovery and development of a novel *ortho*-benzannulation reaction, which will be discussed in great detail in Chapter 4.

Scheme 3.5. A Control Experiment with **181a** under 500 psi of CO



181a

193a n = 3 ?
193b n = 4 ?

3.5 CONCLUSIONS

In summary, the first examples of both inter- and intramolecular cyclopropanation reactions of dienyl chromium carbene complexes under a non-CO atmosphere have been described. The results suggest that the electron density on the olefin can determine whether the reaction will occur in an intermolecular manner. Electron-rich olefins do not undergo cyclopropanation reactions with dienyl carbene complexes, while methyl acrylate, an electron-deficient olefin, reacts with dienyl carbene complexes to give dienylcyclopropanes as a mixture of *trans*- and *cis*-isomers. The intramolecular cyclopropanation reaction of alkenyloxy dienyl carbene complexes with a terminal double bond tethered to the oxygen can occur if the tether length is appropriate. It has also been demonstrated that a tungsten carbene complex affords a high yield of the cyclopropane product in an intramolecular formal [2 + 1] reaction. In all cases, the Diels–Alder reaction which was thought to be a possible competitive reaction did not appear to take place since no [4 + 2] adducts were observed, indicating that the strategy outlined in Figure 3.1 for the synthesis of cyclohexenyl carbene complexes of the type **177** is not viable.

The results demonstrate that cyclopropanes which are tethered to a diene moiety can be efficiently prepared with appropriate substrates involving dienyl carbene complexes. This type of cyclopropane, which may be difficult to prepare by other methods, is useful in organic synthesis,[154] such as metal-catalyzed ring expansions to synthesize medium-sized rings.[155]

CHAPTER FOUR

A NOVEL IRON-MEDIATED THERMAL *ORTHO*-BENZANNULATION OF DIENYL FISCHER CARBENE COMPLEXES: CHROMIUM TO IRON TRANSFER PROCESSES

4.1 BENZANNULATION AND *ORTHO*-BENZANNULATION OF FISCHER CARBENE COMPLEXES: BACKGROUND AND SYNTHETIC APPLICATIONS

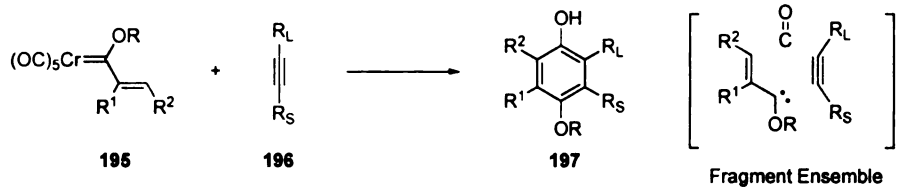
As mentioned in Section 2.1, the study of Fischer carbene complexes during the past forty years has resulted in a large number of new reactions and numerous applications in organic synthesis.[97] The benzannulation reaction (Dötz-Wulff reaction) is one of the most thoroughly studied reactions of Fischer carbene complexes and has been an important method for the synthesis of phenols and, by oxidation thereof, quinones.[156]

4.1.1 Benzannulation of Fischer Carbene Complexes and Their Applications

The benzannulation reaction is a formal [3 + 2 + 1] reaction, where it incorporates the organic portion of an α,β-unsaturated carbene complex **195**, an alkyne **196**, and a CO ligand to form a phenol derivative **197** (Scheme 4.1). The fragment ensemble shows how

the three fragments are connected in the reaction. The α,β-unsaturated carbene complex **195** can be an aryl or alkenyl complex, and as will be discussed later in this section, the metal is not just limited to chromium, but it is the most effective and the most commonly used.

Scheme 4.1. General Scheme of the Benzannulation Reaction



195 **196** **197**

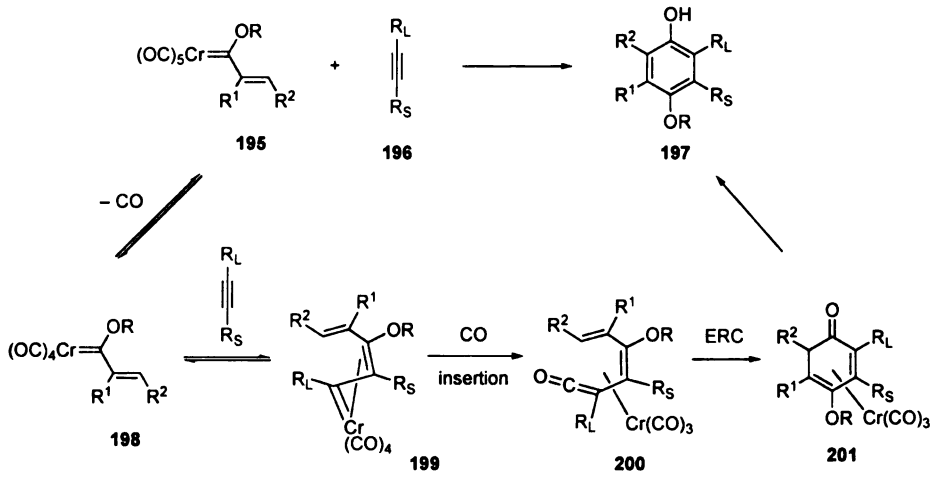
Since its first report by K. H. Dötz in 1975,[157] the benzannulation reaction has been studied extensively, not only because of its mechanistic complexity, but also due to its wide applications in organic synthesis.[156] Thus, it is not possible to give a comprehensive review of the reaction here, and the following description will hopefully serve as a very brief overview of its mechanism, scope and applications.

Mechanistic Considerations and Regioselectivity

The mechanism of the benzannulation reaction is still not fully understood. There have been a few different versions proposed for the reaction that differ mainly in the order of the steps and the nature of the intermediates.[158] The generally accepted mechanism is shown in Scheme 4.2. The first and rate-determining step of the reaction is the dissociation of a CO ligand to generate an unsaturated 16-electron species **198**.[159] Subsequent insertion of an alkyne into the chromium – carbene carbon bond generates the η^1,η^3-vinyl carbene complex **199**. Then CO insertion takes place to give the vinyl ketene complex **200** which undergoes an electrocyclic ring closure (ERC) to provide the

cyclohexadienone complex **201**. Finally, tautomerization and loss of chromium tricarbonyl affords the *p*-alkoxy phenol **197**.

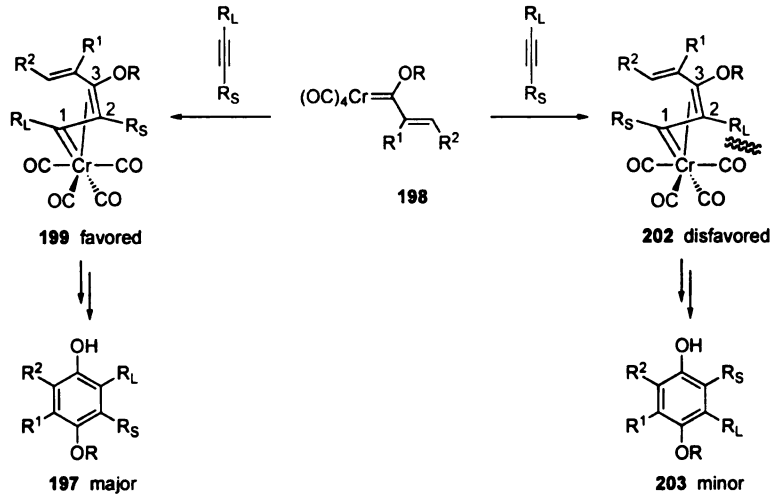
Scheme 4.2. A Simplified Mechanism of the Benzannulation Reaction



During the benzannulation reaction, the regiochemistry of the incorporation of an unsymmetrical alkyne is determined by the steric differences of the acetylene substituents,[160] and the major isomer is the one in which the sterically larger group (R_L) is incorporated adjacent to the phenol functionality. The source of regioselectivity is believed to be from the interaction of the substituents on the alkyne with the carbon monoxide ligands in the vinyl carbene complexes **199** and **202** (Scheme 4.3). Extensive Hückel calculations reveal that the substituent at the 2-position of **199** or **202** is at least one angstrom closer to its nearest CO ligand than that at the 1-position,[161] which accounts for why the intermediate **199** with the sterically smaller group (R_S) at the 2-position is favored as compared to the intermediate **202**. Consequently, the major isomer is the phenol **197** that has the larger group (R_L) adjacent to the newly formed phenol functionality, although it is not clear whether it is a kinetic or thermodynamic outcome. The reaction is highly regioselective with terminal alkynes, but often gives poor

selectivity with an unsymmetrical disubstituted acetylene, in which case the lack of regiocontrol can be overcome in intramolecular annulations in which the acetylene is tethered to the oxygen in the carbene complex.[162]

Scheme 4.3. Regioselectivity of the Benzannulation Reaction



For an α,β-unsaturated carbene complex of the type **204** that is disubstituted at the β-position with carbon substituents, the reaction with an alkyne gives a non-tautomerizable cyclohexa-2,4-dienone **205** as the final product (Scheme 4.4).[163] This reaction is often referred to as the cyclohexadienone annulation. The β,β-disubstituted alkenyl and indolyl carbene complexes both work well in the reaction,[163,164] but aryl carbene complexes that have carbon substituents in both *ortho*-positions usually do not give cyclohexadienone products.[165]

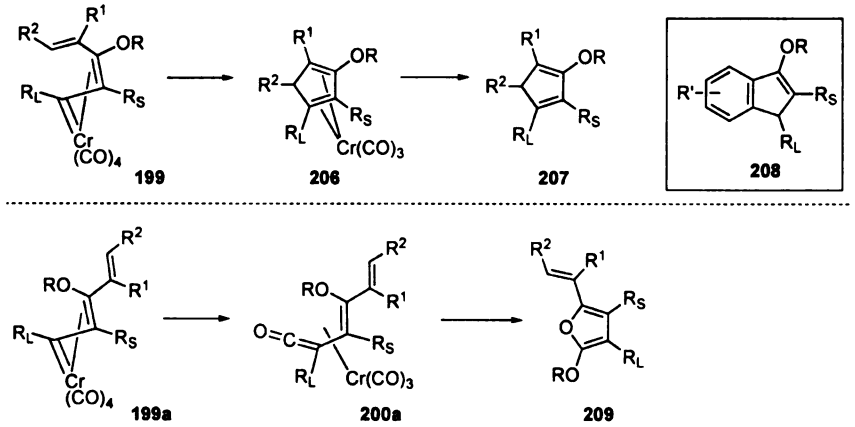
Scheme 4.4. General Scheme of the Cyclohexadienone Annulation

The Scope and Limitations of the Benzannulation Reaction

The benzannulation reaction generally produces good to excellent yields of phenols, however, it can be very sensitive to the reaction conditions and the nature of the substrates. The reaction can form a number of side products, and those most commonly observed include indenes (cyclopentadienes), furans and cyclobutenones.

Chemoselectivity. The indene (cyclopentadiene) side product results from a direct cyclization of the vinyl carbene complexed intermediate **199** without the insertion of a carbon monoxide (Scheme 4.5).[166] While the product **207** is rarely seen from the reaction with alkenyl chromium complexes, aryl carbene complexes are more likely to produce the direct cyclization product, which in this case would be indene **208**. For many reactions, the formation of the indene products can be most detrimental in accounting for the less than optimal yields of the desired phenol products. Since the formation of the *Z*-isomer **199a** is also possible upon the insertion of the alkyne, and since CO insertion gives the vinyl ketene complex **200a** which cannot cyclize to a phenol, this pathway is thought to be the origin of the furan side-product **209**.[167]

Scheme 4.5. The Rationale for the Indene and Furan Formation



Metal Effects. The reactions with tungsten or molybdenum carbene complexes have also been studied, and it has been shown that in general these complexes are much less chemoselective for the formation of the phenol products than the corresponding chromium complexes.[168] One exception is that the reactions of alkenyl carbene complexes with terminal alkynes always give the phenol products in high yields no matter which of the three metals is contained in the carbene complex. Compared to chromium complexes, molybdenum complexes are generally less stable, and while tungsten complexes are generally more stable, their reactions suffer from alkyne polymerization[168b,169] which competes with the formation of the phenol product. A few non-group 6 Fischer carbene complexes, such as iron,[170] cobalt,[171] and manganese[172] complexes, have also been investigated, but none provides a general method for the synthesis of phenols.

Solvent Effects. Studies have shown that the nature of the solvent has more of an effect on the reactions of aryl carbene complexes than on alkenyl complexes.[168a,173] Non-polar and non-coordinating solvents usually favor the formation of phenol product, while in polar and coordinating solvents, such as DMF and acetonitrile, a number of different side products can be formed in significant amounts.

Concentration Effects. The concentration of the reaction can affect the distribution of the products but this is generally limited to the reactions with aryl carbene complexes.[168a,173a,b,174] It has been found that the phenol/indene partition is more favorable at higher concentrations. The distribution is a function of the alkyne concentration and not of the carbene complex concentration.

Temperature Effects. There have not been extensive studies of the effect of the temperature on the product distribution. It has been shown that in some cases the indene side product is favored over phenol at higher temperatures.[173b]

Heteroatom-Stabilizing Substituents. Besides oxygen-stabilized carbene complexes, other hetero-atom stabilized complexes have also been examined, among which the most thoroughly studied is the more electron-rich amino complexes. As expected, the more electron rich substituent increases the electron density on the metal center and strengthens the back bonding from the metal to the CO ligands, which in turn disfavors the insertion of a CO ligand and leads to a decreased amount of the phenol product. Consequently, the formation of the indene product is favored and this is especially true with a polar and coordinating solvent.[175] In fact, the reaction of amino carbene complexes and alkynes in DMF has become an efficient method for the synthesis of indenes, although the efficiency of the reaction is highly dependent on the nature of the substituents on the nitrogen.[176] One exception is the reaction of amino alkenyl carbene complexes and terminal alkynes which gives predominantly the phenol product.[177] It should not be surprising that the reaction of amino carbene complexes can be tuned to give more of the phenol product over the indene product by lowering the electron density on the nitrogen by introducing an electron-withdrawing group. Successful examples of this include installing a carbonyl group on the nitrogen (e.g. forming a carbamate)[178] and using an aromatic pyrrole ring.[179]

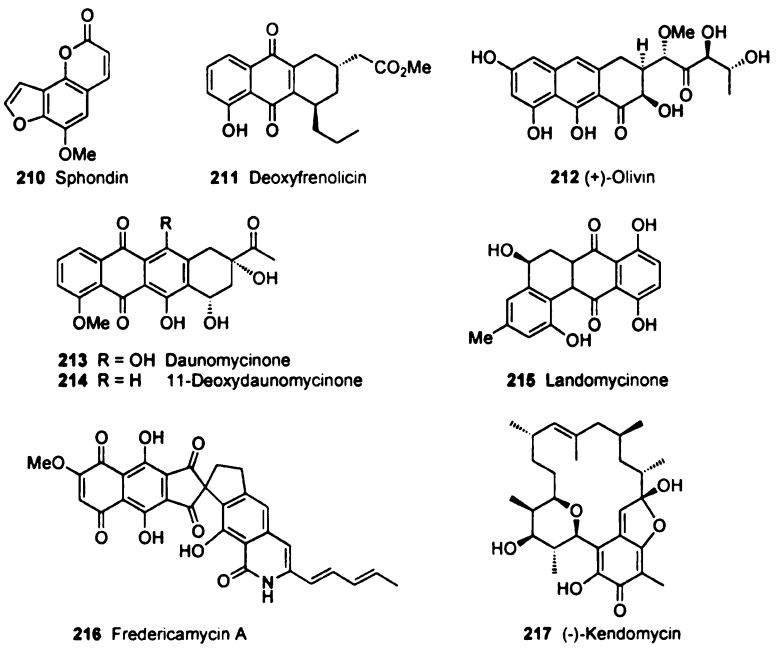
Stereoselectivity. There are a few reports that have examined how the configuration of the newly formed planar center of chirality due to the creation of a chromium tricarbonyl group complexed to an aromatic ring would be influenced by

existing stereogenic centers in the substrate(s), and in some cases high stereoselection can be achieved while in others the stereoselection is limited or the scope has yet to be explored.[180]

Applications in the Synthesis of Complex Molecules

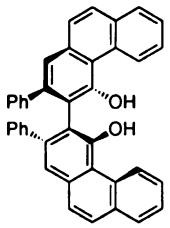
The benzannulation reaction of α,β-unsaturated carbene complexes and alkynes, with its attractive features such as mild reaction conditions and tolerance of a wide range of functional groups, has found applications in the synthesis of a large number of phenol and quinone containing complex molecules. A few examples of natural products are shown in Figure 4.1: sphondin,[181] deoxyfrenolicin,[162b,c,182] (+)-olivin,[183] daunomycinone,[173c,184] 11-deoxydaunomycinone,[185,186] landomycinone,[187] fredericamycin A,[188] and (-)-kendomycin,[189] and each of their syntheses utilizes the benzannulation reaction as the key step.

Figure 4.1. Synthesis of Natural Products Involving Benzannulation Reaction

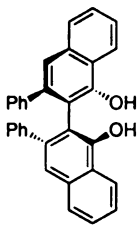


This reaction has also been applied in the synthesis of the vaulted biaryl ligands, VAPOL and VANOL,[190] for use in asymmetric catalysis. The VAPOL and VANOL ligands have been shown as superior ligands in the catalytic asymmetric aziridination reaction,[191] Diels-Alder reaction (VAPOL),[192] and the imino aldol reaction (VAPOL).[193]

Figure 4.2. Structures of VAPOL and VANOL Ligands



218 (*S*)-VAPOL

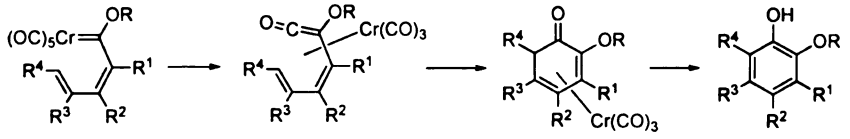


219 (*S*)-VANOL

4.1.2 *ortho*-Benzannulation of Fischer Carbene Complexes and Their Applications

As discussed in Section 4.1.1, the key intermediate in the benzannulation reaction of α,β-unsaturated carbene complexes and alkynes is the vinyl ketene complex **200** (Scheme 4.2). It was then not surprising to propose that if the α,β,γ,δ-unsaturated carbene complex **220** would undergo insertion of a carbon monoxide, the doubly unsaturated vinyl ketene complex **221** would be formed with the alkoxy group attached to the ketene carbon (Scheme 4.6). Similar to **200**, the ketene complex **221** might be expected to undergo an electrocyclic ring closure to give the cyclohexadienone complex **222** which would tautomerize to afford the phenol **223** after the loss of chromium tricarbonyl. The formed phenol **223** has an alkoxy group in the *ortho*-position, thus the reaction is refered to as the *ortho*-benzannulation reaction. This reaction would be a valuable compliment to the benzannulation reaction which produces *p*-alkoxy phenols.

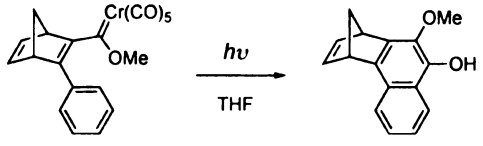
Scheme 4.6. The Strategy for the *ortho*-Benzannulation Reaction



220 221 222 223

Inspired by the pioneering work of Hegedus who found that the photolysis of simple chromium carbene complexes caused insertion of a carbon monoxide ligand to form the corresponding ketene complexes,[194,195] Wulff and coworkers reported in 1989 that the norbornadienyl carbene complex **224**, upon UV irradiation, gave the expected phenol **225** in 18% yield (Scheme 4.7).[196] This was the first example of the *ortho*-benzannulation reaction, which demonstrated that the insertion of a CO ligand was realized photochemically for a doubly unsaturated carbene complex of the type **220**. It was later shown by Merlic that the yield of this reaction could be dramatically improved (93%) if the reaction was performed under an atmosphere of carbon monoxide.[197]

Scheme 4.7. First Example of the *ortho*-Benzannulation Reaction



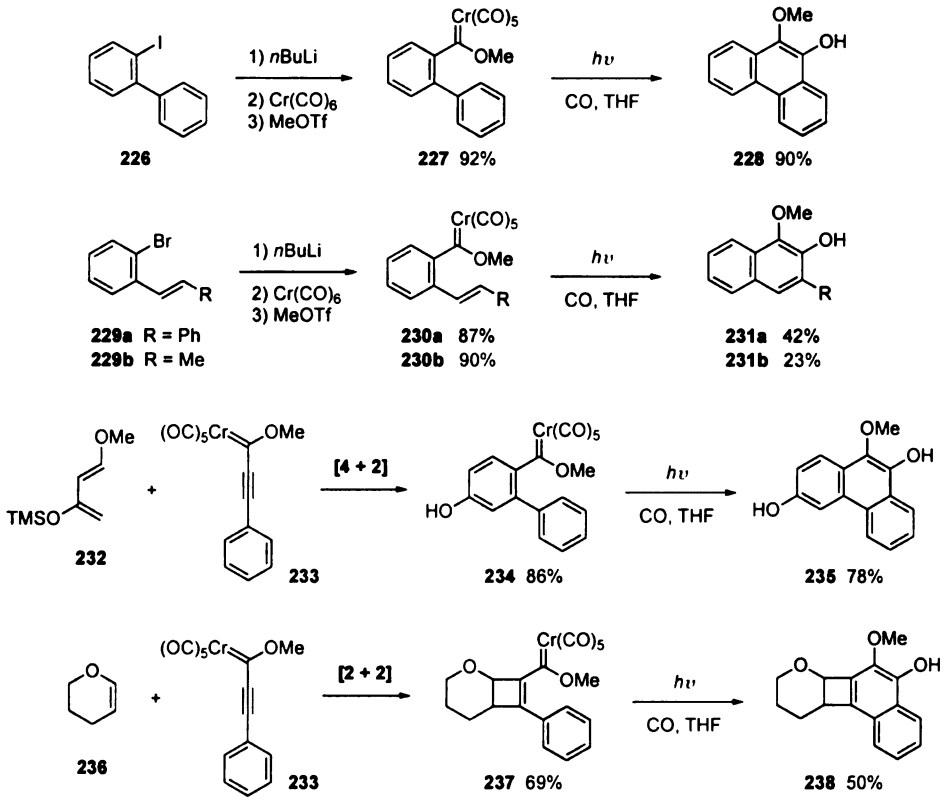
224 225

The Scope and Limitations of the *ortho*-Benzannulation Reaction

The photochemical *ortho*-benzannulation reaction has since been explored and developed as a synthetic method,[197,198] and some examples are illustrated in Scheme 4.8. The reaction requires that the α,β-double bond in the dienyl carbene complex has a cis-disposition. As a consequence of synthetic expediency, most of the carbene complexes

that have been examined either have the α,β-unsaturated double bond incorporated into an aryl ring or are those that can be directly prepared from a [4 + 2] or [2 + 2] cycloaddition onto the alkyne function of an enynyl carbene complex.[199,200] The reaction is independent of the nature of the unsaturation that comprises the dienyl component of the carbene complex and even substrates with aryl groups as both the α,β- and γ,δ-unsaturation are effective for this photochemical *ortho*-benzannulation (e.g. **227** → **228**).

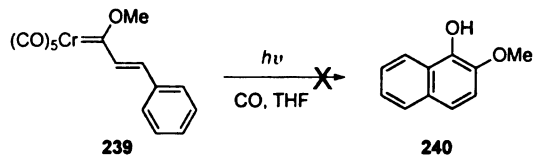
Scheme 4.8. The Photochemical *ortho*-Benzannulation Reaction



However, when the dienyl carbene complex, such as complex **239**, has a *trans*-α,β-double bond, the reaction has been reported to fail under photochemical conditions (Scheme 4.9).[197] As alluded to in Scheme 4.6, during the reaction the α,β-double bond needs to be cis disposed (e.g. in **221**) in order for the cyclization to take place.

Apparently, the isomerization of the *trans*-α,β-double bond of carbene complex **239** could not be realized under the reaction conditions.

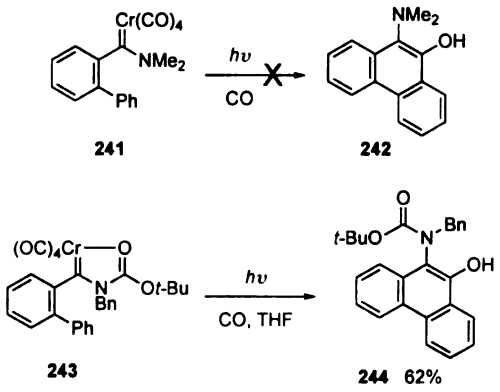
Scheme 4.9. Reported Unsuccessful Example of the *ortho*-Benzannulation



239 **240**

Merlic and coworkers also examined dienyl aminocarbene complexes and found that the photochemical *ortho*-benzannulation was unsuccessful with dialkylaminocarbene complexes with the exception of a single example.[201] Similar to the methods discussed for the optimization of the thermal benzannulation of amino carbene complexes with alkynes (Section 4.1.1), tuning the electron density of the substituents on nitrogen by incorporating a relatively electron-poor carbamate into the carbene complexes (e.g. **243**) favors the formation of the *ortho*-amino phenol products from dienyl amino complexes, and in some cases, giving synthetically useful yields (Scheme 4.10). However, all known examples of this reaction are considerably slower than their corresponding alkoxy carbene complexes.[201]

Scheme 4.10. The *ortho*-Benzannulation of Aminocarbene Complexes

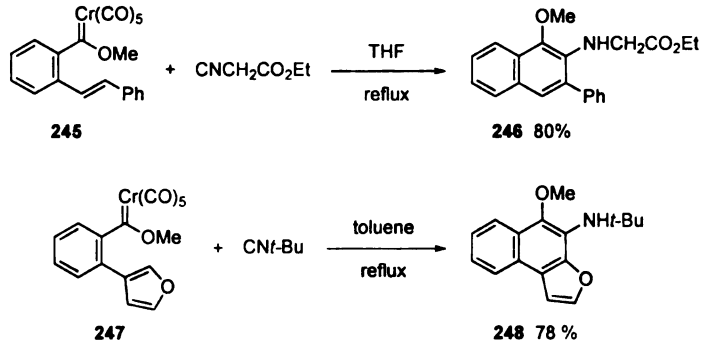


241 **242**

243 **244** 62%

In a related reaction, doubly-unsaturated carbene complexes can react thermally with isonitriles to form *o*-alkoxy aromatic amine derivatives (Scheme 4.11).[202] This reaction presumably proceeds via a dienyketenimine species that is analogous to **221**. Similarly, a structural requirement of the dienyl carbene complexes is a *cis*-α,β-double bond. Alkenyl, aryl and furyl groups can all function as the unsaturation components, except in the case where both the α,β and γ,δ unsaturated units are incorporated into aryl groups. This reaction is different from the *ortho*-benzannulation in the sense that it requires an isonitrile as the reacting partner and the intermediate does not involve a ketene complex.

Scheme 4.11. Formation of *o*-Methoxy Amino Naphthalenes with Isonitriles

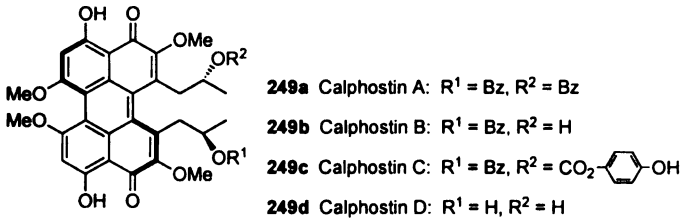


Applications in the Synthesis of Natural Products

The photochemical *ortho*-benzannulation to form *o*-phenols and, by oxidation thereof, *o*-quinones has been applied in the synthesis of complex natural products. For example, as shown in Figure 4.3, Merlic has successfully utilized the reaction in the elegant total syntheses of calphostins A-D,[203] the potent and selective inhibitors of protein kinase C (PKC). The Wulff group has recently applied this reaction to the total

synthesis of carbazoquinocin C,[204] a member of a family of compounds possessing neuronal cell protecting activity.

Figure 4.3. Synthesis of Natural Products Involving the *ortho*-Benzannulation Reaction

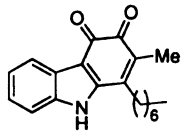


249a Calphostin A: R^1 = Bz, R^2 = Bz

249b Calphostin B: R^1 = Bz, R^2 = H

249c Calphostin C: R^1 = Bz, R^2 = CO_2-C$_6$H$_4$-OH

249d Calphostin D: R^1 = H, R^2 = H

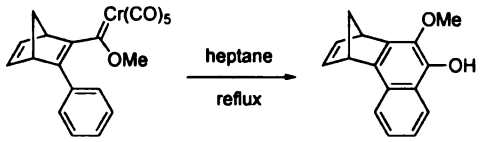


250 Carbazoquinocin C

Examples of the Thermal *ortho*-Benzannulation to Form *o*-Alkoxy Phenols

It was reported by Merlic that, for the thermal reaction of complex **224**, the highest yield that could be obtained was only 29% when the reaction was performed in refluxing heptane (Scheme 4.12).[197] When other dienyl complexes were tested under thermal conditions, little or no benzannulation products were observed.

Scheme 4.12. First Example of the Thermal *ortho*-Benzannulation By Merlic

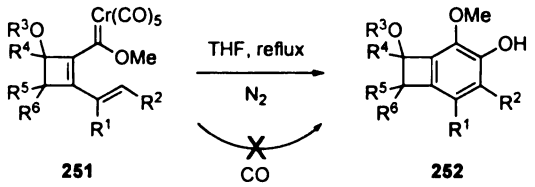


224 **225** 29%

Barluenga has recently reported that, in rare cases, the formation of *o*-methoxy phenols could be induced thermally (Scheme 4.13).[205] All the examples are strictly limited to complexes of the type **251** in which the α,β-double bond is embedded into a strained four-membered ring, and the reactions give good to high yields of *o*-methoxy phenols **252**. It was believed that the unusual reactivity was due to the geometric

restraints of the cyclobutene ring that was introduced in the starting complexes. All the reactions were carried out under an atmosphere of nitrogen, and it was claimed that the reaction failed under a CO atmosphere.

Scheme 4.13. General Scheme of the Thermal Reaction Reported By Barluenga



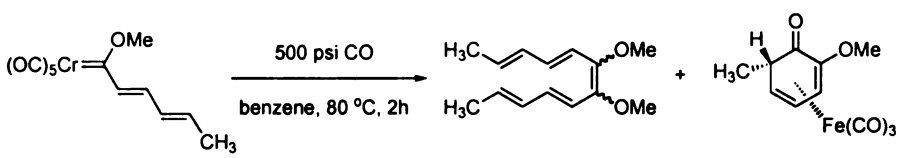
Aumman has also observed the *ortho*-benzannulation products in low to moderate yields with several similar cyclobutene-containing examples of the corresponding tungsten carbene complexes under thermal conditions.[206] Also, there has been a related report on *cis*-styrenyl type chromium carbene complexes with a chalcogen-stabilized iron cluster on the double bond, which can thermally afford both phenol and indene products.[207]

From all the known examples described above, it is clear that the scope of the thermal *ortho*-benzannulation is very limited, and that the *cis*-α,β-unsaturation not only is required but also has to be embedded in a strained ring. This rigid structural requirement in the starting carbene complexes and, therefore the limited geometries in the products, have essentially restricted its use, and as a consequence this thermal reaction has not been of broad interest. These examples were merely viewed as exceptional cases in which the *ortho*-benzannulation reaction be effected under thermal conditions.

4.2 THE DISCOVERY OF A NOVEL THERMAL *ORTHO*-BENZANNULATION MEDIATED BY IRON

As discussed in Chapter 3, the cyclopropanation reaction of dienyl Fischer carbene complexes was examined in both intermolecular and intramolecular fashions. In the course of a control experiment for the cyclopropanation reaction, an unexpected metal carbonyl complex was isolated from the reaction of the *trans,trans*-pentadienyl carbene complex **181a** in benzene at 80 °C under 500 psi of carbon monoxide in a Monel Parr reactor (refer to Scheme 3.5). It took quite a while to finally determine the product as the η^4-dienyl iron tricarbonyl complex **254a** which was isolated in 39% yield (Scheme 4.14).[208] This iron complex had certainly never been expected from the thermolysis of **181a** since only the chromium complex was used and no iron-containing reagent was involved in the reaction. An organic product – the pentaene **253a** – was also isolated in ~30% yield, resulting from dimerization of the carbene ligand, which was not unexpected.[209]

Scheme 4.14. Thermolysis of Pentadienyl Complex **181a** under 500 psi of CO

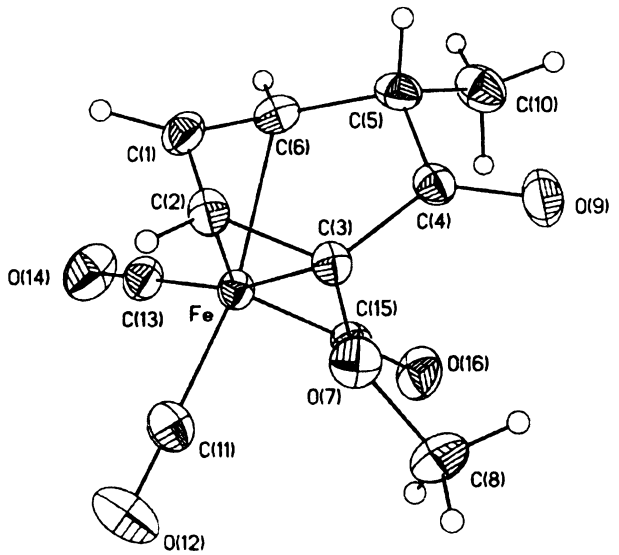


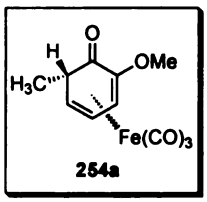
181a **253a** ~30% **254a** 39%

The product **254a** was initially thought to be the cyclohexadienone chromium tricarbonyl complex **193a** on the basis of its NMR spectra (Scheme 3.5). If that structure was correct, it would have a molecular weight of 278; however, the mass spectrum gave a molecule ion of 274. This was the big problem in the assignment of the complex. Another surprising observation was that the complex was very stable in air without any signs of

tautomerization and remained unaffected even upon treatment with strong acids, which did not seem possible for an unsaturated 16-electron group 6 metal complex, such as **193a** (unless it was a ground-breaking discovery in organometallics!).[210] Thus, a tetracarbonyl structure **193b** was suggested for the product which would have 18 electrons on the metal and would be expected to be stable. But again, the molecular weight of **193b** is 302 and this peak was not observed on the mass spectrum. The question that then came to the fore was: which metal would it be if it were not chromium? If this product contained iron, then an iron tricarbonyl complex would fit the high resolution mass spectrum (HRMS), and it could also easily explain the unusual stability that was observed since this complex would be an 18-electron species. As a confirmation, an SEM/EDS analysis[211] was performed to identify which metal was present, and the results clearly showed that the metal in the product was indeed iron and also that the starting complex contained only chromium.[212] The stereochemistry of the methyl group in the complex **254a** was assigned as syn to the iron tricarbonyl group based on its X-ray structure determination (Figure 4.4). Worthy of note is that the X-ray structure was actually taken prior to the SEM/EDS studies but the electron density difference between iron and chromium is small enough that a normal X-ray diffraction analysis cannot distinguish between the two.

Figure 4.4. The X-ray Structure of the Dienone Iron Tricarbonyl Complex **254a**





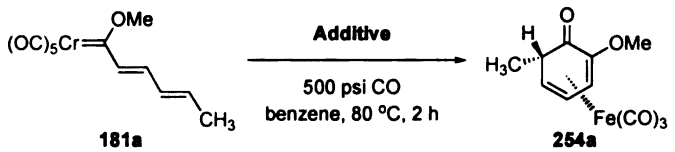
254a

Then the question was: where did iron come from? SEM/EDS analysis ruled out the starting carbene complex **181a** and the benzene solvent was distilled in glass, so the only remaining possible origin would be from the reaction vessel. As mentioned earlier, the reaction was performed in a Monel Parr reactor that is composed of 65% nickel, 33% copper, and only 2% iron and the reactor did not look corroded. On the other hand, the mechanical stirrer appeared to be quite corroded and it was suspected that iron was leached from it.[213]

After determining where iron was coming from, it was decided to pursue other sources of iron to save the mechanical stirrer, and more importantly to be able to maintain rigorous control over the source of the iron. As shown in Table 4.1, the introduction of any of the three iron sources resulted in higher yields of the cyclohexadienone complex **254a**, with diiron nonacarbonyl being superior to triiron dodecacarbonyl and benzylideneacetone tricarbonyl[214] which is known to be an effective iron tricarbonyl transfer agent. It was not necessary to add more than one equivalent of the iron carbonyl

complexes since a slight excess (1.5 equivalents) did not make any difference. In each case, the formation of a trace amount of the pentaene **253a** was also observed.

Table 4.1. Thermolysis under 500 psi of CO with External Iron Sources[a]



181a 254a

Entry	Additive	Equiv.	**254a**, % yield
1	--	--	39
2	$Fe_3(CO)_{12}$	1.0	58
3		1.5	59
4	$Fe(CO)_3(ba)$[b]	1.0	63
5		1.5	63
6	$Fe_2(CO)_9$	1.0	89
7		1.5	89

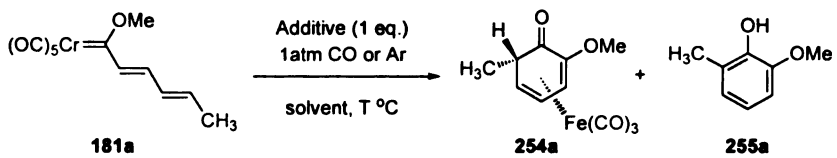
a) All the reactions were carried out at 0.02 M in complex **181a**.

b) Benzylideneacetone iron tricarbonyl.

Since the reaction was performed under 500 psi of CO, a high pressure reactor had to be used. For the purpose of convenience, we sought to carry out the reaction in a glass vessel under one atmosphere of argon or carbon monoxide. Much to our delight, the reaction worked very well and afforded the desired dienone complex **254a** and the corresponding phenol **255a** (Table 4.2). In all cases, no pentaene **253a** was observed when the reaction was performed under 1 atm argon or CO, and the phenol **255a** resulted from the tautomerization of **254a** followed by loss of iron tricarbonyl. It was of interest to note that the overall yields of **254a** and **255a** were only slightly higher under an atmosphere of CO than under argon. The reaction was not very sensitive to the solvent and THF appeared to be slightly better. The reactions in THF or benzene were fairly clean and the separation of the products was not a problem, however, when the reaction

was performed in acetonitrile the purification was not easy due to the presence of some hard-to-separate impurities. As will be shown later, THF and benzene were the solvents that would be used in determining the scope of the reaction. As was observed from the reaction under 500 psi of CO, diiron nonacarbonyl was the better iron source under 1 atm of argon or CO.

Table 4.2. Optimization of the Reaction under 1 atm of Ar or CO[a]



181a **254a** **255a**

Additive	Solvent	CO/Ar	T, °C	Time, h	**254a**, %	**255a**, %	Overall yield, %
$Fe_2(CO)_9$	CH_3CN	CO	80	17	68	12	80
		Ar	80	20	34	8	42
$Fe_2(CO)_9$	heptane	CO	80	36	68	7	75
		Ar	80	20	54	5	59
$Fe_2(CO)_9$	benzene	CO	80	24	70	8	78
		Ar	80	28	58	6	64
$Fe_2(CO)_9$	THF	CO	80	46	61	20	81
		Ar	80	20	50	10	60
$Fe(CO)_3$(ba)	benzene	CO	80	48	60	7	67
		Ar	80	7	18	3	21
- - -	benzene	CO	80	144	- - -	< 0.5	< 0.5[b]
		Ar	80	144	- - -	8	8
$Fe_2(CO)_9$	heptane	CO	60	108	69	5	74
		CO	100	12	59	13	72

a) Unless otherwise specified, all the reactions were carried out at 0.02 M in **181a**.

b) With 70% recovery of **181a**.

The control experiment under argon without a source of iron did produce a small amount of **255a** (8% yield) but only after 144 hours at 80 °C (Table 4.2). After 144 hours at 80 °C under a CO atmostphere, only a trace of **255a** was observed with a 70% recovery

of the starting complex **181a**. Clearly, iron is playing the key role in this carbonylative cyclization.

The temperature study was also carried out under an atmosphere of CO. Heptane was chosen as the solvent simply because it has a high boiling point (98 °C). As can be seen from the last two entries in Table 4.2, the reaction took 108 hours to complete at 60 °C although the overall yield (74%) was essentially the same as the reaction performed at 80 °C (75% yield); while after 12 hours at 100 °C, the reaction gave a slightly lower overall yield (72%). Thus, with both the reaction time and the yield taken into account, it was determined that 80 °C was the temperature that would be used in the study of the scope of the reaction.

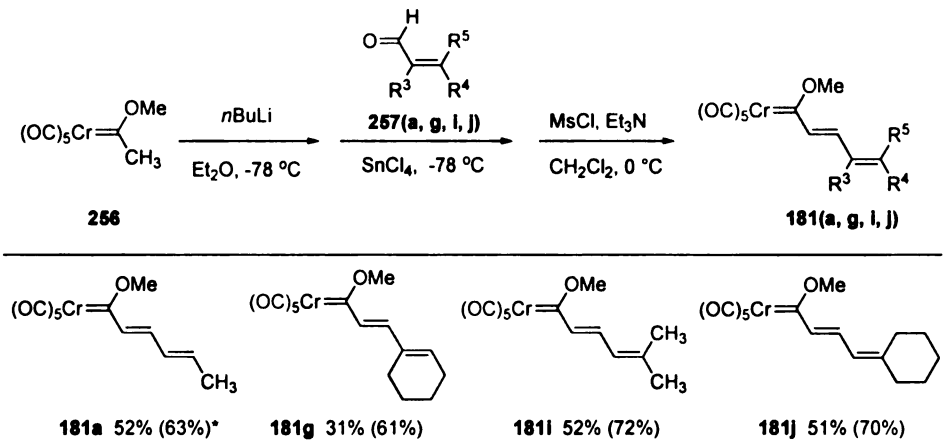
In summary, the first example of the iron-mediated *ortho*-benzannulation of a Fischer carbene complex has been demonstrated. It is the first time that the *ortho*-benzannulation reaction has been realized with a *trans,trans*-dienyl carbene complex. Another feature of this novel reaction is that it is performed under thermal conditions.[215]

The next phase of this study is to investigate the scope of the reaction. The optimized reaction conditions that will be employed are shown as follows: diiron nonacarbonyl used as the iron source, THF or benzene as the solvent, and the reaction would be carried out under one atmosphere of CO at 80 °C.

4.3 PREPARATION OF *TRANS*-α,β-DIENYL CARBENE COMPLEXES

A series of *trans*-α,β-dienyl carbene complexes were synthesized. Most of the carbene complexes were conveniently prepared by an aldol condenstaion of the methyl carbene complex **256** with an unsaturated aldehyde or a ketone.[112] For the reaction of the methyl carbene complex **256** with an aldehyde, the protocol developed by Wulff was used with slight modifications (Scheme 4.15).[112a] The reaction involves the deprotonation of **256** with *n*-BuLi, and then the addition at –78 °C of a pre-mixed solution of the Lewis acid $SnCl_4$ and the aldehye **257**. The resulting aldol adduct is dehydrated upon treatment with MsCl and Et_3N to furnish the dienyl carbene complex **181**. The reaction usually gives moderate to good isolated yields of carbene complexes **181** along with the recovery of some of the starting complex **256**.

Scheme 4.15. Aldol Condensations with Aliphatic Aldehydes

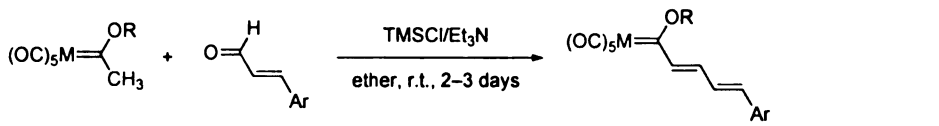


* Yields in prarentheses are based on unrecovered starting material.

This aldol condensation is also effective for cinnamaldehyde, however, for the preparation of this type of dienyl complex with an aryl (or cinnamyl) goup in the δ position, Aumann's procedure using TMSCl and Et_3N was employed (Scheme 4.16).[112b,c] Aumann's procedure is much simpler since it is a one-step reaction which can be

performed at room temperature and usually go to completion after 2–3 days and give good to high yields of the products **181**. However, this procedure can only be used for non-enolizable aldehydes.

Scheme 4.16. Preparation of Dienyl Complexes using Aumman's Method



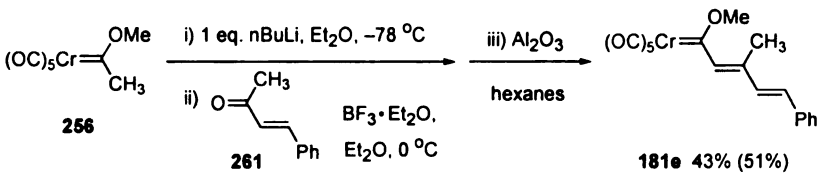
256 M = Cr, R = Me
258 M = W, R = Me
259 M = Cr, R = Et

260a R = Ph
260b R = CH=CHPh

181b M = Cr, R = Me, Ar = Ph; 68%
181c M = W, R = Me, Ar = Ph; 65%
181d M = Cr, R = Et, Ar = Ph; 61%
181h M = Cr, R = Me, Ar = CH=CHPh; 72%

When a ketone was used in the aldol condensation, the better Lewis acid was $BF_3 \cdot OEt_2$ and the dehydrating reagent was alumina as reported by Gilbertson and Wulff.[112d] As shown in Scheme 4.17, the reaction with *trans*-4-phenyl-3-buten-2-one **261** afforded 43% yield of the isolated β-methyl substituted complex **181e** (51% yield based on the recovery of **256**).

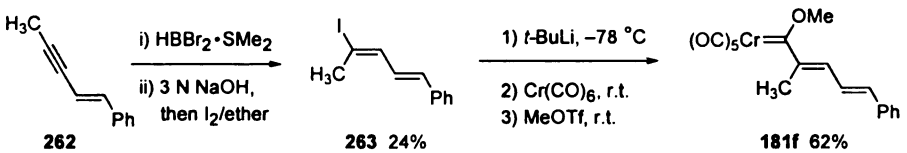
Scheme 4.17. Aldol Condensation with Ketone **261**



The dienyl carbene complex **181f** with a methyl group in the α-position could not be prepared by an aldol condensation since the requisite ethyl methoxy carbene complex and cinnamaldehyde did not give any desired product **181f** under the reaction conditions developed by Wulff,[112a] although the starting carbene complex was all consumed. Thus, this compound was prepared by the Fischer protocol from the dienyl iodide **263**. The synthesis of the precursor iodide **263** involves a one-pot hydroboration/iodination

sequence[216] from 1-((*E*)-pent-1-en-3-ynyl)benzene **262**, which was conveniently prepared by a known procedure[217] from cinnamaldehyde (Scheme 4.18). Considering all the possible isomers that could form in the hydroboration step, it was delightful to be able to isolate the *trans,trans*-iodide **263** in 24% yield which would be difficult to prepare using other methods. The subsequent standard Fischer protocol worked well and gave the α-methyl dienyl complex **181f** in 62% yield.

Scheme 4.18. Preparation of Iodide **263** and Carbene Complex **181f**



262 **263** 24% **181f** 62%

With *trans*-α,β-dienyl carbene complexes **181a-j** in hand, the stage was set for an extensive examination of the efficiency and the scope of the novel *ortho*-benzannulation reaction, which will be discussed in the following section.

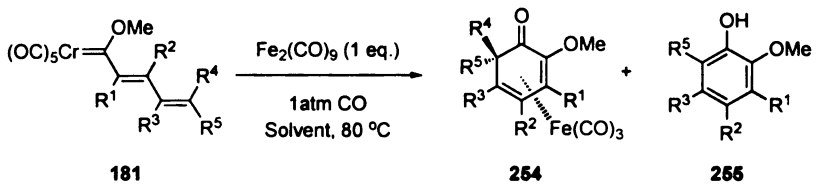
4.4 THE SCOPE AND LIMITATIONS OF THE REACTION

4.4.1 *trans*-α,β-Dienyl Fischer Carbene Complexes

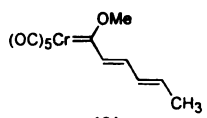
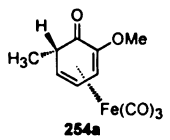
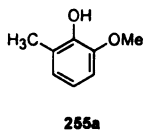
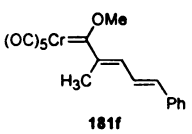
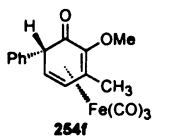
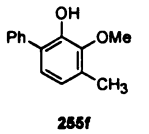
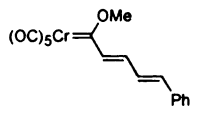
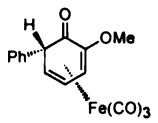
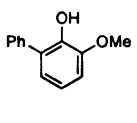
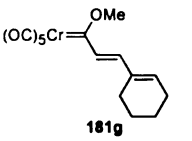
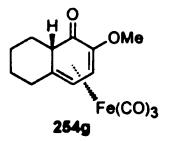
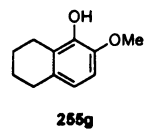
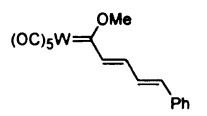
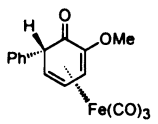
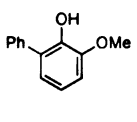
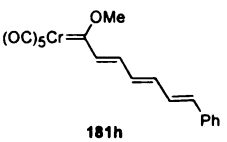
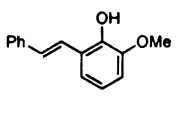
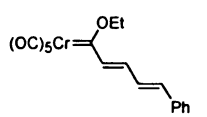
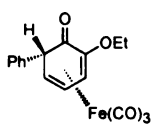
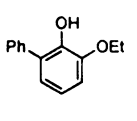
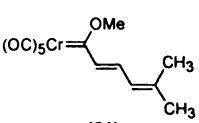
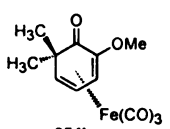
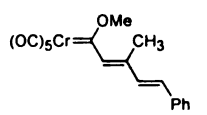
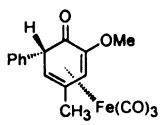
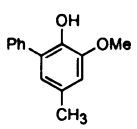
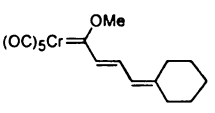
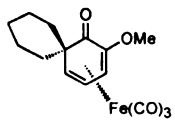
The reactions of *trans*-α,β-dienyl carbene complexes **181a-j** were carried out with one equivalent of $Fe_2(CO)_9$ at 80 °C in THF or benzene under 1 atm of CO, and the results are summarized in Table 4.3. It was delightful to find that the reaction was effective with all the carbene complexes that were examined and gave high to excellent overall yields of the isolated dienone complexes **254** and/or the phenols **255**. In all cases, only a single diastereomer of the dienone complex was formed and the stereochemistry of each was assigned as syn based on the X-ray structure determination of **254a**. For most of the substrates, THF was the optimal solvent. The reaction always gave more of the phenol product in the more polar and coordinating solvent THF than in benzene. Successful substrates include those that have either an alkyl or aryl group at the δ-position (e.g. **181a** and **181b**), and also dienyl complexes that are substituted at the α, β, γ or δ position(s) all worked well. It is also interesting to note that the reaction of the tungsten complex **181c** was superior to that of the corresponding chromium complex, giving 92% overall yield of **254b** and **255b** in THF. Only the phenol **255h** was isolated from the reaction of the trienyl carbene complex **181h**. It is conceivable that the corresponding dienone complex was formed in the reaction but that it was conveted to the phenol **255h** immediately after the reaction mixture was opened to the air.[218] Worthy of mention is that complexes **181i** and **181j** which are disubstituted at the δ-carbon efficiently reacted to give the non-tautomerizable cyclohexadienone iron tricarbonyl complex **254i** (81% yield) and the spiro-complex **254j** (85% yield), respectively. This is

the first time that an "*ortho*-cylcohexadienone annulation" has been realized with a δ,δ-disubstituted dienyl carbene complex.

Table 4.3. The Iron-Mediated Thermal *ortho*-Benzannulation[a]



181 254 255

Carbene Complex 181	Dienone 254	Phenol 255	Carbene Complex 181	Dienone 254	Phenol 255
 181a	 254a	 255a	 181f	 254f	 255f
	THF: 81% (75:25)[b] C_6H_6: 78% (90:10)			THF: 80% (56:44) C_6H_6: 87% (83:17)	
 181b	 254b	 255b	 181g	 254g	 255g
	THF: 82% (40:60) C_6H_6: 80% (56:44)			THF: 91% (93:7) C_6H_6: 88% (98:2)	
 181c	 254b	 255b	 181h		 255h
	THF: 92% (25:75) C_6H_6: 75% (90:10)				THF: 70% C_6H_6: 76%
 181d	 254d	 255d	 181i	 254i	
	THF: 86% (23:77) C_6H_6: 81% (63:37)			THF: 81% C_6H_6: 76%	
 181e	 254e	 255e	 181j	 254j	
	THF: 75% (25:75) C_6H_6: 89% (67:33)			THF: 85% C_6H_6: 81%	

a) Unless otherwise specified, all reactions were carried out at 0.02 M in complex **181**.

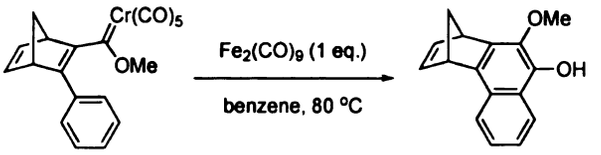
b) The yields are combined yields of isolated **254** and **255**; ratios in parentheses are calculated from the integration of the NMR spectra of the crude reaction mixtures.

The studies demonstrate that the iron-mediated *ortho*-benzannulation of *trans*-α,β-dienyl carbene complexes is broad in scope. The dienyl complex can have substituent(s) at any position(s) of the diene unit. That *trans*-α,β-dienyl complexes are good substrates for this *ortho*-benzannulation greatly increases the power of the *ortho*-benzannulation not only due to the fact that it can now be carried out under thermal conditions, but also because many of the *trans*-substituted dienyl carbene complexes can be easily prepared by an aldol condensation as illustrated in Section 4.3. The *cis*-substituted dienyl complexes that had been previously required for the reaction can be difficult to make unless they are locked into a ring (refer to Schemes 4.8 and 4.13).

4.4.2 *cis*-α,β-Dienyl Fischer Carbene Complexes

Given the effectiveness of the chromium to iron transfer in the thermal *ortho*-benzannulation of *trans*-α,β-dienyl carbene complexes, it was deemed important to determine if this process could be extended to the development of a thermal method for the *ortho*-benzannulation of *cis*-dienyl complexes. The carbene complex **224** was the first of such complexes that were tried, and gratifyingly, it was found that the reaction afforded an 80% yield of the desired naphthol **225** when the reaction was performed under 1 atm of carbon monoxide in the presence of $Fe_2(CO)_9$. The yield was much lower (15%) under argon. Merlic reported that the highest yield that could be obtained under thermal conditions was only 29% when complex **224** was heated in refluxing heptane (in the absence of an iron source).[197] Thus, the iron-mediated *ortho*-benzannulation of **224** was viewed as a great success since previously high yields of **225** could only be obtained under photochemical conditions.

Scheme 4.19. The Iron-Mediated *ortho*-Benzannulation of *cis*-α,β-Complex **224**

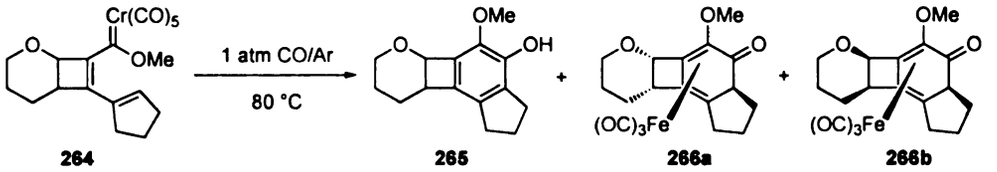


224 **225**

Under 1 atm CO: 80%
Under 1 atm Ar: 15%

Next the *cis*-α,β-dienyl complex **264** was examined. Barluenga reported that complex **264** would give the *ortho*-benzannulated product **265** in 72% yield when simply heated in refluxing THF under an atmosphere of nitrogen.[205] Curiously, it was also claimed that this reaction failed when **264** was heated under an atmosphere of carbon monoxide. In this study, when the reaction was carried out at 80 °C under an argon atmosphere in a Schlenk flask, the best yield obtained was only 40%. Importantly, contrary to what Barluenga claimed, it was found that the reaction actually gave a slightly higher yield (42%) under a CO atmosphere than under an argon atmosphere, as indicated in Table 4.4. It was also found that diiron nonacarbonyl could promote the reaction which gave an increased 68% combined yield of the phenol **265** and the iron complexes **266a** and **266b**. The stereochemistry was tentatively assigned as anti for **266a** and syn for **266b**. These results further demonstrate that the scope of the iron-mediated thermal reaction could be expanded to include *cis*-α,β-dienyl complexes.

Table 4.4. Thermal *ortho*-Benzannulation of *cis*-α,β-Dienyl Complex **264***



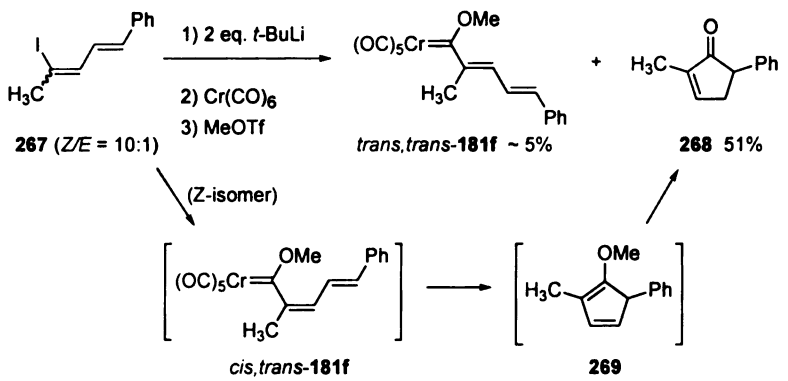
264 **265** **266a** **266b**

Entry	Additive	CO/Ar	Solvent	Time, h	**265**, %	**266a**, %	**266b**, %
1	---	Ar	THF	10	40	---	---
2	---	CO	THF	72	42	---	---
3	$Fe_2(CO)_9$ (1 eq.)	CO	THF	48	49	10	9
4	$Fe_2(CO)_9$ (1 eq.)	CO	Benzene	96	57	7	trace

* Unless otherwise specified, all reactions were carried out at 0.02 M in **264**.

Next it was decided to examine an acylic dienyl complex with a *cis*-α,β-double bond. The *cis,trans*-iodide **267** was obtained in a 10:1 ratio of Z/E isomers using a procedure reported by Zhao for related compounds.[219] However, upon the application of the standard Fischer protocol to the preparation of the *cis,trans*-carbene complex **181f**, none of the desired complex was isolated. These failed attempts included variations with different methylating reagents, such as Meerwein's salt (trimethyl oxonium tetrafluoroborate) and methyl triflate. In addition, an attempt was made to convert the lithium chromium acylate intermediate to the corresponding tetramethyl ammoniuim salt and then methylation, but this also failed to give *cis,trans*-**181f**. In all cases, a small amount of *trans,trans*-carbene complex **181f** (~ 5% yield) was obtained, along with the major product of the reaction which was determined to be the cyclopentenone **268**. Clearly, *cis,trans*-dienyl carbene complex **181f** that was generated from the *Z*-isomer was not stable and underwent spontaneous cyclization (without the insertion of a carbon monoxide) to give the cyclopentadiene **269** which, upon hydrolysis, afforded **268**.

Scheme 4.20. Attempted Preparation of the *cis,trans*-Complex **181f**

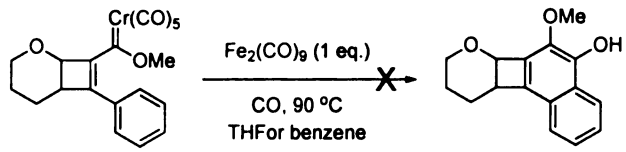


It is known that dienyl carbene complexes, which have an amimo group at the β position and which have the γ,δ-unsaturation and the carbene moiety cis disposed, undergo facile cyclization to give cyclopentadiene derivatives.[220] However, the carbene complexes **224** (Scheme 4.19) and **264** (Table 4.4) also have a cis disposition of the γ,δ-unsaturation and the carbene moiety, and they are clearly stable. This suggests that the exact geometry about the α,β-double bond is important for the stability of the complex. Thus, dienyl complexes can undergo direct cyclization to form cyclopentadiene derivatives at or below room temperature if the angles and lengths of the bonds on the *cis*-α,β-double bond are appropriate. In contrast, the *trans,trans*-carbene complex **181f** is stable and, upon treatment with diiron nonacarbonyl, undergoes the *ortho*-benzannulation to give an 87% yield of the dienone complex **254f** and phenol **255f** (Table 4.3).

Since $Fe_2(CO)_9$ was found to effectively promote the thermal *ortho*-benzannulation of the *cis*-α,β-unsaturated dienyl complex **224** (Scheme 4.19), attention was turned to the investigation of other *cis*-α,β-unsaturated dienyl complexes that Merlic had reported as successful substrates in the photoinduced *ortho*-benzannulation (Scheme 4.8). For example, Merlic reported that complex **237** gave the *o*-methoxy phenol **238** in 50% yield upon photlysis (Scheme 4.8).[197] Treatment of **237** with $Fe_2(CO)_9$ under

thermal conditions in either THF or benzene under 1 atm of CO failed to give any of the cyclized product **238**. This included an attempted reaction under 500 psi of CO in a Parr reaction. In all cases, complex mixtures were obtained and none of the desired **238** was observed while all the starting material was consumed. It is still unclear at this moment why this substrate does not undergo the iron-mediated thermal *ortho*-benzannulation reaction while complex **224** does. Worthy of mention is that all the reactions were heated at 90 °C since the consumption of **237** seemed to be slow at 80 °C.

Scheme 4.21. Attempted Iron-Mediated Thermal *ortho*-Benzannulation of **237**

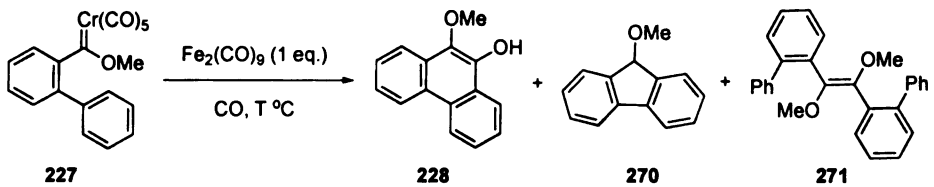


237 **238**

A different but also undesired outcome was observed for the iron-mediated thermal *ortho*-benzannulation of the biphenyl complex **227**. Merlic reported that this complex gave a 90% yield of the *o*-methoxy phenol **228** under photochemical conditions (Scheme 4.8). However, upon heating at 80 °C in the presence of $Fe_2(CO)_9$, the reaction of biphenyl carbene complex **227** was very sluggish and it took days (or even weeks) to consume all the starting material (Table 4.5). Surprisingly, the major product of this reaction was always the direct cyclization product **270**. The *o*-methoxy phenol **228** was the minor product if it was formed at all. In two cases, a small amount of the enol ether **271** was also isolated, resulting from the dimerization of the carbene ligand. The results showed that, under all these conditions that were tried, the insertion of a carbon monoxide was not as fast as the direct cyclization which led to the formation of 9-methoxy fluorene **270**. Given the failure of complexes **227** and **237** to give *ortho*-

benzannulated products in the presence of iron, no other *cis*-α,β-disubstituted dienyl complexes that are known to be photo substrates were not tested in the presence of diiron nonacarbonyl.

Table 4.5. The Iron-Mediated Thermolysis of Carbene Complex **227**.[a]



227 **228** **270** **271**

Entry	CO	Solvent	T, °C	Time, d	**228**, %	**270**, %	**271**, %
1	1 atm	benzene	80	16	20	68	---
2	1 atm	THF	80	7	< 1	79	---
3	1 atm	CH_3CN	80	5	---	77	---
4	1 atm	toluene	130	1	< 1	80	---
5[b]	500 psi	benzene	80	3.6	---	19	8
6	500 psi	toluene	130	0.7	< 2	50	26

a) Unless otherwise specified, all reactions were performed at 0.02 M in **227**.

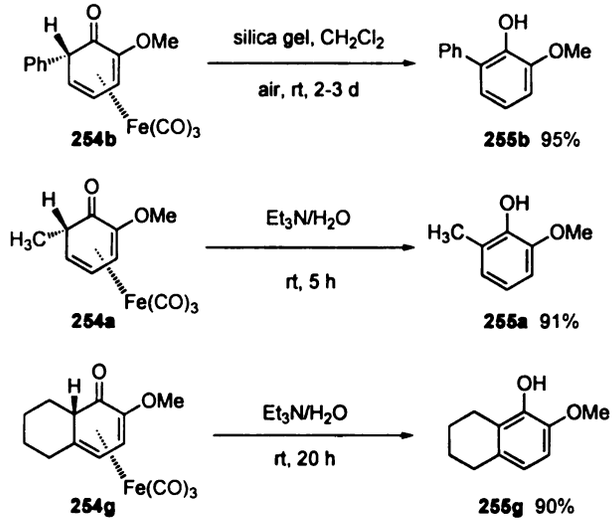
b) With 46% recovery of **227**.

4.4.3 Conversion of the Dienone Iron Tricarbonyl Complexes to Phenols

The demetalation of the iron tricarbonyl complexes can be achieved efficiently to give the corresponding *o*-methoxy phenols. The dienone complex **254b** that has a phenyl group on the sp^3 carbon of the ring was slowly converted to the phenol **255b** even on a silica gel column. Simply stirring **254b** with silica gel in CH_2Cl_2 open to air for a couple of days gave a 95% yield of **255b** (Scheme 4.22). In contrast, the iron tricarbonyl complexes that have an alkyl group on the sp^3 carbon of the ring are quite robust and are not converted to the corresponding phenols on silica gel. However, upon stirring in

Et_3N/H_2O at room temperature for 5 hours, complex **254a** was converted to the phenol **255a** in 91% yield. Alternatively, an 82% yield of the phenol **255a** was obtained after **254a** was refluxed in pyridine for 12 hours under an argon atmosphere.[221] Similarly, the iron complex **254g** was converted to **255g** in 90% yield upon treatment with wet Et_3N.

Scheme 4.22. Demetalation of Iron Tricarbonyl Complexes

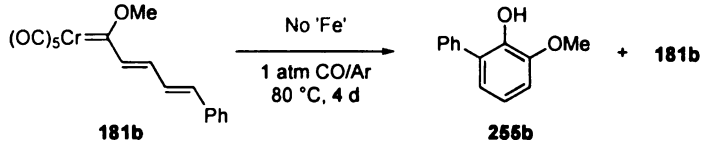


4.4.4 Control Experiments on the *trans,trans*-Dienyl Complex 181b

As shown in Table 4.2, simple thermolysis of the *trans,trans*-pentadienyl carbene complex **181a** without an iron source failed to give the thermal *ortho*-benzannulation product **255a** in any significant yield. Complex **181a** has an alkyl group in the δ-position, and it was decided to run another control experiment with the *trans,trans*-dienyl complex **181b** which has a phenyl group in the δ-position (Scheme 4.23). The outcome was the same when benzene was used as the solvent. After complex **181b** was heated in benzene at 80°C for 4 days under an atmosphere of CO, only a trace of the phenol **255b** was observed along with an 83% recovery of the starting material. A small amount of **255b**

(~7% yield) was obtained from the thermolysis of **181b** under argon along with a 28% recovery of **278b**. These results are remarkably similar to those obtained form the thermal control of **181a**. The thermolysis of **181b** was also examined in THF. Only a trace of phenol was observed under an atmosphere of either argon or CO while all the starting material was consumed. Clearly, all the results further demonstrate that a source of iron tricarbonyl is essential in the thermal *ortho*-benzannulation of *trans,trans*-dienyl carbene complexes.

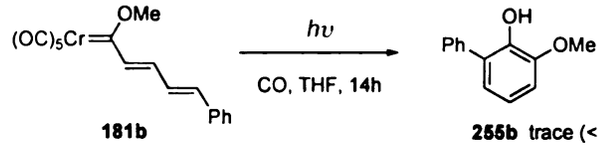
Scheme 4.23. Control Experiments with **181b** in the Absence of an Iron Source



In benzene:	under CO:	< 1% (**255b**) + 83% (**181b**)
	under Ar:	~ 7% (**255b**) + 28% (**181b**)
In THF:	under CO:	< 3% (**255b**)
	under Ar:	< 1% (**255b**)

Given that the *cis*-α,β-unsaturated complexes **237** (Scheme 4.21) and **227** (Table 4.5) will only cleanly give the *ortho*-benzannulation product under photochemical conditions, the question is then raised as to whether the *trans*-α,β-unsaturated dienyl complex **181b** will only give the *ortho*-benzannulation product in the presence of iron. To answer this question, a solution of **181b** in THF was irradiated with a 450 W medium pressure mercury lamp under an atmosphere of carbon monoxide for 14 h until all the staring material was consumed. This reaction only gave a trace amount (< 5% yield) of the *ortho*-benzannulated product **255b** (Scheme 4.24). The failure of the photochemical reaction of *trans,trans*-dienyl complex **181b** is in agreement with Merlic's report on the unsuccessful attempt with the *trans*-styryl complex **239** (Scheme 4.9).

Scheme 4.24. Attempted Photochemical Reaction of *trans,trans*-**181b**



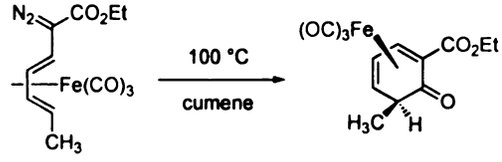
181b **255b** trace (< 5%)

These negative control experiments further demonstrate the uniqueness of the iron-mediated thermal *ortho*-benzannulation reaction of *trans*-α,β-dienyl carbene complexes. In the absence of iron, this reaction does not work under either thermal or photochemical conditions.

4.5 THE MECHANISTIC STUDY

So what does the iron do in this reaction? How does this iron-assisted conversion of the dienyl chromium carbene complex to the iron tricarbonyl cyclohexadienone complex occur? In the only related chemistry, Franck-Neumann reported that the iron tricarbonyl complexed diazo ester **272**, upon heating at 100 °C in cumene, gave the cyclohexadienone complex **273** in 45% yield. This suggests that an iron carbene complexed intermediate could insert CO and cyclize to a dienone (Scheme 4.25).[222]

Scheme 4.25. A Related Literature Example of Cyclohexadienone Formation

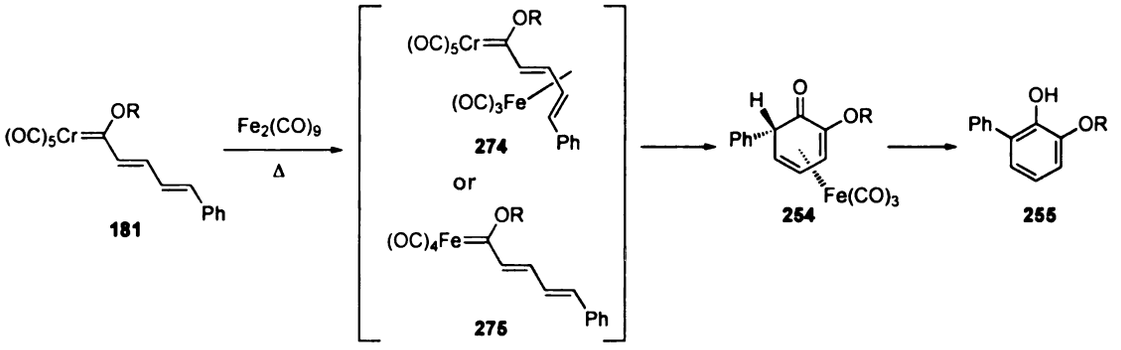


272 **273** 45%

With regard to how the organic fragment is transferred from chromium to iron, there are two most likely possibilities. First, the iron tricarbonyl could become complexed to the dienyl unit in **181** to form an η^4-iron tricarbonyl complex of the type **274** followed

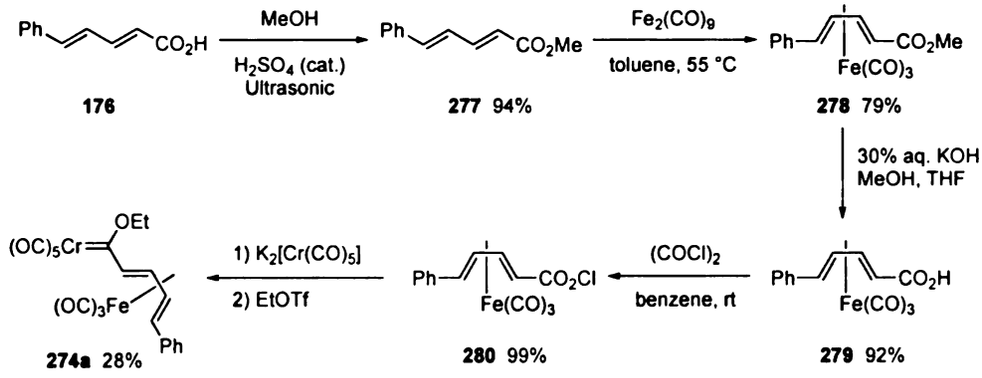
by loss of chromium (Scheme 4.26). Second, there could be a direct transmetalation to give an iron carbene complex of the type **275** which then undergoes internal coordination to the diene in some fashion such that the *trans*-α,β-double-bond is isomerized. To distinguish between these two possibilities, it was decided to prepare both of the complexes **274** and **275** by independent synthesis and test the viability of each in the formation of **254** and **255**.

Scheme 4.26. Mechanistic Considerations for the Iron-Mediated *ortho*-Benzannulation



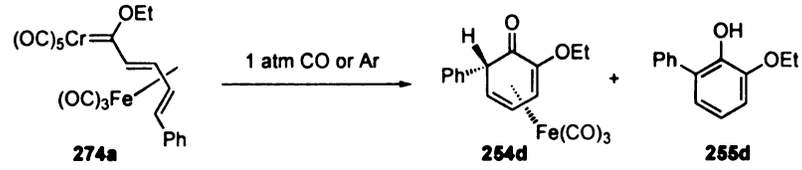
Carbene complex **274a** has not been previously reported and its preparation is shown in Scheme 4.27. The known 5-phenylpent-*2E,4E*-dienoic acid **276**[223] was converted to the corresponding methyl ester **277** which was subsequently complexed with iron tricarbonyl to form the previously unknown dienyl iron tricarbonyl complex **278**.[214] Saponification gave unknown acid **279** and then by treatment with oxalyl chloride afforded the unknown acid chloride **280** in 91% yield over two steps. Then the modified chromate dianion method[224] developed by Hegedus was employed to prepare the complex **274a** in 28% yield.

Scheme 4.27. Preparation of the Iron-Coordinated Chromium Carbene Complex **274a**



With the complex **274a** in hand, its thermolysis at 80 °C in benzene was examined under an atmosphere of argon and carbon monoxide (Table 4.6). Since iron tricarbonyl was already installed in the complex, no external source of iron was added to the reaction. A 71% overall yield of **254d** and **255d** was obtained when the thermolysis was performed under argon; while under CO, the thermolysis gave a 95% overall yield. These results indicate that the complex **274a** is a definite candidate as an intermediate in the *ortho*-benzannulation of dienyl carbene complexes (Scheme 4.26).

Table 4.6. Thermolysis of the Iron-Coordinated Carbene Complex **274a**.[a]



Entry	Additive	Solvent	Temp, °C	Ar/CO	Time, h	Yield, %
1	- - -	benzene	80	Ar	2	71 (4:1)[b]
2	- - -	benzene	80	CO	6	95 (6:1)

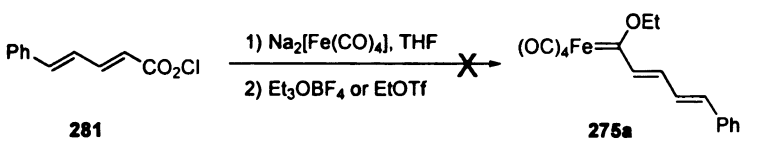
a) Both reactions were carried out at 0.02 M in **274a**.

b) Ratios of **254d/255d** in crude mixtures.

The fact that the iron tricarbonyl coordinated chromium carbene complex **274** will thermally undergo conversion to the *ortho*-benzannulated product does not exclude the possibility that the iron carbene complex **275** is an intermediate in this reaction. However, the reactions of iron tetracarbonyl carbene complexes with alkynes normally do not produce phenols. Furans or pyrones are more typical products from these reaction.[170] There has been only one report of the formation of a *p*-alkoxy phenol and this was from the reaction of the phenyl (ethoxy) tetracarbonyl iron carbene complex with dimethyl acetylenedicarboxylate.[170a] In related chemistry, it has been reported that vinylketene complexes of iron can react with alkynes to form benzannulation products.[225,226] However, whether *o*-alkoxy phenols can be generated from dienyl iron carbene complexes of the type **275** remains unknown.

Attempts were made to generate the iron carbene complex **275a** from the corresponding acid chloride **281** with Collman's reagent – disodium tetracarbonylferrate.[227] This approach was attempted under three different conditions (**a-c** in Scheme 4.28), which included variations in the temperature, the manner of addition, and the ethylating reagent;[228] however, in all cases, none of the desired complex **275a** was isolated. An unexpected iron complex was obtained in each case and its structure was determined to be the diiron complex **282**, which presumably resulted from the acylation of the initial adduct from the acid chloride **281** and $Na_2[Fe(CO)_4]$ with the acid chloride **281**. A couple of related diiron complexes have been reported by Watanabe and coworkers in their efforts to synthesize α,β-unsaturated iron carbene complexes.[229] The yield from the reaction under the conditions shown in (**a**) was 25%, while the yields for (**b**) and (**c**) were not calculated.

Scheme 4.28. Attempted Preparation of the Dienyl Iron Complex **275a**

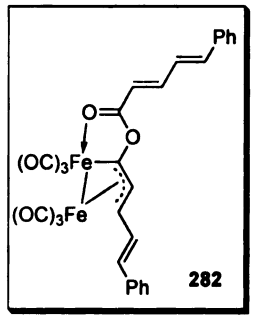


281 **275a**

(a) 1) $Na_2[Fe(CO)_4]$, THF, –78 °C to rt, 6 h; 2) Et_3OBF_4, H_2O (degassed), 0 °C, 1 h.

(b) 1) $Na_2[Fe(CO)_4]$, THF, –78 °C to rt, 5 h; 2) Et_3OBF_4, CH_2Cl_2, 0 °C, 1 h.

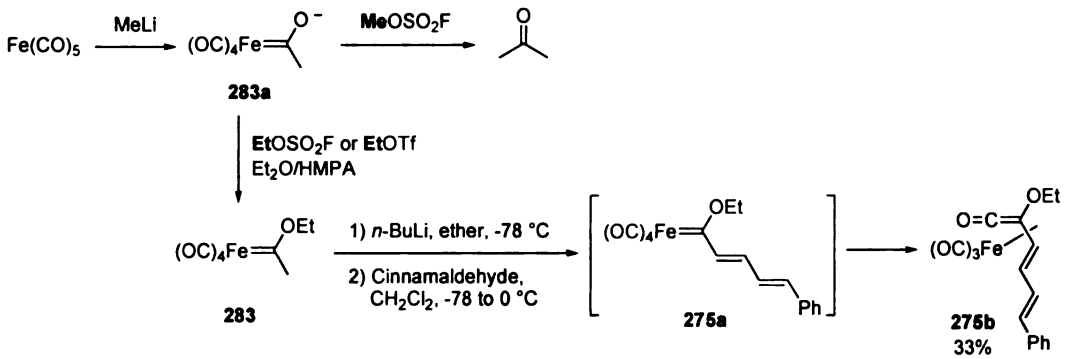
(c) 1) Slow addition of **281** in THF to $Na_2[Fe(CO)_4]$ in THF at rt and stirred for 2 h; 2) EtOTf, ether/HMPA,–78 °C to rt.



282

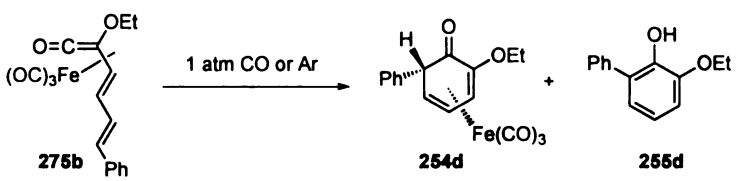
The aldol condensation of the methyl ethoxy iron carbene complex **283** with cinnamaldehyde should provide direct access to the dienyl iron complex **257a**. It was curious to find that there were no known examples of the aldol reaction of iron carbene complexes in the literature. The methyl ethoxy iron carbene complex **283** was prepared according to literature procedure (Scheme 4.29).[228a] It is worthy to note that iron carbene complexes are normally prepared as their ethoxy complexes rather than methoxy analogs. The reason for this is that the tetracarbonyl iron acylate intermedate **283a** can alkylate either on oxygen or on iron. Apparently, the more hindered ethyl substituted electrophiles, such as ethyl fluorosulfonate, give a much higher proportion of alkylation on oxygen than do methyl electophiles.[228a] The aldol reaction of **283** with cinnamaldehyde gave the ketene complex **275b** in 33% yield and none of the iron complex **275a** was isolated (Scheme 4.29). It is clear that the dienyl iron carbene complex **275a** was not stable and underwent spontaneous insertion of a carbon monoxide to generate the previously unkown ketene complex **275b**.[229a,230]

Scheme 4.29. Preparation of the Iron Complexed Ketene **275b**



While the carbene complex **275a** is not stable and isomerizes to the ketene complex **275b**, the ketene complex **275b** will in turn isomerize to the cyclohexadienone complex **254d** when heated at 80 °C in benzene. Thermolysis either under argon or under CO gave the desired dienone complex **254d** and the phenol **255d** in nearly quantative overall yields. Thus it appears that the iron-mediated *ortho*-benzannulation of dienyl chromium carbene complexes could also involve the iron carbene complex **275** resulting from a transmetalation from the chromium complex **181** (Scheme 4.26).

Table 4.7. Thermolysis of the Ketene Complex **275b**.[a]



Entry	Additive	Solvent	Temp, °C	Ar/CO	Time, h	Yield, %
1	- - -	benzene	80	CO	12	96 (3:1)[b]
2	- - -	benzene	80	Ar	22	99 (8:1)

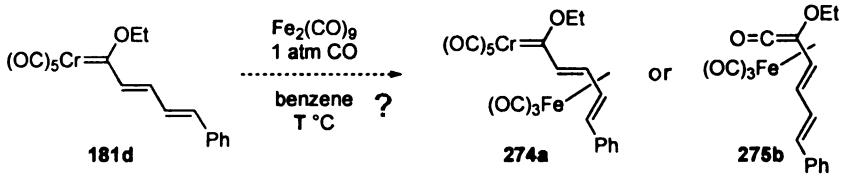
a) Both reactions were carried out at 0.02 M in **275b**.

b) Ratios of **254d/255d** in crude mixtures.

Given that the experiments described above suggest that either the η^4-dienyl iron complex **274** or the η^1-iron carbene complex **275** could be an intermediate in the reaction

(Scheme 4.26), it was decided to stop the reaction early to look for evidence of the presence of either **274** or **275a** or **275b**. A sample of **181d** was heated at 80 °C with one equivalent of $Fe_2(CO)_9$ for only 3 hours, but the NMR spectrum of the crude reaction mixture showed only the starting carbene complex **181d**, the dienone complex **254d** and the phenol **255d** (in a ratio of about 1:10:1). No evidence for the presence of either complex **274a** or **275b** was obtained. It was considered that a lower temperature might help because the conversion of the intermediate **274a** or **275b** to the final products may be faster than the starting material. In the event, a sample of **181d** was heated at 60 °C for 9 hours and then the reaction flask was placed in an ice-bath and the solvent was removed on high vacuum. Unfortunately, only the starting material and the final products were observed in the ^{1}H NMR spectrum of the crude reaction mixture (in a ratio of about 5:20:1 for **181d/254d/255d**).

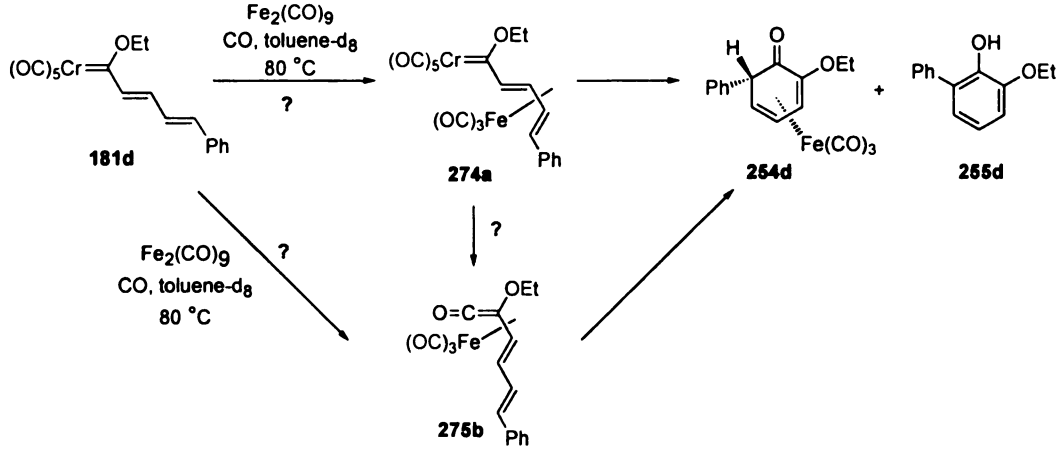
Scheme 4.30. Attempted Detection of Possible Intermediates



Given the failure to detect intermediates **274a** and **275b** in the crude reaction mixtures that were obtained by stopping the reaction short of completion, it was then decided to follow the reaction by ^{1}H NMR. Three reactions were carried out, each having one of the three complexes **181d**, **274a** and **275b** in toluene-d_8 under an atmosphere of carbon monoxide (Scheme 4.31). The reaction of **181d** was performed in the presence of one equivalent of diiron nonacarbonyl in an effort to detect **274a** and/or **275b**. The thermolysis of **274a** was carried out to see if **275b** could be observed. Finally, the thermolysis of **275b** was monitored to probe for intermediates on the way to **254d**.

For each of the three experiments, the temperature was set at 80 °C because the reaction of **181d** seemed to be too slow at lower temperatures (e.g. 40 °C, 60 °C and 70 °C). The ^{1}H NMR spectra were taken every 20–30 minutes for at least 3 hours or until all of the starting material was gone. The thermolysis of **275b** was complete within a half hour, which was much faster than the reactions of **274a** and **181d** (about 20% and 5% conversions, respectively, after a half hour). Unfortunately, in each case, only the starting material and the final products **254d** and **255d** were observed, and none of the possible intermediates were detected. It is reasonable to rationalize that, for the reaction of **181d**, either or both of the complexes **274a** and **275b** are formed gradually in small amounts under the reaction conditions, and that the conversion to the final products is fast, preventing their detection. At this point, both intermediates **274a** and **275b** must be considered as possible intermediates on the pathway.

Scheme 4.31. Attempted In-situ Detection of Possible Intermediates

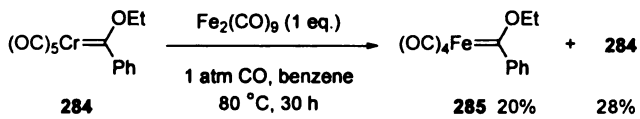


The key transformation that would be required for the formation of iron carbene complex **275** from the chromium carbene complex **181** is the transmetalation of the latter with an iron tetracarbonyl fragment. The transfer of the carbene ligand from group 6 Fischer carbene complexes to other metals has been an active area of interest.[209] The first

known example involves the reaction of a molybdenum carbene complex with photochemically generated $Fe(CO)_4$ to produce an iron carbene complex,[231] however, to the best of our knowledge, there are no known examples of the transfer of a carbene ligand from chromium to iron.

In an effort to demonstrate that a carbene ligand can be transferred from chromium to iron, the chromium carbene complex **284** was heated in benzene at 80 °C under 1 atm CO with one equivalent of $Fe_2(CO)_9$. After 30 hours, the iron carbene complex **285** was isolated in 20% yield with a 28% recovery of **284** (Scheme 4.32). A significant amount of ethyl benzoate was also observed, presumably resulting from the oxidation of the unstable iron complex **285**. This result demonstrates for the first time that the direct carbene ligand transfer from chromium to iron can occur. This of course does not mean that the dienyl complex **274** cannot be an intermediate in the reaction.

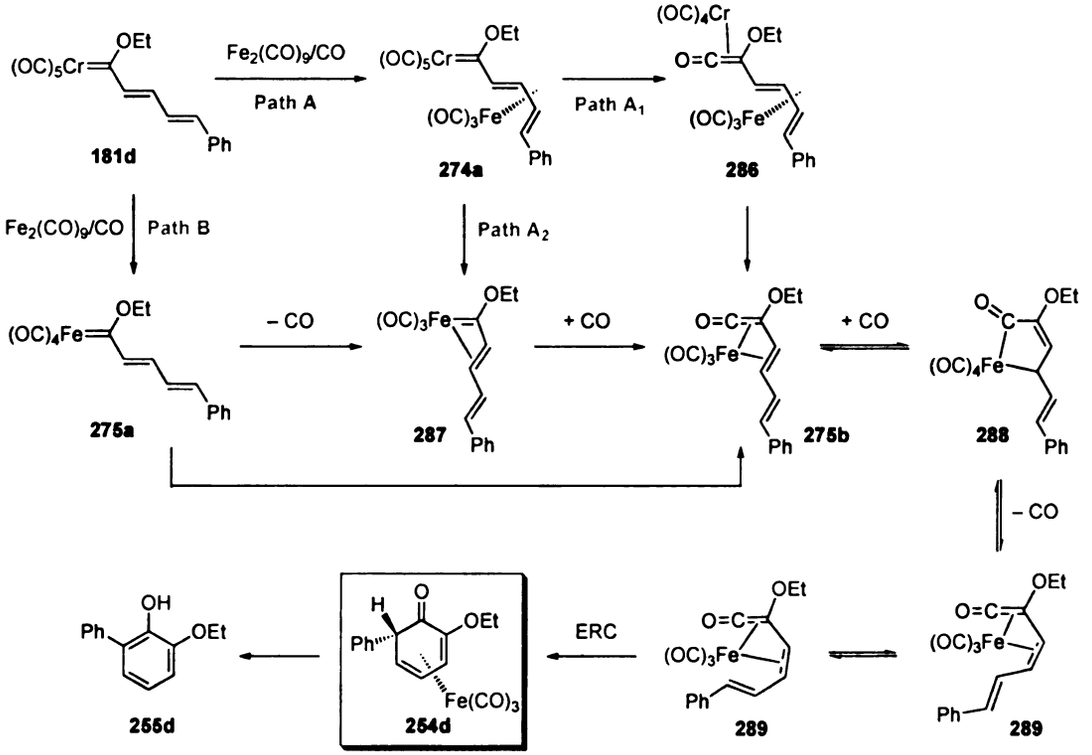
Scheme 4.32. Direct Carbene Ligand Transfer from Chromium to Iron



Based on the above mechanistic studies, a tentative mechanism has been proposed for the thermal *ortho*-benzannulation of *trans*-α,β-dienyl carbene complexes (Scheme 4.33). Complex **181d** could react with an $Fe(CO)_3$ fragment to give **274a** (path A) or undergo transmetalation with an $Fe(CO)_4$ fragment to give the carbene complex **275a** (path B). The resulting complex **274a** may possibly go on to form the ketene complex **286** which could lose chromium to give the ketene complex **275b**. Alternatively, the bi-metallic complex **274a** could lose chromium via the formation of the η^1,η^3-vinyl iron carbene complex **287** which upon CO insertion would give the vinyl ketene complex

275b. The conversion of **275a** to the vinyl ketene complex **275b** may be a one-step process involving simultaneous coordination of the double bond and CO insertion (Scheme 4.29) or a two-step process involving the loss of CO to give complex **287** and then re-incoorporation of CO.[232] The isomerization of the *trans*-α,β-double-bond is proposed to result from the inter conversion of the η^4-vinyl ketene complex **275b** (E configuration) and the η^2-ferracyclopentenone complex **288**. A related η^4 to η^2 conversion has been observed for a cobalt vinyl ketene complex.[233] The η^2-complex **288** should be able to undergo a loss of CO to give either the E or Z isomer of **275b**, depending on the direction of rotation of the styryl group.[233] The *Z*-isomer of **275b**, that is complex **289**, would have the geometry that would allow for the electrocyclic ring closure (ERC) that leads to the observed product **254d.**

Scheme 4.33. Proposed Mechanism for the Iron-Mediated Thermal *ortho*-Benzannulation



4.6 THERMAL *ORTHO*-BENZANNULATION IN THE ABSENCE OF IRON

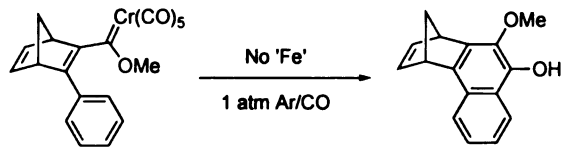
4.6.1 Are Photons Really Necessary?

As discussed in Section 4.4.2, some *cis*-α,β-dienyl complexes, such as **224** (Scheme 4.19) and **264** (Table 4.4), will undergo the *ortho*-benzannulation reaction in the presence of one equivalent of $Fe_2(CO)_9$. It was reported that the photochemical reaction of **224** gave a 93% yield of the phenol **225**, and that complex **224** would undergo the same reaction under strictly thermal conditions giving **225** in 29% when the reaction was performed in the refluxing heptane.[197]

In the course of the present study, it was deemed necessary to perform thermal controls on the *ortho*-benzannulation of complex **224** and the results proved to be quite stunning. As shown in Table 4.8, the thermolysis of **224** in refluxing heptane under argon gave a 28% yield of **225**, which is essentially the same yield reported by Merlic (29%).[197] However, when the reaction was performed under an atmosphere of carbon monoxide, the phenol product **225** was obtained in 75% yield! Apparently the reported 29% yield was from a reaction performed under an inert atmosphere.[197] The thermolysis of **224** was then performed at 80 °C in a number of different solvents, including heptane, CH_3CN, THF and benzene. In all cases, the phenol product **225** was obtained in high to excellent yields from the reactions performed under CO. An astonishing 92% yield was obtained when benzene was used as the solvent! This was a truly stunning finding! Apparently, the thermal cyclization of **224** was never optimized at least according to the published information. However, upon consulting the Ph.D. thesis of D. Xu, it appears that the

proper control experiments were done.[234] It was reported by Xu that the thermolysis of **224** in THF at 90 °C under 50 psi of CO gave an 80% yield of **225**.

Table 4.8. Thermolysis of **224** in the Absence of an Iron Source*



224 **225**

Entry	Additive	Solvent	CO/Ar	T °C	Time, h	Yield, %
1a	- - -	heptane	Ar	100	1.5	28
1b			CO	100	1.5	75
2a	- - -	heptane	Ar	80	39	35
2b			CO	80	42	80
3a	- - -	CH_3CN	Ar	80	4	36
3b			CO	80	8	73
4a	- - -	THF	Ar	80	5	41
4b			CO	80	16	87
5a	- - -	benzene	Ar	80	36	51
5b			CO	80	22	92

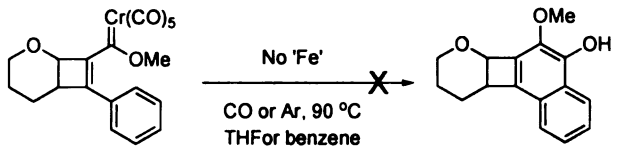
* Unless otherwise specified, all reactions were carried out at 0.02 M in **224**.

So why bother using a photochemical reactor? Are photons really needed for the *ortho*-benzannulation of complexes with a *cis*-α,β-double bond? As was seen for complex **224**, photons are not necessary at all. In addition, complex **264** has been shown to afford the desired phenol in moderate yields under thermal conditions (Table 4.4).

To probe further as to whether photons are necessary, complex **237** was heated at 90 °C in either THF or benzene under 1 atm of CO, but no evidence for the *ortho*-benzannulation product could be obtained (Scheme 4.34). The reaction was also performed in THF under 500 psi of CO and under argon, but in each case, a complex mixture was obtained which did not appear to contain any of the expected product **238**, although Xu reported that a 12% yield of **238** was obtained after complex **237** was heated

at 90 °C in THF under 50 psi of CO for 48 hours.[234] It is unclear at this point why complex **237** failed to give the *ortho*-benzannulation product under thermolysis, given its structure similarity with complex **264** which gives the *o*-methoxy phenol **265** under thermal conditions (Table 4.4). However, this is clearly an example of an *ortho*-benzannulation reaction that requires photolysis since as descired above this reaction will not go under thermolysis or in the presence of $Fe_2(CO)_9$ (Scheme 4.21).

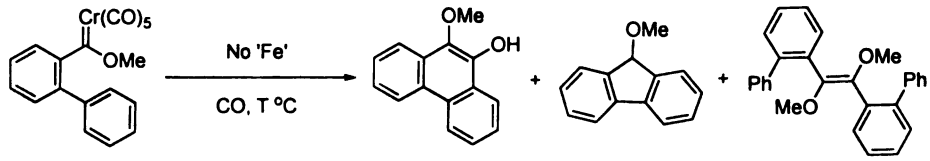
Scheme 4.34. Attempted Thermolysis of **237** without an Iron Source



237 **238**

The thermolysis of the biphenyl complex **227** was also examined and the results are shown in Table 4.9. Under all of the conditions shown in the table, the major product was either the non-CO cyclized product **270** or the alkene **271** which results from dimerization of the carbene ligand. These results mirror those of the iron-mediated reactions of **227** which were presented in Table 4.5. The largest difference between the two is that the reaction in benzene at 80 °C under 1 atm of CO where the iron-mediated reaction gives none of the dimer **271** and the thermal reaction gives a 51% yield of this product. As mentioned earlier in this chapter, the photolysis of complex **227** gives a 90% yield of the *o*-methoxy phenanthrol **228** (Scheme 4.8). Xu also reported that thermolysis of **227** in THF at 90 °C under 50 psi of CO for 7 days gave **270** as the major product (46% yield), along with **271** (26%) and **228** (15%). Thus, complex **227** apprears to be another case where photolysis is required to give the *ortho*-benzannulated product.

Table 4.9. Thermolysis of **227** in the Absence of an Iron Source*



227 **228** **270** **271**

Entry	CO	Solvent	T, °C	Time, d	**228**, %	**270**, %	**271**, %
1	1 atm	benzene	80	12	16	26	51
2	1 atm	THF	80	16	15	58	6
3	1 atm	Toluene	130	0.8	< 1	82	4
4	500 psi	Toluene	130	0.5	< 2	50	38

* Unless otherwise specified, all reactions were carried out at 0.02 M in **227**.

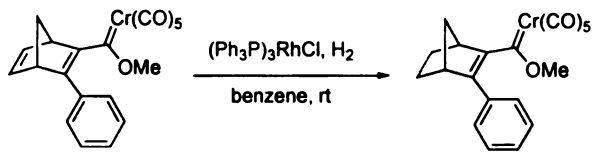
Therefore, it does not seem that all the carbene complexes with a *cis*-α,β-double bond can undergo the *ortho*-benzannulation reaction efficiently under thermal conditions. But what makes the thermal CO insertion process so efficient for the substrate **224** (Table 4.8)? Barluenga claimed that ring strain was responsible for the unusual reactivity of complexes of the type **264** (Scheme 4.13 and Table 4.4).[205] Does it mean that ring strain is the reason why complex **224** reacts thermally? Also, why then does complex **237** not react thermally (Scheme 4.34) since it should have the same ring strain as **264**?

The oxygen in the tetrahydropyran ring in the type **264** and the unconjugated double bond in the norbornadienyl ring in **224** can both provide an additional coordination site for the metal during the reaction. Does this possible extra coordination facilitate the insertion of carbon monoxide which leads to the formation of the desired phenol product?[235,236]

4.6.2 Does Additional Coordination Contribute to the Unusual Reactivity?

To test the idea that the non-conjugated double bond in **224** is coordinating to the chromium during the reaction resulting an acceleration of CO insertion, it was decided to prepare the complex **290**. After a few unsuccessful attempts to prepare the vinyl bromide precursor to the carbene complex **290** that is required for the standard Fischer synthesis, it was pleasing to find that Wilkinson's catalyst – $(Ph_3P)_3RhCl$ – would selectively reduce complex **224** to give the phenylnorbornylenyl complex **290** in 91% yield (Scheme 4.35).

Scheme 4.35. Selective Reduction of **224** with Wilkinson's Catalyst

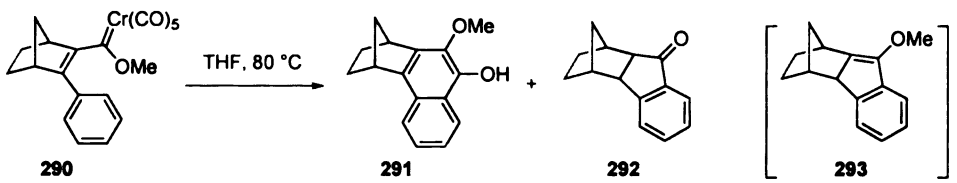


224 **290** 91%

In the absence of any iron source, the thermolysis with **290** under argon only gave a trace (~ 2% yield) of the phenol **291**, and the major product of the reaction was the indanone **292** which was isolated in 43% yield (Table 4.10). The indanone **292** presumably results from the hydrolysis of the non-CO cyclized product **293**. However, under an atmosphere of carbon monoxide, the desired phenol **291** was obtained in 78% yield, along with 9% of the indanone **292**. Thus, in the absence of the unconjugated double bond in **224**, the *ortho*-benzannulation reaction still goes thermally, which suggests that the strain of the ring does in fact contribute to the unusual reactivity in complexes **224** (Table 4.8) and **264** (Table 4.4). The thermolyses of **290** in the presence of one equivalent of $Fe_2(CO)_9$ were also performed under an atmosphere of argon and

carbon monoxide (Entries 3 and 4), which gave results very similar to the thermal reactions in the absence of an iron source.

Table 4.10. Thermal Reaction of the Carbene Complex **290***



290 **291** **292** **293**

Entry	Additive	Ar/CO	Time, h	**291**, %	**292**, %
1	- - -	Ar	7	~2	43
2	- - -	CO	48	78	9
3	$Fe_2(CO)_9$	Ar	12	10	48
4	$Fe_2(CO)_9$	CO	48	76	8

* Unless otherwise specified, all reactions were carried out at 0.02 M in **290**.

4.7 MISCELLANEOUS REACTIONS

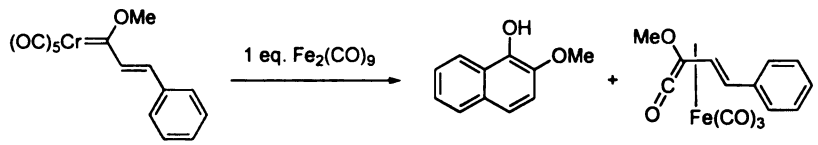
4.7.1 Other Attempted Thermal Reactions

Thermal Reactions of Complex **239** in the Presence of Diiron Nonacarbonyl

As shown in Table 4.11, the reaction of complex **239** in the presence of one equivalent of $Fe_2(CO)_9$ only afforded trace amounts of the *ortho*-benzannulated product **240**. The major product of the reactions at 80°C is the vinyl ketene complex **294**.[237] When the reaction was performed in THF or benzene under 1 atm CO, the ketene complex **294** was isolated in 82% and 80% yields, respectively. When the reaction was carried out in a Parr reactor under 500 psi CO, an 83% yield of **294** was isolated and the phenol **240** was not detected. When the reaction temperature was raised to 100 °C, only

traces of both compounds were observed; and at 130 °C, neither product was detected. So in all cases, only trace or none of the desired **240** was observed.

Table 4.11. Thermal Reactions of **239** in the Presence of $Fe_2(CO)_9$*



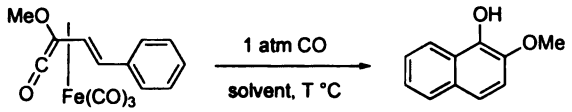
239 **240** **294**

Entry	CO	Solvent	T, °C	Time, h	**240**, %	**294**, %
1	1 atm	THF	80	72	trace	82
2	1 atm	benzene	80	72	trace	80
3	500 psi	benzene	80	24	n.d.	83
4	1 atm	benzene	100	72	trace	trace
5	1 atm	toluene	130	7	n.d.	n.d.

* Unless otherwise specified, all reactions were carried out at 0.02 M in **239**.

The ketene complex **294** was then thermolyzed with the thought that if it were to cyclize to the naphthol **240** then at least a two-step *ortho*-benzannulation of complex **239** could be achieved. Unfortunately, thermolysis at 100 °C and 130 °C under 1 atm CO only gave a trace of the naphthol **240** was observed in both attempts while all the starting complex **239** was consumed (Table 4.12). The results further support the fact that the iron tricarbonyl complexed ketene **294** is unstable at high temperatures and decomposes instead of cyclizing to form the phenol product. It is not clear why the ketene complex **294** does not cyclize. This could be due to the failure of the double bond to isomerize, or to the reluctance the final elecrocyclic ring closure to occur since this would result in the disruption of the aromaticity of the phenyl ring.[238] So the presence of the phenyl ring in the γ,δ-unsaturation unit may be the source for the failure of the cyclization in this case.

Table 4.12. Attempted Conversion of the Ketene Complex **294** to Phenol **240***



294 **240**

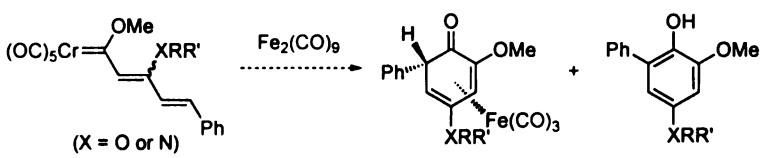
Entry	Solvent	T, °C	Time, h	**240**, % yield
1	benzene	100	43	trace
2	toluene	130	18	trace

* Both reactions were carried out at 0.02 M in **294**.

Phenols with *ortho, para*-Disubstituted Heteroatom Functional Groups

During the studies on the scope of the iron-mediated *ortho*-benzannulation, it was decided to investigate the possibility of generating phenols with *ortho,para*-disubstituted heteroatom functional groups. As shown in Scheme 4.36, the idea was that if complexes of the type **295** could be prepared with an oxygen or a nitrogen functionality at the β-position, an *o*-methoxy *p*-alkoxy (or *p*-amino) phenol **297** would be the eventual product. The preparation of the carbene complexes need not to be stereoselective since both the cis and trans isomers of **295** may undergo the *ortho*-benzannulation reaction.

Scheme 4.36. Generation of *o*-Methoxy *p*-Alkoxy (or *p*-Amino) Phenols

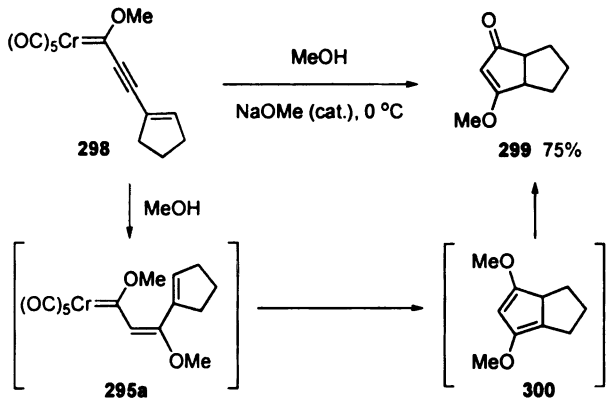


295 **296** **297**

Attempts were then made to prepare the β-methoxy dienyl complex of the type **295**. As shown in Scheme 4.37, when the cyclopentenyl ethynyl complex **298** was dissolved in methanol at 0 °C in the presence of a catalytic amount of sodium methoxide,

the cyclopentenone **299** was isolated in 75% yield and none of the desired dienyl carbene complex **295a** was obtained. Apparently, complex **295a** in which the carbene carbon moiety and the γ,δ-unsaturation are cis disposed did form, but this complex was not stable and cyclized spontaneously at 0 °C to give the cyclopentadiene **300** which was then hydrolyzed to form **299**.[220] This result is consistent with the earlier observation in the attempted preparation of the acyclic *cis,trans*-dienyl complex **181f** (Scheme 4.20). Thus, no further efforts were made to prepare complexes of the type **295** for the iron-mediated thermal *ortho*-benzannulation reaction.

Scheme 4.37. Attempted Preparation of the β-Methoxy Dienyl Complex **295a**

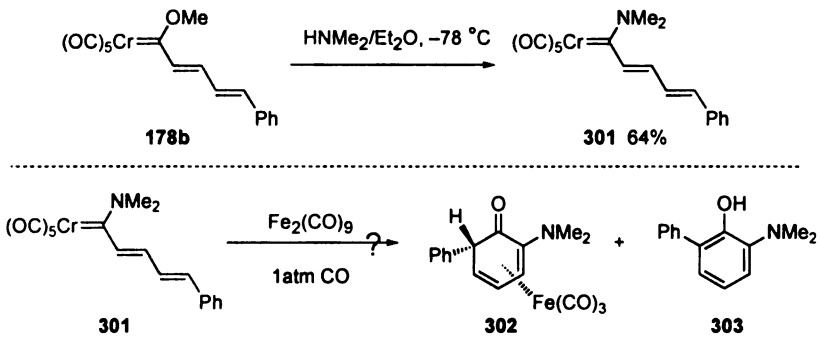


Attempted Preparation of *o*-Amino Phenols

As discussed in Section 4.1.2, with the proper tuning of the electron density on the nitrogen substituents, α,β,γ,δ-doubly unsaturated amino carbene complexes can undergo photochemical *ortho*-benzannulation. Thus, it would be desirable to determine if dialkyl amino complexes could participate in the iron-mediated *ortho*-benzannulation since this would be a potential route to *ortho*-amino phenols. The dimethylamino dienyl carbene complex **301** was prepared in 64% yield from the corresponding methoxy

complex **181b** (Scheme 4.38). After heating **301** at 80 °C in THF for 42 hours, the ^{1}H NMR spectrum of the crude reaction mixture showed that a significant amount of the starting material **301** was still not consumed, along with a new compound **X** whose structure has not yet been determined. After heating in benzene for 96 hours, similar results were obtained with a little higher ratio of **X** : **301** (2 : 3 vs. 1 : 2). However, when the mixture was heated at 110 °C for 48 hours, a complicated mixture was obtained and neither **X** nor **301** was observed. The unknown compound was initially thought to be **302** based on NMR spectra, except that one non-carbonyl carbon was not located in the ^{13}C NMR spectrum. If this structure were true, it would have a molecular weight of 353, however, the mass spectra indicates a molucule ion peak of 313. Nonetheless, the consumption of the starting material **301** was found to be extremely sluggish at 80 °C. It is reasonable to predict that if the electron density on the nitrogen is tuned appropriately by the introduction of electron withdrawing groups, at some point the ready formation of the *ortho*-benzannulated product will be restored as has been shown for amino complexes in the benzannulation reaction.[201]

Scheme 4.38. Preparation of the Amino Complex **301** and Its Thermal Reaction



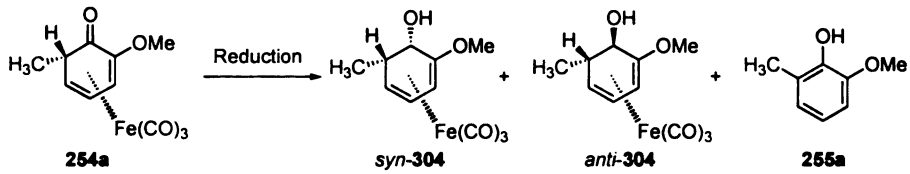
Conditions	Results
THF, 80 °C, 42h	Unknown **X** : **301** = 1 : 2
Benzene, 80 °C, 96 h	Unknown **X** : **301** = 2 : 3
Toluene, 110 °C, 48 h	Complex mixture, No **X** or **301**

4.7.2 Diastereoselective Reduction of Dienone Complexes

As demonstrated in earlier sections, the iron-mediated thermal *ortho*-benzannulation gives dienone iron tricarbonyl complexes in significant amounts especially for carbene complexes with an alkyl group on the δ carbon. If the dienone complex could be reduced to the corresponding alcohol in a diastereoselective manner, the resulting alcohol, after removal of iron tricarbonyl, could be a useful intermediate for further synthetic transformations including acting as a diene in the Diels-Alder reaction.

It was anticipated that the reduction would form *syn*-**304** with high diastereoselectivity because the reducing reagent would be expected to approach the dienone complex of the type **254a** from the top since both the iron tricarbonyl unit and the methyl group sit on the bottom of the ring. However, when $NaBH_4$ was used under different conditions, the best syn/anti ratio of **304** obtained was only about 3.3 : 1. The syn isomer was believed to be the less polar compound since its hydroxy group is sterically shielded.[239] In those cases where bulkier reagents such as $NaBH_3CN$ and $NaBH(OAc)_3$ were used, only the starting material **254a** was recovered and neither **304** or **255a** was observed. More reactive reagents such as Red-Al and L-Selectride gave the phenol **255a** as either the major or the exclusive product, presumably due to the basicity in the reaction mixture that effects the tautomerization of the dienone complex **254a**. Worthy of mention is that the pure *syn*-**304** in $CDCl_3$ in an NMR tube was partially converted to *anti*-**304** at room temperature after a couple of days.

Table 4.13. Diastereoselective Reduction of the Dienone Complex **254a**



254a *syn*-**304** *anti*-**304** **255a**

Conditions	Results
$NaBH_4$ / MeOH, rt, 3 h	**304** ~ 60% (syn/anti = 1 : 0.7); **255a** (~5%)
$NaBH_4$ (in portions) / MeOH, rt, 3 h	Similar as above
$NaBH_4$ (H_2O) / MeOH, 0 °C to rt, 1 h	**304** (syn/anti = 1 : 0.3); **255a** (trace)
$NaBH_4$ / MeOH, -78 °C to rt	**304** (major, syn/anti = 1 : 0.3), **255a** (trace)
$NaBH_4$ (1:1 acetone/AcOH)/acetone, 0 °C to rt	**254a** recovered; No **304** or **255a** observed
$NaBH_3CN$ / MeOH, pH = 4 buffer	**254a** recovered; No **304** or **255a** observed
$NaBH(OAc)_3$, AcOH/CH_2Cl_2, 24 h	**254a** recovered; No **304** or **255a** observed
Red-Al / benzene, 50 °C, 1 h	**255a** (major), **304** (trace)
L-Selectride, -20 °C to rt, 2 h	**255a** only

The low selectivity with $NaBH_4$ was certainly not expected; however, the X-ray structure of **254a** (Figure 4.4) clearly shows that the cyclohexdienone ring is in a twist-boat-like conformation which bends away from the iron tricarbonyl unit, increasing the otherwise less likely attacking from the bottom by $NaBH_4$. This may explain why the formation of *anti*-**304** was not shut down. Since the reduction of dienone complexes was not a priority in this study, no further efforts were made to optimize this reaction.

4.8 CONCLUSIONS

Serendipity has been and continues to be an important source of great discoveries in science. In this chapter, the serendipitous finding and the subsequent development of the highly novel iron-mediated thermal *ortho*-benzannulation of Fischer carbene complexes are discribed. The first examples of the *ortho*-benzannulation reaction have been achieved under thermal conditions in the presence of an iron source. It is the first time that *trans,trans*-α,β,γ,δ-unsaturated Fischer carbene complexes have been employed successfully for the *ortho*-benzannulation reaction, which greatly increases the power of this reaction since many of the *trans*-substituted complexes can be easily prepared by an aldol condensation of the methyl carbene complex with an aldehyde or a ketone. The *cis*-substituted complexes that had been previously required for the reaction can be difficult to make unless they are locked into a ring. The first examples of the "*ortho*-cyclohexadienone annulation" with δ,δ-disubstituted dienyl carbene complexes have also been illustrated. Furthermore, these *trans*-α,β-unsaturated Fischer carbene complexes undergo thermal *ortho*-benzannulation only in the presence of an iron source, and they fail both under thermal conditions in the absence of iron and under photochemical conditions.

The iron-mediated thermal *ortho*-benzannulation also worked with some dienyl carbene complexes having a *cis*-α,β-double bond but failed with others, and the scope for the *cis*-α,β-dienyl substrates has not been established. It is believed that the bond lengths and angles for both double bonds are very important in order for the electrocylic ring closure (ERC) to occur. Otherwise, even after the ketene intermediate is formed during the reaction, it could just decompose if the double bonds are not properly aligned or are

not in the proper position for ring closure to occur. In addition, since the γ,δ-unsaturation and the carbene moiety are cis disposed, it becomes obvious that the insertion of a carbon monoxide must be fast enough to compete with the direct cyclization in order to shut down the formation of the indene product.

Mechanistic studies suggest that two pathways are possible to form the dienone iron tricarbonyl complex and the phenol product. One involves direct transfer of the carbene ligand from Cr to Fe, and the other involves initial coordination of the iron to the diene fragment. A tentative mechanism has been proposed for the chromium to iron transfer process in this iron-assisted conversion of the dienyl chromium carbene complexes to dienone iron tricarbonyl complexes.

Some important findings were also made during the investigation of the thermal *ortho*-benzannulation reaction in the absence of an iron source. It was surprising to find that thermolysis of the norbornadienyl carbene complex **224** worked efficiently to give the phenol product and thus no photons are necessary, which clears away the misinformation about this particular reaction previously presented in the literature. It was also interesting to find that, contrary to what was claimed in the literature, the reaction of the complex **264** gave the desired *o*-methoxy phenol under an atmosphere of carbon monoxide. However, the thermal reaction in the absence of an iron source only worked well with a few *cis*-α,β-dienyl carbene complexes of particular structure types, and the unusual reactivity is believed to result from the geometric restraints in the substrates rather than any possible extra coordination site in the carbene complexes.

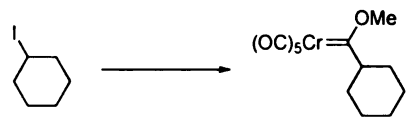
CHAPTER FIVE

EXPERIMENTAL SECTION

5.1. GENERAL INFORMATION

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. Prior to use, tetrahydrofuran and diethyl ether were distilled from Na/benzophenone; methylene chloride was distilled from CaH_2; benzene and toluene were distilled from sodium, all under nitrogen. TLC was performed on Silicyle plastic backed TLC plates (TLP-R10011B-323). Flash chromatography was carried out using 230-400 mesh silica gel. Routine ^1H NMR spectra were recorded on Varian 300 and 500 MHz spectrometers with residue chloroform-*d* (7.24 ppm) as an internal reference. Routine ^{13}C NMR spectra were recorded on Varian 75 and 125 MHz spectrometers with the central peak of the residue chloroform-*d* triplet (77.0 ppm) as an internal reference. Infrared spectra were recorded on a Nicolet 42 FTIR spectrometer. Mass spectral data were obtained at the Michigan State University Mass Spectrometry Facility which is supported, in part, by a grant (DRR-00480) from the Biotechnology Research Technology Program, National Center for Research Resources, National Institutes of Health.

5.2. Experimental Procedures and Characterization Data for Chapter Two



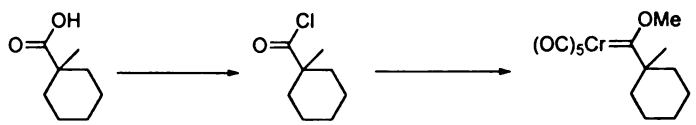
119 63b

The Preparation of Carbene Complex 14b:

In a 250-mL RBF was placed 60 mL of pentane (dried with 4 Å molecular sieves) and cooled to –78 °C, *t*BuLi (1.7 M/pentane, 12.35 mL, 21 mmol) was added under an argon atmosphere. In a separate 100-mL RBF, cyclohexyl iodide **119** (2.10 g, 10 mmol) was dissolved in 40 mL of ether and then transferred via a cannula to the above *t*BuLi solution at –78 °C. The mixture immediately turned milky white and was stirred for 10 min before the cooling bath was removed, and the stirring continued for an additional 0.5 h after the mixture was warmed to room temperature. Then it was cooled down back to –78 °C and transferred into a 200-mL RBF which contained $Cr(CO)_6$ (2.2 g, 10 mmol) and 10 mL of ether at –78 °C. The resulting mixture was stirred for 5 min, and then the bath was removed and the stirring continued for an additional 1 h after it reached room temperature. After the solvents were removed on a rotary evaporator, 20 mL of distilled water and 5 mL of methylene chloride were added, followed by two equivalents of Meerwein's salt while stirring (it should become acidic with pH around 2, if not, more Meerwein's salt needed to be added). The mixture was stirred for about 20 min and extracted with CH_2Cl_2 until the orange-yellow color in the mixture disappeared. The organic extract was then washed with sat. aq. $NaHCO_3$ (30 mL) and brine (30 mL) sequentially, dried with $MgSO_4$ and filtered. After concentration, the orange-yellow oil

was subject to a silica gel chromatography using straight hexanes as the eluent to give carbene complex **63b** (0.80 g) in 25% yield as a yellow-orange solid.

Spectral data for **63b**: mp 52–54 °C. R_f = 0.45 (hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02-1.33 (m, 1H), 1.10 (t, *J* = 12.9 Hz, 2H), 1.24 (t, *J* = 12.9 Hz, 2H), 1.66-1.73 (m, 1H), 1.74 (s, 2H), 1.77 (s, 2H), 3.87 (t, *J* = 11.1 Hz, 1 H), 4.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.64, 25.88, 28.59, 67.93, 71.90, 216.46, 223.30, 366.17; IR (NaCl): 2936s, 2859m, 2062s, 1919vs, 1453s, 1254s, 1232s cm^{-1}; MS (EI) *m/z* (% relative intensity): 318 (M^+, 2), 290 (6), 262 (4), 234 (3), 206 (22), 179 (19), 178 (100), 143 (14), 133 (11), 131 (22), 129 (15), 81 (17), 80 (20), 52 (63), 41 (12). Anal calcd for $C_{13}H_{14}CrO_6$: C, 49.06; H, 4.43. Found: C, 48.95; H, 4.33.



120 **121** **63c**

The Preparation of Carbene Complex 63c:

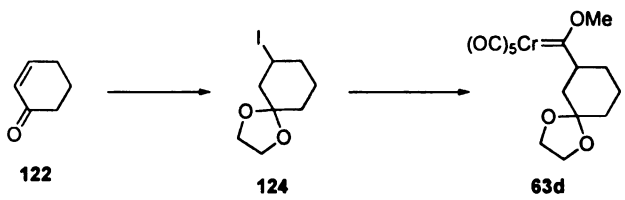
A 100-mL Schlenk flask was charged with graphite powder (0.87 g, 72.7 mmol, 19.5 eq.) and heated in an oil bath to 160 °C under vacuum. Freshly cut potassium metal (0.35 g, 9.0 mmol, 2.42 eq.) was rinsed in dry hexanes and dried before being added portion-wise to the heated flask while stirring and under a continuous flow of argon. (Note: It is important that either good stirring and/or occasional manual shaking of the flask is maintained throughout the heating process to ensure complete intercalation of the potassium metal into the graphite layers. It is also desirable to open the flask under a flow of argon and scrape the melted potassium off the wall of the flask and the surface of the stir bar.) The solid mixture was kept at 160 °C with stirring under argon atmosphere

until the color of the powder turned from black to bronze, indicative of the formation of C_8K. Total heating time once the powder has turned bronze was about 35 min. The solid was then allowed to cool to room temperature and 20 mL of dry THF was added under a positive flow of argon. The bronze suspension was cooled to –78 °C and $Cr(CO)_6$ (0.90 g, 4.1 mmol, 1.1 eq.) was added in one portion. The flask was closed under argon and the dark suspension was allowed to warm to 0 °C and stirred at this temperature for 1.5 h, during which time the color turned from bronze-black to a thick slurry of silvery green in a yellow-green solution. (It was ready to use immediately or could be stored in freezer for days.)

After cooling back down to –78 °C, a solution of acid chloride **121** (0.60 g, 3.7 mmol, 1.0 eq, freshly prepared by refluxing 0.53 g of acid **120** and 2.7 g of thionyl chloride in 10 mL of benzene for 2 h and concentrated under reduced pressure) dissolved in 10 ml THF was added slowly and the reaction mixture was then gradually warmed to room temperature and stirred at this temperature for at least 3 h. The black suspension was then filtered on a sufficiently large coarse fritted funnel packed with Celite, rinsed with either dry THF or ether. The solvent of the filtrate was then removed on a rotary evaporator and the residue was placed on high vacuum for a couple of minutes. The resulting potassium acylate was dissolved in a minimum of water and 5 ml of CH_2Cl_2, and was then treated portion-wise with Meerwein's reagent, Me_3OBF_4 (about 1.09 g, 7.4 mmol, 2 eq.), until the reaction mixture was acidic (pH ~2). The mixture was stirred at room temperature for 20-30 minutes and extracted with CH_2Cl_2 until all of the organge-yellow color was removed from the aqueous layer. The organic extract was washed sequentially with saturated aqueous $NaHCO_3$ solution and brine, dried with $MgSO_4$,

filtered and concentrated under reduced pressure. Silica gel column chromatography (5% EtOAc/hexanes) afforded complex **63c** (0.94 g) in 76% yield as an orange oil, which solidified to an orange-yellow solid upon standing in a freezer at –20 °C.

Spectral data for **63c**: R_f = 0.55 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.11 (s, 3H), 1.24-28 (m, 1H), 1.48-1.55 (m, 5H), 1.62-1.65 (m, 2H), 1.92 (p, *J* = 6.4 Hz, 2H), 4.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.80, 23.10, 25.79, 36.20, 62.51, 68.61, 217.12, 222.66, 374.71; IR (NaCl): 2934m, 2058s, 1916vs, 1453m, 1248s cm^{-1}; MS (EI) *m/z* (% relative intensity): 332 (M^+, 0.4), 304 (4), 276 (9), 248 (5), 220 (17), 193 (13), 192 (100), 189 (13), 175 (12), 158 (30), 145 (15) 143 (38), 95 (35), 82 (16), 52 (62), 41 (11). Anal calcd for $C_{14}H_{16}CrO_6$: C, 50.61; H, 4.85. Found: C, 50.86; H, 4.82.



122 124 63d

The Preparation of Carbene Complex 63d.

To a solution of sodium iodide (8.99 g, 60 mmol) and 2-cyclohexen-1-one **122** (4.81 g, 50 mmol) in 120 mL acetonitrile was rapidly added TMSCl (6.52g, 60 mmol) at room temperature with rigorous stirring under an argon atmosphere. The resulting suspension (yellow precipitate and red-brown liquid) was stirred for an hour before ethylene glycol (3.72 g, 60 mmol) was added rapidly and the mixture was stirred for 20 min. Acetonitrile was then removed on a rotary evaporator and 150 mL of pentane and 50 mL of saturated aqueous $NaHCO_3$ solution were added. The mixture was filtered and

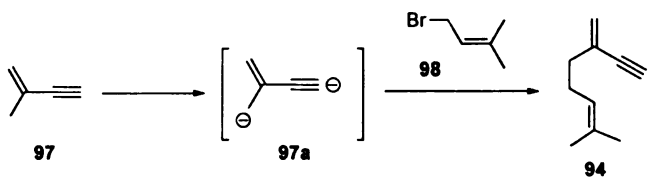
the red organic layer was washed with 50 mL of brine. dried with $MgSO_4$ and filtered through a plug of neutral alumina gel and rinsed with hexanes. After removal of the volatiles, the analytically pure cyclohexyl iodide **124** (10.94 g) was obtained in 82% yield over two steps.

Spectral data for **124**: R_f = 0.58 (20% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$): δ 1.53-1.67 (m, 3H), 1.79-1.91 (m, 2H), 2.14 (t, *J* = 12.6 Hz, 1H), 2.34 (dm, *J* = 12.6 Hz, 1H), 2.48 (dp, *J* = 12.6, 2.1 Hz, 1H), 3.93-3.98 (m, 4H), 4.22 (tt, *J* = 12.6, 4.2 Hz, 1 H). The spectral data are consistent with that reported by Jiang.[123]

In a 100-mL RBF was placed 30 mL pentane (dried with 4 Å molecular sieve) and cooled down to –78 °C, *t*BuLi (1.7 M/pentane, 6.6 mL, 11.1 mmol) was added under an argon atmosphere. In a separate 50-mL RBF, cyclohexyl iodide **124** (1.42 g, 5.3 mmol) was dissolved in 20 mL of ether and transferred to the above *t*BuLi solution via a cannula at –78 °C. The mixture immediately turned milky white and was stirred for 15 min. The cooling bath was then removed and the solution was slowly warmed to room temperature and stirred for an additional an hour at this temperature. Then the solution was cooled down back to –78 °C and transferred via cannula into a 200 ml RBF that contained $Cr(CO)_6$ (1.17 g, 5.3 mmol) in 10 mL of ether, also at –78 °C. The resultant mixture was stirred for half hour before the cold bath was removed and stirring continued for 1.5 hours at room temperature. After removal of the volatiles, 20 mL of distilled water and 5 mL of methylene chloride were added, followed by two equivalents of Meerwein's salt (it should become acidic with pH ~ 2, if not, more Meerwein's salt needed to be added). The mixture was stirred for 20 – 30 minutes and the organic layer was separated and further extraction of the aqueous phase with CH_2Cl_2 was performed

until the yellow color disappeared in the organic layer. The combined organic extracts were washed with 10 mL of sat. aq. $NaHCO_3$ solution and 10 mL of brine sequentially, dried with $MgSO_4$ and filtered. After concentration, the orange-yellow oil was subject to silica gel chromatography using 5–10% EtOAc/hexanes as the eluent to give carbene complex **63d** (1.42 g) in 71% yield as an orange solid.

Spectral data for **63d**: mp = 47–49 °C; R_f = 0.30 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.07 (q, *J* = 12.6 Hz, 1H), 1.27 (t, *J* = 11.9 Hz, 1H), 1.40-1.50 (m, 1H), 1.57 (q, *J* = 13.5 Hz, 1 H), 1.69-1.79 (m, 4 H), 3.90-3.92 (m, 4 H), 4.21 (t, *J* = 11.8 Hz, 1H), 4.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.06, 27.71, 35.30, 36.43, 64.52, 64.57, 68.16, 68.64, 108.62, 216.47, 223.38, 364.56; IR (KBr): 2958m, 2885w, 2061s, 1921vs, 1452m, 1259m, 1232m cm^{-1}; MS (EI) *m/z* (% relative intensity): 376 (M^+, 23), 292 (27), 265 (15), 264 (56), 237 (28), 236 (100), 204(22), 176 (17), 162 (54), 160 (29), 141 (21), 99 (38), 93 (19), 80 (18), 52 (52); HRMS (EI) calcd for $C_{15}H_{16}CrO_8$ *m/z* 376.0250, found 376.0250.



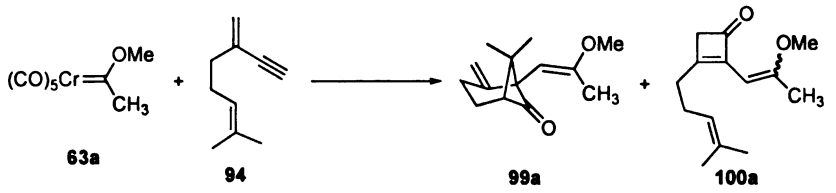
The Preparation of Dienyne 94.

To isopropenyl acetylene **97** (1.21 mL, 12.6 mmol) in 20 mL THF was added *n*BuLi/hexanes (2.29 M, 12.1 mL, 27.7 mmol) at –78 °C under argon atmosphere, followed by freshly prepared KO*t*Bu solution [from KH (1.21 g, 30.1 mmol) and *t*BuOH (2.05 g, 27.7 mmol) in 20 mL THF]. The yellow mixture was stirred for 30 minutes

before warming up to 0 °C for 15 minutes. The reaction was then brought down to –30 °C and a solution of anhydrous LiBr (2.41 g, 12.7 mmol) in 10 mL THF was added slowly. After 20 minutes the yellow-orange solution was cooled to –78 °C and prenyl bromide **98** (1.46 mL, 12.6 mmol) was added dropwise over 10 minutes. The mixture was allowed to warm to room temperature and after an hour, 15 mL of sat. aq. NH_4Cl and 30 mL of pentane was added. The organic phase was separated and washed sequentially with water and brine, dried with $MgSO_4$. Concentration gave the crude dienyne which was further purified by column chromatography using pentane as the eluent to afford dienyne **94** (1.28 g, 76% yield) as a clear colorless liquid.

Spectral data for **94**: R_f = 0.50 (hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (s, 3H), 1.67 (s, 3H), 2.14-2.22 (m, 4H), 2.87 (s, 1H), 5.05-5.10 (m, 1H), 5.28 (s, 1H), 5.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.73, 25.69, 26.55, 37.11, 76.85, 84.10, 122.83, 123.12, 130.50, 132.38; IR (KBr): 3286s, 2966s, 2924s, 2856m, 2362s, 2343m, 1458m, 1377m cm^{-1}; MS (EI) *m/z* (% relative intensity): 134 (M^+, 7), 133 (89), 119 (19), 101 (25), 99 (100), 98 (36), 97 (97), 96 (43), 95 (58), 91 (36), 89 (29), 87 (26), 82 (23), 69 (34), 57(41), 56 (38), 50 (25); HRMS (EI) calcd for $C_{10}H_{14}$ *m/z* 134.1096, found 134.1091.

General Procedure for the Synthesis of Bicycloheptanones 99 and Cyclobutenones 100: Illustrated for 99a and 100a.



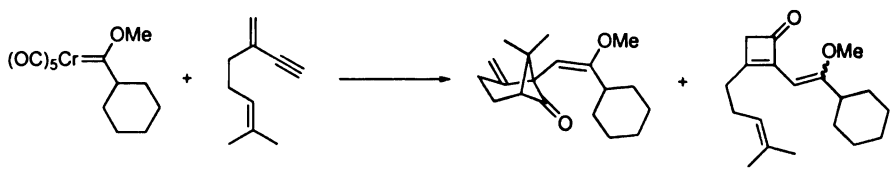
A 10-mL or 100-mL flask with a threaded Teflon high-vacuum stop-cock was charged with carbene complex **63a** (125 mg, 0.50 mmol), dienyne **94** (74 mg, 0.55 mmol) and 5 mL or 50 mL of CH_3CN to make a 0.1 or 0.01 M solution in **63a**. The solution was deoxygenated by the freeze-thaw method (–196/25 °C, 3 cycles), back-filled with argon at room temperature, sealed and then heated at 45 °C for 24 or 48 hours. Then the mixture was transferred to a 100-mL round bottom flask and acetonitrile was removed under reduced pressure. The residue was dissolved in 20 mL CH_2Cl_2 and filtered through a pad of Celite to get rid of green chromium complexes. The yellowish residue was then subjected to silica gel chromatography (5–10% EtOAc/hexanes) to isolate **99a** and **100a**. Careful chromatography was able to provide pure samples of **99a*E***, **100a*E*** and **100a*Z***. The assignment of *E/Z* isomers of **100a** was made by the difference in chemical shift of the enol ether carbons by the method of Strobel.[127] Since **99a** was obtained as a single isomer, it could not be assigned by Strobel's rule, presumably in the *E*-form according to our study on related compounds.[119]

Bicycloheptanone **99a*E***: 44–47% yield. White crystals, mp 61–62 °C. R_f = 0.35 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): 1.08 (s, 3 H), 1.10 (s, 3 H), 1.74 (s, 3 H), 2.05-2.20 (m, 2 H), 2.28-2.37 (m, 1 H), 2.46 (dd, *J* = 16.5, 8.0 Hz, 1 H), 2.68 (dd, *J* = 4.8, 1.5 Hz, 1 H), 3.55 (s, 3 H), 4.23 (s, 1 H), 4.80 (s, 1 H), 4.87 (s, 1 H); ^{13}C NMR

(125 MHz, $CDCl_3$): 17.9, 19.2, 24.6, 25.1, 27.4, 29.7, 54.5, 63.0, 76.1, 89.7, 109.3, 150.4, 156.6, 210.2; IR (NaCl): 2953s, 1777s, 1655s, 1229s cm^{-1}; MS (EI) m/z (relative intensity) 220 (M^+, 45), 205 (20), 192 (95), 177 (100), 161 (34), 145 (75), 135 (45), 110 (30), 105 (45), 91 (40), 77 (25), 69 (25), 59 (20), 55 (2); Anal calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.47; H, 9.52.

Cyclobutenone **100a*E***: 20–24% yield. Colorless viscous oil. R_f = 0.32 (10% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$): 1.63 (s, 3 H), 1.70 (s, 3 H), 2.15 (s, 3 H), 2.29 (q, J = 7.5 Hz, 2 H), 2.58 (t, J = 7.5 Hz, 2 H), 3.11 (s, 2 H), 3.56 (s, 3 H), 4.85 (s, 1 H), 5.11 (t, J = 7.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): 17.8, 19.0, 24.8, 25.7, 29.7, 49.2, 54.9, 87.4 (enol ether), 122.8, 133.1, 143.4, 160.9 (enol ether), 167.2, 187.4; IR (NaCl): 2923s, 1754s, 1657s, 1227s cm^{-1}; MS (EI) m/z (relative intensity): 220 (M^+, 9), 205 (9), 189 (12), 177 (15), 152 (9), 149 (13), 147 (13), 145 (35), 123 (19), 119 (22), 109 (27), 108 (21), 105 (33), 91 (41), 79 (22), 77 (27), 69 (16), 65 (15) 53 (15), 43(100), 41 (65); Anal calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.01; H, 9.48.

Cyclobutenone **100a*Z***: 10–12% yield, Colorless viscous oil. R_f = 0.14 (10% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$): 1.64 (s, 3 H), 1.70 (s, 3 H), 1.96 (s, 3 H), 2.27 (q, J = 7.5 Hz, 2 H), 2.68 (t, J = 7.5 Hz, 2 H), 3.10 (s, 2 H), 3.68 (s, 3 H), 4.80 (s, 1 H), 5.11 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): 17.5, 17.7, 25.1, 25.6, 31.1, 49.6, 55.2, 93.2 (enol ether), 123.2, 132.6, 141.6, 156.3 (enol ether), 168.2, 188.5; IR (NaCl): 2923s, 1761s, 1653m, 1658m, 1223m, 1086m cm^{-1}; MS (EI) *m/z* (relative intensity) 220 (M^+, 55), 205 (20), 189 (20), 179 (30), 163 (15), 145 (22), 135 (22), 123 (20), 117 (10), 109 (30), 89 (65), 84 (63), 69 (100), 77 (15), 65 (10), 59 (24), 55 (27); Anal calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.30; H, 9.36.



63b 94 99b 100b

*Bicycloheptanone **99b** and Cyclobutenone **100b**.*

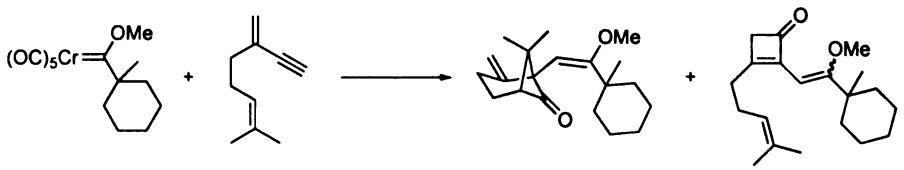
Following the general procedure for the preparation of **99a** and **100a**, the reaction of complex **63b** (148 mg, 0.46 mmol) and dienyne **94** (68 mg, 0.51 mmol) in 5 mL of CH_3CN at 45 °C for 24 h gave **99b*E*** (60 mg, 45% yield) as a white solid as a single isomer, **100b*E*** (40 mg, 30% yield) as a yellowish oil, and **100b*Z*** (15 mg, 11% yield) as a yellowish oil.

Spectral data for **99b*E***: mp 61–63 °C. R_f = 0.50 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (s, 3H), 1.07 (s, 3H), 1.08-1.28 (m, 4H), 1.34-1.46 (m, 2H), 1.56-1.71 (m, 4H), 1.98-2.12 (m, 3H), 2.31-2.41 (m, 2H), 2.63 (dd, *J* = 2.4, 1.2 Hz, 1H), 3.51 (s, 3H), 4.02 (brs, 1H), 4.81 (s, 1H), 4.84 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.72, 24.57, 25.32, 26.14, 26.41, 26.49, 30.73, 37.95, 41.41, 54.52, 62.80, 76.30, 88.07, 109.13, 151.88, 165.09, 209.50; IR (NaCl): 2934s, 2853s, 1779s, 1647s, 1451m, 1211s cm^{-1}; MS (EI) *m/z* (% relative intensity): 288 (M^+, 13), 260 (90), 245 (51), 217 (100), 205 (21), 204 (30), 177 (37), 176 (44), 163 (20), 144 (32), 135 (27), 131 (25), 117 (23), 104 (36), 91 (51), 83 (75), 77 (36), 55 (60), 41 (69). Anal calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.16; H, 9.86.

Spectral data for **100b*E***: R_f = 0.47 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02-1.49 (m, 8H), 1.63 (s, 3H), 1.69 (s, 3H), 1.72-1.74 (m, 2H), 2.03-2.09 (m, 1H), 2.27 (q, *J* = 6.9 Hz, 2 H), 2.57 (t, *J* = 7.5 Hz, 2H), 3.09 (s, 2H), 3.54 (s, 3H), 4.68 (s,

1H), 5.11 (t, J = 7.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.75, 24.87, 25.67, 26.01, 26.16, 29.66, 30.46, 40.81, 49.26, 54.93, 85.38, 122.94, 133.04, 143.52, 166.81, 168.26, 187.16; IR (NaCl): 2928s, 2853s, 1754s, 1647s, 1451m, 1215s cm^{-1}; MS (EI) *m/z* (% relative intensity): 288 (M^+, 7), 260 (12), 245 (16), 217 (27), 205 (27), 177 (37), 145 (32), 105 (31), 91 (51), 83 (56), 79 (26), 69 (29), 55 (73), 41 (100). Anal calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 78.94; H, 9.77.

Spectral data for **100b*Z***: R_f = 0.35 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14-1.27 (m, 8H), 1.60 (s, 3H), 1.67 (s, 3H), 1.75-1.85 (m, 2H), 2.15 (t, J = 11.5 Hz, 1H), 2.25 (q, J = 7.2 Hz, 2 H), 2.63 (t, J = 7.5 Hz, 2H), 3.09 (s, 2H), 3.61 (s, 3H), 4.89 (s, 1H), 5.09 (t, J = 7.2 Hz 1H). Compound **100b*Z*** was easily isomerized to **100b*E*** in $CDCl_3$ in the NMR tube, so other spectra data were not obtained. The assignment of **100b*Z*** was based on the ^{1}H NMR spectrum and by comparison to the related compounds that we have studied.[119]



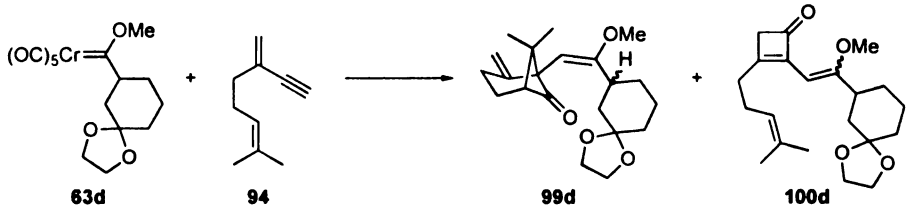
63c **94** **99c** **100c**

*Bicycloheptanone **99c** and Cyclobutenone **100c**.*

Following the general procedure for the preparation of **99a** and **100a**, the reaction of complex **63c** (137 mg, 0.41 mmol) and dienyne **94** (61 mg, 0.45 mmol) in 5 mL of CH_3CN at 45 °C for 24 h gave yellowish oily **99c*E*** (46 mg, 39 % yield) as a single isomer and colorless oily **100c** (43 mg, 36% yield) as a single isomer whose stereochemistry was not determined.

Spectral data for **99c*E***: R_f = 0.40 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (s, 3H), 1.08 (s, 3H), 1.09 (s, 3H), 1.23-1.47 (m, 8H), 1.71-1.76 (m, 2H), 2.06-2.22 (m, 2H), 2.26-2.38 (m, 1H), 2.41-2.46 (m, 1H), 2.63 (dd, *J* = 2.4, 2.1 Hz, 1H), 3.59 (s, 3H), 4.46 (s, 1H), 4.84 (s, 1H), 4.89 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.84, 22.67, 22.73, 24.67, 25.25, 26.39, 27.33, 35.99, 36.50, 41.11, 60.48, 62.89, 77.52, 99.25, 109.76, 149.81, 165.60, 209.56; IR (NaCl): 2930s, 2855s, 1779s, 1642s, 1450m, 1103m cm^{-1}; MS (EI) *m/z* (% relative intensity): 302 (M^+, 23), 247 (14), 205 (73), 191 (33), 177 (22), 163 (26), 145 (81), 139 (100), 105 (42), 97 (36), 91 (44), 55(68), 41 (45). Anal calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.10; H, 9.92.

Spectral data for **100c**: R_f = 0.28 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 3H), 1.22-1.46 (m, 8H), 1.60 (s, 3H), 1.66 (s, 3H), 1.68-1.72 (m, 2H), 2.27 (q, *J* = 7.5 Hz, 2 H), 2.60 (t, *J* = 7.5 Hz, 2H), 3.12 (s, 2H), 3.59 (s, 3H), 5.06-5.10 (m, 1H), 5.09 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.71, 22.41, 24.76, 25.68, 26.27, 30.64, 35.45, 41.02, 49.58, 61.21, 61.24, 95.02, 122.89, 133.07, 143.06, 170.67, 170.74, 188.05; IR (NaCl): 2928s, 2853s, 1761s, 1647s, 1449m, 1100m cm^{-1}; MS (EI) *m/z* (% relative intensity): 302 (M^+, 31), 205 (100), 148 (54), 145 (22), 105 (18), 97 (25), 91 (24), 55 (47), 41 (27). Anal calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.15; H, 10.14.



*Bicycloheptanone **99d** and Cyclobutenone **100d**.*

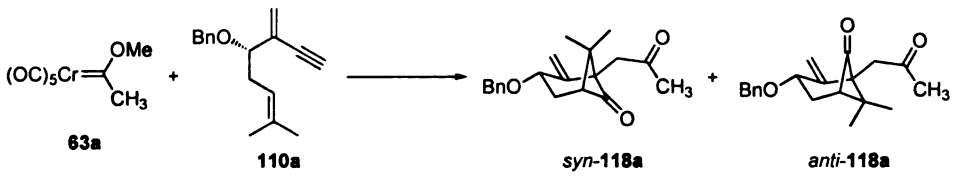
Following the general procedure for the preparation of **99a** and **100a**, except that, before chromatography the CH_2Cl_2 solution was stirred at room temperature under CO overnight and then filtered and concentrated. The reaction of complex **63d** (376 mg, 1.0 mmol) and dienyne **94** (174 mg, 1.3 mmol) in 10 mL of CH_3CN at 45 °C for 40 h gave **99d** (212 mg, 64 % yield), **100d*E*** (58 mg, 17 % yield) and **100d*Z*** (24 mg, 7 % yield), all of which are colorless oils. Compound **99d** existed as a mixture of two inseparable isomers, tentatively assigned as two epimers, in about 1:1 ratio based on the integrations of the relative vinyl proton peaks, the only three partially overlapping peaks of the two isomers (singlets at 4.07(br), 4.78, 4.84, and 4.13(br), 4.80, 4.86 ppm, respectively). Recrystallization in EtOAc/hexanes was able to separate some of **99d-cryst** as a white solid (~ 80 mg) and the rest still contained two isomers.

Spectral data for **99d-cryst**: R_f = 0.41 (30% EtOAc/hexanes); mp = 113–115 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (s, 3H), 1.09 (s, 3H), 1.39-1.76 (m, 7H), 1.89-1.93 (m, 1H), 2.08-2.17 (m, 2H), 2.36-2.45 (m, 3H), 2.62 (dd, J = 4.5, 1.8 Hz, 1H), 3.51 (s, 3H), 3.76-3.92 (m, 4H), 4.07 (brs, 1H), 4.78 (s, 1H), 4.84 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.73, 23.27, 24.54, 25.14, 27.97, 29.25, 35.06, 35.97, 38.80, 54.56, 54.59, 62.89, 63.92, 64.00, 76.36, 88.72, 108.62, 109.34, 152.55, 163.62, 208.74; IR (NaCl): 2946s, 2876m, 1775s, 1658s, 1647s cm^{-1}; MS (EI) m/z (relative intensity): 346 (M^+, 5), 314 (21), 284 (32), 269 (15), 253 (16), 227 (12), 205 (100), 163 (20), 128 (20), 99 (100), 91 (26), 86 (30), 55 (53), 41 (50); Anal calcd for $C_{21}H_{30}O_3$: C, 72.80; H, 8.73. Found: C, 72.49; H, 9.00. The X-ray Structure of **99d-cryst**, which clearly indicates the stereochemistry of the hydrogen, is shown in Appendix 1.

Spectral data for **100d*E***: R_f = 0.36 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.11-1.17 (m, 1H), 1.36-1.50 (m, 3H), 1.60 (s, 3H), 1.58-1.70 (m, 5H), 1.66 (s, 3H), 2.26 (q, *J* = 7.2 Hz, 2H), 2.55 (t, *J* = 7.1 Hz, 2H), 3.08 (s, 2H), 3.51 (s, 3H), 3.89-4.00 (m, 4H), 4.67 (s, 1H), 5.08 (tm, *J* = 7.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.75, 23.09, 24.85, 25.66, 29.52, 29.88, 34.62, 37.71, 38.50, 49.36, 54.97, 64.12, 64.25, 85.60, 109.10, 122.95, 133.01, 143.14, 166.02, 167.69, 187.48; IR (NaCl): 2930s, 1752s, 1653s, 1559s cm^{-1}.

Spectral data for **100d*Z***: R_f = 0.33 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.10-1.19 (m, 1H), 1.36-1.52 (m, 3H), 1.60 (s, 3H), 1.67 (s, 3H), 1.72-1.90 (m, 4H), 2.26 (q, *J* = 7.2 Hz, 2H), 2.47-2.55 (m, 1H), 2.62 (t, *J* = 7.2 Hz, 2H), 3.10 (s, 2H), 3.62 (s, 3H), 3.93-3.95 (m, 4H), 4.89 (s, 1H), 5.08 (tt, *J* = 7.2, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.76, 23.18, 24.99, 25.71, 30.11, 30.81, 34.74, 37.63, 39.50, 49.78, 57.16, 64.28, 64.41, 93.79, 108.88, 123.01, 132.91, 142.02, 164.50, 169.75, 187.97; IR (NaCl): 2924s, 1762s, 1554s cm^{-1}.

General Procedure for the Syntheis of Bicycloheptanones *syn*-118 and *anti*-118: Illustrated for *syn*-118a and *anti*-118a.



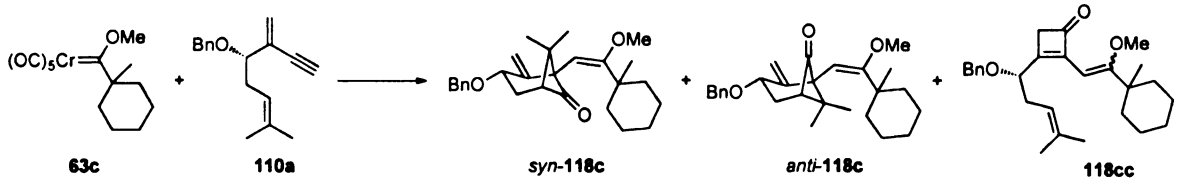
A 10-mL or 50-mL flask with a threaded Teflon high-vacuum stop-cock was charged with carbene complex **63a** (50 mg, 0.22 mmol), dienyne **110a** (53 mg, 0.22

mmol) and 2 or 20 mL of CH_3CN to make a 0.1 or 0.01 M solution in **63a**. The solution was deoxygenated by the freeze-thaw method (–196/25 °C, 3 cycles), back-filled with argon at room temperature, sealed and then heated at 45 °C for 24 hours. Then the mixture was transferred to a 100-mL round bottom flask and CH_3CN was removed on a rotary evaporator. The residue was dissolved in 20 mL CH_2Cl_2 and filtered through a pad of Celite to get rid of green chromium complexes. The crude mixture was then taken up in 5 mL THF/H_2O (4:1) and oxalic acid (50 mg) was added. The hydrolysis was monitored by TLC until the enol ether was all consumed. When the reaction was complete the mixture was diluted with ether and washed sequentially with saturated aqueous $NaHCO_3$ and brine. After drying over $MgSO_4$, the mixture was filtered and the filtrate was concentrated to yield an oily residue which was carefully purified by silica gel column chromatography (10–20% EtOAc/hexanes) to give *syn*-**118a** and *anti*-**118a** as pure compounds. The assignment of the syn/anti isomers was based on their 1D NOESY studies and the X-ray structure of the TROC-protected analog of *syn*-**118a**.[126]

Spectral data for *syn*-**118a**: 63–66% yield. White solid, mp 66–67 °C. R_f = 0.25 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): 1.07 (s, 3 H), 1.10 (s, 3 H), 2.23 (s, 3 H), 2.30 (dd, J = 14.7, 5.4 Hz, 1 H), 2.50 (ddd, J = 14.4, 5.4, 1.2 Hz, 1 H), 2.65 (d, J = 16.8 Hz, 1H), 2.69 (d, J = 4.8 Hz, 1 H), 2.80 (d, J = 16.8 Hz, 1 H), 3.88 (d, J = 4.8 Hz, 1 H), 4.26 (d, J = 12.6 Hz, 1 H), 4.61 (d, J = 12.6 Hz, 1 H), 4.95 (s, 1 H), 5.07 (s, 1 H), 7.21-7.35 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$): 17.87, 23.53, 29.89, 33.32, 36.68, 41.00, 61.07, 68.78, 71.92, 74.28, 113.87, 127.25, 127.40, 128.24, 138.06, 148.17, 203.64, 206.60; IR (NaCl): 2961m, 1788s, 1720s, 1705s, 1267s, 736s cm^{-1}; MS (EI) m/z (relative intensity): 312 (M^+, 0.3), 254 (2), 221 (49), 206 (4), 179 (16), 161 (22), 137

(40), 133 (74), 105 (72), 91 (100), 77 (33), 65 (58), 43 (100), 41 (48); HRMS (EI) calcd for $C_{20}H_{24}O_3$ *m/z* 312.1725, found 312.1724. Anal calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.55; H, 7.90.

Spectral data for *anti*-**118a**: 17-21% yield. Colorless viscous oil. R_f = 0.28 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): 1.04 (s, 3 H), 1.14 (s, 3 H), 2.09-2.14 (m, 1 H), 2.17 (s, 3 H), 2.48-2.58 (m, 1 H), 2.64 (d, *J* = 6.0 Hz, 1 H), 2.69 (d, *J* = 2.4 Hz, 2 H), 4.03 (tt, *J* = 9.0, 2.4 Hz, 1 H), 4.61 (d, *J* = 16.0 Hz, 1 H), 4.67 (d, *J* = 16.0 Hz, 1 H), 4.72 (d, *J* = 2.4 Hz, 1 H), 5.42 (d, *J* = 2.4 Hz, 1 H), 7.26-7.36 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$): 18.16, 23.69, 30.12, 31.83, 35.29, 40.95, 61.41, 71.62, 71.70, 73.46, 107.43, 127.47, 127.76, 128.42, 137.93, 149.30, 205.91, 206.97; IR (NaCl): 3055m, 2961m, 1772s,1723s, 1703s, 1285s, 734s cm^{-1}; MS (EI) m/z (relative intensity): 312 (M^+, 0.3), 297 (2), 221 (11), 204 (19), 178 (19), 161 (29), 146 (22), 133 (51), 120 (56), 109 (17), 91 (100), 65 (84), 55 (51), 43 (100); HRMS (EI) calcd for $C_{20}H_{24}O_3$ *m/z* 312.1725, found 312.1722. Anal calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.65; H, 7.96.



63c **110a** *syn*-**118c** *anti*-**118c** **118cc**

*Bicycloheptanones syn-**118c** and anti-**118c** and Cyclobutenone **118cc**:*

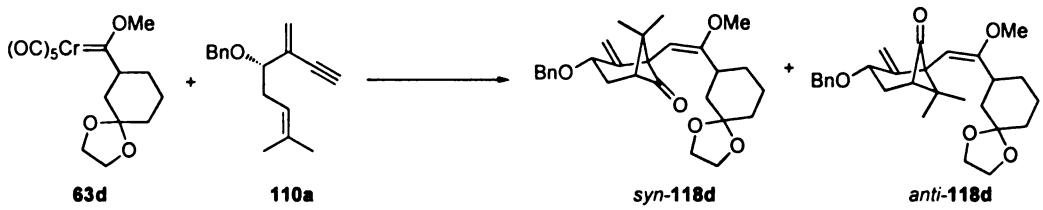
Following the general procedure for the preparation of *syn*-**118a** and *anti*-**118a**, except that the acid hydrolysis was not performed, the reaction of complex **63c** (83 mg, 0.25 mmol) and dienyne **110a** (66 mg, 0.28 mmol) in 2.5 mL of CH_3CN was carried out at 45 °C for 24 h. The purification for this reaction was not easy and performed as

follows. The concentrated yellowish residue was subjected to silica gel chromatography (10% EtOAc/hexanes) to give only one pure isomer of **118cc** (16 mg, 16% yield) as a colorless viscous oil, and the rest was presumably a mixture of isomers of **118c** as well as the other isomer of **118cc** which could not be separated when the solutions of various ratios of EtOAc/hexanes were used as the eluent. Very careful silica gel chromatography, using EtOAc/CH_2Cl_2/hexanes (1:50:49) as the eluent, could isolate the major isomer of *syn*-**118c** (56 mg, 55% yield) as a colorless viscous oil, but the remaining was still not separable. Based on our studies on the related compound **118a** and its analogs, *anti*-**118c** was expected to have the characteristic methine proton (next to BnO- group) to appear around 4.05 ppm as a triplet of multiplets on ^{1}H NMR spectrum, while the corresponding characteristic proton of *syn*-**118c** showed as a doublet at 3.89 ppm. Then the yield (16%) of the presumed *anti*-**118c** was calculated from the ^{1}H NMR spectrum of the crude mixture by comparing the integrations of the relative methine protons after *syn*-**118c** was isolated. The stereochemistry of *syn*-**118c** was assumed to be in the E configuration (same as in the related compounds **99**), and whether **118cc** existed as an E or Z isomer was not determined.

Spectral data for *syn*-**118c**: R_f = 0.33 (10% EtOAc/hexanes); 0.19 (1:50:49 EtOAc/CH_2Cl_2/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (s, 3H), 1.08 (s, 3H), 1.10 (s, 3H), 1.23-1.46 (m, 8H), 1.69-1.77 (m, 2H), 2.38 (ddd, J = 49.8, 14.4, 5.5 Hz, 2H), 2.63 (d, J = 4.7Hz, 1 H), 3.60 (s, 3H), 3.89 (d, J = 5.4 Hz, 1H); 4.39 (s, 1H), 4.45 (dd, J = 76.0, 12.6Hz, 2H), 5.05 (s, 1H), 5.14 (s, 1H), 7.21-7.31 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.00, 22.66, 22.70, 24.83, 26.39, 33.57, 35.94, 36.43, 37.08, 41.20, 60.90, 60.95, 68.75, 73.90, 76.23, 98.69, 114.85, 127.21, 128.27, 138.40, 147.88, 166.55,

204.17; IR (NaCl): 2928s, 2851s, 1771s, 1642s, 1453s, 1065s cm^{-1}; MS (EI) *m/z* (% relative intensity): 408 (M^+, 0.1), 339 (3), 317 (1), 312 (3), 293(3), 221 (10), 175 (18), 161 (10), 149 (60), 127 (9), 105 (12), 97 (15), 91 (100), 77(11), 71 (15), 69 (29), 65 (12), 55 (39), 43 (42), 41 (37). Anal calcd for $C_{27}H_{36}O_3$: C, 79.37; H, 8.88. Found: C, 79.45; H, 9.12.

Spectral data for **118cc**: R_f = 0.26 (10% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$): δ 1.04 (s, 3H), 1.24-1.42 (m, 8H), 1.58 (s, 3H), 1.62-1.64 (m, 2H), 1.67 (s, 3H), 2.47 (m, 2H), 3.18 (s, 2H), 3.63 (s, 3H), 4.49 (t, *J* = 6.4 Hz, 1H), 4.53 (dd, *J* = 53.7, 11.7 Hz, 2H), 5.13 (t, *J* = 7.0 Hz, 1H), 5.17 (s, 1H), 7.28-7.33 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.92, 22.43, 25.81, 26.25, 31.50, 35.50, 35.56, 41.12, 48.11, 61.76, 71.73, 75.80, 95.32, 118.54, 127.70, 127.81, 128.41, 134.83, 137.88, 144.58, 167.08, 171.51, 187.10; IR (NaCl): 2926s, 2855s, 1761s, 1092s cm^{-1}; MS (EI) *m/z* (% relative intensity): 408 (M^+, 0.03), 339 (4), 217 (1), 161 (4), 159 (4), 133 (4), 105 (9), 97 (11), 91 (100), 69 (16), 55 (19), 41 (14). Anal calcd for $C_{27}H_{36}O_3$: C, 79.37; H, 8.88. Found: C, 79.00; H, 9.01.



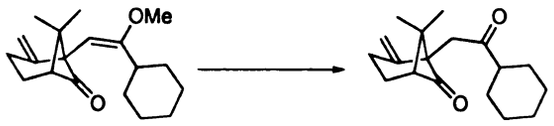
63d **110a** ***syn*-118d** ***anti*-118d**

*Bicycloheptanones syn-**118d** and anti-**118d**:*

Following the general procedure for the preparation of *syn*-**118a** and *anti*-**118a**, except that, before chromatography the CH_2Cl_2 solution was stirred under CO overnight and then filtered and concentrated. The reaction of complex **63d** (210 mg, 0.55 mmol)

and dienyne **110a** (126 mg, 0.53 mmol) in 25 mL of CH_3CN was performed at 47 °C for 25 h afforded *syn*-**118d** (143 mg, 60% yield) which was contaminated with trace of inseparable impurities. All other isomers could not be separated in reasonable purities by silica gel column chromatography using 5-15% EtOAc/hexanes as the eluent. Compound *syn*-**118d** has a characteristic methine proton as a doublet at 3.89 ppm, but the expected triplet of multiplets from *anti*-**118d** was not well separated in the region around 4 ppm in both the crude mixture and eluted fractions. By carefully checking the patterns in the NMR spectra of *syn*-**118a** and *anti*-**118a**, it was determined the two singlet peaks at 5.38 and 4.94 ppm to be from the protons of the exocyclic double bond of *anti*-**118d** and the yield of this tentatively assigned *anti*-**118d** was calculated to be 19% by comparing the integrations of the two peaks with those of *syn*-**118d**.

Spectral data for *syn*-**118d**: R_f = 0.45 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.10 (s, 3H), 1.08 (s, 3H), 1.40-1.45 (m, 1H), 1.50-1.52 (m, 2H), 1.54 (s, 1H), 1.58-1.64 (m, 2H), 1.66-1.69 (m, 1H), 2.21 (d, J = 12.0 Hz, 1H), 2.38 (ddd, J = 29.3, 7.1, 5.3 Hz, 2H), 2.56 (t, J = 2.2 Hz, 1H), 2.64 (d, J = 4.9 Hz, 1H), 3.53 (s, 3H), 3.85-3.87 (m, 2H), 3.89 (d, J = 5.4 Hz, 1H), 3.99-4.02 (m, 2H), 4.17-4.19 (m, 1H), 4.27 (d, J = 13.3 Hz, 1H), 4.78 (d, J = 13.3 Hz, 1H), 4.97 (s, 1H), 5.16 (s, 1H), 7.25-7.34 (m 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.88, 22.87, 24.69, 26.95, 33.70, 35.02, 36.94, 37.60, 54.54, 54.56, 61.03, 63.76, 64.03, 68.22, 72.80, 74.64, 88.14, 108.97, 114.43, 127.22, 127.80, 128.25, 138.67, 150.76, 163.58, 203.83; IR (NaCl): 2940s, 1773s, 1653s, 1456m, 1060s cm^{-1}; MS (EI) *m/z* (% relative intensity): 452 (M^+, 1), 311 (23), 175 (11), 141 (24), 99 (49), 91 (100), 69 (15), 55 (20), 41 (20).



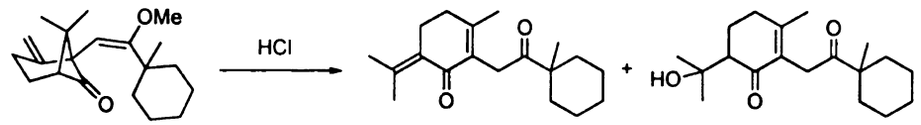
99b **139**

The Hydrolysis of the Enol Ether 99b:

Method A: To a solution of **99b** (14.8 mg, 0.51 mmol) in 5 mL of ether was added 2 mL of HOAc/H_2O (5:2), the resultant mixture was stirred at room temperature for 3 days until TLC showed the disappearance of the starting material. The product was extracted with methylene chloride and washed with H_2O. After concentration, chromatography using 5-10% EtOAc/hexanes as the eluent gave diketone **139** (13.5 mg, 96% yield) as a colorless liquid.

Method B: To a solution of **99b** (9.5 mg, 0.033 mmol) in 2 mL of THF/H_2O (4:1) was added 20 mg of oxalic acid, the resultant mixture was stirred at room temperature for 3 days until TLC showed the disappearance of the starting material. The product was extracted with methylene chloride and washed with H_2O. After concentration, chromatography using 5-10% EtOAc/hexanes as the eluent gave diketone **139** (8.0 mg, 89% yield) as a colorless liquid.

Spectral data for **139**: R_f = 0.33 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (s, 3H), 1.17 (s, 3H), 1.20-1.31 (m, 4H), 1.62-1.85 (m, 6H), 2.02-2.42 (m, 5H), 2.64 (dd, J = 2.5, 1.8 Hz, 1H), 2.77 (d, J = 9.6 Hz, 2H), 4.38 (d, J = 2.4 Hz, 1H), 4.81 (d, J = 1.5 Hz, 1H); IR (NaCl): 2932s, 2855s, 1775s, 1713s, 1451m cm^{-1}; MS (EI) *m/z* (% relative intensity): 274 (M^+, 16), 207 (17), 206 (100), 205 (37), 150 (11), 123 (68), 105 (12), 95 (15), 91 (13), 83 (34), 69 (83), 55 (50), 41 (65).



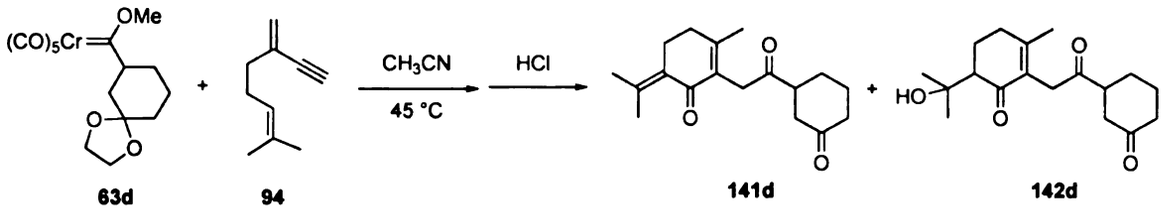
99c **141c** **142c**

The Formation of Diketones 141c and 142c.

A 25-mL RBF was charged with **99c** (45 mg, 0.15 mmol) and added a solution of 0.5 mL of concentrated HCl in ~10 mL of CH_3CN and 1 mL of H_2O. The mixture was stirred at room temperature for 4 hours and worked up as usual. Chromatography on the silica gel column gave diketones **141c** (~15 mg, 35% yield) and **142c** (~16 mg, 35% yield), both as colorless oils.

Spectral data for **141c:** R_f = 0.27 (10% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (s, 3H), 1.28-1.56 (m, 10H), 1.80 (s, 3H), 1.80 (s, 3H), 1.81 (s, 3H), 2.00 (s, 3H), 2.38 (t, *J* = 6.0 Hz, 2H), 3.64 (t, *J* = 6.0 Hz, 2H), 3.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.47, 22.38, 22.94, 22.99, 25.24, 25.90, 27.65, 33.32, 33.99, 34.91, 48.36, 129.06, 131.64, 141.52, 155.39, 190.28, 212.29; IR (NaCl): 2911s, 2849s, 1709s, 1655m, 1456m cm^{-1}; MS (EI) *m/z* (% relative intensity): 288 (M^+, 4), 192 (14), 191 (92), 164 (39), 163 (31), 149 (11), 136 (12), 121 (21), 105 (11), 97 (100), 91 (13), 79 (9), 77 (8), 67 (17), 55 (71), 41 (25). HRMS calcd for $C_{19}H_{28}O_2$ *m/z* 288.2089, meas 288.2090.

Spectral data for **142c:** R_f = 0.05 (10% EtOAc/hexanes); 0.25 (30% EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 1.16 (s, 3H), 1.17 (s, 3H), 1.19 (s, 3H), 1.23-1.60 (m, 8H), 1.1.68-1.78 (m, 1H), 1.82 (s, 3H), 1.96-2.05 (m, 3H), 2.32-2.50 (m, 3H), 3.50 (s, 2H), 5.15 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.62, 22.98, 24.73, 24.79, 25.25, 25.83, 28.48, 32.52, 33.62, 34.88, 48.35, 54.64, 72.51, 130.57, 158.88, 201.90, 212.15; IR (NaCl): 3470br, 2928s, 2851m, 1707s, 1636m, 1379m cm^{-1}; FAB-MS *m/z*: 307 (MH^+), 289 (MH^+–18).



The Formation of Triketones 141d and 142d.

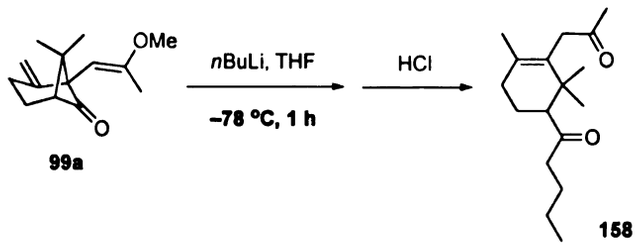
A 50-mL flask with a threaded Teflon high-vacuum stop-cock was charged with carbene complex **63d** (0.376 g, 1.0 mmol), dienyne **94** (0.174 g, 1.3 mmol) and 10 mL of CH_3CN. The solution was deoxygenated by the freeze-thaw method (–196/25 °C, 3 cycles), back-filled with argon at room temperature, sealed and then heated at 45 °C for 47 hours. The flask was then opened and added ~6.0 mL of conc. HCl and 15 mL of H_2O. The resulting yellow-green solution was stirred at room temperature for 4 h. The volatiles were removed on a rotary evaporator and the aqueous solution was extracted with CH_2Cl_2. The organic extract was washed with sat. aq. $NaHCO_3$ and brine sequentially, dried with $MgSO_4$ and concentrated. Purification by silica gel chromatography (10%, then 30%, 50% EtOAc/hexanes) gave **141d** (0.085 g, 30% yield) and **142d** (0.106 g, 35% yield), both as yellowish oils. Triketone **142d** existed as an inseparable mixture of two diastereomers (four enantiomers) and the ^{13}C NMR spectrum showed some doublet-type peaks while others were singlets. The HPLC results (using chiral-AD column) showed that there were four enantiomers in a 1:1:1:1 ratio.

Spectral data for **141d**: R_f = 0.35 (50% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$): δ 1.62-1.72 (m, 2H), 1.76 (s, 3H), 1.80 (s, 3H), 1.93 (s, 3H), 1.95-2.02 (m, 1H), 2.07-2.14 (m, 1H), 2.20-2.25 (m, 2H), 2.30-2.35 (m, 1H), 2.32 (t, J = 6.0 Hz, 2H), 2.40-2.49 (m, 1H), 2.56 (t, J = 6.0 Hz, 2H), 2.92-3.02 (m, 1H), 3.4 (s, 2H); ^{13}C NMR (75

MHz, $CDCl_3$): δ 21.29, 22.18, 22.63, 24.48, 27.17, 27.22, 32.93, 38.02, 40.61, 42.32, 49.42, 128.31, 130.98, 142.24, 156.23, 189.66, 207.90, 209.98; MS (EI) *m/z* (% relative intensity): 288 (M^+, 13), 191 (59), 163 (52), 151 (32), 123 (24), 97 (49), 69 (65), 57 (65), 55 (65), 41 (100) ; HRMS (EI) calcd for $C_{18}H_{24}O_3$ *m/z* 288.1725, meas 288.1729.

Spectral data for **142d**: R_f = 0.12 (50% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 1.14 (s, 3H), 1.18 (s, 3H), 1.65-1.76 (m, 3H), 1.87 (s, 3H), 1.98-2.16 (m, 3H), 2.29-2.53 (m, 7H), 2.95-3.02 (m, 1H), 3.34 (d, *J* = 17.1 Hz, 1H), 3.47 (d, *J* = 17.1 Hz, 1H), 5.02 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.66, 24.62, 24.63, 24.71, 27.41, 28.26, 32.51, 37.69, 40.85, 42.59, 50.01, 54.61, 72.49, 130.06, 159.99, 201.83, 207.56, 210.94 (There are some doublet-type peaks due to the existence of two inseparable diastereomers); IR (KBr): 3465br, 2968m, 1718s, 1631s, 1379m cm^{-1}; MS (EI) *m/z* (% relative intensity): 306 (M^+, 2), 288 (M^+–18, 15), 248 (66), 191 (19), 164 (18), 163 (15), 151 (100), 150 (15), 149 (25), 124 (43), 123 (39), 121 (22), 97 (63), 96 (20), 69 (46), 67 (23), 59 (25), 55 (31); Anal calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.54; H, 8.23. The results of HPLC analysis using the chiral-AD column (40% isopropyl alcohol/hexanes, 1 mL/min) showed 4 well-separated peaks in a 1:1:1:1 ratio with retention times of 7.63, 11.28, 15.03 and 23.05 minutes, respectively.

When the purified **141d** (~10 mg) in 4 N aqueous HCl (1.5 mL) and CH_3CN (1.0 mL) was stirred at room temperature for 10 hours, both **141d** and **142d** were observed from the ^1H NMR spectrum of the crude mixture in a ratio of 4 : 5 in favor of the formation of **142d**. When the purified **142d** was treated with the same conditions, very similar results were observed with a **141d/142d** ratio of 3 : 4.

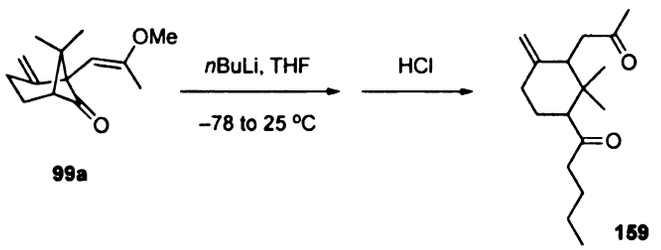


The Preparation of Diketone 158:

A flame dried 25-mL RBF was charged under argon with **99a** (40.0 mg, 0.12 mmol) in 3 mL of THF and cooled to –78 °C. In a separate 10-mL RBF, *n*BuLi (2.5 M, 0.11 mL, 0.27 mmol) was dissolved in 5 mL of THF at –78 °C and was transferred slowly via a cannula to the flask containing **99a**. The resulting mixture was stirred at –78 °C for an hour and subsequently quenched with glacial acetic acid (48 mg, 0.8 mmol). The mixture was then allowed to warm to room temperature. After usual workup, the major compound was isolated as by silica gel chromatography (partially hydrolyzed to **158)** and then treated with a solution of 3 mL of 4 N HCl and 2 mL of THF for 4 hours. The product was extracted with ether (3 x 5 mL), washed sequentially with sat. $NaHCO_3$ aqueous solution and brine, dried with anhydrous Na_2SO_4. Chromatography with 10% EtOAc/hexanes gave diketone **158** (26.2 mg) in 55% yield as a colorless oil.

Spectral data for **158**: R_f = 0.14 (10% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 0.85 (t, J = 7.5 Hz, 3H), 0.92 (s, 3H), 0.93 (s, 3H), 1.21-1.29 (m, 2H), 1.43-1.53 (m, 2H), 1.48 (s, 3H), 1.64-1.81 (m, 2H), 1.92-2.09 (m, 2H), 2.14 (s, 3H), 2.31-2.51 (m, 2H), 2.59 (dd, J = 5.1, 3.3 Hz, 1H), 3.11 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.88, 20.42, 21.87, 22.36, 22.83, 25.74, 27.13, 29.22, 31.16, 37.36, 43.56, 44.37, 57.03, 130.30, 130.81, 207.44, 214.46; IR (KBr): 2959s, 2930s, 1707s cm^{-1}; MS (EI) *m/z* (% relative intensity): 264 (M^+, 33), 246 (23), 231 (21), 221 (16), 206 (14), 191 (27), 161

(43), 151 (25), 147 (120, 137 (43), 135 (16), 121 (100), 119 (20), 109 (13), 107 (20), 105 (28), 93 (16), 91 (22), 85 (34), 77 (16), 57 (54).



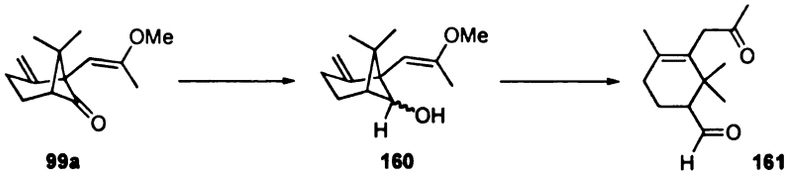
99a **159**

The Formation of Diketone 159:

A flame dried 25-mL RBF was charged under an argon atmosphere with **99a** (51 mg, 0.23 mmol) in 5 mL of THF and cooled to –78 °C. In a separate 10-mL RBF, *n*BuLi (2.5 M, 0.14 mL, 0.35 mmol) was dissolved in 5 mL of THF at –78 °C and was transferred slowly via a cannula to the flask containing **99a**. The resulting mixture was stirred at –78 °C for an hour, and warmed up slowly to room temperature over three hours and then stirred at room temperature for another an hour. After usual workup, the crude mixture was treated with a solution of 3 mL of 4 N HCl and 2 mL of THF for an hour. The product was extracted with ether (3 x 5 mL), washed sequentially with sat. $NaHCO_3$ aqueous solution and brine, dried with anhydrous Na_2SO_4. Silica gel column chromatography with 10% EtOAc/hexanes gave diketone **159** (36.5 mg) in 60% yield as a colorless oil.

Spectral data for **159**: R_f = 0.10 (10% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, J = 7.5 Hz, 3H), 0.87 (s, 3H), 0.97 (s, 3H), 1.22-1.30 (m, 2H), 1.44-1.54 (m, 2H), 1.56-1.70 (m, 2H), 2.08 (s, 3H), 2.10-2.14 (m 2H), 2.40 (td, J = 7.2, 5.7 Hz, 2H), 2.50-2.59 (m, 4H), 4.59 (s, 1H), 4.72 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.88, 22.32, 23.41, 25.64, 25.66, 26.12, 30.06, 30.25, 36.76, 42.98, 44.80, 50.30, 53.74, 110.00,

146.82, 208.16, 213.56; IR (KBr): 2957s, 2926s, 2853m, 1709s cm^{-1}; MS (EI) *m/z* (% relative intensity): 264 (M^+, 23), 246 (19), 231 (24), 206 (14), 191 (30), 161 (79), 138 (47), 137 (27), 121 (100), 119 (27), 107 (18), 95 (13), 91 (18), 85 (35), 84 (24), 79 (13), 77 (13), 57 (66).



The Formation of Aldehyde 161.

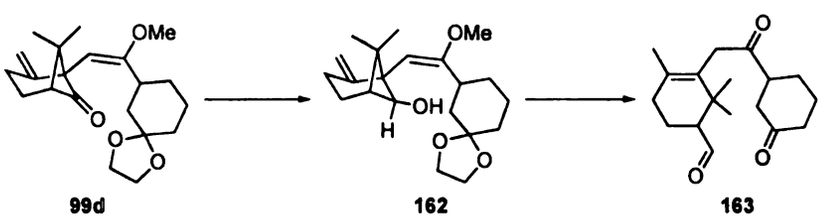
A solution of **99a** (16.5 mg, 0.075 mmol) in 2 mL of THF was added LAH (1.0 M, 0.225 mL, 0.225 mmol) at room temperature and stirred for 6 hours. The reaction mixture was quenched with H_2O and extracted with ether. The organic extracts were washed with sat. aqueous NH_4Cl solution and brine sequentially, dried with anhydrous Na_2SO_4 and concentrated. Purification by silica gel column (5–10% EtOAc/hexanes) gave alcohol **160** (13.1 mg, 79% yield) as a color less oil which solidified in freezer at –20 °C.

Spectral data for **160**: R_f = 0.22 (10% EtOAc/hexanes); ^1H NMR (300 MHz, CD_2Cl_2): δ 0.74 (s, 3H), 1.36 (s, 3H), 1.59 (s, 3H), 1.87-1.98 (m, 4H), 2.30-2.39 (m, 1H), 2.48-2.57 (m, 1H), 3.57 (s, 3H), 4.18 (s, 1H), 4.19 (s, 1H), 4.69 (d, *J* = 0.9 Hz, 1H), 4.70 (d, *J* = 0.9 Hz, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 18.23, 23.38, 23.90, 25.07, 26.36, 41.96, 45.84, 54.81, 57.52, 72.58, 91.16, 106.91, 152.35, 157.34.

To a solution of **160** (10.8 mg, 0.049 mmol) in 1 mL of THF was added 1 mL of 4 N HCl, and the mixture was stirred for 10 hours. The organic product was extracted with ether, washed with brine and dried with anhydrous Na_2SO_4. After removal of the

solvents, the residue was purified by silica gel chromatography (10% EtOAc/hexanes) to give aldehyde **161** (6.3 mg, 62%) as a colorless oil.

Spectral data for **161**: R_f = 0.40 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (s, 3H), 1.08 (s, 3H), 1.50 (s, 3H), 1.71-1.91 (m, 2H), 2.05-2.11 (m, 2H), 2.15 (s, 3H), 2.22 (dt, *J* = 9.9, 3.0 Hz, 1H), 3.17 (s, 2H), 9.84 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.66, 20.43, 23.17, 27.09, 29.40, 30.44, 36.63, 43.25, 57.13, 130.29, 131.37, 206.17, 206.54; IR (KBr): 2932m, 1721s cm^{-1}; MS (EI) *m/z* (% relative intensity): 208 (M^+, 57), 190 (38), 175 (29), 162 (59), 147 (55), 137 (65), 121 (87), 107 (100), 95 (94), 91 (66), 81 (62), 67 (36), 55 (26).



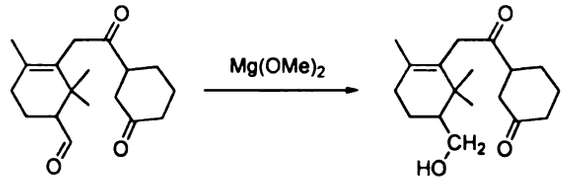
The Formation of Aldehyde 163.

Following the procedure for the preparation of **160**, the reaction of **99d** (121 mg, 0.35 mmol) with LAH (1.0 M, 1.05 mL, 1.05 mmol) in 10 mL THF after 4 h afforded alcohol **162** (108 mg) in 89% yield.

Spectral data for **162**: R_f = 0.30 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, CD_2Cl_2): δ 0.72 (s, 3H), 1.36 (s, 3H), 1.42-1.47 (m, 5H), 1.63-1.71 (m, 3H), 1.83-1.98 (m, 4H), 2.24-2.36 (m, 2H), 2.51-2.63 (m, 1H), 3.54 (s, 3H), 3.74-3.88 (m, 4H), 4.09 (s, 1H), 4.25 (d, J = 2.1 Hz, 1H), 4.66-4.68 (m, 1H), 4.71-4.72 (m, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2): δ 23.43, 23.82, 23.85, 25.43, 26.31, 29.32, 35.33, 36.46, 38.50, 42.33, 45.79, 54.95, 57.55, 64.15, 64.35, 75.57, 89.79, 106.88, 109.20, 153.91, 162.71.

Following the procedure for the preparation of **161**, the reaction of **162** (108 mg, 0.31 mmol) with 4 mL of 4 N HCl in 4 mL of THF after 1 h gave aldehyde **163** (57 mg) in 63% yield. Aldehyde **163** existed as a mixture of two inseparable isomers as evidenced with a few doublet-type peaks in the ^{13}C NMR spectrum.

Spectral data for **163**: R_f = 0.16 (30% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 0.92 (s, 3H), 1.04 (d, J = 3.3 Hz, 3H), 1.43 (d, J = 2.1 Hz, 3H), 1.63-1.89 (m, 4H), 2.04-2.09 (m, 4H), 2.20 (dt, J = 10.2, 3.0 Hz, 1H), 2.29-2.41 (m, 3H), 2.52 (dd, J = 14.4, 11.4 Hz, 1H), 2.91-2.99 (m, 1H), 3.13-3.32 (m, 2H), 9.82 (d, J = 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.68, 20.33, 23.18, 25.00, 27.06, 27.87, 30.38, 36.41, 40.68, 40.69, 42.99, 49.90, 57.00, 129.33, 131.62, 206.12, 207.85, 209.84 (There are a few doublet-type peaks due to the existence of two inseparable isomers); IR (KBr): 2940m, 2871m, 1715s cm^{-1}.



163 **163a**

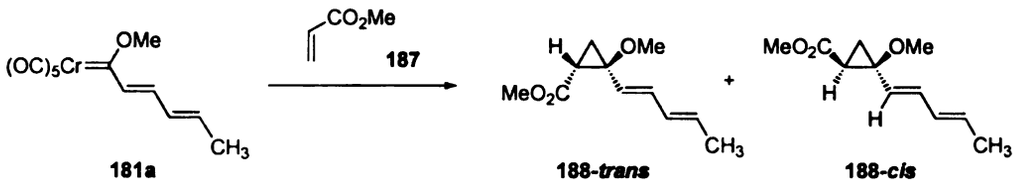
The Formation of Alcohol 163a.

To a solution of **163** (42.0 mg, 0.14 mmol) in 10 mL of THF was added $Mg(OMe)_2$/MeOH (2.0 M, 0.7 mL, 1.4 mmol) and the mixture was heated at 60 °C for 32 h, before 10 mL of ether was added and the mixture was quenched with 5 mL of H_2O. The organic layer was separated and the aqueous phase was further extracted with ether. The combined organic extracts were washed with sat. aqueous NH_4Cl and brine

sequentially, dried with anhydrous Na_2SO_4 and concentrated. Purification by silica gel column (30-50% EtOAc/hexanes) gave alcohol **163a** (17.0 mg) in 40% yield.

Spectral data for **163a**: R_f = 0.17 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.80 (d, *J* = 2.5 Hz, 3H), 0.98 (d, *J* = 6.0 Hz, 3H), 1.46 (d, *J* = 2.0 Hz, 3H), 1.51-1.53 (m, 3H), 1.74-1.78 (m, 2H), 1.89-1.94 (m, 1H), 2.07-2.13 (m, 4H), 2.30-2.43 (m, 3H), 2.56 (dd, *J* = 15, 11.5 Hz, 1H), 2.95-3.01 (m, 1H), 3.16-3.33 (m, 2H), 3.53 (dd, *J* = 10.5, 7.0 Hz, 1H), 3.82 (ddd, *J* = 10.5, 3.0, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.43, 21.82, 22.40, 25.06, 27.32, 27.91, 31.03, 36.44, 40.92, 41.17, 43.03, 46.79, 49.82, 64.15, 129.61, 131.86, 208.58, 210.05; IR (KBr): 3420br, 2938m, 1711s cm^{-1}; MS (EI) *m/z* (% relative intensity): 292 (M^+, 1), 274 (1), 234 (2), 206 (2), 177 (4), 152 (12), 149 (14), 135 (16), 123 (15), 121 (59), 109 (31), 107 (58), 97 (100), 93 (43), 91 (24), 81 (27), 69 (52), 55 (32), 41 (69).

5.3. EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA FOR CHAPTER THREE

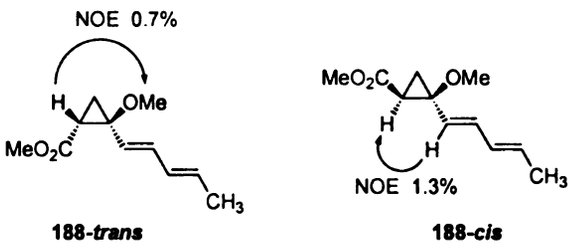


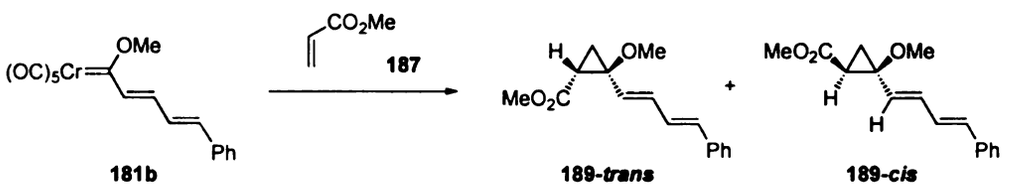
The Preparation of Cyclopropanes 188-*trans* and 188-*cis*.

To a 10-mL flask with a threaded Teflon high-vacuum stop-cock was added carbene complex **181a**[240] (47 mg, 0.15 mmol) and 2 mL of methyl acrylate **187**. The solution was deoxygenated by the freeze-thaw method (–196/25 °C, 3 cycles), back-filled with argon at room temperature, sealed and heated at 80 °C for an hour. The mixture was then cooled down to room temperature and transferred to a 50-mL round bottom flask and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (5–10% EtOAc/hexanes) to give cyclopropanes **188-*trans*** (16.5 mg, 54% yield) and **188-*cis*** (8.4 mg, 28% yield), both as colorless oils. The assignment of *trans*- and *cis*-isomers was based on the NOE results shown below.

Spectral data for **188-*trans***: R_f = 0.27 (10% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42-1.52 (m, 2H), 1.74 (dd, J = 6.9, 1.5 Hz, 3H), 2.12 (dd, J = 9.3, 7.2 Hz, 1H), 3.29 (s, 3H), 3.65 (s, 3H), 5.51 (d, J = 15.0 Hz, 1H), 5.63-5.75 (m, 1H), 6.03-6.11 (m, 1H), 6.31 (dd, J = 15.6, 10.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.13, 21.57, 29.48, 51.84, 55.62, 68.24, 124.43, 129.37, 130.83, 131.45, 171.04; IR (NaCl): 2954m, 1730s, 1439m, 1167m cm^{-1}; MS (EI) m/z (relative intensity): 196 (M^+, 78), 181 (100), 168 (18), 149 (11), 137 (61), 136 (65), 12 (77), 105 (30), 91 (19), 77 (21), 65 (10).

Spectral data for **188-*cis***: R_f = 0.15 (10% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50 (dd, *J* = 8.4, 6.0 Hz, 1H), 1.73 (dd, *J* = 6.6, 1.2 Hz, 3H), 1.78-1.92 (m, 2H), 3.25 (s, 3H), 3.68 (s, 3H), 5.32 (d, *J* = 15.3 Hz, 1H), 5.64-5.75 (m, 1H), 5.98-6.17 (m, 1H), 6.20 (dd, *J* = 15.0, 10.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.13, 19.54, 29.24, 51.97, 56.01, 67.65, 128.80, 130.12, 130.28, 130.62, 169.76; IR (NaCl): 2928m, 1738s, 1439m, 1167m cm^{-1}; MS (EI) m/z (relative intensity): 196 (M^+, 63), 181 (95), 168 (20), 149 (10), 137 (100), 121 (79), 109 (26), 105 (42), 91 (34), 77 (41), 65 (15).



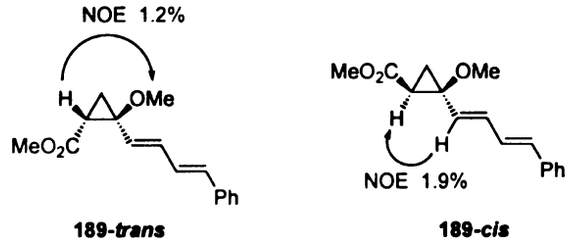


The Preparation of Cyclopropanes 189-*trans* and 189-*cis*.

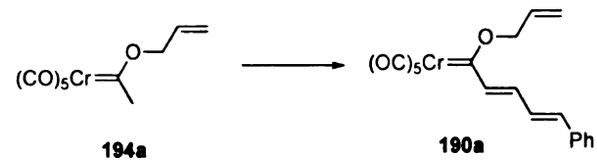
Following the procedure described above for the preparation of **188**, the reaction of carbene complex **181b**[240] (73 mg, 0.2 mmol) and 2 mL of methyl acrylate gave cyclopropanes **189-*trans*** (32 mg, 62% yield) and **189-*cis*** (17 mg, 33% yield), both as colorless oils. The assignment of *trans*- and *cis*-isomers was based on the NOE results shown below.

Spectral data for **189-*trans***: R_f = 0.24 (10% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.49-1.59 (m, 2H), 2.19 (dd, *J* = 9.3, 7.5 Hz, 1H), 3.34 (s, 3H), 3.68 (s, 3H), 5.79 (d, *J* = 15.6 Hz, 1H), 6.48-6.57 (m, 2H), 6.81 (dd, *J* = 15.6, 10.5 Hz, 1H), 7.19-7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.00, 29.82, 51.87, 55.78, 68.40, 126.32, 127.45, 128.22, 128.29, 128.58, 131.21, 131.96, 137.29, 170.99; IR (NaCl): 3024m, 2951m, 1728s, 1439m, 1375m, 1165m cm^{-1}; MS (EI) m/z (relative intensity): 258 (M^+, 100), 199 (70), 198 (60), 183 (16), 167 (57), 155 (28), 141 (15), 128 (17), 115 (17), 91 (34), 77 (10).

Spectral data for **189-*cis***: R_f = 0.12 (10% Et_2O/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20-1.25 (m, 1H), 1.86-2.00 (m, 2H), 3.32 (s, 3H), 3.71 (s, 3H), 5.54 (d, *J* = 15.0 Hz, 1H), 6.39-6.57 (m, 2H), 6.76 (dd, *J* = 15.6, 10.5 Hz, 1H), 7.20-7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.77, 29.70, 52.02, 56.64, 67.76, 126.36, 127.63, 127.66, 128.63, 130.42, 132.45, 132.68, 137.12, 169.54; IR (NaCl): 2951m, 1734s, 1437m, 1167m cm^{-1}; MS (EI) m/z (relative intensity): 258 (M^+, 100), 199 (79), 198 (57), 167 (55), 155 (37), 1541 (18), 121 (15), 115 (19), 91 (34), 77 (11).



189-*trans* **189-*cis***

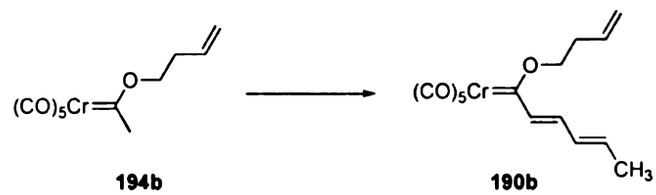


194a 190a

The Preparation of Carbene Complex 190a.

This compound was prepared by Aumann's method for related compounds.[112b] A solution of **194a**[241] (98 mg, 0.355 mmol) in 8 mL of ether was treated with cinnamaldehye (47 mg, 0.355 mmol), TMSCl (135 μL, 1.065 mmol) and Et_3N (198 μL, 1.42 mmol) and stirred at room temperature for 27 hours. The dark red mixture was filtered through a short pad of Celite and concentrated. The residue was subjected to silica gel chromatography (hexanes as the eluent) to afford **190a** (51 mg, 37% yield) as a red solid.

Spectral data for **190a**: R_f = 0.14 (hexanes); 0.45 (10% Et_2O/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 5.42-5.54 (m, 4H), 6.14-6.27 (m, 1H), 6.79-6.85 (m, 2H), 7.04-7.09 (m, 1H), 7.33-7.50 (m, 6H); IR (NaCl): 2054s, 1923vs cm^{-1}.

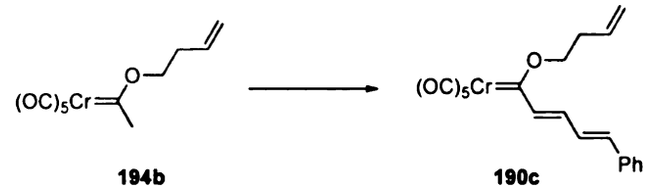


194b 190b

The Preparation of Carbene Complex 190b.

Following a literature procesure for related compounds,[112a] the reaction of **194b**[241] (0.50 g, 1.72 mmol) and crotonaldehyde (0.285 mL, 3.42 mmol) afforded **190b** (0.15 g, 27% yield) as a red solid, along with recovered **194b** (0.23 g, 46%). The yield based on unrecovered starting material was 50%.

Spectral data for **190b**: R_f = 0.20 (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.89 (d, *J* = 6.9 Hz, 3H), 2.72 (q, *J* = 6.6 Hz, 2H), 4.97 (t, *J* = 6.6 Hz, 2H), 5.14-5.23 (m, 2H), 5.83-5.96 (m, 1H), 6.06-6.15 (m, 1H), 6.25-6.36 (m, 1H), 6.60 (dd, *J* = 14.7, 10.8 Hz, 1H), 7.21 (d, *J* = 14.7 Hz, 1H).

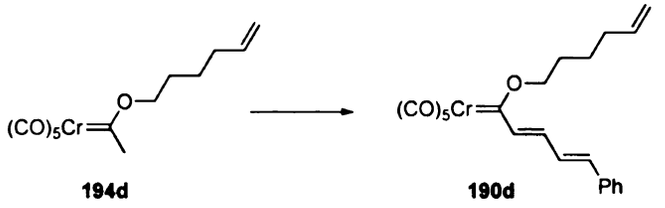


194b **190c**

The Preparation of Carbene Complex 190c.

Following the procedure described above for the preparation of **190a**, the reaction of **194b**[241] (290 mg, 1.0 mmol) and cinnamaldehyde (132 mg, 1.0 mmol) with TMSCl (0.38 mL, 3.0 mmol) and Et_3N (0.56 mL, 4.0 mmol) in 10 mL of ether after 36 hours afforded **190c** (242 mg, 60% yield) as a red solid.

Spectral data for **190c**: R_f = 0.12 (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.76 (q, *J* = 6.6 Hz, 2H), 5.02 (t, *J* = 6.6 Hz, 2H), 5.18-5.27 (m, 2H), 5.89-5.98 (m, 1H), 6.76-6.81 (m, 2H), 7.00-7.05 (m, 1H), 7.31-7.49 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 33.97, 78.58, 118.14, 127.01, 127.37, 128.91, 129.59, 131.06, 133.45, 136.09, 142.87, 145.00, 216.78, 224.50, 329.42.



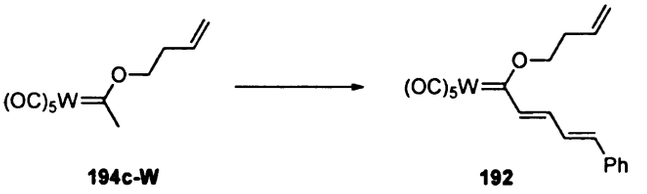
The Preparation of Carbene Complexes 194d and 190d.

A solution of methyl pentacarbonylchromium tetramethylammonium salt (0.62 g, 2 mmol) in CH_2Cl_2 (20 mL) was added freshly prepared 5-hexenyl triflate[242] and stirred at room temperature for 30 minutes. The reaction was quenched with saturated $NaHCO_3$ aqueous solution. The organic layer was separated and the aqueous phase was further extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried with $MgSO_4$, filtered and concentrated. Purification by chromatography with hexanes gave **194d** (0.62g, 96% yield) as an orange oil.

Spectral data for **194d**: R_f = 0.20 (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (p, J = 7.5 Hz, 2H), 1.93-2.03 (m, 2H), 2.14 (q, J = 7.5 Hz, 2H), 2.92 (s, 3H), 4.89 (brs, 2H), 4.96-5.07 (m, 2H), 5.73-5.87 (m, 1H).

Following the procedure described above for the preparation of **190a**, the reaction of **194d** (290 mg, 0.91 mmol) and cinnamaldehyde (120 mg, 0.91 mmol) with TMSCl (0.35 mL, 2.74 mmol) and Et_3N (0.51 mL, 3.65 mmol) in 10 mL of ether after 3 days afforded **190d** (250 mg, 64% yield) as a red oil.

Spectral data for **190d**: R_f = 0.09 (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.64 (q, J = 7.5 Hz, 2H), 1.97-2.07 (m, 2H), 2.18 (q, J = 7.5 Hz, 2H), 4.97 (t, J = 6.6 Hz, 2H), 5.02-5.10 (m, 2H), 5.77-5.90 (m, 1H), 6.72-6.85 (m, 2H), 7.02-7.07 (m, 1H), 7.31-7.49 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.32, 29.03, 33.25, 79.85, 115.24, 127.08, 127.38, 128.92, 129.57, 131.29, 136.18, 138.04, 142.88, 144.82, 216.89, 224.53, 329.67.



194c-W 192

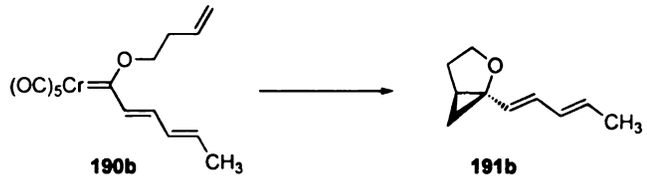
The Preparation of Tungsten Carbene Complex 192.

Following the procedure described above for **194d**, the reaction of the methyl pentacarbonyltungsten tetramethylammonium salt (0.882 g, 2 mmol) and 3-butenyl triflate after 30 minutes afforded **194c-W** (0.763 g, 90% yield) as an orange oil.

Spectral data for **194c-W**: R_f = 0.23 (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.70 (q, J = 6.6 Hz, 2H), 2.86 (s, 3H), 4.82 (brs, 2H), 5.15-5.22 (m, 2H), 5.79-5.92 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 33.39, 52.22, 83.31, 118.44, 132.71, 197.24, 203.43, 330.92.

Following the procedure described above for the preparation of **190a**, the reaction of **194c-W** (371 mg, 0.88 mmol) and cinnamaldehyde (111 μL, 0.88 mmol) with TMSCl (335 μL, 2.64 mmol) and Et_3N (491 μL, 3.53 mmol) in 10 mL of ether after 3 days afforded **192** (210 mg, 45% yield) as a dark red solid.

Spectral data for **192**: R_f = 0.08 (hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.73 (q, J = 6.6 Hz, 2H), 4.84 (t, J = 6.6 Hz, 2H), 5.17-5.26 (m, 2H), 5.85-5.98 (m, 1H), 6.80 (dd, J = 15, 11.1 Hz, 1H), 6.94-7.11 (m, 2H), 7.33-7.51 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 33.73, 81.30, 118.08, 127.28, 127.42, 128.99, 129.65, 133.47, 134.95, 136.33, 144.84, 147.09, 197.63, 203.93, 303.38.

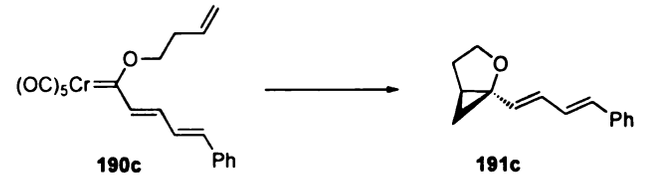


190b **191b**

The Preparation of Cyclopropane 191b.

To a 25-mL flask with a threaded Teflon high-vacuum stop-cock was added carbene complex **190b** (109 mg, 0.34 mmol) and 7 mL of toluene. The solution was deoxygenated by the freeze-thaw method (-196/25 °C, 3 cycles), back-filled with argon at room temperature, sealed and heated at 80 °C for 2 hours. The mixture was then cooled down to room temperature and transferred to a 50-mL round bottom flask and concentrated under reduced pressure. Purification by silica gel column chromatography (0–5% EtOAc/hexanes) afforded **191b** (29.5 mg, 58 % yield) as a colorless oil.

Spectral data for **191b**: R_f = 0.37 (10% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77 (ddd, J = 9.0, 6.3, 0.9 Hz, 1H), 1.12 (t, J = 6.0 Hz, 1H), 1.48 (dt, J = 8.7, 5.1 Hz, 1H), 1.71 (dd, J = 6.2, 1.4 Hz, 3H), 1.91 (ddd, J = 12.0, 7.2, 2.2 Hz, 1H), 2.05-2.15 (m, 1H), 3.56 (td, J = 9.6, 7.2 Hz, 1H), 4.09 (td, J = 9.0, 2.4 Hz, 1H), 5.51 (d, J = 15.0 Hz, 1H), 5.56-5.68 (m, 1H), 5.98-6.07 (m, 1H), 6.27 (dd, J = 15.0, 10.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.42, 18.11, 23.99, 28.75, 66.70, 68.27, 127.65, 127.95, 129.66, 130.92; MS (EI) m/z (relative intensity): 150 (M^+, 100), 135 (38), 107 (19).

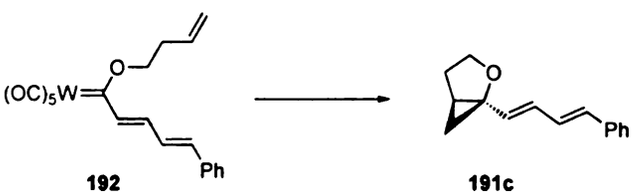


190c **191c**

The Preparation of Cyclopropane 191c.

Following the procedure described above for the preparation of **191b**, the reaction of **190c** (200 mg, 0.49 mmol) in 10 mL of toluene after heating at 80 °C for 6 hours affored **191c** (76 mg, 73% yield) as a colorless oil.

Spectral data for **191c**: R_f = 0.36 (10% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84-0.89 (m, 1H), 1.21 (t, *J* = 6.0 Hz, 1H), 1.54-1.60 (m, 1H), 1.91-1.99 (m, 1H), 2.09-2.21 (m, 1H), 3.61 (td, *J* = 9.3, 6.9 Hz, 1H), 4.14 (td, *J* = 9.0, 2.7 Hz, 1H), 5.76 (d, *J* = 15.3 Hz, 1H), 6.45-6.54 (m, 2H), 6.77 (dd, *J* = 15.3, 10.5 Hz, 1H), 7.14-7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.24, 26.65, 28.77, 66.91, 68.56, 126.18, 127.15, 127.49, 128.53, 128.57, 130.66, 133.54, 137.54; IR (NaCl): 3025m, 2928m, 2874m, 1638m, 1595m, 1063m, 988s cm^{-1}; MS (EI) m/z (relative intensity): 212 (M^+, 100), 197 (15), 183 (10), 157 (12), 141 (16), 128 (36), 115 (14), 91 (13), 77 (11).

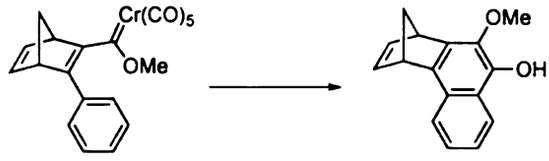


192 **191c**

The Preparation of Cyclopropane 191c from Tungsten Complex 192.

Following the procedure described above for the preparation of **193b**, the reaction of the tungsten carbene complex **192** (84.0 mg, 0.15 mmol) in 3 mL of toluene after heating at 80 °C for an hour gave **191c** (30.1 mg, 91%) as a colorless oil. The spectral data were consistent with those obtained from the reaction wtih **190c** as described above.

5.4. EXPERIMENTAL PROCEDURES AND CHARACTERIZATION DATA FOR CHAPTER FOUR



224 225

The Thermolysis of Complex 224 in the Presence or Absence of $Fe_2(CO)_9$.

General Procedure: A 25-mL flask with a threaded Teflon high-vacuum stop-cock was flushed with nitrogen for 10 minutes before it was charged with the carbene complex **224** (40.2 mg, 0.1 mmol), one equiv of $Fe_2(CO)_9$ (36.4 mg, 0.1 mmol), and 5 mL of the solvent. The mixture was degassed by the freeze-thaw method (–196/25 °C, 3 cycles), back-filled with 1 atm CO or argon at room temperature, sealed and heated at 80 °C until the red color disappeared, indicating all the starting carbene complex was consumed. The mixture was then allowed to cool to room temperature and transferred to a 100-mL round bottom flask and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (5–10% EtOAc/hexanes) to furnish the phenol **225** as a white solid.

Following the general procedure described above, when benzene was used as the solvent and in the presence of 1 atm CO, after 24 h, the reaction gave the phenol **225** (19.0 mg, 80% yield). The same reaction under 1 atm argon for 24 h afforded 15% yield of **225** (3.6 mg).

Spectral data for **225**: R_f = 0.20 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (d, 1H, J = 6.6 Hz), 2.41 (d, 1H, J = 6.6 Hz), 3.96 (s, 3H), 4.36 (s, 1H),

4.44 (s, 1H), 5.98 (s, 1H), 6.89-6.97 (m, 2H), 7.26-7.36 (m, 2H), 7.79 (d, 1H, J = 8.1 Hz), 8.07 (d, 1H, J = 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.74, 49.20, 61.86, 71.52, 121.38, 122.48, 122.72, 123.70, 124.71, 126.05, 138.70, 139.71, 141.07, 141.47, 142.99, 144.34. The spectral data are consistent with the reported data for this compound.[197]

For the reactions that were carried out in the absence of $Fe_2(CO)_9$, the general procedure described above was followed except that none of the iron source was added.

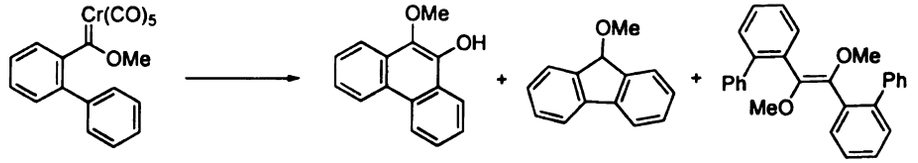
(1) When the reaction was performed in acetonitrile without any iron source in the presence of 1 atm CO for 8 h, a 73% yield of **225** was obtained. The same reaction under 1 atm argon for 4 h gave **225** in 36% yield.

(2) When the reaction was performed in THF without any iron source in the presence of 1 atm CO for 16 h, an 87% yield of **225** was obtained. The same reaction under 1 atm argon for 5 h gave **225** in 41% yield.

(3) When the reaction was performed in benzene without any iron source in the presence of 1 atm CO for 22 h, a 92% yield of **225** was obtained. The same reaction under 1 atm argon for 36 h gave **225** in 51% yield.

(4) When the reaction was performed in heptane without any iron source in the presence of 1 atm CO for 42 h, an 80% yield of **225** was obtained. The same reaction under 1 atm argon for 39 h gave **225** in 35% yield.

(5) When the same reactions as in (4) were performed except that the reaction temperature was at 100 °C, under 1 atm CO after 1.5 h, a 75% yield of **225** was obtained, while under 1 atm argon after 1.5 h **225** was isolated in 28% yield.



227 228 270 271

The Thermolysis of Complex 227 in the Presence or Absence of $Fe_2(CO)_9$.

General Procedure (I) – for reactions performed under 1 atm CO: A 25-mL flask with a threaded Teflon high-vacuum stop-cock was flushed with nitrogen for 10 minutes before it was charged with the carbene complex **227** (77.7 mg, 0.2 mmol), one equiv of $Fe_2(CO)_9$ (72.8 mg, 0.2 mmol), and 10 mL of the solvent. The mixture was degassed by the freeze-thaw method (–196/25 °C, 3 cycles), back-filled with 1 atm CO at room temperature, sealed and heated at 80 °C or 130 °C until the red color disappeared, indicating all the starting carbene complex was consumed. The mixture was then allowed to cool to room temperature and transferred to a 100-mL round bottom flask and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (5–10% EtOAc/hexanes) to give the first eluted 9-methoxy fluorene **270** as the major isomer, followed by the enol ether **271** that was contaminated by a small amount of **270,** and the third eluted phenol product **228** (in the cases that **228** and **271** were also formed).

Following the general procedure (I) described above, when benzene was used as the solvent and at 80 °C, after 16 d, the reaction gave **271** (9.0 mg, 20%) and **270** (26.6 mg, 68%); when THF was used as the solvent and at 80 °C, after 7 d, the reaction gave **270** (30.9 mg, 79%), along with a trace (< 1%) of **228**; when acetonitrile was used as the solvent and at 80 °C, after 5 d, the reaction gave **270** (30.0 mg, 77%); when toluene was

used and at 130 °C, after 1 d, the reaction gave **270** (31.4 mg, 80%) and only trace (< 1%) of **228** was observed.

For the reactions that were carried out in the absence of $Fe_2(CO)_9$, the general procedure (I) described above was followed except that none of the iron source was added. When the reaction was performed in benzene without any iron source at 80 °C for 12 d, **228** (7.0 mg, 16%), **270** (10.0 mg, 26%) and **271** (20.2 mg, 26%) were obtained; when the reaction was performed in THF without any iron source at 80 °C for 16 d, **228** (6.7 mg, 15%) and **270** (22.8 mg, 58%) were obtained, along with trace of **271** (~ 3%); when the reaction was performed in toluene without any iron source at 130 °C for 20 h, **270** (32.0 mg, 82%) was obtained, along with traces of **228** (< 1%) and **271** (~ 2%).

Spectral data for **228**: R_f = 0.18 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.99 (s, 3H), 6.19 (s, 1H), 7.50-7.65 (m, 4H), 7.99 (d, 1H, J = 7.8 Hz), 8.28 (dd, 1H, J = 6.3, 3.6 Hz), 8.61-8.64 (m, 2H); IR (NaCl) 3394 br, 2924s, 2855ms, 1628s, 1453s cm^{-1}. The spectral data are consistent with the reported data for this compound.[197]

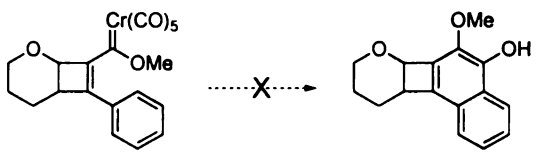
Spectral data for **270**: R_f = 0.34 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.04 (s, 3H), 5.59 (s, 1H), 7.30 (td, 2H, J = 7.5, 1.2 Hz), 7.38 (t, 2H, J = 7.5 Hz), 7.60 (d, 2H, J = 7.2 Hz), 7.66 (d, 2H, J = 7.2 Hz); MS (EI) *m/z* (% relative intensity) 196 (M^+, 100), 195 (75), 181 (31), 165 (87), 152 (21). The spectral data are consistent with the reported data for this compound.[243]

Spectral data for **271**: R_f = 0.32 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.86 (s, 6H), 7.22-7.40 (m, 14H), 7.46 (d, 4H, J = 4.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.52, 125.18, 126.99, 127.03, 127.80, 128.32, 128.58, 130.19, 130.50,

132.10, 141.77, 141.80. MS (EI) *m/z* (% relative intensity) 392 (M^+, 45), 345 (28), 317 (32), 302 (18), 195 (11), 181 (80), 165 (40), 152 (65), 151 (100), 127 (8), 77 (5), 69 (7).

General Procedure (II) – for reactions performed under 500 psi CO: A Monel Paar pressure reactor equipped with a magnetically driven mechanical stirrer was flushed with carbon monoxide for a few minutes before it was charged with the carbene complex **227** (77.7 mg, 0.2 mmol), one equiv of $Fe_2(CO)_9$ (72.8 mg, 0.2 mmol), and 10 mL of benzene or toluene. Then the reactor was further flushed with CO for another 2 minutes and filled with 500 psi CO and heated at 80 or 130 °C with stirring for 0.5–3.6 days. The mixture was transferred to a 100-mL round bottom flask and concentrated on a rotary evaporator. The yields of **228**, **270** and **271** (and unreacted **227**) were calculated from the NMR spectra of the crude mixture using triphenylmethane as the internal standard.

Following the general procedure (II) described above, when benzene was used as the solvent, the reaction at 80 °C for 3.6 d gave **270** (19%) and **271** (4%), along with a 46% recovery of **227**; when toluene was used as the solvent, the reaction at 130 °C for 12 h gave **228** (< 2%), **270** (50%) and **271** (13%); when no iron source was added and toluene was used as the solvent, the reaction at 130 °C for 17 h gave **228** (< 2%), **270** (50%) and **271** (19%);



237 **238**

Attempted Thermolysis of Complex 237 in the Presence or Absence of $Fe_2(CO)_9$.

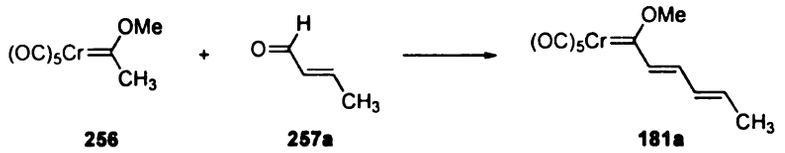
Following the general procedure (I) described above for the thermolysis of **227** under 1 atm CO, the reaction conditions that were tried for **237** included: (1) with one equiv of $Fe_2(CO)_9$ in THF at 80 °C for 24 h and 90 °C for 48 h; (2) with one equiv of $Fe_2(CO)_9$ in benzene at 90 °C for 41 h; (3) without any iron source in THF at 80 °C for 24 h and 90 °C for 48 h; (4) without any iron source in THF at 90 °C for 36 h; (5) without any iron source in benzene at 90 °C for 41 h; (6) without any iron source in THF under 1 atm argon at 65 °C for 60 h. In each of the above cases, all the starting carbene complex **237** was consumed, and a very complex mixture was observed and none of the desired **238** was isolated.

Following the general procedure (II) described above for the thermolysis of **227** under 500 psi CO, the reaction conditions that were tested for **237** included: (1) with one equiv of $Fe_2(CO)_9$ in benzene at 90 °C for 16 h; (2) without any iron source in THF at 90 °C for 22 h. In each of the two cases, all the starting carbene complex **237** was consumed, and a very complex mixture was observed and none of the desired **238** was isolated.

The Preparation of Carbene Complexes 181(a–j).

Carbene complexes *trans,trans*-**181a**[244], *trans,trans*-**181c**[112b,c] and *trans,trans*-**181d**[245] are known in the literature. Aldehydes **257a, 257g, 257i, 260a,** and ketone **261** are commercially available; aldehydes **257j**[246] and **260b**[247] can be readily prepared according to the literature procedures.

General Procedure for the Preparation of Complexes (*trans,trans*-181a, *trans*-181g, *trans*-181i and *trans*-181j): Illustrated for *trans,trans*-181a.

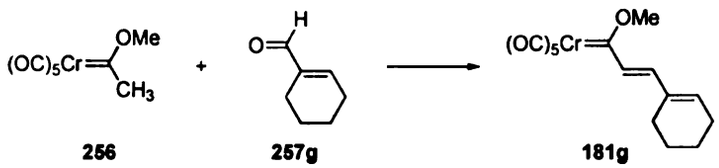


256 **257a** **181a**

Carbene Complex trans,trans-181a. This procedure is similar to one that has been reported for this compound.[112a] The methyl(methoxy)carbene complex **256**[248] (0.25 g, 1 mmol) was dissolved in 30 mL of anhydrous ether and deprotonated with one equivalent of *n*-BuLi (2.5 M in hexanes, 0.4 mL) under argon at –78 °C for 20-30 min. In a separate flask under argon, a solution of crotonaldehyde **257a** (0.41 mL, 5 mmol) in 10 mL of CH_2Cl_2 was cooled to –78 °C and treated with $SnCl_4$ (0.58 mL, 5 mmol) for 20-30 min. Then the solution of the enolate of complex **256** was transferred via cannula to the flask with the aldehyde/$SnCl_4$ complex. The mixture was stirred at –78 °C for two hours before it was quenched by the rapid addition to 50 mL of water. The organic layer was separated and washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the residue was subjected to silica gel chromatography by first elution with pentane to remove the unreacted **256** (46 mg, 18.4% recovery) and subsequent elution with ether/CH_2Cl_2/hexanes (1:1:3) to give the aldol adduct. The aldol adduct, after removal of the solvent, was dissolved in ~ 50 mL of CH_2Cl_2 and cooled to 0 °C, then MsCl (0.16 mL, 2 mmol) and Et_3N (0.31 mL, 2.2 mmol) were added. When the dehydration reaction was complete as indicated by TLC (usually 5-10 min), it was quenched by saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was separated and the aqueous phase was further extracted with ether (2 x 15 mL). The combined organic layer was washed sequentially with aqueous $NaHCO_3$ (30 mL)

solution and brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel with hexanes to afford the carbene complex **181a** (156 mg, 52% yield) as a red solid. The yield based on unrecovered **256** was 63%.

Spectral data for *trans,trans*-**181a**: R_f = 0.24 (hexanes); mp 51–52 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.89 (d, 3H, J = 6.0 Hz), 4.70 (s, 3H), 6.06-6.15 (m, 1H), 6.25-6.35 (m, 1H), 6.10 (dd, 1H, J = 14.7, 11.1 Hz), 7.24 (d, 1H, J = 14.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.40, 66.05, 130.69, 131.99, 141.46, 144.83, 216.84, 224.32, 332.68; IR (NaCl) 2056vs, 1921vs br, 1572s cm^{-1}; MS (EI) *m/z* (% relative intensity) 302 (M^+, 1), 274 (2), 246 (1), 218 (1), 190 (10), 162 (15), 147 (14), 130 (20), 117 (7), 91 (5), 52 (100). Anal calcd for $C_{12}H_{10}CrO_6$: C, 47.69; H, 3.34. Found: C, 47.69; H, 3.44.

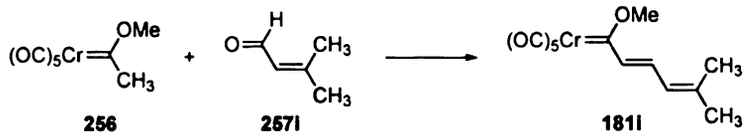


256 **257g** **181g**

*Carbene Complex trans-**181g**.* Following the procedure described above for the preparation of **181a**, the reaction of **256** (250 mg, 1 mmol) and **257g** (0.57 mL, 5 mmol) afforded **181g** (105 mg, 31% yield) as a red solid, along with recovered **256** (124 mg, 50% recovery). The yield based on unrecovered **256** was 61%.

Spectral data for *trans*-**181g**: R_f = 0.24 (hexanes); mp 69–70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60-1.72 (m, 4H), 2.18-2.24 (m, 4H), 4.69 (s, 3H), 6.35 (t, 1H, J = 3.6 Hz), 6.65 (d, 1H, J = 15.3 Hz), 7.26 (d, 1H, J = 15.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.89, 21.96, 24.03, 27.35, 66.02, 135.36, 135.59, 137.20, 145.20, 217.01, 224.34, 332.43; IR (NaCl) 2056vs, 1919vs br, 1570s cm^{-1}; MS (EI) *m/z* (% relative intensity) 342 (M^+, 1), 314 (3), 286 (2), 258 (3), 230 (18), 202 (46), 200 (34), 170 (14), 168 (21),

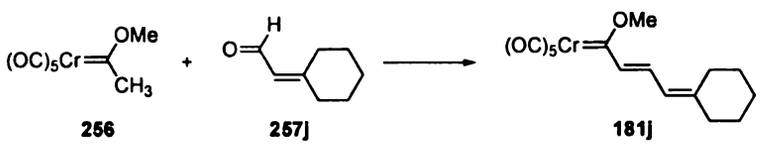
160 (44), 129 (14), 91 (20), 77 (15), 52 (100). Anal calcd for $C_{15}H_{14}CrO_6$: C, 52.64; H, 4.12. Found: C, 52.37; H, 3.97.



256 **257i** **181i**

*Carbene Complex trans-**181i**.* Following the procedure described above for the preparation of **181a** (except that two equivalents of aldehyde/$SnCl_4$ was used), the reaction of **256** (1.0 g, 4 mmol) and **257i** (0.77 mL, 8 mmol) afforded **181i** (0.66 g, 52% yield) as a red solid, along with recovered **256** (0.25 g, 25% recovery). The yield based on unrecovered **256** was 70%.

Spectral data for *trans*-**181i**: R_f = 0.19 (hexanes); mp 67–68 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 1.92 (s, 6H), 4.67 (s, 3H), 5.94 (dt, J = 11.4, 1.2 Hz, 1H), 7.03 (dd, J = 14.4, 11.4 Hz, 1H), 7.20 (d, J = 14.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 19.4, 27.3, 65.8, 124.9, 130.2, 141.0, 153.2, 217.1, 224.4, 331.4; IR (cm^{-1}): 2056vs, 1919vs br, 1561m; MS (EI) m/z (relative intensity) 316 (M^+, 2), 288 (7), 260 (1), 232 (3), 204 (24), 176 (32), 161 (49), 160 (33), 144 (41), 131 (38), 109 (13), 91 (31), 79 (29), 77 (26), 52 (100); Anal. Calcd for $C_{13}H_{12}CrO_6$: C, 49.38; H, 3.82. Found: C, 49.72; H, 3.91.

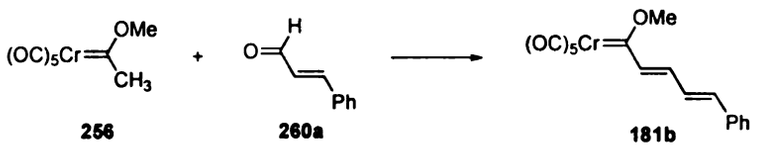


256 **257j** **181j**

*Carbene Complex trans-**181j**.* Following the procedure described above for the preparation of **181a** (except that 2.9 equivalents of aldehyde/$SnCl_4$ was used), the reaction of **256** (0.685 g, 2.74 mmol) and **257j**[246] (1.70 g, 8 mmol) afforded **181j** (0.50 g,

51% yield) as a red solid along with recovered **256** (0.20 g, 29% recovery). The yield based on unrecovered **256** was 72%.

Spectral data for *trans*-**181j**: R_f = 0.24 (hexanes); mp 60–61 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (brs, 6H), 2.24-2.26 (m, 2H), 2.39-2.41 (m, 2H), 4.67 (s, 3H), 5.88 (d, 1H, J = 11.7 Hz), 7.09 (dd, 1H, J = 14.1, 11.7 Hz), 7.25 (d, 1H, J = 14.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.47, 28.12, 28.65, 30.34, 38.47, 65.75, 121.77, 129.16, 141.36, 161.61, 217.09, 224.40, 331.00; IR (NaCl) 2056s, 1919vs br, 1559m cm^{-1}; MS (EI) *m/z* (% relative intensity) 356 (M^+, 1), 328 (5), 300 (3), 272 (3), 244 (35), 216 (35), 214 (52), 184 (41), 161 (43), 160 (66), 121 (40), 91 (63), 77 (30), 52 (77), 51 (100). Anal calcd for $C_{16}H_{16}CrO_6$: C, 53.94; H, 4.53. Found: C, 54.09; H, 4.60.

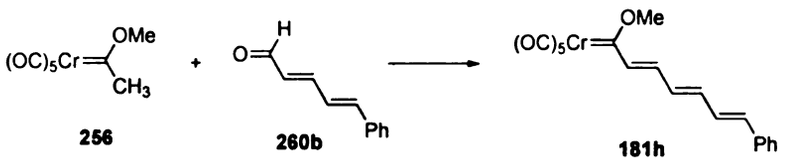


The Preparation of Carbene Complex *trans,trans*-181b.

This compound was prepared by Aumann's method for related compounds.[112b] A solution of **256** (1.25 g, 5 mmol) in 30 mL of ether was treated with cinnamaldehye **260a** (0.66 g, 5 mmol), TMSCl (1.91 mL, 15 mmol) and Et_3N (2.80 mL, 20 mmol) and stirred at room temperature for 3 days. The dark red mixture was filtered through a short pad of Celite and concentrated. The residue was subjected to silica gel chromatography (hexanes as the eluent) to afford **181b** (1.24 g, 68% yield) as a red solid.

Spectral data for *trans,trans*-**181b**: R_f = 0.10 (hexanes); mp = 87–88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.74 (s, 3H), 6.75-6.85 (m, 2H), 7.02-7.07 (m, 1H), 7.31-7.41 (m, 3H), 7.43-7.50 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 66.11, 127.01, 127.39,

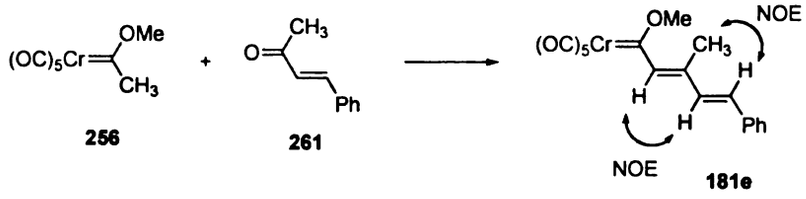
128.90, 129.59, 131.01, 136.11, 142.85, 145.04, 216.80, 224.48, 331.42; IR (NaCl) 2054vs, 1917vs br, 1561s cm^{-1}; MS (EI) *m/z* (% relative intensity) 364 (M^+, 1), 336 (1), 308 (1), 280 (1), 252 (5), 224 (13), 205 (100), 172 (9), 128 (15), 115 (18), 77 (13), 73 (53), 51 (52). Anal calcd for $C_{17}H_{12}CrO_6$: C, 56.05; H, 3.32. Found: C, 56.32; H, 3.55.



The Preparation of Carbene Complex *trans,trans,trans*-181h.

Following the procedure described above for the preparation of **181b**, the reaction of **256** (0.49 g, 1.96 mmol) and **260b**[247] (0.31 g, 1.96 mmol) with TMSCl (0.75 mL, 5.88 mmol) and Et_3N (1.10 mL, 7.84 mmol) in 10 mL of ether afforde **181h** (0.55 g, 72% yield) as a red solid.

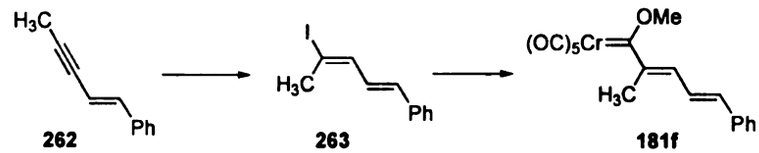
Spectral data for *trans,trans,trans*-**278h**: R_f = 0.10 (hexanes); mp 180 °C (dec). ^1H NMR (300 MHz, $CDCl_3$) δ 4.72 (s, 3H), 6.36 (dd, 1H, J = 14.1, 11.4 Hz), 6.71 (d, 1H, J = 11.4 Hz), 6.76 (d, 1H, J = 12.0 Hz), 6.83-6.95 (m, 2H), 7.26-7.38 (m, 4H), 7.41-7.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 65.98, 127.03, 128.36, 128.55, 128.83, 131.26, 131.30, 136.45, 137.83, 142.41, 145.55, 216.87, 224.56, 330.42; IR (NaCl) 2054vs, 1921vs br cm^{-1}; MS (EI) *m/z* (% relative intensity) 390 (M^+, 1), 362 (1), 334 (2), 306 (1), 278 (21), 250 (63), 218 (29), 198 (23), 167 (29), 165 (26), 152 (18), 149 (29), 129 (18), 128 (18), 115 (10), 103 (50), 77 (33), 52 (87), 51(100). Anal calcd for $C_{19}H_{14}CrO_6$: C, 58.47; H, 3.62. Found: C, 58.10; H, 3.84.



The Preparation of Carbene Complex *trans,trans*-181e.

This compound was prepared by a procedure published for related compounds.[112d] To a solution of the methyl(methoxy)carbene complex **256** (0.25 g, 1 mmol) in 30 mL of ether under argon was added *n*-BuLi (2.5 M in pentane, 0.4 mL, 1 mmol) at –78 °C and stirred for 20 minutes. In a separtate flask, *trans*-4-phenyl-3-buten-2-one **261** (1.46 g, 10 mmol) in 50 mL of ether under argon was treated with BF_3•OEt_2 (1.27 mL, 10 mmol) at 0 °C and stirred for 20 minutes. The solution of the enolate of complex **256** was transferred via cannula to the flask with the **261**/BF_3•OEt_2 complex at 0 °C. The mixture was then allowed to warm to room temperature and stirred for an hour before it was poured into an Erlenmeyer flask with 25 mL of buffer solution (pH = 7). The organic layer was separated and the aqueous phase was further extracted with ether (30 mL). The combined organic layers were washed sequentially with H_2O (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was dissolved in 25 mL of hexanes and Al_2O_3 (Activated, Brockmann I, 2.0 g, 5.0 equivalents by weight) was added and stirred vigorously until TLC showed no aldol adduct was left. The mixture was then filtered and concentrated. Purification by silica gel chromatography afforded **181e** (0.161 g, 43% yield) as a dark red solid, along with recovered **256** (0.040 g, 16% recovery). The yield based on unrecovered starting material was 51%. The stereochemistry of **181e** was confirmed by an NOE study as shown above.

Spectral data for *trans,trans*-**181e**: R_f = 0.13 (hexanes); mp 110–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (s, 3H), 4.76 (s, 3H), 6.76 (d, 1H, J = 16.2 Hz), 6.98 (d, 1H, J = 16.2 Hz), 7.29-7.50 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.51, 66.28, 127.13, 128.85, 128.91, 132.40, 134.59, 136.42, 137.11, 143.57, 216.69, 224.28, 337.66; IR (NaCl) 2053s, 1921vs br, 1536m cm^{-1}; MS (EI) *m/z* (% relative intensity) 378 (M^+, 0.3), 350 (0.2), 322 (1), 294 (0.5), 266 (6), 238 (29), 187 (22), 186 (33), 171 (32), 153 (31), 141 (34), 128 (100), 115 (31), 91 (18), 77 (15), 51 (49). Anal calcd for $C_{18}H_{14}CrO_6$: C, 57.15; H, 3.73. Found: C, 57.41; H, 3.90.



The Preparation of Carbene Complex *trans,trans*-181f.

The vinyl iodide *trans,trans*-**263,** the precursor to **181f,** was prepared using the one-pot hydroboration/iodination[249] sequence as follows. To a solution of 1-((*E*)-pent-1-en-3-ynyl)benzene **262**[250] (0.67 g, 4.7 mmol) in 5 mL of CH_2Cl_2 at 0 °C, $HBBr_2$•SMe_2 (1M in CH_2Cl_2, 4.7 mL, 4.7 mmol) was added dropwise. After the addition was complete, the cold bath was removed and the mixture was allowed to warm to room temperature and stirred for 3 hours. Then the volatiles were removed on a rotary evaporator and the crude borane was added at 0 °C to an aqueous NaOH solution (3N, 8 mL, 5 equivalents) with rapid stirring. After the mixture had been stirred for 30 minutes at 0 °C, 5 mL of ether was added, followed by dropwise addition of I_2 (1.31g, 5.2 mmol) in 15 mL of ether. The reaction mixture was stirred at 0 °C for 30 minutes, followed by warming to room temperature and stirring for an additional 30 minutes. Excess I_2 was then destroyed

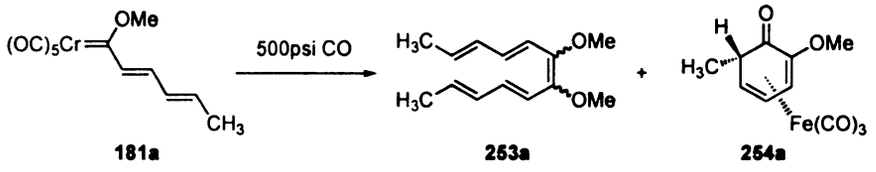
with a few drops of saturated aqueous $Na_2S_2O_3$ solution. The ether layer was separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The residue was subjected to silica gel chromatography (hexanes as the eluent) to give *trans,trans*-**263** (300 mg, 24% yield) as a white solid that was contaminated with a small amount of inseparable impurities, but appeared to be one regioisomer. Some starting enyne was also recovered (106 mg, 16%). The stereochemistry was assigned based on halogen-metal exchange with *n*-BuLi followed by protonation. The resulting *trans,cis*-1-phenylpenta-1,3-diene has NMR data consistent with published data for this compound.[251]

Spectral data for *trans,trans*-**263**: R_f = 0.26 (hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (d, 3H, J = 1.2 Hz), 6.48 (d, 1H, J = 15.0 Hz), 6.83 (dd, 1H, J = 15.0, 10.8 Hz), 6.93 (dd, 1H, J = 10.8, 1.5 Hz), 7.24-7.40 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.26, 97.56, 123.61, 126.49, 127.93, 128.68, 132.78, 136.79, 140.73; MS (EI) *m/z* (% relative intensity) 270 (M^+, 100), 143 (61), 128 (17), 115 (13). Reliable elemental analysis data were not obtained due to the small amount of inseparable impurities.

To a solution of *trans,trans*-**263** (160 mg, 0.60 mmol) in 15 mL of ether at –78 °C was added *t*-BuLi (1.7 M in pentane, 0.71 mL, 1.2 mmol) dropwise. The mixture was then stirred at –78 °C for 2 hours before it was transfered via cannula to $Cr(CO)_6$ (159 mg, 0.72 mmol) in 15 mL of ether at room temperature. The solution was stirred for 3 hours and then cooled to 0 °C. MeOTf (0.12 ml, 1.08 mmol) was added and solution was warmed to room temperature and stirred for 1 hour. The reaction was quenched with aqueous $NaHCO_3$ (10 mL) solution and the organic layer was washed with brine (15

mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel with hexanes to give the carbene complex **181f** as a red solid, contaminated with small amount of impurities. Recrystallication from hexanes at low temperature (–78 °C) afforded pure **181f** (140 mg, 62% yield).

Spectral data for *trans,trans*-**181f**: R_f = 0.10 (hexanes); mp 114–115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96 (s, 3H), 4.66 (s, 3H), 6.89-7.11 (m, 3H), 7.28-7.38 (m, 3H), 7.47-7.50 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.16, 66.39, 123.76, 127.13, 128.82, 128.85, 136.63, 138.23, 139.84, 150.52, 216.76, 223.82, 346.90; IR (NaCl) 2053s, 1917vs, 1904vs cm^{-1}; MS (EI) *m/z* (% relative intensity) 378 (M^+, 0.4), 350 (0.4), 322 (6), 294 (3), 266 (10), 238 (17), 206 (18), 195 (22), 193 (21), 180 (13), 179 (11), 167 (13), 165 (13), 141 (17), 128 (27), 115 (25), 91 (29), 77 (14), 52 (100). Anal calcd for $C_{18}H_{14}CrO_6$: C, 57.15; H, 3.73. Found: C, 57.05; H, 3.67.



181a **253a** **254a**

The Thermolysis of *trans,trans*-181a under 500 psi CO.

A Monel Paar pressure reactor equipped with a magnetically driven mechanical stirrer was flushed with carbon monoxide for a few minutes before it was charged with the carbene complex **181a** (30.2 mg, 0.1 mmol) and 5 mL of benzene. Then the reactor was further flushed with CO for another 2 minutes and filled with 500 psi CO and heated at 80 °C with stirring for 2 hours. The mixture was transfered to a 100-mL round bottom flask and concentrated on a rotary evaporator. The residue was purified by silica gel

chromatography to give **253a** (~6.6 mg, 30%) as a yellowish oil (~1.4:1 mixture of isomers) and **254a** (10.9 mg, 39%) as a yellowish solid.

Spectral data for **253a**: R_f = 0.54 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 1.76-1.80 (m, 6H), 3.59 (s, 3.5H, major isomer), 3.67 (s, 2.5H, minor isomer), 5.72-5.82 (m, 2H), 6.10-6.22 (m, 3H), 6.27-6.46 (m, 3H). This compound was very unstable and other spectral data were not obtained.[252]

Spectral data for **254a**: R_f = 0.14 (10% EtOAc/hexanes); mp 98–99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, 3H, J = 6.6 Hz), 2.30 (q, 1H, J = 6.6 Hz), 2.78 (dt, 1H, J = 6.6, 2.1 Hz), 3.59 (s, 3H), 5.35 (m, 1H), 6.00 (dd, 1H, J = 4.8, 2.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.80, 37.67, 56.95, 61.20, 78.88, 85.37, 110.63, 194.44, 209.60; IR (NaCl) 2054vs, 1981vs br, 1676s cm^{-1}; MS (EI) *m/z* (% relative intensity) 278 (M^+, 3), 250 (8), 222 (47), 194 (25), 179 (100), 164 (26), 162 (23), 134 (20), 95 (22), 83 (17), 56 (53), 41 (18); HRMS-FAB (NBA as the matrix) calcd for $C_{11}H_{11}FeO_5$ (MH^+) *m/z* 278.9956, meas 278.9943. Anal calcd for $C_{11}H_{10}FeO_5$: C, 47.52; H, 3.64. Found: C, 47.34; H, 3.58. The stereochemistry was assigned as syn based on the X-ray structure determination (Appendix 2).

The presence of iron in **254a** was confirmed by SEM/EDS. The analysis was performed using a JEOL JSM-35C scanning electron microscope (SEM) equipped with a Noran energy dispersive spectrometer (EDS). Data were acquired using a 20 kV accelerating voltage and an accumulation time of 60 seconds. The carbene complex **181a** was also subjected to an SEM/EDS analysis which revealed the presence of chromium and the absence of iron. The two spectra are shown in Appendix 3.

For the reactions in the presence of an external source of iron under 500 psi CO, the procedure described above was followed except that one or 1.5 equivalents (as shown in Table 4.1 in the text) of an iron source was also added.

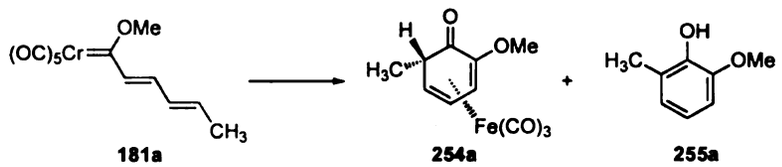
When one equiv of $Fe_3(CO)_{12}$ was present the reaction gave **254a** in 58% yield. The same reaction with 1.5 equiv $Fe_3(CO)_{12}$ afforded a 59% yield of **254a.**

When one equiv of benzylideneacetone iron tricarbonyl ($Fe(CO)_3$(ba)) was present the reaction gave **254a** in 63% yield. The same reaction with 1.5 equiv $Fe(CO)_3$(ba) afforded a 63% yield of **254a** as well.

When one equiv of $Fe_2(CO)_9$ was present the reaction gave **254a** in 89% yield. The same reaction with 1.5 equiv $Fe_2(CO)_9$ afforded the exactly same 89% yield of **254a.**

In each of the above cases, a trace amount (< 5%) of the pentaene **253a** was observed.

General Procedure for the Iron Mediated Carbonylative Cyclization of Carbene Complexes 181 and the Preparation of Iron Tricarbonyl Cyclohexadienone Complexes 254 and Phenols 255: Illustrated for *trans,trans*-Carbene Complex 181a.



181a **254a** **255a**

*Trans,trans-Carbene Complex **181a**.* A 25-mL flask with a threaded Teflon high-vacuum stop-cock was flushed with nitrogen for 10 minutes before it was charged with the carbene complex **181a** (60.4 mg, 0.2 mmol), $Fe_2(CO)_9$ (72.8 mg, 0.2 mmol), and 10

mL of the solvent (THF or benzene in most cases). The mixture was degassed by the freeze-thaw method (–196/25 °C, 3 cycles), back-filled with 1 atm CO (or argon in some cases for the optimization with **181a** in Table 4.2 in the text) at room temperature, sealed and heated at 80 °C until the red color disappeared, indicating all the starting carbene complex was consumed. The mixture was then allowed to cool to room temperature and transferred to a 100-mL round bottom flask and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (5–10% EtOAc/hexanes) to furnish the dienone complex **254a** and the phenol **255a**.

Following the general procedure described above, when THF was used the solvent, after 36 hours, the reaction afforded **254a** (33.9 mg, 61% yield) as a yellowish solid and **255a** (5.5 mg, 20% yield) as a white solid.

Spectral data for **255a**: R_f = 0.26 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3H), 3.85 (s, 3H), 6.69-6.74 (m, 3H); IR (NaCl) 3526s cm^{-1}. The spectral data agree with the data reported in the literature.[253]

*For the optimization of the reaction of **181a*** (Table 4.2 in the text), each was performed on half of the scale that the general procedure indicates.

(1) When benzene was used as the solvent without any iron source and in the presence of 1 atm CO, no detectable amount of **255a** (< 0.5%) was obsereved after 144 hours. In the presence of 1 atm argon a small amount of **255a** (8%) was obtained after 144 hours.

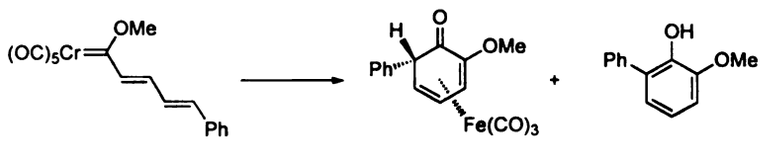
(2) When the reaction was performed in benzene in the presence of $Fe_2(CO)_9$ and 1 atm CO for 18 hours, **254a** (70%) and **255a** (8%) were obtained. The same reaction under 1 atm argon gave **254a** (58%) and **255a** (6%) after 28 hours.

(3) When the reaction was performed in heptane in the presence of $Fe_2(CO)_9$ and 1 atm CO for 36 hours, **254a** (68%) and **255a** (7%) were obtained. The same reaction under 1 atm argon gave **254a** (54%) and **255a** (5%) after 20 hours.

(4) When the reaction was performed in THF in the presence of $Fe_2(CO)_9$ and 1 atm CO for 36 hours, **254a** (61%) and **255a** (20%) were obtained. The same reaction under 1 atm argon gave **254a** (50%) and **255a** (10%) after 20 hours.

(5) When the reaction was performed in CH_3CN in the presence of $Fe_2(CO)_9$ and 1 atm CO for 17 hours, **254a** (68%) and **255a** (12%) were obtained. The same reaction under 1 atm argon gave **254a** (34%) and **255a** (8%) after 20 hours.

(6) When the reaction was performed in benzene in the presence of $Fe(CO)_3$(ba) (benzylidineacetone iron tricarbonyl)[254] (1 equiv) and 1 atm CO for 48 hours, **254a** (60%) and **255a** (7%) were obtained. The same reaction under 1 atm argon gave **254a** (18%) and **255a** (3%) after 7 hours.



181b **254b** **255b**

*Trans,trans-Chromium Carbene Complex **181b**.* A solution of the chromium carbene complex **181b** (0.2 mmol) in THF was reacted with $Fe_2(CO)_9$ according to the general procedure described above for 20 hours. Purification afforded **254b** (5.1 mg, 7.5% yield) as a yellowish solid and **255b** (29.7 mg, 74.3% yield) as a yellowish oil

which solidified in freezer. During silica gel chromatography the complex **254b** was slowly converted to **255b** such that only **255b** could be isolated in the pure form while **254b** was always contaminated with a small amount of **255b**. The dienone complex **254b** could be converted to **255b** in high yield (96-98%) simply by stirring with silica gel in CH_2Cl_2 in open air for a couple of days (this gives a total of 81% yield of **255b**). If the crude mixture was stirred under the same conditions until the conversion of **254b** to **255b** was complete (2–3 d), a 78% yield of **255b** was obtained after chromatography. The same reaction in benzene for 45 h gave **254b** in 5% yield and **255b** in 70% yield.

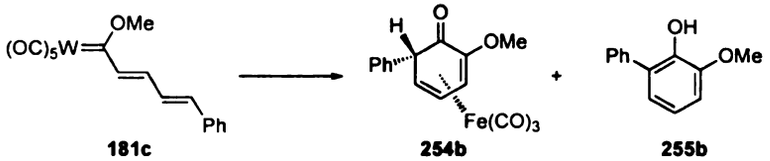
Spectral data for **254b**: R_f = 0.10 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.10 (dm, 1H, J = 6.6 Hz), 3.55 (s, 1H), 3.58 (s, 3H), 5.50 (m, 1H), 6.07 (dd, 1H, J = 4.8, 2.1 Hz) 7.28-7.41 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.70, 53.68, 61.30, 78.97, 85.53, 111.08, 127.13, 128.13, 128.64, 136.57, 191.68, 209.26; IR (NaCl) 2054vs, 1983vs br, 1682s cm^{-1}; MS (EI) *m/z* (% relative intensity) 340 (M^+, 0.7), 312 (2), 284 (41) 256 (37), 226 (87), 208 (34), 200 (21), 18 (20), 157 (35), 141 (42), 129 (100), 127 (53), 115 (37), 84 (24), 77 (13), 57 (27), 56 (62), 51 (11).

Spectral data for **255b**: R_f = 0.18 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3H), 5.85 (s, 1H), 6.84-6.98 (m, 3H), 7.29-7.34 (m, 1H), 7.42 (t, 2H, J = 7.5 Hz), 7.59-7.62 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.14, 109.59, 119.66, 122.68, 127.10, 127.66, 128.18, 129.16, 137.67, 142.75, 146.78; IR (NaCl) 3509br, 2938m, 1590m, 1474s, 1433s, 1269s cm^{-1}; MS (EI) *m/z* (% relative intensity) 200 (M^+, 100), 185 (30), 157 (11). Anal calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.60; H, 5.92.

For the control experiments in the absence of $Fe_2(CO)_9$: following the general procedure described above, the reaction of **181b** (0.2 mmol) in benzene under 1 atm argon for 96 h without any iron source gave **255b** (~ 7%) along with a 28% recovery of **181b**. The same reaction under 1 atm CO for 96 h gave trace (< 1%) of **255b** along with a 83% recovery of **181b**.

The reaction of **181b** (0.2 mmol) in THF under 1 atm argon for 96 h without any iron source gave trace (< 1%) of **255b**. The same reaction under 1 atm CO for 96 h gave trace (< 3%) of **255b**.

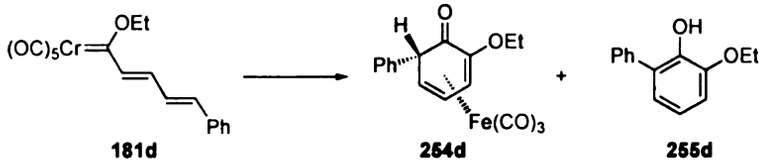
For the reactions under photochemical conditions: A solution of **181b** (182 mg, 0.5 mmol) in 125 mL of dry THF in a quartz photoreactor was purged with nitrogen for 15 min and then with CO for another 15 min. The solution was photolyzed with a 450 W medium pressure mercury lamp for 14 h while slowly sparging with CO. The resulting yellowish solution was allowed to stand over night under 1 atm CO before it was concentrated. Purification by silica gel column chromatography (5–10% EtOAc/hexanes) afforded only a small amount of **255b** (~ 3 mg, 4.3% yield).



181c **254b** **255b**

*Trans,trans-Tungsten Carbene Complex **181c**.* A solution of the tungsten carbene complex **181c** in THF was reacted with was reacted with $Fe_2(CO)_9$ for 72 h following the general procedure described above. Purification gave **254b** (7.0 mg, 10% yield) as a yellowish solid and **255b** (32.7 mg, 82% yield) as a yellowish oil which solidified in freezer. The same reaction in benzene for 24 h gave **254b** in 30% yield and **255b** in 45%

yield. Spectral data for **254b** and **255b** matched those obtained from the reaction of the chromium complex **181b**.



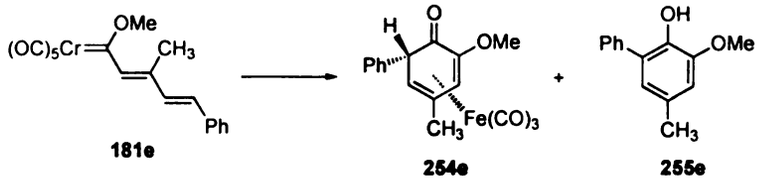
181d **254d** **255d**

*Trans,trans-Chromium Carbene Complex **181d**.* A solution of the ethoxy carbene complex **181d** in THF was reacted with $Fe_2(CO)_9$ for 24 h following the general procedure described above. Purification afforded **254d** (11.0 mg, 16% yield) as a yellowish solid and **255d** (30.0 mg, 70% yield) as a yellowish oil which solidified in freezer. During the silica gel chromatography, **254d** was slowly converted to **255d** such that only **255d** could be isolated in the pure form while **254d** was contaminated with a small amount of **255d**. The same reaction in benzene after 36 h gave **254d** in 20% yield and **255d** in 61% yield.

Spectral data for **254d**: R_f = 0.12 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, 3H, *J* = 6.9 Hz), 3.08-3.12 (m, 1H), 3.14-3.22 (m, 1H), 3.56 (s, 1H), 4.33-4.43 (m, 1H), 5.50 (ddd, 1H, *J* = 6.6, 4.8, 0.9 Hz), 6.08 (dd, 1H, *J* = 4.8, 2.1 Hz), 7.27-7.41 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.36, 46.74, 53.62, 70.07, 79.02, 85.78, 110.37, 127.08, 128.09, 128.64, 136.61, 191.75, 209.42; IR (NaCl) 2054s, 1987vs, 1682m cm^{-1}; MS (EI) *m/z* (% relative intensity) 354 (M^+, 0.3), 326 (1), 298 (54), 270 (65), 226 (100), 214 (11), 208 (28), 185 (15), 164 (39), 152 (24), 133 (41), 128 (43), 78 (27), 56 (41).

Spectral data for **255d**: R_f = 0.25 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (t, 3H, *J* = 7.2 Hz), 4.16 (q, 2 H, *J* = 7.2 Hz), 5.93 (s, 1H), 6.83-6.98 (m,

3H), 7.29-7.35 (m, 1H), 7.39-7.45 (m, 2H), 7.59-7.63 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.992, 64.74, 110.52, 119.60, 122.57, 127.03, 127.60, 128.14, 129.15, 137.78, 142.92, 146.02; IR (NaCl) 3515br, 2980m, 1470s, 1437m cm^{-1}; MS (EI) *m/z* (% relative intensity) 214 (M^+, 80), 186 (100), 157 (10), 139 (12), 128 (36), 115 (19), 102 (12), 77 (23). Anal calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.46; H, 6.45.

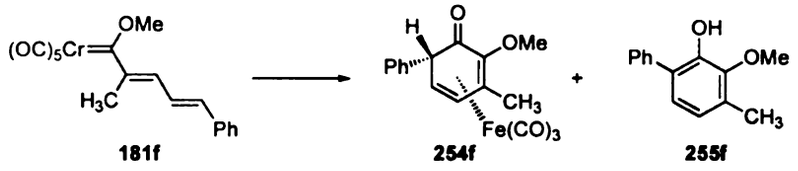


*Trans,trans-Chromium Carbene Complex **181e**.* A solution of the carbene complex **181e** in benzene was reacted with $Fe_2(CO)_9$ for 36 h following the general procedure described above. Purification afforded **254e** (34.9 mg, 49% yield) as a yellowish solid and **255e** (17.2 mg, 40% yield) as a yellowish oil which solidified in freezer. During the silica gel chromatography, **254e** was slowly converted to **255e** such that only **255e** could be isolated in the pure form while **254e** was contaminated with a small amount of **255e**. The same reaction in THF after 36 h gave **254e** in 16% yield and **255e** in 59% yield.

Spectral data for **254e**: R_f = 0.12 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.72 (s, 3H), 3.10 (dd, 1H, *J* = 2.4, 1.5 Hz), 3.56 (s, 1H), 3.57 (s, 3H), 5.98 (d, 1H, *J* = 2.4 Hz), 7.27-7.40 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.36, 46.63, 56.96, 61.16, 85.80, 96.83, 108.16, 127.04, 128.08, 128.63, 136.66, 192.25, 209.33; IR (NaCl) 2050vs, 1979vs br, 1684s cm^{-1}; MS (EI) *m/z* (% relative intensity) 354 (M^+, 0.2), 326

(0.5), 298 (22), 270 (42), 240 (100), 222 (18), 184 (10), 165 (21), 127 (30), 84 (13), 56 (35).

Spectral data for **255e**: R_f = 0.22 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.90 (s, 3H), 5.66 (s, 1H), 6.68 (s, 1H), 6.76 (s, 1H), 7.27-7.32 (m, 1H), 7.37-7,43 (m, 2H), 7.56-7.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.13, 56.13, 110.61, 122.83, 127.02, 127.24, 128.16, 129.04, 129.12, 137.84, 140.44, 146.56; IR (NaCl) 3517br, 2940m, 1601m, 1503s, 1487s cm^{-1}; MS (EI) *m/z* (% relative intensity) 214 (M^+, 100), 199 (45), 184 (47), 153 (12), 128 (25), 115 (13). Anal calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.12; H, 6.67.

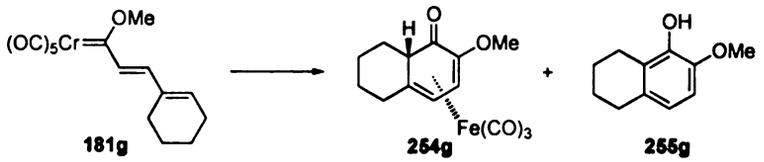


*Trans,trans-Chromium Carbene Complex **181f**.* A solution of the carbene complex **181f** in benzene was reacted with $Fe_2(CO)_9$ for 10 h following the general procedure described above. Purification gave **254f** (51.1 mg, 72% yield) as a yellowish solid and **255f** (6.4 mg, 15% yield) as a yellowish oil which solidified in freezer. During silica gel chromatography, **254f** was slowly converted to **255f**. Thus only **255f** could be isolated in the pure form while **254f** was contaminated with a small amount of **255f**. The same reaction in THF for 36 h gave 44% yield of **254f** and 36% yield of **255f**.

Spectral data for **254f**: R_f = 0.15 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H), 2.94 (d, 1H, *J* = 6.3 Hz), 3.52 (s, 1H), 3.61 (s, 3H), 5.47 (d, 1H, *J* = 6.3 Hz), 7.27-7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.24, 46.58, 49.71, 61.43, 80.26, 103.10, 111.75, 127.01, 128.08, 128.61, 136.87, 192.75, 209.47; IR (NaCl)

2051vs, 1979vs br, 1682s cm^{-1}; MS (EI) *m/z* (% relative intensity) 354 (M^+, 0.3), 326 (1), 298 (41), 270 (44), 240 (100), 222 (31), 184 (14), 178 (14), 166 (22), 153 (11), 141 (16), 128 (21), 115 (20), 56 (21).

Spectral data for **255f**: R_f = 0.18 (10% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.83 (s, 3H), 5.86 (s, 1H), 6.60 (d, 1H, *J* = 8.1 Hz), 7.01 (d, 1H, *J* = 8.1 Hz), 7.28-7.34 (m, 1H), 7.39-7.44 (m, 2H), 7.56-7.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.84, 60.61, 122.10, 125.40, 126.31, 127.03, 128.29, 129.02, 129.79, 137.64, 145.63, 146.00; IR (NaCl) 3497br, 2940m, 1601m, 1487m, 1462m, 1412s cm^{-1}; MS (EI) *m/z* (% relative intensity) 214 (M^+, 100), 200 (26), 199 (10), 141(3), 115(3). Anal calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.22; H, 6.34.

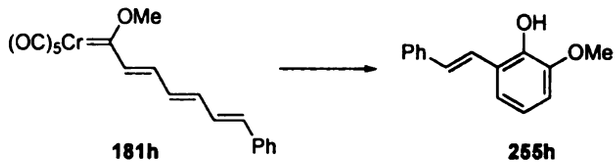


*Trans-Chromium Carbene Complex **181g**.* A solution of the carbene complex **181g** in benzene was reacted with $Fe_2(CO)_9$ for 24 h following the general procedure described above. Purification afforded **254g** (54.5 mg, 86% yield) as a yellowish fluffy solid and **255g** (~ 0.7 mg, 2% yield) as a white solid. The same reaction in THF for 72 h gave 85% yield of **254g** and 6% yield of **255g**.

Spectral data for **254g**: R_f = 0.10 (10% EtOAc/hexanes); mp 154–155 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15-1.58 (m, 4H), 1.77-1.99 (m, 3H), 2.14-2.24 (m, 2H), 3.56 (s, 3H), 5.09 (d, 1H, *J* = 4.5 Hz), 5.91 (d, 1H, *J* = 4.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.84, 25.23, 28.49, 34.94, 43.92, 61.00, 75.66, 79.98, 82.30, 109.21, 194.87, 210.42; IR (NaCl) 2056s, 1989vs br, 1669s cm^{-1}; MS (EI) *m/z* (% relative intensity) 318

(M^+, 2), 290 (3), 262 (46), 234 (36), 219 (100), 200 (24), 177 (11), 115 (13), 91 (14), 77 (11), 55 (18). Anal calcd for $C_{14}H_{14}FeO_5$: C, 52.86; H, 4.44. Found: C, 52.98; H, 4.54.

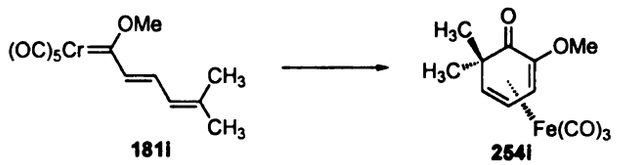
Spectral data for **255g**: R_f = 0.35 (10% EtOAc/hexanes); mp = 92–93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72-1.77 (m, 4H), 2.66-2.70 (m, 4H), 3.83 (s, 3H), 5.63 (s, 1H), 6.56 (d, 1H, J = 8.1 Hz), 6.65 (d, 1H, J = 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.59, 22.97, 23.06, 29.05, 56.15, 108.08, 119.42, 123.63, 130.80, 142.98, 143.75; IR (NaCl) 3407br, 2924m, 1495m, 1271s, 1090m cm^{-1}; MS (EI) *m/z* (% relative intensity) 178 (M^+, 100), 163 (20), 150 (35), 146 (32), 145 (52), 135 (56), 117 (47), 115 (43), 107 (43), 91 (43), 77 (41), 55 (24), 39 (42). Anal calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.18; H, 8.28.



*Trans,trans,trans-Carbene Complex **181h***. A solution of the carbene complex **181h** in benzene was reacted with $Fe_2(CO)_9$ for 8 h following the general procedure described above. Purification afforded **255h** (33.2 mg, 73% yield) as a yellowish solid. The same reaction in THF for 10 h gave a 70% yield of **255h**.

Spectral data for **255h**: R_f = 0.14 (10% EtOAc/hexanes); mp 72-73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3H), 5.96 (s, 1H), 6.75 (dd, 1H, J = 8.1, 1.8 Hz), 6.83 (t, 1H, J = 8.1 Hz), 7.14-7.24 (m, 3H), 7.30-7.45 (m, 3H), 7.51-7.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.10, 109.40, 118.80, 119.53, 122.97, 123.73, 126.55, 127.37, 128.57, 129.38, 137.88, 143.48, 146.73; IR (NaCl) 3507br, 3023m, 2939m, 1588m, 1476s, 1265s cm^{-1}; MS (EI) *m/z* (% relative intensity) 226 (M^+, 100), 211 (11), 194 (12),

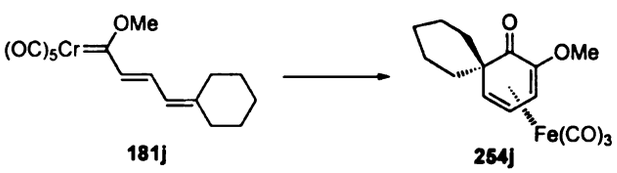
193 (24), 165 (66), 152 (20), 115 (15), 82 (21), 76 (26), 63 (12). Anal calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.42; H, 6.37.



181i **254i**

*Trans-Chromium Carbene Complex **181i**.* A solution of the carbene complex **181i** in THF was reacted with $Fe_2(CO)_9$ for 48 h following the general procedure described above. Purification afforded **254i** (47.5 mg, 81% yield) as a yellowish solid. The same reaction in benzene for 72 h gave a 76% yield of **254i**.

Spectral data for **254i**: R_f = 0.22 (10% EtOAc/hexanes); mp 34–35 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 0.91 (s, 3H), 1.26 (s, 3H), 2.87 (dd, *J* = 6.6, 2.1 Hz, 1H), 3.59 (s, 3H), 5.23 (dd, *J* = 6.6, 4.8 Hz, 1H), 5.99 (dd, *J* = 4.8, 2.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 25.8, 33.7, 41.4, 61.2, 63.3, 77.8, 85.1, 108.9, 197.2, 209.6; IR (cm^{-1}): 2054vs, 1981vs br, 1678s; MS (EI) m/z (relative intensity) 292 (M^+, 4), 264 (11), 236 (56), 208 (32), 193 (100), 178 (90), 176 (31), 162 (33), 121 (15), 109 (19), 96 (15), 84 (20), 81 (18), 79 (15), 56 (28); Anal. Calcd for $C_{12}H_{12}FeO_5$: C, 49.35; H, 4.14. Found: C, 49.37; H, 4.05.

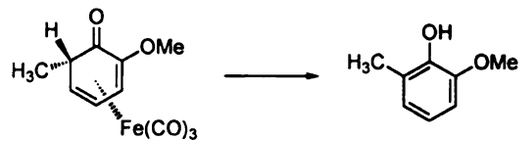


181j **254j**

*Trans-Chromium Carbene Complex **181j**.* A solution of the carbene complex **181j** in THF was reacted with $Fe_2(CO)_9$ for 24 h following the general procedure

described above. Purification afforded **254j** (56.6 mg, 85% yield) as a yellow oil. The same reaction in benzene for 72 h gave an 81% yield of **254j**.

Spectral data for **254j**: R_f = 0.24 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03-1.07 (m, 1H), 1.22-1.28 (m, 1H), 1.31-1.45 (m, 5H), 1.53-1.54 (m, 1H), 1.75 (dt, 1H, *J* = 13.2, 4.2 Hz), 1.92 (td, 1H, *J* = 13.2, 4.2 Hz), 3.18 (dd, 1H, *J* = 6.6, 5.0 Hz), 3.59 (s, 3H), 5.28 (dd, 1H, *J* = 6.6, 5.0 Hz), 5.98 (dd, 1H, *J* = 5.0, 2.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.09, 21.61, 25.61, 32.83, 43.09, 44.57, 59.22, 61.18, 77.43, 85.18, 109.01, 196.79, 209.61; IR (NaCl) 2932m, 2054vs, 1979vs br, 1680s cm^{-1}; MS (EI) *m/z* (% relative intensity) 332 (M^+, 2), 304 (11), 276 (100), 248 (62), 233 (95), 228 (16), 216 (27), 177 (70), 95 (31), 91 (26), 56 (75), 41 (20). Anal calcd for $C_{15}H_{16}FeO_5$: C, 54.24; H, 4.86. Found: C, 54.64; H, 4.93.

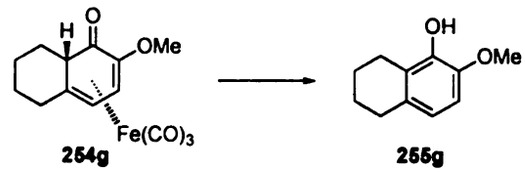


254a **255a**

Demetalation of the Iron Tricarbonyl Complex 254a.

The iron tricarbonyl complexes of the type **254** not having a phenyl group on the sp^3-ring carbon are quite robust and are not converted to the phenols **255** on silica gel. A 25-mL round bottom flask was charged with **254a** (27.8 mg, 0.1 mmol), 5 mL of Et_3N and 0.5 mL of H_2O. This mixture was stirred at room temperature under argon for 5 hours. Then Et_3N was removed on a rotary evaporator and 10 mL of ether was added followed by 10 mL of saturated aqueous NH_4Cl solution. The organic phase was separated and the aqueous layer was further extracted with ether (2x10 mL). The combined ether layer was dried over Na_2SO_4 and concentrated. The residue was loaded

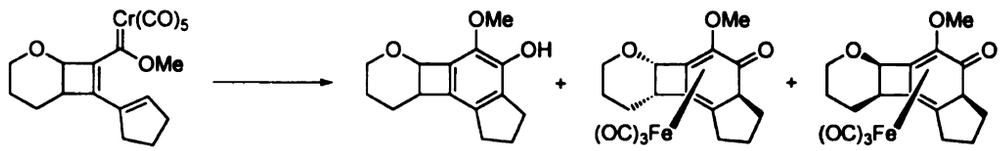
onto a silica gel chromatography to afford **255a** (12.5 mg, 91% yield) as a white solid. Alternatively, when a solution of **254a** (19.5 mg, 0.07 mmol) in 5 mL of pyridine was refluxed under argon for 12 hours, phenol **255a** was obtained in 82% yield (7.9 mg).



254g **255g**

Demetalation of the Iron Tricarbonyl Complex 254g.

Following the procedure described above for the demetalation of **254a**, after stirring with Et_3N/H_2O for 20 h, the complex **254g** (31.8 mg, 0.1 mmol) was converted to the phenol **255g** (16.0 mg, 90% yield) as a white solid.



264 **265** **266a** **266b**

The Thermolysis of Complex 264 in the Presence or Absence of $Fe_2(CO)_9$.

General Procedure: A 25-mL flask with a threaded Teflon high-vacuum stop-cock was charged with the carbene complex **264**[205] (40.1 mg, 0.1 mmol), $Fe_2(CO)_9$ (36.4 mg, 0.1 mmol), and 5 mL of THF or benzene. The mixture was degassed by the freeze-thaw method (–196/25 °C, 3 cycles), back-filled with 1 atm CO or argon at room temperature, sealed and heated at 80 °C until the red color disappeared, indicating all the starting carbene complex was consumed. The mixture was then allowed to cool to room temperature and transferred to a 100-mL round bottom flask and concentrated under

reduced pressure. The residue was subjected to silica gel chromatography (5–10% EtOAc/hexanes) to furnish the phenol **265** and the iron complexes **266a** and **266b**.

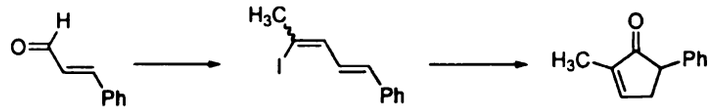
Following the general procedure described above, when the reaction was performed in THF under 1 atm CO for 48 h, **265** (12.0 mg, 49%), **266a** (4.0 mg, 10%) and **266b** (3.6 mg, 9%) were obtained. The stereochemistry was tentatively assigned as anti for **266a** (presumably less polar) and syn for **266b**. During the silica gel chromatography, **266a/b** were slowly converted to **265** such that only **265** could be isolated in the pure form while **266a/b** were contaminated with a small amount of **72.** The same reaction in benzene for 96 h gave **265** (13.9 mg, 57%) and **266a** (2.6 mg, 7%) along with trace (< 2%) of **266b**.

Spectral data for **265**: R_f = 0.14 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41-1.60 (m, 2H), 1.81-1.91 (m, 1H), 2.02-2.14 (m, 3H), 2.68 (t, 2H, J = 7.5 Hz), 2.83 (t, 2H, J = 7.5 Hz), 3.55 (q, 1H, J = 5.1 Hz), 3.68-3.85 (m, 2H), 3.97 (s, 3H), 5.17 (d, 1H, J = 5.1 Hz), 5.35 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.61, 22.85, 26.18, 29.01, 29.55, 41.64, 57.87, 61.40, 72.91, 126.13, 132.44, 132.62, 132.76, 140.38, 140.84. The spectral data are consistent with the reported data for this compound.[205]

Spectral data for **266a**: R_f = 0.20 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72-2.09 (m, 9H), 2.20-2.25 (m, 1H), 2.57 (td, 1H, J = 4.8, 0.9 Hz), 3.67-3.71 (m, 1H), 3.76 (s, 3H), 3.89-3.92 (m, 1H), 4.08-4.14 (m, 1H), 5.65 (d, 1H, J = 2.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.37, 22.83, 25.03, 26.65, 30.56, 45.34, 49.92, 59.05, 62.01, 74.13, 77.49, 99.60, 101.50, 112.97, 184.23, 209.72; IR (NaCl) 2041s, 1970vs, 1669m cm^{-1}; MS (EI) *m/z* (% relative intensity) 386 (M^+, 1), 358 (2), 330 (31), 302 (3), 272 (100), 257 (17), 246 (11), 240 (38), 231 (14), 149 (11), 115 (17), 91 (16), 56 (22).

Spectral data for **266b**: R_f = 0.08 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.03 (m, 9H), 2.17-2.22 (m, 1H), 2.47-2.50 (m, 1H), 3.57 (td, 1H, J = 4.5, 3.3 Hz), 3.71 (s, 3H), 3.77-3.81 (m, 1H), 4.05-4.10 (m, 1H), 5.15 (d, 1H, J = 3.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.62, 25.17, 26.22, 26.59, 30.71, 41.82, 50.11, 59.03, 61.39, 64.14, 71.71, 71.96, 103.78, 109.80, 185.97, 210.27; IR (NaCl) 2041s, 1968vs, 1669m cm^{-1}; MS (EI) *m/z* (% relative intensity) 386 (M^+, 1), 358 (1), 330 (29), 302 (2), 272 (75), 246 (14), 240 (28), 231 (20), 149 (18), 121 (21), 111 (21), 97 (27), 95 (22), 83 (31), 71 (76), 69 (47), 57 (100), 43 (34).

For the reactions that were carried out in the absence of $Fe_2(CO)_9$, the general procedure described above was followed except that none of the iron source was added. When THF was used as the solvent under 1 atm of *argon* without any iron source, after 10 h, the reaction gave **265** (9.8 mg, 40%) as a white solid. The same reaction under 1 atm CO afforded **265** in 42% yield (10.3 mg).



260a **267** (*Z*/*E* = 10 : 1) **268**

Preparation of Dienyl Iodide *cis,trans*-267 and its Conversion to Cyclopentenone 268 via the *cis,trans*-Carbene Complex 181f.

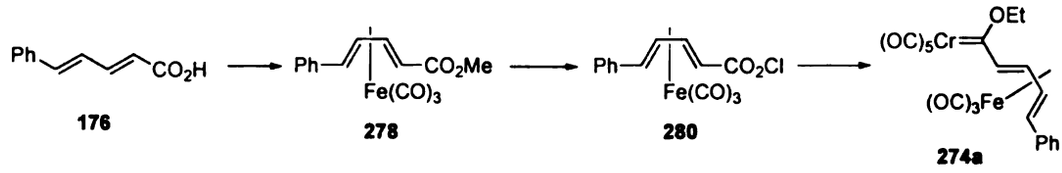
The iodide *cis,trans*-**267** was prepared by a procedure reported by Zhao for related compounds.[255] To a stirred suspension of (ethyl)triphenylphosphonium iodide (3.36 g, 8.0 mmol) in 40 mL THF was added *n*-BuLi (1.6 M in hexane, 5.0 mL, 8.0 mmol) at room temperature. After the disappearance of the solid material, the solution

was transferred via cannula to a flask with iodine (1.83 g, 7.2 mmol) in 80 mL of THF at –78 °C. The resulting suspension was vigorously stirred for 5 minutes and warmed to –20 °C, then sodium bis(trimethylsilyl)amide (1M in THF, 6.8 mL, 6.8 mmol) was added to produce a red solution and the mixture was stirred for 5 minutes. *Trans*-cinnamaldehyde **260a** (0.85 mL, 6.7 mmol) was added and the solution was stirred for 10 minutes. The reaction was quenched with saturated aqueous NH_4Cl solution (100 mL) and diluted with ether (100 mL). The mixture was filtered through a short pad of Celite. The organic layer was separated and the aqeous phase was further extracted with ether (2 x 50 mL). The combined organic layers were washed sequentially with saturated aqueous NH_4Cl solution (100 mL), H_2O (100 mL) and brine (100 mL) and then dried with anhydrous $MgSO_4$ and concentrated. Silica gel chromatography (hexanes as the eluent) afforded *cis,trans*-**267** (1.17 g, 65% yield) as a white solid (Z/E = 10:1). The stereochemistry was assigned based on halogen-metal exchange with *n*-BuLi followed by protonation. The resulting mixture of *trans,trans*-1-phenylpenta-1,3-diene and *trans,cis*-1-phenylpenta-1,3-diene have NMR data consistent with published data for these two compounds.[251]

Spectral data for *cis,trans*-**267**: R_f = 0.26 (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.627-2.630 (m, 3H), 6.48 (dq, 1H, J = 5.7, 0.3 Hz), 6.67 (d, 1H, J = 9.3 Hz), 6.80 (dd, 1H, J = 9.3, 5.7 Hz) 7.22-7.25 (m, 1H), 7.30-7.33 (m, 2H), 7.42-7.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.12, 102.51, 126.59, 127.94, 128.65, 131.04, 134.27, 134.39, 136.99; MS (EI) *m/z* (% relative intensity) 270 (M^+, 100), 143 (70), 141 (25), 128 (68), 127 (17), 115 (25). Anal calcd for $C_{11}H_{11}I$: C, 48.91; H, 4.10. Found: C, 48.88; H, 4.11.

To a solution of *cis,trans*-**267** (0.37 g, 1.37 mmol, Z/E = 10:1) in 30 mL of THF was added two equivalents of *t*-BuLi (1.7 M in pentane, 1.61 mL, 2.74 mmol) dropwise at -78 °C. The mixture was stirred for 2 hours at this temperature before it was transferred via cannula to a solution of $Cr(CO)_6$ (0.33 g, 1.51 mmol) in 30 mL of THF at room temperature and stirred for 2 hours. Then MeOTf (0.28 mL, 2.47 mmol) was added at 0 °C and stirred for 30 minutes. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with ether (3 x 30 mL). The combined ether extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The residue was subjected to silica gel chromatography (0-10% EtOAc/hexanes) to afford cyclopentenone **268** (120 mg, 51% yield) as a colorless oil, along with a small amount of carbene complex *trans,trans*-**181f** (from the small amount of the minor *E*-isomer of the starting material).

Spectral data for **268**: R_f = 0.16 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82 (d (showing additional splitting, 3H), J = 2.4 Hz), 2.64 (dm, 1H, J = 18.9 Hz), 3.08 (dm (m shows 8 lines), 1H, J = 18.9 Hz), 3.54 (dd, 1H, J = 6.9, 2.4 Hz), 7.10-7.43 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.41, 36.38, 50.98, 126.74, 127.53, 128.68, 139.76, 141.04, 157.04, 208.93; IR (NaCl) 3029m, 2923m, 1705s, 1638m, 1495m cm^{-1}; MS (EI) *m/z* (% relative intensity) 172 (M^+, 100), 129(11), 1128 (20), 115(5), 104 (6), 103 (6). The ^{1}H NMR data of **268** are consistent with those reported for this compound.[256] The proton on the methylene that is *trans* to the phenyl group of **268** shows a particularly characteristic 8-line pattern.[256]



The Preparation of Carbene Complex 274a.

A solution of **176**[257] (1.75 g, 10 mmol) in 20 mL methanol was added 0.5 mL of concentrated H_2SO_4, and the mixture was exposed to ultrasound for 4 h. The reaction was worked up by adding 25 mL of water and the product was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were washed successively with 10% $NaHCO_3$ aqueous solution and brine, dried with anhydrous $MgSO_4$ and concentrated to give analytically pure ester **277** (1.76 g, 94%).

Spectral data for **277**: R_f = 0.30 (10% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 3H), 5.97 (d, 1H, J = 15.3 Hz), 6.85-6.87 (m, 2H), 7.28-7.36 (m, 3H), 7.39-7.47 (m, 3H). The spectral data are consistent with the reported data for this compound.[258]

To a dry 100 mL flask under argon was added **277** (1.74 g, 9.25 mmol), $Fe_2(CO)_9$ (3.54 g, 9.72 mmol) and degassed toluene (20 mL). The mixture was heated at 55 °C for 15 h before it was filtered through a short pad of Celite. After the removal of the solvent, the residue was subject to silica gel column (5% EtOAc/hexanes) to give **278** (1.67 g, 54%) as a yellow solid, along with recovery of **277** (0.52 g, 30%). The yield based on unrecovered **277** was 79%.

Spectral data for **278**: R_f = 0.26 (10% EtOAc/hexanes); mp 115-116 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (dm, 1H, J = 7.2 Hz), 2.35 (dm, 1H, J = 8.7 Hz), 3.67 (s, 3H), 5.88-5.96 (m, 2H), 7.17-7.28 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.47, 51.65, 82.35, 83.10, 126.23, 127.07, 128.75, 138.56, 172.48, 208.82 (br); IR (NaCl) 2054s,

1987vs, 1713m cm^{-1}; MS (EI) *m/z* (% relative intensity) 328 (M^+, 2), 300 (6), 272 (21), 244 (50), 214 (31), 186 (29), 184 (65), 128 (100), 127 (62), 115 (12), 81 (11), 77 (12), 57 (40), 56 (50). Anal calcd for $C_{15}H_{12}FeO_5$: C, 54.91; H, 3.69. Found: C, 55.06; H, 3.79.

A solution of **278** (0.60 g, 1.83 mmol) in 10 mL of CH_3OH under argon was added 10 mL of 30% KOH aqueous solution and 10 mL of THF. The mixture was stirred at room temperature for 8 h before it was acidified with 10% HCl solution to a pH of about 2 with external cooling. Extraction with ether (3 x 30 mL) followed by drying with Na_2SO_4, and concentration gave a yellow solid. The product was purified by dissolving it in a 30% NaOH solution, washing several times with ether, and then acidifying with 10% HCl solution. The organic layer was separated and the aqueous phase was further extracted with ether (3 x 20 mL). The combined organic phase was dried with Na_2SO_4, and concentrated to give a pure yellow crystalline solid **279** in 92% yield (0.53 g).

Spectral data for **279**: mp 195 °C (dec); ^1H NMR (300 MHz, $CDCl_3$ with drops of DMSO-d_6) δ 1.18 (dm, 1H, *J* = 7.5 Hz), 2.20 (dm, 1H, J = 8.7), 5.74-5.81 (m, 2H), 6.99-7.27 (m, 5H), acid OH not observed; ^{13}C NMR (125 MHz, $CDCl_3$) δ 46.20, 62.00, 81.98, 83.33, 125.92, 126.62, 128.39, 138.46, 173.45, 209.26 (br); IR (NaCl) 2002s, 1975vs, 1669s cm^{-1}; MS (EI) *m/z* (% relative intensity) 314 (M^+, 1), 286 (1), 258 (2), 230 (8), 184 (9), 174 (11), 135 (20), 129 (89), 128 (100), 117 (40), 115 (47), 107 (38), 105 (22), 97 (26), 95 (18), 91 (49), 77 (35), 69 (22), 55 (20).

To a stirred solution of **279** (0.50 g, 1.59 mmol) in 10 mL benzene at room temperature as added oxalyl chloride (0.63 mL, 7.16 mmol), and the mixture was stirred under argon for 5 h. The volatiles were removed on a rotary evaporator to give crude acid chloride **280** (0.55 g, 99%) which was used directly for the next step.

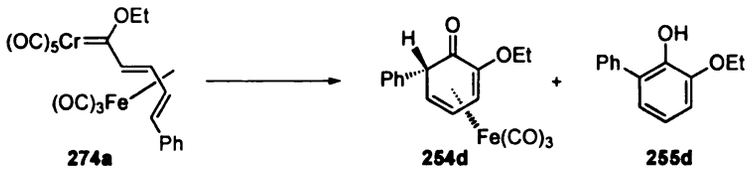
Spectral data for **280**: ^{1}H NMR (300 MHz, $CDCl_3$ with drops of DMSO-d_6) δ 1.55 (d, 1H, J = 6.9 Hz), 2.62 (d, 1H, J = 8.7 Hz), 5.90-5.99 (m, 2H), 7.22-7.38 (m, 5H).

To a 100-mL Schlenk flask was added graphite powder (0.37 g, 30.81 mmol, 19.5 equiv), and the flask was then placed in an oil bath and heated to 160 °C under vacuum. During this time of heating, the freshly cut potassium metal (0.15 g, 3.84 mmol, 2.43 equiv) was rinsed in dry hexane and added portion-wise to the heated flask while stirring and under a continuous flow of argon. (Note: It is important that either good stirring and/or occasional manual shaking of the flask is maintained throughout the heating process to ensure complete intercalation of the potassium metal into the graphite layers. It is also desirable to open the flask under a flow of argon and scrape the melted potassium off the wall of the flask and the surface of the stir bar.) The solid mixture was kept at 160 °C with stirring under argon atmosphere until the color of the powder turned from black to bronze, indicative of the formation of C_8K. Total heating time once the powder had turned bronze was about 35 min. The solid was then allowed to cool to room temperature and 15 mL of dry THF was added under a positive flow of argon. The bronze suspension was cooled to –78 °C and chromium hexacarbonyl (0.38 g, 1.74 mmol, 1.1 equiv) was added in one portion. The flask was closed under argon and the dark suspension was allowed to warm to 0 °C where it was stirred for 1.5 h, during which time the color turned from bronze-black to a thick slurry of silvery green in a yellow-green solution. (It was ready to use immediately or could be stored in freezer for days.)

After cooling back down to –78 °C, a solution of **280** (0.55g, 1.58 mmol, 1 equiv) in 10 ml of THF was added slowly and the reaction mixture was then gradually warmed

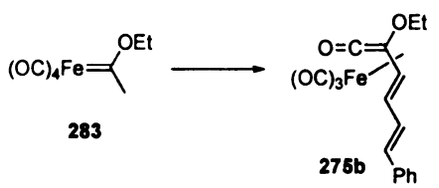
to room temperature and stirred at this temperature for at least 3 h. The black suspension was then filtered on a sufficiently large coarse fritted funnel packed with Celite, rinsing with either dry THF or ether. The solvent of the filtrate was then removed on a rotavopor and the residue was placed on high vaccuum for 20 min. The resulting potassium acylate was dissolved 20 ml of CH_2Cl_2, and the mixture was cooled to 0 °C. EtOTf (0.31 mL, 2.37 mmol, 1.5 equiv) was added slowly and the solution was stirred for 30 min before being quenched with sat. $NaHCO_3$ solution (20 mL). The organic layer was separated and the aqueous phase was further extracted with CH_2Cl_2 until all the red color was removed. The combined organic extract was washed with brine and dried with Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatography using 0-5% EtOAc/hexanes as the eluent afforded **274a** (0.23 g, 28%) as a dark red solid.

Spectral data for **274a**: R_f = 0.06 (hexanes); mp 115 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (t, 3H, J = 7.2 Hz), 2.81 (d, 1H, J = 8.4 Hz), 2.84 (d, 1H, J = 9.99 Hz), 4.80-4.97 (m, 2H), 5.75 (ddd, 1H, J = 8.4, 5.1, 1.0 Hz), 5.90 (dd, 1H, J = 9.9, 5.1 Hz), 7.20-7.29 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.72, 63.32, 73.16, 76.04, 77.41, 82.60, 126.46, 127.54, 128.98, 137.92, 209.04 (br), 216.84, 223.65, 335.19; IR (NaCl) 2066s, 2045vs, 2000s, 1923vs cm^{-1}; MS (EI) *m/z* (% relative intensity) 518 (M^+, 1), 503 (3), 490 (3), 462 (2), 434 (8), 429 (11), 415 (3), 406 (13), 401 (3), 382 (5), 378 (21), 355 (19), 350 (9), 338 (16), 322 (18), 294 (78), 281 (21), 270 (29), 266 (21), 265 (80), 250 (70), 227 (23), 221 (27), 207 (19), 197 (22), 193 (20), 192 (20), 184 (22), 157 (13), 147 (35), 142 (20), 141 (53), 129 (42), 128 (43), 115 (47), 109 (28), 108 (30), 107 (26), 105 (20), 97 (25), 91 (15), 83 (41), 80 (30), 69 (39), 57 (51), 55 (47), 52 (100), 43 (38). Anal calcd for $C_{21}H_{14}CrFeO_9$: C, 48.68; H, 2.72. Found: C, 48.88; H, 2.91.



The Thermolysis of Complex 274a.

A 25-mL flask with a threaded Teflon high-vacuum stop-cock was flushed with nitrogen for 10 minutes before it was charged with the carbene complex **274a** (51.8 mg, 0.1 mmol) and 5 mL of benzene. The mixture was degassed by the freeze-thaw method (–196/25 °C, 3 cycles), back-filled with 1 atm argon at room temperature, sealed and heated at 80 °C until the red color disappeared (2 h), indicating all the starting carbene complex was consumed. The mixture was then allowed to cool to room temperature and transferred to a 50-mL round bottom flask and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (5–10% EtOAc/hexanes) to furnish the dienone complex **254d** (9.9 mg, 28%) and the phenol **255d** (9.2 mg, 43%). The same reaction under 1 atm CO for 6 h gave **254d** (12.4 mg, 35%) and **255d** (12.9 mg, 60%). Their spectral data are identical with those from the reaction of **181d**.

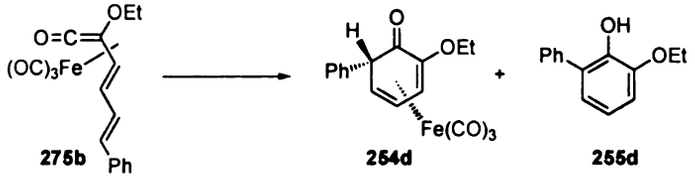


The Preparation of the Ketene Complex 275b.

To a solution of **283**[228a] (0.54 g, 2.25 mmol) in 30 mL of ether at –78 °C was added *n*BuLi (2.5 M in hexanes, 0.9 mL, 2.25 mmol), and the resulting yellow mixture was stirred for 15 min. Cinnamaldehyde (0.57 mL, 4.50 mmol) was then added to the

above solution and stirred for 10 min at –78 °C before the cold bath was replaced by an ice bath and continued stirring for an hour. The solvent was removed on a rotary evaporator and the product was purified by silica gel column chromatography (0–5% EtOAc/hexanes) to afford **275b** (0.26g, 33%) as a yellow solid.

Spectral data for **275b**: R_f = 0.24 (10% EtOAc/hexanes); mp 77–78 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 6.9 Hz), 2.82 (dd, 1H, J = 10.2, 8.4 Hz), 3.72-3.96 (m, 2H), 5.98 (d, 1H, J = 8.4 Hz), 6.49 (dd, 1H, J = 15.6, 10.2 Hz), 6.65 (d, 1H, J = 15.6 Hz), 7.24-7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.76, 53.46, 65.38, 87.63, 95.87, 126.28, 128.08, 128.81, 129.30, 132.49, 136.50, 207.36 (br), 235.35; IR (NaCl) 2056s, 1987vs, 1746s cm^{-1}; MS (EI) *m/z* (% relative intensity) 354 (M^+, 1), 326 (3), 298 (14), 270 (89), 258 (5), 242 (66), 228 (63), 226 (95), 214 (42), 198 (25), 196 (31), 184 (53), 172 (15), 157 (82), 146 (33), 141 (27), 133 (100), 129 (65), 128 (65), 115 (40), 110 (45), 91 (23), 81 (47), 77 (37), 57 (39), 56 (51). Anal calcd for $C_{17}H_{14}FeO_5$: C, 57.66; H, 3.98. Found: C, 57.88; H, 4.11.

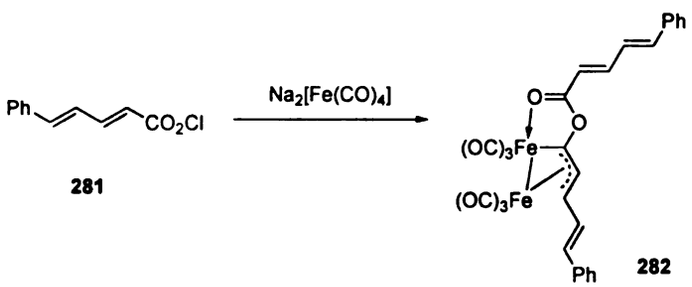


275b 254d 255d

The Thermolysis of Complex 275b.

A 25-mL flask with a threaded Teflon high-vacuum stop-cock was flushed with nitrogen for 10 minutes before it was charged with the carbene complex **275b** (35.4 mg, 0.1 mmol) and 5 mL of benzene. The mixture was degassed by the freeze-thaw method (–196/25 °C, 3 cycles), back-filled with 1 atm argon at room temperature, sealed and heated at 80 °C until the red color disappeared (22 h), indicating all the starting carbene

complex was consumed. The mixture was then allowed to cool to room temperature and transferred to a 50-mL round bottom flask and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (5–10% EtOAc/hexanes) to furnish the dienone complex **254d** (18.8 mg, 53%) and the phenol **255d** (9.8 mg, 46%). The same reaction under 1 atm CO for 12 h gave **254d** (10.4 mg, 29%) and **255d** (14.3 mg, 67%). Their spectral data are identical with those from the reaction of **181d**.



281 **282**

The Reaction of Acid Chloride 281 with $Na_2[Fe(CO)_4]$.

Under an atmosphere of argon, a solution of disodium tetracarbonylferrate – dioxane complex (1:1.5), $Na_2Fe(CO)_4 \cdot 1.5C_4H_8O_2$ (1.08 g, 3.1 mmol), in 20 mL of THF at –78 °C was added slowly a solution of **281** (0.60 g, 3.1 mmol) in 15 mL of THF. The mixture was then gradually warmed to room temperature and stirred for 6 h. The solvent was removed in vacuo and the flask was backfilled with argon, and about 1.0 g of Et_3OBF_4 was added before 20 mL of degassed ice-cold water was added with rapid stirring. Then ether (10 mL) was added and more Et_3OBF_4 was added until the solution turned acidic (pH ~ 2).[259] The organic layer was separated and the aqueous phase was further extracted with either until all the red color disappeared. The combined organic extract was washed with brine and dried with Na_2SO_4 and concentrated. The residue was

subjected to silica gel chromatography (0–10% EtOAc/hexanes) to furnish the iron complex **282** (0.23 g, 25%) as a red solid.

Spectral data for **282**: R_f = 0.25 (10% EtOAc/hexanes); mp 220 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23 (t, 1H, *J* = 9.3 Hz), 6.12 (d, 1H, *J* = 15.3 Hz), 6.24 (d, 1H, *J* = 9.0 Hz), 6.49 (dd, 1H, *J* = 15.3, 10.2 Hz), 6.72 (d, 1H, *J* = 15.6 Hz), 6.90 (dd, 1H, *J* = 15.6, 11.4 Hz), 7.10 (d, 1H, *J* = 15.3 Hz), 7.21-7.25 (m, 1H), 7.31 (t, 2H, *J* = 7.5 Hz), 7.36-7.41 (m, 5H), 7.48-7.51 (m, 2H), 7.60 (dd, 1H, *J* = 15.6, 11.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 62.94, 89.90, 114.37, 125.42, 126.21, 127.58, 127.77, 128.73, 129.02, 130.18, 131.11, 131.24, 135.32, 137.11, 145.08, 150.17, 176.70, 203.08, 210.96, 211.86; IR (NaCl) 2060vs, 2010vs, 1966vs, 1618m, 1568s cm^{-1}; MS (FAB, NBA) *m/z* 594 (M^+), 566 (M-CO), 538 (M-2CO), 510 (M-3CO), 482 (M-3CO), 454 (M-5CO), 426 (M-6CO). Anal calcd for $C_{28}H_{18}Fe_2O_8$: C, 56.60; H, 3.05. Found: C, 56.99; H, 3.15.

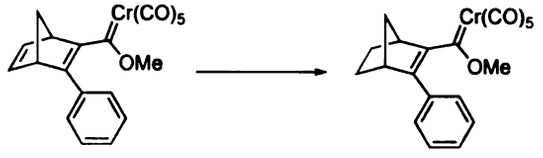
284 **285**

Direct Carbene Ligand Transfer from Chromium Complex 284.

A 25-mL flask with a threaded Teflon high-vacuum stop-cock was flushed with nitrogen for 10 minutes before it was charged with the carbene complex **284** (65.2 mg, 0.2 mmol), $Fe_2(CO)_9$ (72.8 mg, 0.2 mmol), and 10 mL of benzene. The mixture was degassed by the freeze-thaw method (–196/25 °C, 3 cycles), back-filled with 1 atm CO at room temperature, sealed and heated at 80 °C for 30 h. The mixture was then allowed to cool to room temperature and transferred to a 50-mL round bottom flask and concentrated under reduced pressure. The residue was subjected to silica gel

chromatography (5–10% EtOAc/hexanes) to furnish the iron carbene complex **285** (12.1 mg, 28%) along with a recovery of **284** (18.0 mg, 28%). A significant amount (about 37% yield, calculated from the NMR spectrum of the crude mixture) of ethyl benzoate was also observed.

Spectral data for **285:** R_f = 0.30 (hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (t, 3H, *J* = 7.2 Hz), 5.14 (q, 2H, *J* = 7.2 Hz), 7.34-7.44 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.74, 77.84, 125.99, 127.71, 131.26, 154.33, 200.00, 213.30, 323.04; IR (NaCl) 2052s, 1935vs cm^{-1}. The spectral data are consistent with the reported data.[228a]



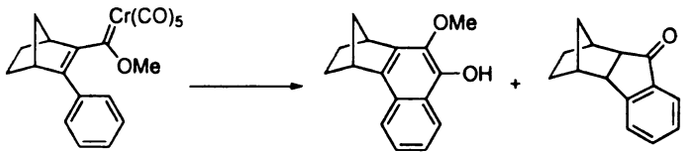
224 **290**

The Preparation of Carbene Complex 290.

A solution of **224** (1.21 g, 3.0 mmol) in 50 mL of degassed benzene was added $(Ph_3P)_3RhCl$ (0.42 g, 0.45 mmol) under at atmosphere of hydrogen and stirred at room temperature for 8 h. The mixture was then passed through a short pad of alumina and concentrated. The residue was then subjected to silica gel column chromatography (0–5% EtOAc/hexanes) to afford **290** (1.10 g, 91%) as a red solid.

Spectral data for **290**: R_f = 0.13 (hexanes); mp 89–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (dm, 1H, *J* = 8.7 Hz), 1.44-1.50 (m, 1H), 1.82-1.97 (m, 4H), 3.22 (s, 1H), 3.42 (s, 1H), 4.29 (s, 3H), 7.05-7.09 (m, 2H), 7.22-7.31 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.72, 27.15, 46.84, 47.63, 49.15, 65.42, 127.39, 127.73, 128.54, 134.50, 138.51, 216.26, 223.96, 352.49 (one aromatic/vinyl carbon not located); IR (NaCl)

2060s, 1929vs cm^{-1}; MS (EI) *m/z* (% relative intensity) 404 (M^+, 1), 376 (1), 348 (1), 320 (15), 292 (5), 264 946), 232 (24), 221 (25), 204 (50), 193 (18), 153 (14), 117 (24), 91 (11), 52 (100). Anal calcd for $C_{20}H_{16}CrO_6$: C, 59.41; H, 3.99. Found: C, 59.40; H, 4.07.



290 **291** **292**

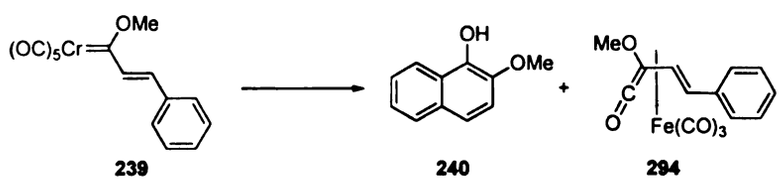
The Thermolysis of Complex 290 in the Absence or Presence of $Fe_2(CO)_9$.

A 25-mL flask with a threaded Teflon high-vacuum stop-cock was charged with the carbene complex **290** (40.4 mg, 0.1 mmol) and 5 mL of THF. The mixture was degassed by the freeze-thaw method (–196/25 °C, 3 cycles), back-filled with 1 atm CO at room temperature, sealed and heated at 80 °C until the red color disappeared (48 h), indicating all the starting carbene complex was consumed. The mixture was then allowed to cool to room temperature and transferred to a 50-mL round bottom flask and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (0–5% EtOAc/hexanes) to furnish the phenol **291** (18.8 mg, 78%) that was contaminated with a small amount of **292**, and the ketone **292** (1.7 mg, 9%) as a white solid. The same reaction under 1 atm argon for 7 h gave **291** (~ 2%) and **292** (43%).

When the thermolysis of **290** was carried out in the presence of $Fe_2(CO)_9$, the above procedure was followed except that one equivalent of the iron source was added. The reaction with $Fe_2(CO)_9$ under 1 atm CO for 48 h gave **291** (76%) and **292** (8%), while the same thermolysis with $Fe_2(CO)_9$ under 1 atm argon for 12 h gave **291** (10%) and **292** (48%).

Spectral data for **291**: R_f = 0.18 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11-1.26 (m, 2H), 1.577-1.62 (m, 1H), 1.80-1.84 (m, 1H), 1.93-2.03 (m, 2H), 3.77 (s, 1H), 3.87 (s, 1H), 3.97 (s, 3H), 6.00 (s, 1H), 7.31-7.39 (m, 2H), 7.79-7.82 (m, 1H), 8.10-8.13 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.62, 27.81, 40.76, 42.25, 49.68, 61.41, 122.43, 122.78, 123.29, 123.83, 124.72, 124.98, 136.64, 137.06, 137.25, 140.60; IR (NaCl) 3442 br, 2963s, 2869m, 1587m, 1460s, 1356s, 1302s cm^{-1}; MS (EI) *m/z* (% relative intensity) 240 (M^+, 63), 212 (100), 197 (66), 169 (19), 168 (18), 151 (23), 139 (19), 115 (15), 76 (10), 75 (11).

Spectral data for **292**: R_f = 0.22 (10% EtOAc/hexanes); mp 57–58 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.58-0.65 (m, 1H), 1.01-1.09 (m, 1H), 1.20-1.37 (m, 2H), 1.65 (dt, 1H, J = 9.9, 1.5 Hz), 1.78-1.82 (m, 1H), 2.64 (t, 1H, J = 4.2 Hz), 2.72 (t, 1H, J = 4.2 Hz), 2.94 (ddd, 1H, J = 8.1, 5.4, 1.8 Hz), 3.66 (dd, 1H, J = 8.4, 5.1 Hz), 7.31-7.38 (m, 2H), 7.55 (td, 1H, J = 7.8, 1.2 Hz), 7.67 (d, 1H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.15, 24.92, 40.21, 40.23, 43.08, 47.76, 55.22, 123.58, 126.75, 127.57, 134.53, 138.56, 156.22, 208.86; IR (NaCl) 2957m, 2874w, 1711s, 1603m cm^{-1}; MS (EI) *m/z* (% relative intensity) 198 (M^+, 10), 132 (100), 130 (20), 115 (11), 91 (4), 77 (6), 67 (5). Anal calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.69; H, 7.50.



239 **240** **294**

The Thermolysis of 239 and the Formation of Complex 294.

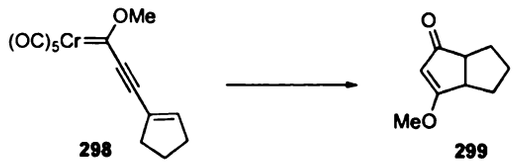
A 25-mL flask with a threaded Teflon high-vacuum stop-cock was flushed with nitrogen for 10 minutes before it was charged with the carbene complex **239** (67.6 mg,

0.2 mmol), $Fe_2(CO)_9$ (72.8 mg, 0.2 mmol), and 10 mL of THF. The mixture was degassed by the freeze-thaw method (–196/25 °C, 3 cycles), back-filled with 1 atm of CO at room temperature, sealed and heated at 80 °C until the red color disappeared (72 h), indicating all the starting carbene complex was consumed. The mixture was then allowed to cool to room temperature and transferred to a 100-mL round bottom flask and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (5–10% EtOAc/hexanes) to furnish the ketene complex **294** (51.5 mg, 82%) as a yellow solid, with trace of **240** observed from the NMR spectra of the crude mixture.

The same reaction in benzene for 72 h gave **294** (50.2 mg, 80%) and trace of **240**. When the reaction was performed at 100 °C in benzene for 72 h, a messy mixture was obtained and only traces of **294** and **240** were observed; when the reaction temperature was at 130 °C in toluene for 7 h, a messy mixture was obtained and none of **294** and **240** were observed.

When the reaction that was performed under 500 psi of CO, the following procedure was used. A Monel Paar pressure reactor equipped with a magnetically driven mechanical stirrer was flushed with carbon monoxide for a few minutes before it was charged with the carbene complex **239** (67.6 mg, 0.2 mmol), $Fe_2(CO)_9$ (72.8 mg, 0.2 mmol), and 10 mL of THF. Then the reactor was further flushed with CO for another 2 minutes and filled with 500 psi CO and heated at 80 °C with stirring for 24 hours. The mixture was transfered to a 100-mL round bottom flask and concentrated on a rotary evaporator. Purification with silica gel chromatography (5–10% EtOAc/hexanes) gave the ketene complex **294** (51.9 mg, 83%) and none of **240** was detected.

Spectral data for **294**: R_f = 0.22 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.93 (d, 1H, *J* = 8.7 Hz), 3.64 (s, 3H), 6.46 (d, 1H, *J* = 8.7 Hz), 7.23-7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.00, 56.50, 86.02, 96.56, 126.73, 127.38, 129.12, 138.45, 207.02 (br), 234.79; IR (NaCl) 2060vs, 1985vs br, 1740s cm^{-1}; MS (EI) *m/z* (% relative intensity) 314 (M^+, 1), 286 (10), 258 (6), 230 (13), 202 (43), 162 (28), 159 (93), 148 (98), 133 (100), 131 (85), 115 (44), 103 (67), 84 (24), 77 (47), 56 (51), 51 (18). Anal calcd for $C_{14}H_{10}FeO_5$: C, 53.54; H, 3.21. Found: C, 53.40; H, 3.35.

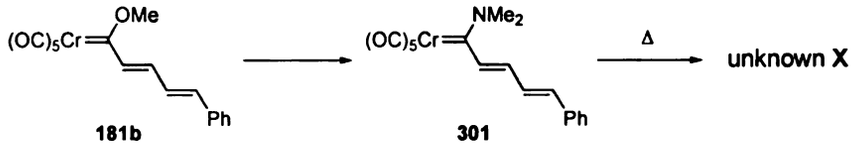


The Formation of 299 from Carbene Complex 298.

To a freshly prepared MeONa/MeOH solution (0.02 M, 7 mL) at 0 °C was added the carbene complex **298**[205] (230 mg, 0.7 mmol) and the mixture was stirred for 10 min (the color of the solution turned from red to red-orange). An ice-cold sat. $NaHCO_3$ aqueous solution (10 mL) was then added and the product was extracted by ether (3 x 10 mL), dried by Na_2SO_4 and concentrated. (During the extraction and concentration, the red-orange color became lighter and the greenish solid covered the inner wall of the flask after removal of the solvent on a rotary evaporator.) Purification on the silica gel column (10–20% EtOAc/hexanes) afforded **299** (80 mg, 75%) as a colorless liquid.

Spectral data for **299**: R_f = 0.10 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21-1.35 (m, 1H), 1.53-1.67 (m, 3H), 1.80-1.95 (m, 2H), 2.82 (t, 1H, *J* = 7.5 Hz), 3.13 (t, 1H, *J* = 7.5 Hz), 3.79 (s, 3H), 5.23 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.64, 28.45, 29.03, 45.68, 50.90, 58.76, 104.80, 192.04, 208.35; IR (NaCl) 2946m,

1694s, 1591s, 1360m cm^{-1}; MS (EI) *m/z* (% relative intensity) 152 (M^+, 51), 127 (14), 124 (100), 121 (35), 111 (55), 69 (28).



The Preparation of Amino Carbene Complex 301 and Its Thermolysis.

A solution of **181b** (0.38 g, 1.04 mmol) in 10 mL of ether at –78 °C under an atmosphere of argon was added freshly prepared Me_2NH/ether solution (2.0 M, 0.74 mL, 1.47 mmol) via syringe. The color of the mixture changed immediately from red to orange-yellow and the solution was stirred for 5 min before the volatiles were removed. Purification on the silica gel column (10% EtOAc/hexanes) afforded **301** (0.25 g, 64%) as a orange-yellow oil which solidified in the freezer to form a yellow solid.

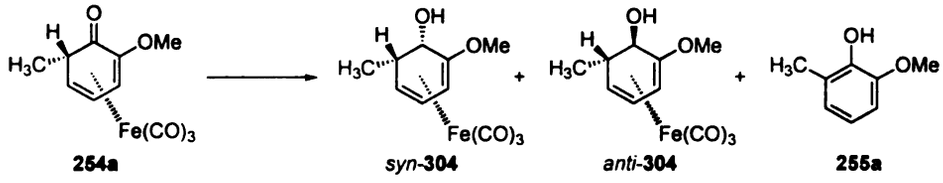
Spectral data for **301**: R_f = 0.08 (10% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.86 (s, 3H), 5.71 (dd, 1H, *J* = 15.9, 10.2 Hz), 6.60(d, 1H, *J* = 15.6 Hz), 6.69-6.81 (m, 2H), 7.20-7.24 (m, 1H), 7.31 (t, 2H, *J* = 7.2 Hz), 7.40 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.85, 51.02, 122.54, 126.44, 127.73, 127.90, 128.67, 134.52, 136.78, 140.72, 217.43, 223.56, 269.33; IR (NaCl) 2053vs, 1972s, 1908vs br, 1537m cm^{-1}; MS (EI) *m/z* (% relative intensity) 377 (M^+, 1), 349 (12), 321 (9), 293 (3), 265 (26), 237 (52), 201 (46), 194 (19), 159 (33), 157 (98), 128 (100), 115 (27), 95 (40), 86 (40), 77 (31), 57 (66), 52 (87), 43 (67), 41 (55).

A 25-mL flask with a threaded Teflon high-vacuum stop-cock was flushed with nitrogen for 10 minutes before it was charged with the carbene complex **301** (89.0 mg, 0.236 mmol), $Fe_2(CO)_9$ (85.9 mg, 0.236 mmol), and 12 mL of THF. The mixture was

degassed by the freeze-thaw method (–196/25 °C, 3 cycles), back-filled with 1 atm CO at room temperature, sealed and heated at 80 °C for 42 h. The mixture was then allowed to cool to room temperature and transferred to a 100-mL round bottom flask and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (5–10% EtOAc/hexanes) to furnish a very polar unknown compound **X** (18.0 mg) as a yellowish oil, the structure of which has not been fully characterized. And some of the starting complex **301** (36 mg, 40%) was recovered. The NMR spectrum of the crude mixture indicated that the ratio of **X/301** = 1 : 2.

The same reaction in benzene for 96 h resulted in a ratio of **X/301** = 2 : 3. And the reaction in toluene at 110 °C for 48 h gave a messy complex that did not appear to contain **X** and no starting complex **301** was recovered.

Spectral data for **X**: R_f = 0.07 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (d, 1H, J = 3.6 Hz), 2.34 (d, 1H, J = 5.7 Hz), 2.99 (s, 3H), 3.17 (s, 3H), 6.00 (d, 1H, J = 4.5 Hz), 6.17 (s, 1H), 7.21-7.31 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.99, 37.10, 45.85, 61.98, 82.61, 83.54, 126.21, 126.99, 128.79, 138.91, 170.54, 209.16 (br); IR (NaCl) 2041vs, 1975vs br, 1624s cm^{-1}; MS (EI) *m/z* (% relative intensity) 313 (M^+, 8), 285 (32), 257 (100), 213 (7), 201 (14), 185 (64), 157 (45), 128 (94), 84 (14), 77 (14), 56 (84).



254a *syn*-**304** *anti*-**304** **255a**

Reduction of 254a for the Preparation of Complex 304.

A typical procedure: A solution of **254a** (67.2 mg, 0.24 mmol) in 15 mL of methanol was treated with $NaBH_4$ (92 mg, 2.42 mmol) for 3 h. The reaction was then quenched with 3 mL of H_2O and stirred for 5 min. The products were extracted with ether (3 x 10 mL) and the organic extracts were washed with brine and dried with Na_2SO_4. After removal of the solvent, the residue was subjected to silica gel column chromatography (10–20% EtOAc/hexanes) to afford *syn*-**304** (24 mg, 36%) and *anti*-**304** (17 mg, 25%), along with a trace (< 5%) of **255a** was seen on the NMR spectrum of the crude mixture.

Spectral data for *syn*-**304**: R_f = 0.20 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, 3H, J = 7.8 Hz), 1.97 (tt, 1H, J = 7.2, 1.2 Hz), 2.27 (d, 1H, J = 3.0 Hz), 2.54 (dt, 1H, J = 6.6, 1.5 Hz), 3.50 (s, 3H), 3.98 (dd, 1H, J = 7.2, 2.7 Hz), 4.99-5.03 (m, 1H), 5.26 (dd, 1H, J = 4.5, 1.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.13, 34.45, 56.73, 64.14, 70.32, 74.32, 75.74, 121.89, 212.19; IR (NaCl) 3465w br, 2039vs, 1966vs cm^{-1}; MS (EI) *m/z* (% relative intensity) 252 (M^+–CO, 2), 224 (9), 196 (4), 181 (18), 178 (86), 166 (11), 148 (14), 122 (89), 129 (25), 91 (78), 77 (52), 57 (82), 56 (77), 43 (100).

Spectral data for *anti*-**304**: R_f = 0.09 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, 3H, J = 6.9 Hz), 1.65-1.71 (m, 1H), 2.00 (d, 1H, J = 4.2 Hz), 2.38 (dt, 1H, J = 6.3, 1.5 Hz), 3.47 (s, 3H), 3.98-4.01 (m, 1H), 5.19-5.23 (m, 1H), 5.37 (dt, 1H, J = 4.8, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.64, 36.96, 56.58, 57.93, 75.96, 77.70, 78.71, 116.32, 211.84; IR (NaCl) 3397s br, 2041vs, 1960vs cm^{-1}.

REFERENCES AND NOTES

[1] Taxol® is a registered trademark of Bristol-Myers Squibb Company. The approved generic name is paclitaxel. The chemical compound will be referred to as taxol thereafter as named by Wani and Wall in his original paper in 1971 (Ref. 17). No infringement of the BMS trademark is intended or implied by this usage.

[2] Goodman, J.; Walsh, V. *The Story of Taxol: Nature and Politics in the Pursuit of an Anti-cancer Drug*; Cambridge University Press: New York, 2001.

[3] Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15.

[4] For detailed accounts of the history of the development of Taxol, see: (a) Suffness, M.; Wall, M. E. In *Taxol: Science and Applications*; Suffness, M., Ed.; CRC Press: Baca Raton, FL, 1995. (b) Wall, M. E.; Wani, M. C. In *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1994. (c) Ref. 2.

[5] For a review on taxane diterpenoids, see: (a) Baloglu, E.; Kingston, D. G. I. *J. Nat. Prod.* **1999**, *62*, 1448. (b) Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, C., Eds.; Springer-Verlag: New York, 1993.

[6] Taxotere® is a registered trademark of Rhone-Poulenc, and it is marketed in the U.S. by Sanofi-aventis. Its generic name is docetaxel.

[7] For bioactivity of other taxanes, see: (a) Rose, W. C. In *Taxol: Science and Applications*; Suffness, M., Ed.; CRC Press: Baca Raton, FL, 1995. (b) Kingston, D. G. I. *Pharmacol. Ther.* **1991**, *52*, 1. (c) Appendino, G. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1995; pp 237-268. (d) Appendino, G. In *The Chemistry and Pharmacology of Taxol and its Derivatives*; Farina, V., Ed.; Elsevier Science: New York, 1995; pp 7-53.

[8] (a) Kobayashi, J.; Ogiwara, A.; Hosoyama, H.; Shigemori, H.; Yoshida, N.; Sasaki, T.; Li, Y.; Iwasaki, S.; Naito, M.; Tsuruo, T. *Tetrahedron* **1994**, *50*, 7401. (b) Morita, H.; Wei, L.; Gouda, A.; Takeya, K.; Itokawa, H.; Fukaya, H.; Shigemori, H.; Kobayashi, J. *Tetrahedron* **1997**, *53*, 4621.

[9] (a) Goodman, L. S.; Wintrobe, M. M.; Dameshek, W.; Goodman, M. J.; Gilman, A.; McLennan, M. T. *J. Am. Med. Assoc.* **1946**, *132*,126. (b) Farber, S.; Diamond, L. K.; Mercer, R. D.; Sylvester, R. F., Jr.; Wolff, J. A. *N. Engl. J. Med.* **1948**, *238*, 787. (c) Burchenal, J. H.; Murphy, M. L.; Ellison, R. R.; Sykes, M. P.; Tan, T. C.; Leone, L. A.; Karnofsky, D. A.; Craver, L. F.; Dargeon, H. W.; Rhoads, C. P. *Blood* **1953**, *8*, 965.

[10] Zubrod, C. G.; Shepartz, S.; Leiter, J.; Endicott, K. M.; Carrese, L. M.; Baker, C. G. *Cancer Chemother. Rep.* **1966**, *50*, 349.

[11] (a) Schepartz, S. A. *Cancer Treat. Rep.* **1976**, *60*, 975. (b) Suffness, M. *Gann Monogr. Cancer Res.* **1989**, *36*, 21.

[12] McCracken, R. J. *Cancer Treat. Rep.* **1976**, *60*, 973.

[13] William, J. J.; Schubert, B. G. *Economic Botany* **1955**, *9*, 141.

[14] Wall, M. E.; Wani, M. C.; Taylor, H. L. *Cancer Treat. Rep.* **1976**, *60*, 1011.

[15] Wall, M. E.; Wani, M. C. *Cancer Res.* **1995**, *55*, 753.

[16] Wall, M. E.; Wani, M. C. *The American Chemical Society 153rd National Meeting*, Paper M-006, Miami Beach, FL, 1967.

[17] Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

[18] Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425.

[19] (a) Suffness, M.; Douros, J. *J. Nat. Prod.* **1982**, *45*, 1. (b) Borman, S. *Chem. Eng. News* **1991**, *69*, 11.

[20] Fuchs, D. A.; Johnson, R. K. *Cancer Treat. Rep.* **1978**, *62*, 1219.

[21] Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665.

[22] The promotion of microtubule assembly and inhibition of its disassembly results in blocking a cell's ability to break down the mitotic spindle during mitosis (cell division). With the spindle still in place the cell cannot divide into daughter cells, eventually leading to cell death.

[23] Rowinsky, E. K.; Donehower, R. C. *Pharmacol. Ther.* **1991**, *52*, 35.

[24] (a) Lee, V. D.; Huang, B. *Plant Cell* **1990**, *2*, 1051. (b) Wilson, L. *Life Sci.* **1975**, *17*, 303. (c) Bai, R.; Pettit, G. R.; Hamel, E. *J. Biol. Chem.* **1990**, *265*,17141.

[25] Purich, D. L.; Kristofferson, D. *Adv. Protein Chem.* **1984**, *36*, 133.

[26] (a) Humar, N. *J. Biol. Chem.* **1981**, *256*, 10435. (b) Vallee, R. B. *J. Cell Biol.* **1982**, 435. (c) Vallee, R. B.; Collins, C. A. *Methods Enzymol.* **1986**, *134*, 116.

[27] Schiff, P. B.; Horwitz, S. B. *Biochemistry* **1981**, *20*, 3247.

[28] Heidemann, S. R.; Gallas, P. T. *Developmental Biol.* **1980**, *80*, 489.

[29] (a) Keller, H. U.; Zimmerman, A. *Invasion Metathesis* **1986**, *6*, 33. (b) Komiya, Y.; Tashiro, T. Cell Motil. *Cytoskeleton* **1988**, *11*, 151. (c) Rainey, W. E.; Kramer, R. E.; Mason, J. I.; Shay, J. W. *J. Cell Physiol.* **1985**, *123*, 17. (d) Mattson, M. P. *Brain Res.* **1992**, *582*, 107.

[30] (a) Ucker, D. S. *New Biol.* **1991**, *3*, 103. (b) Colombel, M.; Olsson, C. A.; Ng, P. Y.; Buttyan, R. *Cancer Res.* **1992**, *52*, 4313. (c) Lee, S.; Christakos, S.; Small, M. B. *Curr. Opin. Cell Biol.* **1993**, *5*, 286. (d) Jordon, M. A.; Wilson, L. In *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1994. pp138-153.

[31] For reviews on clinical usage of Taxol, see: (a) Rowinsky, E. K.; Cazenave, L. A.; Donehower, R. C. *J. Natl. Cancer Inst.* **1990**, *82*, 1247. (b) Rowinsky, E. K.; Donehowever, R. C. *idbd.* **1991**, *83*, 1778. (c) Rowinsky, E. K.; Onetto, N.; Canetta, R. M.; Arbuck, S. G. *Semin. Oncol.* **1992**, *19*, 646. (d) Arbuck, S. G.; Christian, M. C.; Fisherman, J. S.; Cazenave, L. S.; Sarosy, G.; Suffness, M.; Adams, J.; Canetta, R.; Kole, K. E.; Friedman, M. A. *Monogr. Natl. Cancer Inst.* **1993**, *15*, 11. (e) Goldspiel, B. R. *Pharmacotherapy* 1997, 17, 110S-125S.

[32] (a) Riondel, J.; Jacrot, M.; Picot, F.; Beriel, H.; Mouriquand, C.; Potier, P. *Cancer Chemother. Pharmacol.* **1986**, *17*, 137. (b) Jacrot, M.; Riondel, J.; Picot, F.; Leroux, D.; Mouriquand, H.; Beriel, P.; Potier, P. *Seances Acad. Sci. Ser. 3* **1983**, *247*, 597.

[33] *National Cancer Institute Clinical Brochure: Taxol (NSC1259973)*, National Cancer Institute, Division of Cancer Treatment, Bethesda, MD, 1983, 6-12.

[34] Adam, J. D.; Flora, K. F.; Goldspiel, B. R.; Wilson, J. W.; Arbuck, S. G.; Finley, R. *Monogr. Natl. Cancer Inst.* **1993**, *15*, 141.

[35] For details of clinical studies (including phase I) with Taxol, see: (a) Ref. 31. (b) Arbuck, S. G.; Blaylock, B. A. In *Taxol: Science and Applications*; Suffness, M., Ed.; CRC Press: Baca Raton, FL, 1995.

[36] (a) Weiss, R. B.; Donehower, R. C.; Wiernik, P. H.; Ohnuma, T.; Gralla, R. J.; Trump, D. L.; Baker, J. R., Jr.; Van Echo, D. A.; Von Hoff, D. D.; Leyland-Jones, B. *J. Clin. Oncol.* **1990**, *8*, 1263. (b) Brown, T.; Havlin, K.; Weiss, G.; Cagnola, J.; Koeller, J.; Kuhn, J.; Rizzo,J.; Craig, J.; Phillips, J.; Von Hoff, D. *J. Clin. Oncol.* **1991**, *9*, 1261. (c) Onetto, N.; Canetta, R.; Winograd, B.; Catane, R.; Dougan, M.; Grechko, J.; Burroughs, J.; Rozencweig, M. *J. Natl. Cancer Inst., Monographs* **1993**, 131.

[37] Rowinsky, E. K.; Eisenhauer, E. A.; Chaudhry, V.; Arbuck, S. G.; Donehower, R. C. *Semin. Oncol.* **1993**, *20*, 1.

[38] Cisplatin, discovered to be highly active against cancers in 1965 by Professor Barnett Rosenberg of Michigan State University, had been the major anticancer drug before Taxol was used, along with its later-introduced analog carboplatin, and both are still widely used. For related information, see: *Chem. Eng. News* **2005**, *83*, (June 20, Issue 25).

[39] McGuire, W. P.; Rowinsky, E. K.; Rosenheim, N. B.; Grumbine, F. C.; Ettinger, D. S.; Armstrong, D. K.; Donehower, R. C. *Ann. Inter. Med.* **1989**, *111*, 273.

[40] From 1969 to 1990, a period of over 20 years, the total production of Taxol by NCI contractors was 3.7 kg, most of which was produced in the last 5 years of that period. (See: Ref. 4a)

[41] (a) Thigpen, T.; Blessing, J.; Ball, H.; Hummel, S.; Barret, R. *Proc. Annu. Meet. Am. Soc. Clin. Oncol.* 1990, 9 (Abstract 604). (b) Ozols, R. F. *Curr. Probl. Cancer* **1992**, *16*, 63.

[42] Holmes, F. A.; Walters, R. S.; Theriault, R. L.; Forman, A. D.; Newton, L. K.; Raber, M. N.; Buzdar, A. U.; Frye, D. H.; Hortobagyi, G. N. *J. Natl. Cancer Inst.* **1991**, *83*, 1797.

[43] a) Murphey, W. K.; Winn, R. J.; Fossella, F. V.; Shin, D. M.; Hynes, H. E.; Gross, H. M.; Davila, E.; Leimert, J. T.; Dhingra, H. M.; Raber, M. N.; Krakoff, I. H.; Hong, W. K. *Proc. Annu. Meet. Am. Soc. Clin. Oncol.* **1992**, *11*, 294 (Abstract 985). b) Chang, A.; Kim, K.; Glick, J.; Anderson, T.; Karp, D.; Johnson, D. *ibid.* **1992**, *11*, 293 (Abstract 981).

[44] Trojanowski, J.; Lee, V. M. Y. *Am. J. Pathology* **2005**, *167*, 1183.

[45] *Chem. Eng. News* **2002**, *80*, 13 (June 10, issue 23); **2005**, *83*, (June 20, Issue 25).

[46] (a) A typical treatment regimen for a 165-lb patient suffering from breast cancer involves repeated infusion of a 300-mg dose every three weeks for three months. The cost of the 1.2 g of Taxol required for this course of treatment was approximately $10,000 in 2002. (b) Testicular cancer survivor Lance Armstrong, who is most famous for winning the Tour de France a record seven consecutive times from 1999 to2005, was cured with three BMS drugs (including Taxol) in 1996.

[47] For recent biosynthesis studies, see: (a) Walker, K.; Long, R.; Croteau, R. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 9166. (b) Jennewein, S.; Wildung, M. R.; Chau, M.; Walker, K.; Croteau, R. *Proc. Nat. Acad. Sci. USA* **2004**, *101*, 9149-9154. (c) Loncaric, C.; Merriweather, E.; Walker, K. D. *Chemistry and Biology* **2006**, *13*, 309-317. For reviews,

see: (d) Walker, K.; Croteau, R. *Recent Adv. Phytochem.* **1999**, *33*, 31. (e) Floss, H. G.; Mocek, U. In *Taxol: Science and Applications*; Suffness, M., Ed.; CRC Press: Baca Raton, FL, 1995. (f) Takeya, K. In *Taxus: The Genus Taxus*; Itokawa, H., Lee, K.-H., Eds.; Taylor and Francis: London, 2003, chap. 5. (g) Kingston, D. G. I. In *Anticancer Agents from Natural Products*; Cragg, G. M., Kingston, D. G. I., Newman, D. J., Eds.; CRC Press LLC: Boca Raton, FL, 2005; pp 89-122. (h) Rohr, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2190.

[48] For reviews, see: (a) Wuts, P. G. M. *Curr. Opin. Drug Disc. Devel.* **1998**, *1*. 329. (b) Holton, R. A.; Biediger, R. J.; Boatman, P. D. In *Taxol: Science and Applications*; Suffness, M., Ed.; CRC Press: Baca Raton, FL, 1995.

[49] For Taxol production by plant tissue culture methods, see: (a) Zhong, J.-J. *J. Biosci. Bioeng.* **2002**, *94*, 591. (b) Tabata, H. *Adv. Biochem. Eng./Biotechnol.* **2004**, *7*, 1.

[50] Gueritte-Voegelein, F.; Senilh, V.; David, B.; Guenard, D.; Potier, P. *Tetrahedron* **1986**, *42*, 4451.

[51] (a) Barasoain, I.; Des Ines, D.; Duz, F.; Andreia, J. M.; Peyrot, V.; Leynadier, D.; Garcia, P.; Briand, C.; De Suusa, G.; Rahmani, R. *Proc. Am. Assoc. Cancer Res.* **1991**, *32*, 329. (b) Ringel, I.; Horwitz, S. B. *J. Natl. Cancer Inst.* **1991**, *83*, 288.

[52] Fromes, V.; Guonon, P.; Bissery, M. C.; Fellous, A. *Proc. Am. Assoc. Cancer Res.* **1992**, *33*, 511.

[53] Joel, S. P. *Chemistry and Industry* **1994** (March 7), 172.

[54] 10-DAB is present in a number of *Taxus* species, including *Taxus brevifolia* and *Taxus wallichiana,* a species growing in the Himalayan region.

[55] (a) Senilh, V.; Gueritte, F.; Guenard, D.; Colin, M.; Potier, P. *Comptes rendus del' Academie des Sciences de Paris, Serie II* **1984**, *299*, 1039. (b) Bissery, M.-C.; Lavelle, F. In *Cancer Therapeutics: Experimental and Clinical Agents*; Teicher, B. A., Ed.; Humana Press: Totowa, NJ; 1997, pp 175-193.

[56] (a) Denis, J. N.; Greene, A. E.; Guenard, D.; Gueritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917. (b) Mangatal, L.; Adeline, M. T.; Guenard, D.; Gueritte-Voegelein, F.; Potier, P. *Tetrahedron* **1989**, *45*, 4177.

[57] (a) Holton, R. A. *European Patent Application 400971*, **1990**; US Patent 5015744, **1991**. (b) Holton, R. A. *European Patent Application 428376*, **1991**; US Patent 5175315, **1992**. (c) Holton, R. A.; Biediger, R. J.; Boatman, P. D. In *Taxol: Science and Applications*; Suffness, M., Ed.; CRC Press: Baca Raton, FL, 1995.

[58] (a) Ojima, I.; Habus, I.; Zhao, M.; Georg, G.; Jayasinghe, L. R. *J. Org. Chem.* **1991**, *56*, 1681. (b) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y.-H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985.

[59] (a) Bredt, J.; Thouet, H.; Schnitz, J. *Liebigs Ann.* **1924**, *437*, 1. (b) For a review, see: K. J. Shea, K. J. *Tetrahedron* **1980**, *36*, 1683.

[60] Nicolaou, K. C.; Guy, R. K.; Potier, P. *Scientific American* **1996**, *274*, 84.

[61] (a) Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. S.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597. (b) Holton, R. A.; Kim, H. B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. S.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599.

[62] (a) Nicolaou, K. C.; Zang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*,630. (b) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Coulandouros, E. A.; Sorensen, E. J. *J. Am. Chem Soc.* **1995**, *117*, 624. (c) Nicolaou, K. C.; Liu, J. J.; Yang, H.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C. K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem Soc.* **1995**, *117*, 634. (d) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem Soc.* **1995**, *117*, 645. (e) Nicolaou, K. C.; Ueno, H.; Liu, J. J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653.

[63] Anon. *Chemistry and Industry* **1994** (February 21), 125.

[64] Holton, R. A.; Juo, R. R.; Kim, H. B.; Williams, A. D.; Harusawa, S.; Lowenthal, R. E.; Yogai, S. *J. Am. Chem. Soc.* **1988**, *110*, 6558.

[65] Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843.

[66] (a) Samaranayake, G.; Magri, N. F.; Jitrangsri, C.; Kingston, D. G. I. *J. Org. Chem.* **1991**, *56*, 5114. (b) Chen, S.; Huang, S.; Wei, J.; Farina, V. *Tetrahedron* **1993**, *49*, 2805.

[67] (a) Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Gränicher, C.; Houze, J. B.; Jänichen, J.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciaro, T. P.; Mühlebach, M.; Natchus, M. G.; Paulsen, H.; Rawlins, D. B.; Satkofsky, J.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E.; Tomooka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2755. (b). Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.;

Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *J. Am. Chem. Soc.* **1997**, *119*, 2757.

[68] (a) Morihira, K.; Hara, R.; Kawahara, S.; Nishimori, T.; Nakamura, N.; Kusama, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120*, 12980. (b) Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 3811.

[69] Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. Eur. J.* **1999**, *5*, 121 and references therein.

[70] Wender, P. A.; Natchus, M. G.; Shuker, A. J. In *Taxol: Science and Applications*; Suffness, M., Ed.; CRC Press: Baca Raton, FL, 1995.

[71] For an excellent review on the synthetic efforts through the middle of 1991, see: Swindell, C. S. *Org. Prep. Proceed. Int.* **1991**, *23*, 465.

[72] (a) Swindell, C. S.; deSolms, S. J.; Springer, J. P. *Tetrahedron Lett.* **1984**, *25*, 3797. (b) Swindell, C. S.; deSolms, S. J. *ibid.* **1984**, *25*, 3801. (c) Swindell, C. S.; Patel, B. P.; deSolms, S. J.; Springer, J. P. *J. Org. Chem.* **1987**, *52*, 2346. (d) Swindell, C. S.; Patel, B. P. *Tetrahedron Lett.* **1987**, *28*, 5275. (e)) Swindell, C. S.; Patel, B. P. *J. Org. Chem.* **1990**, *55*, 3.

[73] Neh, H.; Blechert, S.; Schnick, W.; Jansen, M. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 905.

[74] (a) Winkler, J. D.; Subrahmanyam, D.; Hsung, R. P. *Tetrahedron* **1992**, 48, 7049; corrigendum: *ibid.* **1993**, *49*, 291. (b) Winkler, J. D.; Lee, C.-S.; Rubo, L.; Muller, C. L.; Squattrito, P. J. *J. Org. Chem.* **1989**, *54*, 4491.

[75] Jackson, R. W.; Higby, R. G.; Gilman, J. W.; Shea, K. J. *Tetrahedron* **1992**, *48*, 7013.

[76] Bonnert, R. V.; Jenkins, P. R. *J. Chem. Soc. Perkin Trans. 1* **1989**, 413 and references therein.

[77] Winkler, J. D.; Kim, H. S.; Kim, S. *Tetradedron Lett.* **1995**, *36,* 687.

[78] Blechert, S.; Muller, R.; Beitzel, M. *Tetrahedron* **1992**, *48*, 6953.

[79] Trost, B. M.; Hiemstra, H. *J. Am. Chem. Soc.* **1982**, *104*, 886.

[80] (a) Kress, M. H.; Ruel, R.; Milller, W.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 5999; **1993**, *34*, 6003.

[81] Paquette, L. A.; Zhao, M.; Montgomery, F.; Zeng, Q.; Wang, T. Z.; Elmore, S.; Combrink, K.; Wang, H.-L.; Bailey, S.; Su, Z. In *Current Trends in Organic Synthesis*; Scolastico, C., Nicotra, F., Eds.; Kluwer Academic/Plenum Publishers: New York, 1999. pp 25-34.

[82] Funk, R. L.; Daily, W. J.; Parvez, M. *J. Org. Chem.* **1988**, *53*, 4141.

[83] Yadav, J. S.; Ravishankar, R. *Tetrahedron Lett.* **1991**, *32*, 2629.

[84] Hitchcock, S. A.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 4843; corrigendum: *ibid.* **1992**, *33*, 7448.

[85] Wang, Z.; Warder, S. E.; Perrier, H.; Grimm, E. L.; Bernstein, M. A.; Ball, R. G. *J. Org. Chem.* **1993**, *58*, 2931.

[86] A prodrug is a pharmacological substance (drug) which is administered in an inactive (or significantly less active) form. Once administered, the prodrug is metabolized in the body in vivo into the active compound.

[87] For an overview of prodrugs for Taxol, see: Kingston, D. G. I.; Jagtap, P. G.; Yuan, H.; Samala, L. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Falk, H., Kirby, G. W., Eds.; Springer-Verlag Wien: New York, 2002.

[88] For reviews, see: (a) Zefirova, O. N.; Nurieva, E. V.; Ryzhov, A. N.; Zyk, N. V.; Zefirov, N, S. *Russ. J. Org. Chem.* **2005**, *41*, 315. (b) Kingston, D. G. I. *J. Nat. Prod.* **2000**, *63*, 726.

[89] (a) Ojima, I.; Lin, S.; Inoue, T.; Miller, M. L.; Borella, C. P.; Geng, X.; Walsh, J. J. *J. Am. Chem. Soc.* **2000**, *122*, 5343. (b) Ganesh, T.; Guza, R. C.; Bane, S.; Ravindra, R.; Shanker, N.; Lakdawala, A. S.; Snyder, J. P.; Kingston, D. G. I. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 10006. (c) Boge, T. C.; Wu, Z.-J.; Himes, R. H.; Vander Velde, D. G.; Georg, G. I. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3047. (d) Yuan, H.; Kingston, D. G. I. *Tetrahedron* **1999**, *55*, 9707.

[90] He, L.; Jagtap, P. G.; Kingston, D. G. I.; Shen, H.-J.; Orr, G. A.; Horwitz, S. B. *Biochemistry* **2000**, *39*, 3972.

[91] (a) Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325. (b) Koalski, R. J.; Giannakakou, P.; Hamel, E. *J. Biol. Chem.* **1997**, *272*, 2534.

[92] Ter Harr, E.; Kowalski, R. J.; Hamel, E.; Lin, C. M.; Longley, R. E.; Gunasekera, S. P.; Rosenkranz, H. S.; Day, B. W. *Biochemistry* **1996**, *35*, 243.

[93] Lindel, T.; Jensen, P. R.; Fenical, W.; Long, B. H.; Casazza, A. M.; Carboni, J.; Fairchild, C. R. *J. Am. Chem. Chem.* **1997**, *119*, 8744.

[94] (a) Ojima, I.; Chakravarty, S.; Tadashi, I.; Lin, S.; He, L.; Horwitz, S. B.; Kuduk, S. B.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 4256. (b) Ojima, I.; Lin, S.; Inoue, T.; Miller, M. L.; Borella, C. P.; Geng, X.; Walsh, J. J. *J. Am. Chem. Soc.* **2000**, *122*, 5343,

[95] Fischer, E. O.; Maasböl, A. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 580.

[96] Dötz, K. H.; Fischer, H.; Hofmann, P.; Kreissl, F. R.; Schubert, U.; Weiss, K. *Transition Metal Carbene Complexes*, Verlag Chemie: Weinheim; Deerfield Beach, Florida; 1983.

[97] For reviews on the chemistry of Fischer carbene complexes and their synthetic applications, see: (a) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587. (b) Wulff, W. D. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1989; Vol. 1. pp 209-393. (c) Wulff, W. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol 5. (d) Wulff, W. D. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, UK, 1995; Vol. 12, pp 469-547. (e) Hegedus, L. S. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, pp 549-576. (f) Doyle, M. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, pp 387-420. (g) Harvey, D. F.; Sigano. D. M. *Chem. Rev.* **1996**, *96*, 271. (h) de Meijere, A.; Schirmer, H.; Duetsch, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3964. (i) Dötz, K. H.; Tomuschat, P. *Chem. Soc. Rev.* **1999**, *28*, 187. (j) Herndon, J. W. *Coord. Chem. Rev.* **1999**, *181*, 177. (k) *Metal Carbenes in Organic Synthesis*; Dörwald, F. Z., Ed.; Wiley-VCH: New York, 1999. (l) *Metal Carbenes in Organic Synthesis. Topics in Organometallic Chemistry, 13*; Dötz, K. H., Ed.; Springer-Verlag: Berlin, Heidelberg. 2004. (m) Barluenga, J.; Fernandez-Rodriguez, M. A.; Aguilar, E. *J. Organomet. Chem.* **2005**, *690*, 539.

[98] Schrock, R. R. *J. Am. Chem. Soc.* **1974**, *96*, 6796.

[99] For an introduction to the metal carbene complexes, see: (a) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*, 3rd Ed.; John Wiley & Sons, Inc: New York, 2001. (b) Spessard, G. O.; Miessler, G. L. *Organometallic Chemistry*; Prentice Hall: Upper Saddle River, New Jersey, 1996.

[100] Aumann, R.; Fischer, E. O. *Chem. Ber.* **1968**, *101*, 954.

[101] (a) Harvey, D. F.; Brown, M. F. *Tetrahedron Lett.* **1990**, *31*, 2529. (b) Alkyl fluorosulfonates were used before, see: Casey, C. P.; Cyr, C. R.; Boggs, R. A. *Synth. Inorg. Met. Org. Chem.* **1973**, *3*, 249.

[102] Connor, J. A.; Jones, E. M. *J. Chem. Soc. A* **1971**, 3368.

[103] Ref. 96, p 153.

[104] (a) Semmelhack, M. F.; Lee, G. R. *Organometallics* **1987**, *6*, 1839. (b) Imwinkeried, R.; Hegedus, L. S. *Organometallics* **1988**, *7*, 702. (c) Schwindt, M. A.; Lejon, T.; Hegedus, L. S. *Organometallics* **1990**, *9*, 2814. (d) Bueno, A. B.; Moser, W. H.; Hegedus, L. S. *J. Org. Chem.* **1998**, *63*, 1462.

[105] (a) Dötz, K. H.; Sturm, W.; Alt, H. G. *Organometallics* **1987**, *6*, 1424. (b) Alt, H. G.; Englhardt, H. F.; Steinlein, E.; Rogers, R. D. *J. Orgnomet. Chem.* **1988**, *344*, 321. (c) Parlier, A.; Rudler, H. *J. Chem. Soc., Chem. Commun.* **1986**, 514.

[106] For reviews, see: (a) Ref. 97(g); (b) Brookhart, M.; Studabaker, W. B. *Chem. Rev.* **1987**, *87*, 411. (c) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919.

[107] For a review for the preparation of 5-membered carbocyclic rings, see: Herndon, J. W. *Tetrahedron* **2000**, *56*, 1257.

[108] (a) Wulff, W. D.; Yang, D. C. *J. Am. Chem. Soc.* **1983**, *105*, 6726. (b) Wulff, W. D.; Bauta, W. E.; Kaesler, R. W.; Lankford, P. J.; Miller, R. A.; Murray, C. K.; Yang, D. C. *J. Am. Chem. Soc.* **1990**, *112*, 3642 and references therein. (c) Anderson, B. A.; Wulff, W. D.; Powers, T. S.; Tribbitt, S.; Rheingold, A. L. *J. Am. Chem. Soc.* **1992**, *114*, 10784. (d) Wulff, W. D.; Powers, T. S. *J. Org. Chem.* **1993**, *58*, 2381. (e) Powers, T. S.; Jiang, W.; Su, J.; Wulff, W. D. *J. Am. Chem. Soc.* **1997**, *119*, 6438.

[109] a) Faron, K. L.; Wulff, W. D. *J. Am. Chem. Soc.* **1988**, *110*, 8727. (b) Wulff, W. D.; Faron, K. L.; Su, J.; Springer, J. P.; Rheingold, A. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 197 and references therein.

[110] (a) Fischer, E. O.; Kalder, H. J. *J. Orgnomet. Chem.* **1977**, *13*, 57. (b) Pipoh, R.; van Eldik, R.; Henkel, G. *Organometallics* **1993**, *12*, 2236 and references therein.

[111] For example, the pK_a value of α-protons in methyl(methoxycarbene)pentacarbonyl chromium(0) is about 8, see: Casey, C. P.; Anderson, R. L. *J. Am. Chem. Soc.* **1974**, *96*, 1230.

[112] (a) Wang, H.; Hsung, R. P.; Wulff, W. D. *Tetrahedron Lett.* **1998**, *39*, 1849. (b) Aumann, R.; Heinen, H. *Chem. Ber.* **1987**, *120*, 537. (c) Dötz, K. H.; Noack, R.; Harms, K. *Tetrahedron* **1990**, *46*, 1235. (d) Wulff, W. D.; Gilbertson, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 503.

[113] Wulff, W. D.; Kaesler, R. W. *Organometallics* **1985**, *4*, 1461-1463.

[114] (a) Snider, B. B. *Chem. Rev.* **1988**, *88*, 793. (b) Chen, L. Y.; Ghosez, L. *Tetrahedron: Aymmetry* **1991**, *2*, 1181. (c) Xu, S. L.; Xia, H. J.; Moore, H. W. *J. Org. Chem.* **1991**, *56*, 6094. (d) Baeckstrom, P.; Li, L.; Polec, I.; Unelius, C. R.; Wimalasiri, W. R. *J. Org. Chem.* **1991**, *56*, 3358. (e) Snider, B. B.; Allentoff, A. J. *J. Org. Chem.* **1991**, *56*, 321. (f) Lee, S. Y.; Kulkarni, Y. S.; Burbaum, B. W.; Johnston, M. I.; Snider, B. B. *J. Org. Chem.* **1988**, *53*, 1848. (g) Snider, B. B.; Walner, M. *Tetrahedron* **1989**, *45*, 3171.

[115] Bellus, D.; Ernst, G. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 797.

[116] Kim, O. K.; Wulff, W. D.; Jiang, W. *J. Org. Chem.* **1993**, *58*, 5571-5573.

[117] Kim, O. K. Ph.D. Thesis, The University of Chicago, 1990.

[118] For a related metal-free crossed [2 + 2] cycloaddition, see Ref. 20(a), (e), (f) and (g).

[119] Jiang, W.; Fuertes, M. J.; Wulff, W. D. *Tetrahedron* **2000**, *56*, 2183.

[120] (a) Kulkarni, Y. S.; Snider, B. B. *J. Org. Chem.* **1985**, *50*, 2809. (b) Widmark, G. *Acta Chem. Scand.* **1955**, *9*, 941.

[121] Klusener, P. A.; Kulik, W.; Brandsma, L. *J. Org. Chem.* **1987**, *52*, 5261.

[122] (a) Lochmann, L; Pospisil, J.; Lim, D. *Tetrahedron Lett.* **1966**, 257. (b) Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9.

[123] Jiang, W. Ph.D. Thesis, The University of Chicago, 1996.

[124] There existed some inconsistencies in the spectra that were not very convincing for the proposed tricyclic structure. For example, the ^{13}C NMR spectrum showed three carbons above 200 ppm which better fit the triketone structure, while DEPT spectrum showed six quaternary carbons above 70 ppm that indicated the β-diketone should be in the enol form. Furthermore, the exchangeable proton at 5 ppm to be assigned from the β-hydroxy group was not very reasonal since it is expected to be above 10 ppm.

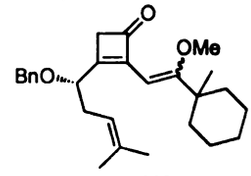
[125] (a) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535. (b) For a recent synthetic application of the Grob fragmentaion, see: Molander, G. A.; Huerou, Y. L.; Brown, G. A. *J. Org. Chem.* **2001**, *66*, 4511.

[126] Fuertes, M. J. Ph.D. Thesis, The University of Chicago, 2001.

[127] Strobel, M. P.; Andrieu, C. G.; Paquer, D.; Vazeux, M.; Parm, C. C. *Nouv. J. Chim.* **1980**, *4*, 101.

[128] The reaction of **63b** and **110a** was performed by Fuertes (see Ref. 126).

[129] When complex **63c** was used in the reaction, the cyclobutenone product **118cc** was isolated in 16% yield as a single isomer, whose stereochemistry was not determined.



118cc

[130] Chan, K. S.; Peterson, G. A.; Brandvold, T. A.; Faron, K. L.; Challener, C. A.; Hyldahl, C.; Wulff, W. D. *J. Organomet. Chem.* **1987**, *334*, 9.

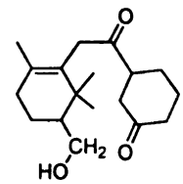
[131] Jiang also carried out the hydrolysis of **99a** and obtained very similar results, see: Ref 123.

[132] Aoyama, H.; Tokunaga, M.; Hiraiwa, S.-I.; Shirogane, Y.; Obora, Y.; Tsuji, Y. *Org. Lett.* **2004**, *6*, 509.

[133] Wijkens, P.; Vermeer, P. *J. Organomet. Chem.* **1986**, *301*, 247.

[134] Similar fragmentation for a related compound has been reported, see: (a) Kulkarni, Y. S.; Niwa, M.; Ron, E.; Snider, B. B. *J. Org. Chem.* **1987**, *52*, 1568. (b) Hebrault, D.; Uguen, D. *Tetrahedron Lett.* **1998**, *39*, 6699.

[135] The corresponding alcohol **163a** was formed in ~ 40% yield.



163a

[136] For an introduction to *N*-acylimidazoles, see: (a) Fife, T. H. *Acc. Chem. Res.* **1993**, *26*, 325 and reference therein. (b) Zaramella, S.; Stromberg, R.; Yeheskiely, E. *Eur. J. Org. Chem.* **2002**, 2633.

[137] Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis,* 3rd ed.; John Wiley & Sons, Inc: New York, 1999.

[138] For an inverse electron demand [4 + 2] reaction involving pyranylidene carbene complexes , see: Wang, S. L. B.; Wulff, W. D. *J. Am. Chem. Soc.* **1990**, *112*, 4550.

[139] For recent examples of diastereo- and enantioselective cyclopropanation with Fischer carbene complexes, see: (a) Barluenga, J.; Suarez-Sobrino, A. L.; Tomas, M.; Garcia-Granda, S.; Santiago-Garcia, R. *J. Am. Chem. Soc.* **2001**, *123*, 10494. (b) Barluenga, J.; Bernad, P., Jr.; Concellon, J. M. *J. Org. Chem.* **1997**, *62*, 6870.

[140] (a) Fischer, E. O.; Dötz, K. H. *Chem. Ber.* **1970**, *103*, 1273. (b) Dötz, K. H.; Fischer, E. O. *Chem. Ber.* **1972**, *105*, 1356. (c) Wienand, A.; Reissig, H.-U. *Tetrahedron Lett.* **1988**, *29*, 2315. (d) Herndon, J. W.; Tumer, S. U. *Tetrahedron Lett.* **1989**, *30*, 4771. (e) Harvey, D. F.; Brown, M. F. *Tetrahedron Lett.* **1990**, *31*, 2529. (f) Wienand, A.; Reissig, H.-U. *Organometallics* **1990**, *9*, 3133. (g) Herndon, J. W.; Tumer, S. U. *J. Org. Chem.* **1991**, *56*, 286. (h) Wienand, A.; Reissig, H.-U. *Chem. Ber.* **1991**, *124*, 957.

[141] (a) Fischer, E. O.; Dötz, K. H. *Chem. Ber.* **1972**, *105*, 3966. (b) Dorrer, B.; Fischer, E. O.; Kalbfus, W. *J. Organomet. Chem.* **1974**, *81*, C20. (c) Wulff, W. D.; Yang, D. C.; Murray, C. K. *Pure Appl. Chem.* **1988**, *60*, 137.

[142] Barluenga, J.; López, S.; Trabanco, A. A.; Fernández-Acebes, A.; Flórez, J. *J. Am. Chem. Soc.* **2000**, *122*, 8145.

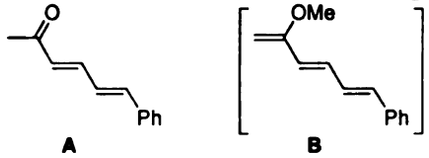
[143] For a review on dienyl carbene complexes (1-metalla-1,3,5-hexatrienes), see: Aumann, R. *Eur. J. Org. Chem.* **2000**, 17.

[144] Murray, C. K.; Yang, D. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1990**, *112*, 5660.

[145] An example of cyclopropanation with acyloxy dienyl carbene complex has also been reported, see: Ref. 144.

[146] (a) Zheng, Q.-H.; Su, J. *Synth. Commun.* **1999**, 3467. (b) Nandanan, E.; Jang, S.-Y.; Moro, S.; Kim, H. O.; Siddiqui, M. A.; Russ, P.; Marquez, V. E.; Busson, R.; Herdewijn, P.; Karden, T. K.; Boyer, J. L.; Jacobson, K. A. *J. Med. Chem.* **2000**, *43*, 829. (c) Venneri, P. C.; Warkentin, J. *Can. J. Chem.* **2000**, *78*, 1194.

[147] In the case when **181b** was treated with ethyl enol ether **185**, about 20% of ketone **A** was obtained, presumably hydrolyzed from the metathesis product **B**. This type of metathesis is well documented in the literature, for an example, see: Ref. 141(c).



A **B**

[148] For the preparation of methyl alkenyloxy chromium carbene complexes, see: (a) Söderberg, B. C.; Hegedus, L. S.; Sierra, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 4364. (b) Christoffers, J.; Dötz, K. H. *Organometallics* **1994**, *13*, 4189. (c) Xu, Y.-C.; Wulff, W. D. *J. Org. Chem.* **1987**, *52*, 3263.

[149] Söderberg, B. C.; Hegedus, L. S. *Organometallics* **1990**, *9*, 313.

[150] Dötz, K. H.; Noack, R.; Harms, K. *Tetrahedron* **1990**, *46*, 1235.

[151] Barluenga, J.; Aznar, F.; Palomero, M. A. *J. Org. Chem.* **2003**, *68*, 537.

[152] Wulff, W. D.; Yang, D. C.; Murray, C. K. *J. Am. Chem. Soc.* **1988**, *110*, 2653.

[153] Intramolecular cyclopropanation with acyloxycarbene complexes has been reported, see: Barluenga, J.; Aznar, F.; Gutierrez, I.; Martin, J. A. *Org. Lett.* **2002**, *4*, 2719.

[154] For applications of cyclopropanes in organic synthesis, see: (a) Reissig, H.-U. *Top. Curr. Chem.* **1988**, *144*, 73. (b) Reissig, H.-U. In The Chemistry of the Cyclopropyl Group; Patai, S.; Rappoport, A., Eds.; John Wiley and Sons: New York, 1987; Chapter 8.

[155] For examples, see: (a) Taber, D. F.; Joshi, P. V.; Kanal, K. *J. Org. Chem.* **2004**, *69*, 2268. (b) Zuo, G.; Louie, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2777.

[156] For reviews on the benzannulation reaction: see: (a) Ref. 97. (b) Waters, M. L.; Wulff, W. D. *Org. Reactions* in press.

[157] Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 587.

[158] For discussions on the mechanistic issues, see: (a) Waters, M. L.; Bos, M. E.; Wulff, W. D., *J. Am. Chem. Soc.*, **1999**, *121*, 6403, and references therein. (b) Barluenga, J.; Aznar, F.; Gutierrez, I.; Martin, A.; Garcia-Granda, S.; Llorca-Baragano, M. *J. Am. Chem. Soc.* **2000**, *122*, 1314 and references therein. (c) Ref. 97.

[159] Fischer, H.; Mühlemeier, J.; Märkl, R.; Dötz, K, H. *Chem. Ber.* **1982**, *115*, 1355.

[160] (a) Wulff, W. D.; Tang, P.-C.; McCallum, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 7677. (b) Dötz, K, H.; Mühlemeier, J.; Schubert, U.; Orama, O. *J. Organomet. Chem.* **1983**, *247*, 187. (c) Wulff, W. D.; Chan, K.-S.; Tang, P.-C. *J. Org. Chem.* **1984**, *49*, 2293. (d) Yamashita, A.; Toy, A. *Tetrahedron Lett.* **1986**, *27*, 3471.

[161] Hoffman, P.; Hämmerle, M.; Unfried, G. *New J. Chem.* **1991**, *15*, 769.

[162] (a) Gross, M. F.; Finn, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 10921. (b) Semmelhack, M. F.; Bozell, J. J.; Keller, L.; Sato, T.; Spiess, E. J.; Wulff, W. D.; Zack, A. *Tetrahedron* **1985**, *41*, 5803. (c) Semmelhack, M. F.; Bozell, J. J.; Sato, T.; Spiess, E. J.; Wulff, W.; Zack, A. *J. Am. Chem. Soc.* **1982**, *104*, 5850.

[163] (a) Tang, P.-C.; Wulff, W. D. *J. Am. Chem. Soc.* **1984**, *106*, 1132. (b) Wulff, W. D.; Gilbertson, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 503. (C) Gilbertson, S. R.; Wulff, W. D. *Synlett* **1989**, 47.

[164] Bauta, W. E.; Wulff, W. D.; Pavkovic, S. F.; Zaluzec, E. J. *J. Org. Chem.* **1989**, *54*, 3249.

[165] (a) Dötz, K, H.; Dietz, R.; Kappenstein, C.; Neugebauer, D.; Schubert, U. *Chem. Ber.* **1979**, *112*, 3682. (b) Quinn, J. F.; Bos, M. E.; Wulff, W. D. *Org. Lett.* **1999**, *1*, 161.

[166] (a) Dötz, K, H. *J. Organomet. Chem.* **1977**, *140*, 177. (b) Yamashita, A. *Tetrahedron Lett.* **1986**, *27*, 5915.

[167] McCallum, J. S.; Kunng, R.-A.; Gilbertson, S. R.; Wulff, W. D. *Organometallics* **1988**, *7*, 2346.

[168] (a) Wulff, W. D.; Bax, B. M.; Brandvold, T. A.; Chan, K. S.; Gilbert, A. M.; Hsung, R. P.; Mitchell, J.; Clardy, J. *Organometallics* **1994**,13, 102. (b) Foley, H. C.; Strubinger, L. M.; Targos, T. S.; Geoffroy, G. L. *J. Am. Chem. Soc.* **1983**, *105*, 3064. (c) Dötz, K, H.; Larbig, H. *J. Organomet. Chem.* **1991**, *405*, C38. (d) Dötz, K, H.; Larbig, H. *Bull. Soc. Chim. Fr.* **1992**, *129*, 579.

[169] Katz, T. J.; Lee, S. J. *J. Am. Chem. Soc.* **1980**, *102*, 422.

[170] (a) Ur-Rahman, A.; Schnatter, W. F. K.; Manolache, N. *J. Am. Chem. Soc.* **1993**, *115*, 9848. (b) Semmelhack, M. F.; Park, T. *Organometallics* **1986**, *5*, 2550. (c) Semmelhack, S. F.; Tamura, R.; Schnatter, W.; Springer, J. *J. Am. Chem. Soc.* **1984**, *106*, 5363.

[171] Wulff, W. D.; Gilbertson, S. R.; Springer, J. P. *J. Am. Chem. Soc.* **1986**, *108*, 520.

[172] (a) Balzer, B. L.; Cazanoue, M.; Sabat, M.; Finn, M. G. *Organometallics* **1992**, *11*, 1759. (b) Balzer, B. L.; Cazanoue, M.; Finn, M. G. *J. Am. Chem. Soc.* **1992**, *114*, 8735.

[173] (a) Chan, K. S.; Peterson, G. A.; Brandvold, T. A.; Faron, K. L.; Challener, C. A.; Hyldahl, C.; Wulff, W. D. *J. Organomet. Chem.* **1987**, *334*, 9. (b) Bos, M. E.; Wulff, W. D.; Miller, R. A.; Chamberlin, S.; Brandvold, T. A. *J. Am. Chem. Soc.* **1991**, *113*, 9293. (c) Wulff, W. D.; Tang, P.-C.; Chan, K. S.; McCallum, J. S.; Yang, D. C.; Gilbertson, S. R. *Tetrahedron* **1985**, *41*, 5813.

[174] Gross, M. F.; Finn, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 10921.

[175] Liptak, V.; Wulff, W. D. unpublished results.

[176] Yamashita, A. *Tetrahedron Lett.* **1986**, *27*, 5915.

[177] (a) Wulff, W. D.; Gilbert, A. M.; Hsung, R. P.; Rahm, A. *J. Org. Chem.* **1995**, *60*, 4566. (b) Barluenga, J.; Aznar, F.; Gutierrez, I.; Martin, A.; Garcia-Granda, S.; Llorca-Baragano, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 1314.

[178] (a) Dötz, K. H.; Grotjahn, D.; Harms, K. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1384. (b) Grotjahn, D. B.; Kroll, F. E. K.; Schäfer, T.; Harms, K.; Dötz, K. H. *Organometallics* **1992**, 11, 298.

[179] Merino, I.; Hegedus, L. S. *Organometallics* **1995**, *14*, 2522.

[180] (a) Wulff, W. D. *Organometallics* **1998**, *17*, 3116, and references therein. (b) Hsung, R. P.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 6449. (c) Hsung, R. P.; Wulff, W. D.; Challener, C. A. *Synthesis* 1996, 773. (d) Dötz, K. H.; Stinner, C. *Tetrahedron: Asymmetry* **1997**, *8*, 1751.

[181] Wulff, W. D.; McCallum, J. S.; Kunng, F. A. *J. Am. Chem. Soc.* **1988**, *110*, 7419.

[182] Xu, Y.-C.; Kohlman, D. T.; Liang, S. X.; Erikkson, C. *Org. Lett.* **1999**, *1*, 1599.

[183] The total synthesis has been finishied in our group, but yet to be published. For preliminary synthetic studies, see: Liptak, V. P; Wulff, W. D. *Tetrahedron* **2000**, *56*, 10229.

[184] Wulff, W. D.; Tang, P.-C. *J. Am. Chem. Soc.* **1984**, *106*, 434.

[185] (a) Dötz, K, H.; Popall, M.; Müller, G. *J. Organomet. Chem.* **1987**, *334*, 57. (b) Dötz, K, H.; Popall, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1158. (c) Dötz, K, H.; Popall, M. *Chem. Ber.* **1988**, *121*, 665.

[186] Wulff, W. D.; Xu, Y.-C. *J. Am. Chem. Soc.* **1988**, *110*, 2312.

[187] Roush, W. R.; Neitz, R. J. *J. Org. Chem.* **2004**, *69*, 4906.

[188] (a) Boger, D. L.; Jacobson, I. C. *Tetrahedron Lett.* **1989**, *30*, 2037. (b) Boger, D. L.; Jacobson, I. C. *J. Org. Chem.* **1990**, *55*, 1919. (c) Boger, D. L.; Jacobson, I. C. *J. Org. Chem.* **1991**, *56*, 2115. (d) Boger, D. L.; Hüter, O.; Mbiya, K.; Zhang, M. *J. Am. Chem. Soc.* **1995**, *117*, 11839.

[189] The synthesis of the major portion of (-)-kendomycin has been reported: White, J. D.; Smits, H. *Org. Lett.*, **2005**, *7*, 235.

[190] Bao, J.; Wulff, W. D.; Dominy, J. B.; Fumo, M. J.; Grant, E. B.; Rob, A. C.; Whitcomb, M. C.; Yeung, S.-M.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 3392.

[191] (a) Antilla, J. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 5099. (b) Antilla, J. C.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4518.

[192] (a) Bao, J.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 3814. (b) Heller, D. P.; Goldberg, D. R.; Wulff, W. D. *J. Am. Chem. Soc.* **1997**, *119*, 10551.

[193] Xue, S.; Yu, S.; Deng, Y.; Wulff, W. D. *Angew. Chem. Int. Ed.* **2001**, *40*, 2271.

[194] (a) McGuire, M. A.; Hegedus, L. S. *J. Am. Chem. Soc.* **1982**, *104*, 5538. (b) Hegedus, L. S.; deWeck, G.; D'Andreas, S. *J. Am. Chem. Soc.* **1988**, *110*, 2122. (c) Hegedus, L. S.; Schwindt, M. A.; De Lombaer, S.; Imwinkelried, R. *J. Am. Chem. Soc.* **1990**, *112*, 2264. (d) Söderberg, B. C.; Hegedus, L. S.; Sierra, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 4364.

[195] For reviews of photochemistry of Fischer carbene complexes, see: (a) Ref. 1e. (b) Hegedus, L. S. *Tetrahedron* **1997**, *53*, 4105.

[196] (a) Wulff, W. D. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1989; Vol. 1, p 336. (b) Yang, D. C. Ph.D. Thesis, University of Chicago, 1986, p 28.

[197] Merlic, C. A.; Xu, D. *J. Am. Chem. Soc.* **1991**, *113*, 7418.

[198] Merlic, C. A.; Roberts, W. M. *Tetrahedron Lett.* **1993**, *34*, 7379.

[199] For [4 + 2] cycloaddition of alkynyl carbene complexes with 1,3-dienes, see: Wulff, W. D.; Yang, D. C. *J. Am. Chem. Soc.* **1984**, *106*, 7565.

[200] For [2 + 2] cycloaddition of alkynyl carbene complexes with alkenes, see: (a) Faron, K. L.; Wulff, W. D. *J. Am. Chem. Soc.* **1988**, *110*, 8727. (b) Wulff, W. D.; Faron, K. L.; Su, J.; Springer, J. P.; Rheingold, A. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 197.

[201] Merlic, C. A.; Xu, D.; Gladstone, B. G. *J. Org. Chem.* **1993**, *58*, 538.

[202] (a) Merlic, C. A.; Burns, E. E.; Xu, D.; Chen, S. Y. *J. Am. Chem. Soc.* **1992**, *114*, 8722. (b) Merlic, C. A.; Burns, E. E. *Tetrahedron Lett.* **1993**, *34*, 5401.

[203] (a) Merlic, C. A.; Aldrich, C. C.; Albaneze-Walker, J.; Saghatelian, A. *J. Am. Chem. Soc.* **2000**, *122*, 3224. (b) Merlic, C. A.; Aldrich, C. C.; Albaneze-Walker, J.; Saghatelian, A.; Mammen, J. *J. Org. Chem.* **2001**, *66*, 1297.

[204] Manish, R.; Wulff, W. D. *Org. Lett.* **2004**, *6*, 329.

[205] (a) Barluenga, J.; Aznar, F.; Palomero, M. A. *J. Org. Chem.* **2003**, *68*, 537. (b) Barluenga, J.; Aznar, F.; Palomero, M. A. Barluenga, S. *Org. Lett.* **1999**, *1*, 541.

[206] Wu, H.-P.; Aumann, R.; Fröhlich, R.; Wibbeling, B. *Eur. J. Org. Chem.* **2000**, 1183.

[207] Mathur, P.; Ghosh, S.; Sarkar, A.; Rheingold, A. L.; Guzei, I. A. *Tetrahedron* **2000**, *56*, 4995.

[208] For organo-iron chemistry including η^4-dienyl complexes, see: *The Organic Chemistry of Iron, Vols. 1 and 2*; Koerner von Gustorf, E. A., Grevels, F.-W., Fischler, I., Eds.; Academic Press: New York; 1978 (Vol. 1) and 1981 (Vol. 2).

[209] Gomez-Gallego, M.; Mancheno, M. J.; Sierra, M. A. *Acc. Chem. Res.* **2005**, *38*, 44 and references therein.

[210] For electron figurations of metals in organometallic complexes, see: (a) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*, 3rd Ed.; John Wiley & Sons, Inc: New York, 2001. (b) Spessard, G. O.; Miessler, G. L. *Organometallic Chemistry*; Prentice Hall: Upper Saddle River, New Jersey, 1996.

[211] For an introduction to SEM/EDS analysis, see: Flegler, S. L.; Heckman, J. W.; Klomparens, K. L. *Scanning and Transmission Electron Microscopy: An Introduction*; Oxford University Press: New York, 1993.

[212] The SEM/EDS analysis results of both **254a** and **181a** are included in Appendix 3.

[213] It was known a long time ago that iron could be converted to iron carbonyl at high temperature in the presence of carbon monoxide, see: (a) Hieber, W. A. *Z. Anorg. Allegem. Chem.* **1940**, *245*, 295. (b) *Handbook of Organometallic Compounds*; Hagihara, N., Kumada, M., Okawara, R., Eds.; W. A. Benjamin, Inc.: New York, 1968; p 886.

[214] (a) Howell, J. A. S.; Johnson, B. F. G.; Josty, O. L.; Lewis, J. *J. Orgnomet. Chem.* **1972**, *39*, 329. (b) Barton, D. H. R.; Gunatilaka, A. A. L.; Nakanishi, T.; Patin, H.; Widdowson, D. A.; Worth, B. R. *J. Chem. Soc., Perkin I* **1976**, 821.

[215] A preliminary communication has been published, see: Lian, Y.; Wulff, W. D. *J. Am. Chem. Soc.* **2005**, *127*, 17162.

[216] (a) Brown, H. C.; Campbell, J. B., Jr. *J. Org. Chem.* **1980**, *45*, 389. (b) Brown, H. C.; Chandrasekharan, J. *J. Org. Chem.* **1983**, *48*, 644.

[217] (a) Wang, Z.-X.; Gao, G.-A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646. (b) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

[218] It was observed that the reaction mixture turned from clear yellowish solution to gray suspension immediately after the mixture was opened to air, suggesting the loss of iron tricarbonyl from the complex.

[219] Chen, J.; Wang, T.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 2827.

[220] (a) Aumann, R.; Fröhlich, R.; Prigge, J.; Meyer, O. *Organometallics* **1999**, *18*, 1369. (b) Wu, H.-P.; Aumann, R.; Fröhlich, R.; Wibbeling, B. *Eur. J. Org. Chem.* **2000**, 1183. (c) Duetsch, M.; Stein, F.; Lackmann, R.; Pohl, E.; Herbst-Irmer, R.; de Meijere, A.

Chem. Ber. **1992**, *125*, 2051. (d) Wu, Y.-T.; Schirmer, H.; Noltemeyer, M.; de Meijere, A. *Eur. J. Org. Chem.* **2001**, 2501. (e) For a related microreview, see: Aumann, R. *Eur. J. Org. Chem.* **2000**, 17.

[221] Demetalation by $FeCl_3$ or $Ce(NH_4)_2(NO_3)_6$ is not effective. For other possible methods, see: Franck-Neumann, M.; Geoffroy, P.; Gassmann, D. *Synlett* **2002**, 2054.

[222] Franck-Neumann, M.; Geoffroy, P.; Winling, A. *Synlett* **1995**, 341.

[223] Crombie, L.; Crombie, W. M. L. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1267.

[224] (a) Semmelhack, M. F.; Lee, G. R. *Organometallics* **1987**, *6*, 1839. (b) Schwindt, M. A.; Lejon, T.; Hegedus, L. S. *Organometallics* **1990**, *9*, 2814. (c) Bueno, A. B.; Moser, W. H.; Hegedus, L. S. *J. Org. Chem.* **1998**, *63*, 1462.

[225] (a) Darbasie, N. D.; Schnatter, W. F. K.; Warner, K. F.; Manolache, N. *Tetrahedron Lett.* **2006**, *47*, 963. (b) Morris, K. G.; Saberi, S. P.; Salter, M. M.; Thomas, S. E.; Ward, M. F.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1993**, *49*, 5617. (c) Benyunes, S. A.; Gibson, S. E.; Peplow, M. A. *Tetrahedron: Asymmetry* **1997**, *8*, 1535.

[226] (a) For a comprehensive review of vinylketene transition metal complexes, see: Gibson, S. E.; Peplow, M. A. *Adv. Organomet. Chem.* **1999**, *44*, 275. (b) For a related reaction of vinylketene cobalt(I) complexes and alkynes, see: Huffman, M. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 8617.

[227] Collman, J. P. *Acc. Chem. Res.* **1975**, *8*, 342.

[228] (a) Semmelhack, M. F.; Tamura, R. *J. Am. Chem. Soc.* **1983**, *105*, 4099. (b) Chen, J.-B.; Lei, G.-X.; Yin, J.-G. *Acta Chimica Sinica* **1989**, *47*, 1105.

[229] (a) Mitsudo, T.; Ishihara, A.; Kadokura, M.; Watanabe, Y. *Organometallics* **1986**, *5*, 238. (b) Mitsudo, T.; Watanabe, H.; Sasaki,T.; Takegami, Y.; Watanabe, Y. *Organometallics* **1989**, *8*, 368.

[230] (a) Alcock, N. W.; Richards, C. J.; Thomas, S. E. *Organometallics* **1991**, *10*, 231. (b) For a related isolated chromium(0) vinylketene complex, see: Anderson, B. A.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1990**, *112*, 8615.

[231] (a) Fischer, E. O.; Beck, H. J. *Angew. Chem., Int. Ed.* **1970**, *9*, 72. (b) Fischer, E. O.; Beck, H. J.; Kreiter, C. G.; Lynch, J.; Mueller, J.; Winkler, E. *Chem. Ber.* **1972**, *105*, 162.

[232] (a) Alcock, N. W.; Richards, C. J.; Thomas, S. E. *Organometallics* **1991**, *10*, 231. (b) Mitsdo, T.; Watanabe, H.; Sasaki, T.; Takegami, Y.; Watanabe, Y. *Organometallics* **1989**, *8*, 368.

[233] Huffman, M. A.; Liebeskind, L.; Pennington, W. T. *Organometallics* **1992**, *11*, 255.

[234] Xu, D. Ph.D. Thesis, Universisty of California, Los Angeles, 1991.

[235] For an η^2,η^4-norbornadienyl iron dicarbonyl ketene complex, see: (a) Park, J.; Kang, S.; Whang, D.; Kim, K. *Organometallics* **1991**, *10*, 3413. (b) Park, J.; Kang, S.; Whang, D.; Kim, K. *Organometallics* **1992**, *11*, 1738.

[236] There are examples of carbonyl-vinylketene coupling by addition of donor ligands, see: (a) Mitsudo, T.-A.; Sasaki, T.; Watanabe, Y.; Takegami, Y. *J. Chem. Soc., Chem. Commun.* **1978**, 252. (b) Mayr, A.; Asaro, M. F.; Glines, T. J. *J. Am. Chem. Soc.* **1987**, *109*, 2215.

[237] An ethoxy analog of **294** has very recently reported, see: Ref 225(a).

[238] For reactions of vinylketene iron complexes with alkynes, see: Refs. 225 and 226.

[239] Kuhn, D. E.; Lillya, C. P. *J. Am. Chem. Soc.* **1972**, *94*, 1682.

[240] For the preparation of **181a** and **181b**, see: Ref. 215; or Section 5.4 in the text.

[241] Söderberg, B. C.; Hegedus, L. S.; Sierra, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 4364.

[242] Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.

[243] Wright, B. B.; Platz, M. S. *J. Am. Chem. Soc.* **1984**, *106*, 4175.

[244] (a) Ref. 112a; (b) Anderson, R. L. Ph. D. Thesis, University of Wisconisn, 1974, p. 60.

[245] For the preparation of ethoxy carbene complex, see: Ref. 112b.

[246] Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, 7.

[247] Reid, M.; Rowe, D. J.; Taylor, R. J. K. *Chem. Commun.* **2003**, 2284.

[248] Hegedus, L. S.; McGuire, M. A.; Schultze, L. M. *Org. Synth. Coll. Vol. VIII,* **1993**, 216.

[249] Brown, H. C.; Campbell, J. B., Jr. *J. Org. Chem.* **1980**, *45*, 389. (b) Brown, H. C.; Chandrasekharan, J. *J. Org. Chem.* **1983**, *48*, 644.

[250] (a) Wang, Z.-X.; Gao, G.-A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646. (b) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

[251] (a) Chen, J.; Che, C.-M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4950. (b) Chinkov, N.; Majumdar, S.; Marek, I. *J. Am. Chem. Soc.* **2003**, *125*, 13258.

[252] For an analog of **60a**, see: Sierra, M. A.; del Amo, J. C.; Mancheño, M. J.; Gómez-Gallego, M. *J. Am. Chem. Soc.* **2001**, *123*, 851.

[253] Lai, C.-H.; Shen, Y.-L.; Wang, M.-N.; Rao, N. S. K.; Liao, C.-C. *J. Org. Chem.* **2002**, *67*, 6493.

[254] Howell, J. A. S.; Johnson, B. F. G.; Josty, P. L.; Lewis, J. *J. Organometal. Chem.* **1972**, *39*, 329.

[255] Chen J.; Wang, T.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 2827.

[256] Khand, I. U.; Pauson, P. L. *J. Chem. Res. (S)* **1977**, 9.

[257] Crombie, L.; Crombie, W. M. L. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1267.

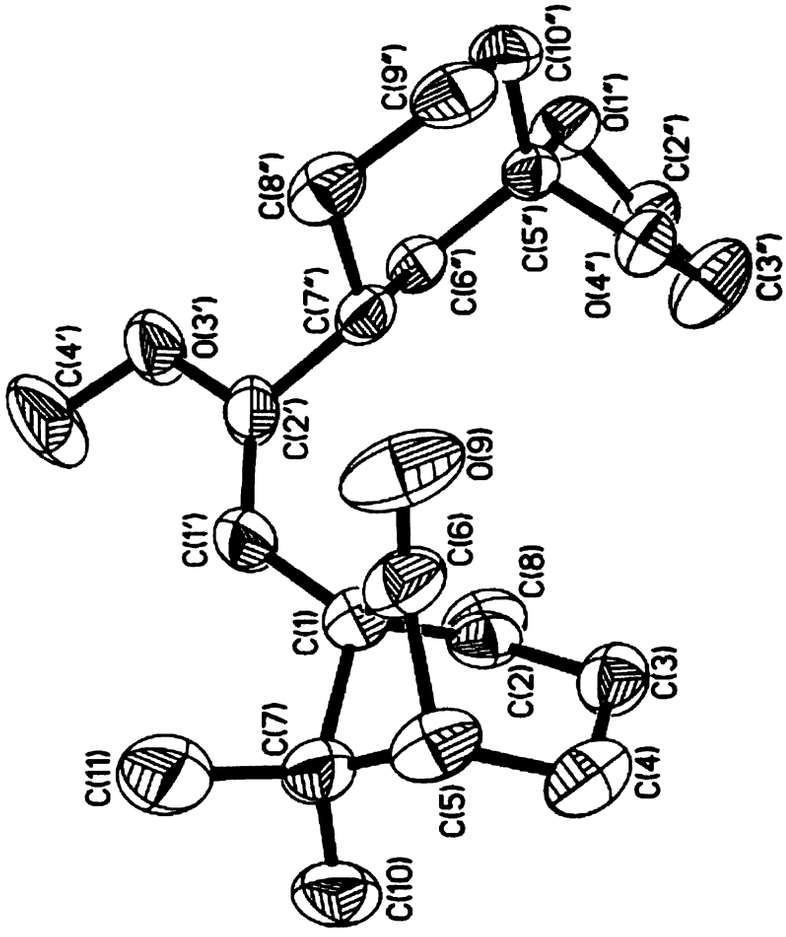
[258] Drew, J.; Letellier, M.; Morand, P.; Szabo, A. G. *J. Org. Chem.* **1987**, *52*, 4047.

[259] The (anticipated) ethylation followed the literature procedure for the preparation of iron carbene complexes, see: Ref. 228(b).

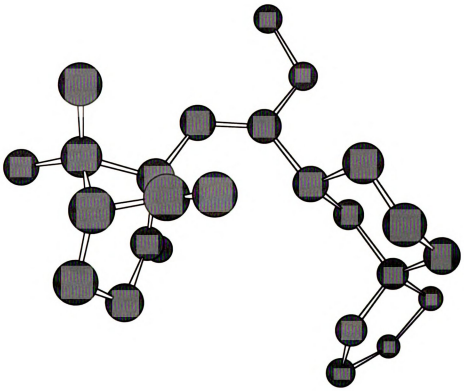
APPENDICES

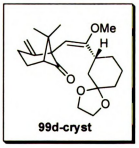
APPENDIX 1

X-RAY STRUCTURE AND CRYSTAL DATA FOR **99d-cryst**



ORTEP Diagram of **99d-cryst**





X-ray Structure of **99d-cryst** (Displayed in Chem Draw®)

X-ray Crystallographic Data for **99d-cryst**

Table 1. Crystal data and structure refinement for 1-[2'-(1",4"-Dioxa-spiro[4.5]dec-7"-yl)-2'-methoxy-vinyl]-7,7-dimethyl-2-methylene-bicyclo[3.1.1]heptan-6-one

Identification code	shelxl
Empirical formula	C21 H30 O4
Formula weight	346.45
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system	monoclinic
Space group	P 2(1)/c
Unit cell dimensions	a = 24.575(5) A b = 8.6136(17) A c = 18.416(4) A alpha = 90 deg. beta = 95.55(3) deg. gamma = 90 deg.
Volume	3880.0(13) A^3
Z	8
Density (calculated)	1.186 Mg/m^3
Absorption coefficient	0.080 mm^-1
F(000)	1504
Crystal size	0.6 x 0.3 x 0.3 mm
Theta range for data collection	1.67 to 28.33 deg.
Index ranges	-32<=h<=31, -11<=k<=11, -23<=l<=23
Reflections collected / unique	45301 / 9406 [R(int) = 0.2185]
Completeness to theta = 28.33	97.0%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9406 / 0 / 512
Goodness-of-fit on F^2	0.935
Final R indices [I>2sigma(I)]	R1 = 0.0748, wR2 = 0.1225

R indices (all data)	R1 = 0.2663, wR2 = 0.1734
Extinction coefficient	0.0023(3)
Largest diff. peak and hole	0.241 and -0.193 e.A^-3

Table 2. Atomic coordinates (x 10^4), equivalent isotropic displacement parameters (A^2 x 10^3), and occupancies for 1-[2'-(1",4"-Dioxa-spiro[4.5]dec-7"-yl)-2'-methoxy-vinyl] -7,7-dimethyl-2-methylene-bicyclo[3.1.1]heptan-6-one

	x	y	z	U(eq)	Occ.
C(1)	1076(1)	5731(4)	4109(2)	45(1)	1
C(2)	1383(2)	4311(4)	4407(2)	43(1)	1
C(3)	1932(2)	4660(4)	4809(2)	50(1)	1
C(4)	1948(2)	6197(4)	5226(2)	56(1)	1
C(5)	1543(2)	7340(5)	4840(2)	53(1)	1
C(6)	1505(2)	7010(4)	4030(2)	52(1)	1
C(7)	950(2)	6749(5)	4803(2)	56(1)	1
C(8)	1191(2)	2883(5)	4326(2)	65(1)	1
O(9)	1685(1)	7634(3)	3520(1)	79(1)	1
C(10)	765(2)	5873(5)	5458(2)	69(1)	1
C(11)	545(2)	8050(6)	4586(3)	102(2)	1
C(1')	622(2)	5460(5)	3520(2)	58(1)	1
C(2')	688(2)	4994(4)	2847(2)	52(1)	1
O(3')	268(1)	4729(4)	2313(1)	76(1)	1
C(4')	-270(2)	4929(10)	2502(3)	152(3)	1
O(1")	1799(1)	1110(3)	1696(1)	50(1)	1
C(2")	1958(2)	94(4)	2281(2)	52(1)	1
C(3")	2287(2)	1098(4)	2835(2)	70(1)	1
O(4")	2214(1)	2638(3)	2582(1)	41(1)	1
C(5")	1792(1)	2636(4)	1988(2)	36(1)	1
C(6")	1249(1)	2999(4)	2270(2)	36(1)	1
C(7")	1223(1)	4668(4)	2545(2)	38(1)	1
C(8")	1343(2)	5788(4)	1929(2)	49(1)	1
C(9")	1897(2)	5431(4)	1683(2)	53(1)	1
C(10")	1934(2)	3777(4)	1420(2)	47(1)	1
C(21)	3921(1)	6564(4)	2318(2)	29(1)	1
C(22)	3910(1)	4848(4)	2526(2)	34(1)	1
C(23)	3413(2)	4379(4)	2899(2)	49(1)	1
C(24)	3200(2)	5667(4)	3377(2)	50(1)	1
C(25)	3341(1)	7257(4)	3087(2)	41(1)	1
C(26)	3327(1)	7183(4)	2261(2)	33(1)	1
C(27)	3969(1)	7514(4)	3068(2)	35(1)	1
C(28)	4296(2)	3857(4)	2395(2)	42(1)	1
O(29)	3030(1)	7699(2)	1761(1)	40(1)	1
C(30)	4366(2)	6868(5)	3680(2)	49(1)	1
C(31)	4085(2)	9238(4)	2952(2)	46(1)	1
C(21')	4279(1)	6995(3)	1743(2)	29(1)	1

C(22')	4190(1)	6579(3)	1045(2)	28(1)	1
O(23')	4511(1)	7012(2)	508(1)	35(1)	1
C(24')	4981(1)	7919(4)	712(2)	46(1)	1
O(21")	3733(1)	1517(3)	-69(1)	49(1)	1
C(22")	3700(4)	421(6)	471(3)	129(2)	1
C(23")	3361(2)	1043(5)	1017(2)	65(1)	1
O(24")	3191(1)	2526(2)	748(1)	44(1)	1
C(25")	3512(1)	2942(4)	171(2)	34(1)	1
C(26")	3966(1)	4022(3)	455(2)	31(1)	1
C(27")	3738(1)	5541(3)	729(2)	27(1)	1
C(28")	3361(1)	6292(4)	117(2)	33(1)	1
C(29")	2910(1)	5195(4)	-182(2)	38(1)	1
C(30")	3140(1)	3659(4)	-429(2)	35(1)	1

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table 3. Bond lengths [A] and angles [deg] for 1-[2'-(1",4"-Dioxa-spiro[4.5]dec-7"-yl)-2'-methoxy-vinyl] -7,7-dimethyl-2-methylene-bicyclo[3.1.1]heptan-6-one

C(1)---C(1')	1.498(5)
C(1)---C(2)	1.513(5)
C(1)---C(6)	1.542(5)
C(1)---C(7)	1.604(5)
C(2)---C(8)	1.321(5)
C(2)---C(3)	1.503(5)
C(3)---C(4)	1.530(5)
C(3)---H(3A)	0.9700
C(3)---H(3B)	0.9700
C(4)---C(5)	1.525(5)
C(4)---H(4A)	0.9700
C(4)---H(4B)	0.9700
C(5)---C(6)	1.513(5)
C(5)---C(7)	1.540(5)
C(5)---H(5)	0.9800
C(6)---O(9)	1.203(4)
C(7)---C(11)	1.526(5)
C(7)---C(10)	1.528(5)
C(8)---H(8A)	0.9300
C(8)---H(8B)	0.9300
C(10)--H(10A)	0.9600
C(10)--H(10B)	0.9600
C(10)--H(10C)	0.9600
C(11)--H(11A)	0.9600
C(11)--H(11B)	0.9600
C(11)--H(11C)	0.9600
C(1')--C(2')	1.327(4)
C(1')--H(1')	0.9300
C(2')--O(3')	1.375(4)
C(2')--C(7")	1.503(5)

O(3')--C(4')	1.411(5)
C(4')--H(4'A)	0.9600
C(4')--H(4'B)	0.9600
C(4')--H(4'C)	0.9600
O(1")--C(2")	1.414(4)
O(1")--C(5")	1.421(4)
C(2")--C(3")	1.511(5)
C(2")--H(2"A)	0.9700
C(2")--H(2"B)	0.9700
C(3")--O(4")	1.412(4)
C(3")--H(3"A)	0.9700
C(3")--H(3"B)	0.9700
O(4")--C(5")	1.434(3)
C(5")--C(10")	1.501(4)
C(5")--C(6")	1.509(4)
C(6")--C(7")	1.528(4)
C(6")--H(6"A)	0.9700
C(6")--H(6"B)	0.9700
C(7")--C(8")	1.539(4)
C(7")--H(7")	0.9800
C(8")--C(9")	1.508(5)
C(8")--H(8"A)	0.9700
C(8")--H(8"B)	0.9700
C(9")--C(10")	1.511(5)
C(9")--H(9"A)	0.9700
C(9")--H(9"B)	0.9700
C(10")-H(10D)	0.9700
C(10")-H(10E)	0.9700
C(21)--C(21')	1.487(4)
C(21)--C(22)	1.528(4)
C(21)--C(26)	1.548(4)
C(21)--C(27)	1.601(4)
C(22)--C(28)	1.315(4)
C(22)--C(23)	1.514(4)
C(23)--C(24)	1.539(5)
C(23)--H(23A)	0.9700
C(23)--H(23B)	0.9700
C(24)--C(25)	1.522(5)
C(24)--H(24A)	0.9700
C(24)--H(24B)	0.9700
C(25)--C(26)	1.520(4)
C(25)--C(27)	1.564(4)
C(25)--H(25)	0.9800
C(26)--O(29)	1.204(3)
C(27)--C(30)	1.523(4)
C(27)--C(31)	1.531(4)
C(28)--H(28A)	0.9300
C(28)--H(28B)	0.9300
C(30)--H(30A)	0.9600
C(30)--H(30B)	0.9600
C(30)--H(30C)	0.9600
C(31)--H(31A)	0.9600
C(31)--H(31B)	0.9600
C(31)--H(31C)	0.9600
C(21')-C(22')	1.333(4)
C(21')-H(21')	0.9300
C(22')-O(23')	1.375(3)

C(22')-C(27")	1.500(4)
O(23')-C(24')	1.416(3)
C(24')-H(24C)	0.9600
C(24')-H(24D)	0.9600
C(24')-H(24E)	0.9600
O(21")-C(22")	1.380(5)
O(21")-C(25")	1.430(3)
C(22")-C(23")	1.468(6)
C(22")-H(22A)	0.9700
C(22")-H(22B)	0.9700
C(23")-O(24")	1.419(4)
C(23")-H(23C)	0.9700
C(23")-H(23D)	0.9700
O(24")-C(25")	1.429(3)
C(25")-C(30")	1.496(4)
C(25")-C(26")	1.507(4)
C(26")-C(27")	1.529(4)
C(26")-H(26A)	0.9700
C(26")-H(26B)	0.9700
C(27")-C(28")	1.530(4)
C(27")-H(27")	0.9800
C(28")-C(29")	1.518(4)
C(28")-H(28C)	0.9700
C(28")-H(28D)	0.9700
C(29")-C(30")	1.526(4)
C(29")-H(29A)	0.9700
C(29")-H(29B)	0.9700
C(30")-H(30D)	0.9700
C(30")-H(30E)	0.9700

C(1')--C(1)---C(2)	116.6(3)
C(1')--C(1)---C(6)	120.8(3)
C(2)---C(1)---C(6)	106.9(3)
C(1')--C(1)---C(7)	118.3(3)
C(2)---C(1)---C(7)	106.3(3)
C(6)---C(1)---C(7)	82.6(3)
C(8)---C(2)---C(3)	122.4(4)
C(8)---C(2)---C(1)	123.4(4)
C(3)---C(2)---C(1)	114.1(3)
C(2)---C(3)---C(4)	113.5(3)
C(2)---C(3)---H(3A)	108.9
C(4)---C(3)---H(3A)	108.9
C(2)---C(3)---H(3B)	108.9
C(4)---C(3)---H(3B)	108.9
H(3A)--C(3)---H(3B)	107.7
C(5)---C(4)---C(3)	109.9(3)
C(5)---C(4)---H(4A)	109.7
C(3)---C(4)---H(4A)	109.7
C(5)---C(4)---H(4B)	109.7
C(3)---C(4)---H(4B)	109.7
H(4A)--C(4)---H(4B)	108.2
C(6)---C(5)---C(4)	108.2(3)
C(6)---C(5)---C(7)	85.7(3)
C(4)---C(5)---C(7)	112.3(3)
C(6)---C(5)---H(5)	115.6
C(4)---C(5)---H(5)	115.6
C(7)---C(5)---H(5)	115.6

O(9)---C(6)---C(5)	133.9(4)
O(9)---C(6)---C(1)	134.4(3)
C(5)---C(6)---C(1)	91.1(3)
C(11)--C(7)---C(10)	109.4(4)
C(11)--C(7)---C(5)	111.1(4)
C(10)--C(7)---C(5)	118.7(3)
C(11)--C(7)---C(1)	111.4(3)
C(10)--C(7)---C(1)	117.0(3)
C(5)---C(7)---C(1)	87.8(3)
C(2)---C(8)---H(8A)	120.0
C(2)---C(8)---H(8B)	120.0
H(8A)--C(8)---H(8B)	120.0
C(7)---C(10)--H(10A)	109.5
C(7)---C(10)--H(10B)	109.5
H(10A)-C(10)--H(10B)	109.5
C(7)---C(10)--H(10C)	109.5
H(10A)-C(10)--H(10C)	109.5
H(10B)-C(10)--H(10C)	109.5
C(7)---C(11)--H(11A)	109.5
C(7)---C(11)--H(11B)	109.5
H(11A)-C(11)--H(11B)	109.5
C(7)---C(11)--H(11C)	109.5
H(11A)-C(11)--H(11C)	109.5
H(11B)-C(11)--H(11C)	109.5
C(2')--C(1')--C(1)	124.9(3)
C(2')--C(1')--H(1')	117.6
C(1)---C(1')--H(1')	117.6
C(1')--C(2')--O(3')	124.5(3)
C(1')--C(2')--C(7")	126.4(3)
O(3')--C(2')--C(7")	109.1(3)
C(2')--O(3')--C(4')	117.4(3)
O(3')--C(4')--H(4'A)	109.5
O(3')--C(4')--H(4'B)	109.5
H(4'A)-C(4')--H(4'B)	109.5
O(3')--C(4')--H(4'C)	109.5
H(4'A)-C(4')--H(4'C)	109.5
H(4'B)-C(4')--H(4'C)	109.5
C(2")--O(1")--C(5")	107.2(2)
O(1")--C(2")--C(3")	104.6(3)
O(1")--C(2")--H(2"A)	110.8
C(3")--C(2")--H(2"A)	110.8
O(1")--C(2")--H(2"B)	110.8
C(3")--C(2")--H(2"B)	110.8
H(2"A)-C(2")--H(2"B)	108.9
O(4")--C(3")--C(2")	105.8(3)
O(4")--C(3")--H(3"A)	110.6
C(2")--C(3")--H(3"A)	110.6
O(4")--C(3")--H(3"B)	110.6
C(2")--C(3")--H(3"B)	110.6
H(3"A)-C(3")--H(3"B)	108.7
C(3")--O(4")--C(5")	108.1(3)
O(1")--C(5")--O(4")	104.8(2)
O(1")--C(5")--C(10")	109.2(3)
O(4")--C(5")--C(10")	109.2(3)
O(1")--C(5")--C(6")	111.5(3)
O(4")--C(5")--C(6")	109.6(2)
C(10")-C(5")--C(6")	112.2(3)

C(5")--C(6")--C(7")	112.1(3)
C(5")--C(6")--H(6"A)	109.2
C(7")--C(6")--H(6"A)	109.2
C(5")--C(6")--H(6"B)	109.2
C(7")--C(6")--H(6"B)	109.2
H(6"A)-C(6")--H(6"B)	107.9
C(2')--C(7")--C(6")	111.4(3)
C(2')--C(7")--C(8")	113.1(3)
C(6")--C(7")--C(8")	109.2(3)
C(2')--C(7")--H(7")	107.7
C(6")--C(7")--H(7")	107.7
C(8")--C(7")--H(7")	107.7
C(9")--C(8")--C(7")	109.6(3)
C(9")--C(8")--H(8"A)	109.8
C(7")--C(8")--H(8"A)	109.8
C(9")--C(8")--H(8"B)	109.8
C(7")--C(8")--H(8"B)	109.8
H(8"A)-C(8")--H(8"B)	108.2
C(8")--C(9")--C(10")	112.0(3)
C(8")--C(9")--H(9"A)	109.2
C(10")-C(9")--H(9"A)	109.2
C(8")--C(9")--H(9"B)	109.2
C(10")-C(9")--H(9"B)	109.2
H(9"A)-C(9")--H(9"B)	107.9
C(5")--C(10")-C(9")	111.6(3)
C(5")--C(10")-H(10D)	109.3
C(9")--C(10")-H(10D)	109.3
C(5")--C(10")-H(10E)	109.3
C(9")--C(10")-H(10E)	109.3
H(10D)-C(10")-H(10E)	108.0
C(21')-C(21)--C(22)	116.4(3)
C(21')-C(21)--C(26)	119.0(3)
C(22)--C(21)--C(26)	108.2(3)
C(21')-C(21)--C(27)	119.1(3)
C(22)--C(21)--C(27)	106.3(2)
C(26)--C(21)--C(27)	82.7(2)
C(28)--C(22)--C(23)	122.5(3)
C(28)--C(22)--C(21)	123.6(3)
C(23)--C(22)--C(21)	113.9(3)
C(22)--C(23)--C(24)	113.7(3)
C(22)--C(23)--H(23A)	108.8
C(24)--C(23)--H(23A)	108.8
C(22)--C(23)--H(23B)	108.8
C(24)--C(23)--H(23B)	108.8
H(23A)-C(23)--H(23B)	107.7
C(25)--C(24)--C(23)	110.3(3)
C(25)--C(24)--H(24A)	109.6
C(23)--C(24)--H(24A)	109.6
C(25)--C(24)--H(24B)	109.6
C(23)--C(24)--H(24B)	109.6
H(24A)-C(24)--H(24B)	108.1
C(26)--C(25)--C(24)	109.2(3)
C(26)--C(25)--C(27)	84.8(2)
C(24)--C(25)--C(27)	113.2(3)
C(26)--C(25)--H(25)	115.3
C(24)--C(25)--H(25)	115.3
C(27)--C(25)--H(25)	115.3

O(29)--C(26)--C(25)	134.8(3)
O(29)--C(26)--C(21)	132.6(3)
C(25)--C(26)--C(21)	91.0(2)
C(30)--C(27)--C(31)	110.1(3)
C(30)--C(27)--C(25)	119.7(3)
C(31)--C(27)--C(25)	109.7(3)
C(30)--C(27)--C(21)	116.1(3)
C(31)--C(27)--C(21)	112.0(3)
C(25)--C(27)--C(21)	87.5(2)
C(22)--C(28)--H(28A)	120.0
C(22)--C(28)--H(28B)	120.0
H(28A)-C(28)--H(28B)	120.0
C(27)--C(30)--H(30A)	109.5
C(27)--C(30)--H(30B)	109.5
H(30A)-C(30)--H(30B)	109.5
C(27)--C(30)--H(30C)	109.5
H(30A)-C(30)--H(30C)	109.5
H(30B)-C(30)--H(30C)	109.5
C(27)--C(31)--H(31A)	109.5
C(27)--C(31)--H(31B)	109.5
H(31A)-C(31)--H(31B)	109.5
C(27)--C(31)--H(31C)	109.5
H(31A)-C(31)--H(31C)	109.5
H(31B)-C(31)--H(31C)	109.5
C(22')-C(21')-C(21)	124.5(3)
C(22')-C(21')-H(21')	117.8
C(21)--C(21')-H(21')	117.8
C(21')-C(22')-O(23')	124.7(3)
C(21')-C(22')-C(27")	125.5(3)
O(23')-C(22')-C(27")	109.7(3)
C(22')-O(23')-C(24')	117.9(2)
O(23')-C(24')-H(24C)	109.5
O(23')-C(24')-H(24D)	109.5
H(24C)-C(24')-H(24D)	109.5
O(23')-C(24')-H(24E)	109.5
H(24C)-C(24')-H(24E)	109.5
H(24D)-C(24')-H(24E)	109.5
C(22")-O(21")-C(25")	108.3(3)
O(21")-C(22")-C(23")	108.7(4)
O(21")-C(22")-H(22A)	110.0
C(23")-C(22")-H(22A)	110.0
O(21")-C(22")-H(22B)	110.0
C(23")-C(22")-H(22B)	110.0
H(22A)-C(22")-H(22B)	108.3
O(24")-C(23")-C(22")	104.9(4)
O(24")-C(23")-H(23C)	110.8
C(22")-C(23")-H(23C)	110.8
O(24")-C(23")-H(23D)	110.8
C(22")-C(23")-H(23D)	110.8
H(23C)-C(23")-H(23D)	108.8
C(23")-O(24")-C(25")	108.7(3)
O(24")-C(25")-O(21")	105.6(2)
O(24")-C(25")-C(30")	108.2(3)
O(21")-C(25")-C(30")	110.4(3)
O(24")-C(25")-C(26")	109.9(3)
O(21")-C(25")-C(26")	110.2(3)
C(30")-C(25")-C(26")	112.3(3)

C(25")-C(26")-C(27")	111.1(3)
C(25")-C(26")-H(26A)	109.4
C(27")-C(26")-H(26A)	109.4
C(25")-C(26")-H(26B)	109.4
C(27")-C(26")-H(26B)	109.4
H(26A)-C(26")-H(26B)	108.0
C(22')-C(27")-C(26")	110.9(2)
C(22')-C(27")-C(28")	114.0(3)
C(26")-C(27")-C(28")	109.5(2)
C(22')-C(27")-H(27")	107.4
C(26")-C(27")-H(27")	107.4
C(28")-C(27")-H(27")	107.4
C(29")-C(28")-C(27")	111.8(3)
C(29")-C(28")-H(28C)	109.2
C(27")-C(28")-H(28C)	109.2
C(29")-C(28")-H(28D)	109.2
C(27")-C(28")-H(28D)	109.2
H(28C)-C(28")-H(28D)	107.9
C(28")-C(29")-C(30")	111.7(3)
C(28")-C(29")-H(29A)	109.3
C(30")-C(29")-H(29A)	109.3
C(28")-C(29")-H(29B)	109.3
C(30")-C(29")-H(29B)	109.3
H(29A)-C(29")-H(29B)	107.9
C(25")-C(30")-C(29")	110.7(3)
C(25")-C(30")-H(30D)	109.5
C(29")-C(30")-H(30D)	109.5
C(25")-C(30")-H(30E)	109.5
C(29")-C(30")-H(30E)	109.5
H(30D)-C(30")-H(30E)	108.1

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 1-[2'-(1",4"-Dioxa-spiro[4.5]dec-7"-yl)-2'-methoxy-vinyl] -7,7-dimethyl-2-methylene-bicyclo[3.1.1]heptan-6-one

	U11	U22	U33	U23	U13	U12
C(1)	45(2)	54(3)	36(2)	-4(2)	0(2)	3(2)
C(2)	49(2)	49(3)	34(2)	3(2)	11(2)	-10(2)
C(3)	48(3)	55(3)	47(2)	13(2)	4(2)	-2(2)
C(4)	58(3)	64(3)	43(3)	10(2)	-5(2)	-19(2)
C(5)	74(3)	44(3)	40(2)	0(2)	-2(2)	-8(2)
C(6)	73(3)	45(3)	38(2)	5(2)	-1(2)	6(2)
C(7)	66(3)	62(3)	37(2)	-10(2)	-3(2)	16(2)
C(8)	78(3)	61(3)	54(3)	0(2)	2(3)	-13(3)
O(9)	136(3)	55(2)	45(2)	11(2)	2(2)	-22(2)
C(10)	56(3)	104(4)	47(3)	-27(3)	7(2)	-12(3)

C(11)	135(5)	110(4)	58(3)	-27(4)	-2(4)	59(4)
C(1')	44(3)	88(3)	42(2)	-20(2)	0(2)	19(2)
C(2')	43(2)	65(3)	46(2)	-13(2)	-8(2)	21(2)
O(3')	44(2)	127(3)	52(2)	-36(2)	-10(1)	31(2)
C(4')	47(3)	313(9)	88(5)	-98(6)	-22(3)	67(4)
O(1")	69(2)	39(2)	40(2)	-7(1)	-2(1)	10(1)
C(2")	69(3)	33(2)	52(3)	2(2)	-2(2)	8(2)
C(3")	96(4)	39(3)	67(3)	7(2)	-23(3)	3(3)
O(4")	41(1)	42(2)	40(1)	1(1)	-4(1)	0(1)
C(5")	39(2)	39(2)	30(2)	-4(2)	1(2)	3(2)
C(6")	39(2)	37(2)	32(2)	0(2)	-1(2)	-3(2)
C(7")	41(2)	43(2)	30(2)	-1(2)	-4(2)	3(2)
C(8")	70(3)	35(3)	41(2)	1(2)	-3(2)	3(2)
C(9")	70(3)	49(3)	41(2)	15(2)	6(2)	-12(2)
C(10")	55(3)	51(3)	37(2)	8(2)	12(2)	3(2)
C(21)	32(2)	30(2)	25(2)	1(2)	6(2)	0(2)
C(22)	35(2)	36(2)	29(2)	4(2)	2(2)	2(2)
C(23)	47(2)	48(3)	53(2)	18(2)	6(2)	-3(2)
C(24)	41(3)	68(3)	43(2)	18(2)	10(2)	4(2)
C(25)	40(2)	55(3)	30(2)	2(2)	7(2)	15(2)
C(26)	35(2)	31(2)	35(2)	2(2)	4(2)	-2(2)
C(27)	36(2)	42(2)	28(2)	-2(2)	4(2)	3(2)
C(28)	46(2)	39(3)	41(2)	2(2)	1(2)	-3(2)
O(29)	39(1)	43(2)	37(1)	6(1)	1(1)	7(1)
C(30)	52(3)	62(3)	33(2)	-4(2)	1(2)	9(2)
C(31)	52(3)	42(2)	45(2)	-10(2)	6(2)	2(2)
C(21')	28(2)	32(2)	28(2)	-5(2)	2(2)	-5(2)
C(22')	28(2)	26(2)	31(2)	4(2)	9(2)	0(2)
O(23')	39(1)	36(1)	33(1)	-4(1)	9(1)	-11(1)
C(24')	45(2)	49(3)	45(2)	-7(2)	11(2)	-18(2)
O(21")	59(2)	23(1)	64(2)	-11(1)	5(1)	1(1)
C(22")	247(8)	43(4)	108(4)	32(3)	79(5)	42(4)
C(23")	85(3)	45(3)	62(3)	25(2)	-11(3)	-7(3)
O(24")	54(2)	38(2)	42(1)	11(1)	14(1)	-5(1)
C(25")	44(2)	24(2)	36(2)	-1(2)	11(2)	0(2)
C(26")	36(2)	27(2)	30(2)	-4(2)	3(2)	-2(2)
C(27")	32(2)	23(2)	27(2)	0(2)	6(2)	-1(2)
C(28")	41(2)	27(2)	31(2)	1(2)	5(2)	0(2)
C(29")	39(2)	39(2)	33(2)	6(2)	-2(2)	0(2)
C(30")	41(2)	33(2)	31(2)	-1(2)	2(2)	-9(2)

The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

Table 5. Hydrogen coordinates (x 10^4), isotropic displacement parameters (A^2 x 10^3), and occupancies for 1-[2'-(1",4"-Dioxa-spiro[4.5]dec-7"-yl)-2'-methoxy-vinyl] -7,7-dimethyl-2-methylene-bicyclo[3.1.1]heptan-6-one

	x	y	z	U(eq)	Occ.
H(3A)	2204	4688	4461	53(11)	1
H(3B)	2029	3825	5150	56(11)	1
H(4A)	1855	6019	5719	49(10)	1
H(4B)	2314	6628	5253	57(11)	1
H(5)	1597	8431	4979	71(12)	1
H(8A)	1396	2049	4520	78(15)	1
H(8B)	849	2712	4074	62(13)	1
H(10A)	699	6599	5835	95(15)	1
H(10B)	1045	5156	5638	94(17)	1
H(10C)	435	5314	5311	111(18)	1
H(11A)	477	8636	5012	94(15)	1
H(11B)	208	7612	4371	180(30)	1
H(11C)	694	8722	4240	74(16)	1
H(1')	266	5630	3635	67(12)	1
H(4'A)	-525	4699	2088	170(20)	1
H(4'B)	-319	5984	2652	180(30)	1
H(4'C)	-332	4242	2896	130(30)	1
H(2"A)	2178	-752	2122	70(13)	1
H(2"B)	1640	-334	2484	89(15)	1
H(3"A)	2156	984	3313	130(20)	1
H(3"B)	2671	812	2869	113(19)	1
H(6"A)	1190	2291	2665	34(9)	1
H(6"B)	959	2836	1882	31(8)	1
H(7")	1515	4796	2943	32(8)	1
H(8"A)	1064	5678	1522	54(11)	1
H(8"B)	1335	6851	2102	65(12)	1
H(9"A)	2175	5603	2086	58(11)	1
H(9"B)	1968	6134	1292	54(11)	1
H(10D)	1687	3639	981	47(10)	1
H(10E)	2303	3575	1298	53(11)	1
H(23A)	3504	3476	3201	47(10)	1
H(23B)	3123	4083	2530	46(10)	1
H(24A)	2806	5574	3377	51(10)	1
H(24B)	3362	5553	3875	71(12)	1
H(25)	3142	8130	3278	39(9)	1
H(28A)	4269	2823	2533	77(14)	1
H(28B)	4596	4189	2164	53(11)	1
H(30A)	4363	7516	4103	57(11)	1
H(30B)	4728	6846	3525	51(11)	1
H(30C)	4258	5833	3796	59(12)	1
H(31A)	4108	9768	3413	88(14)	1
H(31B)	3794	9680	2631	77(13)	1
H(31C)	4424	9349	2739	88(15)	1
H(21')	4586	7596	1881	9(7)	1
H(24C)	5165	8150	288	67(12)	1
H(24D)	5223	7353	1057	52(11)	1
H(24E)	4875	8870	931	62(12)	1

H(22A)	4063	181	698	380(70)	1
H(22B)	3539	-527	263	260(40)	1
H(23C)	3049	378	1066	160(20)	1
H(23D)	3572	1134	1489	124(19)	1
H(26A)	4196	4243	69	25(8)	1
H(26B)	4189	3520	850	39(9)	1
H(27")	3513	5280	1123	17(7)	1
H(28C)	3199	7220	302	37(9)	1
H(28D)	3575	6599	-275	17(7)	1
H(29A)	2698	5683	-591	42(9)	1
H(29B)	2667	4996	193	38(9)	1
H(30D)	2842	2952	-573	29(8)	1
H(30E)	3341	3836	-850	47(10)	1

Table 6. Torsion angles [deg] for
1-[2'-(1",4"-Dioxa-spiro[4.5]dec-7"-yl)-2'-methoxy-vinyl]
-7,7-dimethyl-2-methylene-bicyclo[3.1.1]heptan-6-one

C(6)	C(1)	C(2)	C(3)	22.9(4)
C(6)	C(1)	C(2)	C(8)	-157.0(3)
C(7)	C(1)	C(2)	C(3)	-64.1(4)
C(7)	C(1)	C(2)	C(8)	115.9(4)
C(1')	C(1)	C(2)	C(3)	161.6(3)
C(1')	C(1)	C(2)	C(8)	-18.4(5)
C(1)	C(2)	C(3)	C(4)	34.1(4)
C(8)	C(2)	C(3)	C(4)	-145.9(4)
C(2)	C(3)	C(4)	C(5)	-29.7(4)
C(3)	C(4)	C(5)	C(6)	-31.5(4)
C(3)	C(4)	C(5)	C(7)	61.4(4)
C(4)	C(5)	C(6)	C(1)	84.6(3)
C(4)	C(5)	C(6)	O(9)	-103.8(5)
C(7)	C(5)	C(6)	C(1)	-27.5(3)
C(7)	C(5)	C(6)	O(9)	144.1(5)
C(2)	C(1)	C(6)	C(5)	-78.4(3)
C(2)	C(1)	C(6)	O(9)	110.1(5)
C(7)	C(1)	C(6)	C(5)	26.5(3)
C(7)	C(1)	C(6)	O(9)	-145.0(5)
C(1')	C(1)	C(6)	C(5)	145.1(3)
C(1')	C(1)	C(6)	O(9)	-26.4(6)
C(4)	C(5)	C(7)	C(1)	-81.6(3)
C(4)	C(5)	C(7)	C(10)	38.2(5)
C(4)	C(5)	C(7)	C(11)	166.3(3)
C(6)	C(5)	C(7)	C(1)	26.4(3)
C(6)	C(5)	C(7)	C(10)	146.1(4)
C(6)	C(5)	C(7)	C(11)	-85.8(4)
C(2)	C(1)	C(7)	C(5)	79.5(3)
C(2)	C(1)	C(7)	C(10)	-41.8(4)
C(2)	C(1)	C(7)	C(11)	-168.7(4)
C(6)	C(1)	C(7)	C(5)	-26.0(3)
C(6)	C(1)	C(7)	C(10)	-147.3(4)
C(6)	C(1)	C(7)	C(11)	85.8(4)

C(1')	C(1)	C(7)	C(5)	-147.2(3)
C(1')	C(1)	C(7)	C(10)	91.6(4)
C(1')	C(1)	C(7)	C(11)	-35.3(5)
C(2)	C(1)	C(1')	C(2')	-69.0(5)
C(6)	C(1)	C(1')	C(2')	63.6(5)
C(7)	C(1)	C(1')	C(2')	162.3(4)
C(1)	C(1')	C(2')	O(3')	179.2(4)
C(1)	C(1')	C(2')	C(7")	-0.6(7)
C(1')	C(2')	O(3')	C(4')	-1.7(7)
C(7")	C(2')	O(3')	C(4')	178.1(5)
C(5")	O(1")	C(2")	C(3")	-25.6(4)
O(1")	C(2")	C(3")	O(4")	9.5(5)
C(2")	C(3")	O(4")	C(5")	9.9(5)
C(2")	O(1")	C(5")	O(4")	32.0(3)
C(2")	O(1")	C(5")	C(6")	-86.5(3)
C(2")	O(1")	C(5")	C(10")	149.0(3)
C(3")	O(4")	C(5")	O(1")	-25.6(4)
C(3")	O(4")	C(5")	C(6")	94.1(4)
C(3")	O(4")	C(5")	C(10")	-142.5(3)
O(1")	C(5")	C(6")	C(7")	-176.7(3)
O(4")	C(5")	C(6")	C(7")	67.8(3)
C(10")	C(5")	C(6")	C(7")	-53.8(4)
C(1')	C(2')	C(7")	C(6")	121.4(4)
C(1')	C(2')	C(7")	C(8")	-115.2(4)
O(3')	C(2')	C(7")	C(6")	-58.5(4)
O(3')	C(2')	C(7")	C(8")	64.9(4)
C(5")	C(6")	C(7")	C(2')	-178.1(3)
C(5")	C(6")	C(7")	C(8")	56.4(4)
C(2')	C(7")	C(8")	C(9")	177.3(3)
C(6")	C(7")	C(8")	C(9")	-58.1(4)
C(7")	C(8")	C(9")	C(10")	58.4(4)
O(1")	C(5")	C(10")	C(9")	176.3(3)
O(4")	C(5")	C(10")	C(9")	-69.7(4)
C(6")	C(5")	C(10")	C(9")	52.1(4)
C(8")	C(9")	C(10")	C(5")	-55.2(4)

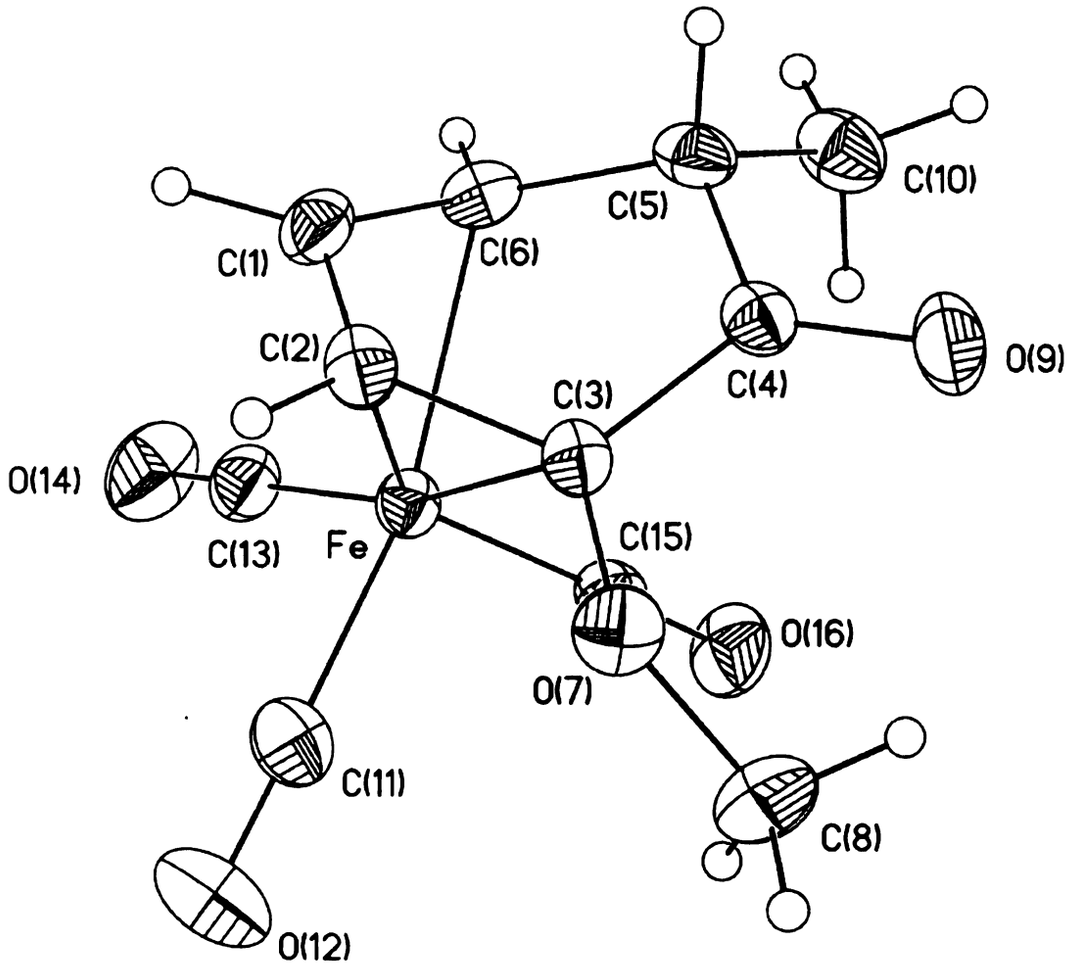
C(21')	C(21)	C(22)	C(28)	20.1(4)
C(26)	C(21)	C(22)	C(28)	157.3(3)
C(27)	C(21)	C(22)	C(28)	-115.2(3)
C(21')	C(21)	C(22)	C(23)	-159.8(3)
C(26)	C(21)	C(22)	C(23)	-22.6(4)
C(27)	C(21)	C(22)	C(23)	64.9(3)
C(28)	C(22)	C(23)	C(24)	147.1(3)
C(21)	C(22)	C(23)	C(24)	-33.0(4)
C(22)	C(23)	C(24)	C(25)	27.8(4)
C(23)	C(24)	C(25)	C(26)	33.3(4)
C(23)	C(24)	C(25)	C(27)	-59.4(4)
C(24)	C(25)	C(26)	O(29)	109.8(4)
C(27)	C(25)	C(26)	O(29)	-137.4(4)
C(24)	C(25)	C(26)	C(21)	-84.3(3)
C(27)	C(25)	C(26)	C(21)	28.5(2)
C(21')	C(21)	C(26)	O(29)	19.2(5)
C(22)	C(21)	C(26)	O(29)	-116.7(4)
C(27)	C(21)	C(26)	O(29)	138.5(4)
C(21')	C(21)	C(26)	C(25)	-147.3(3)
C(22)	C(21)	C(26)	C(25)	76.8(3)
C(27)	C(21)	C(26)	C(25)	-28.0(2)

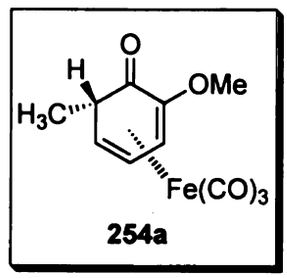
C(26)	C(25)	C(27)	C(30)	-146.3(3)
C(24)	C(25)	C(27)	C(30)	-37.6(4)
C(26)	C(25)	C(27)	C(31)	84.9(3)
C(24)	C(25)	C(27)	C(31)	-166.3(3)
C(26)	C(25)	C(27)	C(21)	-27.5(2)
C(24)	C(25)	C(27)	C(21)	81.2(3)
C(21')	C(21)	C(27)	C(30)	-91.6(4)
C(22)	C(21)	C(27)	C(30)	42.3(4)
C(26)	C(21)	C(27)	C(30)	149.2(3)
C(21')	C(21)	C(27)	C(31)	36.1(4)
C(22)	C(21)	C(27)	C(31)	170.0(3)
C(26)	C(21)	C(27)	C(31)	-83.1(3)
C(21')	C(21)	C(27)	C(25)	146.4(3)
C(22)	C(21)	C(27)	C(25)	-79.8(3)
C(26)	C(21)	C(27)	C(25)	27.1(2)
C(22)	C(21)	C(21')	C(22')	68.1(4)
C(26)	C(21)	C(21')	C(22')	-64.3(4)
C(27)	C(21)	C(21')	C(22')	-162.5(3)
C(21)	C(21')	C(22')	O(23')	178.0(3)
C(21)	C(21')	C(22')	C(27")	-3.7(5)
C(21')	C(22')	O(23')	C(24')	2.3(4)
C(27")	C(22')	O(23')	C(24')	-176.2(3)
C(25")	O(21")	C(22")	C(23")	10.5(7)
O(21")	C(22")	C(23")	O(24")	1.7(7)
C(22")	C(23")	O(24")	C(25")	-13.3(5)
C(23")	O(24")	C(25")	O(21")	19.7(3)
C(23")	O(24")	C(25")	C(30")	137.9(3)
C(23")	O(24")	C(25")	C(26")	-99.1(3)
C(22")	O(21")	C(25")	O(24")	-18.5(5)
C(22")	O(21")	C(25")	C(30")	-135.2(5)
C(22")	O(21")	C(25")	C(26")	100.1(5)
O(24")	C(25")	C(26")	C(27")	-62.9(3)
O(21")	C(25")	C(26")	C(27")	-178.9(2)
C(30")	C(25")	C(26")	C(27")	57.5(4)
C(21')	C(22')	C(27")	C(26")	-114.1(3)
O(23')	C(22')	C(27")	C(26")	64.4(3)
C(21')	C(22')	C(27")	C(28")	121.8(3)
O(23')	C(22')	C(27")	C(28")	-59.7(3)
C(25")	C(26")	C(27")	C(22')	177.2(3)
C(25")	C(26")	C(27")	C(28")	-56.1(3)
C(22')	C(27")	C(28")	C(29")	-179.9(3)
C(26")	C(27")	C(28")	C(29")	55.3(3)
C(27")	C(28")	C(29")	C(30")	-54.6(4)
O(24")	C(25")	C(30")	C(29")	65.9(3)
O(21")	C(25")	C(30")	C(29")	-179.0(3)
C(26")	C(25")	C(30")	C(29")	-55.5(4)
C(28")	C(29")	C(30")	C(25")	53.8(4)

Symmetry transformations used to generate equivalent atoms:

APPENDIX 2

X-RAY STRUCTURE AND CRYSTAL DATA FOR **254a**





254a

ORTEP Diagram of **254a**

X-ray Crystallographic Data for **254a**

Table 1. Crystal data and structure refinement for wf072604

Identification code	wf072604
Empirical formula	C11 H10 Fe O5
Formula weight	278.04
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 12.152(2) A
	b = 7.3323(15) A
	c = 13.315(3) A
	alpha = 90 deg.
	beta = 108.59(3) deg.
	gamma = 90 deg.
Volume	1124.5(4) A^3
Z	4
Density (calculated)	1.642 Mg/m^3
Absorption coefficient	1.347 mm^-1
F(000)	568
Crystal size	0.25 x 0.1 x 0.05 mm
Theta range for data collection	1.77 to 28.32 deg.
Index ranges	-16<=h<=16, -9<=k<=9, -17<=l<=17
Reflections collected / unique	12943 / 2711 [R(int) = 0.0523]
Completeness to theta = 28.32	97.0%

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2711 / 0 / 194
Goodness-of-fit on F^2	0.746
Final R indices [I>2sigma(I)]	R1 = 0.0344, wR2 = 0.0904
R indices (all data)	R1 = 0.0623, wR2 = 0.1091
Largest diff. peak and hole	0.413 and -0.304 e.A^-3

Table 2. Atomic coordinates (x 10^4), equivalent isotropic displacement parameters (A^2 x 10^3), and occupancies for wf072604

	x	y	z	U(eq)	Occ.
Fe	2142(1)	540(1)	969(1)	20(1)	1
C(1)	3847(2)	152(4)	1076(2)	27(1)	1
C(2)	3607(2)	2030(4)	1081(2)	23(1)	1
C(3)	3179(2)	2675(3)	1905(2)	20(1)	1
C(4)	3651(2)	1888(3)	2983(2)	22(1)	1
C(5)	4044(2)	-81(4)	3019(2)	26(1)	1
C(6)	3645(2)	-865(4)	1907(2)	26(1)	1
O(7)	2833(2)	4480(2)	1812(2)	27(1)	1
C(8)	1858(3)	4870(4)	2172(3)	35(1)	1
O(9)	3718(2)	2768(3)	3779(1)	34(1)	1
C(10)	3645(3)	-1203(5)	3808(3)	34(1)	1
C(11)	1259(2)	2130(4)	8(2)	30(1)	1
O(12)	721(2)	3145(3)	-603(2)	48(1)	1
C(13)	1636(2)	-1365(4)	89(2)	29(1)	1
O(14)	1312(2)	-2577(3)	-459(2)	46(1)	1
C(15)	1239(2)	195(4)	1787(2)	26(1)	1
O(16)	646(2)	-17(3)	2293(2)	41(1)	1

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table 3. Bond lengths [A] and angles [deg] for wf072604

Fe-C(15)	1.794(3)
Fe-C(13)	1.801(3)
Fe-C(11)	1.809(3)
Fe-C(1)	2.051(3)
Fe-C(2)	2.053(2)
Fe-C(6)	2.122(3)
Fe-C(3)	2.142(2)
C(1)-C(2)	1.408(4)
C(1)-C(6)	1.420(4)
C(2)-C(3)	1.436(3)
C(3)-O(7)	1.382(3)
C(3)-C(4)	1.482(3)
C(4)-O(9)	1.221(3)
C(4)-C(5)	1.516(4)
C(5)-C(6)	1.516(4)
C(5)-C(10)	1.530(4)
O(7)-C(8)	1.442(4)
C(11)-O(12)	1.142(3)
C(13)-O(14)	1.138(3)
C(15)-O(16)	1.143(3)
C(15)-Fe-C(13)	97.90(12)
C(15)-Fe-C(11)	100.38(12)
C(13)-Fe-C(11)	92.13(13)
C(15)-Fe-C(1)	137.62(12)
C(13)-Fe-C(1)	93.76(12)

C(11)-Fe-C(1)	119.80(12)
C(15)-Fe-C(2)	135.66(11)
C(13)-Fe-C(2)	124.64(11)
C(11)-Fe-C(2)	90.78(11)
C(1)-Fe-C(2)	40.13(11)
C(15)-Fe-C(6)	98.78(11)
C(13)-Fe-C(6)	93.31(12)
C(11)-Fe-C(6)	159.15(11)
C(1)-Fe-C(6)	39.73(11)
C(2)-Fe-C(6)	69.64(11)
C(15)-Fe-C(3)	96.31(10)
C(13)-Fe-C(3)	163.91(10)
C(11)-Fe-C(3)	92.69(11)
C(1)-Fe-C(3)	70.57(10)
C(2)-Fe-C(3)	39.97(9)
C(6)-Fe-C(3)	77.06(10)
C(2)-C(1)-C(6)	115.0(2)
C(2)-C(1)-Fe	70.02(15)
C(6)-C(1)-Fe	72.83(15)
C(1)-C(2)-C(3)	116.8(2)
C(1)-C(2)-Fe	69.85(15)
C(3)-C(2)-Fe	73.35(14)
O(7)-C(3)-C(2)	114.8(2)
O(7)-C(3)-C(4)	118.2(2)
C(2)-C(3)-C(4)	119.3(2)
O(7)-C(3)-Fe	122.79(17)
C(2)-C(3)-Fe	66.68(14)
C(4)-C(3)-Fe	104.68(16)
O(9)-C(4)-C(3)	122.2(2)

O(9)-C(4)-C(5)	122.8(2)
C(3)-C(4)-C(5)	115.0(2)
C(4)-C(5)-C(6)	109.3(2)
C(4)-C(5)-C(10)	111.6(2)
C(6)-C(5)-C(10)	113.2(2)
C(1)-C(6)-C(5)	118.8(2)
C(1)-C(6)-Fe	67.44(15)
C(5)-C(6)-Fe	109.74(17)
C(3)-O(7)-C(8)	114.7(2)
O(12)-C(11)-Fe	178.6(2)
O(14)-C(13)-Fe	179.3(3)
O(16)-C(15)-Fe	178.8(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for wf072604

	U11	U22	U33	U23	U13	U12
Fe	20(1)	21(1)	20(1)	-2(1)	7(1)	-2(1)
C(1)	20(1)	35(2)	27(1)	-6(1)	11(1)	-1(1)
C(2)	20(1)	29(1)	21(1)	-1(1)	7(1)	-7(1)
C(3)	20(1)	22(1)	19(1)	-1(1)	6(1)	-4(1)
C(4)	18(1)	26(1)	21(1)	1(1)	5(1)	-3(1)
C(5)	18(1)	31(1)	27(1)	5(1)	5(1)	1(1)
C(6)	24(1)	23(1)	32(1)	0(1)	10(1)	3(1)
O(7)	32(1)	19(1)	31(1)	1(1)	11(1)	-2(1)
C(8)	38(2)	26(2)	45(2)	-2(1)	17(1)	7(1)

O(9)	39(1)	42(1)	20(1)	-4(1)	8(1)	-2(1)
C(10)	32(2)	38(2)	31(2)	9(1)	8(1)	-2(1)
C(11)	28(1)	30(1)	26(1)	-2(1)	4(1)	-6(1)
O(12)	45(1)	45(1)	41(1)	15(1)	-2(1)	-1(1)
C(13)	28(1)	33(2)	28(1)	-3(1)	12(1)	-1(1)
O(14)	44(1)	44(1)	51(1)	-26(1)	15(1)	-10(1)
C(15)	22(1)	26(1)	25(1)	-2(1)	3(1)	0(1)
O(16)	34(1)	58(1)	38(1)	-1(1)	21(1)	-5(1)

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U11 + \ldots + 2 h k a^* b^* U12]$$

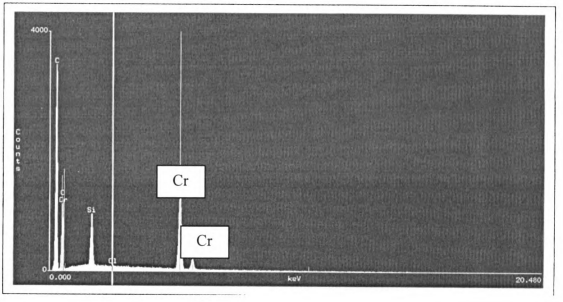
Table 5. Hydrogen coordinates (x 10^4), isotropic displacement parameters (A^2 x 10^3), and occupancies for wf072604

	x	y	z	U(eq)	Occ.
H(1)	4020(30)	-320(40)	460(20)	28(8)	1
H(2)	3640(20)	2810(40)	550(20)	21(7)	1
H(5)	4860(30)	0(40)	3270(20)	19(7)	1
H(6)	3630(20)	-2190(40)	1890(20)	21(7)	1
H(8A)	1760(30)	6130(50)	2090(30)	41(9)	1
H(8B)	2020(30)	4550(50)	2900(30)	47(10)	1
H(8C)	1090(40)	4100(60)	1870(40)	90(15)	1
H(10A)	2750(30)	-1150(40)	3600(20)	31(8)	1
H(10B)	4020(30)	-790(50)	4500(30)	55(11)	1
H(10C)	3830(30)	-2380(50)	3780(30)	48(10)	1

APPENDIX 3

SEM/EDS SPECTRA FOR **181a** AND **254a**

SEM/EDS Spectra for Chromium Complex **181a**



SEM/EDS Spectra for Iron Complex **254a**