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CHLORINATIVE REARRANGEMENTS OF BICYCLIC AND MONOCYCLIC CARBINOLS VIA THE ACTION OF BLEACH AND VINEGAR

presented by

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has been accepted towards fulfillment
of the requirements for the

Doctoral degree in Chemistry

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Major Professor's Signature

1/28/03
Date

CHLORINATIVE REARRANGEMENTS OF BICYCLIC AND MONOCYCLIC CARBINOLS *VIA* THE ACTION OF BLEACH AND VINEGAR

By

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ABSTRACT

CHLORINATIVE REARRANGEMENTS OF BICYCLIC AND MONOCYCLIC CARBINOLS *VIA* THE ACTION OF BLEACH AND VINEGAR

By

Erik L. Ruggles

Investigation into a NaOCl/AcOH induced *exo*-olefin insertion/ring expansion of bicyclic vinyl carbinols led to a systematic study of this rearrangement. This ring expansion/elimination reaction proceeds first through a chlorinative ring enlargement to form a β-chloroketone. Elimination of HCl follows to produce *exocyclic* enones in good yields and regioselectivity. Interestingly in the bicyclic [2.2.2] chlorinative ring expansions, each diastereomeric starting carbinol rearranges stereospecifically to produce bicyclic β-chloroketones. Other issues addressed include substrate scope, as well as the chemo-, regio-, and diastereoselectivity of these chlorinative ring expansions. Subsequent experimentation with other non-vinylogous carbinols led to the observation of a number of other chlorinative rearrangements. The information gleaned from this methodology is an important addition to the database of rearrangements in bicyclic and monocyclic carbinols.

To Me, Myself and I

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On a personal note, upon my arrival at MSU, I had only one family but upon my departure I have been blessed with a lovely wife, Ali, and son, Sayler. You both are the love of my life. I am forever grateful for Ali's gentle prodding over the years and her understanding of late nights and endless work, I will make it up. Also my heart sings for Sayler, whose smile, laughter, and antics have always lifted my spirits immeasurably. I must thank my family for their love and support throughout my long academic studies. In particular I thank my parents, Ed and Bev, for encouraging me to follow my dreams and my sister and brother, Whitney and Seth, for their encouragement and friendship. Last but not least, I want to also express thanks to my Mammaw Ruggles, Mammaw and Pappaw Morehead, Snook and Glenn, and Michael Riordan whom always have lent a compassionate ear and were always there to help out in any way. My family has been the wind behind my sails on this long voyage and I thank you all.

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LIST OF ABBREVIATIONS

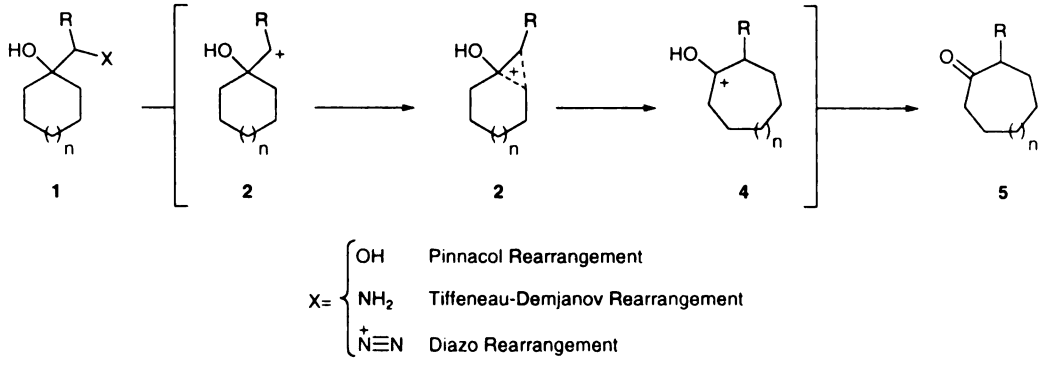
AcOH	acetic acid
CH_2Cl_2	dichloromethane
CCl_4	carbon tetrachloride
CI	chemical ionization
DAID	diacetoxyiodobenzene
DHF	dihydrofuranyl
DHP	dihydropyranyl
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
EI	electric ionization
Et_2O	diethyl ether
eq	equation
FAB	fast atom bombardment
g	gram
h	hour
HDA	hetero Diels-Alder
HMPA	hexamethyl phosphoramide
HPLC	high performance liquid chromatography
H_2O	water
HRMS	high resolution mass spectrometry
IR	infrared spectroscopy
LRMS	low resolution mass spectrometry

$LiAlD_4$	lithium aluminum deuteride
min	minute
mL	milliliter
mmol	millimole
MS	molecular sieves
$NaBH_4$	sodium borohydride
NaOCl	sodium hypochlorite
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance spectroscopy
NOE	nuclear Overhauser effect
PhH	benzene
i-Pr_2EtN	di-*iso*-propyl ethyl amine
RCM	ring closing metathesis
r.t.	room temperature
THF	tetrahydrofuran

Chapter 1. Introduction of Ideas

The ring enlargement of organic molecules by one carbon atom is a powerful transformation.[1] A common feature among the classic Pinacol,[2] Tiffeneau-Demjanov,[3] and diazo methods,[4] is the formation of a carbinol cation, **4**, accompanying ring expansion, **2**→**4** (Scheme 1). These [1,2]-shifts can be broadly termed as Wagner-Meerwein rearrangements.[5] Within this broad classification, the chemo-, regio-, and stereoselectivities observed are often dependent on various issues. Ring size, substitution

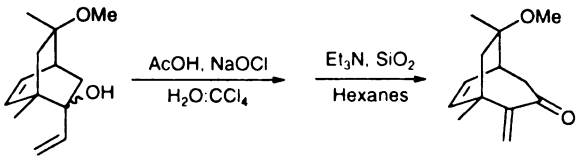
Scheme 1. General Carbinol Cation Ring Expansion



pattern, and/or reagents often dictate the observed selectivities.[6] That being said, there are generalities among ring enlargements: (1) the ability to expand increases (a) as the donor ability of electrons adjacent to the carbocation increases, (b) as the size of the expanding ring decreases, and (c) as the ease of carbonium ion formation decreases; (2) upon examination of the migrating termini, the higher degree of alkyl substitution normally produces the regioselectivity observed.

During experimentation, originally aimed at the development of a radical oxy-Cope rearrangement, an interesting one-carbon ring expansion was observed (Scheme 2). Contrary to the aforementioned processes that expand *via* a leaving group, in our case (Scheme 2), the vinyl group attacks an electrophilic source prior to expansion. Both

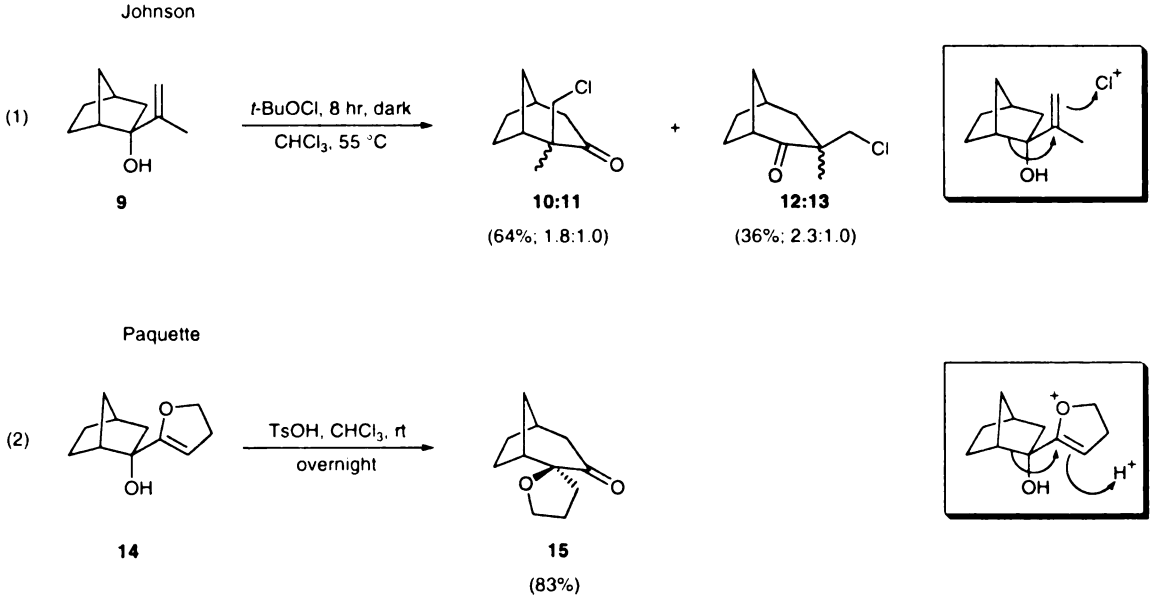
Scheme 2. One Carbon Expansion Impetus



6:7 **8**

Johnson[7] and Paquette[8] have observed similar rearrangements in vinyl [2.2.1] carbinols (equations 1 and 2 respectively, Scheme 3). Johnson uses *t*-BuOCl as a source of electrophilic chlorine and proposes that it is the preferential orientation of the *iso*-propenyl substituent that imparts the observed diastereoselectivity, with bridgehead migration being favored. Paquette employs protonation of a vinyl group to evoke a similar ring expansion of hydrofuranyl carbinols. In this case, bridgehead migration is

Scheme 3. Johnson and Paquette Expansions



absolute. The observed diastereoselectivity arises from a proposed *anti* relationship between the hydroxyl and furanyl oxygens (Scheme 3).

As a result of the interesting nature of these rearrangements, it was decided to further examine the expansion of vinyl carbinols to understand the scope, mechanism and

synthetic utility of this reaction. The chapters that follow will delve into the chemo-, regio-, and diastereoselectivity observed in the NaOCl/AcOH mediated chlorinative ring expansion on a variety of substrates. However as the impetus of this ring expansion rests in our labors toward a radical oxy-Cope rearrangement, a discussion of these studies shall be presented first in Chapter 2.

Chapter 2. Radical Oxy-Cope Attempts

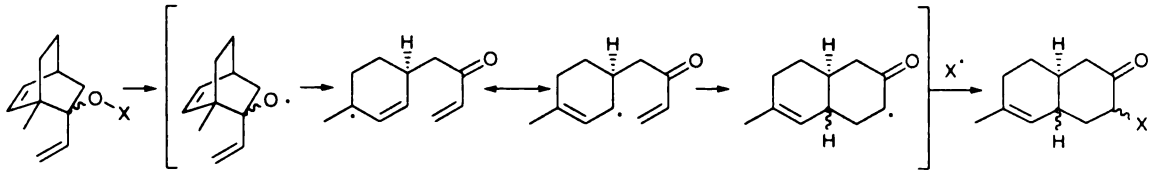
2.1. Introduction to the Radical oxy-Cope

Concerted rearrangements of organic molecules have long been exploited for their simplicity and ability to impart high levels of stereo and regiocontrol during transformations. As an example the oxy-Cope rearrangement has been used extensively for ring expansions as well as the elaboration of polycyclic backbones.[9] The oxy-Cope is highly valued in these endeavors as a result of its ability to impart chirality at one or more centers during the concerted rearrangement. Although most radical carbon-carbon bond forming processes occur in a stepwise fashion, it is possible for the bond reorganization of such a sequence to resemble those observed in concerted reactions. Radical cyclizations do have the ability to impart regio- and stereoselectivity during the course of a reaction,[10] and radical reactions have mimicked thermal concerted processes.[11,12,13,14,15] However, the use of an oxygen-centered radical for the acceleration and/or genesis of an oxy-Cope rearrangement has, to the best of our knowledge, not yet been investigated.[16]

The proposed radical oxy-Cope rearrangement requires first the formation of a suitable oxygen bond that could cleave homolytically under the right conditions, **16**.[17] The envisioned process begins with homolytic cleavage of the O-X bond to form alkoxy radical **17**. Subsequent β-cleavage during carbonyl formation produces allylic radical **18a**, and its resonance contributor **18b**. Literature precedent would have the allylic radical to add from the least substituted carbon, **18b→19**, in order to form the more substituted olefin center.[18] After which, recombination produces an oxy-Cope product, **20**, *via* a radical rearrangement.

This type of stepwise radical promoted oxy-Cope rearrangement could potentially

Scheme 4. Radical Oxy-Cope Rearrangement



16 17 18a 18b 19 20

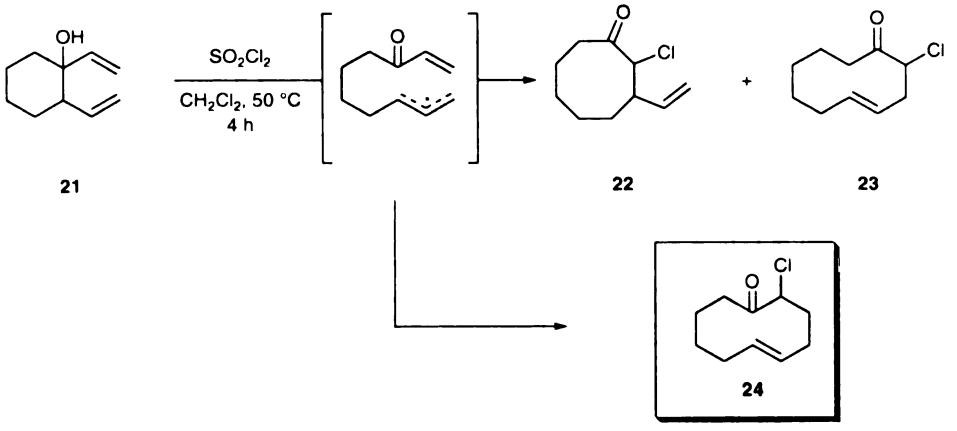
complement its thermal and anionic counterparts. For example in contrast to a concerted reaction, a stepwise process may be stereoselective but independent of stereochemistry in the starting bicyclic vinyl alcohol. As illustrated above, upon reaching radical **18a**, the stereochemistry in the starting substrate is inconsequential (Scheme 4). So either diastereomeric alcohol can be employed. This is quite unlike the thermal/anionic counterpart in which only one diastereomeric alcohol has the proper orbital alignment for sigmatropic rearrangement. Thus the vinyl Grignard addition can be non-selective in a radical initiated oxy-Cope. Secondly, radical rearrangements are considered neutral processes; hence substrates with base or thermal sensitive substituents could now be employed. There have also been theoretical estimates opening up the possibility of rate enhancement under these neutral conditions.[19] Finally there is also the prospect of a stereo outcome opposite that produced by traditional means. That is formation of **20** may, based on related radical cyclization, afford the *trans* fused product.[20] Given these possibilities and questions, the radical oxy-Cope was viewed as an intriguing complement to the traditional [3,3] sigmatropic rearrangement.

2.2. Prior Art

In the late 80's, Bulliard and coworkers published a rearrangement of carbinol **21**.[21] Upon treatment with SO_2Cl_2, **21** reportedly rearranged to give chloroketones, **22** and **23** as a 1:1 mixture (Scheme 5). Both products are described to be the product of

alkoxy fragmentation after hypochlorite formation followed by cyclization in either an *exo*, **22**, or *endo*, **23**, fashion. This literature report is troublesome, since product **23** is not what would be expected from *endo* cyclization. The expected product, **24**, would have both the carbonyl and chloro substituents juxtaposed by one carbon. Moreover **24** could be viewed as arising from the first radical oxy-Cope rearrangement. However this was never claimed, nor were spectral data for the products detailed in the letter. Whether ketone **23** was truly constructed or merely a typo led us to try and reproduce Bulliard's work. However upon subjecting **21** to their conditions only ketone **22** was observed along with a number of other products. Attempts at reaching any of the three authors did not help in the elucidation of whether this truly was a radical oxy-Cope rearrangement. Our inability to repeat the reaction and less than clear correspondence with the authors led to the conclusion of this route.

Scheme 5. Bulliard's Reaction

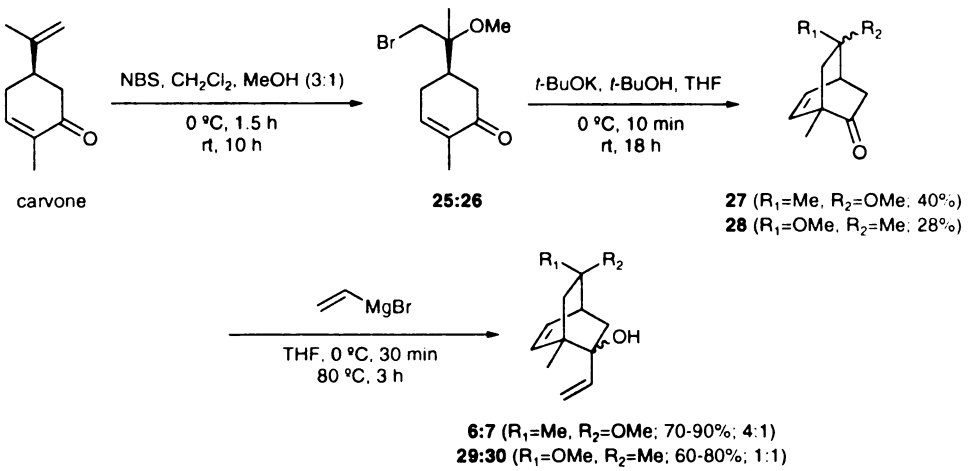


2.3. Substrate Synthesis

The beginning of the second-generation radical oxy-Cope investigation entailed the construction of a suitable carbinol that would undergo the standard oxy-Cope rearrangement. A [2.2.2] bicyclic construct was chosen since only one diastereomer has the proper orbital alignment for thermal or anionic rearrangement while under radical

conditions either diastereomer should react in the same fashion. Also, [2.2.2] carbinol systems can be somewhat sluggish toward [3,3]-sigmatropic rearrangement and often need to be transformed into their potassium salt prior to rearrangement making base sensitive substitutions problematic.[22] Furthermore even under anionic acceleration, heat is often necessary for the rearrangement to proceed. It was hoped that radical conditions would provide a neutral way to accelerate such reactions and also be stereoconvergent with both carbinol diastereomers being able to rearrange similiarly. Thus the [2.2.2] system emerged as one of the most suitable substrates to address such questions.

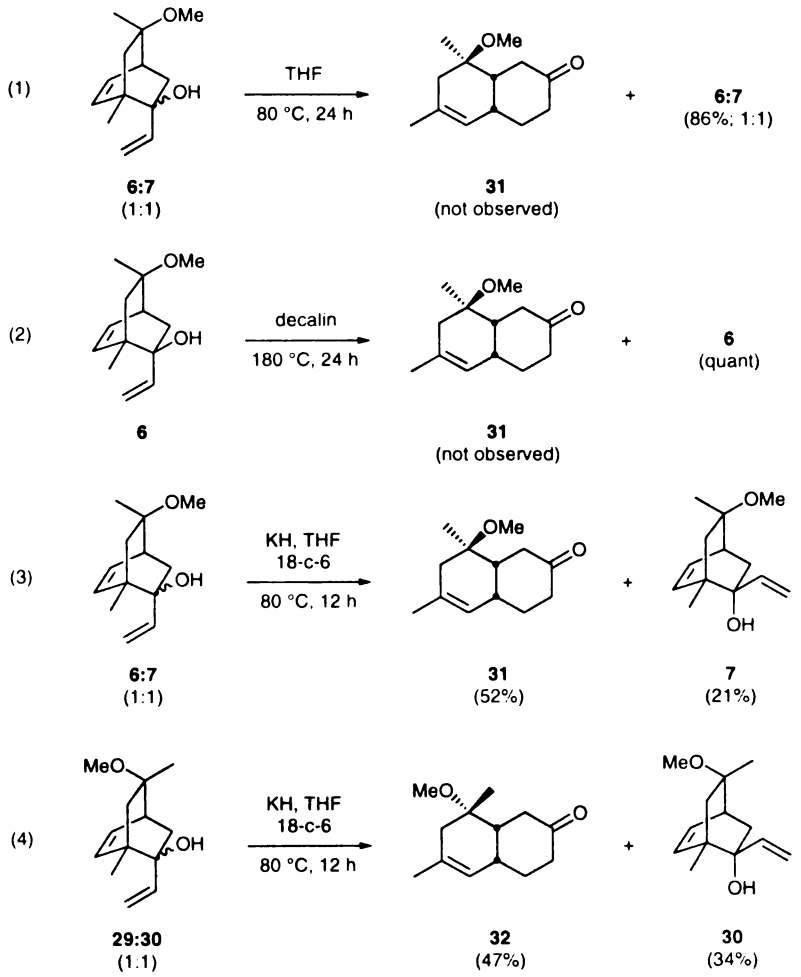
Scheme 6. Carvone Derived Substrates[23]



A short route to [2.2.2] systems has been developed by Srikrishna,[24] which utilizes carvone as a chiral starting synthon (Scheme 6). Use of *N*-bromosuccinimide (NBS) and methanol (MeOH) generates bromomethoxy carvone **25:26**. Treatment with base then provides the [2.2.2] core *via* an intramolecular substitution reaction. Vinyl Grignard addition provides the desired oxy-Cope precursors, **6:7** and **29:30**. Another easily accessible oxy-Cope substrate is **21**,[25] which is available from successive vinyl addition across α-chlorocyclohexanone.[26]

To establish the spectroscopic and chemical properties of the starting materials and rearranged products, the starting carbinols were subjected to the standard oxy-Cope conditions (Scheme 7). First, the diastereomeric bicyclic carbinols, **6** and **7** were thermalized. After heating at either 80 °C or 180 °C for 24 hrs only starting material was recovered (equations 1 and 2, Scheme 7). Upon treatment with KH, all carbinols rearranged smoothly at 80 °C in 12 hrs to provide the predicted [4.4.0] bicycles, **31** and **32**, along with recovered *endo* carbinols **7** and **30** (equations 3 and 4, Scheme 7). With the desired products isolated and identified spectroscopically the radical oxy-Cope could be investigated.

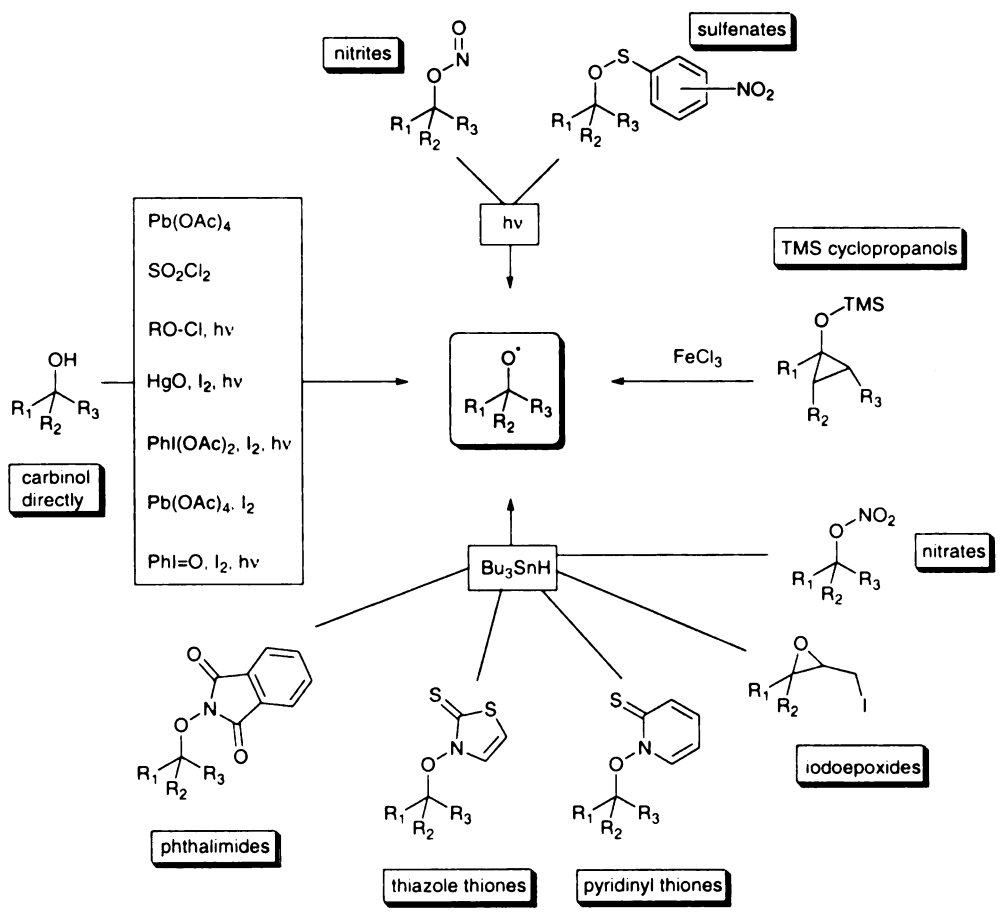
Scheme 7. Anionic oxy-Cope Controls[23]



2.4. Radical oxy-Cope

The literature provides many ways to produce alkoxy radicals directly (Figure 1). The photolysis of nitrites;[27] carbinol oxidation *via* $Pb(OAc)_4$,[28] $Pb(OAc)_4/Cu(OAc)_2$,[29] $Pb(OAc)_2/O_2$,[30] Mn(2-pyridinecarboxylato)$_3$,[31] and $Mn(OAc)_3$;[31c,f,g] irradiation of sulfenates;[32] action of $FeCl_3$ on fused cyclopropylsiloxanes;[33] treatment of alcohols with sulfuryl chloride;[21] hypochlorite[34] and hypoiodite fragmentation;[35] as well as the tin hydride reduction of iodoepoxides,[36] nitrate esters,[37] pyridinyl thiones,[38] thiazole thiones,[39] and phthalimides[40] are all methods for the generation of such radicals.

Figure 1. Methods for Generating Oxygen Centered Radicals



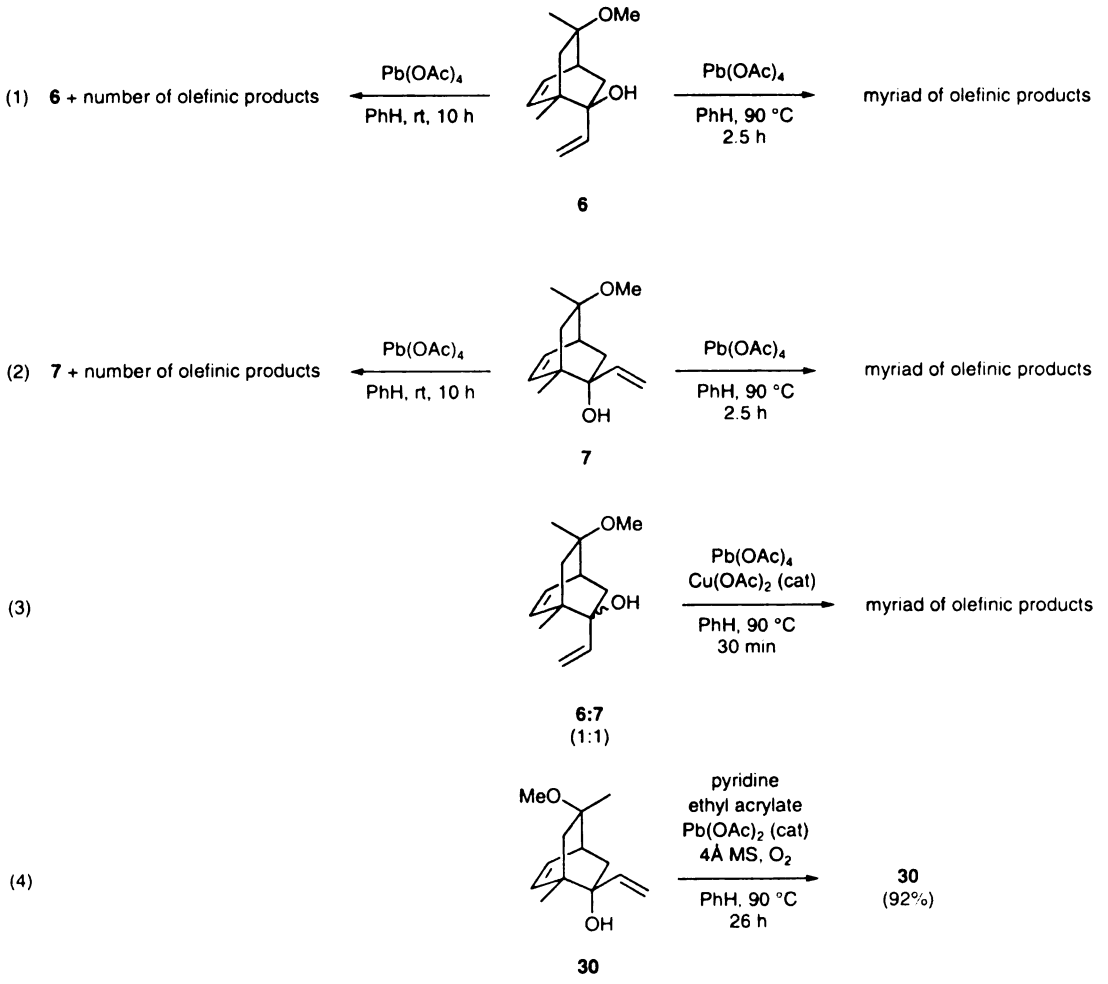
Though the ways of alkoxy radical generation are numerous, not all cater to the allylic-homoallylic nature of the starting tertiary bicyclic carbinol. Pyridinyl and thiazole

thiones as well as phthalimides rely on substitution chemistry for their construction. The bicyclic tertiary nature of the system would require a S_N1 process, allowing for the possibility of products derived *via* cationic bicyclic rearrangements.[41] As a result, these methods were not attempted. Generation of nitrate esters and their subsequent reduction was thought promising, however early attempts resulted in complete decomposition of the starting substrates. Thus further study of nitrate esters was avoided.

2.4.1. Lead

The use of $Pb(OAc)_4$ for decarboxylation and oxidative cyclization is well known.[28c] It also has been used to create oxygen radicals from secondary bicyclic and

Scheme 8. $Pb(OAc)_4$ Attempts

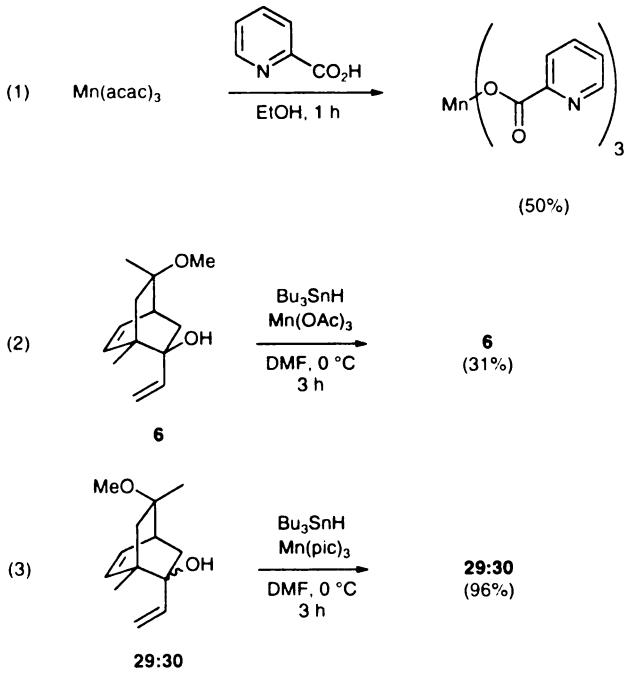


monocyclic carbinols as well.[28ab] Unfortunately, with our substrates clean reactions were not observed when $Pb(OAc)_4$ mediated rearrangements were attempted at ambient or reflux temperatures (equations 1 and 2, Scheme 8). Recently, Rigby has shown that use of $Cu(OAc)_2$ as a catalytic additive can oxidize carbinols as well.[29d] However these conditions proved even more harsh than $Pb(OAc)_4$ alone, rapidly providing a myriad of molecules (equation 3, Scheme 8). Lead (II) was studied next as the use of $Pd(OAc)_2$ in an oxygen atmosphere has triggered the oxidative ring cleavage of cyclobutanols.[30] However, as before, exposure of our substrate to standard Pb(II) conditions gave no reaction (equation 4, Scheme 8). This prompted the dismissal of lead based reagents.

2.4.2. Manganese

Tris-(2-pyridinecarboxylato)manganese(III) or $Mn(pic)_3$ has been used to generate alkoxy radicals of carboxylic acids,[31b,g] as well as with cyclopropanols.[31c-e,g,i]

Scheme 9. $Mn(pic)_3$ and $Mn(OAc)_3$ Attempts

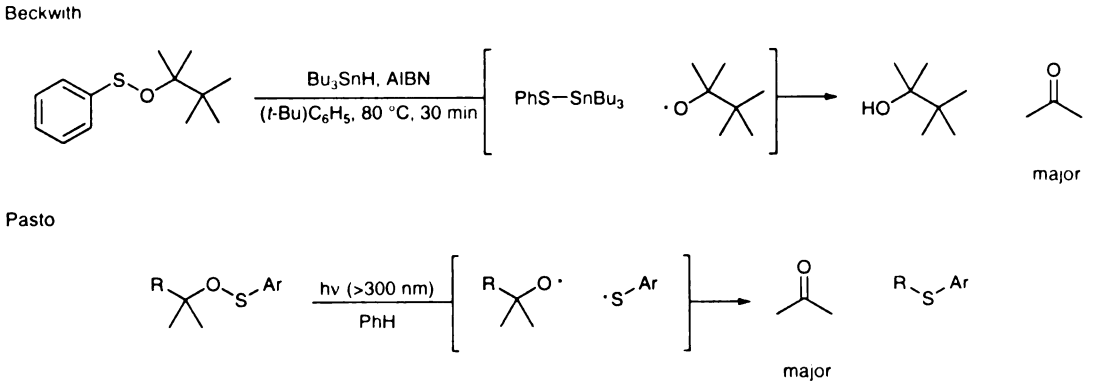


This reagent can be easily synthesized from the readily available $Mn(acac)_3$ (equation 1, Scheme 9).[31a] Trisacetoxymanganese(III) or $Mn(OAc)_3$ has been used to generate carboxylic radicals as well, and also to produce alkyl radicals of β-ketoesters.[31b,g-h] Bicyclic carbinol **6** did not undergo the desired rearrangement and was recovered in low yield (equation 2, Scheme 9). Use of $Mn(pic)_3$ resulted in high recovery of starting material (equation 3, Scheme 9). Like the lead-based reagents, this method was abandoned.

2.4.3. Sulfenate Ester

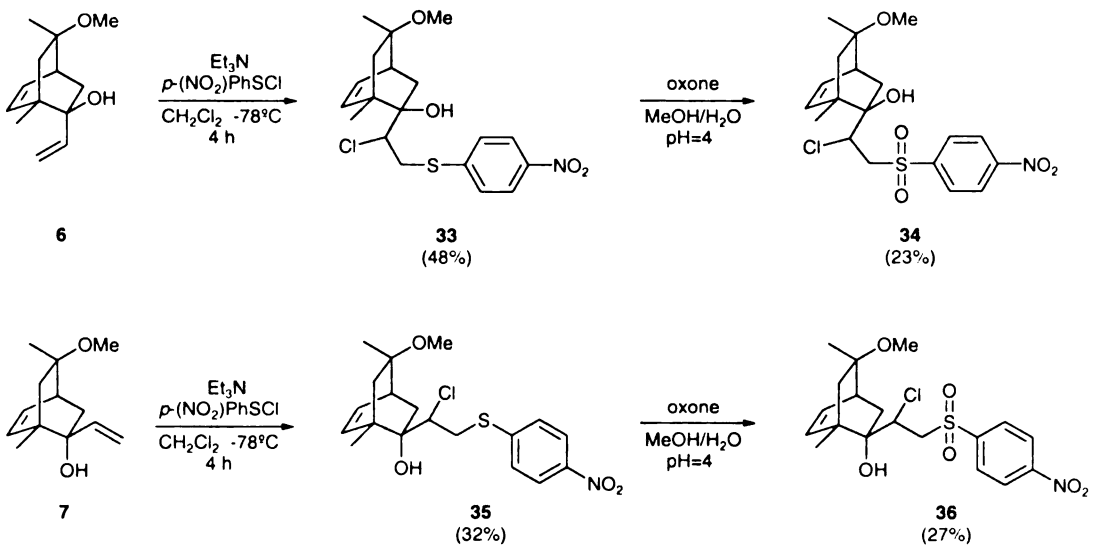
The use of a sulfur-oxygen bond for the generation of oxygen-centered radicals began with Beckwith in the late 80's (Figure 2).[32a] The ability to cleave a sulfur-oxygen bond homolytically makes sense since related peroxide bonds can be cleaved in this manner. Also it is known that Bu_3SnH can be used as an initiation reagent for alkyl radicals upon treatment with alkyl halogens (Cl, Br, I) and dialkyl chalcogenides (S, Se, Te),[42] It naturally followed that the sulfur-oxygen bond could be cleaved in a homolytic fashion as well.

Figure 2. Sulfenate Ester Homolysis



Soon after Beckwith's work, Pasto discovered that sulfur-oxygen bonds not only cleave under Bu_3SnH conditions, but also by light when the S–O bearing groups are properly substituted (Figure 2).[32b-d] Electron withdrawing groups, such as nitro, located on the aromatic ring enhance this desired homolytic fission.

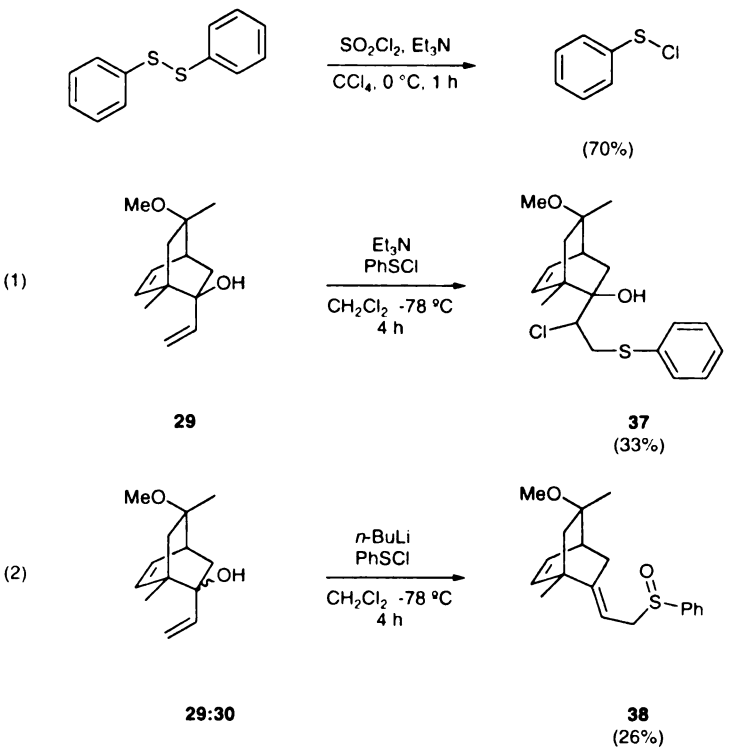
Scheme 10. Nitrophenyl Sulfenate Attempts[23]



Unfortunately, in our hands, formation of the S-O bond was never observed (Scheme 10). Carbinol treatment with *p*-nitrophenylsulfenyl chloride and base[43] only resulted in addition across the vinylic portion of the substrate.[44,45] This addition was thought to be a result of the enhanced polarization of the sulfur-chlorine bond due to the electron withdrawing nitro substituent. To rule out the possible sulfenate [2,3]-sigmatropic rearrangement,[46] both **33** and **35** were oxidized via oxone to produce sulfones **34** and **36** in low yield. In hopes to avoid the addition problem, unsubstituted phenyl sulfenyl chloride was used (equations 1 and 2, Scheme 11).[47] Treatment of the readily available diphenyl disulfide with sulfuryl chloride produced phenyl sulfenyl chloride in good yield.[48] However, as observed in the nitro case, addition across the vinyl olefin was the only observable product when Et_3N was used as the base.[49] Use of *n*-BuLi

as a base produced the [2,3]-sigmatropic product, **38**, even at -78 °C. As a result, the sulfenate avenue for oxygen centered radical formation was abandoned.

Scheme 11. Phenyl Sulfenate Attempts[23]

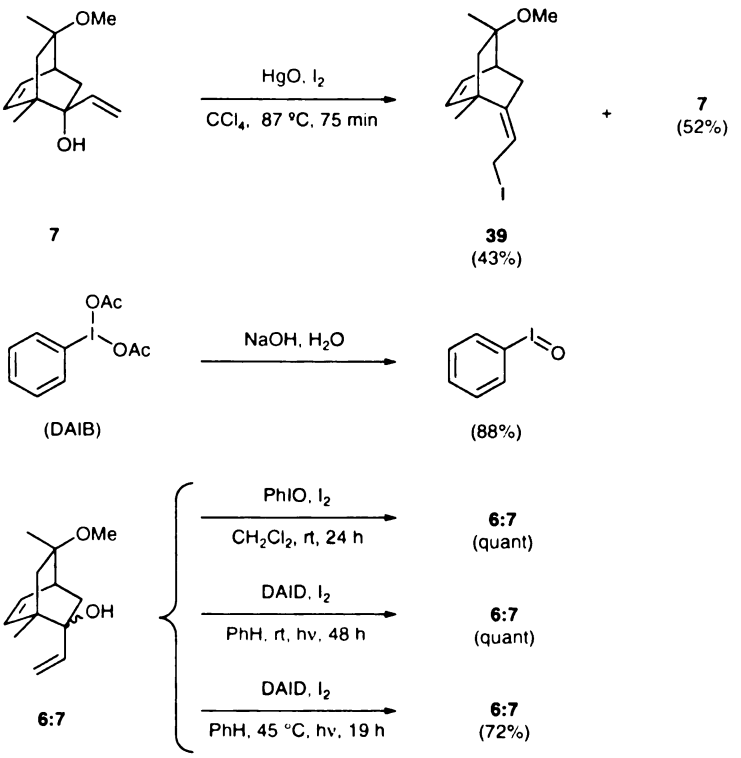


2.4.4. Hypoiodites

There are a number of ways to generate alkoxy radicals by way of hypoiodites. Heterolytic cleavage by HgO/I_2 was originally pioneered by Petrov and later by Barton, who developed methods for homolytic cleavage.[35a,b,50] Hypoiodite fragmentation has also been observed with $Pb(OAc)_4/I_2$,[51] and hypervalent iodine species have been used extensively by Suaréz and Suginome for the generation of anomeric alkoxy radicals in hemiacetals and other systems as well. [35c-l] The reaction of HgO/I_2 with carbinol **7** did not generate the oxy-Cope like product. Nor was the iodoepoxide observed, despite such species being previously reported to come from the hypoiodination of allylic alcohols.[36] Besides starting material the only product isolated, was believed to be iodo **39** (Scheme

12).[52] Treatment with $Pb(OAc)_4/I_2$ provided a complex reaction mixture, as expected from the previous results (Scheme 8). Lastly, use of hypervalent iodines such as diacetoxyiodobenzene (DIAD)[53] and iodosylbenzene,[54] which is readily available from DIAD,[55] was uneventful with only starting material recovered (Scheme 12).

Scheme 12. Hypoiodite Attempts

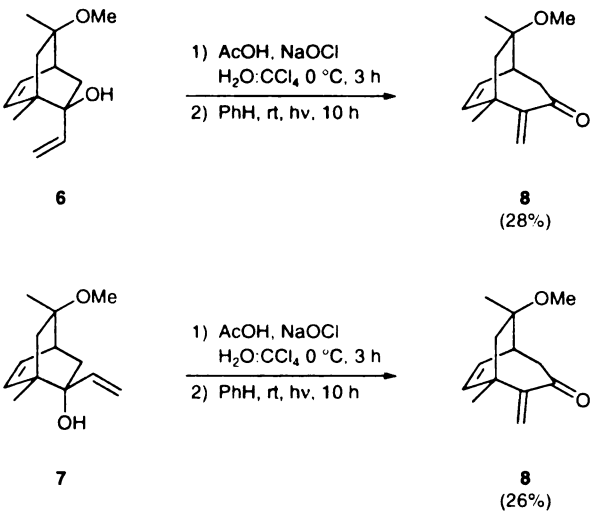


2.4.5. Hypochlorites

In conjunction with hypoiodites, hypochlorites have been extensively used for alkoxy radical generation.[34] The reaction conditions can be quite simple with bleach (NaOCl) and vinegar (AcOH) being among the common reactants.[56] The first attempt at hypochlorite formation and fragmentation yielded enone **8** regardless of carbinol stereochemistry, albeit in low yield (Scheme 13). Importantly, as predicted earlier, the presumed stepwise sequence was selective with respect to product formation, but this selectivity was independent of the starting carbinol stereochemistry. The hypochlorite

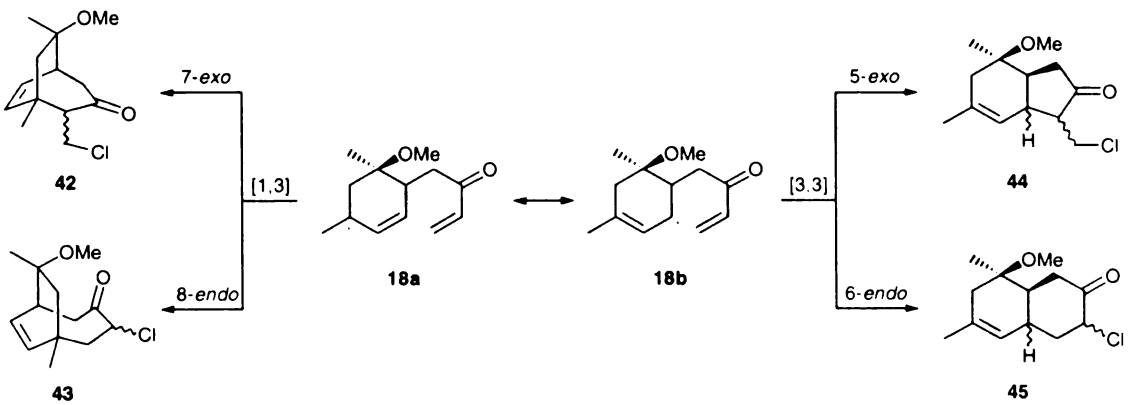
conditions only yielded one product resultant from a 7-*exo* cyclization, **42**, even though there are other more favorable cyclization modes (Figure 3). The fact that there were no

Scheme 13. Hypochlorite Attempts[23]



products isolated from reaction by the allylic resonance form, including the "favored" 5-*exo* cyclization was surprising. If this reaction is proceeding *via* free radicals it would appear that after C–C homolysis, the vinyl sector is in an excellent position for attack by the newly formed radical center.

Figure 3. Possible Radical Cyclizations



2.5. Conclusions

Given the interesting features of the bleach/vinegar induced rearrangement, namely (1) the single mode of cyclization coupled with ready loss of HCl to produce an

exocyclic enone, and (2) the inexpensive and environmentally friendly, or "green", reagents used a more in-depth study of this reaction was undertaken.[57]

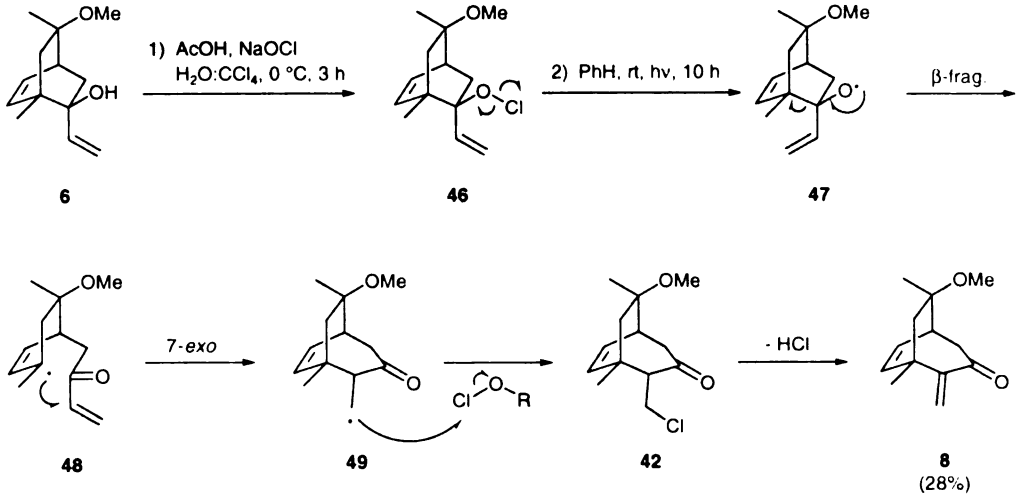
Chapter 3. NaOCl/AcOH Promoted Ring Expansions

3.1. Introduction

The ability of simple reagents like NaOCl and AcOH to promote an *exo*-olefin ring expansion regardless of carbinol geometry was intriguing. Given the possible synthetic utility of such a transformation, studies aimed at optimization of the observed ring expansion/*exo*-olefin insertion were undertaken. In conjunction with these studies, mechanistic insight into this process was sought.

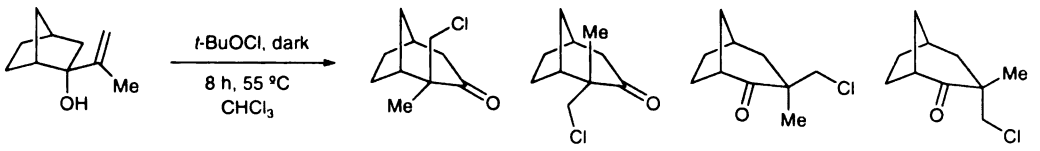
Initially the observed expansion was thought to be radical in nature (Scheme 14), as the conditions employed were those that have generated alkoxy radicals in the past.[58] One can envision after alkoxy radical formation and β-fragmentation, allylic radical **48** undergoing a 7-*exo* cyclization to generate radical **49**. Subsequent propagation of the

Scheme 14. Proposed Radical Mechanism



radical chain, and loss of HCl would generate the observed enone **8**. The above Scheme is somewhat counter intuitive given what is known about free radicals. Generally allylic radicals add to give the more thermodynamically stable product, which was not observed, and 7-*exo* radical cyclizations are not favored when compared to 5-*exo* or even 6-*endo* cyclizations.

Scheme 15. Johnson's [2.2.1] Chlorinative Ring Expansion



9 **10** (41%) **11** (23%) **12** (25%) **13** (11%)

The generation of β-chloroketones *via* a ring expansion of vinyl substituted carbinols are known. Johnson has described the chlorinative ring homologation of simple cyclobutanes, -pentanes, and -hexanes and isopropenyl [2.2.1]-heptanol, **9**.[59] As reported, treatment of a warm, *dark* solution of **9** with *t*-BuOCl afforded a mixture of [3.2.1]-β-chloroketones (Scheme 15). Though several mechanistic pictures were described for this rearrangement, both concerted and free radical sequences were ruled out. Since the experimental conditions were not free radical, i.e. running the reaction in the dark, it was argued that if **9** was being transformed into a hypochlorite prior to a concerted intramolecular rearrangement, a higher degree of diastereoselectivity would have been observed. Thus, Johnson surmised that a cationic mechanism was the most probable. Despite the relatively mild nature of the chlorinative rearrangement, experimentation with bicyclic substrates beyond the [2.2.1] system was not undertaken by Johnson or others.

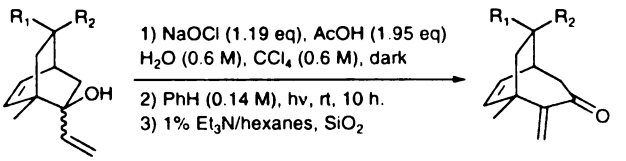
It is interesting that Johnson observed ring expansion in the dark, conditions that should not allow for free radical formation while we observed similar enlargement, albeit without isolation of the pre-supposed chloroketone, under conditions that form free radicals. The ability for these bicyclic systems to undergo similar ring expansions in different environments, light vs. dark, while being subjected to hypochlorite forming

conditions led us to further investigate the necessary reagents and conditions for this reaction.

3.2. Understanding the Reaction Conditions

Refinement of the initial rearrangement and workup conditions allowed for significant improvement in enone isolated yield. It was assumed that the reaction was producing a β-chloroketone, **42**, which was subsequently undergoing elimination. This process significantly simplified the rearrangement by avoiding the issue of the α-keto stereochemistry of **42**. Use of triethylamine (Et_3N) buffered silica allowed for major strides in ease of purification, as well as helping the elimination process.

Table 1. Temperature and Sequence of Reagent Addition Experiments[23]



Entry	Carbinol	Procedure	Product (yield)[a]
(1)	**6** *exo*-OH; R_1=Me; R_2=OMe	A	**8** (28%) R_1=Me; R_2=OMe
(2)	**7** *endo*-OH; R_1=Me; R_2=OMe	A	**8** (26%)
(3)	**7**	B	**8** (26%)
(4)	**6**	C	**8** (35%)
(5)	**6**	D	**8** (28%)
(6)	**6**	E	**8** (60%)

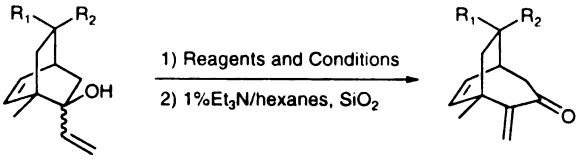
Procedure A: Addition of room temperature AcOH/substrate/CCl_4 solution to chilled (0 °C) NaOCl/H_2O solution. Procedure B: Addition of room temperature substrate/CCl_4 solution to chilled (0 °C) AcOH/NaOCl/H_2O solution. Procedure C: Addition of chilled (0 °C) substrate/CCl_4 solution to chilled (0 °C) AcOH/NaOCl/H_2O solution. Procedure D: Simultaneous addition of chilled (0 °C) substrate/CCl_4 solution and AcOH to chilled (0 °C) NaOCl/H_2O solution. Procedure E: Addition of chilled (0 °C) AcOH/substrate/CCl_4 solution to chilled (0 °C) NaOCl/H_2O solution.
[a] Isolated yield.

Screening of the reagents revealed that the AcOH and NaOCl were absolutely necessary for the reaction to take place. If water (H_2O) or carbon tetrachloride (CCl_4) were excluded sharp decreases in yields were observed. With knowledge of the necessary ingredients, the temperature and sequence of addition were investigated, still under the presumption that a hypochlorite intermediate needed to be formed and irradiated (Table 1). We hypothesized, if reaction conditions were found to enhance hypochlorite formation then an increase in enone should also be observed. These data showed that the media of this biphasic reaction needed to be chilled prior to their combination (entries 1, 2, and 3 vs. entries 4 and 6, Table 1). Even if one of the components was not chilled, a decrease in yield was observed (entry 5, Table 1). The best yield of enone **8** thus far occurred when a chilled solution (0 °C) of substrate (1.00 eq) and AcOH (1.95 eq) in CCl_4 (0.6 M with respect to substrate) was added to a chilled solution (0 °C) of NaOCl (1.19 eq), in H_2O (0.6 M with respect to substrate) after irradiation and purification *via* Et_3N buffered silica chromatography (entry 6, Table 1).

The improvement is isolated enone yield was dependent on the temperature and sequence of reagent addition in the hypochlorite-forming first step of the three step sequence. The next set of experiments involved the use of free radical and non-free radical forming conditions to get an understanding of what intermediates, hypochlorite vs. cationic, were involved. It was believed that the stereochemistry of the methoxy bearing carbon was inconsequential to the rearrangement and both **6:7** and **29:30** were used interchangeably. The first experiment was to run the bleach/vinegar conditions in the presence of normal room light. The reaction proceeded without the formation of a large body of byproducts (entries 1 and 2, Table 2). The second set of experiments

enlisted a radical scavenger, di-*tert*-butylhydroxytoluene (BHT). The isolated yields were lower when BHT was an additive, however the reaction took place regardless of whether BHT was present in the first or second step (entries 3 and 4, Table 2). Ring expansion in ambient light and a radical scavenger points toward a reaction that is not

Table 2. Mechanistic Experiments[23]



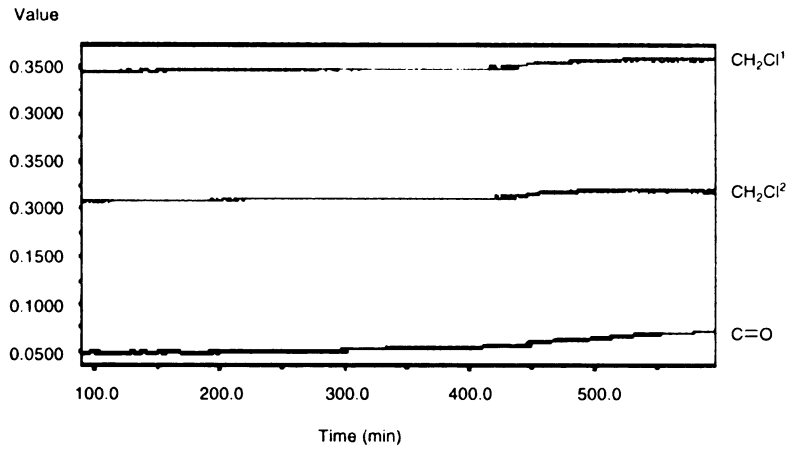
Entry	Substrate	Conditions	Product (yield[a])
(1)[b]	**6:7**	A	**8** (37%)
(2)[b]	**29:30**	A	**50** (48%)
(3)	**6:7**	B	**8** (41%)
(4)[b]	**29:30**	C	**50** (33%)
(5)[b]	**6**	D	**8** (45%)
(6)[b]	**7**	D	**8** (48%)
(7)[b]	**6:7**	D	**8** (53%)
(8)	**6:7**	E	**8** (62%)

Reagents and Conditions: A: NaOCl (1.19 eq.), AcOH (1.95 eq.), H_2O (0.6 M), CCl_4 (0.6 M), 0 °C, 2.5 h. B: 1) NaOCl (1.19 eq), AcOH (1.95 eq), H_2O (0.6 M), CCl_4 (0.6 M), 0 °C, dark, 3 h. 2) BHT (1.6 eq), PhH (0.14 M), rt, hv, 8 h. C: 1) BHT (1.6 eq), NaOCl (1.19 eq), AcOH (1.95 eq), H_2O (0.6 M), CCl_4 (0.6 M), 0 °C, dark, 3 h. 2) PhH (0.14 M), rt, hv, 10 h. D: NaOCl (1.19 eq.), AcOH (1.95 eq.), H_2O (0.6 M), CCl_4 (0.6 M), 0 °C, dark, 3 h. E: 1) NaOCl (1.19 eq), AcOH (1.95 eq), H_2O (0.6 M), CCl_4 (0.6 M), 0 °C, dark, 3 h. 2) PhH (0.14 M), rt, hv, 10 h.

[a] Isolated yields. [b] Recovered starting material.

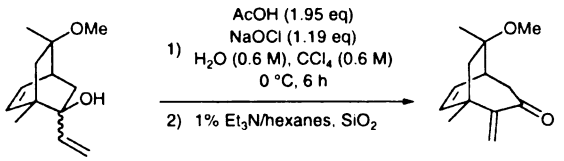
under free radical control. As a result, the likelihood of a hypochlorite intermediate seemed small. We became curious if there was any chemistry occurring during the irradiation step. Use of NMR and React-IR™ techniques , Figure 4, to follow the irradiation of the reaction suggests that very little chemistry was occurring at this stage of the process. Removal of the irradiation step provided proof that the rearrangement

Figure 4. React-Ir Analysis of Irradiation



was occurring during the biphasic portion of the reaction, albeit in somewhat lower isolated yield (entries 5, 6, and 7, Table 2). The lower isolated yields when compared to entry 8 (Table 2), and recovery of starting carbinols were interpreted to be the result of not letting the reaction run to completion. Residual chlorinating agents in the irradiation step would explain why there was a slightly better yield for entry 8, Table 2. Indeed when the reaction time was extended to 6 hrs, yields improved from 37% to 92% (Scheme 16). The excellent isolated yield led to the understanding that the

Scheme 16. Standard Set of Conditions[23]



6:7

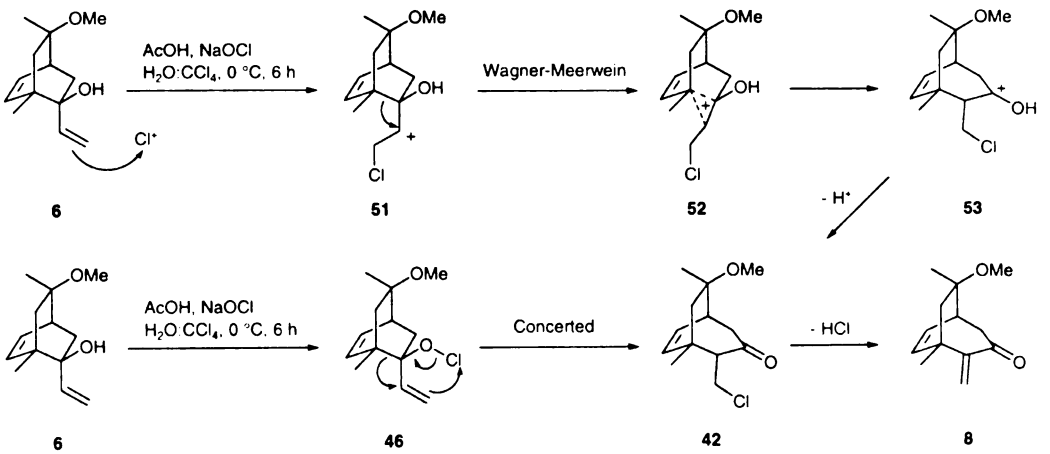
8
(92%; trial 1)
(95%; trial 2)

rearrangement was occurring during the biphasic portion, or step 1, of this multistep reaction and that these reactions could be run in the presence of normal laboratory lighting. As a result we adopted this set of conditions, as our "standard set of conditions" for all subsequent substrates studied.

3.3. Proposed Mechanism

The previous experiments also gave some additional insight into the mechanism of this rearrangement. The fact that the product composition is not affected by the addition of radical scavenger nor by the presence or absence of light discredits the proposed radical mechanism (Scheme 14). Given these observations and other reports, a mechanism involving cationic character appears the most probable and is illustrated in Scheme 17.[59,60,61] The combination of NaOCl and AcOH is a source of Cl^+. After Cl^+ capture by the vinyl portion of the carbinol, a Wagner-Meerwein shift of the bridgehead produces carbinol cation **53**. Loss of H^+ would generate **42** and again, loss of HCl. One other possible mechanism would be the concerted rearrangement of an *in-situ* generated hypochlorite. Though possible, this mechanism seems unlikely since a concerted rearrangement should impart a higher level of stereoselectivity than that was observed in the products (Scheme 15). Also when hypochlorites are reacted in the presence of light, at least trace amounts of oxy-radical derived products are expected.[58] None were observed. Moreover, attempts to purposely prepare hypohalites of **6** or **7** by alternative methods (Chapter 2) never afforded enone **8** or its haloketone analogues. Lastly, use of

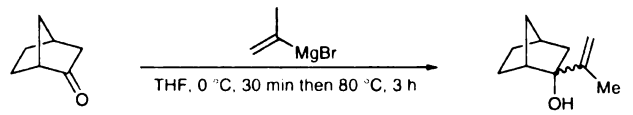
Scheme 17. Proposed Cationic and Concerted Mechanisms



React-IR™ showed no formation of an oxygen chlorine bond.[62] These facts all support a cationic rearrangement.

3.4. Chlorinative [2.2.1] Ring Expansions

Scheme 18. Synthesis of **9**[23]

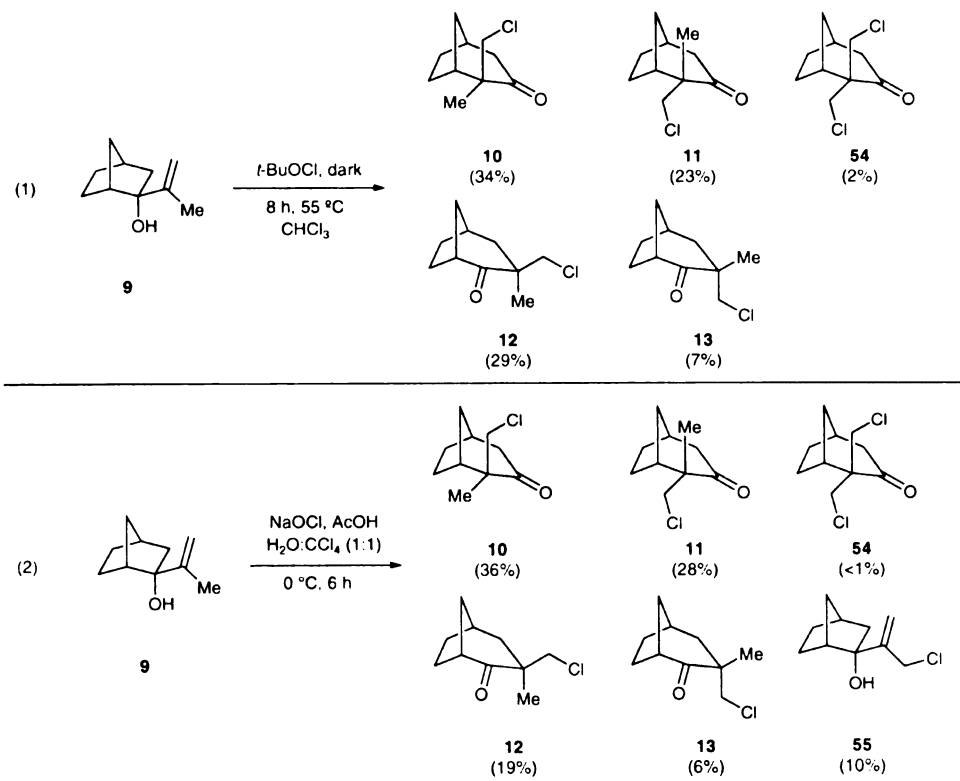


norcamphor

9
(64%; 50:1)

As stated in Chapter 1, a related chlorinative ring enlargement has been reported by Johnson in a number of *iso*-propenyl carbinols.[59] Given the similarities of both ring expansions, namely the vinyl carbinol substrate and use of a hypochlorite reagent, it was thought prudent to submit isopropenyl [2.2.1] carbinol **9** to both Johnson's and our

Scheme 19. *t*-BuOCl vs. NaOCl in Johnson's System[23]

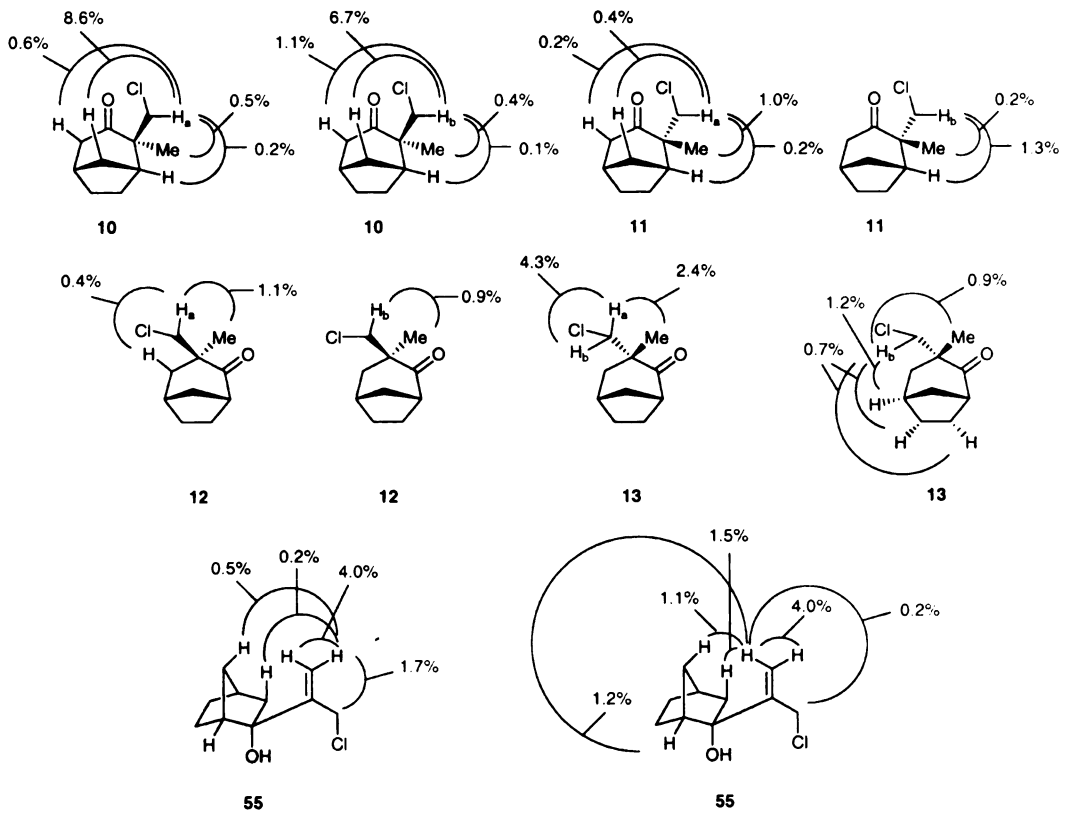


conditions. Also with the advances in structural elucidation since the time of the original report, the structures of chloroketones **10-13** could be more firmly established. In addition, a preparative method needed to be developed so as to ascertain the isolated yields of these products.[63]

3.4.1. Results and Structural Assignment

Isopropenyl carbinol **9** is readily available from Grignard addition across norcamphor in a ratio of 50:1 (Scheme 18). Treatment of **9** with Johnson's conditions gave a ratio of products similar to that described in the original report, plus the formation of a dichloro product, **54**.[64] Johnson reported six products whose yields were obtained from gas-liquid phase chromatography (GLC). Only four of these products, **10-13**, were

Figure 5. 1D-NOE Support of Johnson's Products

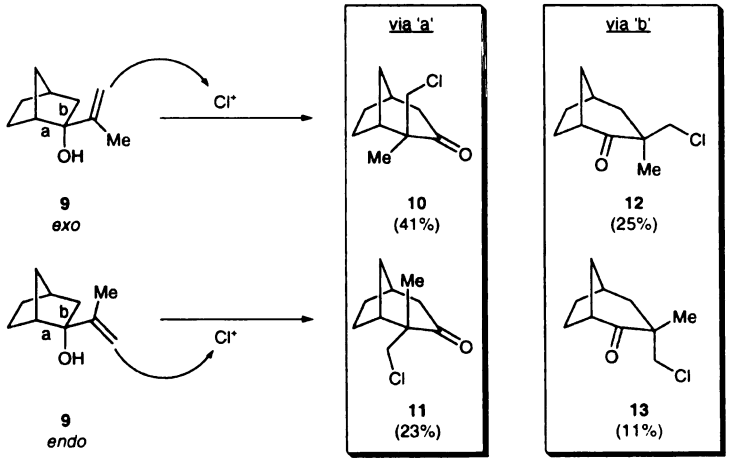


isolated. It is likely that one of the two unidentified products in Johnson's study was dichloroketone **54**. Exposure to the standard NaOCl/AcOH conditions derived above produced the same compounds that were observed under Johnson's conditions, plus a chlorinated carbinol, **55** (Scheme 19). All structural data, high-field NMR and one-dimensional nuclear Overhauser enhancement (1D-NOE), were in good agreement with the original assigned structures (Figure 5).[59,65] Johnson used aromatic solvent-induced shifts, observed previously in methylcyclohexanones, to distinguish the stereochemical configurations of **10-13**. Use of 1D-NOE experiments also confirmed that **55** still retained the same carbinol geometry as **9**. Dichloro product **54** was ascertained by comparison with the other [3.2.1]-ketones with the diagnostic downfield shift of the methylenic protons adjacent to the carbonyl observed in **10** and **11**.

3.4.2. Mechanistic Considerations

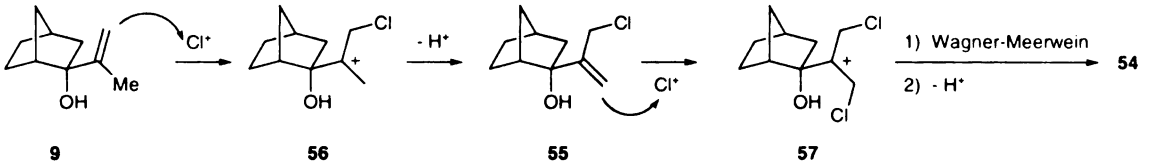
Both reactions are slightly regioselective with the bridgehead carbon 'a' bond preferentially migrating vs. 'b' bond cleavage (Scheme 20). The diastereoselectivity results from the reacting rotomeric isopropenyl conformer. Orientation of the methylene in an *exo* fashion is preferred by ~2:1 over the *endo*.

Scheme 20. Johnson Regio and Diastereoselectivity



There also appears to be a secondary pathway to products **54** and **55**. The initial Cl^+ capture occurs to generate cation **56**, which undergoes loss of H^+ and generates **55**. Wagner-Meerwein shift occurs after a second abstraction of electrophilic Cl^+ to produce dichloroketone **54**.

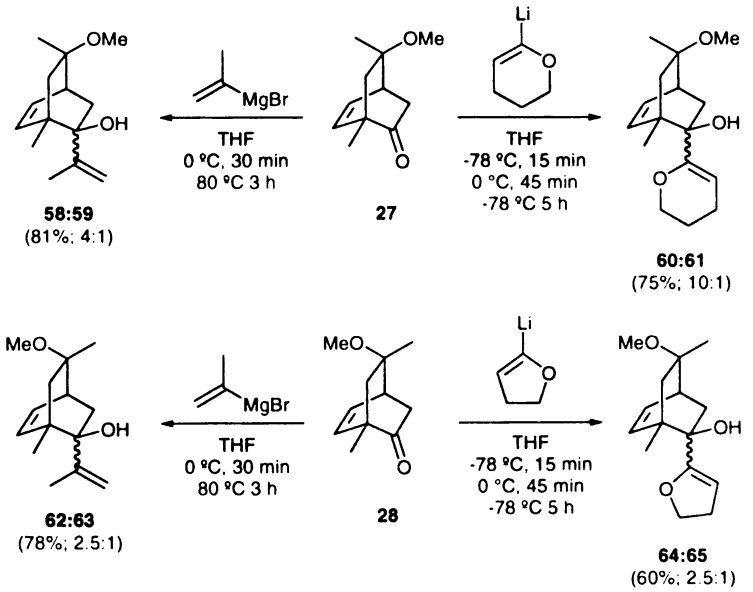
Scheme 21. Secondary Cationic Mechanism



3.5. Further Unsaturated [2.2.2] Substrate Synthesis

The conditions derived above mimicked Johnson's relatively well. Examination of the literature reveals little regarding cationic rearrangements of vinyl substituted [2.2.2] carbinols. To more fully appreciate the selectivity, scope and mechanism of this chlorinative rearrangement, a series of carvone-derived "vinyl" [2.2.2]-bicyclocarbinols were subjected to NaOCl and AcOH.

Scheme 22. "Vinyl" Substrate Synthesis[23]



The substrate synthesis was fairly straightforward. *Iso*-propenyl, dihydropyranyl (DHP), and dihydrofuranyl (DHF) anions all added, rather cleanly, across Srikrishna's ketones **27** and **28** and the addition products were all isolated in reasonable yield (Scheme 22).[66] It should be noted that the methoxy group blocks the *exo* attack to some degree in **58** through **61**, achieving modest diastereoselectivity. The methyl group shields the *exo* face only slightly to yield some diastereomeric favoritism, **62** through **65**. The resultant allylic alcohols (**58** through **65**) were then subjected to the standard bleach and acetic acid chlorinative ring expansion conditions (Table 3).

3.6. Chlorinative Ring Expansions of "Vinyl" [2.2.2] Carbinols

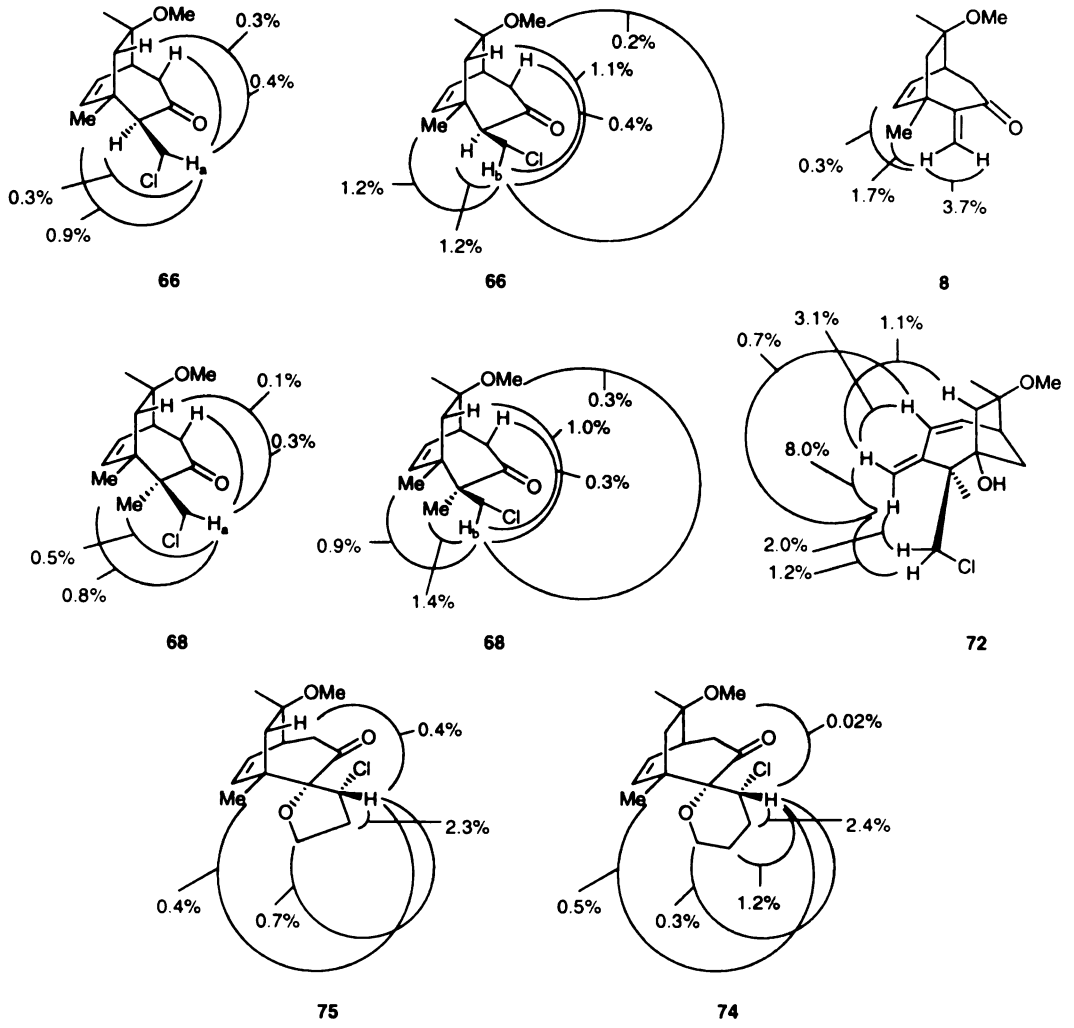
3.6.1. Results and Structural Assignment

All vinyl carbinols investigated, Table 3, rearranged smoothly and surprisingly in a diastereoselective manner. The stereochemistry of the *exo*-carbinol vinyl, *iso*-propenyl, DHP and DHF rearrangement products, **8**, **66**, **68**, **72**, **74**, and **75**, were assigned on the basis of 1D-NOE experiments (Figure 6). In the chlorinative ring expansions the through space effects of note are between the CH_2Cl or CHCl protons and their interaction with hydrogens on the top face of the ring (Figure 6). The stereochemistry of the other diastereomeric chloroketones was assigned by default, since by ^{1}H-NMR all these species possessed the signature α-keto methylene protons thus establishing the regiochemistry of their rearrangement.

The vinyl carbinol set (entries 1-2, Table 1) revealed that the rearrangement is also diastereospecific. The *exo*-carbinol produced the *exo*-chloroketone, **66**, selectively while the *endo*-carbinol yields the *endo*-chloroketone, **67** (entries 1 and 2 respectively,

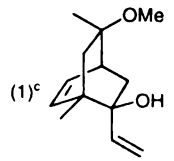
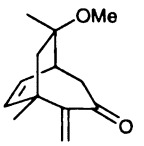
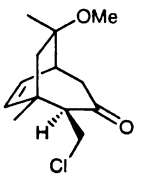
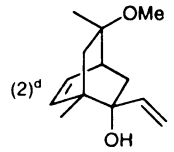
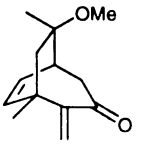
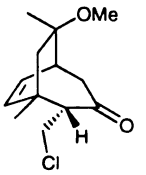
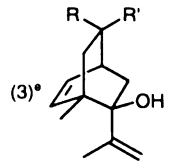
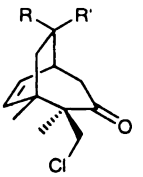
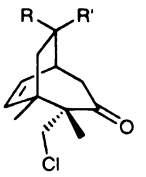
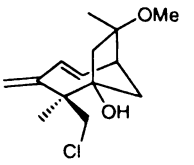
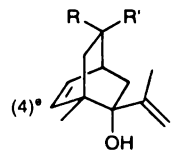
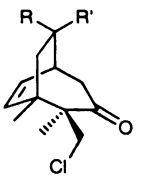
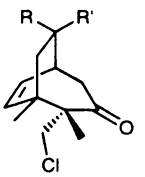
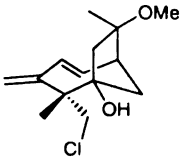
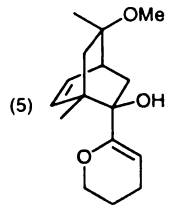
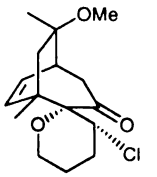
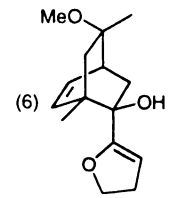
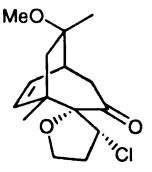
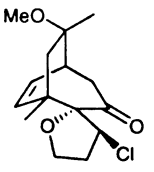
Table 3). The β-chloroketones, **66:67**, were prone to eliminate HCl, as can be seen from of enone **8**. It is possible that in both cases the minor chloromethyl diastereomers

Figure 6. 1D-NOE Support of Chlorinative Diastereoselectivities



are produced but not observed due to this elimination. Crude ^{1}H-NMR analysis of both *exo*- and *endo*-carbinols, **6** and **7**, showed that these rearrangements were not completely diastereoselective with observed **66:67** ratios of 16:1 and 1:14 respectively. *Iso*-propenyl bearing substrates (entries 3-4, Table 3) were then studied since the rearrangement products of these species cannot eliminate. Like the vinyl bearing carbinols, **6** and **7**, the *iso*-propenyl carbinols, **58:59** and **62:63**, rearranged in a diastereospecific manner. Both diastereomers were isolated, supporting the previous notion of facile HCl

Table 3. Chlorinative Ring Expansions of [2.2.2] Bicyclics[23]

Entry	Substrate	Products (yield[a]; ratio)[b]		
(1)[c]				
	6	**8** (48%)	**66** (32%)	
(2)[d]				
	7	**8** (47%)	**67** (36%)	
(3)[e]				
	58 (R_1=Me; R_2=OMe) **62** (R_1=OMe; R_2=Me)	**68:69** (86%; 20:1) **70:71** (78%; 15:1)		**72** (10%)
(4)[e]				
	59 (R_1=Me; R_2=OMe) **63** (R_1=OMe; R_2=Me)	**68:69** (82%; 1:12) **70:71** (76%; 1:11)		**73** (16%)
(5)				
	60	**74** (90%)		
(6)				
	64	**75:76** (43%; 7:1)		

Reagents and conditions: 1) NaOCl (1.19 eq), AcOH (1.95 eq), CCl_4 (0.6 M), H_2O (0.6 M), 0 °C, 6 h. [a] Isolated yields. [b] Ratios determined by ^{1}H-NMR. [c] Crude ^{1}H-NMR shows a 16:1 mixture of **66:67**. [d] Crude ^{1}H-NMR shows a 1:14 mixture of **66:67**. [e] Analagous [4.2.1]-carbinols were not isolated for **62** and **63**.

elimination masking the diastereoselectivity of the rearrangements of **6** and **7**. The *iso*-propenyl *exo*-carbinols, **58** and **62**, were more selective than their *endo* counterparts, **59** and **63**. The *exo*-carbinols generate α-*exo*-chloroketones, **68** and **70** preferentially, and vice versa for the *endo*-set, **69** and **71** (entries 3 and 4, Table 3).

3.6.2. Mechanistic Considerations

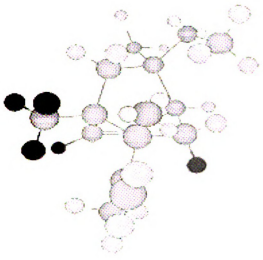
The greater selectivity observed by *exo*-carbinols **58** and **62** is believed to be a consequence of sterics. The *iso*-propenyl unit of **58** and **62**, has a large degree of rotomeric freedom, with its *exo*- and *endo*-olefinic rotomers being nearly equivalent in energy (Figure 7). This freedom enables **58** to adopt the reactive *cisoid* conformer and achieve enhanced selectivity. On the other hand, **59** and **63** have a number of substituents to accommodate and thus the *exo*- and *endo*-olefinic species have significantly different environments. A constriction of rotomeric freedom allows for the reaction of the *transoid* conformer and the observed loss in selectivity. Accompanying each chloroketone was a [3.2.1]-bicyclocarbinol, **72** and **73**, with the migrating carbon stereochemistry remaining intact. Surprisingly no other vinyl substrate investigated rearranged to produce this bicyclic skeleton. DHP and DHF carbinols were also investigated (entries 5-6, Table 3). They also follow this trend with both *exo*-carbinols resulting in the chlorocarbon *exo* to the ring.

Data on the rearrangements presented in Table 3 suggest that, in contrast to **10** (equation 1, Figure 8),[59] the [2.2.2]-bicycles rearrange *via* conformers that place the olefin and the hydroxyl *syn* to each other. Paquette has described a similar relationship during proton mediated ring expansions of DHF substituted [2.2.1]-carbinols,[60] pointing to a

Figure 7. Rotomeric Constraints

58

59



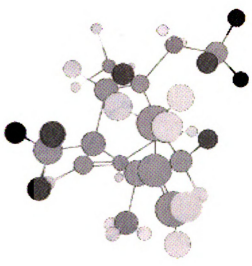
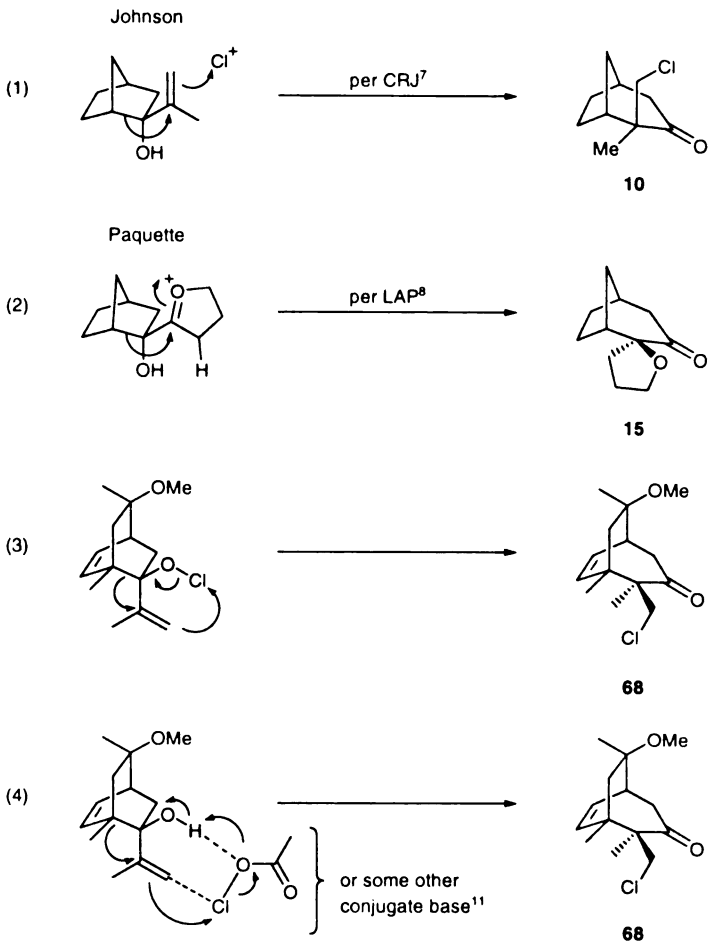


Figure 8. Mechanistic Arguements

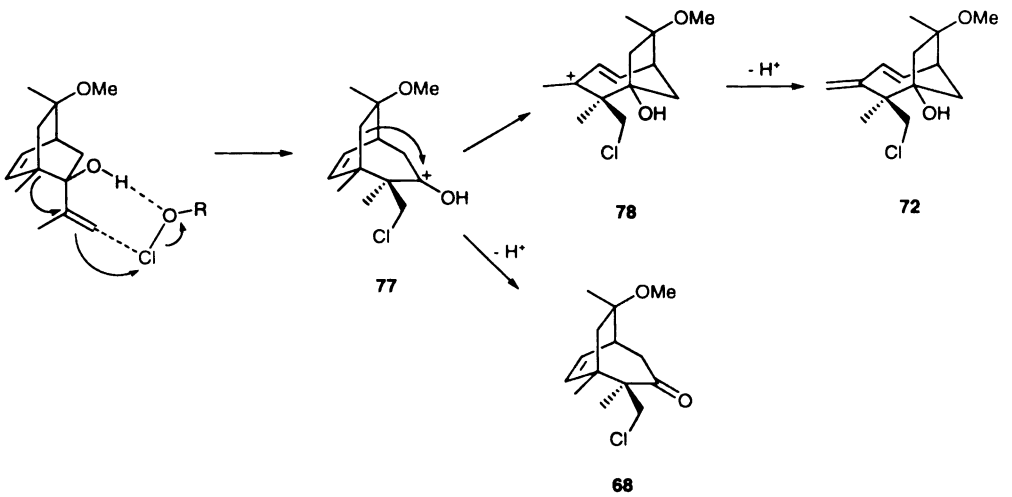


preferred *anti* relationship between the ring oxygen and the hydroxyl (equation 2, Figure 8). However entries 1-4 (Table 3) suggest that, in our reactions, the heteroatom may not be the primary stereocontrol element. Furthermore, the resultant stereochemistry of the chlorine-bearing carbons in entries 5 and 6 (Table 3) indicates that the same conformer undergoes both chlorination and ring expansion. For reasons stated earlier it seems unlikely that the [2.2.2] systems are being converted to their hypochlorites prior to a concerted rearrangement (equation 3, Figure 8). It is possible that the Wagner-Meerwein shift is in concert with, or *via* a late transition state, chlorination by a hypochlorite species (equation 4, Figure 8). The rotomeric preference is possibly the result of hydrogen

bonding between the carbinol and hypochlorite, allowing for a predisposition of the reactive site to be on the exterior of the ring. In either event the facile nature of electrophilic Cl^+ capture and Wagner-Meerwein shift would explain the observed diastereoselectivities.

Lastly, the generation of secondary rearrangement products, albeit only in the *iso*-propenyl case, *via* a subsequent alkyl [1,3]-shift points toward a cationic intermediate, **77** (Scheme 23). All these observations lead to the conclusion that this rearrangement,

Scheme 23. *Iso*-propenyl Carbinol Secondary Mechanism

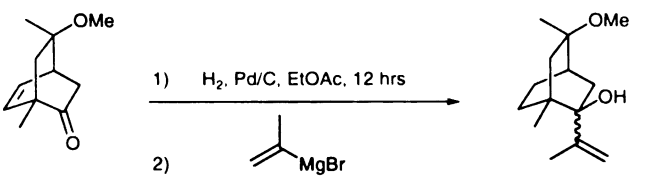


like Johnson's, is cationic in nature. Chlorination occurs *via* acetyl hypochlorite, or some other conjugate hypochlorite,[67] and the carbinol's *cisoid* rotomeric geometry (equation 4, Figure 8). Wagner-Meerwein rearrangement ensues to produce the observed β-chloroketones. Furthermore, in terms of chemoselectivity, ether oxygens did not interfere with the expansion and, to reiterate, no reaction with the bridging olefin was observed during the rearrangement.

3.6.3. Rotomeric Carbinol Investigation

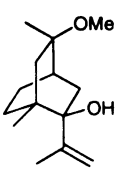
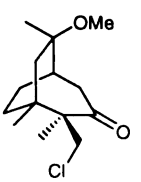
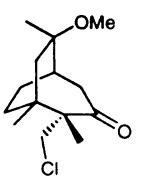
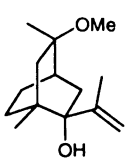
The observed diastereoselectivity of unsaturated [2.2.2] *iso*-propenyl carbinols was hypothesized to be the result of a preferred, more reactive *iso*-propenyl rotomer. The *iso*-propenyl unit of *exo*-carbinol **58** has more rotomeric freedom, than diastereomer

Scheme 24. Synthesis of Saturated **80** and **81**[23]



59. As a result, **58** can easily access the more reactive rotomer allowing for better diastereoselectivity. In order to explore this hypothesis, the internal olefin was saturated to produce compounds **80** and **81**. Hydrogenation of **27** followed by addition of *iso*-propenyl Grignard produced the saturated *iso*-propenyl carbinols in good yield and reasonable diastereoselectivity (Scheme 24). If the diastereoselectivity was a result of the

Table 4. Chlorinative Ring Expansions of Saturated [2.2.2] Isopropenyl Carbinols[23]

Entry	Carbinol	Products (yield\; ratio)	
(1)			
	80	**82**	**83**
		(82% 10:1)	
(2)		**82**	**83**
		(79%; 1:14)	
	81		

Reagents and conditions: 1) NaOCl (1.19 eq), AcOH (1.95 eq), CCl_4 (0.6 M), H_2O (0.6 M), 0 °C, 6 h. [a] Isolated yield. [b] Ratio determined by ^{1}H-NMR.

aforementioned rotomeric constraint, then a loss of selectivity would be observed in carbinol **80**, as a result of the new hydrogen substituents, while a similar ratio of diastereomers would be observed for **81**.

Upon treatment with the standard NaOCl/AcOH conditions, both *exo*- and *endo*-carbinols rearranged smoothly to produce chloroketones **82:83** in a diastereoselective manner (Table 4). Indeed, a loss of selectivity in the rearrangement of **80** was observed, while similar diastereoselectivity to that of **59** was observed with **81**. These data provide support for a preferred rotomeric carbinol and that the rotomeric environment can dictate the observed selectivity. This issue of rotomeric constriction could be explored further by submitting other alkyl substituted vinyl moieties to our standard set of conditions.

3.6.4. Summary of Chlorinative [2.2.2] Bicyclic Expansions

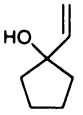
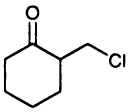
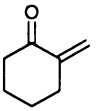
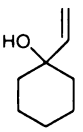
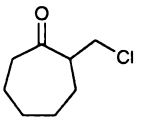
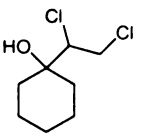
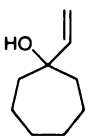
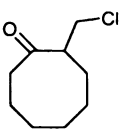
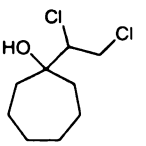
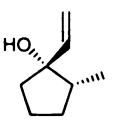
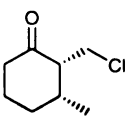
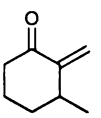
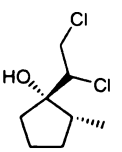
These examples establish bleach and acetic acid as effective promoters of chlorinative one-carbon ring expansions of [2.2.1]- and [2.2.2]-bicyclic molecules. Rearrangement of vinyl-, *iso*-propenyl-, DHF-, and DHP-substituted [2.2.2]-bicyclo-carbinols were chemo-, regio-, and stereoselective, affording β-chloro-[3.2.2]-bicycloketones in respectable yields. The selectivity of these rearrangements appears to be derived from reaction of a preferred conformer in which the hydroxyl and the reacting vinyl groups are in a *syn* orientation.

3.7. Chlorinative Ring Expansions of Monocyclic Vinyl Carbinols

To emphasize the generality of this rearrangement, a set of simple vinyl cycloalkanols were selected and subjected to standard conditions. The substrates were readily available *via* vinyl Grignard addition across commercially available cyclopentanone, cyclohexanone and cycloheptanone with little product purification.

3.7.1. Results and Structural Assignment

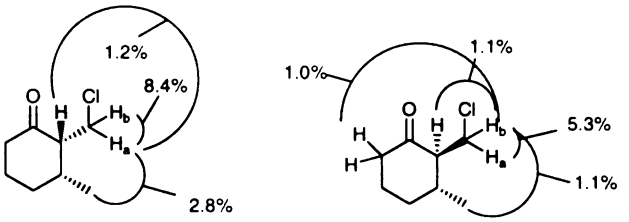
Table 5. Chlorinative Expansions of Monocyclics[23]

Entry	Carbinol[a]	Products (yield[b])			
(1)					
	84 (98%)	**89** (69%)	**90** (10%)		
(2)					
	85 (quant)	**91** (65%)	**92** (12%)		
(3)					
	86 (97%)	**93** (62%)	**94** (18%)		
(4)[d]					
	87:88 (86%; 10:1)	**95:96** (71%; 5:1)	**97** (10%)	**98** (<2%)	

Reagents and conditions: 1) NaOCl (1.19 eq), AcOH (1.95 eq), CCl_4 (0.6 M), H_2O (0.6 M), 0 °C, 6 hrs. [a] CH_2=CHMgBr,0 °C, 30 min, 80 °C, 1 hr. [b] Isolated yields. [d] Major isomer shown.

Indeed, all carbinols underwent expansion to produce their respective β-chloroketones in reasonable yield (Table 5). Unfortunately accompanying the ring expansion in this series were chlorinated carbinols **92** and **94**. Methyl vinyl cyclohexanol **87** rearranged smoothly to provide the β-chlorocyclohexanones, **95:96**, in respectable yield and diastereoselectivity (entry 4, Table 5). The stereochemistry of **95** and **96** were determined by 1D-NOE experiments (Figure 9).

Figure 9. 1D-NOE Support of Methyl β-Chlorocyclohexanones **95:96**

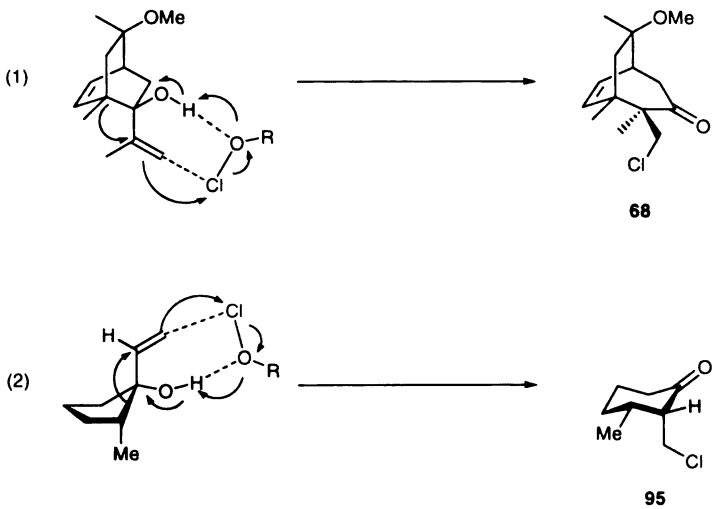


95 **96**

3.7.2. Mechanistic Considerations

Importantly, the mneumonic, described previously (Figure 10), holds true in this monocyclic case. The *cisoid* geometry, of the hydroxy and vinyl moiety, is again favored (5:1) in this simple system. There was also a small amount of elimination that had occurred prior to column chromatography to produce **97**. A minute amount of dichlorocarbinol **98** was also observed, however this compound was never cleanly isolated so its structure remains tentative.

Figure 10. Predictive Diastereoselective Pneumonic



3.7.3. Summary of Chlorinative Monocyclic Expansions

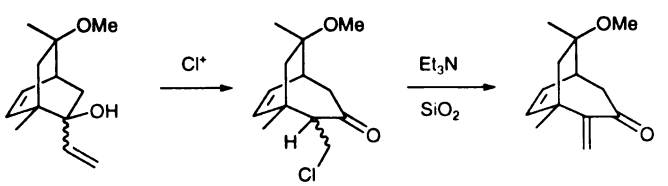
These examples show how commercially inexpensive and environmentally benign NaOCl and AcOH can chlorinatively ring expand a variety of "vinyl" substituted

carbinols with excellent chemoselectivity, in reasonable regio and diastereoselectivity and in good yield. The β-chloroketones isolated can be transformed into a variety of species making this process synthetically attractive. One such process, which is quite facile for the vinyl carbinols, is the elimination of HCl to produce *exocyclic* enones.

3.8. Exo-Olefin Insertion/One Carbon Ring Expansions

Enones are found in a number of biologically active compounds.[68] Their chemical prowess has long been exploited as these compounds can be manipulated at either the α, β, or γ-positions. The construction of *exocyclic* enones can be accomplished in a number of ways. Eliminations of oxalates,[69] pyrrolidines,[70] β-selenyl ketones,[71] α-methoxymethyl ketones,[72] β-metallo ketones,[73] as well as dehydrosulfenylation,[74] and α-methenylation,[75] are all suitable methods. However these methods can suffer from a lack of regioselectivity, low yields, or intricate synthetic procedures. To the best of our knowledge a synthetic route to *exocyclic* enones *via* a one-carbon expansion protocol has not been established.[76] Thus we sought to optimize not only the observed chlorinative rearrangement, but also the facile elimination of the β-chloroketones, **66:67**, to generate an *exocyclic* enone, **8**, (Scheme 25). In doing so we also aimed to address other questions. Can this facile elimination be observed in other bicyclic and monocyclic systems? *Exocyclic* enones **8** and **50** could not internalize their olefinic moiety per

Scheme 25. *Exo*-Olefin Insertion/One Carbon Ring Expansion



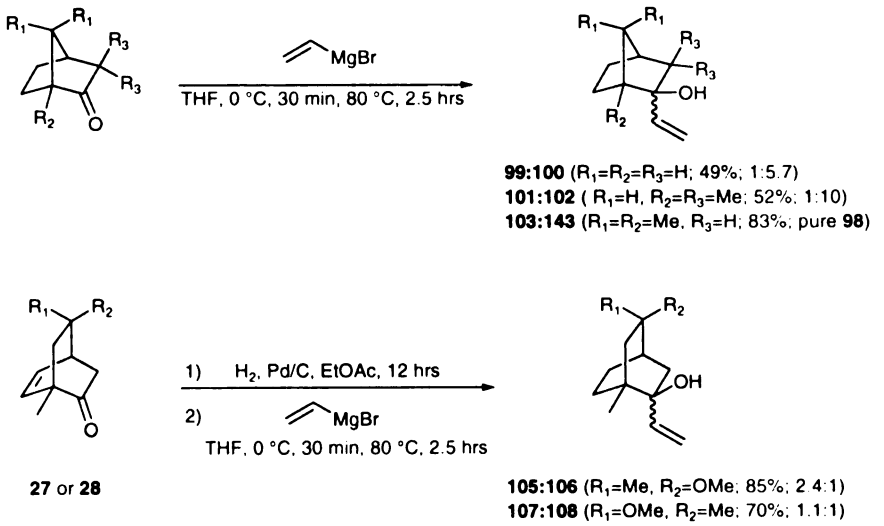
6:7 66:67 8

Bredt's rule. Will this internalization occur in suitably substituted substrates? Both questions needed to be addressed.

3.9. Saturated [2.2.1] and [2.2.2] Substrate Synthesis

The vinyl [2.2.1] bicyclics were readily available from their respective commercially available ketones (Scheme 26). Quick purification *via* an alumina plug provided the substrates in good yield. The selectivity of the 1,2-addition observed in the [2.2.1] constructs complements the literature with the norcamphor and fenchone bicycles yielding primarily *endo*-carbinols, **100** and **102** respectively. The internally saturated [2.2.2] series mimicked what was previously observed (Scheme 6, Chapter 2) with the methoxy substituent being able to shield the *exo*-face of the carbonyl. However, the saturated bridging carbons block *endo* attack to some degree resulting in a loss of selectivity (**6:7**; 4:1 vs. **105:106**; 2.4:1).

Scheme 26. Saturated [2.2.1] and [2.2.2] Substrate Synthesis[23]

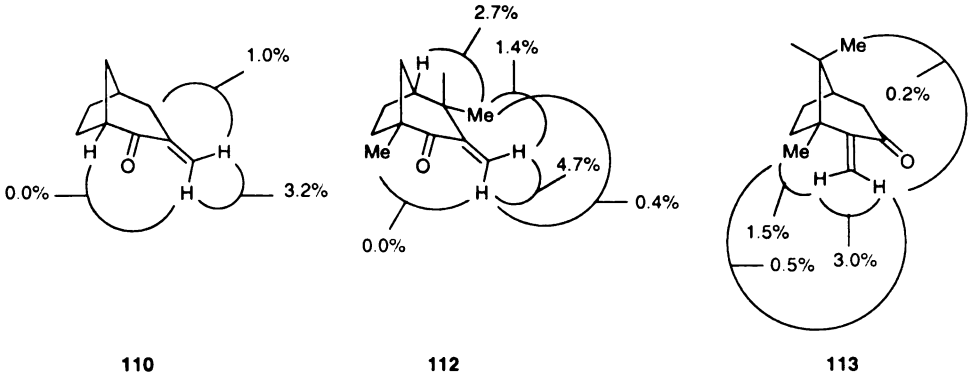


3.10. [2.2.2] and [2.2.1] Exo-Olefin Insertion/One Carbon Ring Expansions

3.10.1. Results and Structural Assignment

All vinyl [2.2.1] and [2.2.2] carbinols examined rearranged smoothly to produce [3.2.1]- and [3.2.2]-bicycloenones respectively (entries 1-11, Table 6), with the regioisomeric enones being assigned by 1D-NOE through space couplings (Figure 11). The lack of regioselectivity observed in the [2.2.1] substrates was nominal, but not surprising considering similar rearrangements (entries 1-3, Table 6).[59,60,61] Investigation into the homologous [2.2.2] systems (entries 4-5, Table 6) revealed complete regioselectivity, as observed by its unsaturated predecessor (entries 6-11, Table 6).

Figure 11. 1D-NOE Support of **110**, **112**, and **113**

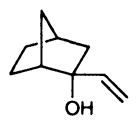
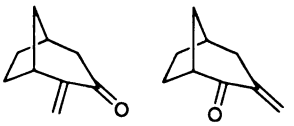
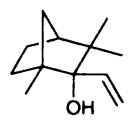
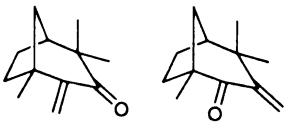
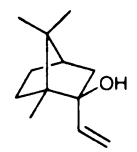
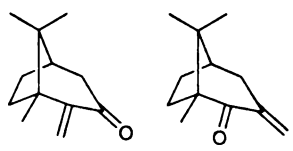
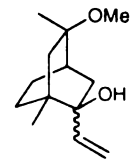
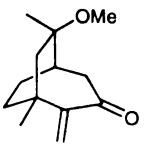
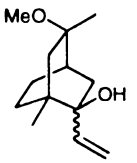
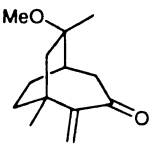


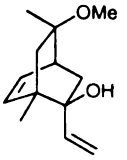
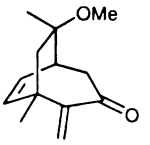
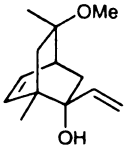
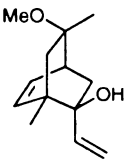
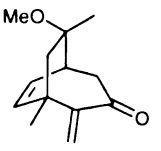
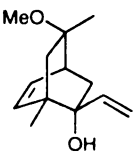
110 **112** **113**

3.10.2. Mechanistic Considerations

The lack of regioselectivity observed in the [2.2.1] system has been attributed to anchimeric assistance following carbocation formation, as well as bond angle distortion present in both the substrate and intermediate.[77] The anchimeric assistance available to the cationic intermediate can be seen upon examination of the antibonding molecular orbitals found in the two possible migrating carbon-carbon bonds (C1-C2 and C1-C3; Figure 12). This cationic intermediate can effectively interact with either

Table 6. Bicyclic *Exo*-Olefin Insertion One Carbon Expansion Results[23]

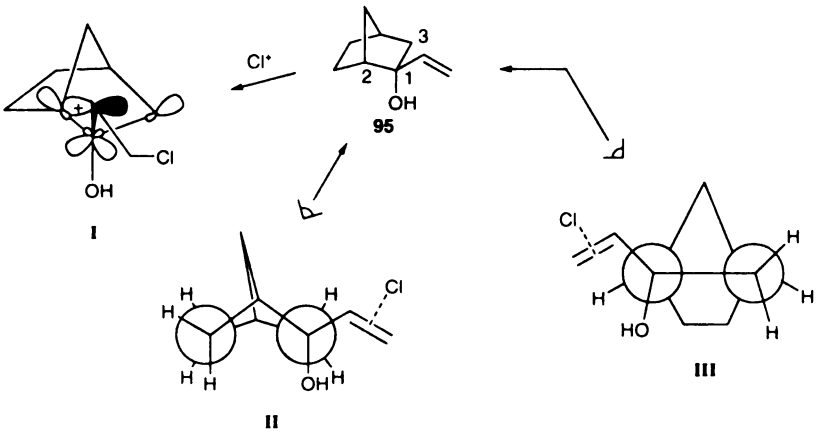
Entry	Carbinol	Products (yield[a]; ratio[b])
(1)		
	100	**109:110** (82%; 1.0:1.6)
(2)		
	102	**111:112** (86%; 1.0:1.5)
(3)		
	103	**113:114** (96%; 3.0:1.0)
(4)		
	105:106 (1:1)	**115** (90%)
(5)		
	107:108 (1:1)	**116** (88%)

Entry	Carbinol	Product (yield[a])
(6)		
	6	**8** (92%)
(7)		**8** (88%)
	7	
(8)		
	29	**50** (95%)
(9)		**50** (87%)
	30	
(10)	**6:7**	**8** (95%)
(11)	**29:30**	**50** (91%)

Reagents and conditions: 1) NaOCl (1.19 eq), AcOH (1.95 eq), CCl_4 (0.6 M), H_2O (0.6 M), 0 °C, 6 h. 2) 1% Et_3N/hexanes, SiO_2. [a] Isolated yields. [b] Ratios determined by ^{1}H-NMR.

antibonding orbital as depicted in **I**. Newman projections **II** and **III**, depict eclipsing interactions along the C1-C3 bond axis while a gauche interaction is present along the C1-C2 bond (Figure 12). This interaction can induce preferential migration of the C1-C3 bond to relieve this eclipsing strain. This influence is observed with both the norcamphor and fenchone derived carbinols, **100** and **102** (entries 1 and 2, Table 6). In these cases the

Figure 12. Molecular Orbital and Newman Representations



electronics slightly favor migration of the bridgehead carbon (hydro dialkyl vs. dihydro alkyl and methyl dialkyl vs. dimethyl alkyl). Yet the C1-C3 bond preferentially migrates. The camphor substrate, **103**, enhances the migratory aptitude of the bridgehead carbon (methyl dialkyl vs. dihydro alkyl) which was observed preferentially (entries 3, Table 6). These examples demonstrate that the simple mneumonic of nucleophilicity and migration might not hold true for other ring systems and does not hold for the [2.2.1] bicyclic system (entries 1-3, Table 6).

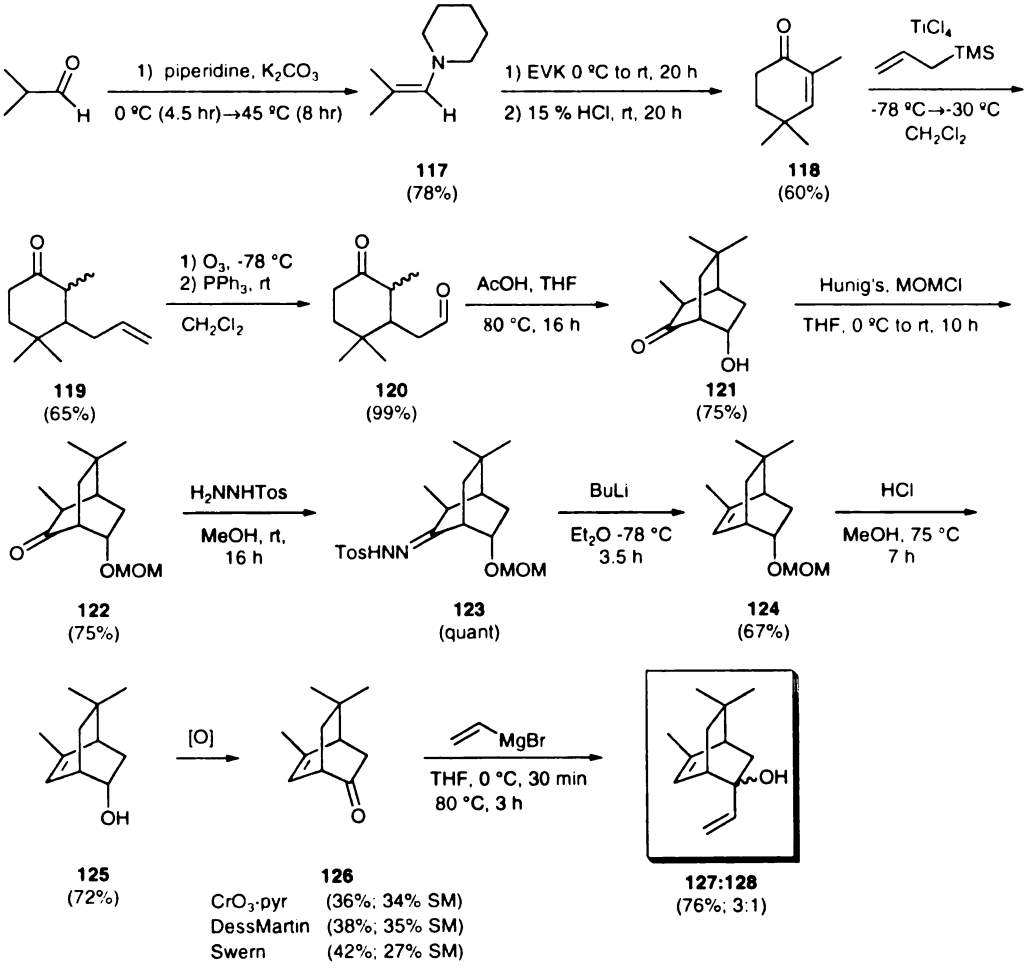
To see if the loss of regioselectivity observed in the [2.2.1] system was an artifact of the missing internal olefin, the homologous [2.2.2] saturated system was explored (entries 4 and 5, Table 6). This system, though a diastereomeric mixture, rearranged with excellent regioselectivity. Selective migration of the bridgehead was observed in both cases with the ethereal unit surviving the reaction and workup conditions. Lastly, the original control substrates, **6:7** and **26:27**, (entries 6-11, Table 6) were investigated under the optimized standard conditions. Again, as expected, both the *exo* and *endo* diastereomeric carbinols produce the same *exocyclic* enone with absolute regioselectivity.

3.11. Influence of Bridgehead Methyl Group in [2.2.2] Expansion

3.11.1. Substrate Synthesis

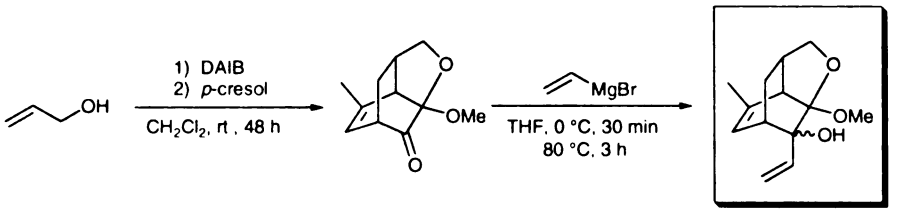
In order to test the electronics of migration further, the bridgehead methyl group needed to be transposed to the back-bridging olefin. Fashioning this in a simple system is not trivial, while the converse is true for a more complicated structure. Following a procedure of Paquette and Maleczka,[78] tandem aldol/michael condensation generates **117** (Scheme 27).[79] Subsequent Sakurai reaction, ozonolysis and another aldol generates the [2.2.2] skeleton, **121**.[80] Protection of the hydroxyl ensues followed by hydrazone formation and Shapiro reaction to install the olefin moiety with the backside

Scheme 27. Synthesis of Paquette's [2.2.2] Backside Methyl System[23]



methyl substituent in place, **124**.[81] Deprotection, oxidation, and vinyl Grignard addition produces carbinols **127:128** in a 3:1 mixture. The somewhat more manly ketal complex **130:131** was obtained by an intramolecular Diels-Alder reaction of masked benzoquinones in moderate yield and diastereoselectivity (Scheme 28).[82]

Scheme 28. Ketal Carbinol Synthesis[23]



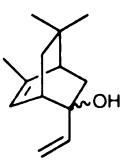
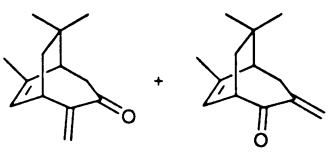
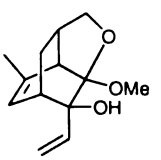
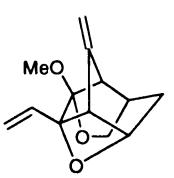
129
(73%)

130:131
(56%; 10:1)

3.11.2. Results

The expansion of vinyl carbinols **127:128** results in a 5:1 mixture of regioisomeric *exocyclic* enones, with no internalization of the olefin observed. It appears that the bridgehead methyl substituent is the important factor for the complete regioselective ring expansion of the [2.2.2] systems investigated thus far. The electronics

Table 7. [2.2.2] Backside Methyl Ring Expansion/Eliminations[23]

Entry	Substrate	Products (yield[a]; ratio[b])
(1)		
	127:128 (3:1)	**132** + **133** (81%; 5:1)
(2)		
	130	**134** (42%)

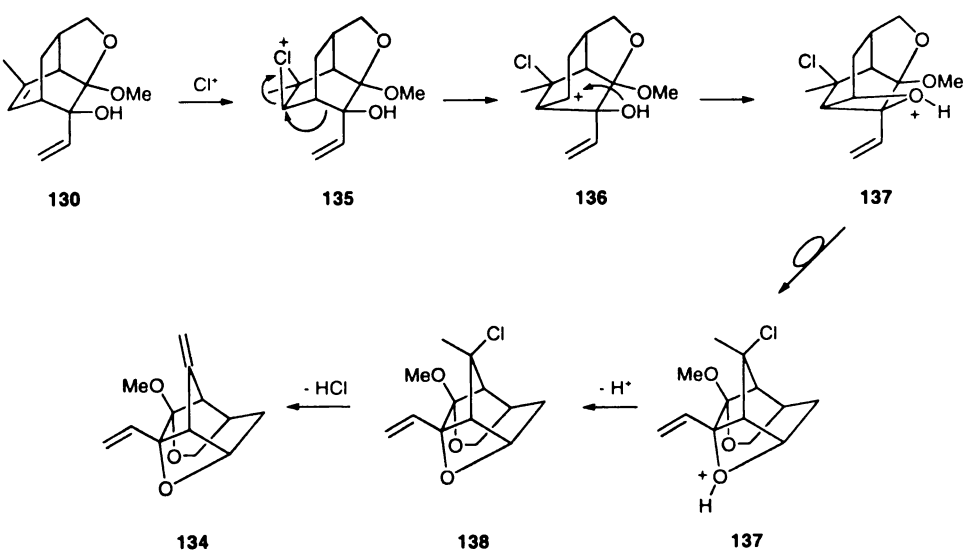
Reagents and conditions: 1) NaOCl (1.19 eq), AcOH (1.95 eq), CCl_4 (0.6 M), H_2O (0.6 M), 0 °C, 6 h. 2) 1% Et_3N/hexanes, SiO_2.
[a] Isolated yield. [b] Ratios determined by ^{1}H-NMR.

of the internal olefin do favor bridgehead migration, though somewhat less than the previous [2.2.2] examples. The rearrangement of **130** was very difficult to discern. After in-depth analysis of ^{1}H, ^{13}C, DEPT, and mass spectroscopy, structure **134** was deemed most consistent with the data. This structure is tentative due to our inability to obtain 1D-NOE spectral data. It is believed that tetracycle **134** arises from Cl^{+} abstraction *via* the internal olefin (Scheme 29).

3.11.3. Mechanistic Considerations

Rearrangement of vinyl carbinol **130** is the first example where the bridging double bond prefers to capture Cl^{+}. This olefin is more electron rich as a result of the methyl substituent, however this reaction path was not observed in carbinols **127:128**. It is possible that the ketal portion of the molecule is having some effect here. Wagner-Meerwein shift of **135** generates cation **136**, which is captured by the hydroxyl substituent to produce **137**. Subsequent loss of a proton followed by loss of HCl generates **134**.

Scheme 29. Possible Mechanism for **129**



3.11.4. Summary of Bicyclic Exo-Olefin Insertion/One Carbon Expansions

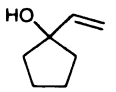
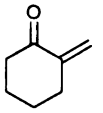
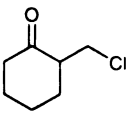
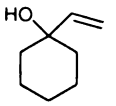
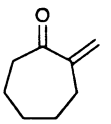
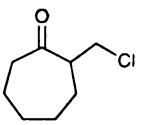
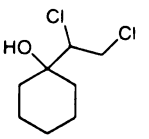
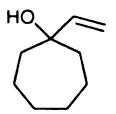
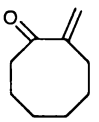
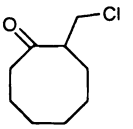
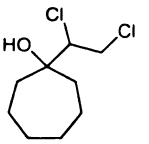
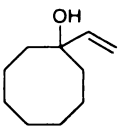
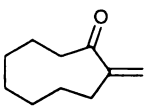
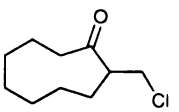
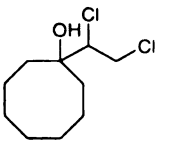
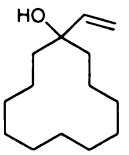
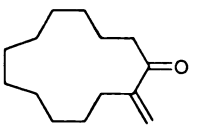
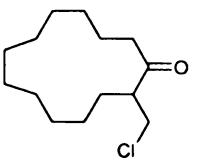
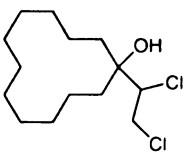
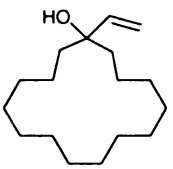
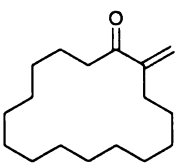
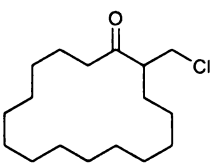
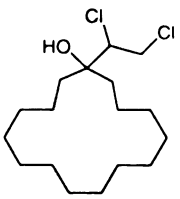
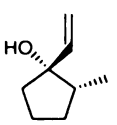
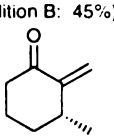
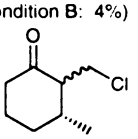
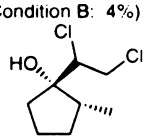
These examples emphasize how this chemistry allows for an unselective Grignard addition prior to the selective rearrangement. As observed earlier, this rearrangement is generally chemoselective, with no observable products derived from the bridging olefinic moiety, except possibly **134**. For [2.2.2] systems a bridgehead substitution is necessary for complete regioselectivity, while the internal olefin is inconsequential. Lastly, [2.2.1] constructs tend to be only moderately selective, if selective at all.

3.12. Monocyclic Exo-Olefin Insertion Ring Expansions

3.12.1. Results and Discussion

Earlier in the monocyclic chlorinative ring expansion of **84**, enone **90** was observed with no internalization of the olefinic moiety. To expand the scope of this rearrangement/elimination and to address the possibility of internalization a variety of homologous monocyclic carbinols were investigated. The ketone precursors for entries 1-7 (Table 8), are all commercially available. All carbinol substrates were obtained *via* vinyl Grignard addition across a suitable carbonyl in respectable yields with no purification necessary. The carbinols investigated rearranged to give their respective enones with moderate yields. The ring expansions and elimination of five, six, and seven membered carbinols (entries 1-3, Table 8) were facile, albeit they gave lower isolated yields than expected. The lower isolated yields, when compared to their chlorinated analogues (Table 5), may be a result of the enone's volatility. This would explain why the five to six expansion affords lower yields than both the six to seven, and seven to eight transformations. The expected ring size trend is observed in the larger ring systems (entries 4-6, Table 8). Of synthetic importance, there was no internalization of the

Table 8. Monocyclic *Exo*-Olefin Insertion One Carbon Expansion Results[23]

Entry	Carbinol	Products (Condition A yield[a]; Condition B yield[a])		
(1)	 **84**	 **90** (Condition A: 56%) (Condition B: 67%)	 **89** (Condition A: 12%) (Condition B: 0%)	
(2)	 **85**	 **142** (Condition A: 62%) (Condition B: 72%)	 **91** (Condition A: 10%) (Condition B: 0%)	 **92** (Condition A: 16%) (Condition B: 3%)
(3)	 **86**	 **143** (Condition A: 60%) (Condition B: 70%)	 **93** (Condition A: 14%) (Condition B: 0%)	 **94** (Condition A: 19%) (Condition B: 4%)
(4)	 **139**	 **144** (Condition A: 42%) (Condition B: 63%)	 **145** (Condition A: 0%) (Condition B: 0%)	 **146** (Condition A: 18%) (Condition B: 6%)
(5)	 **140**	 **147** (Condition A: 28%) (Condition B: 53%)	 **148** (Condition A: 27%) (Condition B: 3%)	 **149** (Condition A: 5%) (Condition B: 3%)
(6)	 **141**	 **150** (Condition A: 26%) (Condition B: 45%)	 **151** (Condition A: 31%) (Condition B: 4%)	 **152** (Condition A: 8%) (Condition B: 4%)
(7)	 **87**	 **97** (Condition A: ---) (Condition B: 79%)	 **95:96** (Condition A: ---) (Condition B: 0%)	 **98** (Condition A: ---) (Condition B: ~2%)

Reagents and conditions: Conditions A: NaOCl (1.19 eq), AcOH (1.95 eq), CCl_4 (0.6 M), H_2O (0.6 M), 0 °C, 6 h. 2) 1% Et_3N/hexanes, SiO_2. Conditions A: NaOCl (1.19 eq), AcOH (1.95 eq), CCl_4 (0.6 M), H_2O (0 3 M), 0 °C, 6 h. 2) 2-3% Et_3N/hexanes, SiO_2. [a] Isolated yields.

olefinic moiety during the reaction or upon purification. The regioselectivity of this rearrangement still held when a methyl group was added to the five membered case (entry 7, Table 8). Only the enone from migration of the more nucleophilic carbon was isolated. This level of regioselectivity has been observed in [2.2.2] bicyclic systems (Table 3, entries 4-11 Table 6), but not in simple five membered arrays (entries 1-3, Table 6).

3.12.2. Dilution Experiments

As observed previously (Table 5), the monocyclic systems produced an intrusive amount of chlorinated carbinol resultant from Cl_2 addition across the substrate's vinyl portion. The chlorine addition is a bimolecular reaction, resulting first from its production from bleach and second, its subsequent addition across the olefin. Dilution of the aqueous phase could slow the production of Cl_2 and thus circumvent the byproduct chlorocarbinol's formation. Treatment under standard conditions, augmented by a two-fold dilution of the aqueous layer, resulted in a significant decrease in the production of chlorocarbinols in all ring sizes (all entries, Conditions B, Table 8). These monocyclic examples demonstrate that the tandem chlorinative ring expansion/elimination sequence is a general reaction of vinyl-substituted cyclocarbinols.

3.13. Conclusions

In summary; a one-carbon expansion of 'vinyl' bicyclocarbinols has been developed to yield β-chlorobicyclocarbinones in respectable yield. Utilizing a facile elimination to produce *exocyclic* enones has furthered this process. Bond migration in these ring expansions can be regioselective, but data suggest this is substrate dependent, e.g. [2.2.1] vs. [2.2.2]. The [2.2.2] system investigated was not only regioselective but

also diastereoselective. This diastereoselectivity results from the population of a preferred "vinyl" rotomeric species prior to the Wagner-Meerwein shift. In these cases a *cisoid* rotomer, between "vinyl" and hydroxyl, is preferred. This geometry seems to be optimal for rearrangement and can even be observed in simple ring systems. Clearly the scope of the rearrangement and synthetic utility of the products, be they chloroketone or enone, coupled with the inexpensive reagents all contribute to this reaction's synthetic appeal.

Chapter 4. Additional NaOCl/AcOH Promoted Chlorinative Rearrangements

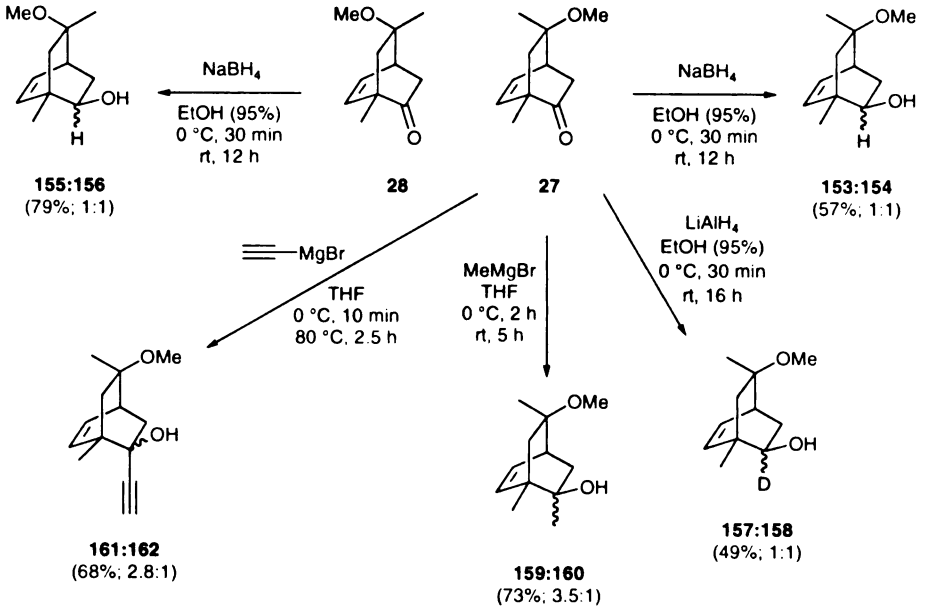
4.1. Introduction

Treatment of vinyl carbinols with NaOCl and AcOH promoted a one-carbon expansion to produce *exocyclic* enones (Chapter 3). To see how non-vinyl substitution at the carbinol carbon would affect its reactivity with the standard set of NaOCl/AcOH conditions, a series of secondary (2°), methyl-substituted tertiary (3°), and alkynyl substituted 3°-carbinols were constructed. These substrates would address a number of questions: 1) Without a vinyl substituent, would hypohalite formation result followed by free radical processes? 2) The chemoselectivity observed in substrate carbinols **6:7** and **29:30** was interesting in that reaction at the vinyl portion of the molecule superseded any at the bridging olefin. Would reactivity of the bridging olefin be observed? 3) Would the same chlorinative ring expansion, with or without elimination, be observed with alkynyl-substituted substrates?

4.2. Substrate Preparation

The necessary substrates were easily prepared *via* the carvone pipeline.[83] Srikrishna's ketones **27:28** were again treated with the appropriate nucleophiles. The 2°-carbinols, **153** through **158**, were produced by hydride and deuteride reduction. Both reductions occurred in moderate yield to afford equal amounts of diastereomeric carbinols (Scheme 30). Treatment of **27** with ethynyl Grignard generated alkynyl carbinols, **161:162**, in good yield with slight diastereoselectivity. The methyl carbinols, **159:160**, were more diastereoselective and similarly available *via* methyl Grignard addition. These three nucleophilic additions demonstrate nicely how the selectivity of the Grignard reaction with **27** can increase as size of the nucleophile increases.

Scheme 30. Preparation of H(D), Me, and Alkynyl Carbinols[23]



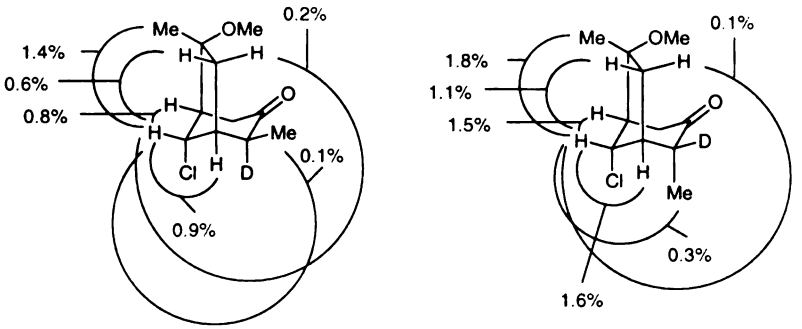
4.3. Rearrangement of Secondary Carbinols

4.3.1. Results and Structural Assignment

The 2°-carbinols, **153:154**, **155:156** and **157:158**, were treated with NaOCl and AcOH. These experiments showed that, despite our earlier results, the bicyclic olefin was not inert to the reaction conditions as the starting substrates were transformed into γ-chloro-[3.2.1]-ketones in moderate yields and diastereoselectivities (Table 9). There was no elimination of HCl after Et_3N buffered chromatography, which supports a bridging chlorocarbon. The stereochemistry at the chlorocarbon was determined by ^{1}H-NMR. There is a slight downfield shift of this proton upon comparison of **163** (4.37 ppm) to **165** (4.74 ppm). This results from the difference in the orientation of the methoxy substituent. If the stereochemistry at this position were reversed, there would be little if any change in these δ-values given their similar environments. The stereochemistry α to the ketone was also determined initially by ^{1}H-NMR. This methyl group in both **163** (0.96 ppm) and **165** (0.97 ppm) appear to be in similar environments. It has been

established that cyclohexanones with α-methyl substituents show distinct δ-values for axial and equatorial protons. This had been exemplified previously with the chlorinative ring expansions of Johnson's substrate, isopropenyl-[2.2.1]-cycloheptanol (Scheme 19, Section 3.4).[84] NMR data suggested that the carbonyl's α-methyl group was

Figure 13. 1D-NOE Support of **167:168**

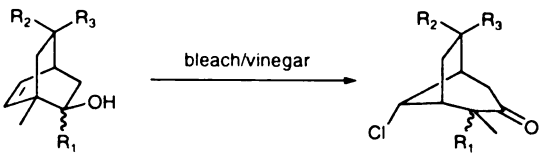


167 **168**

oriented in an up or equatorial position. Chloroketones **167** and **168** were also subjected to 1D-NOE experiments to further support the stereochemical assignment of the chlorocarbon (Figure 13).[85] Clearly the chlorocarbon's proton displays a through-space interaction with the left half of the bicyclic molecule but lacks interaction with the carbonyl's α-protons. Both observations support the stereochemical assignment.

At first it was unclear whether or not the reaction conditions were producing a hypochlorite. First, the reaction was run in ambient light (entries 1-3, Table 9). The reaction proceeded without a large body of byproducts to generate the [3.2.1]-ketones in good yield and modest diastereoselectivity, after lengthening the reaction time to 6 h. Similar yields, entry 1 vs. entries 4-6 (Table 9), were obtained when the first step of the reaction, NaOCl/AcOH, was carried out in a dark room followed by subsequent irradiation (entries 4-6, Table 9). However, only one diastereomer was isolated. Again, as in the vinyl ring expansions, we questioned whether irradiation was necessary.

Table 9. Secondary Carbinol Rearrangements[23]



Entry	Carbinol	Conditions	Products (yield[a];ratio[b])	Recovered Substrate (yield[a]; ratio[b])
(1)	**153:154** R_1=H; R_2=Me; R_3=OMe	A	**163:164** (35%; 3:1) R_1=H; R_2=Me; R_3=OMe	**153:154** (39%; 1:2.3)
(2)	**155:156** R_1=H; R_2=OMe; R_3=Me	B	**165:166** (52%; 3:1) R_1=H; R_2=OMe; R_3=Me	**155:156** (12%; 1:2.3)
(3)	**157:158** R_1=D; R_2=Me; R_3=OMe	B	**167:168** (60%; 2:1) R_1=D; R_2=Me; R_3=OMe	**157:158** (7%; 1:1)
(4)[c]	**153:154**	C	**163** (45%)	**153:154** (36%; 1:3)
(5)[c]	**155:156**	C	**165** (33%)	**155:156** (42%; 1:2.4)
(6)	**157:158**	C	**167** (37%)	**157:158** (32%; 1:3.2)
(7)	**157:158**	D	**167:168** (58%; 1.2:1)	**157:158** (36%; 1:1)
(8)	**157:158**	E	**167:168** (45%; 1.5:1)	**157:158** (26%; 1:1)

Reagents and Conditions: A: NaOCl (1.19 eq), AcOH (1.95 eq), H_2O (0.6 M), CCl_4 (0.6 M), 0 °C, 3 h. B: NaOCl (1.19 eq), AcOH (1.95 eq), H_2O (0.6 M), CCl_4 (0.6 M), 0 °C, 6 h. C: 1) NaOCl (1.19 eq), AcOH (1.95 eq), H_2O (0.6 M), CCl_4 (0.6 M), 0 °C, dark, 3 h. 2) PhH (0.03 M), hv, rt, 7 h. D: NaOCl (1.19 eq), AcOH (1.95 eq), H_2O (0.6 M), CCl_4 (0.6 M), 0 °C, dark, 6 h. E: BHT (1.10 eq), NaOCl (1.19 eq), AcOH (1.95 eq), H_2O (0.6 M), CCl_4 (0.6 M), 0 °C, 6 h.

[a] Isolated yields. [b] Ratios's determined by ^{1}H-NMR. [c] Minor product not isolated.

Upon subjection of **157:158** to the reaction conditions in the absence of light, no loss of isolated yield was observed (entry 7, Table 9).

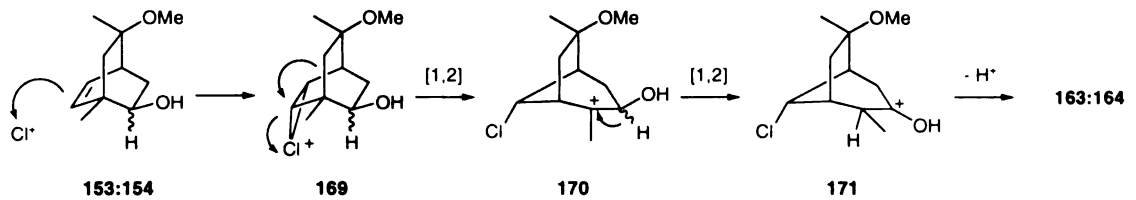
The lower diastereoselectivity observed with conditions A, B, D and E is believed to arise from the prolonged reaction time. From the ratio of recovered starting material it appears that the *exo*-carbinol reacts in a more facile nature than its diastereomer though both rearrange. Interestingly, this rearrangement is somewhat hindered by the addition of BHT and a slight loss of stereoselectivity is observed when the reaction is carried out in

the dark. In both these cases there was also significant recovery of starting material (entries 8 and 7 respectively, Table 9). Furthermore, the stereochemistry α to the ketone goes from a 2:1 to a 1.2:1 mixture when the reaction is run dark (entry 3 vs. entry 7, Table 9). Thus, the mechanistic nature of this rearrangement is not completely understood.

4.3.2. Mechanistic Considerations

Even though there is not a full understanding of all the mechanistic paths, a cationic pathway is proposed for the formation of the [3.2.1] chloroketones. A cationic mechanism is apparent due to the ability of this rearrangement to proceed whether the reaction is run in the dark or in the presence of a radical scavenger. As with the vinyl substrates, electrophilic chlorine (Cl^+) is likely captured by the double bond to generate

Scheme 31. Secondary Carbinol Cationic Mechanism



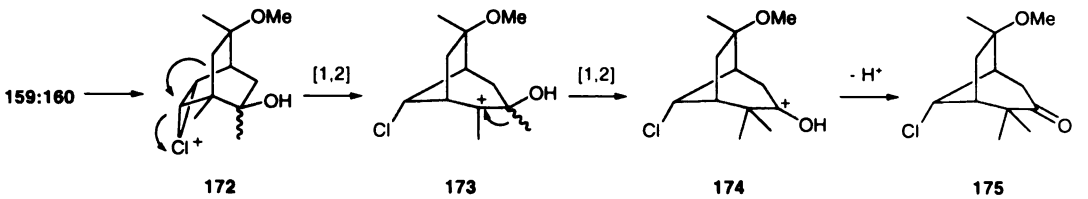
species **169** (Scheme 31). This initiates a [1,2] shift of the front bridging carbon to produce cation **170**. A subsequent [1,2] shift of a hydrogen or deuterium atom generates carbinol cation **171** and loss of a proton generates the observed γ-chloro-[3.2.1]-bicycloketones **163:164**.

4.4. Rearrangement of Methyl Substituted Tertiary Carbinols

In order to further explore possible involvement of the bicyclic olefin the 2°-carbinol was changed to a methyl substituted 3°-alcohol. This substrate lacks any protons for the putative [1,2]-shift. However a [1,2]-methyl migration would be

available. Thus, capture of Cl^+ followed by two sequential [1,2] shifts would produce chloroketone **175**. This was not the case.

Scheme 32. Anticipated 3°-Carbinol Rearrangement

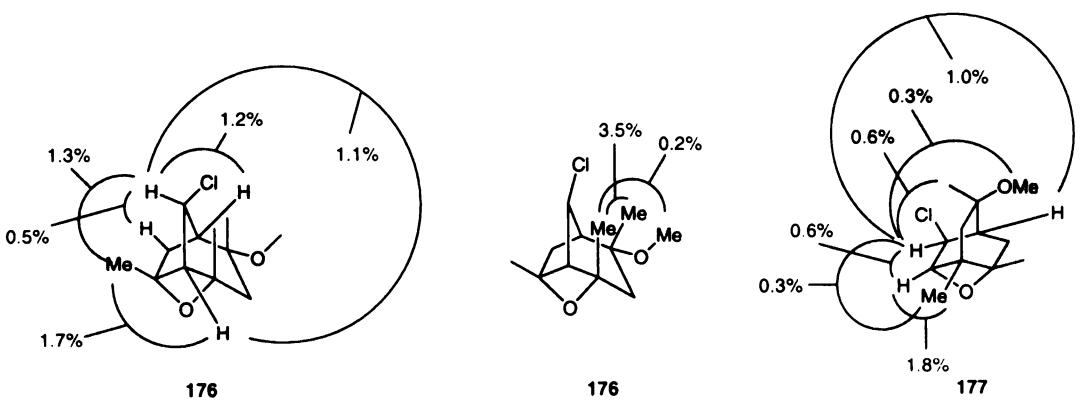


172 **173** **174** **175**

4.4.1. Results and Structural Assignment

The formation of **175** or any ketonic structure was not observed. Instead one of two rearranged products, **176** and **177**, were observed depending on which diastereomeric carbinol was subjected to the standard conditions (Table 10). The structures of the proposed rearrangement products were not easy to ascertain. Use of ^{13}C-NMR coupled with DEPT spectroscopy elucidated the two 3°-carbons present in the oxetane substructure of **176**. Similarly the 2°- and 3°-carbons of epoxide **177** were deduced. The use of 1D-NOE also supported the structure assignments. The stereochemistry of chlorocarbon **176** was also ascertained by the observation of through space interactions with the left half of the tricycle. There was also a strong methyl-methyl interaction

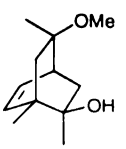
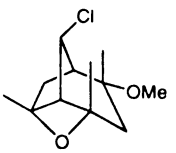
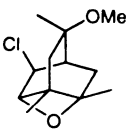
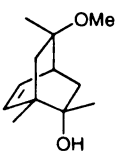
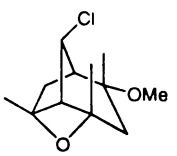
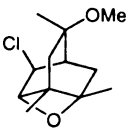
Figure 14. 1D-NOE Support of **176** and **177**



176 **176** **177**

indicative of the 1,3-diaxial orientation. Analysis of bicycle **177** also showed through space interactions that support the proposed structure. Carbinol **159** yielded an ethereal tricycle **176**, which was accompanied by bicycle **177**. Diastereomeric carbinol **160** also produced **177**, but did not generate the tricyclic ether **176**.

Table 10. Methyl Substituted 3°-Carbinol Rearrangements[23]

Entry	Substrate	Products (yield[a]; ratio[b])		
(1)				
	159	**176** (34%)	**177** (28%)	
(2)[c]				
	160	**176** (not observed)	**177** (57%)	

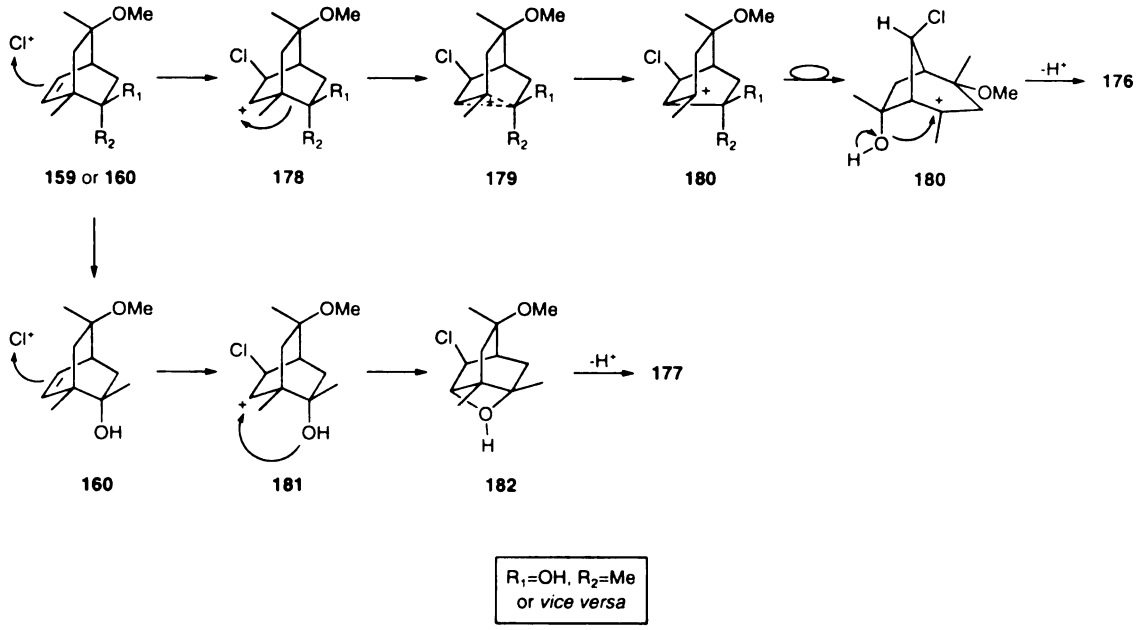
Reagents and conditions: NaOCl (1.19 eq), AcOH (1.95 eq), CCl_4 (0.6 M), H_2O (0.6 M), 0 °C, 6 h. [a] Isolated yields. [b] Ratios determined by ^{1}H-NMR. [c] Recovery of **160** (6%).

4.4.2. Mechanistic Considerations

The ability of both carbinols to produce the same rearranged epoxide, **176**, coupled with the observation that only one of the alcohols produced tricycle **177** is interesting. This implies the operation of two mechanisms, one of which is stereospecific in relation to the hydroxyl carbon.

Tricycle **176** is envisioned to form *via* abstraction of Cl^+ by the olefin (Scheme 33). Cation **178** undergoes an alkyl [1,2]-shift to produce **180** by way of a three coordinate non-classical cation. The 3°-cation **180** is in close proximity to the lone pair of electrons residing on the hydroxyl, and subsequent attack of the hydroxyl followed by loss of H^+ produces **176**. This sequence cannot occur with *endo*-carbinol **160** since

Scheme 33. Methyl Substituted 3°-Carbinol Cationic Mechanisms



the hydroxyl is on the bottom face of the bicycle and the oxygen's lone pair is to far removed from the cation. The putative mechanism shared by both carbinols is interesting, in that this sequence involves loss of H_2O. This has not been observed upon reaction of any other carbinol studied. Loss of H_2O followed by hydroxide capture would generate carbinol **160**, which can undergo electrophilic capture of Cl^+ to produce **181**. Capture of the cation by the hydroxyl ensues, followed by loss of H^+ to generate **177**.

4.4.3. Summary of Methyl Carbinols

The ability of cations to undergo different rearrangement pathways is not new.[86] So it is not surprising that diastereomeric carbinols could rearrange *via* different routes. This makes the rearrangement of carbinol **159** unattractive since products from each pathway are formed. This prohibits the use of the convenient protocol of subjecting a diastereomeric mixture of carbinols, as in the case of the vinyl carbinols, to the conditions since mixtures would result. Thus separation is necessary at the carbinol stage. The

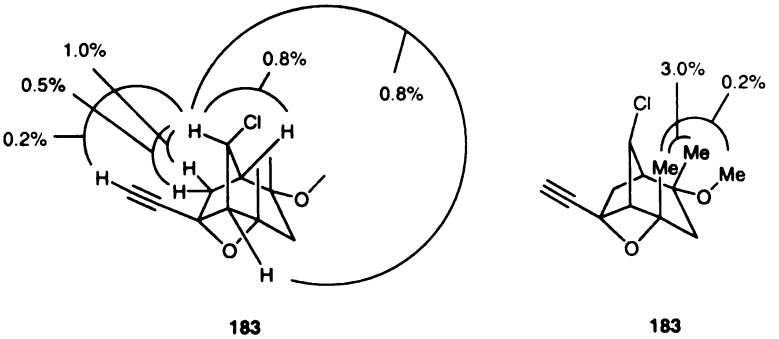
ability of *endo*-carbinol **160** to generate the chloroepoxide diastereomerically is appealing even with the modest yield. To further explore the cationic rearrangement that NaOCl/AcOH can evoke, alkynyl carbinols were next subjected to the standard conditions.

4.5. Rearrangements of Ethynyl Substituted Tertiary Carbinols

4.5.1. Results and Structural Assignment

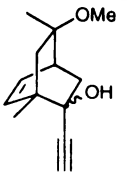
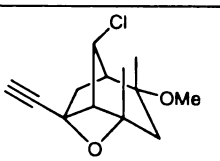
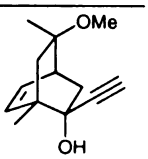
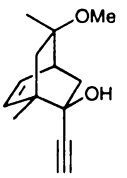
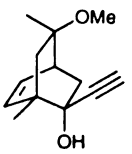
Alkynyl substituted carbinols were employed to see if a ring expansion related to those observed previously with vinyl substituted alcohols, or another rearrangement would operate. Upon exposure to the standard conditions, a 1:1 diastereomeric mixture of **161:162** produced the familiar tricyclic ether **183** along with recovered *endo*- carbinol **162** (entry 1, Table 11). The geometry of **183** was established *via* NOE interactions with the left or cyclopentyl portion of the tricycle, while the aliphatic methyl substituents also showed a strong diaxial through-space interaction. This was reminiscent of the methyl carbinols, in that it appeared that only the *exo*-carbinol was rearranging to produce the four-membered ethereal unit. Treatment of **161** gave solely **183** in moderate yield with a small recovery of starting material. Exposure of **162** to NaOCl/AcOH only resulted in the recovery of starting material (entries 2 and 3, Table 11).

Figure 15. 1D-NOE Support of **183**



183 **183**

Table 11. Ethynyl Substituted 3°-Carbinol Rearrangements[23]

Entry	Substrate	Products (yield[a])	
1			
	161:162 (1:1)	**183** (39%)	**162** (36%)
2		**183** (63%)	**162** (2%)
	161		
3		**183** (not observed)	**162** (76%)
	162		

Reagents and conditions: NaOCl (1.19 eq), AcOH (1.95 eq), CCl_4 (0.6 M), H_2O (0.6 M), 0 °C, 6 h.
[a] Isolated yields.

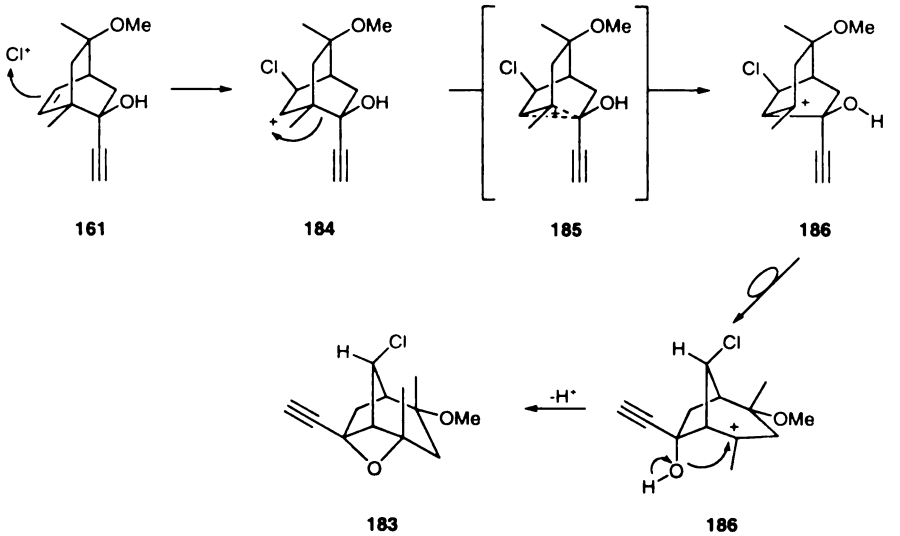
4.5.2. Mechanistic Considerations

The fact that **162** is inert to the conditions is not completely understood. In all carbinol cases to this point, there was some rearrangement observed whether the alcohols were *exo* or *endo*. Be that as it may, the ability of **161** to produce only one product is synthetically appealing. Again, as in the methyl case, separation of the carbinols becomes an issue. However, the "other" carbinol does not taint the product composition, and the ether is easily separated from the unreactive alcohol.

The mechanism envisioned would be similar to that proposed for the methyl *exo*-carbinol (Scheme 33). Carbinol **161** undergoes Cl^+ abstraction followed by an alkyl [1,2]-shift to generate cation **186**. Attack of the hydroxyl followed by loss of a proton

generates the tricyclic **183**. Again, the hydroxyl geometry present at carbocation **163** is essential for heterocyclic ring closure.

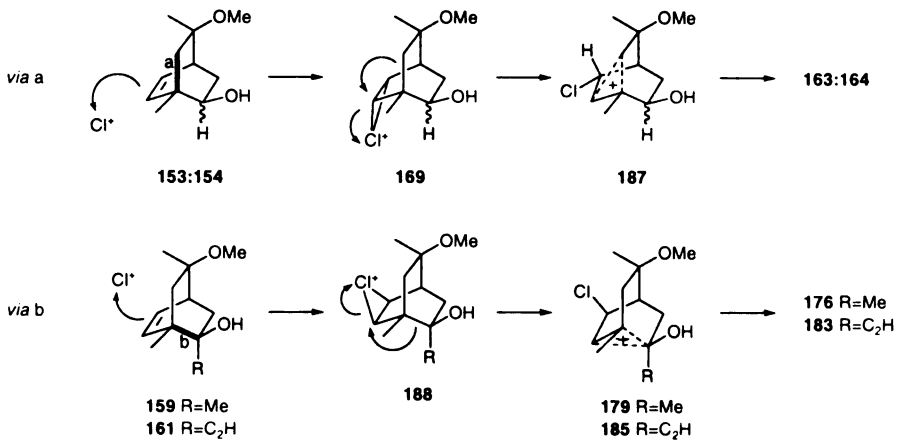
Scheme 34. Ethynyl Substituted 3°-Carbinol Cationic Mechanism



4.6. Conclusions

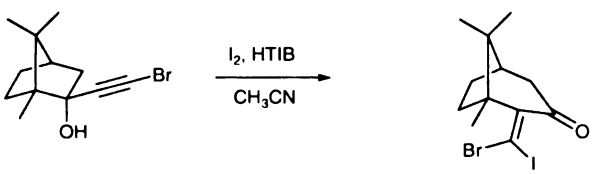
The examples discussed above demonstrate that the internal olefin present in the carbinol substrates is not chemically inert to the reaction conditions as observed in the vinyl substrates. The aforementioned rearrangements appear to be primarily cationic in nature. This double bond's reactivity and subsequent alkyl [1,2]-shift is sensitive to the nature of the hydroxyl's substitution. When there is no substitution, i.e. only hydrogen or deuterium, then migration of the 'a' bond is preferred due to abstraction of Cl^+ from the bottom face of the olefin (Scheme 35). Conversely, with the methyl or ethynyl substitution migration of the 'b' bond is preferred. Now Cl^+ abstraction occurs from the top face of the substrate followed by an alkyl [1,2]-shift of the 'b' bond. The mode of Cl^+ abstraction seems to be influenced by the sterics of the bottom face of the bicycle. It appears that Cl^+ capture occurs *via* the least sterically hindered face followed by rearrangment. In all the above rearrangements the preferred

Scheme 35. Differing Mechanistic Pathways



migratory bond is the antiperiplanar one. It was somewhat surprising that the alkynyl substrates did not undergo the ring expansion observed previously in the vinyl series. Ethynyl carbinols have been ring expanded in [2.2.1] systems *via* suggested bromonium and iodium ion intermediates (Scheme 36).[87] These examples however lacked the

Scheme 36. McNelis Expansion of [2.2.1] Alkynyl Carbinols



HTIB=[hydroxy(tosyloxy)iodo]benzene (60%)

internal unsaturation present in the substrates above and can be rationalized upon examination of the cation intermediates. The 2°-cationic intermediate (*via* olefin) is more stable than the disubstituted vinyl carbocation (*via* alkyne) and as a result the alkene portion of the substrate is far more reactive than the alkyne.

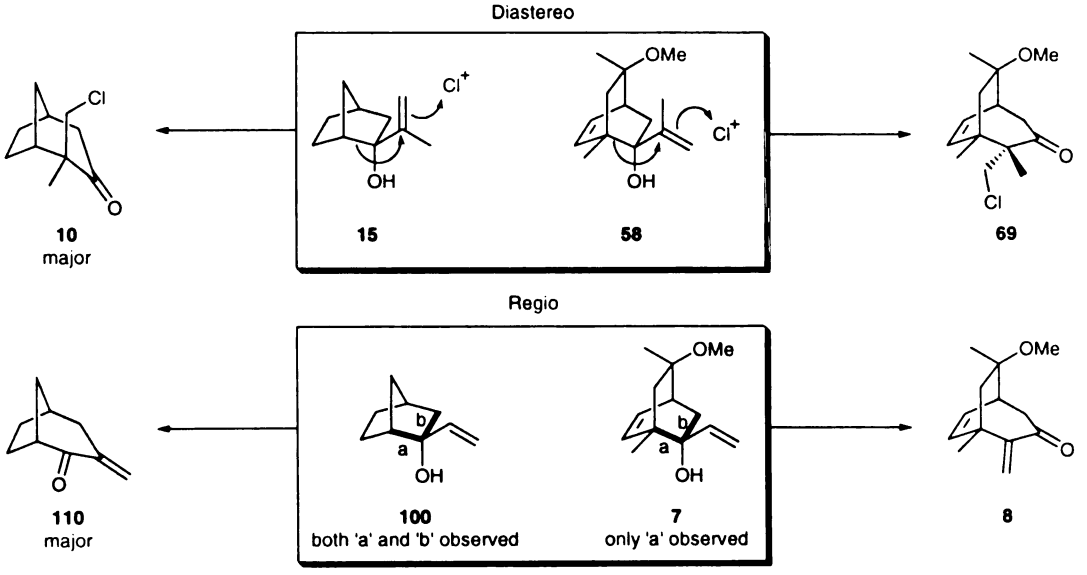
These examples demonstrate the ability of the simple NaOCl/AcOH conditions to evoke a number of cationic rearrangements as long as there is an olefinic moiety present in the substrate and that such cationic intermediates can rearrange in a regio and diastereoselective manner.

Chapter 5. Theoretical Investigation

5.1. Introduction

The ring expansions of vinyl-substituted carbinols have been shown to be chemo- regio- and diastereoselective (Chapter 3). However there have been some discrepancies. Most notable is the preferred *anti* orientation in Johnson's [2.2.1] bicycle while the carvone derived [2.2.2] bicycles prefer *syn.* As a result the ability to predict the stereo-outcome of these chlorinative ring expansions is not absolute. Another discrepancy of note is the ability for the [2.2.2] system to expand in a completely regioselective manner while the [2.2.1] constructs respond unselectively. It is obvious that these differences

Figure 16. Regio and Diastereo Discrepancies



could be the result of the different systems, [2.2.1] vs. [2.2.2]. However it would be advantageous to be able to predict the regioselectivity of these ring expansions along with the diastereoselectivity as well.

Molecular force field calculations were made to estimate the relative strain energies (SE) present in these systems.[88] It was hoped that the difference in strain energies (ΔSE) between the substrate and products, and also between the regio- and

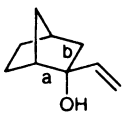
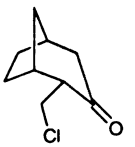
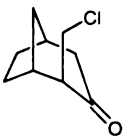
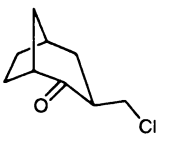
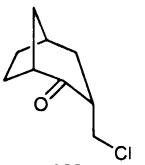
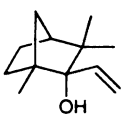
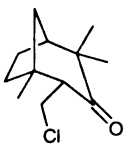
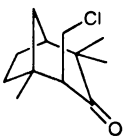
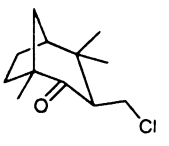
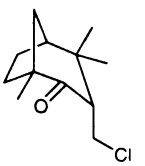
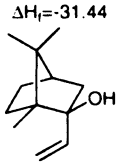
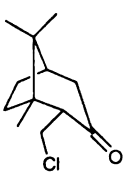
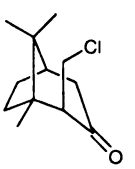
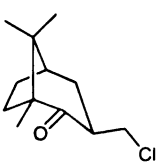
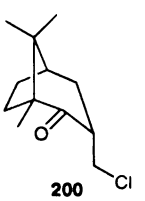
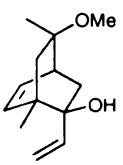
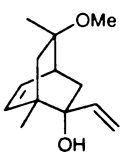
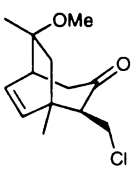
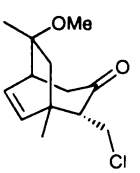
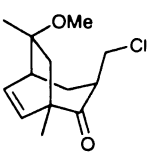
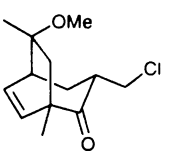
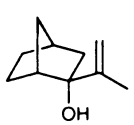
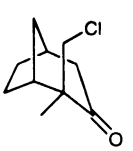
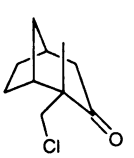
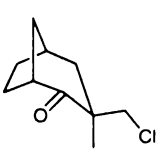
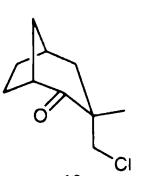
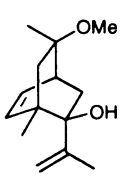
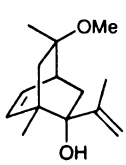
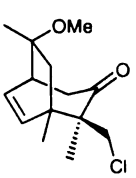
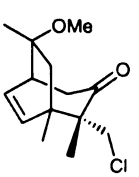
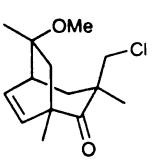
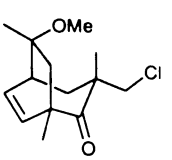
diastereomeric products would be predictive. All calculations were conducted using a Spartan program package (version 5.0, Wavefunction Inc.) on a SGI Indigo II machine. The minimum energy conformers were located with the Osawa searching method and were found within 3.0 kcal/mol of the global minimum.[89]

5.2. Theoretical Investigation of Chlorinative Ring Expansion

The theoretical study began with the analysis of a few select vinyl substituted carbinols at the MMFF94 level (Table 12).[88] The starting substrate's SE was compared to that of both regio and diastereomeric chloroketones. It would not be prudent to compare the carbinol to that of the enone, as it is the product of elimination and not expansion. In conjunction with the molecular mechanics study, a semi-empirical calculation was performed at the AM1 level on the MMFF94 conformers to get an idea of these compounds heat of formation (ΔH_f).

An interesting trend surfaces upon comparison of the starting substrates with the regiochemistry of the product ketones. It was observed previously that norcamphor, fenchone, and camphor derived vinyl carbinols were regiochemically unselective, when subjected to our standard set of bleach/vinegar conditions (entries 1-3, Table 6, Section 3.10.1). Analysis of the ΔSE and $\Delta\Delta H_f$ energies reveal that there is not a significant difference in ΔSE (>4.0 kcal/mole) between the two regiochemistries, which supports what was observed experimentally (entries 1-3, Table 13). The $\Delta\Delta H_f$ energies for the most part complement the ΔSE calculated. The ΔSE of entries 1 and 2, Table 13, favor migration of the 'b' bond which is what observed. In the camphor case, entry 3 Table 13, migration of the 'a' bond was preferred by 3:1 experimentally, but the ΔSE and $\Delta\Delta H_f$ energies favor 'b' bond migration. It appears in this case that the electronics of the ring

Table 12. Select Bicyclic Strain Energies (SE) and Heats of Formation (ΔH_f)

Substrate	Product (Migration of 'a')		Product (Migration of 'b')	
				
100 SE=+33.04 ΔH_f=-27.99	**189** SE=+16.94 ΔH_f=-64.25	**190** SE=+17.80 ΔH_f=-64.04	**191** SE=+16.80 ΔH_f=-64.05	**192** SE=+16.85 ΔH_f=-63.38
				
102 SE=+62.94 ΔH_f=-31.44	**193** SE=+42.36 ΔH_f=-66.81	**194** SE=+44.29 ΔH_f=-65.99	**195** SE=+41.69 ΔH_f=-66.18	**196** SE=+45.71 ΔH_f=-62.71
				
103 SE=+62.48 ΔH_f=-29.63	**197** SE=+47.15 ΔH_f=-64.19	**198** SE=+49.93 ΔH_f=-62.90	**199** SE=+43.99 ΔH_f=-68.68	**200** SE=+45.14 ΔH_f=-66.70
 				
6 **7** SE=+83.63 SE=+89.16 ΔH_f=-54.26 ΔH_f=-47.69	**66** SE=+61.12 ΔH_f=-73.18	**67** SE=+57.89 ΔH_f=-73.39	**201** SE=+69.44 ΔH_f=-78.11	**202** SE=+73.36 ΔH_f=-74.88
				
9 SE=+36.59 ΔH_f=-32.21	**10** SE=+29.83 ΔH_f=-60.08	**11** SE=+29.42 ΔH_f=-60.41	**12** SE=+32.97 ΔH_f=-65.50	**13** SE=+33.85 ΔH_f=-63.38
 				
58 **59** SE=+98.46 SE=+92.72 ΔH_f=-50.87 ΔH_f=-52.00	**68** SE=+74.43 ΔH_f=-67.17	**69** SE=+71.63 ΔH_f=-70.31	**203** SE=+82.90 ΔH_f=-74.24	**204** SE=+86.35 ΔH_f=-73.40

expansion are dictating migration and not the release of strain energy. The vinyl carbinol ΔSE calculations, entries 4 and 5 Table 13, clearly favor migration of the 'a' bond by ≥ 8 kcal/mol, which was observed experimentally. Analyses of the isopropenyl substrates, entries 6 through 8 Table 13, also show preference for migration of the 'a' bond. In the

Table 13. Chloroketone Carbinol ΔSE and $\Delta\Delta H_f$ Values

Entry	Substrate	Product	ΔSE	$\Delta\Delta H_f$	Product	ΔSE	$\Delta\Delta H_f$	Product	ΔSE	$\Delta\Delta H_f$	Product	ΔSE	$\Delta\Delta H_f$
(1)	**100**	**189**	-16.10	-36.26	**190**	-15.24	-36.05	**191**	-16.24	-36.06	**192**	-16.19	-35.39
(2)	**102**	**193**	-20.58	-35.37	**194**	-18.65	-34.55	**195**	-21.25	-34.74	**196**	-17.23	-31.27
(3)	**103**	**197**	-15.33	-34.56	**198**	-12.55	-33.27	**199**	-18.49	-39.05	**200**	-17.34	-37.07
(4)	**6**	**66**	-22.51	-18.92	**67**	-25.74	-19.13	**201**	-14.19	-23.85	**202**	-10.27	-27.19
(5)	**7**	**66**	-28.04	-25.49	**67**	-31.27	-25.70	**201**	-19.72	-30.42	**202**	-15.80	-27.19
(6)	**9**	**10**	-6.76	-27.87	**11**	-7.17	-28.20	**12**	-3.62	-33.29	**13**	-2.74	-31.17
(7)	**58**	**68**	-24.03	-16.30	**69**	-26.83	-19.44	**203**	-15.56	-23.37	**204**	-12.11	-22.53
(8)	**59**	**68**	-18.29	-15.17	**69**	-22.41	-18.31	**203**	-18.48	-22.24	**204**	-19.32	-21.40

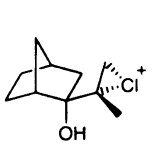
Δ = Chloroketone Energy - Substrate Energy (kcal/mol)

case of Johnson's substrate **9**, the ΔSE is not as great as in the [2.2.2] bicycles. This would predict a mixture of regioisomers with the 'a' bond migration predominating, which was indeed observed experimentally. The $\Delta\Delta H_f$ energies in entries 4 though 8, Table 13, do not complement the ΔSE energies calculated. This demonstrates that these ring expansions seem to be influenced by the release of strain energy coupled with the electronics of migration and not necessarily by the heats of formation. These examples demonstrate that the ΔSE at the MMFF94 level can be used to predict whether a ring expansion will give a mixture of regioisomers (< 4 kcal/mol) or be more selective (> 8 kcal/mol). However, such calculations are not exact in predicting which regiochemical isomer will predominate, entry 3 (Table 13).

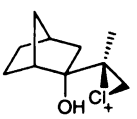
5.3. Theoretical Investigation of Chlorinative Transition State

When considering the regioselectivities of these bicyclic ring expansions, the calculations can be predictive of whether the ring expansions will be regioselective or not. That being said, the actual diastereoselectivities observed experimentally do not agree with the calculations, upon comparison of the ΔSE or $\Delta\Delta H_f$ energies (entries 4 through 8, Table 13). This is understandable since the diastereoselectivity is likely derived from a transition structure. Thus the difference in energies of the transition states needed to be calculated. Though there is the question of the exact nature of the transition state, it was assumed to involve a chloronium ion. The single point energy (SPE) calculation on this transition state mimicked the diastereoselectivities observed. In every example the observed diastereoselectivity matches the minimum SPE calculation for the chloronium ion transition state. Of course this mneumonic relies on the assumption that a chloronium ion is being formed. With this assumption in mind, it does predict that Johnson's substrate should adopt a *transoid* conformation in this transitions state to orient

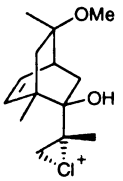
Figure 17. Singe Point Energies (SPE) of Chloronium Transition States



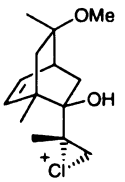
9-TS-anti
SPE=+82.89



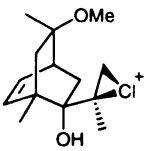
9-TS-syn
SPE=+84.57



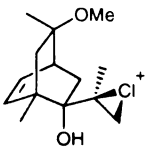
58-TS-anti
SPE=+140.98



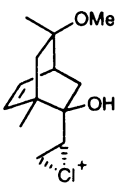
58-TS-syn
SPE=+132.70



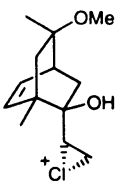
59-TS-anti
SPE=+141.76



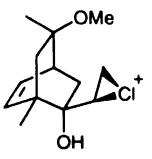
59-TS-syn
SPE=+138.45



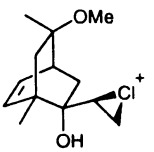
6-TS-anti
SPE=+107.82



6-TS-syn
SPE=+103.27



7-TS-anti
SPE=+114.21



7-TS-syn
SPE=+112.35

the chloromethyl substituent in an up position, which was observed (~2:1). The ΔSPE for **9-TS-anti** and **9-TS-syn** is only 1.68 kcal/mol. This small difference predicts a mixture of diastereomers, which is observed by the small (~2:1) ratio. Analysis of the *i*-Pr and vinyl transitions states, **58-TS-anti** vs. **58-TS-syn** and **59-TS-anti** vs. **59-TS-syn**; **6-TS-anti** vs. **6-TS-syn** and **7-TS-anti** vs. **7-TS-syn**, reveal that now a *cisoid* geometry is favored, which is also observed experimentally. The ΔSPE is much greater for the *exo*-carbinols **58** and **7** which carries over to the observed diastereoselectivities, **58** (20:1) vs. **59** (1:12) and **6** (16:1) vs **7** (1:14). Even though this pneumonic is based on certain assumptions it does mimic the observed diastereoselectivities by predicting the favored diastereomer.

5.4. Conclusions

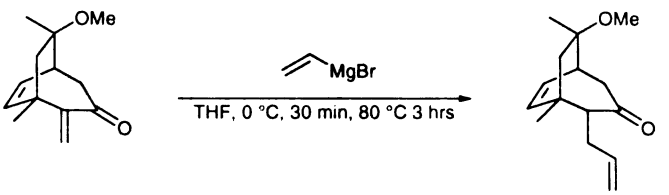
The above calculations support what was observed in Chapter 3, though this theoretical investigation is just that, theoretical. It does however allow the chemist an idea of whether the desired chlorinative ring expansion will be regioselective or not, and also which diastereomer will be preferred. In the end of course, one needs to perform the reaction to determine the actual regio- and diastereoselectivity.

Chapter 6. Future Synthetic Investigations

6.1. Nucleophilic Addition to Ring Expanded Enones

Nucleophiles can add into enones in a variety of ways. Additions can occur in either a 1,2- or 1,4-manner. While electrophilic processes can occur the α,β, or γ positions.[90] This enables enones to be transformed into a myriad of chemically

Scheme 37. Vinyl Grignard Addition of **8**

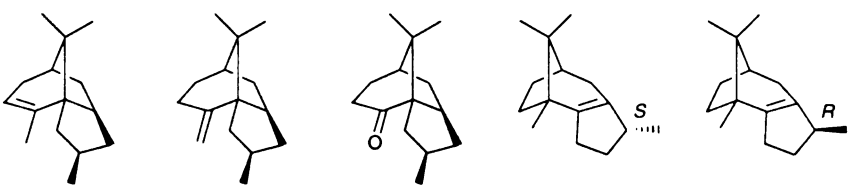


8 **205**

substituted species. To probe the reactivity of our rearrangement products, enone **8** was subjected to vinyl Grignard addition (Scheme 37). Interestingly the vinyl addition occurred in a 1,4-manner as opposed to a 1,2-addition. Additional effort should be expended to induce these *exocyclic* enones to undergo a 1,2-addition, since it appears that 1,4-additons are very facile.

6.2. Patchoulenes

Figure 18. Patchoulenes

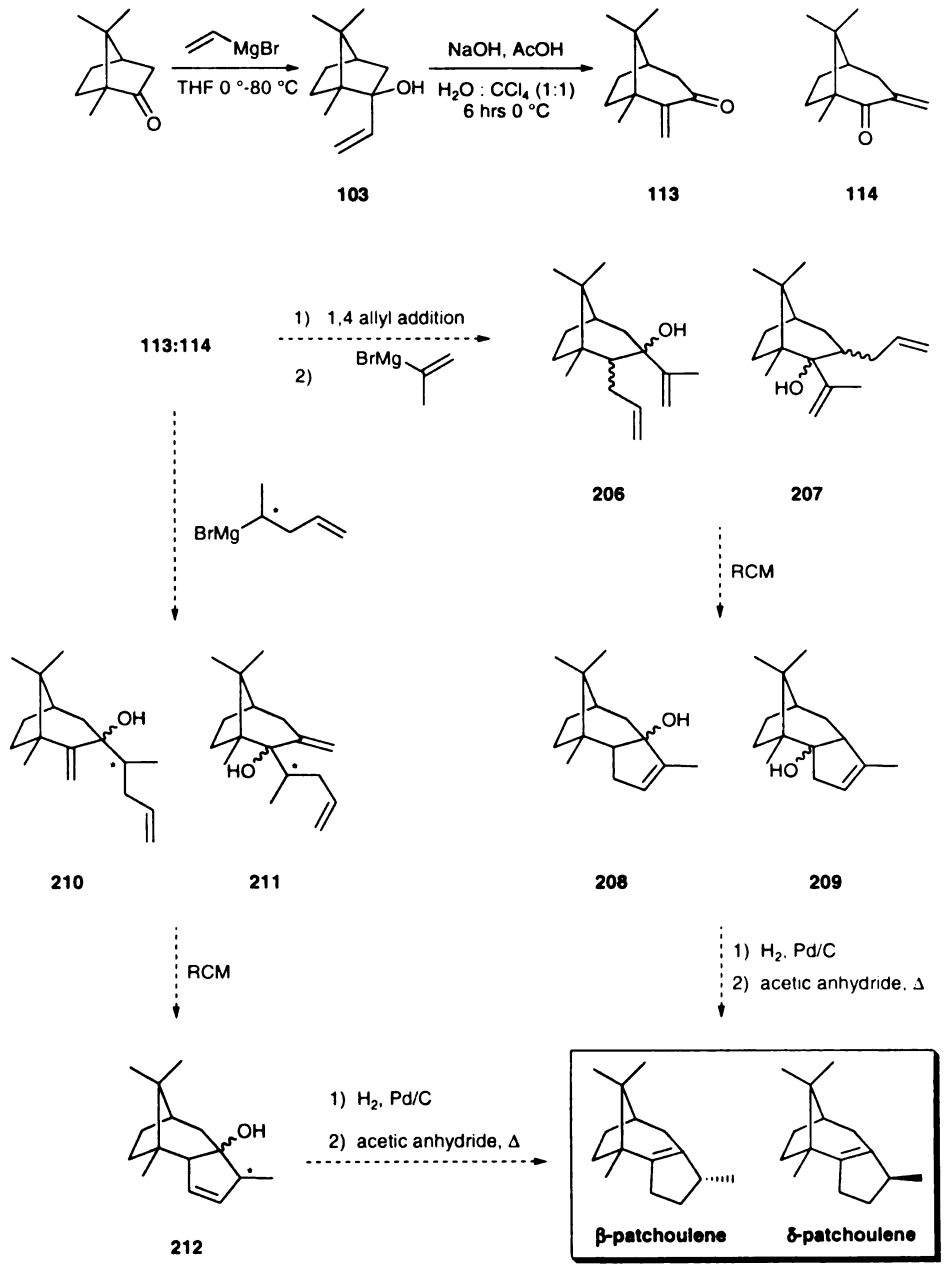


α-patchoulene γ-patchoulene norpatchoullone β-patchoulene δ-patchoulene

The ease of 1,4 addition may make these rearrangement useful in the synthesis of natural bicyclics. One such class of compounds are the patchoulenes (Figure 18). For over the past 130 years, the patchoulenes have been of interest, largely due to their importance in the perfume industry. As such they have been the subject of total synthesis

and derivitization.[91] The patchoulenes are also prized as key synthetic intermediates to other more complex natural products.[92] The two earliest synthetic routes have begun with homocamphor, which already has the desired [3.2.1] construct installed. Our ring expansion would provide the [3.2.1] bicyclic core *via* the ring expansion of (+)-camphor. Vinyl addition across (+)-camphor generates **103**, which subsequently provides the

Scheme 38. Proposed Synthetic Routes to β- and δ-Patchoulenes

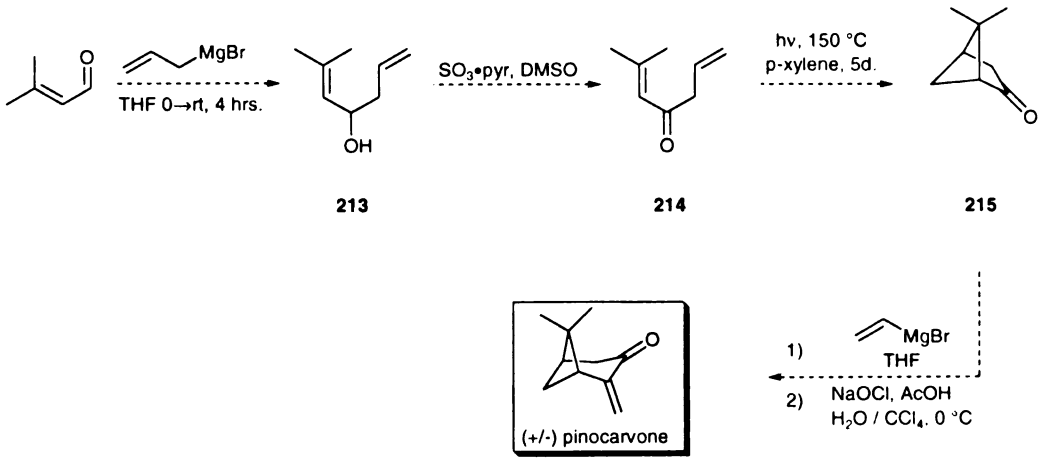


[3.2.1]-bicyclic enones **113:114** after ring expansion/elimination (entry 3, Table 6, Chapter 3). Subsequent transformations would allow for both β- and δ-patchoulenes to be realized. It has been previously observed that the [3.2.2] enones undergo facile 1,4-addition (Scheme 37). This type of reaction followed the addition of isopropenyl Grignard would produce ketones **206:207** in a mixture of diastereomers. Ring closing metathesis (RCM), followed by hydrogenation and elimination of H_2O would produce the desired patchoulenes after separation (Scheme 38). If a 1,2-addition could be optimized than use of chiral Grignard reagent would allow for the installation of either stereogenic center present in the fused cyclopentyl substructure. After carbinol separation, compound **210** would be subjected to RCM, followed by hydrogenation and elimination of H_2O, as in the first route, to produce either of the desired natural products.[93]

6.3. Pinocarvone

Another natural product to be targeted is pinocarvone (Scheme 39).[94] Though commercially available through Interbioscreen Ltd. of Russia, pinocarvone is quite expensive ($250/50 mg; $390/100 mg; $490/150 mg). The synthesis of this deceivingly

Scheme 39. Proposed Synthetic Route to (+/-)-Pinocarvone



simple molecule could begin with allyl Grignard addition across 3-methyl-2-butenal followed by oxidation to produce ketone **214** in reasonable yield. Irradiation of the ketone at high temperature should produced (+/-)-[2.1.1]-bicycle **215**. Subsequent 1,2-vinyl addition followed by use of the standard NaOCl/AcOH conditions, with basic purification, should produce (+/-)-pinocarvone. It is hoped that the rearrangement will be selective and occur *via* the bridgehead bond ('a'-route). The strained nature of the bicyclic substrate however, could produce poor regioselectivity.

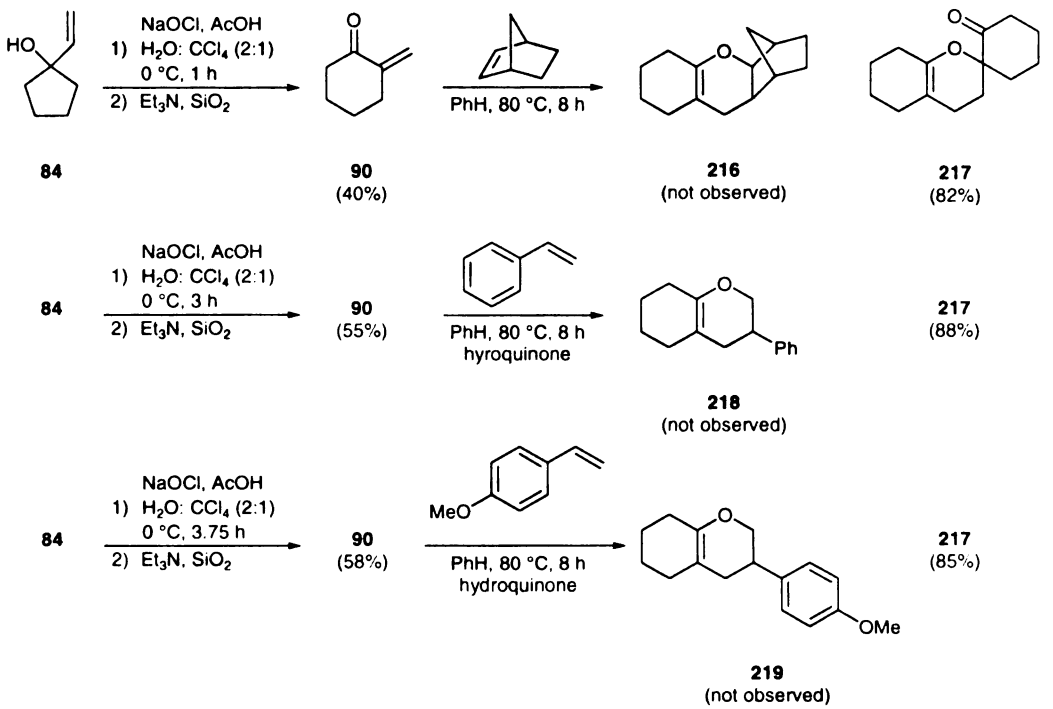
6.4. Enone Diels-Alder Cycloadditions

Diels-Alder reactions have long been exploited for their ability to produce carbocyclic structures from relative simple alkene starting materials.[95] While a Wittig reaction could transform the ring expanded *exocyclic* enone into a suitable *s-cis*-diene for cycloaddition, *s-cis* enones themselves have been used as dienophiles or dienes as well. This flexibility to react in a variety of ways allows our method for the construction of *s-cis*-enones to be synthetic starting point for a variety of carbo- and heterocyclic ring systems.

In conjunction with the Diels-Alder, the standard set of ring expansion/*exo*-olefin insertion conditions were explored. In order to obtain the desired *exocyclic* enones in a more rapid manner deviations in reaction time and workup were implemented. A shorter reaction time resulted in slightly lower isolated yields, however streamlined the workup and allowed for quick and clean isolation of the desired enone. In these examples, Scheme 40, workup consisted of addition of a cold aqueous solution 3% K_2CO_3 to the reaction followed by stirring for 5 min. Standard separation and concentration allowed for the enone to be quickly purified *via* a short silica plug while eluting with 1%

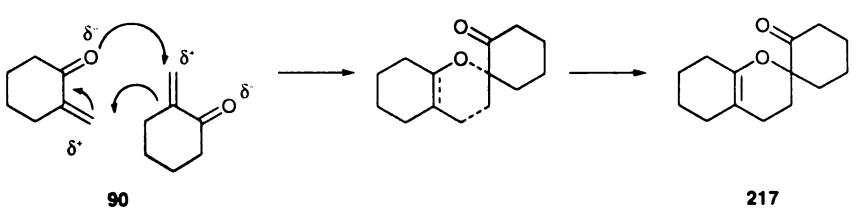
Et_3N/hexanes. The enone elutes first, compared to the chloroketone precursor, and was used directly in the Diels-Alder. These modifications allowed for the rapid transformation of simple cyclic vinyl carbinols into more complex moieties.

Scheme 40. Diels-Alder Diene Participation of Enone **90**[23]



In preliminary investigations 2-methylenecyclohexanone, **90**, was exposed to a dienophile. The anticipated intramolecular hetero Diels-Alder (HAD) was not observed for **90**. Instead enone **90** diemerized, in the presence of either norbornylene or styrene, *via* HAD to generate spiral **217** (Scheme 40). This type of thermal dimerization of enones has been observed in the literature.[96] Given the inherent resonance structures of enones it was thought that an electron rich dienophile might aid in achieving the desired

Scheme 41. Diemerization of Enones

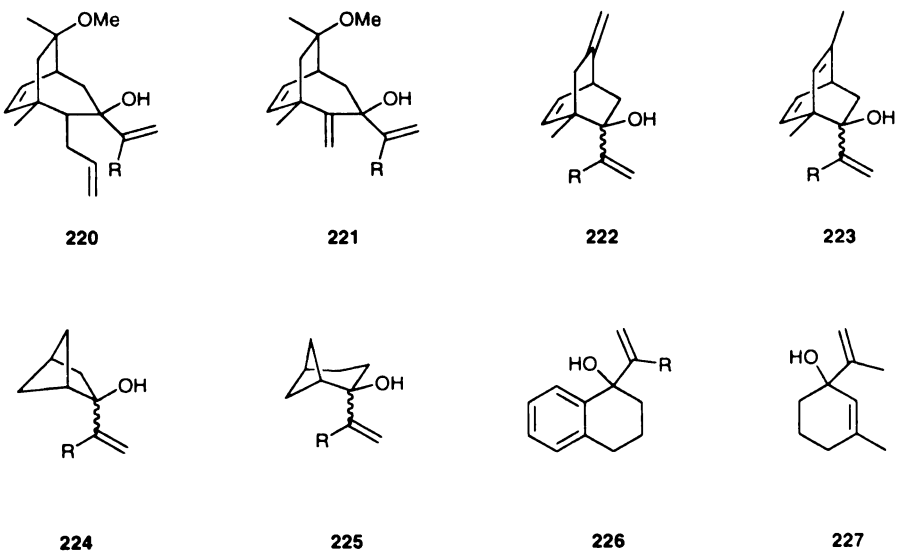


cycloaddition. However, use of *p*-methoxystyrene was unsuccessful. Though these are not promising results there is still much room for experimentation.

6.5. Increase in Substrate Scope

There is always room for broadening of the substrate scope. This study involved simple monocyclic, as well as [2.2.1] and [2.2.2] bicyclic systems. There are a number of other bicyclic systems, for example **224** and **225**, which also could be investigated. More in-depth study of the chemoselectivity could be achieved by the addition of olefins, **222** and **223**. Also study of sp^2 vs. sp^3 migration could be achieved with substrates like **221**, **226** and **227**. Initial studies with **226** show that arene migration is preferred over sp^3-hybridized methylene. A few of these substrates are shown below (Figure 19).

Figure 19. Possible Substrates



6.6. Final Thoughts

The research described herein has completed a broad investigation into the ability for bleach and vinegar to be able to generate a number of cationic rearrangements, which are often selective in some manner. A good understanding of the chemo-, regio-, and diastereoselectivity of the chlorinative ring expansion/elimination were gained along side

observations of other interesting rearrangements. The ability to ring expand general vinyl carbinols *via* simple conditions, coupled with the ability to transform the resultant chloroketones into more complex materials adds to the synthetic prowess of this protocol. Certainly this body of research has made a contribution to the area of cationic chemistry. Developing an understanding of these rearrangements and their synthetic subtleties has been most rewarding to myself.

Experimental Details

Materials and Methods:

All air or moisture sensitive reactions were carried out in oven- or flame-dried glassware under a nitrogen atmosphere unless otherwise noted. All commercial reagents were used without purification. All solvents were reagent grade. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone under nitrogen. Benzene (PhH), dimethyl sulfoxide (DMSO) and diisopropylethylamine (*i*-Pr_2EtN) were freshly distilled from calcium hydride under nitrogen. Except as otherwise noted, all reactions were magnetically stirred and monitored by thin-layer chromatography with 0.25-mm precoated silica gel plates or capillary GC with a fused silica column. Flash chromatography was performed with silica gel 60 Å (particle size 230-400 mesh ASTM) or basic alumina (particle size ~150 mesh). High performance liquid chromatography (HPLC) was performed with Ranin component analytical/ semiprep system. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Melting points were determined on a Thomas-Hoover Apparatus, uncorrected. Infrared spectra were recorded on a Nicolet IR/42 spectrometer. Proton and carbon NMR spectra were recorded on a Varian Gemini-300, VXR 500 or INOVA 600 spectrometer. Chemical shifts for ^{1}H-NMR and ^{13}C-NMR are reported in parts per million (ppm) relative to $CDCl_3$ (δ = 7.24 ppm for ^{1}H-NMR or δ = 77.0 ppm for ^{13}C-NMR). Optical rotations were measured with a Perkin-Elmer Model 341 polarimeter. High resolution mass spectra (HRMS) data were obtained at either the Michigan State University Mass Spectrometry Service Center or at the Mass Spectrometry Laboratory of the University of South Carolina, Department of

Chemistry & Biochemistry. GC/MS were performed with a fused silica column (30 m by 0.25 mm i.d.).

General Procedures:

General Procedure I: Preparation of Bicyclic Vinyl and *Iso*-propenyl carbinols.

A vinyl or isopropenyl magnesium bromide/THF (1.0 M and 0.5 M respectively, 3.00 eq) solution was chilled to 0 °C prior to the dropwise addition of **27**, or **28**, (1.00 eq), in THF (~2.0 M). After complete addition the reaction was stirred at 0 °C for 0.5 hrs and then warmed to reflux (80 °C). Reflux was maintained for 3 hrs The reaction was then cooled to 0 °C and quenched with an aqueous solution of $NH_4Cl_{(sat)}$. After partitioning with Et_2O and separation, the ethereal layer was washed two times with an aqueous solution of $NH_4Cl_{(sat)}$ and once with H_2O. The combined aqueous layers were extracted two times with Et_2O. The combined ethereal layers were dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified *via* flash alumina chromatography with hexanes/EtOAc as the eluent (30 g basic alumina per 1 g compound; Activity III).

General Procedure II: Preparation of Bicyclic DHF and DHP Carbinols.

A solution of (5.00 eq) dihydrofuran or dihydropyran in 15 mL THF (1.8 M) was chilled to –78 °C prior to the dropwise addition of (5.05 eq) a *t*-BuLi/pentane (1.7 M) solution. After 15 min the reaction temperature was raised to 0 °C for 45 min Subsequent cooling to –78 °C was followed by the dropwise addition of **27**, or **28**, (1.00 eq) in THF (1.1 M). After 15 min the reaction temperature was raised to 0 °C and stirred for 5 hrs The reaction was quenched with the addition of an aqueous solution of $NH_4Cl_{(sat.)}$ and partitioned with Et_2O. After separation, the ethereal layer was washed two

times with an aqueous solution of $NH_4Cl_{(sat.)}$. The combined aqueous layers were extracted two times with Et_2O. The combined ethereal layers were washed once with brine and then dried over $MgSO_4$, filtered, and concentrated. The residue was purified *via* flash alumina chromatography with hexanes/EtOAc as the eluent (30 g basic alumina per 1 g cmpd; Activity III).

General Procedure III: Preparation of Monocyclic Vinyl Carbinols.

A vinyl magnesium bromide/THF (1.0 M, 3.00 eq) solution was chilled to 0 °C prior to the dropwise addition of ketone (1.00 eq) in THF (~2.0 M). After complete addition the reaction was stirred at 0 °C for 0.5 hrs and then warmed to reflux (80 °C). Reflux was maintained until the reaction was judged complete by TLC (1-3 hrs). The reaction was then cooled to 0 °C and quenched with an aqueous solution of $NH_4Cl_{(sat)}$. After partitioning with Et_2O and separation, the ethereal layer was washed two times with an aqueous solution of $NH_4Cl_{(sat)}$ and once with H_2O. The combined aqueous layers were extracted two times with Et_2O. The combined ethereal layers were dried over $MgSO_4$, filtered, and concentrated. If necessary the crude residue was purified *via* flash alumina chromatography with hexanes/EtOAc as the eluent (30 g alumina per 1 g compound; basic Activity III).

General Procedure IV: Preparation of Bicyclic 2°-Carbinols.

A solution of **27**, or **28**, (1.00 eq) in 30 mL 95% EtOH (0.37 M) was cooled to 0 °C, afterwhich $NaBH_4$ or $LiAlD_4$ (4.00 eq), was added in one portion. The reaction was kept at 0 °C for 30 min, then warmed to room temperature and stirred for 16 hrs The reaction was then quenched with an aqueous solution of $NH_4Cl_{(sat)}$ and further partitioned with Et_2O. After separation the ethereal phase was washed two consecutive times with

an aqueous solution of $NH_4Cl_{(sat)}$. The combined aqueous layers were extracted two consecutive times with Et_2O. The combined ethereal layers were dried over $MgSO_4$, filtered, and concentrated to afford a ~1:1 mixture carbinols.

General procedure V: Rearrangements Induced by NaOCl and AcOH.

A solution of bicyclocarbinol (1.00 eq) in CCl_4 (0.6 M) was chilled to 0 °C. After 10 min at 0 °C, AcOH (1.95 eq) was added rapidly to the CCl_4 solution. This solution was stirred at 0 °C for an additional 5 min and then added rapidly to a 0 °C solution of NaOCl (0.75 M 1.19 eq) in H_2O (same volume as CCl_4). The biphasic reaction was vigorously stirred for 6 hrs at 0 °C. The reaction was then poured into a cold solution of 3% K_2CO_3 in H_2O and partitioned with the addition of room temperature CH_2Cl_2. After separation the organic layer was washed three times with a cold solution of 3% K_2CO_3 in H_2O. The combined aqueous washes were extracted three times with ambient CH_2Cl_2. The combined CH_2Cl_2 layers were then dried over $MgSO_4$, filtered, and concentrated. The residual was purified *via* flash silica chromatography with hexanes/EtOAc (chlorinative ring expansion) or 1% Et_3N/hexanes (ring expansion/*exo*-olefin insertion) as the eluent (10 g SiO_2 per 1 g cmpd).

General Procedure VI: Preparation of oxy-Cope Products.

A 35% wt/wt KH/oil suspension (1.37 eq) was washed three consecutive times with 1 mL hexanes prior to the dropwise addition of a solution containing a 1:1 mixture of **1:2,** or **29:30**, (1.00 eq) in 20 mL THF. After complete addition the reaction was heated to reflux (80 °C) and maintained overnight. Subsequent cooling to 0 °C and quenching with 25 mL NH_4Cl resulted in a biphasic solution. After partitioning with Et_2O and separation, the ethereal layer was washed two times with an aqueous solution of

$NH_4Cl_{(sat)}$ and once with H_2O. The combined aqueous layers were extracted two times with Et_2O. The combined ethereal layers were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified *via* flash alumina chromatography as the eluent (30 g basic alumina; Activity II; 30%Et_2O/hexanes).

General Procedure VII: Preparation of Chlorosulfides (sulfenate attempts).

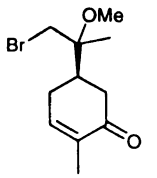
The following experiments were carried out in a darkened hood and an aluminum wrapped round bottom flask. To a chilled (-78 °C) solution of **1**, or **2**, or **29** (1.00 eq) in 5.0 mL CH_2Cl_2 (0.24 M) was added Et_3N (2.00 eq). The reaction was stirred for 15 min, afterwhich p-NO_2PhSCl (1.11 eq) in 0.40 mL CH_2Cl_2 (4.0 M), was added dropwise *via* syringe. The reaction was stirred at -78 °C for 4 hrs and then partitioned with 10 mL CH_2Cl_2 and 10 mL 3% aqueous HCl. After separation the CH_2Cl_2 layer was washed once with 10 mL 3% aqueous HCl and two times with 10 mL H_2O. The CH_2Cl_2 layer was then dried over Na_2SO_4, filtered, and concentrated. After concentration the yellow oil was purified *via* prep-HPLC (Rainin si-80-199-C5 column; 10:1 hexanes/EtOAc, 60 min).

General Procedure VIII: Preparation of Sulfones (sulfide oxidation).

Oxone® (2.09 eq) in 2 mL H_2O (0.21 M), was buffered to a pH = 4 by addition of Na_2HPO_4 and subsequently chilled to 0 °C. Addition of **33**, or **35**, (1.00 eq) in 1mL MeOH (0.20 M) followed, with an additional 1 mL MeOH added to facilitate stirring of the resultant slurry. The reaction was warmed to room temperature and agitated for 12 hrs The reaction was partitioned with 15 mL CH_2Cl_2 and separated. The aqueous layer was extracted three times with 15 mL CH_2Cl_2. The combined CH_2Cl_2 layers were washed two times with 15 mL H_2O and one time with 15 mL brine. The CH_2Cl_2 layer

was then dried over Na_2SO_4, filtered, and concentrated to afford a brown oil. The oil was purified *via* prep-HPLC (Rainin si-80-199-C5 column; 100% hexanes, 45 min; 10% EtOAc/hexanes, 60 min; 16% EtOAc/hexanes, 60 min).

Specific Procedures and Spectral Data:



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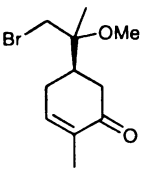


26

(5*R)-5-[(1*R**)-1-bromomethyl-1-methoxyethyl]-2-methylcyclohexa-2-enone (25) and (5*R**)-5-[(1*S**)-1-bromomethyl-1-methoxyethyl]-2-methylcyclohexa-2-enone (26).**

A solution of 20.00 g (133.1 mmol, 1.00 equivalent) (*R*)-(–)-carvone in 200 mL of a 3:2 CH_2Cl_2/MeOH solvent system was charged with N_2 and chilled to 0 °C. Over a period of 4 hrs, 29.36 g (164.9 mmol, 1.24 eq) of *N*-bromosuccinimide was added portion wise. Upon complete NBS addition the reaction was allowed to come to room temperature and stir for 16 hrs The reaction was then partitioned with 100 mL CH_2Cl_2 and 100 mL 2% $NaOH_{aq}$. The phases were separated, and the organic CH_2Cl_2 phase was subject to two more 100 mL 2% $NaOH_{aq}$ washes and one subsequent 75 mL brine wash. The CH_2Cl_2 phase was dried with Na_2SO_4, filtered, and concentrated to afford an orange viscous oil. The epimeric oil was purified *via* flash silica chromotography (300 g; 10:1 hexanes/EtOAc) to quantitative yield a 1:1 mixture of **25:26**.

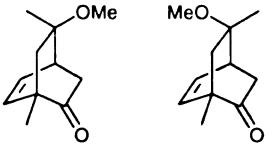
25: R_f = 0.24 (10:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.75 (m, 1 H), 3.43 (AB_q, J = 11.1, 4.2 Hz, 2 H), 3.22 (s, 3 H), 2.34 (series of m, 4 H), 1.75 (p, J = 1.2 Hz, 3 H), 1.24 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 199.2 (C), 145.0 (CH), 135.0 (C), 75.8

(C), 49.5 (CH_2), 40.8 (CH_2), 38.9 (CH_3), 36.5 (CH_3), 26.0 (CH_2), 17.9 (CH_3), 15.5 (CH); LRMS (EI) *m/z* 260.1 (M^+), 262.2 (M^{+2}), 228.1 (M^+-MeOH), 230.1 (M^{+2}-MeOH).

26: R_f = 0.24 (10:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.70 (m, 1 H), 3.40 (AB_q, *J* = 10.9, 4.9 Hz, 2 H), 3.19 (s, 3 H), 2.48 (m, 2 H), 2.23 (m, 2 H), 1.72 (m, 3 H), 1.21 (s, 3 H); LRMS (EI) *m/z* 260.1 (M^+), 262.1 (M^{+2}).

25:26: IR (CH_2Cl_2) 3250 (m), 3190 (s), 2950 (s), 1720 (s), 1670 (m), 1410 (s), 1395 (s), 1280 (s), 1150 (s), 930 (s), 780 (s), 590 (s) cm^{-1}.

For original synthesis see: Srikrishna, A.; Sharma, V. R.; Danieldoss, J.; Hemamalini, P. *J. Chem. Soc. Perkin Trans. I* **1996**, 1305-1311.



27 **28**

(1*S, 4*S**, *8R**)-1,8-dimethyl-8-methoxybicyclo[2.2.2]oct-5-en-2-one (27) and (1*S**, 4*S**, 8*S**)-1,8-dimethyl-8-methoxybicyclo[2.2.2]oct-5-en-2-one (28).**

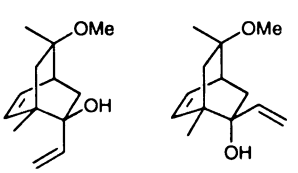
A solution containing 28.98 g (133.1 mmol) bromocarvone **25:26**, in 300 mL ^{t}BuOH and 350 mL THF was chilled to 0 °C, and 17.50 g (155.9 mmol, 1.17 eq.) of ^{t}BuOK was added in portons. Upon complete addtion of the base, the reaction was stirred at 0 °C for 10 min and then warmed to room temperature and stirred for 18 hrs The reaction was then poured into 300 mL of acidic brine (150 mL 3% HCl_{aq} / 150 mL brine). The aqueous mixture was partitioned with 150 mL Et_2O and separated. The ethereal solution was washed two additional times with 300 mL acidic brine. The ethereal layer was dried with Na_2SO_4, filtered and concentrated. The resultant brown oil was purified *via* flash silica chromotography (180 g; 4:1 hexanes/EtOAc) to yield 9.67 g

(40%) of **27**, 6.67 g (28%) of **28** and 4.79 g (20%) of **27:28,** as a 1:5 mixture of diastereomers, as a clear oils.

27: R_f = 0.53 (4:1 hexanes/EtOAc); $[\alpha]_D^{20}$ = -383.8 (*c* 1.49, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.41 (t, *J* = 7.5 Hz, 1 H), 5.81 (d, *J* = 8.1 Hz, 1 H), 3.15 (s, 3 H), 2.88 (m, 1 H), 2.50 (dd, *J* = 18.0, 3.3 Hz, 1 H), 1.84 (dt, *J* = 18.3, 3.3 Hz, 1 H), 1.73 (dd, *J* = 13.5, 3.3 Hz, 1 H), 1.42 (dd, *J* = 13.8, 3.3 Hz, 1 H), 1.23 (s, 3 H), 1.12 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 212.9 (C), 135.7 (CH), 134.4 (CH), 78.8 (C), 50.2 (C), 49.6 (CH_3), 45.9 (CH_2), 41.5 (CH), 34.6 (CH_2), 24.8 (CH_3), 17.1 (CH_3); IR (neat) 3090 (w), 2970 (m), 2930 (m), 2828 (w), 1724 (s), 1454 (w), 1371 (w), 1082 (m), 754 (w) cm^{-1}; LRMS (EI) *m/z* 180.6 (M^+).

28: R_f = 0.33 (4:1 hexanes/EtOAc); $[\alpha]_D^{20}$ = -377.9 (*c* 1.72, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.42 (t, *J* = 8.1 Hz, 1 H), 5.88 (d, *J* = 8.1 Hz, 1 H), 3.13 (s, 3 H), 2.97 (m, 1 H), 2.05 (m, 2 H), 1.61 (AB_q, *J* = 15.0 Hz, 2 H), 1.32 (s, 3 H), 1.14 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 212.8 (C), 135.7 (CH), 134.4 (CH), 78.8 (C), 50.2 (C), 49.6 (CH_3), 45.9 (CH_2), 41.5 (CH), 34.6 (CH_2), 24.8 (CH_3), 17.2 (CH_3); IR (neat) 3090 (w), 2970 (m), 2933 (m), 2826 (w), 1724 (s), 1452 (w), 1375 (w), 1132 (m), 1080 (m), 1012 (w), 920 (w), 848 (w), 748 (m) cm^{-1}; LRMS (EI) *m/z* 180.0 (M^+).

For original synthesis see: Srikrishna, A., Sharma, V. R., Danieldoss, J., Hemamalini, P. *J. Chem. Soc. Perkin Trans. I* **1996**, 1305-1311.



6 **7**

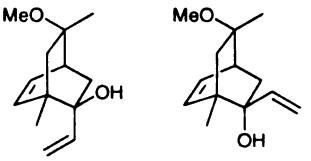
(1*S, 2*S**, 4*S**, 8*R**)-1,8-dimethyl-2-ethenyl-8-methoxybicyclo[2.2.2]oct-5-en-2-ol (6) and (1*S**, 2*R**, 4*S**, 8*R**)-1,8-dimethyl-2-ethenyl-8-methoxybicyclo[2.2.2]oct-5-en-2-ol (7).**

Following general procedure I, the reaction of 1.2 g (6.7 mmol) of starting ketone **27**, afforded 0.98 g (70%) of **6:7** as a 4:1 diastereomeric mixture after purification *via* flash alumina chromatography (60 g; 100:1 hexanes/EtOAc).

6: R_f = 0.42 (5:1 hexanes/EtOAc); $[\alpha]_D^{20}$ = -40.0 (*c* 1.19, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.17 (t, *J* = 6.9 Hz, 1 H), 5.86 (d, *J* = 8.1 Hz, 1 H), 5.53 (dd, *J* = 16.8, 10.5 Hz, 1 H), 5.17 (dd, *J* = 17.1, 2.1 Hz, 1 H), 4.92 (dd, *J* = 10.8, 2.1 Hz, 1 H), 3.17 (s, 3 H), 2.85 (s, 1 H), 2.61 (m, 1 H), 1.92 (d, *J* = 14.1 Hz, 1 H), 1.82 (dd, *J* = 13.8, 3.0 Hz, 1 H), 1.47 (dd, *J* = 14.1, 2.4 Hz, 1 H), 1.09 (s, 3 H), 0.98 (d, *J* = 13.5 Hz, 1 H) 0.94 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 144.2 (CH), 139.7 (CH), 133.5 (CH), 110.8 (CH_2), 78.4 (C), 75.5 (C), 49.6 (CH_3), 45.7 (CH_2), 43.2 (C), 40.7 (CH_2), 40.1 (CH), 24.5 (CH_3), 18.8 (CH_3); IR (neat) 3439 (br s), 3092 (w), 3042 (w), 2934 (s), 2831 (m), 1650 (w), 1454 (m), 1367 (m), 1116 (s), 1062 (s), 1003 (m), 918 (m), 844 (w), 740 (w-m) cm^{-1}; HRMS (EI) *m/z* 208.1465 [(M^+), calcd. for $C_{13}H_{20}O_2$: 208.1463].

7: R_f = 0.33 (5:1 hexanes/EtOAc); $[\alpha]_D^{20}$ = -97.3 (*c* 1.25, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.37 (t, *J* = 7.8 Hz, 1 H), 6.07 (dd, *J* = 17.7, 11.1 Hz, 1 H), 5.89 (d, *J* = 7.8 Hz, 1 H), 5.31 (dd, *J* = 17.7, 2.1 Hz, 1 H), 5.11 (dd, *J* = 10.5, 1.5 Hz, 1 H), 3.14 (s, 3 H), 2.57 (m, 1 H), 2.34 (dd, *J* = 13.8, 2.1 Hz, 1 H), 1.60 (d, *J* = 13.8 Hz, 1 H), 1.51 (s, 1 H), 1.19 (dd, *J* = 13.5, 3.3 Hz, 1 H), 1.09 (s, 3 H), 1.01 (d, *J* = 14.4 Hz, 1 H), 1.00 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 140.7 (CH), 137.9 (CH), 134.5 (CH), 113.2 (CH_2), 79.6 (C),

78.9 (C), 49.3 (CH_3), 44.3(CH_2), 43.4 (C), 40.3 (CH), 39.4 (CH_2), 24.7 (CH_3), 18.1 (CH_3); HRMS (EI) *m/z* 208.1461 [(M^+), calcd. for $C_{13}H_{20}O_2$: 208.1463].



29 **30**

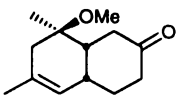
(1*S, 2*S**, 4*S**, 8*S**)-1,8-dimethyl-2-ethenyl-8-methoxybicyclo[2.2.2]oct-5-en-2-ol (29) and (1*S**, 2*R**, 4*S**, 8*S**)-1,8-dimethyl-2-ethenyl-8-methoxybicyclo[2.2.2]oct-5-en-2-ol (30).**

Following general procedure I, the reaction of 0.8 g (4.6 mmol) of starting ketone **28**, afforded 0.61 g (63%) of **29:30** as a 1:1 diastereomeric mixture after purification *via* flash alumina chromatography (60 g; 100:1 hexanes/EtOAc).

29: R_f = 0.25 (5:1 hexanes/EtOAc); $[\alpha]_D^{20}$ = -69.3 (*c* 1.45, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.25 (AB_q, *J* = 8.1, 1.8 Hz, 1 H), 5.93 (d, *J* = 8.4 Hz, 1 H), 5.77 (dd, *J* = 17.3, 10.8 Hz, 1 H), 5.12 (dd, *J* = 17.1, 1.2 Hz, 1 H), 4.97 (dd, *J* = 10.8, 1.2 Hz, 1 H), 3.13 (s, 3 H), 2.66 (m, 1 H), 2.00 (d, *J* = 13.5 Hz, 1 H), 1.69 (dd, *J* = 14.4, 2.4 Hz, 1 H), 1.60 (dd, *J* = 14.4, 3.3 Hz, 1 H), 1.58 (s, 1 H), 1.43 (s, 3 H), 1.17 (d, *J* = 13.5 Hz, 1 H), 0.95 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 146.2 (CH), 136.5 (CH), 133.4 (CH), 110.3 (CH_2), 79.1 (C), 77.7 (C), 48.9 (CH_3), 44.1 (CH_2), 43.0 (C), 40.2 (CH), 39.6 (CH_2), 21.9 (CH_3), 18.5 (CH_2); IR (neat) 3470 (m br), 3070 (w) 3020 (w), 2963 (s), 2936 (s), 2874 (s), 1726 (s), 1462 (s), 1371 (s), 1286 (s), 1147 (s), 1078 (s), 1001 (s), 918 (s), 733 (s) cm^{-1}; HRMS (EI) *m/z* 208.1461 [(M^+), calcd. for $C_{13}H_{20}O_2$: 208.1463].

30: R_f = 0.11 (5:1 hexanes/EtOAc); $[\alpha]_D^{20}$ = -125.4 (*c* 1.24, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.41 (AB_q, *J* = 6.6, 1.5 Hz, 1 H), 5.98 (d, *J* = 8.4 Hz, 1 H), 5.87 (dd, *J* = 17.1,

10.8 Hz, 1 H), 5.32 (dd, J = 17.4, 1.8 Hz, 1 H), 5.14 (dd, J = 10.5, 1.5 Hz, 1 H), 3.09 (s, 3 H), 2.67 (m, 1 H), 1.94 (dd, J = 15.3, 1.8 Hz, 1 H), 1.67 (s, 1 H), 1.43 (d, J = 13.8 Hz, 1 H), 1.42 (d, J = 15.3 Hz, 1 H), 1.29 (s, 3 H), 1.28 (d, J = 13.2 Hz, 1 H), 1.03 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 139.7 (CH), 136.3 (CH), 134.3 (CH), 114.2 (CH_2), 79.1 (C), 77.1 (C), 49.1 (CH_3), 44.9 (CH_2), 43.4 (C), 40.7 (CH_2), 39.9 (CH), 22.0 (CH_3), 18.4 (CH_3); IR (neat) 3470 (m br), 3070 (w) 3020 (w), 2963 (s), 2936 (s), 2874 (s), 1726 (s), 1462 (s), 1371 (s), 1286 (s), 1147 (s), 1078 (s), 1001 (s), 918 (s), 733 (s) cm^{-1}; HRMS (EI) *m/z* 208.1463 [(M^+), calcd. for $C_{13}H_{20}O_2$: 208.1463].

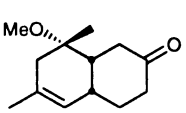


31

(8*R, 9*R**, 10*S**)-6,8-dimethyl-8-methoxybicyclo[4.4.0]dec-5-en-2-one (31).**

Following general procedure VI, the reaction of 0.49 g (2.4 mmol) of starting carbinols **1:2**, as a 4:1 mixture, afforded 0.23 g (47%) of **31** after purification *via* flash alumina chromatography (30 g; neutral, Activity I, 30% Et_2O/hexanes).

31: R_f = 0.33 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.27 (s, 1 H), 2.72 (br s, 1 H), 2.40-1.86 (series of m, 12 H), 1.63 (s, 3 H), 1.09 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 211.9 (C), 132.9 (C), 122.8 (CH), 75.6 (C), 42.6 (CH_2), 48.7 (CH), 40.5 (CH_3), 37.9 (CH_2), 37.5 (CH_3), 30.6 (CH), 30.4 (CH_3), 23.1 (CH_2), 21.3 (CH_2); IR (neat) 3015 (w), 1713 (s), 1580 (w), 1068 (s), 841 (m) cm^{-1}; HRMS (EI) *m/z* 208.1471 [(M^+), calcd. for $C_{13}H_{20}O_2$: 208.1463].

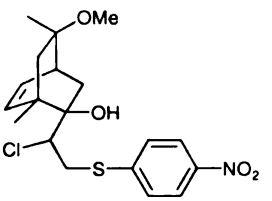


32

(8*S, 9*R**, 10*S**)-6,8-dimethyl-8-methoxybicyclo[4.4.0]dec-5-en-2-one (32).**

Following general procedure VI, the reaction of 0.47 g (2.3 mmol) of starting carbinols **29:30**, as a 1:1 mixture, afforded 0.24 g (50%) of **32** after purification *via* flash alumina chromatography (30 g; neutral, Activity I, 30% Et_2O/hexanes).

32: R_f = 0.26 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.09 (s, 1 H), 3.13 (s, 3 H), 2.44 (m, 2 H), 2.40-1.60 (series of m, 8 H), 1.67 (s, 3 H), 1.17 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 212.8 (C), 134.2 (C), 122.1 (CH), 75.4 (C), 48.1 (CH), 42.4 (CH_2), 39.2 (CH_3), 38.8 (CH_2), 37.4 (CH_3), 33.3 (CH_3), 30.9 (CH), 23.3 (CH_2), 22.0 (CH_2); IR (neat) 3010 (w), 1714 (s), 1680 (m), 1060 (s), 910 (m); HRMS (EI) *m/z* 208.1455 [(M^+), calcd. for $C_{13}H_{20}O_2$: 208.1463].



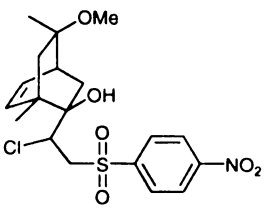
33

(1*S, 2*S**, 4*S**, 8*R**)-2-[1-chloro-2-(4-nitro-phenylsulfanyl)-ethyl]-8-methoxy-1,8-dimethyl-bicyclo[2.2.2]oct-5-en-2-ol (33).**

Following general procedure VII, the reaction of 0.30 g (1.4 mmol) of starting carbinol **1**, afforded 0.22 g (48%) of **33** as one isomer after purification *via* prep-HPLC (Rainin si-80-199-C5 column; 10:1 hexanes/EtOAc, 60 min).

33: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.3 Hz, 2 H), 7.49 (d, *J* = 9.0 Hz, 2 H), 6.09 (t, *J* = 7.5 Hz, 1 H), 6.02 (d, *J* = 7.8 Hz, 1 H), 4.24 (dd, *J* = 14.8, 7.5 Hz, 1 H), 4.03 (br s, 1 H), 3.70 (dd, *J* = 14.8, 7.2 Hz, 1 H), 3.68 (s, 1 H), 3.23 (s, 3 H), 2.74 (m, 1 H), 1.99 (d, *J* = 13.8 Hz, 1 H), 1.81 (dd, *J* = 14.1, 3.6 Hz, 1 H), 1.52 (dd, *J* = 13.8, 3.1 Hz, 1 H), 1.14 (s, 3 H), 1.06 (s, 3 H), 0.97 (d, *J* = 13.5 Hz, 1 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ

146.1 (C), 145.5 (C), 141.5 (CH), 130.4 (CH), 127.9 (CH), 123.9 (CH), 78.4 (C), 77.3 (C), 55.3 (CH), 49.8 (CH_3), 47.9 (CH_2), 47.1 (CH_2), 44.2 (C), 39.9 (CH), 37.5 (CH_2), 24.5 (CH_3), 17.7 (CH_3); IR (NaCl, neat) 3431 (br s), 3047 (w), 2963 (s), 1577, (w), 670 (s); HRMS (FAB) *m/z* 397.1955 [(M^+), calcd. for $C_{19}H_{24}ClNO_4S$: 397.1115].

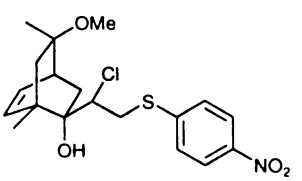


34

(1*S, 2*S**, 4*S**, 8*R**)-2-[1-chloro-2-(4-nitro-benzenesulfonyl)-ethyl]-8-methoxy-1,8-dimethyl-bicyclo[2.2.2]oct-5-en-2-ol (34).**

Following general procedure VIII, the reaction of 40.0 mg (0.10 mmol) of starting sulfide **33**, afforded 11.8 mg (27%) of **34** after purification *via* prep-HPLC (Rainin si-80-199-C5 column; 100% hexanes, 45 min; 10% EtOAc/hexanes, 60 min; 16% EtOAc/hexanes, 60 min).

34: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.39 (d, *J* = 9.0 Hz, 2 H), 8.08 (d, *J* = 9.3 Hz, 2 H), 6.29 (t, *J* = 7.8 Hz, 1 H), 6.18 (d, *J* = 8.4 Hz, 1 H), 4.22 (dd, *J* = 13.2, 1.5 Hz, 1 H), 4.05 (s, 1 H), 3.66 (dd, *J* = 12.9, 5.7 Hz, 1 H), 3.52 (dd, *J* = 4.5, 1.5 Hz, 1 H), 3.22 (s, 3 H), 2.75 (m, 1 H), 2.37 (dd, *J* = 14.4, 1.8 Hz, 1 H), 2.07 (d, *J* = 14.4 Hz, 1 H), 1.81 (dd, *J* = 13.8, 3.3 Hz, 1 H), 1.40 (s, 3 H), 1.16 (s, 3 H), 1.08 (d, *J* = 14.1 Hz, 1 H); LRMS (EI) *m/z* 429.1 (M^+).

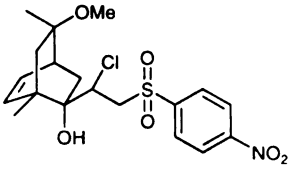


35

(1*S, 2*R**, 4*S**, 8*R**)-2-[1-chloro-2-(4-nitro-phenylsulfanyl)-ethyl]-8-methoxy-1,8-dimethyl-bicyclo[2.2.2]oct-5-en-2-ol (35).**

Following general procedure VII, the reaction of 0.30 g (1.4 mmol) of starting carbinol **2**, afforded 0.11 g (32%) of **35** as one isomer after purification *via* prep-HPLC (Rainin si-80-199-C5 column; 10:1 hexanes/EtOAc, 60 min).

35: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 9.0 Hz, 2 H), 7.54 (d, *J* = 9.0 Hz, 2 H), 6.37 (t, *J* = 6.6 Hz, 1 H), 5.81 (d, *J* = 7.5 Hz, 1 H), 4.32 (dd, *J* = 11.7 Hz, 3.0 Hz, 1 H), 3.93 (dd, *J* = 8.4, 3.0 Hz, 1 H), 3.75 (dd, *J* = 11.7, 8.7 Hz, 1 H), 3.23 (s, 1 H), 3.03 (s, 3 H), 2.55 (m, 1 H), 2.00 (d, *J* = 14.4 Hz, 1 H), 1.36 (dd, *J* = 13.8, 3.9 Hz, 1 H), 1.25 (s, 3 H), 1.22 (d, *J* = 14.7 Hz, 1 H), 1.13 (d, *J* = 14.7 Hz, 1 H), 1.09 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 147.6 (C), 145.4 (C), 139.3 (CH), 135.2 (CH), 128.0 (CH), 123.9 (CH), 79.5 (C), 78.8 (C), 59.8 (CH), 49.4 (CH_3), 47.9 (CH_2), 44.9 (C), 44.4 (CH_2), 40.8 (CH), 39.9 (CH), 24.6 (CH_3), 20.5 (CH_3); IR (NaCl, neat) 3440 (br s), 3035 (w), 2980 (s), 1575, (w), 665 (s); HRMS (FAB) *m/z* 397.2003 [(M^+), calcd. for $C_{19}H_{24}ClNO_4S$: 397.1115].

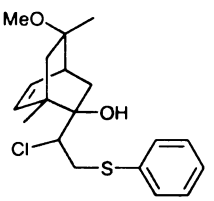


36

(1*S, 2*R**, 4*S**, 8*R**)-2-[1-chloro-2-(4-nitro-benzenesulfonyl)-ethyl]-8-methoxy-1,8-dimethyl-bicyclo[2.2.2]oct-5-en-2-ol (36).**

Following general procedure VIII, the reaction of 80.5 mg (0.20 mmol) of starting sulfide **35**, afforded 19.5 mg (23%) of **36** after purification *via* prep-HPLC (Rainin si-80-199-C5 column; 100% hexanes, 45 min; 10% EtOAc/hexanes, 60 min; 16% EtOAc/hexanes, 60 min).

36: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.40 (d, *J* = 9.0 Hz, 2 H), 8.16 (d, *J* = 9.0 Hz, 2 H), 6.34 (t, *J* = 6.9 Hz, 1 H), 5.79 (d, *J* = 7.8 Hz, 1 H), 4.38 (dd, *J* = 14.1, 1.2 Hz, 1 H), 4.06 (dd, *J* = 6.3, 1.2 Hz, 1 H), 3.84 (dd, *J* = 14.4, 6.3 Hz, 1 H), 3.17 (s, 1 H), 3.07 (dd, *J* = 14.1, 2.4 Hz, 1 H), 2.95 (s, 3 H), 2.59 (m, 1 H), 1.58 (d, *J* = 14.7 Hz, 1 H), 1.42 (dd, *J* = 14.1, 3.3 Hz, 1 H), 1.35 (s, 3 H), 1.15 (d, *J* = 14.1 Hz, 1 H), 1.09 (s, 3 H); LRMS (EI) *m/z* 429.1 (M^+).

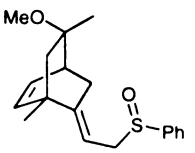


37

(1*S, 2*S**, 4*S**, 8*S**)-2-(1-chloro-2-phenylsulfanyl-ethyl)-8-methoxy-1,8-dimethyl-bicyclo[2.2.2]oct-5-en-2-ol (37).**

Following general procedure VII, the reaction of 0.10 g (0.51 mmol) of starting carbinol **29**, afforded 53.7 mg (33%) of **37** after purification *via* prep-HPLC (Rainin si-80-199-C5 column; 10:1 hexanes/EtOAc, 60 min).

37: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.47 (m, 2 H), 7.28 (m, 3 H), 6.22 (AB_q, *J* = 7.8, 1.2 Hz, 1 H), 5.96 (dd, *J* = 7.8, 1.2 Hz, 1 H), 3.95 (dd, *J* = 11.7, 5.7 Hz, 1 H), 3.53 (dd, *J* = 7.2 Hz, 1 H), 3.39 (dd, *J* = 5.4 Hz, 1 H), 3.12 (s, 3 H), 2.70 (m, 1 H), 2.14 (d, *J* = ,1H), 1.82 (dd, *J* = 14.7, 2.1 Hz, 1 H), 1.66 (dd, *J* = 5.3, 4.5 Hz, 1 H), 1.62 (s, 1 H), 1.45 (s, 3 H), 1.22 (s, 3 H), 1.05 (d, *J* = 13.2 Hz, 1 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 136.9 (CH), 135.5 (C), 132.9 (CH), 131.6 (CH), 131.6 (CH), 129.1 (CH), 127.5 (CH), 78.7 (C), 77.6 (C), 48.9 (CH_3), 46.1 (CH), 46.0 (CH_2), 44.3 (CH_2), 40.3 (CH), 37.7 (C), 21.5 (CH_3), 19.2 (CH_3); IR (NaCl, neat) 3425 (br s), 3010 (w), 2988 (s), 1590, (w), 675 (s); HRMS (FAB) *m/z* 352.1483 [(M^+), calcd. for $C_{19}H_{25}ClO_2S$: 352.1264].



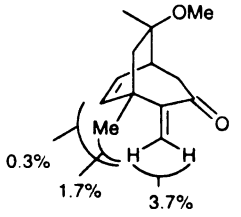
38

Preparation of (1*S, 4*S**, 5*S**)-7-(2-benzenesulfinyl-ethylidene)-5-methoxy-1,5-dimethyl-bicyclo[2.2.2]oct-2-ene (38).**

The following experiment was carried out in a darkened hood, and an aluminum wrapped round bottom flask. To a chilled (-78 °C) solution of 0.10 g **29** (0.48 mmol, 1.00 eq) in 10.0 mL THF was added 0.28 mL of a 1.7 M *n*-BuLi/hexanes solution (2.00 eq). The reaction was stirred for 30 min, afterwhich 0.07 g PhSCl (0.50 mmol, 1.11 eq) in 5 mL THF was added dropwise *via* syringe. The reaction was stirred at -78 °C for 2 hrs, then warmed to 0 °C and quenched with aqueous $NH_4Cl_{(sat)}$. The aqueous was extracted two times with 20 mL Et_2O. The combined ethereal layers were then dried over $MgSO_4$, filtered, and concentrated. After concentration the yellow oil was purified *via* prep-HPLC (Rainin si-80-199-C5 column; 10:1 hexanes/EtOAc, 60 min) to afford 39.5 mg (26%) of **38**.

38: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.54 (m, 2 H), 7.48 (m, 3 H), 6.21 (m, 1 H), 5.87 (d, *J* = 8.1 Hz, 1 H), 5.06 (tt, *J* = 7.8, 2.4 Hz, 0.5H), 4.93 (tt, *J* = 7.8, 2.4 Hz, 0.75H), 3.48 (pd, *J* = 8.1 Hz, 1 H), 3.09 (s, 3 H), 2.71 (m, 1 H), 2.16 (dt, *J* = 16.8 Hz, 1 H), 1.82 (dd, *J* = 10.9, 3.3 Hz, 1 H), 1.79 (dt, *J* = 16.2 Hz, 1 H), 1.47 (d, *J* = 12.9 Hz, 1 H), 1.21 (d, *J* = 13.2 Hz, 1 H), 1.15 (s, 3 H), 1.12 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 151.9 (C), 135.4 (CH), 135.3 (C), 132.9 (CH), 131.0 (CH), 128.9 (CH), 124.4 (CH), 104.5 (CH), 78.9 (C), 56.5 (CH_2), 50.0 (CH_3), 49.1 (CH_2), 41.7 (C), 39.8 (CH), 29.6 (CH_2), 22.6 (CH_3), 21.2

(CH_3); IR (NaCl, neat) 3047 (w), 2963 (s), 1577, (w), 1180 (s); HRMS (FAB) *m/z* 316.11587 [(M^+), calcd. for $C_{19}H_{24}O_2S$: 316.1497].

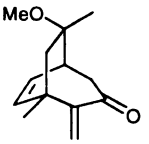


8

(1*S, 5*S**, 9*R**)-1,9-dimethyl-9-methoxy-2-methylenebicyclo[3.2.2]non-6-en-3-one (8).**

Following general procedure V, the reaction of 0.11 g (0.52 mmol) of starting carbinols **1:2**, as a 4:1 mixture, afforded 0.10 g (93%) of **8** after purification *via* flash silica chromatography (1.2 g; 1% Et_3N/hexanes).

8: R_f = 0.40 (5:1 hexanes/EtOAc); $[\alpha]_D^{20}$ = -53.5 (*c* 1.05, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.21 (AB_q, *J* = 8.1, 1.2 Hz, 1 H), 5.82 (d, *J* = 0.9 Hz, 1 H), 5.77 (d, *J* = 8.7 Hz, 1 H), 5.15 (d, *J* = 0.6, Hz, 1 H), 3.16 (s, 3 H), 2.99 (dd, *J* = 18.0, 3.6 Hz, 1 H), 2.59 (m, 1 H), 2.27 (dd, *J* = 18.3, 4.2 Hz, 1 H), 1.99 (d, *J* = 14.4 Hz, 1 H), 1.57 (d, *J* = 14.1 Hz, 1 H), 1.25 (s, 3 H), 1.23 (s, 3 H); For 1-D NOE correlations see figure shown above; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 202.2 (C), 154.4 (C), 137.4 (CH), 132.6 (CH), 116.9 (CH_2), 78.1 (C), 49.6 (CH_2), 49.3 (CH_3), 42.2 (CH_2), 40.0 (CH), 38.2 (C), 26.8 (CH_3), 26.4 (CH_3); IR (neat) 3040 (m), 2970 (s), 2965 (s), 2860 (m), 1710 (m), 1684 (s), 1599 (s), 1450 (s), 1371 (s), 1136 (s), 1064 (s), 960 (m), 765 (m) cm^{-1}; HRMS (EI) *m/z* 206.1298 [(M^+); calcd. for $C_{13}H_{18}O_2$: 206.1307].

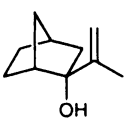


50

(1S*, 5S*, 9S*)-1,9-dimethyl-9-methoxy-2-methylenebicyclo[3.2.2]non-6-en-3-one (50).

Following general procedure V, the reaction of 0.12 g (0.57 mmol) of starting carbinols **29:30**, as a 1:1 mixture, afforded 0.10 g (91%) of **50** after purification *via* flash silica chromatography (1.2 g; 1% Et_3N/hexanes).

50: R_f = 0.26 (5:1 hexanes/EtOAc); $[\alpha]_D^{20}$ = -84.6° (*c* 1.57 ,$CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.22 (AB_q, *J* = 6.9, 0.24 Hz, 1 H), 5.84 (d, *J* = 8.7 Hz, 1 H), 5.78 (d, *J* = 0.9 Hz, 1 H), 5.15 (d, *J* = 0.6 Hz, 1 H), 3.11 (s, 3 H), 2.70 (d, *J* = 16.2, 3.6 Hz, 1 H), 2.67 (m, 1 H), 2.41 (d, *J* = 14.7 Hz, 1 H) 1.87 (d, *J* = 15.3 Hz, 1 H), 1.74 (d, *J* = 14.7 Hz, 1 H), 1.28 (s, 3 H), 1.27 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 202.4 (C), 154.5 (C), 136.3 (CH), 131.9 (CH), 117.0 (CH_2), 78.7 (C), 49.7 (CH_2), 49.3 (CH_3), 43.6 (CH_2), 38.3 (CH), 37.1 (C), 26.3 (CH_3), 23.8 (CH_3); IR (neat) 3070 (w), 2970 (s), 2937 (s), 2830 (m), 1695 (w), 1682 (s), 1510 (m), 1435 (m), 1375 (s), 1128 (s), 1080 (s), 940 (m), 758 (m-s) cm^{-1}; HRMS (EI) *m/z* 206.1304 [(M^+); calcd. for $C_{13}H_{18}O_2$: 206.1307].



9

(+/-)-(1*R, 2*R**, 4*S**)-2-isopropenyl-bicyclo[2.2.1]heptan-2-ol (9).**

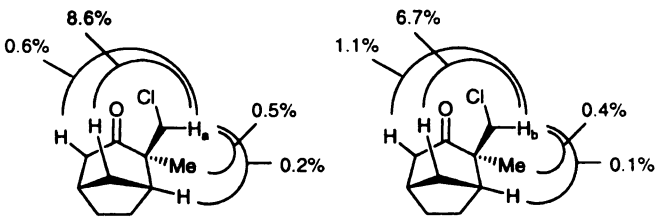
Following general procedure I, the reaction of 5.1 g (46.3 mmol) of norcamphor, afforded 4.5 g (64%) of **9**, as a 50:1 mixture of diastereomers, after purification *via* flash alumina chromatography (120 g; basic, Activity III; 100:1 hexanes/EtOAc).

9: $R_f = 0.40$ (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.85 (s, 1 H), 4.72 (d, *J* = 3.9 Hz, 1 H), 2.35 (m, 1 H), 2.14 (m, 1 H), 1.98 (d, *J* = 0.9, Hz, 1 H), 1.86 (m, 2 H), 1.76 (s, 3 H), 1.46 (d, *J* = 9.9 Hz, 1 H), 1.37-1.18 (series of m, 4 H), 1.12 (dd, *J* = 13.2, 3.3 Hz, 1 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 149.8 (C), 108.8 (CH_2), 80.8 (C), 44.6 (CH), 43.7 (CH_2), 38.7 (CH_3), 36.8 (CH), 28.6 (CH_2), 21.9 (CH_2), 18.4 (CH_2); IR (neat) 3366 (br s), 2088 (w), 2968 (s), 2872 (s), 1643 (m), 1454 (s), 1373 (m), 1307 (s), 1163 (s), 1147 (s), 1026 (s), 993 (s), 897 (s), 868 (m), 734 (m) cm^{-1}; HRMS (EI) *m/z* 152.1198 [(M^+) calcd. for $C_{10}H_{16}O$: 152.1201].

For previous synthesis see: Johnson, C. R.; Herr, R. W. *J. Org. Chem.* **1973**, *38*, 3153-3159.

Rearrangement of *i*-propenyl[2.2.1]heptanol *via* Johnson's conditions.

A solution of 0.58 g (3.8 mmol, 1.00 eq) **9** in 19 mL (0.2 M) $CHCl_3$ was heated to 55 °C, in a dark room, prior to the addition of 0.45 mL (4.0 mmol, 1.05 eq) *t*-BuOCl. The reaction was heated (55 °C) for 8 h in a dark room. The reaction was concentrated and the crude oil was purified *via* flash silica chromatography (18 g; 50:1 hexanes/EtOAc) to afford 0.24 g (34%) **10**, 0.16 g (23%) **11**, 0.21 g (29%) **12**, 0.05 g (7%) **13**, 0.01 g (2%) **54**.

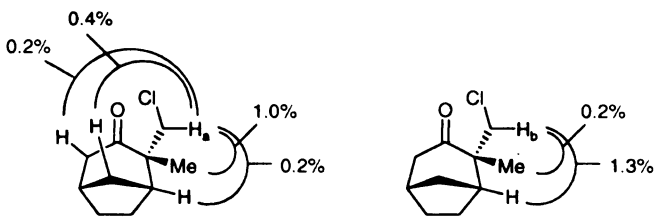


10 **10**

(+/-)-(1*R, 2*S**, 5*S**)-2-chloromethyl-2-methyl-bicyclo[3.2.1]octan-3-one (10).**

Following general procedure V, the reaction of 0.52 g (3.4 mmol) of starting carbinol **9**, afforded 0.23 g (36%) of **10** after purification *via* flash silica chromatography (20 g; 50:1 hexanes/EtOAc).

10: R_f = 0.73 (5:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.71 (d, *J* = 6.6 Hz, 1 H), 3.52 (d, *J* = 6.6 Hz, 1 H), 2.49 (m, 2 H), 2.36 (m, 1 H), 2.21 (dm, *J* = 15.0 Hz, 1 H), 2.13 (d, *J* = 12.5 Hz, 1 H), 1.72-1.63 (series of m, 3 H), 1.52 (m, 1 H), 1.39 (m, 1 H), 1.15 (s, 3 H); For 1-D NOE correlations see figure shown above; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 212.0 (C), 54.9 (C), 50.7 (CH_2), 47.7 (CH_2), 43.6 (CH), 36.0 (CH_2), 33.7 (CH_2), 28.5 (CH), 25.0 (CH_2), 18.7 (CH_3); IR (neat) 2957 (s), 2878 (s), 1709 (s), 1462 (s), 1377 (s) , 1290 (s), 1084 (m), 1041 (m), 964 (w), 916 (w), 881 (m), 733 (s) cm^{-1}; HRMS (EI) *m/z* 186.0807 [(M^+) calcd. for $C_{10}H_{15}O^{35}Cl$: 186.0811].



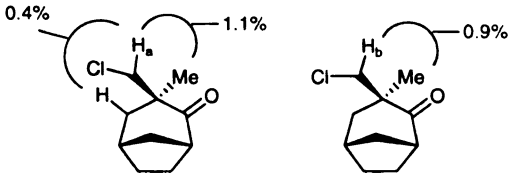
11 **11**

(+/-)-(1*R, 2*R**, 5*S**)-2-chloromethyl-2-methyl-bicyclo[3.2.1]octan-3-one (11).**

Following general procedure V, the reaction of 0.52 g (3.4 mmol) of starting carbinol **9**, afforded 0.18 g (28%) of **11** after purification *via* flash silica chromatography (20 g; 50:1 hexanes/EtOAc).

11: R_f = 0.61 (5:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.78 (d, *J* = 7.2 Hz, 1 H), 3.68 (d, *J* = 6.9 Hz, 1 H), 2.61 (dm, *J* = 9.6 Hz, 1 H), 2.51 (series of m, 2 H), 2.12 (series of m, 2 H), 1.77-1.52 (series of m, 4 H), 1.23 (m, 1 H), 1.26 (s, 3 H); ^{1}H-NMR (500 MHz, C_6D_6) δ 3.86 (d, *J* = 11.7 Hz, 1 H), 3.66 (d, *J* = 11.7 Hz, 1 H), 2.30 (t, *J* = 4.4

Hz, 1 H), 2.10 (dd, J = 12.6, 4.4 Hz, 1 H), 1.91 (t, J = 4.4 Hz, 1 H), 1.86 (d, J = 3.8 Hz, 1 H), 1.56 (d, J = 12.0 Hz, 1 H), 1.28 (m, 3 H), 1.04 (m, 1 H), 1.00 (m, 1 H), 0.96 (d, J = 0.9 Hz, 3 H); For 1-D NOE correlations see figure shown above; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 214.3 (C), 53.0 (C), 50.1 (CH), 47.3 (CH_2), 41.7 (CH), 35.6 (CH), 33.6 (CH_2), 28.2 (CH_2), 24.8 (CH_2), 22.0 (CH_3); IR (neat) 2953 (s), 2878 (ms), 1703 (s), 1460(m), 1288 (m), 1066 (m), 981 (w), 887 (w), 713 (m) cm^{-1}; HRMS (EI) *m/z* 186.0808 [(M^+) calcd. for $C_{10}H_{15}O^{35}Cl$: 186.0811].

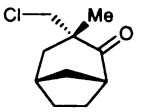


12 12

(+/-)-(1*R, 3*R**, 5*S**)-3-chloromethyl-3-methyl-bicyclo[3.2.1]octan-2-one (12).**

Following general procedure V, the reaction of 0.52 g (3.4 mmol) of starting carbinol **9**, as a 4:1 mixture, afforded 0.12 g (19%) of **12** after purification *via* flash silica chromatography (20 g; 50:1 hexanes/EtOAc).

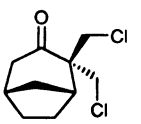
12: R_f = 0.61 (5:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.82 (d, J = 6.3 Hz, 1 H), 3.10 (d, J = 6.3 Hz, 1 H), 2.77 (t, J = 3.0 Hz, 1 H), 2.49 (m, 1 H), 2.32 (dd, J = 8.4, 2.7 Hz, 1 H), 1.94 (series of m, 4 H), 1.69 (series of m, 2 H), 1.58 (dt, J = 8.4, 1.5 Hz, 1 H), 1.20 (s, 3 H); For 1-D NOE correlations see figure shown above; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 214.8 (C), 53.1 (CH_2), 50.8 (CH), 47.7 (C), 40.8 (CH_2), 34.7 (CH), 34.3 (CH_2), 28.7 (CH_2), 28.3 (CH_3), 28.1 (CH_2); IR (neat) 2955 (s), 2876 (s), 1709 (s), 1448 (s), 1288 (s), 1068 (m), 960 (m), 918 (m), 736 (s) cm^{-1}; HRMS (EI) *m/z* 186.0801 [(M^+) calcd. for $C_{10}H_{15}O^{35}Cl$: 186.0811].



13

(+/-)-(1*R, 3*S**, 5*S**)-3-chloromethyl-3-methyl-bicyclo[3.2.1]octan-2-one (13).**

Following general procedure V, the reaction of 0.52 g (3.4 mmol) of starting carbinol **9**, afforded 0.03 g (6%) of **19**, based on ^{1}H-NMR. Compound **13** was never isolated in pure form and as a result spectral information is not available. It's isolation as a mixture with other regio and diastereomers allowed for its identification due to its inherent signature ^{1}H-NMR signals and 1-D NOE correlations. See Johnson, C. R.; Herr, R. W. *J. Org. Chem.* **1973**, *38*, 3153-3159.



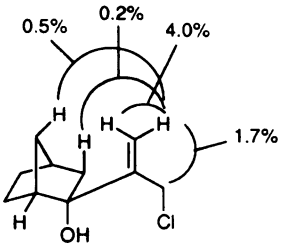
54

(+/-)-(1*R, 5*S**)-2,2-bis-chloromethyl-bicyclo[3.2.1]octan-3-one (54).**

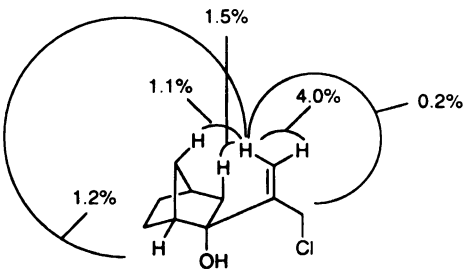
Following general procedure V, the reaction of 0.52 g (3.4 mmol) of starting carbinol **9**, as a 4:1 mixture, afforded 6.1 mg (~1%) of **54** after purification *via* flash silica chromatography (20 g; 50:1 hexanes/EtOAc).

54: R_f = 0.59 (5:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.18 (d, *J* = 7.5 Hz, 1 H), 4.00 (dd, *J* = 6.9, 0.9 Hz, 1 H), 3.85 (d, *J* = 6.9 Hz, 1 H), 3.64 (dd, *J* = 7.2, 0.9 Hz, 1 H), 2.59 (m, 3 H), 2.24 (dt, *J* = 8.7, 1.8 Hz, 1 H), 2.13 (d, *J* = 7.5 Hz, 1 H), 1.71 (m, 2 H), 1.58 (m, 2 H), 1.40 (m, 1 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 209.1 (C), 57.7 (C), 47.8 (CH_2), 45.0 (CH_2), 44.8 (CH_2), 40.9 (CH), 36.4 (CH), 33.6 (CH_2), 27.6 (CH_2), 25.2 (CH_2); IR (neat) 2959 (s), 2880 (m), 1714 (s), 1460 (m), 1439 (m), 1288 (m), 1190 (w),

1097 (w), 870 (w), 787 (s), 761 (s) cm^{-1}; HRMS (EI) *m/z* 220.0426 [(M^+) calcd. for $C_{10}H_{14}O^{35}Cl_2$: 220.0422].



55

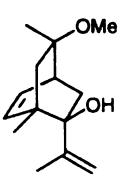


55

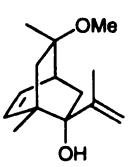
(+/-)-(1*R, 2*S**, 4*R**)-2-(1-chloromethyl-vinyl)-bicyclo[2.2.1]heptan-2-ol (55).**

Following general procedure V, the reaction of 0.52 g (3.4 mmol) of starting carbinol **9**, as a 4:1 mixture, afforded 0.06 g (10%) of **55** after purification *via* flash silica chromatography (20 g; 50:1 hexanes/EtOAc).

55: R_f = 0.45 (5:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.33 (s, 1 H), 5.26 (s, 1 H), 4.24 (d, *J* = 12.5 Hz, 1 H), 4.20 (d, *J* = 12.5 Hz, 1 H), 2.44 (m, 1 H), 2.38 (br s, 1 H), 2.23 (m, 1 H), 2.04 (dm, *J* = 5.1 Hz, 2 H), 1.60 (series of m, 2 H), 1.42 (dt, *J* = 7.5, 2.7 Hz, 1 H), 1.36 (m, 1 H), 1.30 (dp, *J* = 6.0, 1.2 Hz, 1 H), 1.22 (dd, *J* = 7.8, 2.1 Hz, 1 H); For 1-D NOE correlations see figure shown above; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 150.22 (C), 114.2 (CH_2), 81.0 (C), 45.7 (CH), 45.0 (CH_2), 44.8 (CH_2), 38.7 (CH_2), 37.0 (CH), 28.6 (CH_2), 21.9 (CH_2); IR (neat) 3428 (br m), 2959 (s), 2872 (m), 1690 (w), 1610 (w), 1454 (m), 1309 (m), 1163 (m), 1026 (m), 958 (m), 912 (m), 788 (s), 761 (s) cm^{-1}; HRMS (EI) *m/z* 186.0815 [(M^+) calcd. for $C_{10}H_{15}O^{35}Cl$: 186.0811].



58



59

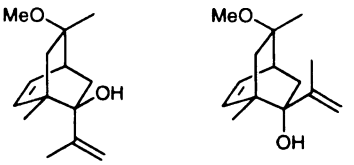
(1*S*, 2*R***, 4*S***, 8*R***)-1,8-dimethyl-2-isopropenyl-8-methoxybicyclo[2.2.2]oct-5-en-2-ol (58) and (1*S***, 2*S***, 4*S***, 8*R***)-1,8-dimethyl-2-isopropenyl-8-methoxybicyclo[2.2.2]oct-5-en-2-ol (59).**

Following general procedure I, the reaction of 1.00 g (5.5 mmol) of starting ketone **27**, afforded 0.91 g (81%) of **58:59**, as a 4:1 diastereomeric mixture, after purification *via* flash alumina chromatography (25 g; basic Activity III, 50:1 hexanes/EtOAc).

58: R_f = 0.42 (5:1 hexanes/EtOAc); $[\alpha]_{546}^{20}$ = -50.1 (*c* 0.63, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.11 (t, *J* = 6.6 Hz, 1 H), 5.94 (d, *J* = 7.2 Hz, 1 H), 5.11 (d, *J* = 2.4 Hz, 1 H), 4.78 (AB_q, *J* = 2.4, 1.2 Hz, 1 H), 3.19 (s, 3 H), 2.68 (m, 1 H), 2.24 (d, *J* = 13.8 Hz, 1 H), 1.98 (d, *J* = 13.8 Hz, 1 H), 1.76 (dd, *J* = 14.4, 3.3 Hz, 1 H), 1.66 (dd, *J* = 13.8, 2.4 Hz, 1 H), 1.58 (s, 3 H), 1.38 (s, 1 H), 1.11 (s, 3 H), 0.94 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 148.7 (C), 141.5 (CH), 131.7 (CH), 111.6 (CH_2), 78.7 (C), 77.6 (C), 49.8 (CH_3), 47.3 (CH_2), 43.7 (C), 40.6 (CH), 30.3 (CH_2), 24.7 (CH_3), 21.5 (CH_3), 18.7 (CH_3); IR (neat) 3493 (m), 3040 (w), 2961 (s), 2872 (m), 1680 (w), 1620 (w), 1452 (s), 1371 (s), 1101 (s), 1062 (s), 918 (m), 904 (m), 879 (w), 736 (m) cm^{-1}; HRMS (EI) *m/z* 222.1622 [(M^+) calcd. for $C_{14}H_{22}O_2$: 222.1620].

59: R_f = 0.21 (5:1 hexanes/EtOAc); $[\alpha]_{546}^{20}$ = -81.0 (*c* 0.65, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.33 (t, *J* = 6.9 Hz, 1 H), 5.83 (d, *J* = 7.8 Hz, 1 H), 5.20 (d, *J* = 1.8 Hz, 1 H), 4.99 (t, *J* = 1.8 Hz, 1 H), 3.10 (s, 3 H), 2.54 (m, 1 H), 2.53 (d, *J* = 12.6 Hz, 1 H), 1.86 (d, *J* = 14.1 Hz, 1 H), 1.82 (s, 3 H), 1.21 (s, 1 H), 1.14 (d, *J* = 14.4 Hz, 1 H), 1.12 (d, *J* = 13.8 Hz, 1 H), 1.07 (s, 3 H), 1.00 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 147.1 (C), 138.0 (CH), 135.0 (CH), 114.0 (CH_2), 79.8 (C), 79.4 (C), 49.2 (CH_3), 45.8 (C), 41.4 (CH_2),

41.0 (CH), 40.9 (CH_2), 24.9 (CH_3), 22.1 (CH_3), 19.5 (CH_3); IR (neat) 3501 (br m), 3090 (w), 2966 (s), 2932 (s), 2878 (m), 2826 (m), 1697 (m), 1664 (s), 1454 (s), 1367 (s), 1101 (s), 1072 (s), 939 (m), 810 (w), 690 (w) cm^{-1}; HRMS (EI) *m/z* 222.1624 [(M^+) calcd. for $C_{14}H_{22}O_2$: 222.1620].



62 **63**

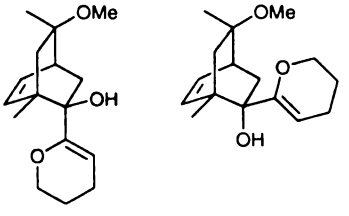
(1*S, 2*R**, 4*S**, *8S**)-1,8-dimethyl-2-isopropenyl-8-methoxybicyclo[2.2.2]oct-5-en-2-ol (62) and (1*S**, 2*S**, 4*S**, 8*S**)-1,8-dimethyl-2-isopropenyl-8-methoxybicyclo[2.2.2]oct-5-en-2-ol (63).**

Following general procedure I, the reaction of 2.00 g (11.1 mmol) of starting ketone **28**, afforded 1.93 g (78%) of **62:63**, as a 2.5:1 diastereomeric mixture, after purification *via* flash alumina chromatography (60 g; basic Activity III, 50:1 hexanes/EtOAc).

62: R_f = 0.64 (5:1 hexanes/EtOAc); $[\alpha]_{546}^{20}$ = -64.2 (*c* 0.80, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.19 (AB_q, *J* = 6.3, 1.8 Hz, 1 H), 5.96 (d, *J* = 7.8 Hz, 1 H), 4.99 (d, *J* = 1.2 Hz, 1 H), 4.81 (t, *J* = 1.5 Hz, 1 H), 3.13 (s, 3 H), 2.69 (m, 1 H), 2.06 (d, *J* = 12.9 Hz, 1 H), 1.73 (dd, *J* = 14.1, 3.3 Hz, 1 H), 1.63, (d, *J* = 0.6 Hz, 3 H), 1.62 (dd, *J* = 13.8, 3.0 Hz, 1 H), 1.46 (s, 3 H), 1.22 (s, 1 H), 1.10 (d, *J* = 12.9 Hz, 1 H), 0.947 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 151.2 (C), 137.5 (CH), 132.2 (CH), 111.3 (CH_2), 79.1 (C), 78.9 (C), 48.8 (CH_3), 45.7 (CH_2), 43.3 (C), 40.6 (CH), 39.2 (CH_2), 22.5 (CH_3), 21.6 (CH_3), 18.7 (CH_3); IR (neat) 491 (br m), 3040 (m), 2932 (s), 2824 (s), 1726 (s), 1710 (w), 1454 (s), 1373 (s),

1134 (s), 1080 (s), 991 (m), 897 (m), 733 (s) cm^{-1}; HRMS (EI) *m/z* 222.1624 [(M^+) calcd. for $C_{14}H_{22}O_2$: 222.1620].

63: R_f = 0.52 (5:1 hexanes/EtOAc); $[\alpha]_{546}^{20}$ = -76.0 (*c* 0.25, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.45 (AB_q, *J* = 6.3 Hz, 1 H), 5.91 (d, *J* = 7.2 Hz, 1 H), 5.04 (t, *J* = 1.5 Hz, 1 H), 4.87 (s, 1 H), 3.15 (s, 3 H), 2.99 (m, 1 H), 2.09 (d, *J* = 13.5 Hz, 1 H), 1.86 (d, *J* = 0.6 Hz, 3 H), 1.69 (dd, *J* = 14.7, Hz, 1 H), 1.42 (dd, *J* = 11.1, 2.1 Hz, 1 H), 1.34 (s, 3 H), 1.33 (s, 1 H), 1.22 (d, *J* = 12.9 Hz, 1 H), 1.16 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 136.8 (C), 135.4 (CH), 132.5 (CH), 113.0 (CH_2), 79.2 (C), 77.2 (C), 49.4 (CH_3), 46.3 (CH_2), 41.2 (CH), 40.5 (C), 36.2 (CH_2), 22.3 (CH_3), 19.8 (CH_3), 17.2 (CH_3); IR (neat) 3491 (s), 3090 (w), 2932 (s), 2824 (s), 1701 (s), 690 (w), 1454 (s), 1336 (s), 1115 (s), 1080 (s), 1010 (m), 897 (s), 680 (m-s) cm^{-1}; HRMS (EI) *m/z* 222.1708 [M^+) calcd. for $C_{14}H_{22}O_2$: 222.1620].



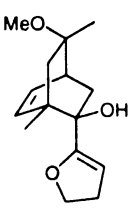
60 **61**

(1*S, 2*R**, 4*S**, 8*R**)-2-(2,3)-dihyropyranyl-8-methoxy-1,8-dimethyl-bicyclo[2.2.2]oct-5-en-2-ol (60) and (1*S**, 2*S**, 4*S**, 8*R**)-2-(2,3)-dihyropyranyl-8-methoxy-1,8-dimethyl-bicyclo[2.2.2]oct-5-en-2-ol (61).**

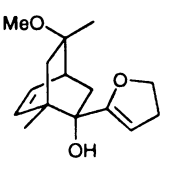
Following general procedure II, the reaction of 1.99 g (11.08 mmol) of starting ketone **27**, afforded 2.19 g (75%) of **60:61**, as a 10:1 diastereomeric mixture, after purification *via* flash alumina chromatography (60 g; basic Activity III, 50:1 hexanes/EtOAc).

60: R_f = 0.50 (5:1 hexanes/EtOAc); $[\alpha]_{546}^{20}$ = -51.0 (*c* 0.19, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.07 (t, *J* = 7.5 Hz, 1 H), 5.93 (d, *J* = 7.8 Hz, 1 H), 4.96 (t, *J* = 3.6 Hz, 1 H), 3.88 (m, 2 H), 3.61 (s, 1 H), 3.21 (s, 3 H), 2.64 (m, 1 H), 2.02 (m, 2 H), 1.96 (d, *J* = 13.8 Hz, 1 H), 1.74 (m, 4 H), 1.12 (s, 3 H), 0.96 (s, 3 H), 0.95 (d, *J* = 13.8 Hz, 1 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 152.7 (C), 138.2 (CH), 132.3 (CH), 98.8 (CH), 79.5 (C), 78.1 (C), 65.9 (CH_2), 49.1 (CH_3), 44.4 (C), 42.1 (CH_2), 40.6 (CH), 37.4 (CH_2), 24.9 (CH_3), 22.1 (CH_2), 20.2 (CH_2), 19.4 (CH_3); IR (neat) 3543 (br s), 3050 (w), 2937 (s), 2874 (m), 2830 (m), 1714 (s), 1458 (m), 1369 (m), 1284 (w), 1105 (s), 1066 (s), 796 (m), 680 (m) cm^{-1}; HRMS (EI) *m/z* 264.1719 [M^+) calcd. for $C_{16}H_{24}O_3$: 264.1725].

61: R_f = 0.30 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.25 (t, *J* = 7.8 Hz, 1 H), 5.82 (d, *J* = 7.8 Hz, 1 H), 5.19 (t, *J* = 3.9 Hz, 1 H), 3.95 (t, *J* = 5.4 Hz, 2 H), 3.15 (s, 3 H), 2.52 (m, 1 H), 2.40 (dd, *J* = 14.4, 1.8 Hz, 1 H), 2.04 (m, 2 H), 1.85 (d, *J* = 13.8 Hz, 1 H), 1.77 (m, 2 H), 1.37 (s, 1 H), 1.30 (dd, *J* = 14.4, 3.3 Hz, 1 H), 1.08 (s, 3 H), 0.98 (s, 3 H), 0.82 (d, *J* = 13.8 Hz, 1 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 155.6 (C), 140.2 (CH), 134.5 (CH), 95.8 (CH), 80.1 (C), 78.6 (C), 66.4 (CH_2), 49.2 (CH_3), 45.3 (C), 42.2 (CH_2), 40.8 (CH), 37.6 (CH_2), 25.3 (CH_3), 22.9 (CH_2), 20.3 (CH_2), 19.9 (CH_3); IR (neat) 3439 (br s), 3044 (w), 2934 (s), 2872 (s), 2826 (m), 1709 (s), 1458 (s), 1365 (s), 1255 (m), 1085 (s), 1066 (s), 987 (w), 846 (w), 734 (m) cm^{-1}; HRMS (EI) *m/z* 264.1739 [M^+) calcd. for $C_{16}H_{24}O_3$: 264.1725].



64



65

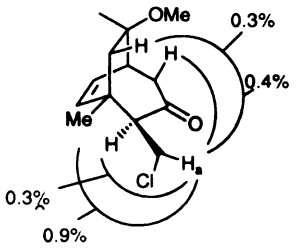
(1*S*, 2*R***, 4*S***, 8*S***)-1,8-dimethyl-2-(2,3)-dihydrofuryl-8-methoxybicyclo[2.2.2]oct-5-en-2-ol (64) and (1*S***, 2*S***, 4*S***, 8*S***)-1,8-dimethyl-2-(2,3)-dihydrofuryl-8-methoxybicyclo[2.2.2]oct-5-en-2-ol (65).**

Following general procedure II, the reaction of 0.97 g (5.3 mmol) of starting ketone **28**, afforded 0.79 g (75%) of **64:65**, as a 2.5:1 diastereomeric mixture, after purification *via* flash alumina chromatography (40 g; neutral Activity III, 30:1 hexanes/EtOAc).

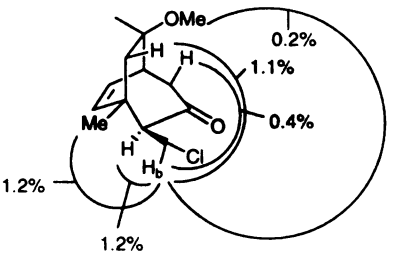
64: R_f = 0.15 (4:1 hexanes/EtOAc); $[\alpha]_{546}^{20}$ = -67.0 (*c* 0.32, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.39 (AB_q, *J* = 8.1, 1.5 Hz, 1 H), 5.97 (d, *J* = 8.1 Hz, 1 H), 4.92 (t, *J* = 2.4 Hz, 1 H), 4.32 (t, *J* = 9.6 Hz, 2 H), 3.09 (s, 3 H), 2.68 (m, 1 H), 2.62 (td, *J* = 9.3, 2.7 Hz, 2 H), 2.23 (dd, *J* = 15.0, 1.5 Hz, 1 H), 2.04 (s, 1 H), 1.82 (d, *J* = 14.1 Hz, 1 H), 1.35 (s, 3 H), 1.21 (d, *J* = 9.3 Hz, 1 H), 1.13 (d, *J* = 9.3 Hz, 1 H), 1.09 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.4 (C), 136.1 (CH), 133.9 (CH), 97.2 (CH), 79.5 (C), 76.5 (C), 70.2 (CH_2), 48.9 (CH_3), 43.7 (CH_2), 43.4 (C), 39.9 (CH), 38.6 (CH_2), 29.9 (CH_2), 21.1 (CH_3), 19.3 (CH_3); IR (neat) 3466 (br m), 3090 (w), 2936 (s), 2872 (s), 2824 (m), 1707 (m), 1680 (w), 1456 (s), 1136 (s), 1080 (s), 970 (s), 941 (s), 830 (w), 731 (s) cm^{-1}; HRMS (EI) *m/z* 250.1568 [(M^+), calcd. for $C_{15}H_{22}O_3$: 250.1569].

65: R_f = 0.31 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.30 (t, *J* = 7.2 Hz, 1 H), 5.85 (d, *J* = 8.1 Hz, 1 H), 5.08 (t, *J* = 2.4 Hz, 1 H), 4.32 (dt, *J* = 9.3, 3.3 Hz, 2 H), 3.17 (s, 3 H), 2.65 (series of m, 2 H), 2.55 (m, 1 H), 2.49 (dd, *J* = 13.8, 2.1 Hz, 1 H), 1.86 (d, *J* = 13.8 Hz, 1 H), 1.63 (d, *J* = 14.7 Hz, 1 H), 1.38 (dd, *J* = 14.4, 3.3 Hz, 1 H), 1.22 (s, 1 H), 1.11 (s, 3 H), 1.07 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.7 (C), 137.6 (CH), 133.0 (CH), 97.7 (CH), 79.3 (C), 76.1 (C), 69.8 (CH_2), 49.2 (CH_3), 44.0 (CH_2), 42.5

(CH), 40.4 (CH_2), 38.5 (C), 30.5 (CH_2), 24.8 (CH_3), 19.4 (CH_3); IR (neat) 3468 (br s), 3061 (m), 2974 (s), 1710 (m), 1651 (s), 1456 (s), 1365 (s), 1163 (s), 1070 (s), 1008 (s), 939 (s), 852, (m), 733 (s) cm^{-1}; HRMS (EI) *m/z* 250.1572 [(M^+), calcd. for $C_{15}H_{22}O_3$: 250.1569].



66



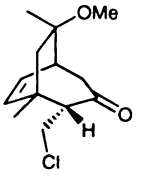
66

(1*S, 2*S**, 5*S**, 9*R**)-2-chloromethyl-1,9-dimethyl-9-methoxybicyclo[3.2.2]non-6-en-3-one (66).**

Following general procedure V, the reaction of 0.35 g (1.4 mmol) of starting carbinol **1**, afforded 0.11 g (32%) of **66** after purification *via* flash silica chromatography (3 g; 75:1 hexanes/EtOAc).

66: R_f = 0.33 (5:1 hexanes/EtOAc); $[\alpha]_{546}^{20}$ = -49.4 (*c* 0.68, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.28 (AB_q, *J* = 7.8, 1.2 Hz, 1 H), 5.83 (d, *J* = 9.0 Hz, 1 H), 3.74 (dd, *J* = 11.4, 4.2 Hz, 1 H), 3.49 (dd, *J* = 11.4, 8.4 Hz, 1 H), 3.15 (s, 3 H), 2.79 (dd, *J* = 15.9, 5.4 Hz, 1 H), 2.64 (m, 1 H), 2.59 (dd, *J* = 8.4, 4.2 Hz, 1 H), 2.19 (dd, *J* = 13.2, 2.4 Hz, 1 H), 1.94 (d, *J* = 14.4 Hz, 1 H), 1.43 (d, *J* = 15.0 Hz, 1 H), 1.23 (s, 3 H), 1.17 (s, 3 H); For 1-D NOE correlations see figure shown above; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 208.5 (C), 136.1 (CH), 133.6 (CH), 78.5 (C), 66.6 (CH), 49.7 (CH_2), 49.3 (CH_3), 42.6 (CH_2), 41.3 (CH_2), 40.3 (CH), 36.5 (C), 29.6 (CH_3), 26.9 (CH_3); IR (neat) 3070 (w), 2961 (s), 2928

(s), 2855 (m), 1684 (s), 1599 (m), 1462 (s), 1371 (s), 1257 (m), 1134 (s), 1064 (s), 765 (m) cm^{-1}; HRMS (EI) *m/z* 242.1163 [(M^+); calcd. for $C_{13}H_{19}O_2{}^{35}Cl$: 242.1074].

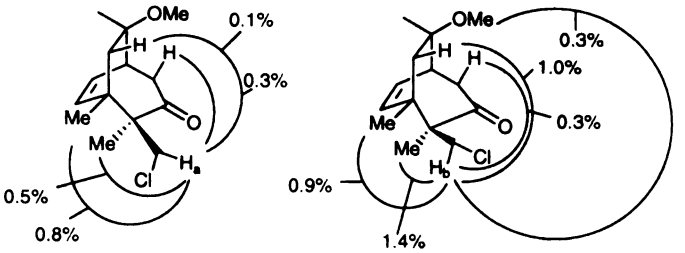


67

(1*S, 2*R**, 5*S**, 9*R**)-2-chloromethyl-1,9-dimethyl-9-methoxybicyclo[3.2.2]non-6-en-3-one (67).**

Following general procedure V, the reaction of 0.12 g (0.57 mmol) of starting carbinol **2**, afforded 0.05 g (36%) of **67** after purification *via* flash silica chromatography (3.5 g; 5:1 hexanes/EtOAc).

67: R_f = 0.26 (5:1 hexanes/EtOAc); $[\alpha]_{546}^{20}$ = -20.0 (*c* 0.14, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.28 (AB_q, *J* = 8.7, 1.1 Hz, 1 H), 5.84 (d, *J* = 9.3 Hz, 1 H), 3.74 (dd, *J* = 11.5, 3.9 Hz, 1 H), 3.50 (dd, *J* = 11.5, 8.2 Hz, 1 H), 3.16 (s, 3 H), 2.78 (dd, *J* = 15.3, 4.9 Hz, 1 H), 2.65 (m, 1 H), 2.60 (dd, *J* = 7.7, 3.3 Hz, 1 H), 2.19 (dd, *J* = 15.9, 2.7 Hz, 1 H), 1.93 (d, *J* = 14.2 Hz, 1 H), 1.35 (d, *J* = 14.3 Hz, 1 H), 1.18 (s, 3 H), 1.17 (s, 3 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 224.1 (C), 136.8 (CH), 132.2 (CH), 78.3 (C), 78.0 (CH), 50.0 (CH_3), 49.7 (CH_2), 41.0 (CH), 34.5 (CH_2), 29.9 (CH_2), 28.0 (CH_3), 24.3 (C), 22.6 (CH_3); IR (neat) 3023 (w), 2918 (s), 2849 (s), 1724 (w), 1603 (w), 1462 (m), 1379 (m), 1120 (ms), 1074 (m), 935 (w), 844 (w), 758 (m) cm^{-1}; HRMS (EI) *m/z* 242.1087 [(M^+); calcd. for $C_{13}H_{19}O_2{}^{35}Cl$: 242.1074].

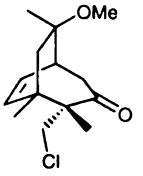


68 68

(1*S, 2*S**, 5*S**, 9*R**)-2-chloromethyl-1,2,9-trimethyl-9-methoxybicyclo[3.2.2]non-6-en-3-one (68).**

Following general procedure V, the reaction of 67.8 mg (0.30 mmol) of starting carbinol **58**, afforded 67.2 mg (86%) of **68:69**, as a 20:1 diastereomeric mixture, and 7.8 mg (10%) of **72** after purification *via* flash silica chromatography (1.0 g; 50:1 to 5:1 hexanes/EtOAc).

68: R_f = 0.83 (5:1 hexanes/EtOAc); $[\alpha]_{546}^{20}$ = -60.0 (*c* 0.10, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.20 (AB_q, *J* = 8.8, 1.3 Hz, 1 H), 5.82 (d, *J* = 8.8 Hz, 1 H), 3.87 (d, *J* = 11.0 Hz, 1 H), 3.77 (d, *J* = 11.4 Hz, 1 H), 3.17 (s, 3 H), 2.94 (dd, *J* = 15.9, 3.9 Hz, 1 H), 2.63 (d, *J* = 15.4 Hz, 1 H), 2.54 (m, 1 H), 2.32 (dd, *J* = 15.9, 3.9 Hz, 1 H), 1.25 (d, *J* = 15.4 Hz, 1 H), 1.19 (s, 3 H), 1.15 (s, 3 H), 1.06 (s, 3 H); For 1-D NOE correlations see figure shown above; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 209.9 (C), 139.8 (CH), 132.7 (CH), 78.3 (C), 58.1 (C), 49.3 (CH_3), 47.2 (CH_2), 45.9 (CH_2), 40.8 (CH_2), 40.0 (CH), 39.4 (C), 27.1 (CH_3), 24.6 (CH_3), 21.2 (CH_3); IR (neat) 3034 (m), 2932 (s), 2828 (m), 1701 (s), 1458 (s), 1371 (s), 1277 (m), 1140 (s), 1064 (s), 916 (m), 738 (s), 680 (s) cm^{-1}; HRMS (EI) *m/z* 256.1238 [(M^+); calcd. for $C_{14}H_{21}O_2{}^{35}Cl$: 256.1230].

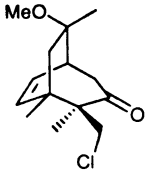


69

(1*S, 2*R**, 5*S**, 9*R**)-2-chloromethyl-1,2,9-trimethyl-9-methoxybicyclo[3.2.2]non-6-en-3-one (69).**

Following general procedure V, the reaction of 0.14 g (0.65 mmol) of starting carbinol **59**, afforded 0.13 g (82%) of **68:69**, as a 1:12 diastereomeric mixture, and 26.9 mg (16%) of **73** after purification *via* flash silica chromatography (1.0 g; 50:1 to 5:1 hexanes/EtOAc).

69: R_f = 0.42 (5:1 hexanes/EtOAc); $[\alpha]_{546}^{20}$ = -48.0 (*c* 0.02, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.29 (AB_q, *J* = 8.7, 0.9 Hz, 1 H), 5.90 (d, *J* = 9.0 Hz, 1 H), 3.64 (d, *J* = 3.0 Hz, 2 H), 3.15 (s, 3 H), 2.82 (dd, *J* = 15.6, 5.1 Hz, 1 H), 2.57 (m, 1 H), 2.37 (dd, *J* = 15.6, 2.7 Hz, 1 H), 2.06 (d, *J* = 15.3 Hz, 1 H), 1.16 (s, 3 H), 1.15 (s, 3 H), 1.12 (d, *J* = 15.6 Hz, 1 H), 1.07 (s, 3 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 212.3 (C), 135.7 (CH), 134.4 (CH), 78.8 (C), 56.9 (C), 50.3 (CH_3), 49.6 (CH_2), 45.9 (CH_2), 41.6 (CH), 40.8 (CH_2), 34.6 (C), 29.6 (CH_3), 24.8 (CH_3), 22.6 (CH_3); IR (neat) 3093 (w), 2986 (s), 2804 (s), 2777 (s), 1728 (s), 1705 (m), 1458 (s), 1383 (s), 1298 (m), 1116 (s), 1076 (s), 935 (m), 844 (m), 752 (m) cm^{-1}; HRMS (EI) *m/z* 256.1233 [(M^+); calcd. for $C_{14}H_{21}O_2{}^{35}Cl$: 256.1230].

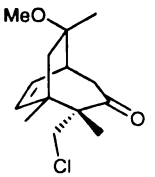


70

(1*S, 2*S**, 5*S**, 9*S**)-2-chloromethyl-1,2,9-trimethyl-9-methoxybicyclo[3.2.2]non-6-en-3-one (70).**

Following general procedure V, the reaction of 0.30 g (1.3 mmol) of starting carbinol **62**, afforded 0.27 g (78%) of **70:71**, as a 15:1 diastereomeric mixture, after purification *via* flash silica chromatography (1.0 g; 50:1 to 5:1 hexanes/EtOAc).

70: R_f = 0.25 (4:1 hexanes/EtOAc); $[\alpha]_{546}^{20}$ = -72.0 (*c* 0.15, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.28 (AB_q, *J* = 7.2, 1.5 Hz, 1 H), 5.87 (d, *J* = 9.0 Hz, 1 H), 3.91 (d, *J* = 11.4 Hz, 1 H), 3.57 (d, *J* = 12.0 Hz, 1 H), 3.08 (s, 3 H), 2.96 (m, 1 H), 2.57 (d, *J* = 15.6 Hz, 1 H), 2.48 (d, *J* = 13.8 Hz, 1 H), 1.72 (d, *J* = 14.7 Hz, 1 H), 1.56 (d, *J* = 15.3 Hz, 1 H), 1.21 (s, 3 H), 1.19 (s, 3 H), 1.03 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 211.1 (C), 138.2 (CH), 132.5 (CH), 79.2 (C), 58.1 (C), 49.4 (CH_3), 46.3 (CH_2), 46.1 (CH_2), 41.2 (CH), 37.7 (C), 36.2 (CH_2), 23.9 (CH_3), 23.1 (CH_3), 17.2 (CH_3); IR (neat) 3090 (w), 2972 (s), 2934 (s), 2826 (m), 1724 (s), 1697 (s), 1454 (m), 1375 (m), 1134 (s), 1082 (s), 848 (w), 750 (s), 682 (m) cm^{-1}; HRMS (EI) *m/z* 256.1240 [(M^+); calcd. for $C_{14}H_{21}O_2{}^{35}Cl$: 256.1230].



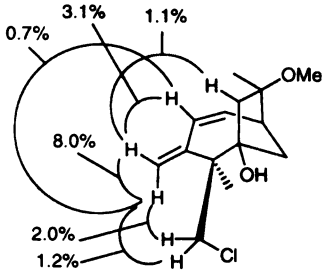
71

(1*S, 2*R**, 5*S**, 9*S**)-2-chloromethyl-1,2,9-trimethyl-9-methoxybicyclo[3.2.2]non-6-en-3-one (71).**

Following general procedure V, the reaction of 0.32 g (1.4 mmol) of starting carbinol **63**, afforded 0.28 g (76%) of **70:71**, as a 1:11 diastereomeric mixture, after purification *via* flash silica chromatography (1.0 g; 50:1 to 5:1 hexanes/EtOAc).

71: R_f = 0.42 (5:1 hexanes/EtOAc); $[\alpha]_{546}^{20}$ = -53.0 (*c* 0.06, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.44 (AB_q, *J* = 6.3, 1.8 Hz, 1 H), 5.90 (d, *J* = 7.2 Hz, 1 H), 3.45 (d, *J* = 12.6 Hz, 1 H), 3.38 (d, *J* = 12.0 Hz, 1 H), 3.14 (s, 3 H), 2.96 (m, 1 H), 2.56 (d, *J* = 17.4 Hz, 1 H),

2.45 (d, J = 14.1 Hz, 1 H), 1.33 (s, 3 H), 1.21 (s, 3 H), 1.18 (d, J = 16.2 Hz, 1 H), 1.15 (s, 3 H), 1.11 (d, J = 15.6 Hz, 1 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 212.3 (C), 135.4 (CH), 131.8 (CH), 79.3 (C), 69.3 (C), 65.8 (CH_2), 49.1 (CH_3), 46.8 (CH_2), 41.9 (CH_2), 38.3 (CH), 35.0 (C), 22.3 (CH_3), 22.0 (CH_3), 15.2 (CH_3); IR (neat) 3090 (w), 2972 (s), 2934 (s), 2826 (m), 1724 (s), 1697 (s), 1454 (m), 1375 (m), 1134 (s), 1082 (s), 848 (w), 750 (s), 682 (m) cm^{-1}; HRMS (EI) *m/z* 256.1248 [(M^+); calcd. for $C_{14}H_{21}O_2{}^{35}Cl$: 256.1230].



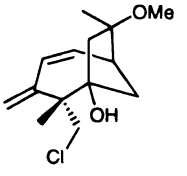
72

(1*R, 2*R**, 6*R**, 9*R**)-2-chloromethyl-2,9-dimethyl-9-methoxy-3-methylene-bicyclo[4.2.1]non-4-en-1-ol (72).**

Following general procedure V, the reaction of 67.8 mg (0.30 mmol) of starting carbinol **58**, afforded 67.2 mg (86%) of **68:69**, as a 20:1 diastereomeric mixture, and 7.8 mg (10%) of **72** after purification *via* flash silica chromatography (1.0 g; 50:1 to 5:1 hexanes/EtOAc).

72: R_f = 0.35 (5:1 hexanes/EtOAc); $[\alpha]_D^{20}$ = -15.9 (*c* 0.33, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.24 (t, J = 7.7 Hz, 1 H), 5.98 (d, J = 7.7 Hz, 1 H), 5.34 (d, J = 1.1 Hz, 1 H), 5.29 (s, 1 H), 4.17 (dd, J = 13.2, 1.1 Hz, 1 H), 4.05 (dd, J = 13.2, 1.1 Hz, 1 H), 3.52 (s, 1 H), 3.22 (s, 3 H), 2.72 (m, 1 H), 1.99 (d, J = 13.7 Hz, 1 H), 1.97 (dd, J = 14.3, 3.3 Hz, 1 H), 1.79 (dd, J = 13.7, 2.2 Hz, 1 H), 1.14 (s, 3 H), 0.98 (s, 3 H), 0.97 (d, J = 13.7 Hz, 1 H); For 1-D NOE correlations see figure shown above; ^{13}C-NMR (75 MHz, $CDCl_3$) δ

150.1 (C), 140.3 (CH), 133.4 (CH), 115.4 (CH_2), 78.5 (C), 76.8 (C), 49.7 (CH_3), 46.9 (CH_2), 45.5 (CH_2), 44.6 (C), 43.4 (CH_2), 40.7 (CH), 24.6 (CH_3), 18.8 (CH_3); IR (NaCl, neat) cm^{-1} 3560 (br m), 3015 (w), 2961 (s), 2934 (s), 2871 (m), 1728 (s), 1630 (w), 1590 (w), 1462 (m), 1379 (m), 1286 (s), 1124 (s), 1124 (s), 1072 (s), 962 (w), 918 (w), 742 (m); HRMS (EI) *m/z* 256.1219 [(M^+); calcd. for $C_{14}H_{21}ClO_2$: 256.7680].



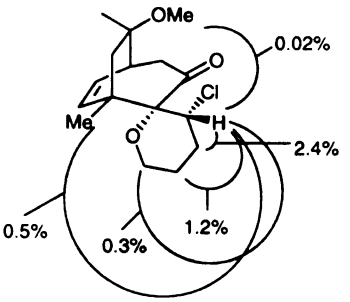
73

(1*R, 2*S**, 6*R**, 9*R**)-2-chloromethyl-2,9-dimethyl-9-methoxy-3-methylene-bicyclo[4.2.1]non-4-en-1-ol (73).**

Following general procedure V, the reaction of 0.14 g (0.65 mmol) of starting carbinol **59**, afforded 0.13 g (82%) of **68:69**, as a 1:12 diastereomeric mixture, and 26.9 mg (16%) of **73** after purification *via* flash silica chromatography (1.0 g; 50:1 to 5:1 hexanes/EtOAc).

135b: R_f = 0.42 (5:1 hexanes/EtOAc); $[\alpha]_D^{20}$ = -14.0 (*c* 0.17, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.40 (t, *J* = 7.7 Hz, 1 H), 5.89 (d, *J* = 8.2 Hz, 1 H), 5.71 (s, 1 H), 5.60 (s, 1 H), 4.33 (d, *J* = 12.6 Hz, 1 H), 4.20 (d, *J* = 12.6 Hz, 1 H), 3.18 (s, 3 H), 2.62 (m, 1 H), 2.57 (d, *J* = 14.8 Hz, 1 H), 1.77 (d, *J* = 14.8 Hz, 1 H), 1.56 (s, 1 H), 1.40 (dd, *J* = 14.8, 3.8 Hz, 1 H), 1.12 (s, 3 H), 1.02 (s, 3 H), 0.92 (d, *J* = 14.8 Hz, 1 H) ^{13}C-NMR (75 MHz, $CDCl_3$) δ 147.2 (C), 137.6 (CH), 135.2 (CH), 118.6 (CH_2), 80.1 (C), 79.4 (C), 49.3 (CH_3), 46.3 (CH_2), 45.2 (C), 42.0 (CH_2), 41.7 (CH_2), 41.0 (CH_2), 24.9 (CH_3), 19.2 (CH_3); IR (NaCl, neat) cm^{-1} 3544 (br w), 3015 (w), 2980 (s), 2932 (s), 2860 (s), 1706 (w), 1623

(w), 1458 (s), 1383 (s), 1350 (s), 1278 (m), 1124 (s), 1072 (s), 933 (m), 844 (m), 724 (m); HRMS (EI) *m/z* 256.3248 [(M^+); calcd. for $C_{14}H_{21}ClO_2$: 256.7680].

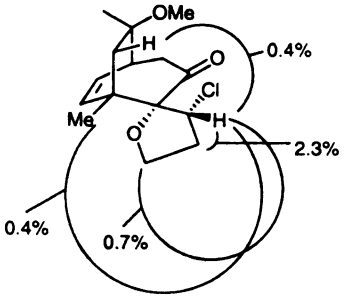


74

(1*S, 2*R**-(3*R**), 5*S**, 9*R**)-2-(3-chloro)-spiropyranyl-1,9-dimethyl-9-methoxybicyclo[3.2.2]non-6-en-3-one (74).**

Following general procedure V, the reaction of 0.12 g (0.48 mmol) of starting carbinol **60**, afforded 0.13 g (90%) of **74**, after purification *via* flash silica chromatography (1.0 g; 50:1 to 5:1 hexanes/EtOAc).

74: R_f = 0.08 (5:1 hexanes/EtOAc); $[\alpha]_{546}^{20}$ = +24.0 (*c* 0.20, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.16 (t, *J* = 6.6 Hz, 1 H), 6.02 (d, *J* = 6.6 Hz, 1 H), 4.96 (dd, *J* = 8.7, 3.8 Hz, 1 H), 3.65 (t, *J* = 5.5 Hz, 2 H), 3.21 (s, 3 H), 2.75 (m, 1 H), 1.95 (dd, *J* = 13.7, 3.3 Hz, 1 H), 1.93 (d, *J* = 14.2 Hz, 1 H), 1.86-1.75 (series of m, 4 H), 1.70 (dd, *J* = 13.7, 2.7 Hz, 1 H), 1.62 (m, 1 H), 1.13 (s, 3 H), 0.97 (s, 3 H), 0.94 (d, *J* = 14.2 Hz, 1 H); For 1-D NOE correlations see figure shown above; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 208.0 (C), 140.1 (CH), 131.3 (CH), 82.3 (C), 78.3 (C), 61.9 (CH_2), 57.4 (C), 49.7 (CH_3), 46.2 (CH_2), 43.7 (C), 42.2 (CH_2), 40.3 (CH), 29.1 (CH_2), 29.0 (CH_2), 24.4 (CH_3), 18.5 (CH_3); IR (neat) 3049 (w), 2932 (s), 1724 (s), 1643 (w), 1460 (s), 1367 (s), 1334 (s), 1286 (s), 1224 (s), 1169 (s), 1105 (s), 1062 (s), 910 (s), 846 (m), 756 (m), 731 (m), 704 (m), 667 (s) cm^{-1}; HRMS (EI) *m/z* 298.1244 [(M^+); calcd. for $C_{16}H_{23}O_3{}^{35}Cl$: 298.8047].

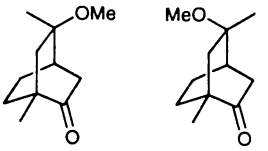


74

(1*S, 2*R**, 5*S**, 9*S**)-2-(3-chloro)-spirofuranyl-1,9-dimethyl-9-methoxybicyclo[3.2.2]non-6-en-3-one (75).**

Following general procedure V, the reaction of 0.35 g (1.4 mmol) of starting carbinol **64**, afforded 0.17 g (43%) of **75:76**, as a 7:1 diastereomeric mixture, after purification *via* flash silica chromatography (1.0 g; 50:1 to 5:1 hexanes/EtOAc).

75: R_f = 0.56 (4:1 hexanes/EtOAc); $[\alpha]_{546}^{20}$ = -91.0 (*c* 0.16, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.32 (AB_q, *J* = 8.3, 1.9 Hz, 1 H), 5.82 (d, *J* = 7.3 Hz, 1 H), 4.06 (m, 2 H), 3.03 (s, 3 H), 3.00 (t, *J* = 5.8 Hz, 1 H), 2.71 (dd, *J* = 7.3, 2.9 Hz, 2 H), 2.65 (m, 1 H), 2.42 (dd, *J* = 14.1, 7.3 Hz, 1 H), 2.33 (dd, *J* = 15. 1, 2.44 Hz, 1 H), 1.91 (d, *J* = 14.6 Hz, 1 H), 1.33 (d, *J* = 14.6 Hz, 1 H), 1.29 (s, 3 H), 1.06 (s, 3 H); For 1-D NOE correlations see figure shown above; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 208.5 (C), 135.2 (CH), 133.4 (CH), 111.6 (C), 85.4 (CH), 67.9 (C), 65.7 (CH_2), 43.8 (CH_3), 38.4 (CH_2), 37.2 (CH_2), 34.9 (C), 33.7 (CH), 25.9 (CH_2), 24.4 (CH_3), 19.0 (CH_3); IR (neat) 3110 (w), 2932 (s), 1721 (m), 1705 (m), 1454 (s), 1369 (s), 1300 (s), 1242 (s), 1217 (s), 1174 (s), 1082 (s), 925 (s), 879 (s), 781 (m), 756 (m), 734 (mw), 677 (mw) cm^{-1}; HRMS (EI) *m/z* 284.1205 [(M^+); calcd. for $C_{15}H_{21}O_3{}^{35}Cl$: 284.1179].



78 79

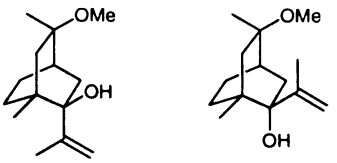
(1*S, 4*R**, 8*R**)-1,8-dimethyl-8-methoxybicyclo[2.2.2]octan-2-one (78) and (1*S**, 4*R**, 8*S**)-1,8-dimethyl-8-methoxybicyclo[2.2.2]octan-2-one (79).**

A solution containing 1.01 g (5.6 mmol, 1.00 eq) **27:28** and a spatula tip of Pd/C in 150 mL EtOAc was purged *via* an aspirator and subsequently charged with H_2. The reaction was stirred at room temperature for 16 hrs The reaction was then gravity filtered through celite and concentrated. The resultant oil was purified *via* flash silica chromatography (15 g; 4:1 hexanes/EtOAc) to afford 0.52 g (51%) of saturated **78** and 0.47 g (47%) of saturated **79** both as clear oils.

78: R_f = 0.75 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.01 (s, 3 H), 2.2-1.2 (series of m, 9 H), 1.04 (s, 3 H), 0.72 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 216.1 (C), 74.6 (C), 49.1 (CH_3), 45.9 (CH_2), 43.5 (C), 40.7 (CH), 35.9 (CH_2), 28.8 (CH_2), 22.7 (CH_3), 20.5 (CH_2), 19.6 (CH_3); IR (neat) 2934 (s), 2820 (m), 1720 (s), 1454 (s), 1454 (s), 1346 (s), 1134 (s), 1076 (s), 981 (w), 844 (w), 790 (m) cm^{-1}; HRMS (EI) *m/z* 182.1302 [(M^+), calcd. for $C_{11}H_{18}O_2$: 182.1307].

79: R_f = 0.50 (4:1 hexanes/EtOAc); $[\alpha]_D^{20}$ = -8.0 (*c* 0.12, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.93 (s, 3 H), 2.40 (dt, *J* = 18.9, 2.7 Hz, 1 H), 2.01 (t, *J* = 3.0 Hz, 1 H), 1.77 (dd, *J* = 18.6, 2.7 Hz, 1 H), 1.48 (d, *J* = 13.8 Hz, 1 H), 1.34 (d, *J* = 14.4 Hz, 1 H), 1.7-1.4 (series of m, 4 H), 1.14 (s, 3 H), 0.71 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 215.5 (C), 74.3 (C), 48.7 (CH_3), 45.6 (CH_2), 43.2 (CH_2), 40.3 (CH), 35.6 (C), 28.5 (CH_2), 22.3 (CH_3), 20.2 (CH_2), 19.3 (CH_3); IR (neat) 2930 (s), 2828 (m), 1722 (s), 1456 (m), 1375

(m), 1174 (m), 1086 (s), 981 (w), 947 (w), 868 (w) cm^{-1}; HRMS (EI) *m/z* 182.1310 [(M^+), calcd. for $C_{11}H_{18}O_2$: 182.1307].



80 **81**

(1*S, 2*R**, 4*S**, 8*R**)-2-isopropenyl-5-methoxy-1,5-dimethyl-bicyclo[2.2.2]octan-2-ol (80) and (1*S**, 2*S**, 4*S**, 8*R**)-2-isopropenyl-5-methoxy-1,5-dimethyl-bicyclo[2.2.2]octan-2-ol (81).**

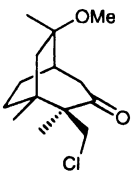
Following general procedure I, the reaction of 2.2 g (12.3 mmol) of starting ketone **78**, afforded 0.91 g (81%) of **80:81**, as a 2.5:1 diastereomeric mixture, after purification *via* flash alumina chromatography (25 g; basic Activity III, 50:1 hexanes/EtOAc).

80: R_f = 0.42 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.07 (d, *J* = 2.0 Hz, 1 H), 4.74 (d, *J* = 2.0, Hz, 1 H), 3.15 (s, 3 H), 2.64 (m, 1 H), 2.20 (d, *J* = 13.4 Hz, 1 H), 1.93 (d, *J* = 13.4 Hz, 1 H), 1.78 (dd, *J* = 14.2, 3.5 Hz, 1 H), 1.62 (dd, *J* = 13.4, 2.0 Hz, 1 H), 1.60 (s, 3 H), 1.40 (s, 1 H), 1.13 (s, 3 H), 1.11 (s, 1 H), 1.05 (series of m, 4 H), 0.98 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 148.0 (C), 110.5 (CH_2), 77.9 (C), 77.4 (C), 50.0 (CH_3), 47.8 (CH_2), 43.3 (C), 41.2 (CH), 30.8 (CH_2), 30.6 (CH_2), 25.7 (CH_3), 22.1 (CH_3), 21.9 (CH_2), 17.9 (CH_3); LRMS (EI) *m/z* 224.1 (M^+ ^{35}Cl), 226.1 (M^+ ^{37}Cl).

81: R_f = 0.21 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.98 (d, *J* = 1.7 Hz, 1 H), 4.80 (t, *J* = 1.7 Hz, 1 H), 3.12 (s, 3 H), 2.69 (m, 1 H), 2.14 (d, *J* = 12.2 Hz, 1 H), 1.69 (d, *J* = 14.4 Hz, 1 H), 1.65 (s, 3 H), 1.55 (m, 1 H), 1.48 (s, 3 H), 1.17 (s, 1 H), 1.15 (d, *J* = 14.4 Hz, 1 H), 1.10 (series of m, 4 H), 1.09 (d, *J* = 12.8 Hz, 1 H), 0.96 (s, 3 H); ^{13}C-

NMR (75 MHz, $CDCl_3$) δ 146.2 (C), 115.3 (CH_2), 79.6 (C), 79.1 (C), 49.8 (CH_3), 46.1 (C), 42.1 (CH_2), 40.9 (CH), 40.6 (CH_2), 24.9 (CH_2), 23.9 (CH_3), 22.9 (CH_2), 22.7 (CH_3), 19.3 (CH_3); LRMS (EI) *m/z* 224.1 (M^+), 226.1 ($M^{+\,37}Cl$).

202:203: IR (neat) 2958 (s), 2880(s), 1720 (s), 1620 (w), 1452 (s), 1371 (s), 1110 (s), 1064 (s), 920 (m), 899 (m), 856 (w), 720 (m) cm^{-1}.

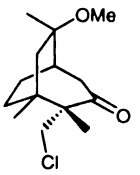


82

(1*S, 2*S**, 5*S**, 9*R**)-2-chloromethyl-1,2,9-trimethyl-9-methoxybicyclo[3.2.2]non-3-one (82).**

Following general procedure V, the reaction of 80.5 mg (0.35 mmol) of starting carbinol **80**, afforded 74.0 mg (82%) of **82:83**, as a 10:1 diastereomeric mixture, after purification *via* flash silica chromatography (1.0 g; 50:1 to 5:1 hexanes/EtOAc).

82: R_f = 0.65 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.85 (d, *J* = 10.7 Hz, 1 H), 3.75 (d, *J* = 10.7 Hz, 1 H), 3.19 (s, 3 H), 2.76 (dd, *J* = 16.0, 4.0 Hz, 1 H), 2.64 (d, *J* = 14.4 Hz, 1 H), 2.55 (m, 1 H), 2.34 (dd, *J* = 16.0, 4.0 Hz, 1 H), 1.27 (d, *J* = 14.4 Hz, 1 H), 1.20 (s, 3 H), 1.18 (series of m, 4 H), 1.17 (s, 3 H), 1.08 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 209.7 (C), 78.5 (C), 58.4 (C), 49.7 (CH_3), 47.6 (CH_2), 46.2 (CH_2), 40.6 (CH_2), 40.1 (CH), 39.8 (C), 28.2 (CH_2), 27.6 (CH_3), 24.9 (CH_2), 24.8 (CH_3), 21.6 (CH_3); IR (neat) 3034 (m), 2932 (s), 2828 (m), 1701 (s), 1458 (s), 1371 (s), 1277 (m), 1140 (s), 1064 (s), 916 (m), 738 (s), 680 (s) cm^{-1}; HRMS (EI) *m/z* 258.6305 [(M^+); calcd. for $C_{14}H_{23}O_2{}^{35}Cl$: 258.7842].

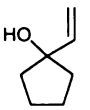


83

(1*S, 2*R**, 5*S**, 9*R**)-2-chloromethyl-1,2,9-trimethyl-9-methoxybicyclo[3.2.2]non-3-one (83).**

Following general procedure V, the reaction of 81.2 mg (0.36 mmol) of starting carbinol **81**, afforded 73.4 mg (79%) of **82:83**, as a 14:1 diastereomeric mixture, after purification *via* flash silica chromatography (1.0 g; 50:1 to 5:1 hexanes/EtOAc).

83: R_f = 0.38 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.62 (d, *J* = 2.8 Hz, 2 H), 3.17 (s, 3 H), 2.85 (dd, *J* = 15.4, 5.0 Hz, 1 H), 2.59 (m, 1 H), 2.39 (dd, *J* = 14.9, 3.0 Hz, 1 H), 2.08 (d, *J* = 14.9 Hz, 1 H), 1.51 (dd, *J* = 15.2, 4.9 Hz, 1 H), 1.39 (dd, *J* = 8.9, 4.9 Hz, 1 H), 1.18 (s, 3 H), 1.14 (s, 3 H), 1.12 (series of m, 3 H), 1.09 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 210.9 (C), 78.4 (C), 57.0 (C), 51.1 (CH_3), 49.8 (CH_2), 45.7 (CH_2), 41.3 (CH), 41.2 (CH_2), 34.9 (C), 29.9 (CH_3), 29.7 (CH_2), 25.5 (CH_2), 25.1 (CH_3), 23.0 (CH_3); IR (neat) 3093 (w), 2986 (s), 2804 (s), 2777 (s), 1728 (s), 1705 (m), 1458 (s), 1383 (s), 1298 (m), 1116 (s), 1076 (s), 935 (m), 844 (m), 752 (m) cm^{-1}; HRMS (EI) *m/z* 258.7513 [(M^+); calcd. for $C_{14}H_{23}O_2{}^{35}Cl$: 258.7842].



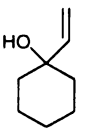
84

1-vinyl-cyclopentanol (84).

Following general procedure III, the reaction of 2.10 mL (23.8 mmol) of cylcopentanone, afforded 2.61 g (98%) of **84** with no need of purification.

84: R_f = 0.48 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.00 (dd, *J* = 17.1, 10.5 Hz, 1 H), 5.24 (dd, *J* = 17.4, 1.5 Hz, 1 H), 5.00 (dd, *J* = 10.8, 1.2 Hz, 1 H), 1.80 (m, 3 H), 1.65 (series of m, 6 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 144.4 (CH), 111.0 (CH_2), 82.1 (C), 40.2 (2 CH_2), 23.6 (2 CH_2); IR (neat) 3372 (br s), 3088 (w), 2961 (s), 2874 (s), 1641 (m), 1439 (m), 1415 (m), 1321 (m), 1228 (m), 1192 (m), 1064 (m), 993 (s), 916 (s) cm^{-1}; LRMS (EI) *m/z* 112.1 (M^+).

For previous syntheses see: (a) Johnson, C. R.; Cheer, C. J.; Goldsmith, D. *J. Org. Chem.* **1964**, *29*, 3320-3323. (b) Marcou, A.; Normant, H. Bull. Soc. Chim. France **1965**, 3491-3494.



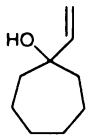
85

1-vinyl-cyclohexanol (85).

Following general procedure III, the reaction of 1.06 mL (10.1 mmol) of cylcohexanone, afforded 1.28 g (quantitative) of **85** with no need of purification.

85: R_f = 0.42 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.94 (dd, *J* = 17.4, 10.6 Hz, 1 H), 5.24 (dd, *J* = 17.1, 1.2 Hz, 1 H), 5.02 (dd, *J* = 10.8, 1.5 Hz, 1 H), 1.53 (series of m, 11 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ. ^{13}C-NMR (75 MHz, $CDCl_3$) δ 145.9 (CH), 111.4 (CH_2), 71.5 (C), 37.5 (CH_2), 25.4 (2 CH_2), 21.9 (2 CH_2); IR (neat) 3385 (br s), 3086 (m), 3007 (m), 2934 (s), 2858 (s), 1652 (m), 1448 (s), 1352 (m), 1265 (m), 1175 (m), 1053 (s), 993 (s), 962 (s), 922 (s), 852 (m) cm^{-1}; LRMS (EI) *m/z* 126.0 (M^+).

Commerically available or for original synthesis see: Marcou, A.; Normant, H. *Bull. Soc. Chim. Fr.* **1965**, 3491-3494.



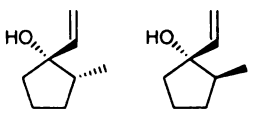
86

1-vinyl-cycloheptanol (86).

Following general procedure III, the reaction of 1.50 mL (12.7 mmol) of cylcoheptanone, afforded 1.72 g (97%) of **86** with no need of purification.

86: $R_f = 0.57$ (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.93 (ddd, J = 17.4, 10.8, 1.8 Hz, 1 H), 5.09 (dd, J = 17.4, 1.5 Hz, 1 H), 4.87 (dd, J = 10.8, 1.5 Hz, 1 H), 1.95 (m, 1 H), 1.60 (series of m, 6 H), 1.39 (series of m, 6 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 146.4 (CH), 109.9 (CH_2), 75.3 (C), 40.8 ($2CH_2$), 29.3 ($2CH_2$), 21.9 ($2CH_2$); IR (neat) 3379 (br s), 3084 (w), 3007 (w), 2939 (s), 2858 (s), 1625 (w), 1460 (s), 1415 (m), 1344 (m), 1203 (m), 1089 (m), 1030 (s), 995 (s), 954 (m), 918 (s), 844 (m) cm^{-1}; LRMS (EI) m/z 140.2 (M^+).

For original synthesis see: Marcou, A.; Normant, H. *Bull. Soc. Chim. Fr,* **1965**, 3491-3494.



87 88

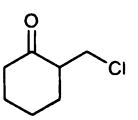
(1*S, 2*S**)-2-methyl-1-vinyl-cyclopentanol (87) and (1*R**, 2*S**)-2-methyl-1-vinyl-cyclopentanol (88).**

Following general procedure III, the reaction of 2.00 g (20.3 mmol) of methylcyclopentanone, afforded 2.21 g (86%) of **87:88**, as a 10:1 mixture of diastereomers, after purification *via* flash alumina chromatography (60 g; basic Activity III, 50:1 hexanes/EtOAc).

87: R_f = 0.43 (4:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.78 (dd, *J* = 17.2, 10.6 Hz, 1 H), 5.19 (d, *J* = 17.2 Hz, 1 H), 5.01 (d, *J* = 11.0 Hz, 1 H), 1.71 (series of m, 4 H), 1.58 (m, 1 H), 1.43 (m, 2 H), 0.80 (d, *J* = 6.6 Hz, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.7 (CH), 111.9 (CH_2), 82.4 (C), 43.4 (CH), 40.2 (CH_2), 31.5 (CH_2), 21.3 (CH_2), 11.7 (CH_3); IR (neat) 3453 (br s), 3088 (w), 2963 (s), 2974 (s), 1722 (s), 1456 (s), 1375 (m), 1155 (m), 1045 (m), 999 (m), 947 (m), 916 (m), 734 (m) cm^{-1}; LRMS (EI) *m/z* 126.1 (M^+).

88: R_f = 0.67 (4:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.63 (dd, *J* = 17.2, 10.6 Hz, 1 H), 5.05 (dd, *J* = 17.2, 1.7 Hz, 1 H), 4.85 (dd, *J* = 11.0, 1.3 Hz, 1 H), 1.84 (m, 2 H), 1.54 (series of m, 4 H), 1.05 (m, 1 H), 0.62 (d, *J* = 7.0 Hz, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.1 (CH), 111.6 (CH_2), 82.0 (C), 44.7 (CH), 37.5 (CH_2), 31.2 (CH_2), 20.5 (CH_2), 15.9 (CH_3); IR (neat) 3447 (br s), 3092 (w), 2961 (s), 2874 (s), 1732 (m), 1456 (m), 1375 (m), 1109 (m), 995 (s), 949 (s), 918 (s), 734 (m) cm^{-1}; LRMS (EI) *m/z* 126.1 (M^+).

For original synthesis see: Battioni, J. P.; Capmau, M. L.; Chodkiewicz, W. *Bull. Soc. Chim. Fr.* **1969**, 976-981.



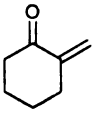
89

2-chloromethyl cyclohexanone (89).

Following general procedure V, the reaction of 0.25 g (2.2 mmol) of **84**, afforded 0.23 g (69%) of **89**, and 0.025 g (10%) **90** after purification *via* flash silica chromatography (12 g; 10:1 hexanes/EtOAc).

89: R_f = 0.46 (5:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.84 (dd, *J* = 11.5, 4.9 Hz, 1 H), 3.41 (dd, *J* = 11.5, 7.6 Hz, 1 H), 2.62 (dt, *J* = 7.6, 4.9 Hz, 1 H), 2.37 (m, 2 H), 2.28 (m, 1 H), 2.07 (m, 1 H), 1.90 (m, 1 H), 1.65 (m, 2 H), 1.42 (m, 1 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 222.8 (C), 56.8 (CH), 39.2 (CH_2), 38.6 (CH_2), 36.1 (CH_2), 26.3 (CH_2), 20.2 (CH_2); IR (neat) 3056 (w), 2930 (s), 2860 (s), 1707 (s), 1448 (s), 1373 (m), 1267 (m), 1130 (m), 1074 (m), 974 (w), 951 (w), 734 (m) cm^{-1}; HRMS (EI) *m/z* 146.0508 [(M^+); calcd. for $C_7H_{11}{}^{35}ClO$: 146.0498].

For original synthesis see: Portnyagin, Y. M.; Chernysh, O. N. *Zh. Org. Khim.* **1974**, *10*, 2117-2119.



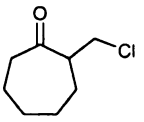
90

2-methylene-cyclohexanone (90).

Following general procedure V, the reaction of 0.51 g (4.6 mmol) of **84**, afforded 0.28 g (56%) of **90** after purification *via* flash silica chromatography (15 g; 1% Et_3N/hexanes).

90: R_f = 0.67 (5:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.80 (d, *J* = 1.5 Hz, 1 H), 5.10 (d, *J* = 1.5 Hz, 1 H), 2.55 (t, *J* = 6.0 Hz, 1 H), 2.42 (t, *J* = 6.5 Hz, 1 H), 1.87 (t, *J* = 6.5 Hz, 1 H), 1.83 (m, 1 H), 1.74 (t, *J* = 6.5 Hz, 1 H), 1.70 (m, 1 H), 1.59 (m, 1 H), 1.50 (m, 1 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 211.9 (C), 145.3 (C), 120.1 (CH_2), 40.7 (CH_2), 34.6 (CH_2), 32.8 (CH_2), 25.2 (CH_2); IR (neat) 3012 (w), 2932 (s), 2862 (s), 1718 (s), 1654 (m), 1446 (m), 1377 (m), 1269 (m), 1120 (s), 1068 (s), 1047 (m), 999 (m), 960 (m), 906 (m), 887 (m) cm^{-1}; HRMS (EI) *m/z* 110.0726 [(M^+) calcd. for $C_7H_{10}O$: 110.0732].

For previous syntheses see: (a) Muehlstaedt, M.; Herzschuh, R. *J. Prakt. Chem.* **1963**, *20*, 20-34. (b) Muehlstaedt, M.; Zach, L.; Becwar-Reinhardt, H. *J. Prakt. Chem.* **1965**, *29*, 158-172. (c) Ksander, G. M.; McMurry, J. E.; Johnson, M. *J. Org. Chem.* **1977**, *42*, 1180-1185.



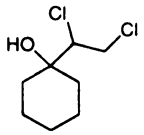
91

2-chloromethyl cycloheptanone (91).

Following general procedure V, the reaction of 0.36 g (2.9 mmol) of **85**, afforded 0.30 g (65%) of **91** and 68.6 mg (12%) of **92** after purification *via* flash silica chromatography (14 g; 10:1 hexanes/EtOAc).

91: R_f = 0.52 (5:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.76 (dd, *J* = 10.9, 6.0 Hz, 1 H), 3.45 (dd, *J* = 10.9, 7.1 Hz, 1 H), 2.86 (m, 1 H), 2.48 (m, 2 H), 1.85 (m, 4 H), 1.64 (m, 2 H), 1.43 (m, 2 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 212.8 (C), 53.8 (CH), 45.2 (CH_2), 43.7 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 23.6 (CH_2); IR (neat) 2930 (s), 2855 (s), 1699 (s), 1452 (m), 1331 (w), 1221 (w), 1143 (w), 1107 (w), 939 (w), 835 (w) cm^{-1}; HRMS (EI) *m/z* 160.0652 [(M^+) calcd. for $C_8H_{13}{}^{35}ClO$: 160.0655].

For original synthesis see: Ryu, I.; Ogawa, A.; Sonoda, N. *Nippon Kagaku Kaishi* **1985**, 442-444

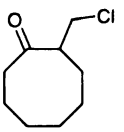


92

1-(1,2-dichloro-ethyl)-cyclohexanol (92).

Following general procedure V, the reaction of 0.36 g (2.9 mmol) of **85**, afforded 0.30 g (65%) of **91** and 68.6 mg (12%) of **92** after purification *via* flash silica chromatography (14 g; 10:1 hexanes/EtOAc).

92: R_f = 0.40 (5:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.06 (dd, *J* = 11.9, 3.0 Hz, 1 H), 3.98 (dd, *J* = 8.8, 3.0 Hz, 1 H) 3.66 (dd, *J* = 11.9, 8.8 Hz, 1 H), 2.01 (s, 1 H), 1.75 (d, *J* = 12.8 Hz, 2 H), 1.68 (d, *J* = 13.2 Hz, 2 H), 1.55 (m, 6 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 73.3 (C), 72.3 (CH), 45.8 (CH_2), 34.8 (CH_2), 34.0 (CH_2), 25.3 (CH_2), 21.6 (CH_2), 21.4 (CH_2); IR (neat) 3456 (br s), 2936 (s), 2858 (s), 1448 (m), 1377 (m), 1319 (m), 1261 (m), 1149 (m), 1041 (m), 981 (m), 902 (m), 852 (w), 765 (m), 727 (m) cm^{-1}; HRMS (EI) *m/z* 196.0425 [(M^+) calcd. for $C_8H_{14}{}^{35}Cl_2O$: 196.0422].



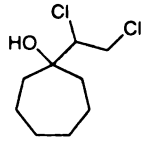
93

2-chloromethyl cyclooctanone (93).

Following general procedure V, the reaction of 0.42 g (3.2 mmol) of **86**, afforded 0.35 g (62%) of **93** and 0.12 g (18%) of **94** after purification *via* flash silica chromatography (15 g; 10:1 hexanes/EtOAc).

93: R_f = 0.56 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.70 (dd, *J* = 10.4, 8.7 Hz, 1 H), 3.33 (dd, *J* = 10.4, 5.4 Hz, 1 H), 3.04 (m, 1 H), 2.39 (ddd, *J* = 14.8, 7.1, 3.2 Hz, 1 H), 2.29 (ddd, *J* = 14.8, 10.9, 3.2 Hz, 1 H), 2.01 (m, 1 H), 1.83 (ddd, *J* = 13.7, 6.5, 3.2 Hz, 1 H), 1.72 (m, 1 H), 1.60 (m, 1 H), 1.48 (m, 4 H), 1.34 (m, 1 H), 1.00 (m, 1 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 216.5 (C), 51.4 (CH), 44.8 (CH2), 44.0 (CH_2), 31.9 (CH_2), 27.8 (CH_2), 24.5 (CH_2), 24.3 (CH_2), 23.3 (CH_2); IR (neat) 2928 (s), 2856 (s), 1701

(s), 1484 (s), 1448 (s), 1332 (m), 1199 (m), 1084 (m), 962 (w), 850 (w), 717 (s) cm^{-1}; HRMS (EI) *m/z* 174.0853 [(M^+) calcd. for $C_9H_{15}{}^{35}ClO$: 174.0811].

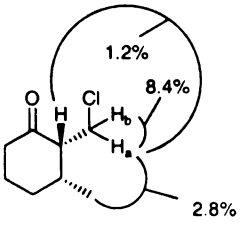


94

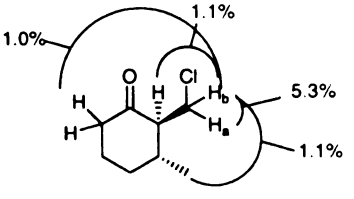
1-(1,2-dichloro-ethyl)-cycloheptanol (94).

Following general procedure V, the reaction of 0.42 g (3.2 mmol) of **86**, afforded 0.35 g (62%) of **93** and 0.12 g (18%) of **94** after purification *via* flash silica chromatography (15 g; 10:1 hexanes/EtOAc).

94: R_f = 0.44 (5:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.02 (dd, *J* = 5.7, 3.9 Hz, 1 H), 3.96 (d, *J* = 6.1 Hz, 2 H), 2.33 (s, 1 H), 1.97 (dd, *J* = 14.5, 9.7 Hz, 1 H), 1.81 (dd, *J* = 14.1, 9.2 Hz, 1 H), 1.65 (m, 4 H), 1.56 (m, 4 H), 1.40 (m, 2 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 77.3 (C), 72.6 (CH), 64.0 (CH_2), 38.3 (CH_2), 38.3 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 22.2 (CH_2), 22.2 (CH_2); IR (neat) 3449 (br m), 2928 (s), 2858 (s), 1460 (s), 1317 (m), 1253 (m), 1192 (m), 1120 (m), 1049 (m), 929 (m), 707 (m) cm^{-1}; HRMS (EI) *m/z* 210.0563 [(M^+) calcd. for $C_9H_{16}{}^{35}Cl_2O$: 210.0578].



95

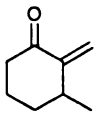


96

2-chloromethyl-3-methyl-cyclohexanone (95).

Following general procedure V, the reaction of 0.90 g (7.1 mmol) of **87**, afforded 0.81 g (71%) of **95:96**, as a 5:1 diastereomeric mixture, 88.6 mg (18%) of **97**, and (<2%) **98** after purification *via* flash silica chromatography (20 g; 10:1 hexanes/EtOAc).

95: R_f = 0.67 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.78 (dd, *J* = 11.5, 6.0 Hz, 1 H), 3.37 (dd, *J* = 11.5, 8.7 Hz, 1 H), 2.79 (dt, *J* = 8.7, 5.4 Hz, 1 H), 2.61 (m, 1 H), 2.25 (m, 2 H), 1.86 (m, 2 H), 1.68 (m, 1 H), 1.01 (m, 1 H), 0.74 (d, *J* = 7.1 Hz, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 208.2 (C), 57.7 (CH), 41.0 (CH_2), 39.9 (CH_2), 35.7 (CH_2), 33.3 (CH_2), 24.8 (CH), 19.9 (CH_3); IR (neat) 2932 (s), 2870 (s), 1709 (s), 1456 (s), 1377 (m), 1267 (w), 1155 (m), 1126 (w), 1080 (w), 1047 (w), 1016 (w), 991 (w), 951 (w), 736 (m) cm^{-1}; HRMS (EI) *m/z* 160.0655 [(M^+) calcd. for $C_8H_{13}{}^{35}Cl_2O$: 160.0655].

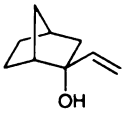


97

3-methyl-2-methylene-cyclohexanone (97).

Following general procedure V, the reaction of 0.90 g (7.1 mmol) of **87**, afforded 0.81 g (71%) of **95:96**, as a 5:1 diastereomeric mixture, 88.6 mg (18%) of **97**, and (<2%) **98** after purification *via* flash silica chromatography (20 g; 10:1 hexanes/EtOAc).

97: R_f = 0.61 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.66 (s, 1 H), 5.01 (s, 1 H), 2.45 (m, 1 H), 2.38 (dt, *J* = 16.8, 5.4 Hz, 1 H), 2.25 (ddd, *J* = 5.9, 10.2, 5.1 Hz, 1 H), 1.74 (series of m, 4 H), 1.02 (d, *J* = 6.6, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 202.3 (C), 151.0 (C), 117.5 (CH_2), 40.3 (CH_2), 36.3 (CH), 32.3 (CH_2), 21.7 (CH_2), 19.1 (CH_3); IR (neat) 3055 (w), 2932 (s), 2868 (s), 1707 (s), 1635 (m), 1458 (s), 1377 (s), 1265 (s), 1188 (s), 1124 (s), 1051 (s), 1018 (s), 968 (s), 920 (s), 736 (s) cm^{-1}; HRMS (EI) *m/z* 124.0890 [(M^+) calcd. for $C_8H_{12}O$: 124.0888].



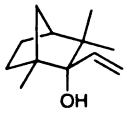
100

(+/-)-(1*R, 2*R**, 4*S**)-2-vinyl-bicyclo[2.2.1]heptan-2-ol (100).**

Following general procedure I, the reaction of 2.15 g (19.5 mmol) of norcamphor, afforded 0.93 g (49%) of **99:100**, as a 1:5.7 diastereomeric mixture, after purification *via* flash alumina chromatography (60 g; basic, Activity III; 20:1 hexanes/EtOAc).

100: R_f = 0.44 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.97 (ddd, *J* = 17.4, 10.8, 0.9 Hz, 1 H), 5.10 (dt, *J* = 17.4, 1.2 Hz, 1 H), 5.91 (dt, *J* = 10.8, 1.2 Hz, 1 H), 2.16 (br s, 1 H), 2.03 (br s, 1 H), 1.97 (m, 1 H), 1.86 (br s, 1 H), 1.79 (dAB_q, *J* = 13.2, 4.5, 1.5 Hz, 1 H), 1.49 (dq, *J* = 13.9, 8.1 Hz, 1 H), 1.47 (d, *J* = 10.2 Hz, 1 H), 1.40-1.18 (series of m, 3 H), 1.12 (dd, *J* = 12.9, 3.6 Hz, 1 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 145.4 (CH), 110.1 (CH_2), 79.0 (C), 47.1 (CH), 44.6 (CH_2), 38.1 (CH_2), 37.0 (CH), 28.7 (CH_2), 21.7 (CH_2); IR (neat) 3370 (br s), 3070 (w), 2955 (s), 2872 (s), 1630 (w), 1454 (m), 1410 (m), 1307 (s), 1163 (m), 1072 (m), 1054 (m), 993 (s), 981 (s), 916 (s), 881 (w), 844 (w), 734 (m) cm^{-1}; HRMS (EI) *m/z* 138.1042 [(M^+) calcd. for $C_9H_{14}O$: 138.1045].

For previous synthesis see: Sundararaman, P.; Fallis, A. G. *J. Org. Chem.* **1977**, *42*, 813-819.



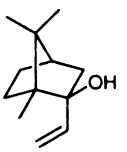
102

(+/-)-(1*R, 2*S**, 4*S**)-1,3,3-trimethyl-2-vinyl-bicyclo[2.2.1]heptan-2-ol (102).**

Following general procedure I, the reaction of 2.02 g (13.2 mmol) of fenchone, afforded 1.14 g (52%) of **101:102**, as a 1:10 diastereomeric mixture, after purification *via* flash alumina chromatography (60 g; basic, Activity III; 50:1 hexanes/EtOAc).

102: R_f = 0.67 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.91 (dd, *J* = 17.1, 10.8 Hz, 1 H), 5.10 (dd, *J* = 17.1, 1.8 Hz, 1 H), 4.95 (dd, *J* = 10.5, 1.8 Hz, 1 H), 1.90 (m, 1 H), 1.66 (d, 1 H), 1.64 (m, 2 H), 1.42-1.30 (series of m, 2 H), 1.10 (d, *J* = 9.0 Hz, 1 H), 0.95 (dd, *J* = 12.9, 3.9 Hz, 1 H), 0.88 (s, 3 H), 0.85 (s, 3 H), 0.84 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 142.7 (CH), 110.0 (CH_2), 82.2 (C), 52.0 (C), 48.3 (CH), 44.2 (C), 40.5 (CH_2), 29.1 (CH_2), 28.5 (CH_3), 25.4 (CH_2), 21.8 (CH_3), 17.1 (CH_3); IR (neat) 3507 (br w), 3086 (w), 2961 (s), 2934 (s), 2876 (m), 1670 (w), 1460 (m), 1385 (m), 1319 (w), 1261 (w), 1169 (w), 1134 (m), 1099 (m), 1080 (m), 1022 (w), 995 (m), 912 (m) cm^{-1}; HRMS (EI) *m/z* 180.1355 [(M^+) calcd. for $C_{12}H_{20}O$: 180.1514].

For previous synthesis see Keegan, D. S.; Midland, M. M.; Werley, R. T.; McLoughlin, J. I. *J. Org. Chem.* **1991**, *56*, 1185-1191.



103

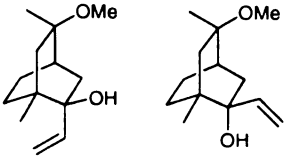
(+/-)-(1*R, 2*R**, 4*R**)-1,7,7-trimethyl-2-vinyl-bicyclo[2.2.1]heptan-2-ol (103).**

Following general procedure I, the reaction of 11.2 g (0.07 mol) of camphor, afforded 11.0 g (83%) of **103** after purification *via* flash alumina chromatography (300 g; basic, Activity III; 100:1 hexanes/EtOAc).

103: R_f = 0.59 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.01 (dd, *J* = 17.1, 10.8 Hz, 1 H), 5.19 (dd, *J* = 17.4, 1.2 Hz, 1 H), 5.03 (dd, *J* = 10.8, 1.5 Hz, 1 H), 2.31 (dt,

J = 18.3, 3.6 Hz, 1 H), 1.92 (m, 2 H), 1.89 (d, J = 18.6 Hz, 2 H), 1.47 (s, 1 H), 1.32 (m, 2 H), 1.10 (s, 3 H), 0.79 (s, 3 H), 0.78 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.8 (CH), 112.0 (CH_2), 81.4 (C), 60.3 (C), 42.9 (C), 31.1 (CH_2), 29.8 (CH), 26.9 (CH_2), 19.7 (CH_2), 14.1 (CH_3), 9.6 (CH_3), 9.2 (CH_3); IR (neat) 3508 (br s), 3058 (w), 2972 (s), 1625 (m), 1454 (s), 1398 (s), 1371 (s), 1325 (m), 1275 (s), 1069 (s), 999 (m), 972 (m), 918 (s), 736 (s) cm^{-1}; LRMS (EI) *m/z* 180.1 (M^+).

For previous synthesis see: Capman, M. L.; Chodkiewicz, W.; Cadiot, P. *Tetrahedron Lett.* **1965**, 1619-1624. Keegan, D. S.; Midland, M. M.; Werley, R. T.; McLoughlin, J. I. *J. Org. Chem.* **1991**, *56*, 1185-1191.



105 **106**

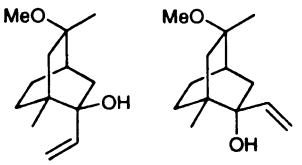
(1*S, 2*S**, 4*R**, 8*R**)-1,8-dimethyl-2-ethenyl-8-methoxybicyclo[2.2.2]octan-2-ol (105) and (1*S**, 2*R**, 4*R**, 8*R**)-1,8-dimethyl-2-ethenyl-8-methoxybicyclo[2.2.2]octan-2-ol (106).**

Following general procedure I, the reaction of 0.52 g (2.8 mmol) of starting ketone **78**, afforded 0.51 g (85%) **105:106**, as a 2.5:1 diastereomeric mixture, after purification *via* flash alumina chromatography (3 g; basic, Activity III; 100:1 hexanes/EtOAc).

105: R_f = 0.37 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.88 (dd, J = 17.1, 10.8 Hz, 1 H), 5.27 (dd, J = 17.4, 2.4 Hz, 1 H), 5.05 (dd, J = 10.8, 2.1 Hz, 1 H), 3.18 (s, 3 H), 1.89 (m, 1 H), 1.80 (dd, J = 12.9, 1.8 Hz, 1 H), 1.79 (m, 1 H), 1.73 (m, 1 H), 1.63 (dd, J = 14.4, 2.1 Hz, 1 H), 1.48 (series of m, 3 H), 1.29 (br s, 1 H), 1.22 (s, 3 H), 1.10 (d, J =

15.0 Hz, 1 H), 0.69 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.2 (CH), 112.4 (CH_2), 76.5 (C), 73.5 (C), 49.3 (CH_3), 45.3 (CH_2), 39.3 (CH_2), 36.8 (C), 33.8 (CH), 29.2 (CH_2), 23.5 (CH_2), 22.2 (CH_3), 21.3 (CH_3); IR (NaCl, neat) 3458 (br m), 3015 (w), 2949 (s), 2870 (m), 2829 (w), 1740 (w), 1450 (m), 1373 (m), 1140 (m), 1064 (s), 989 (m), 945 (w), 920 (m) cm^{-1}; HRMS (EI) *m/z* 210.1629 [(M^+), calcd. for $C_{13}H_{22}O_2$: 210.1620].

106: R_f = 0.25 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.10 (dd, *J* = 17.4, 10.8 Hz, 1 H), 5.16 (dd, *J* = 17.1, 1.5 Hz, 1 H), 5.01 (dd, *J* = 10.8, 1.5 Hz, 1 H), 3.09 (s, 3 H), 2.14 (dt, *J* = 14.1, 3.0 Hz, 1 H), 1.76 (m, 2 H), 1.59 (dd, *J* = 14.2 Hz, 2 H), 1.51 m, 1 H), 1.31 (s, 1 H), 1.25 (dd, *J* = 14.4, 3.3 Hz, 1 H), 1.21 (s, 3 H), 1.10 (d, *J* = 14.4 Hz, 1 H), 0.88 (s, 1 H), 0.64 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.7 (CH), 111.2 (CH_2), 76.0 (C), 74.7 (C), 48.6 (CH_3), 46.0 (CH_2), 38.2 (CH_2), 36.7 (C), 33.8 (CH), 27.6 (CH_2), 23.9 (CH_3), 22.3 (CH_2), 20.9 (CH_3); IR (NaCl, neat) 3466 (br s), 3084 (w), 2947 (s), 2826 (m), 1722 (m), 1639 (w), 1450 (m), 1373 (m), 1271 (m), 1167 (m), 118 (m), 1066 (m), 991 (m), 945 (w), 918 (m) cm^{-1}; HRMS (EI) *m/z* 210.1614 [(M^+), calcd. for $C_{13}H_{22}O_2$: 210.1620].



107 **108**

(1*S, 2*S**, 4*R**, 8*S**)-1,8-dimethyl-2-ethenyl-8-methoxybicyclo[2.2.2]octan-2-ol (107) and (1*S**, 2*R**, 4*R**, 8*S**)-1,8-dimethyl-2-ethenyl-8-methoxybicyclo[2.2.2]octan-2-ol (108).**

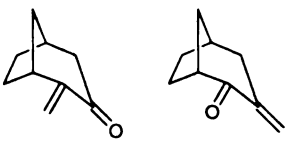
Following general procedure I, the reaction of 0.75 g (4.1 mmol) of starting ketone **79**, afforded 0.61 g (70%) **107:108**, as a 1.1:1 diastereomeric mixture, after

purification *via* flash alumina chromatography (3 g; basic, Activity III; 100:1 hexanes/EtOAc).

107: R_f = 0.44 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.95 (dd, *J* = 17.1, 10.8 Hz, 1 H), 5.13 (dd, *J* = 16.5, 1.5 Hz, 1 H), 4.97 (dd, *J* = 11.1, 1.5 Hz, 1 H), 3.07 (s, 3 H), 2.20-1.23 (series of m, 9 H), 1.22 (s, 3 H), 1.13 (s, 1 H), 0.61 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.9 (CH), 111.4 (CH_2), 75.5 (C), 74.8 (C), 48.7 (CH_3), 45.5 (CH_2), 40.3 (CH_2), 36.4 (C), 34.2 (CH), 28.6 (CH_2), 22.6 (CH_3), 21.0 (CH_3), 20.4 (CH_2); HRMS (EI) *m/z* 210.1615 [(M^+), calcd. for $C_{13}H_{22}O_2$: 210.1620].

108: R_f = 0.37 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.87 (dd, *J* = 16.8, 10.8 Hz, 1 H), 5.13 (dd, *J* = 16.5, 0.9 Hz, 1 H), 4.97 (dd, *J* = 10.8, 1.5 Hz, 1 H), 3.08 (s, 3 H), 2.20-1.23 (series of m, 9 H), 1.12 (s, 3 H), 0.82 (s, 1 H), 0.59 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.1 (CH), 111.7 (CH_2), 75.7 (C), 75.0 (C), 49.1 (CH_3), 44.0 (CH_2), 39.9 (CH_2), 36.1 (C), 33.8 (CH), 27.4 (CH_2), 22.8 (CH_3), 21.1 (CH_2), 19.7 (CH_3); HRMS (EI) *m/z* 210.1622 [(M^+), calcd. for $C_{13}H_{22}O_2$: 210.1620].

107:108: IR (neat) 3460 (br s), 3084 (w), 2934 (s), 2826 (m), 1637 (m), 1456 (s), 1373 (s), 1246 (s), 1076 (s), 995 (s), 920 (s) cm^{-1}.



109 110

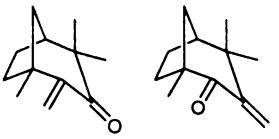
(+/-)-(1*R, 5*S**)-2-methylene-bicyclo[3.2.1]octan-3-one (109) and (+/-)-(1*R**, 5*S**)-3-methylene-bicyclo[3.2.1]octan-2-one (110).**

Following general procedure V, the reaction of 0.51 g (3.6 mmol) of **100**, afforded 0.41 g (82%) **109:110**, as a 1:1.6 regiomeric mixture, after purification *via* flash silica chromatography (15 g; 1% Et_3N/hexanes).

109: R_f = 0.56 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.94 (s, 1 H), 5.15 (s, 1 H), 2.75 (t, *J* = 2.7 Hz, 1 H), 2.51 (m, 1 H), 2.39 (series of m, 2 H), 1.93-1.45 (series of m, 6 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 203.1 (C), 142.4 (C), 122.5 (CH_2), 49.7 (CH), 39.2 (CH_2), 35.6 (CH_2), 34.1 (CH), 28.8 (CH_2), 28.2 (CH_2); IR (neat) 3092 (w), 2955 (s), 2874 (s), 1697 (s), 1612 (m), 1450 (m), 1286 (m), 1188 (m), 1107 (s), 1057 (m), 981 (w), 939 (m), 916 (m), 734 (s) cm^{-1}; LRMS (EI) *m/z* 136.0 (M^+).

110: R_f = 0.57 (5:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.66 (d, *J* = 2.0 Hz, 1 H), 4.98 (d, *J* = 1.5 Hz, 1 H), 3.04 (t, *J* = 4.5 Hz, 1 H), 2.51 (d, *J* = 2.5 Hz, 1 H), 2.43 (m, 1 H), 2.38 (dd, *J* = 7.5, 4.0 Hz, 1 H), 1.85 (m, 2 H), 1.77 (d, *J* = 12.0 Hz, 1 H), 1.71 (m, 1 H), 1.55 (m, 1 H), 1.49 (m, 1 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 201.6 (C), 151.4 (C), 117.1 (CH_2), 49.3 (CH), 42.7 (CH), 37.3 (CH_2), 34.0 (CH_2), 31.4 (CH_2), 29.3 (CH_2); IR (neat) 3092 (w), 2955 (s), 2874 (s), 1697 (s), 1612 (m), 1450 (m), 1286 (m), 1188 (m), 1107 (s), 1057 (m), 981 (w), 939 (m), 916 (m), 734 (s) cm^{-1}; HRMS (EI) *m/z* 136.0887 [(M^+) calcd. for $C_9H_{12}O$: 136.0888].

For original synthesis of **105** see: Keenan, M.; Rocco, V. P.; Takeuchi, K.; Tupper, D. E.; Vixien, V. Patent GB2367554. **2002**.



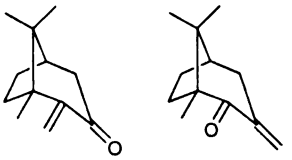
111 **112**

(+/-)-(1*R, 5*S**)-1,4,4-trimethyl-2-methylene-bicyclo[3.2.1]octan-3-one (111) and (+/-)-(1*R**, 5*S**)-1,4,4-trimethyl-3-methylene-bicyclo[3.2.1]octan-3-one (112).**

Following general procedure V, the reaction of 0.50 g (3.0 mmol) of **102**, afforded 0.43 g (86%) **111:112**, as a 1:1.5 regiomeric mixture, after purification *via* flash silica chromatography (15 g; 1% Et_3N/hexanes).

111: R_f = 0.71 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.74 (s, 1 H), 5.09 (s, 1 H), 1.98 (d, *J* = 12.6 Hz, 2 H), 1.83 (series of m, 2 H), 1.55-1.27 (series of m, 3 H), 1.10 (s, 3 H), 1.07 (s, 3 H), 0.98 (s, 3 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 205.4 (C), 173.5 (C), 114.4 (CH_2), 57.5 (C), 42.6 (C), 40.0 (CH), 35.0 (CH_2), 34.3 (CH_2), 30.3 (CH_2), 21.8 (CH_3), 19.8 (CH_3), 19.3 (CH_3); IR (NaCl, neat) 3081 (w), 2968 (s), 2874 (s), 1695 (s), 1610 (m), 1462 (s), 1385 (m), 1267 (m), 1051 (s), 1030 (m), 935 (m), 908 (m), 736 (s) cm^{-1}; LRMS (EI) *m/z* 178.2 (M^+).

112: R_f = 0.74 (5:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.54 (d, *J* = 1.5 Hz, 1 H), 5.02 (d, *J* = 1.5 Hz, 1 H), 2.02 (m, 1 H), 2.00 (s, 1 H), 1.98 (d, *J* = 11.7 Hz, 1 H), 1.77 (series of m, 2 H), 1.51 (m, 2 H), 1.24 (s, 3 H), 1.10 (s, 3 H), 1.04 (s, 3 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 207.9 (C), 154.8 (C), 114.5 (CH_2), 48.7 (C), 46.8 (C), 45.5 (CH), 41.5 (CH_2), 37.4 (CH_2), 26.5 (CH_2), 26.4 (CH_3), 23.2 (CH_3), 23.1 (CH_3); IR (NaCl, neat) 3081 (w), 2968 (s), 2874 (s), 1695 (s), 1610 (m), 1462 (s), 1385 (m), 1267 (m), 1051 (s), 1030 (m), 935 (m), 908 (m), 736 (s) cm^{-1}; HRMS (EI) *m/z* 178.1358 [(M^+) calcd. for $C_{12}H_{18}O$: 178.1358].



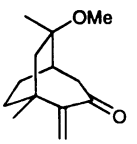
113 114

(1*R, 5*R**)-1,8,8-trimethyl-2-methylene-bicyclo[3.2.1]octan-3-one (113) and (1*R**, 5*R**)-1,8,8-trimethyl-3-methylene-bicyclo[3.2.1]octan-2-one (114).**

Following general procedure V, the reaction of 0.50 g (2.7 mmol) of **103**, afforded 0.47 g (96%) **113:114**, as a 3:1 regiomeric mixture, after purification *via* flash silica chromatography (15 g; 1% Et_3N/hexanes).

113: R_f = 0.63 (5:1 hexanes/EtOAc); $[\alpha]_D^{20}$ = -46.8 ° (*c* 1.40); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.63 (m, 1 H), 4.86 (m, 1 H), 2.46 (dm, *J* = 9.6 Hz, 1 H), 2.01 (dq, *J* = 11.1, 1.8 Hz, 2 H), 1.78 (t, *J* = 2.7 Hz, 2 H), 1.50-1.30 (series of m, 2 H), 0.66 (s, 3 H), 0.59 (s, 3 H), 0.53 (s, 3 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 203.9 (C), 141.8 (C), 121.1 (CH_2), 46.0 (C), 44.6 (C), 42.5 (CH_2), 42.4 (CH), 29.2 (CH_2), 26.4 (CH_2), 19.1 (CH_3), 18.5 (CH_3), 8.6 (CH_3); IR (NaCl, neat) 3098 (m), 2910 (s), 2868 (s), 1615 (m), 1462 (s), 1387 (s), 1282 (s), 1236 (s), 1130 (s), 1086 (s), 1016 (s), 995 (s), 960 (s), 918 (s), 740 (m) cm^{-1}; HRMS (EI) *m/z* 178.2701 [(M^+) calcd. for $C_{11}H_{18}O$: 178.2707].

114: R_f = 0.58 (5:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.48 (d, *J* = 0.9 Hz, 1 H), 4.79 (d, *J* = 0.6 Hz, 1 H), 2.36 (ddd, *J* = 11.1, 2.7, 1.5 Hz, 1 H), 2.10 (dt, *J* = 9.6, 0.6 Hz, 2 H), 1.63 (t, *J* = 2.3 Hz, 2 H), 1.20-1.09 (series of m, 2 H), 0.71 (s, 3 H), 0.67 (s, 3 H), 0.59 (s, 3 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 201.1 (C), 154.2 (C), 115.2 (CH_2), 56.8 (C), 45.9 (C), 44.5 (CH), 36.2 (CH_2), 35.4 (CH_2), 34.3 (CH_2), 23.5 (CH_3), 16.5 (CH_3), 12.9 (CH_3); IR (NaCl, neat) 3098 (m), 2910 (s), 2868 (s), 1615 (m), 1462 (s), 1387 (s), 1282 (s), 1236 (s), 1130 (s), 1086 (s), 1016 (s), 995 (s), 960 (s), 918 (s), 740 (m) cm^{-1}; LRMS (EI) *m/z* 178.1 (M^+).

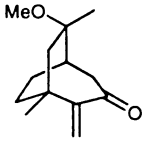


115

(1*S, 5*R**, 9*R**)-1,9-dimethyl-9-methoxy-2-methylenebicyclo[3.2.2]nonan-3-one (115).**

Following general procedure V, the reaction of 0.10 g (0.48 mmol) of starting carbinols **105:106**, as a 1:1 mixture, afforded 90.3 mg (90%) of **115** after purification *via* flash silica chromatography (3 g; 1% Et_3N/hexanes).

115: R_f = 0.38 (5:1 hexanes/EtOAc); $[\alpha]_D^{20}$ = -24.3 (*c* 0.38); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.75 (d, *J* = 0.9 Hz, 1 H), 5.17 (d, *J* = 0.9 Hz, 1 H), 3.17 (s, 3 H), 3.15 (d, *J* = 12.0 Hz, 1 H), 2.66 (dt, *J* = 18.9, 3.3 Hz, 1 H), 2.53 (dd, *J* = 19.5, 4.8 Hz, 1 H), 2.11 (m, 1 H), 1.87 (dd, *J* = 15.0, 3.6 Hz, 1 H), 1.75 (dd, *J* = 15.3, 0.9 Hz, 1 H), 1.52 (dd, *J* = 17.1, 1.5 Hz, 1 H), 1.50 (m, 1 H), 1.49 (dd, *J* = 17.4, 2.4 Hz, 1 H), 1.17 (s, 3 H), 1.12 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 205.1 (C), 158.1 (C), 118.4 (CH_2), 75.0 (C), 49.0 (CH_3), 46.5 (CH_2), 46.4 (CH_2), 34.7 (C), 34.3 (CH), 33.4 (CH_2), 29.4 (CH_3), 23.7 (CH_2), 29.4 (CH_3); IR (neat) 3090 (w), 2928 (s), 2826 (m), 1722 (s), 1684 (s), 1464 (s), 1375 (s), 1118 (s), 1078 (s), 981 (w), 943 (m), 916 (m), 823 (w) cm^{-1}; HRMS (EI) *m/z* 208.1468 [(M^+); calcd. for $C_{13}H_{20}O_2$: 208.1463].



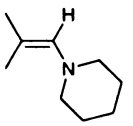
116

(1*S, 5*R**, 9*S**)-1,9-dimethyl-9-methoxy-2-methylenebicyclo[3.2.2]nonan-3-one (116).**

Following general procedure V, the reaction of 0.13 g (0.63 mmol) of starting carbinols **107:108**, as a 1:1 mixture, afforded 0.11 g (88%) of **116** after purification *via* flash silica chromatography (3 g; 1% Et_3N/hexanes).

116: R_f = 0.44 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.89 (d, *J* = 1.2 Hz, 1 H), 5.17 (d, *J* = 0.9 Hz, 1 H), 3.11 (d, *J* = 14.4 Hz, 1 H), 3.06 (s, 3 H), 2.95 (dd, *J* =

18.3, 5.7 Hz, 1 H), 2.31 (dd, J = 18.3, 2.4 Hz, 1 H), 2.10 (p, J = 2.7 Hz, 1 H), 1.72 (d, J = 15.0 Hz, 1 H), 1.68 (d, J = 16.2 Hz, 1 H), 1.54 (series of m, 2 H), 1.45 (d, J = 14.4 Hz, 1 H) 1.23 (s, 3 H), 1.12 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 202.5 (C), 156.2 (C), 118.1 (CH_2), 76.1 (C), 48.8 (CH_3), 46.4 (CH_2), 44.3 (CH_2), 37.4 (CH), 34.7 (C), 32.5 (CH_2), 29.6 (CH_2), 24.7 (CH_3), 24.6 (CH_3); IR (neat) 3090 (w), 2928 (s), 2826 (s), 1722 (s), 1684 (m), 1597 (w),1464 (s), 1375 (s), 1118 (s), 1078 (s), 981 (m), 943 (m), 916 (m), 823 (w) cm^{-1}; HRMS (EI) m/z 208.1463 [(M^+); calcd. for $C_{13}H_{20}O_2$: 208.1463].



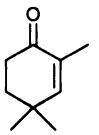
117

1-(2-methyl-propenyl)-piperidine (117).

To a stirring chilled, 0 °C, heterogeneous solution of 12.04 g K_2CO_3 (87.1 mmol, 35 mol%) in 58 mL piperidine (586.4 mmol, 2.36 eq), was added 22.6 mL *iso*-butryaldehyde (248.8 mmol, 1.00 eq) in a dropwise manner over 1.5 hrs After complete addition the reaction was stirred at 0 °C for 3 hrs, then warmed to room temperature and agitated an additional 8 hrs The reaction was gravity filtered, dried over $MgSO_4$, filtered, and concentrated to produce a yellow oil. The oil was purified *via* short path distillation at room temperature under aspirator pressure. To prevent severe foaming, 5 mL silicon oil was added to the distillation mixture. The distilation produced 27.12 g (78%) of the desired piperidine enamine, **117**, as a water white oil.

117: bp = 22 °C (15 mmHg); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.30 (q, J = 1.2 Hz, 1 H), 2.75 (t, J = 5.1 Hz, 2 H), 2.50 (t, J = 5.1 Hz, 2 H), 1.62 (s, 3 H), 1.55 (d, J = 1.2 Hz, 3 H), 1.52-1.36 (series of m, 6 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 136.1 (CH), 120.8 (C), 54.0 (CH_2), 47.2 (CH_2), 27.0 (CH_2), 25.7 (CH_2), 24.0 (CH_2), 22.2 (CH_3), 17.3 (CH_3); IR (neat)

3010 (w), 2932 (s), 2853 (m), 27m), 1089 (m), 2737 (m), 1678 (w), 1441 (m), 1386 (m), 1269 (w), 1180 (m), 1111 (m), 1035 (m), 987 (w), 862 (m) cm^{-1}; LRMS (EI) *m/z* 139.2 (M^+), 140.2 (M^+ +H), 124.1 (M^+ -Me).



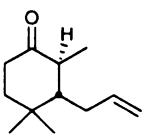
118

(2, 4, 4)-trimethylcyclohexanes-2-en-1-one (118).

Enamine **117** was chilled to 0 °C and 25.0 mL ethyl vinyl ketone (251.1 mmol, 1.01 eq) was added dropswise *via* addition funnel over a period of 45 min After complete addition the reaction was warmed to room temperature and stirred for 24 hrs The addition of 300 mL of an aqueous 15% HCl solution followed with aggitation for an additional 48 hrs at room temperature. The reaction was then brought to reflux (110 °C) for 1 hr and then cooled to room temperature. The reaction was partitioned with brine and the reaction mixture was extracted four times with 50 mL Et_2O. The combined ethereal layers was dried over $MgSO_4$, filtered, and concentrated to produce a yellow oil. The oil was distilled *via* the short-path at aspirator pressure (15 mmHg) with heating to produce 20.92 g (60%) of **118** as a water-white oil.

118: bp = 74-76 °C (15 mm Hg); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.32 (s, 1 H), 2.36 (t, *J* = 6.6 Hz, 2 H), 1.74 (t, *J* = 6.6 Hz, 2 H), 1.64 (d, *J* = 1.5 Hz, 3 H), 1.04 (s, 6 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 199.6 (C), 155.0 (CH), 132.3 (C), 36.2 (CH_2), 34.3 (CH_2), 32.8 (C), 27.8 (CH_3), 15.8 (CH_3); IR (neat) 3300 (w), 2926 (s), 2868 (s), 1716 (m), 1678 (s), 1448 (s), 1361 (s), 1176 (s), 1087 (s), 1023 (s), 981 (w), 916 (m), 883 (m) cm^{-1}, 752 (w); LRMS (EI) *m/z* 139.0 (M^{+1}), 138.0 (M^+); HRMS (EI) *m/z* 138.1044 [(M^+), calcd. for $C_9H_{14}O$: 138.1045].

For previous synthesis see: Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107-124.



119

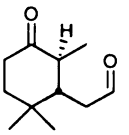
(+/-)-(2*S, 3*S**)-3-allyl-(2, 4, 4)-trimethylcyclohexanone (119).**

A solution of 13.30 g **118** (96.2 mmol, 1.00 eq) in 180 mL CH_2Cl_2 was chilled to -78 °C. To this solution, 15.0 mL $TiCl_4$ (136.7 mmol, 1.42 eq) was added in a dropwise manner slowly turning the solution from clear to dark red and finally to a bright yellow slurry. After the complete addition of $TiCl_4$ the reaction was kept at –78 °C for an additional 10 min To this, 14.77 mL allyltrimethylsilane (92.9 mmol, 0.96 eq) in 20 mL CH_2Cl_2 was added dropwise turning the solution a ruddy red The reaction temperature was kept at -78 °C after the silanes complete addition for 3 hrs The reaction was warmed to 0 °C, quenched with H_2O and partitioned with 100 mL Et_2O. After separation the aqueous layer was extracted two times with 100 mL Et_2O. The combined ethereal layers were washed once with 100 mL H_2O and once with 150 mL brine. The organics were dried over $MgSO_4$, filtered, and concentrated to afford a clear oil. The oil was purified *via* flash silica chromotography (400 g; 30:1 hexanes/EtOAc) to provide 11.27 g (65%) of racemic diastereomer **119** as a transparent oil.

119: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.71 (ABsext, *J* = 17.1, 10.2, 6.9 Hz, 1 H), 4.91 (dd, *J* = 17.1, 1.5 Hz, 1 H), 4.84 (dd, *J* = 10.2, 1.5 Hz, 1 H), 2.35 (td, *J* = 14.1, 6.6 Hz, 1 H), 2.23 (dq, *J*= 14.6, 6.3 Hz, 1 H), 2.18 (m, 2 H), 1.98 (dt, *J* = 15.3, 6.9 Hz, 1 H), 1.55 (dd, *J* = 6.3, 3.0 Hz, 1 H), 1.50 (dd, *J* = 13.8, 4.8 Hz, 1 H), 1.19 (dt, *J* = 11.4, 5.1 Hz, 1 H), 0.96

(s, 3 H), 0.94 (d, J = 6.6 Hz, 3 H), 0.90 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 212.8 (C), 138.4 (CH), 115.0 (CH_2), 52.9 (CH), 46.2 (CH), 41.1 (CH_2), 37.8 (CH_2), 34.4 (CH_2), 34.1 (C), 29.4 (CH_3), 19.8 (CH_3), 12.5 (CH_3); IR (neat) 3076 (m-w), 2970 (s), 2937 (s), 2872 (s), 1714 (s), 1678 (s), 1639(m), 1469 (s), 1437 (m), 1390 (m), 1369 (m), 1311 (m), 1248 (w), 1153 (m), 1010 (m), 995 (m), 910 (s) cm^{-1}; HRMS (EI) *m/z* 180.1507 [(M^+), calcd. for $C_{12}H_{20}O$: 180.1514].

For previous synthesis see: Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107-124.



120

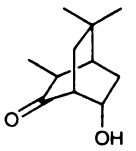
(+/-)-(2*S, 3*S**)-(2,2,6-trimethyl-5-oxo-cyclohexyl)-acetaldehyde (120).**

A solution of 11.8162 g **119** (65.5 mmol, 1.00 eq) in 250 mL CH_2Cl_2 was charged with N_2 at –78 °C. Ozone was bubbled into the reaction until a clear blue solution was produced, ~2 hr. Nitrogen was then bubbled through the reaction, to removing excess ozone, until a water white solution was generated. The reaction was worked up in a reductive manner by the dropwise addition of 51.95 g Ph_3P (198.0 mmol, 3.02 eq) in 200 mL CH_2Cl_2. After overnight stirring, 12 hrs, at room temperature the yellow green heterogeneous solution was gravity filtered and concentrated to afford a yellow white solid. The solid was taken up in 200 mL Et_2O and gravity filtered onto a silica column and purified *via* flash silica chromotography (200 g; 20%EtOAc/hexanes) to provide 11.81 g (98%) of the desired aldehyde **120** as a white solid.

120: mp = 115-120 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.75 (dd, J = 2.1, 0.9 Hz, 1 H), 2.90-2.15 (series of m, 4 H), 2.05-1.95 (series of m, 1 H), 1.80-1.60 (series of m, 2 H),

1.04 (s, 3 H), 0.97 (d, J = 6.3 Hz, 1 H), 0.94 (s, 3 H), 0.92 (d, J = 6.6 Hz, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 211.6 (C), 201.3 (CH), 45.4 (CH), 40.9 (CH), 40.6 (CH_2), 38.0 (CH_2), 35.8 (CH_2), 33.7 (C), 29.4 (CH_3), 19.6 (CH_3), 12.6 (CH_3); HRMS (EI) *m/z* 182.1302 [(M^+), calcd. for $C_{11}H_{18}O_2$: 182.1307].

For previous synthesis see: Maleczka, Jr., R. E. Ph.D. Dissertation, Ohio State University , 1992.



121

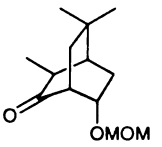
(+/-)-(1*R, 3*R**, 4*S**, 6*S**)-6-hydroxy-3,8,8-trimethylbicyclo[2.2.2]oct-2-one (121).**

A solution of 98.0 mL AcOH (1.7 mols, 26.1 eq) in 125 mL THF was prepared, to which 11.94 g **120** (major) (65.5 mmol, 1.00 eq) was added. The reaction was refluxed (95 °C) for 10 hrs and then partitioned with 75 mL Et_2O and 75 mL of an aqueous 1 M NaOH solution. After separation the ethereal layer was washed two times with 75 mL of an aqueous 1 M NaOH solution. The combined aqueous layers were extracted two times with 50 mL Et_2O. The combined ethereal layers were dried over $MgSO_4$, filtered, and concentrated to produce a white solid. The solid was purified *via* alumina chromatography (300 g; basic Activity III; 30:1 hexanes/EtOAc) to yield 8.9486 g (75%) of racemic diasteromer **121** as a white solid.

121: mp = 92-94 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.22 (dt, J = 9.3, 3.6, 1 H), 2.61 (AB_q, J = 7.2, 5.1, 2.1 Hz, 1 H), 2.40 (dAB_q, J = 9.3, 2.1, 1.2 Hz, 1 H), 2.30 (q, J = 3.0 Hz, 1 H), 1.63 (br s, 1 H), 1.60 (q, J = 2.4 Hz, 1 H), 1.52 (dd, J = 6.6, 3.0 Hz, 2 H), 1.48 (q, J = 3.0 Hz, 1 H), 1.17 (d, J = 7.5 Hz, 3 H), 1.09 (s, 3 H), 1.05 (s, 3 H); ^{13}C-NMR (75

MHz, $CDCl_3$) δ 219.2 (C), 69.0 (CH), 53.1 (CH), 45.0 (CH), 42.7 (CH), 36.0 (CH_2), 30.6 (C), 30.5 (CH_3), 29.3 (CH_3), 28.0 (CH_2), 12.9 (CH_3); IR (neat) 3431 (br s), 2966 (s), 2872 (s), 1724 (s), 1452 (s), 1388 (s), 1294 (m), 1170 (m), 1103 (s), 1032 (s), 1005 (m), 916 (m), 733 (s) cm^{-1}; HRMS (EI) *m/z* 182.1307 [(M^+), calcd. for $C_{11}H_{18}O_2$: 182.1307].

For previous synthesis see: Paquette, L. A.; Maleczka, Jr., R. E.; Qiu, F. *J. Org. Chem.* **1991**, *56*, 2455-2461.



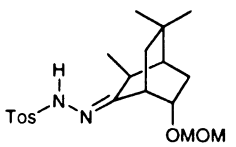
122

(+/-)-(1*R, 3*R**, 4*S**, 6*S**)-6-methoxymethoxy-3,8,8-trimethylbicyclo[2.2.2]oct-2-one (122).**

A solution of 8.9486 g **121** (49.0 mmol, 1.00 eq) in 30 mL THF was cooled to 0 °C. To this chilled solution, 9.40 mL $^iPr_2NEt$ (54.0 mmol, 1.01 eq) was added in a dropwise manner. After complete addition the reaction was stirred at 0 °C for 15 min which was followed by addition of 4.3 mL methoxymethylchloride (56.6 mmol, 1.15 eq) in 20 mL THF. Upon complete addition the reaction was warmed to room temperature and stirred for 30 hrs The reaction was taken up in 30 mL Et_2O and partitioned with 30 mL H_2O. After separation the ethereal layer was washed three times with 30 mL H_2O. The combined aqueous layers were extracted once with 30 mL Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated to provide a pale yellow oil. The oil was purified *via* flash silica chromatography (250 g; 4:1 hexanes/EtOAc) to yield 8.31 g (75%) of **122**.

122: R_f = 0.57 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.43 (d, *J* = 6.6 Hz, 1 H), 4.42 (d, *J* = 6.6 Hz, 1 H), 3.87 (m, 1 H), 3.15 (s, 3 H), 2.44 (m, 1 H), 2.28 (m, 1 H), 2.21 (m, 1 H), 1.54 (dt, *J* = 9.0, 1.8 Hz, 1 H), 1.37 (dd, *J* = 11.7, 1,8 Hz, 1 H), 1.32 (m, 2 H), 1.00 (d, *J* = 4.5 Hz, 3 H), 0.95 (s, 3 H), 0.89 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 216.2 (C), 94.5 (CH_2), 73.7 (CH), 54.9 (CH_3), 49.6 (CH), 44.7 (CH), 42.2 (CH), 36.3 (CH_2), 30.5 (CH_3), 30.2 (C), 29.0 (CH_3), 26.1 (CH_2), 12.8 (CH_3); IR (neat) 2963 (s), 2824 (m), 2788 (w), 1724 (s), 1456 (m), 1369 (m), 1217 (m), 1145 (s), 1101 (s), 1037 (s), 918 (m), 883 (w), 733 (m), 648 (m) cm^{-1}; HRMS (EI) *m/z* 226.1568 [(M^+), calcd. for $C_{13}H_{22}O_3$: 226.1569].

For previous synthesis see: Paquette, L. A.; Maleczka, Jr., R. E.; Qiu, F. *J. Org. Chem.* **1991**, *56*, 2455-2461.



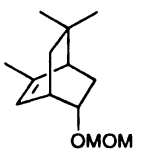
123

(+/-)-(1*R, 3*R**, 4*S**, 6*S**)-6-methoxymethoxy-3,8,8-trimethylbicyclo[2.2.2]oct-2-one tosylhydrazone (123).**

To a room temperature stirring solution of 8.31 g **122** (36.7 mmol, 1.00 eq) in 50 mL MeOH, was added 8.26 g tosylhydrazide (44.3 mmol, 1.21 eq). The reaction was stirred at room temperature for 36 hrs After concentration and PhH azeotrope, the residue was taken up consecutively in cold (0 °C) ether and filtered. The filtrate was then concentrated to produce 14.45 g (quantitative yield) of **123** as a white gel like material. Only one isomer was observed *via* NMR.

123: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.47 (br s, 1 H), 7.80 (d, *J* = 8.1 Hz, 2 H), 7.23 (d, *J* = 7.8 Hz, 2 H), 4.46 (AB_q, *J* = 4.5, 6.0 Hz, 2 H), 3.80 (m, 1 H), 3.22 (s, 3 H), 3.01 (q, *J* = 3.0 Hz, 1 H), 2.38 (s, 3 H), 2.12 (m, 1 H), 1.35 (m, 2 H), 1.29 (dd, *J* = 5.1, 2.4 Hz, 1 H), 1.25 (dd, *J* = 4.8, 2.4 Hz, 1 H), 1.20 (m, 1 H), 1.02 (s, 3 H), 1.01 (s, 3 H), 0.98 (d, *J* = 6.0 Hz, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.5 (C), 143.2 (C), 135.7 (C), 128.9 (CH), 128.1 (CH), 97.1 (CH_2), 78.7 (CH), 54.8 (CH_3), 44.8 (CH), 37.4 (CH), 36.1 (CH_2), 35.3 (CH), 30.5 (CH_3), 30.4 (C), 29.1 (CH_3), 26.4 (CH_2), 21.5 (CH_3), 16.0 (CH_3); IR (neat) 3500 (br m), 3123 (s), 2966 (s), 1915 (w), 1736 (s), 1645 (s), 1599 (s), 1495 (s), 1334 (s), 1163 (s), 943 (s), 814 (s), 760 (s), 730 (s), 705 (s) cm^{-1}; HRMS (EI) *m/z* 394.1918 [(M^+), calcd. for $C_{20}H_{30}N_2O_4S$: 394.1926].

For previous synthesis see: Paquette, L. A.; Maleczka, Jr., R. E.; Qiu, F. *J. Org. Chem.* **1991**, *56*, 2455-2461.



124

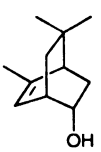
(+/-)-(1*R, 4*S**, 6*S**)-6-methoxymethoxy-3,8,8-trimethylbicyclo[2.2.2]oct-2-ene (124).**

To a cold (0 °C) magnetically stirred solution of 3.51 g **123** (8.9 mmol, 1.00 eq) in 40 mL PhH, 22.3 mL *n*-BuLi (1.6 M/hexanes, 4.01 eq) was added in a dropwise manner. After complete addition the reaction was stirred at 0 °C for 3 hrs The reaction was quenched with an aqueous solution of $NH_4Cl_{(sat)}$ and stirred at room temperature for 2 hrs The reaction was separated and the aqueous layer extracted once with 50 mL Et_2O. After separation the ethereal layer was washed three times with 40 mL of an aqueous soluton of $NH_4Cl_{(sat)}$. The combined aqueous layers were extracted once with 50 mL Et_2O. The

combined organics were was washed once with 30 mL brine, then dried over $MgSO_4$, filtered, and concentrated to produce an oil. The oil was purified *via* flash silica chromatography (25 g; 10%EtOAc/hexanes) to yield 1.2496 g **124** (67%) as an oil.

124: R_f = 0.61 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.68 (d, *J* = 6.3 Hz, 1 H), 4.62 (d, *J* = 6.9 Hz, 1 H), 4.58 (d, *J* = 6.9 Hz, 1 H), 3.82 (dt, *J* = 8.7, 3.3 Hz, 1 H), 3.31 (s, 3 H), 2.59 (sextet, *J* = 2.7 Hz, 1 H), 2.27 (ddd, *J* = 13.8, 8.4, 3.0 Hz, 1 H), 1.83 (s, 3 H), 1.81 (m, 1 H), 1.12 (m, 2 H), 1.03 (m, 1 H), 0.95 (s, 3 H), 0.79 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 145.0 (C), 120.3 (CH), 94.7 (CH_2), 75.5 (CH), 55.1 (CH_3), 47.7 (CH), 39.6 (CH_2), 36.8 (CH), 31.8 (CH_2), 31.5 (C), 31.0 (CH_3), 29.3 (CH_3), 22.0 (CH_3); IR (NaCl, neat) cm^{-1} 3015 (w), 2930 (s), 2864 (m), 2822 (w), 1464 (w), 1444 (w), 1363 (w), 1143 (m), 1101 (s), 1043 (s), 1027 (m), 991 (w), 945 (w), 918 (m), 802 (w); HRMS (CI) m/z 228.1976 [(M^+ NH_4), calcd. for $C_{13}H_{22}O_2$: 228.1964].

For previous synthesis see: Paquette, L. A.; Maleczka, Jr., R. E.; Qiu, F. *J. Org. Chem.* **1991**, *56*, 2455-2461.



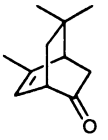
125

(+/-)-(1*R*, 2*S*, 4*S*)- 5,8,8-trimethyl-bicyclo[2.2.2]oct-5-en-2-ol (120).

To a stirring solution of 0.5575 g **124** (2.6 mmol, 1.00 eq) in 30 mL MeOH was added three drops of an aqueous 12 M HCl solution. The reaction was heated at 70 °C for 5 hrs, afterwhich the reaction was cooled to room temperature and concentrated. The residue was purified *via* flash chromotography (5 g; 5% EtOAc/hexanes) to provide 0.32 g (72%) of **125** as a white solid.

125: mp = 58-60 °C R_f = 0.32 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.64 (dd, *J* = 6.3, 1.2 Hz, 1 H), 3.84 (m, 1 H), 2.49 (sext, *J* = 3.0 Hz, 1 H), 2.32 (ddd, *J* = 19.5, 8.1, 2.7 Hz, 1 H), 1.82 (d, *J* = 1.8 Hz, 3 H), 1.79 (m, 1 H), 1.38 (br s, 1 H), 1.09 (m, 2 H), 0.93 (s, 3 H), 0.85 (dt, *J* = 14.1, 3.0 Hz, 1 H), 0.78 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 146.5 (C), 119.6 (CH), 70.2 (CH), 48.0 (CH), 39.8 (CH), 39.2 (CH_2), 34.7 (CH_2), 32.0 (C), 30.9 (CH_3), 29.2 (CH_3), 22.0 (CH_3); IR (KBr) cm^{-1} 3356 (br s), 3038 (m), 2945 (s), 2864 (s), 1623 (m), 1444 (s), 1361 (s), 1155 (m), 1130 (m), 1082 (s), 1060 (s), 1035 (m), 962 (m), 814 (m), 802 (m); HRMS (EI) *m/z* 166.1353 [(M^+), calcd. for $C_{11}H_{18}O$: 166.1358].

For previous synthesis see: Paquette, L. A.; Maleczka, Jr., R. E.; Qiu, F. *J. Org. Chem.* **1991**, *56*, 2455-2461.



126

(+/-)-(1*R*, 4*S*)- 5,8,8-trimethyl-bicyclo[2.2.2]oct-5-en-2-one (126).

CrO_3•pyridine Oxidation: To a stirring solution of 0.395 mL pyridine (4.8 mmol, 1.20 eq) in 25 mL CH_2Cl_2, 0.2497 g CrO_3 (2.4 mmol, 61 mol%) was added. The reaction was stirred for 15 min afterwhich, 0.6758 g **125** (4.0 mmol, 1.00 eq) in 6 mL CH_2Cl_2 was added dropwise. The reaction was stirred for an additional 15 min, then partitioned with the addition of 30 mL of an aqueous 1 M NaOH solution. After separation the CH_2Cl_2 phase was washed once with 30 mL of an aqueous 1 M NaOH solution, two times with 30 mL of an aqueous 1 M HCl solution, and two times with 30 mL of an aqueous solution of $NaHCO_{3(sat)}$.. The CH_2Cl_2 phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified *via* flash chromotography (7 g;

5%EtOAc/hexanes) to provide 0.2403 g (36%) of **126** as well as 0.2302 g (34% recovery) of **125**.

Dess-Martin Oxidation: To a stirring solution of 48.3 mg **125** (0.29 mmol, 1.00 eq) in 2.5 mL CH_2Cl_2, was added 0.1519 g Dess-Martin periodinane (0.35 mmol, 1.23 eq). The reaction was stirred at room temperature for 7 hrs and then partitioned with 5 mL CH_2Cl_2 and 6 mL of a 1:1 10% aqueous solution of $Na_2S_2O_3/NaHCO_{3(sat)}$. The biphasic reaction was stirred for 1 hr. After separation the aqueous layer was extracted twice with 15 mL CH_2Cl_2. The combined CH_2Cl_2 layers was dried over $MgSO_4$, filtered and concentrated to afford an oil. The oil was purified *via* flash chromotography (1 g; 5% EtOAc/hexanes) to provide 17.8 mg (38%) of **126** as well as 16.9 mg (35% recovery) of **125**.

Dess-Martin Periodinane: (a) Martin, J. C.; Dess, D. B. *J. Org. Chem.* **1983**, *48*, 4155-4156. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

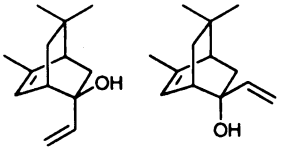
Swern Oxidation: A solution of 0.051 mL oxalyl chloride (0.5 mmol, 1.20 eq) in 2 mL CH_2Cl_2 was chilled to -78 °C, afterwhich 0.076 mL DMSO (1.0 mmol, 2.20 eq) was added in a dropwise manner. The reaction was stirred for 15 min before the dropwise addition of 81.0 mg **125** (0.48 mmol, 1.00 eq) in 1 mL CH_2Cl_2. After complete addition the reaction was stirred an additional 15 min before the dropwise addition of 0.34 mL $^iPr_2EtN$ (2.4 mmol, 5.00 eq). After its complete addition the reaction was warmed to room temperature and partitioned with the addition of 10 mL Et_2O and 10 mL H_2O. After separation the ethereal layer was washed two times with 10 mL H_2O. The combined aqueous layers were washed two times with 20 mL Et_2O. The combined ethereal layers were dried over $MgSO_4$, filtered and concentrated. The residue was

purified *via* flash chromotography (1 g; 5% EtOAc/hexanes) to provide 33.6 mg (42%) of the desired **126** as well as 22.2 mg (27% recovery) of **125**.

Swern Oxidation: Swern, D.; Mancuso, A. J. *Synthesis* **1981**, 165-184.

126: R_f = 0.56 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.69 (d, *J* = 3.0 Hz, 1 H), 2.87 (p, *J* = 2.4 Hz, 1 H), 2.29 (dd, *J* = 18.3, 2.1 Hz, 1 H), 2.15 (m, 1 H), 1.89 (dd, *J* = 18.6, 3.0 Hz, 1 H), 1.85 (d, *J* = 1.8 Hz, 3 H), 1.56 (dd, *J* = 13.2, 2.4 Hz, 1 H), 1.40 (dd, *J* = 13.2, 3.3 Hz, 1 H), 1.06 (s, 3 H), 0.94 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 213.6 (C), 147.7 (C), 118.5 (CH), 49.9 (CH), 49.5 (CH), 38.7 (CH_2), 36.2 (CH_2), 33.5 (C), 31.1 (CH_3), 28.4 (CH_3), 22.1 (CH_3); LRMS (EI) *m/z* 164.0 (M^+), 165.1 (M^{+1}).

For previous synthesis see: Paquette, L. A.; Maleczka, Jr., R. E.; Qiu, F. *J. Org. Chem.* **1991**, *56*, 2455-2461.



127 128

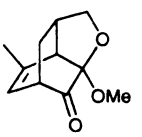
(+/-)-(1*R, 2*R**, 4*S**)-2-ethenyl-5,8,8-trimethyl-bicyclo[2.2.2]oct-5-en-2-ol (127) and (1*R**, 2*S**, 4*S**)-2-ethenyl-5,8,8-trimethyl-bicyclo[2.2.2]oct-5-en-2-ol (128).**

Following general procedure I, the reaction of 0.12 g (0.76 mmol) of starting ketone **126**, afforded 0.11 g (76%) of **127:128**, as a 3:1 diastereomeric mixture, after purification *via* flash silica chromatography (1.5 g; basic Activity III; 5% EtOAc/hexanes).

127: R_f = 0.60 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.88 (dd, *J* = 17.4, 10.5 Hz, 1 H), 5.67 (dt, *J* = 6.6, 1.5 Hz, 1 H), 5.08 (dd, *J* = 17.4, 1.5 Hz, 1 H), 4.87 (dd, *J* = 10.5, 1.5 Hz, 1 H), 2.18 (dt, *J* = 6.6, 2.7 Hz, 1 H), 1.92 (dd, *J* = 12.6, 2.4 Hz, 1 H), 1.83

(dd, J = 17.7, 2.4 Hz, 1 H), 1.81 (s, 1 H), 1.76 (d, J = 1.5 Hz, 3 H), 1.41 (dd, J = 17.1, 2.4 Hz, 1 H), 1.39 (d, J = 11.1 Hz, 1 H), 1.14 (s, 3 H), 0.92 (d, J = 12.6 Hz, 1 H), 0.81 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 147.9 (CH), 144.1 (C), 122.8 (CH), 109.2 (CH_2), 75.6 (C), 48.7 (CH), 43.7 (CH), 36.7 (CH_2), 35.3 (CH_2), 32.3 (C), 31.7 (CH_3), 28.0 (CH_3), 21.8 (CH_3); HRMS (EI) *m/z* 192.1521 [(M^+); calcd. for $C_{13}H_{20}O$: 192.1514].

128: R_f = 0.48 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.09 (dd, J = 17.0, 10.4 Hz, 1 H), 5.79 (dt, J = 6.0, J = 1.6 Hz, 1 H), 5.35 (dd, J = 17.5 Hz, 1.6 Hz, 1 H), 5.12 (dd, J = 10.9 Hz, 1.6 Hz, 1 H), 2.35 (m, 1 H), 2.22 (dd, J = 14.9 Hz, 2.2 Hz, 1 H), 1.84 (d, J = 1.6 Hz, 3 H), 1.37 (dd, J = 14.2 Hz, 1.6 Hz, 1 H), 1.22 (br s, 1 H), 1.21 (dd, J = 14.8, 2.7 Hz, 1 H), 1.11 (d, J = 7.1 Hz, 1 H), 0.99 (s, 3 H), 0.96 (d, J = 8.7 Hz, 1 H), 0.81 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 146.7 (CH), 142.7(C), 121.4 (CH), 113.3 (CH_2), 75.3 (C), 48.7 (CH), 37.9 (CH), 36.2 (CH_2), 36.1 (CH_2), 34.7 (C), 32.5 (CH_3), 31.3 (CH_3), 28.1 (CH_3); HRMS (EI) *m/z* 192.1521 [(M^+); calcd. for $C_{13}H_{20}O$: 192.1514].



129

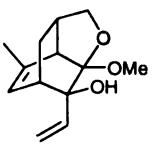
(+/-)-(1*S, 3*R**, 6*S**, 7*R**)-3-methoxy-8-methyl-4-oxa-tricyclo[4.3.1.0^{3,7}]dec-8-en-2-one (129).**

A solution of 4.92 mL 2-propenol (72.3 mmol, 5.00 eq), 5.59 g diacetoxyiodobenzene (17.3 mmol, 1.20 eq) in 25 mL CH_2Cl_2 was stirred at room temperature for 10 min afterwhich 1.83 mL *p*-cresol (14.4 mol, 1.00 eq) in 25 mL CH_2Cl_2 was added dropwise over the course of an hour. After complete addition the reaction was stirred at room temperature for 48 hrs The reaction was then concentrated and the

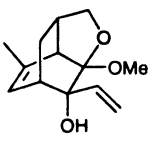
residual purified *via* flash silica chromatography (80 g; 30% EtOAc/hexanes) to provide 2.0552 g (73%) of **129** as a clear oil.

129: R_f = 0.19 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.86 (dt, *J* = 6.9, 1.8 Hz, 1 H), 4.05 (dd, *J* = 7.8, 3.6 Hz, 1 H), 3.70 (d, *J* = 7.8 Hz, 1 H), 3.44 (s, 3 H), 3.09 (dd, *J* = 4.2, 2.1 Hz, 1 H), 3.00 (dt, *J* = 6.6, 2.7 Hz, 1 H), 2.45 (m, 1 H), 1.83 (d, *J* = 1.5 Hz, 3 H), 1.70-1.80 (series of m, 2 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 201.7 (C), 139.1 (C), 122.5 (CH), 100.7 (C), 73.8 (CH_2), 51.0 (CH_3), 47.1 (CH), 45.1 (CH), 34.9 (CH), 31.2 (CH_2), 21.1 (CH_3); IR (NaCl, neat) cm^{-1} 3090 (w), 2947 (m), 1743 (s), 1442 (m), 1375 (m), 1298 (m), 1246 (s), 1167 (m), 1087 (ms), 1049 (ms), 1006 (m), 960 (ms), 916 (m), 827 (m), 765 (m), 733 (ms); HRMS (EI) *m/z* 194.1021 [(M^+); calcd. for $C_{11}H_{14}O_3$: 194.0943].

For previous synthesis see: Liao, C.; Chu, C.; Lee. T.; Rao, P. D.; Song, L. *J. Org. Chem.* **1999**, *64*, 4111-4118.



130



131

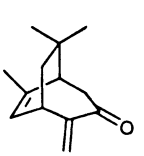
(+/-)-(1*S, 2*S**, 3*R**, 6*S**, 7*R**)-3-methoxy-8-methyl-2-vinyl-4-oxa-tricyclo[4.3.1.0^{3,7}]dec-8-en-2-ol (130) and (+/-)-(1*S**, 2*R**, 3*R**, 6*S**, 7*R**)-3-methoxy-8-methyl-2-vinyl-4-oxa-tricyclo[4.3.1.0^{3,7}]dec-8-en-2-ol (131).**

Following general procedure I, the reaction of 2.05 g (10.5 mmol) of starting ketone **129**, afforded 1.32 g (56%) of **130:131**, as a 10:1 diastereomeric mixture, after purification *via* flash silica chromatography (80 g; basic Activity III; 25:1 hexanes/EtOAc).

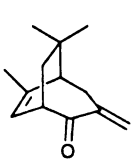
130: R_f = 0.35 (4:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.27 (dd, *J* = 17.4, 10.8 Hz, 1 H), 5.97 (dt, *J* = 6.6, 1.8 Hz, 1 H), 5.48 (dd, *J* = 17.4, 2.4 Hz, 1 H), 5.18 (dd, *J* = 10.8, 2.1 Hz, 1 H), 3.98 (dd, *J* = 7.5, 3.3 Hz, 1 H), 3.64 (d, *J* = 7.5 Hz, 1 H), 3.38 (s, 3 H), 2.81 (dd, *J* = 4.2, 1.2 Hz, 1 H), 2.72 (s, 1 H), 2.48 (dt, *J* = 6.6, 2.7 Hz, 1 H), 2.17 (m, 1 H), 1.85 (d, *J* = 1.5 Hz, 3 H), 1.61-1.51 (series of m, 2 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 138.1 (CH), 133.6 (C), 127.0 (CH), 113.1 (CH_2), 109.6 (C), 79.0 (C), 72.0 (CH_2), 50.9 (CH_3), 46.3 (CH), 41.8 (CH), 34.6 (CH), 30.6 (CH_2), 20.5 (CH_3); LRMS (EI) *m/z* 222.0 (M^+), 223.2 (M^{+1}); HRMS (EI) *m/z* 222.1260 [(M^+); calcd. for $C_{13}H_{18}O_3$: 222.1256].

131: R_f = 0.19 (4:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.87 (m, 2 H), 5.37 (dd, *J* = 17.2, 2.2 Hz, 1 H), 4.94 (dd, *J* = 10.6, 2.2 Hz, 1 H), 3.97 (dd, *J* = 7.5, 3.5 Hz, 1 H), 3.84 (s, 1 H), 3.67 (d, *J* = 7.5 Hz, 1 H), 3.25 (s, 3 H), 2.84 (d, *J* = 5.7 Hz, 1 H), 2.19 (m, 1 H), 2.16 (m, 1 H), 1.77 (d, *J* = 1.7 Hz, 3 H), 1.46-1.28 (series of m, 2 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 140.0 (CH), 138.9 (C), 127.4 (CH), 111.6 (CH_2), 108.50 (C), 80.0 (C), 72.9 (CH_2), 50.6 (CH_3), 47.1 (CH), 43.9 (CH), 35.7 (CH), 29.8 (CH_2), 21.0 (CH_3); LRMS (EI) *m/z* 222.0 (M^+), 223.2 (M^{+1}); HRMS (EI) *m/z* 222.1249 [(M^+); calcd. for $C_{13}H_{18}O_3$: 222.1256].

130:131: IR (neat) 3550 (br m), 3500 (br m), 3091 (w), 3020 (m), 2945 (s), 2874 (s), 1675 (w), 1625 (w), 1439 (s), 1329 (s), 1284 (s), 1253 (s), 1149 (s), 1081 (s), 1037 (s), 999 (s), 958 (s), 920 (s), 825 (s), 733 (s) cm^{-1}.



132



133

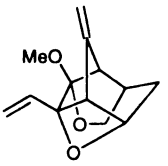
(+/-)-(1*S, 5*R**)-6,9,9-trimethyl-2-methylene-bicyclo[3.2.2]non-6-en-3-one (132) and (+/-)-(1*S**, 5*R**)-6,9,9-trimethyl-3-methylene-bicyclo[3.2.2]non-6-en-2-one (133).**

Following general procedure V, the reaction of 0.50 g (2.6 mmol) of starting carbinols **127:128**, as a 3:1 mixture, afforded 0.40 g (81%) of **132:133**, as a 5:1 regiomeric mixture, after purification *via* flash silica chromatography (4.5 g; 1% Et_3N/hexanes).

132: R_f = 0.52 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.86 (m, 1 H), 5.58 (d, 7.1 Hz, 1 H), 5.20 (m, 1 H), 3.01 (t, *J* = 7.6 Hz, 1 H), 2.91 (dd, *J* = 17.0, 4.4 Hz, 1 H), 2.82 (dd, *J* = 17.2, 4.4 Hz, 1 H), 2.54 (q, *J* = 2.7 Hz, 1 H), 1.91 (d, *J* = 7.7 Hz, 1 H), 1.83 (d, *J* = 1.6 Hz, 3 H), 1.20 (d, *J* = 7.1 Hz, 1 H), 1.13 (s, 3 H), 0.94 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 213.8 (C), 154.2 (C), 147.9 (C), 118.8 (CH), 116.0 (CH_2), 50.0 (CH), 48.3 (CH), 39.2 (CH_2), 36.8 (CH_2), 34.2 (C), 30.1 (CH_3), 28.9 (CH_3), 21.2 (CH_3); HRMS (EI) *m/z* 190.1347 [(M^+); calcd. for $C_{13}H_{18}O$: 190.1358].

133: R_f = 0.48 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.77 (d, *J* = 7.1 Hz, 1 H), 5.72 (d, *J* = 2.2 Hz, 1 H), 5.03 (d, *J* = 2.2 Hz, 1 H), 3.10 (t, *J* = 7.1 Hz, 1 H), 2.48 (q, *J* = 2.7 Hz, 1 H), 2.31 (dd, *J* = 19.2, 3.8 Hz, 1 H), 1.89 (d, *J* = 7.7 Hz, 1 H), 1.81 (d, *J* = 1.6 Hz, 3 H), 1.66 (dd, *J* = 19.5, 3.8 Hz, 1 H), 1.01 (d, *J* = 7.1 Hz, 1 H), 1.04 (s, 3 H), 0.96 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 215.1 (C), 153.1 (C), 148.2 (C), 119.1 (CH), 116.4 (CH_2), 54.0 (CH), 52.7 (CH), 39.5 (CH_2), 35.9 (CH_2), 31.5 (C), 29.4 (CH_3), 22.5 (CH_3), 20.5 (CH_3); LRMS (EI) *m/z* 190.1 (M^+).

132:133: IR (neat) 3041 (m), 2975 (s), 2962 (s), 1715 (s), 1680 (m), 1448 (s), 1373 (s), 1130 (s), 958 (m), 760 (m) cm^{-1}.

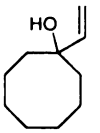


134

(+/-)-(1*S*, 2*R***, 7*R***, 8*S***, 10*S***)-(2, 10)-epoxy-7-methoxy-9-methylene-10-vinyl-6-oxa-tricyclo[5.2.1.0^{1,10}]dec-3-en-10-ol (134).**

Following general procedure V, the reaction of 0.14 g (0.65 mmol) of starting carbinols **130**, afforded 60.4 mg (90%) of **134** after purification *via* flash silica chromatography (3 g; 1% Et_3N/hexanes).

134: R_f = 0.48 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.29 (dd, *J* = 17.4, 10.8 Hz, 1 H), 5.44 (dd, *J* = 17.1, 1.8 Hz, 1 H), 5.42 (s, 1 H), 5.29 (s, 1 H), 5.26 (m, 1 H), 5.21 (dd, *J* = 11.1, 1.5 Hz, 1 H), 3.95 (dd, *J* = 7.2, 3.0 Hz, 1 H), 3.58 (d, *J* = 7.5 Hz, 1 H), 3.35 (s, 3 H), 3.06 (m, 1H), 2.83 (d, *J* = 4.2 Hz, 1 H), 2.63 (m, 1 H), 2.46 (dm, *J* = 10.8 Hz, 1 H), 2.11 (q, *J* = 3.0 Hz, 1 H) ^{13}C-NMR (125 MHz, $CDCl_3$) δ 142.8 (C), 137.7 (CH), 118.6 (CH_2), 114.2 (CH_2), 107.9 (C), 78.7 (C), 74.1 (CH_2), 56.4 (CH), 49.8 (CH_3), 44.8 (CH), 43.4 (CH), 36.0 (CH), 23.6 (CH_2); HRMS (EI) *m/z* 220.1186 [(M^+); calcd. for $C_{13}H_{16}O_3$: 220.2643].



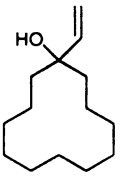
139

1-vinyl-cyclooctanol (139).

Following general procedure III, the reaction of 2.0 g (15.8 mmol) of cyclooctanone, afforded 2.19 g (90%) of **139** after purification *via* flash silica chromatography (60 g; basic Activity III; 20:1 hexanes/EtOAc).

139: R_f = 0.25 (9:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.94 (dd, *J* = 17.5, 10.5 Hz, 1 H), 5.15 (dd, *J* = 17.5, 1.5 Hz, 1 H), 4.94 (dd, *J* = 10.5, 1.5 Hz, 1 H), 2.33 (m, 1 H), 1.80 (m, 1 H), 1.70 (m, 2 H), 1.58 (m, 6 H), 1.44 (m, 4 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 145.8 (CH), 111.1 (CH_2), 125.0 (C), 41.7 (CH_2), 36.0 ($2CH_2$), 28.1 ($2CH_2$), 21.8 ($2CH_2$); IR (neat) 3420 (br s), 3065 (w), 3015 (w), 2926 (s), 2856 (s), 1693 (m), 1473 (m), 1448 (m), 1414 (m), 1334 (w), 1242 (w), 1161 (w), 1093 (w), 995 (s), 918 (s), 734 (m) cm^{-1}; LRMS (EI) *m/z* 152.2 (M^+).

Commerically available or for original synthesis see: Marcou, A.; Normant, H. *Bull. Soc. Chim. Fr.* **1965**, 3491-3494.



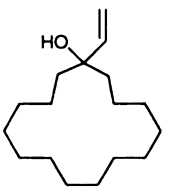
140

1-vinyl-cyclododecanol (140).

Following general procedure III, the reaction of 2.0 g (10.9 mmol) of cyclododecanone, afforded 2.03 g (88%) of **140** after purification *via* flash silica chromatography (60 g; basic Activity III; 20:1 hexanes/EtOAc).

140: R_f = 0.12 (95:5 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.93 (dd, *J* = 17.5, 11.0 Hz, 1 H), 5.17 (dd, *J* = 17.5, 1.5 Hz, 1 H), 4.97 (dd, *J* = 11.0, 1.5 Hz, 1 H), 1.59 (m, 2 H), 1.40 (m, 4 H), 1.31 (m, 17 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 145.3 (CH), 111.0 (CH_2), 73.3 (C), 34.6 ($2CH_2$), 26.3 ($2CH_2$), 25.9 ($2CH_2$), 22.5 ($2CH_2$), 22.1 ($2CH_2$), 19.5 (CH_2); IR (neat) 3414 (br s), 3092 (w), 2939 (s), 2853 (s), 1620 (m), 1471 (s), 1448 (s), 1348 (m), 1365 (m), 1170 (m), 1062 (s), 997 (s), 918 (s), 738 (s) cm^{-1}; LRMS (EI) *m/z*

210.0 (M^+). For original synthesis see: Marcou, A.; Normant, H. *Bull. Soc. Chim. France* **1965**, 3491-3494.

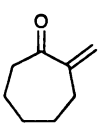


141

1-vinyl-cyclopentadecanol (141).

Following general procedure III, the reaction of 2.0 g (8.9 mmol) of cyclopentadecanone, afforded 1.75 g (78%) of **141** after purification *via* flash silica chromatography (60 g; basic Activity III; 20:1 hexanes/EtOAc).

141: R_f = 0.50 (9:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.96 (dd, *J* = 17.5, 11.0 Hz, 1 H), 5.21 (d, *J* = 17.5 Hz, 1 H), 5.03 (d, *J* = 11.0 Hz, 1 H), 1.51 (m, 4 H), 1.36 (m, 25 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 145.4 (CH), 111.4 (CH_2), 75.1 (C), 38.2 ($2CH_2$), 27.7 ($2CH_2$), 26.9 ($2CH_2$), 26.7 ($2CH_2$), 26.7 ($2CH_2$), 26.3 ($2CH_2$), 21.8 ($2CH_2$); IR (neat) 3377 (br m), 3084 (w), 3011 (w), 2932 (s), 2858 (s), 1639 (w), 1458 (m), 1412 (w), 1350 (w), 1280 (w), 1155 (w), 1133 (w), 995 (m), 918 (s), 734 (s) cm^{-1}; HRMS (EI) *m/z* 252.2453 [(M^+) calcd. for $C_{17}H_{32}O$: 252.2453].



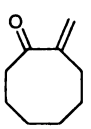
142

2-methylene-cycloheptanone (142).

Following general procedure V, the reaction of 0.21 g (1.6 mmol) of starting carbinol **80** and afforded 0.15 g (72%) of **142** after purification *via* flash silica chromatography (3 g; 2% Et_3N/hexanes).

142: R_f = 0.53 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.92 (d, *J* = 2.1 Hz, 1 H), 5.22 (d, *J* = 2.1 Hz, 1 H), 2.57 (d, *J* = 11.1 Hz, 2 H), 2.46 (d, *J* = 9.6 Hz, 2 H), 1.66 (series of m, 6 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 203.6 (C), 148.3 (C), 122.4 (CH_2), 43.4 (CH_2), 33.8 (CH_2), 31.2 (CH_2), 30.4 (CH_2), 25.2 (CH_2); IR (neat) 3065 (w), 2928 (s), 2858 (s), 1703 (s), 1610 (w), 1452 (s), 1317 (w), 1230 (m), 1167 (m), 1135 (m), 1105 (m), 1049 (m), 978 (m), 943 (m), 748 (w) cm^{-1}; HRMS (EI) *m/z* 124.0890 [(M^+) calcd. for $C_8H_{12}O$: 124.0888].

For previous syntheses see: (a) Muehlstaedt, M.; Herzschuh, R. *J. Prakt. Chem.* **1963**, *20*, 20-34. (b) Muehlstaedt, M.; Zach, L.; Becwar-Reinhardt, H. *J. Prakt. Chem.* **1965**, *29*, 158-172. (c) Ksander, G. M.; McMurry, J. E.; Johnson, M. *J. Org. Chem.* **1977**, *42*, 1180-1185.



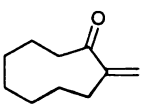
143

2-methylene-cyclooctanone (143).

Following general procedure V, the reaction of 0.25 g (1.7 mmol) of starting carbinol **81** and afforded 0.15 g (70%) of **143** after purification *via* flash silica chromatography (3 g; 2% Et_3N/hexanes).

143: R_f = 0.51 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.75 (d, *J* = 2.4 Hz, 1 H), 5.12 (d, *J* = 2.1 Hz, 1 H), 2.48 (m, 2 H), 1.67 (m, 2 H), 1.50 (series of m, 6 H), 1.35 (m, 2 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 206.6 (C), 148.4 (C), 121.8 (CH_2), 39.2 (CH_2), 31.0 (CH_2), 30.5 (CH_2), 28.8 (CH_2), 28.9 (CH_2), 25.2 (CH_2); IR (neat) 2928 (s), 2856 (s), 1701 (s), 1466 (s), 1373 (m), 1240 (s), 1172 (w), 1128 (s), 1087 (w), 1047 (m), 935 (w), 910 (w), 733 (w) cm^{-1}; HRMS (EI) *m/z* 138.1055 [(M^+) calcd. for $C_9H_{14}O$: 138.1045].

For previous syntheses see: (a) Muehlstaedt, M.; Herzschuh, R. *J. Prakt. Chem.* **1963**, *20*, 20-34. (b) Muehlstaedt, M.; Zach, L.; Becwar-Reinhardt, H. *J. Prakt. Chem.* **1965**, *29*, 158-172. (c) Ksander, G. M.; McMurry, J. E.; Johnson, M. *J. Org. Chem.* **1977**, *42*, 1180-1185.



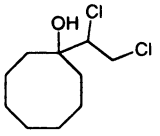
144

2-methylene-cyclononanone (144).

Following general procedure V, the reaction of 0.29 g (1.4 mmol) of starting carbinol **139** and afforded 0.19 g (53%) of **144** and 26.5 mg (6%) **146** after purification *via* flash silica chromatography (3 g; 2% Et_3N/hexanes).

144: R_f = 0.74 (4:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.43 (d, *J* = 0.8 Hz, 1 H), 5.34 (d, *J* = 0.8 Hz, 1 H), 2.59 (m, 2 H), 2.42 (td, *J* = 6.1, 0.8 Hz, 2 H), 1.79 (p, *J* = 6.1 Hz, 2 H), 1.49 (series of m, 4 H), 1.36 (series of m, 4 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 210.8 (C), 152.2 (C), 118.5 (CH_2), 41.5 (CH_2), 32.6 (CH_2), 26.7 (CH_2), 26.1 (CH_2), 24.3 (CH_2), 24.2 (CH_2), 22.4 (CH_2); IR (neat) 3088 (w), 3065 (w), 2932 (s), 2874 (m). 1682 (s), 1620 (w), 1469 (m), 1444 (m), 1361 (w), 1298 (w), 1267 (w), 1205 (w), 1147 (w), 1113 (w), 1089 (w), 1039 (w), 922 (m), 908 (m), 736 (m) cm^{-1}; HRMS (EI) *m/z* 152.1201 [(M^+) calcd. for $C_{10}H_{16}O$: 152.1201].

For previous syntheses see: (a) Muehlstaedt, M.; Herzschuh, R. *J. Prakt. Chem.* **1963**, *20*, 20-34. (b) Muehlstaedt, M.; Zach, L.; Becwar-Reinhardt, H. *J. Prakt. Chem.* **1965**, *29*, 158-172. (c) Ksander, G. M.; McMurry, J. E.; Johnson, M. *J. Org. Chem.* **1977**, *42*, 1180-1185.

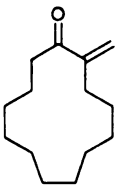


146

1-(1,2-dichloro-ethyl)-cyclooctanol (146).

Following general procedure V, the reaction of 0.29 g (1.4 mmol) of starting carbinol **139** and afforded 0.19 g (53%) of **144** and 26.5 mg (6%) **146** after purification *via* flash silica chromatography (3 g; 2% Et_3N/hexanes).

146: R_f = 0.42 (4:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.04 (m, 2 H), 3.67 (AB_q, J = 12.8, 3.0 Hz, 1 H), 1.90 (m, 3 H), 1.77 (m, 1 H), 1.60 (series of m, 7 H), 1.35 (series of m, 4 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 76.4 (C), 71.7 (CH), 46.1 (CH_2), 34.5 (CH_2), 33.9 (CH_2), 28.6 (CH_2), 27.1 (CH_2), 25.0 (CH_2), 22.1 (CH_2), 22.0 (CH_2); IR (neat) 3462 (br m), 2924 (s), 2856 (m), 1471 (m), 1367 (m), 1251 (m), 1068 (m), 1016 (m), 939 (m), 734 (m) cm^{-1}; HRMS (EI) *m/z* 224.0721 [(M^+) calcd. for $C_{10}H_{18}O^{35}Cl_2$: 224.0735].



147

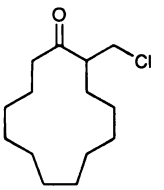
2-methylene-cyclotridecanone (147).

Following general procedure V, the reaction of 0.29 g (1.4 mmol) of starting carbinol **140** and afforded 0.15 g (53%) of **147**, 10.4 mg (3%) **148** and 11.9 mg (3%) **149** after purification *via* flash silica chromatography (3 g; 3% Et_3N/hexanes).

147: R_f = 0.78 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.93 (s, 1 H), 5.68 (s, 1 H), 2.70 (m, 1 H), 2.31 (m, 1 H), 1.95 (m, 2 H), 1.65 (m, 2 H), 1.53 (m, 2 H), 1.24 (series of m, 14 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 204.2 (C), 149.4 (C), 125.3 (CH_2),

37.1 (CH_2), 31.0 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 25.3 (CH_2), 24.7 (CH_2), 24.5 (CH_2), 24.1 (CH_2); IR (neat) 2932 (s), 2862 (s), 1716 (m), 1672 (m), 1462 (m), 1444 (m), 1360 (w), 1267 (w), 1111 (w), 1070 (w), 933 (w), 733 (m) cm^{-1}; LRMS (EI) m/z 208.1 (M^+).

For previous syntheses see: Muehlstaedt, M.; Remane, H.; Graefe, J. *Z. Chem.* **1969**, *9*, 303-305. (b) Muehlstaedt, M.; Koehler, H. J.; Porzig, D.; Scholz, M. *J. Prakt. Chem.* **1970**, *312*, 292-299. (c) Marshall, J. A.; Audia, v. H. *J. Org. Chem.* **1985**, *50*, 1607-1611.

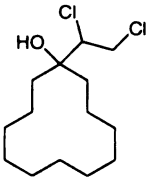


148

2-chloromethyl-cyclotridecanone (148).

Following general procedure V, the reaction of 0.29 g (1.4 mmol) of starting carbinol **140** and afforded 0.15 g (53%) of **147**, 10.4 mg (3%) **148** and 11.9 mg (3%) **149** after purification *via* flash silica chromatography (3 g; 3% Et_3N/hexanes).

148: R_f = 0.80 (5:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.67 (dd, *J* = 11.0, 9.2 Hz, 1 H), 3.39 (dd, *J* = 10.6, 5.3 Hz, 1 H), 2.88 (m, 1 H), 2.72 (ddd, *J* = 18.1, 10.1, 3.0 Hz, 1 H), 2.37 (ddd, *J* = 18.1, 6.6, 3.5 Hz, 1 H), 1.94 (m, 1 H), 1.51 (m, 2 H), 1.26 (series of m, 17 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 212.1 (C), 54.1 (CH), 44.4 (CH_2), 42.7 (CH_2), 30.1 (CH2), 26.3 (CH_2), 26.2 (CH_2), 26.1 (CH_2), 24.8 (CH_2), 24.4 (CH_2), 24.0 (CH_2), 23.8 (CH_2), 23.4 (CH_2), 21.6 (CH_2); IR (neat) 2930 (s), 2858 (s), 1709 (s), 1462 (s), 1410 (s), 1371 (m), 1286 (m), 1168 (m), 1115 (m), 1087 (m), 1030 (m), 916 (m), 733 (s) cm^{-1}; HRMS (EI) *m/z* 244.1623 [(M^+) calcd. for $C_{14}H_{25}{}^{35}ClO$: 244.1594].

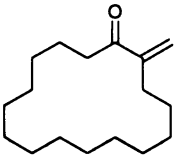


149

1-(1,2-dichloro-ethyl)-cyclododecanol (149).

Following general procedure V, the reaction of 0.29 g (1.4 mmol) of starting carbinol **140** and afforded 0.15 g (53%) of **147**, 10.4 mg (3%) **148** and 11.9 mg (3%) **149** after purification *via* flash silica chromatography (3 g; 3% Et_3N/hexanes).

149: R_f = 0.35 (5:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.09 (dd, *J* = 13.2, 6.1 Hz, 1 H), 3.96 (m, 2 H), 2.33 (br s, 1 H), 1.78 (m, 2 H), 1.54 (dt, *J* = 11.9, 4.8 Hz, 1 H), 1.34 (series of m, 19 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 77.5 (C), 70.8 (CH), 64.1 (CH2), 33.3 (CH_2), 31.7 (CH_2), 26.4 (CH_2), 26.2 (CH_2), 25.9 (CH_2), 22.5 (CH_2), 22.4 (CH_2), 22.1 (CH_2), 22.0 (CH_2), 19.6 (CH_2), 19.1 (CH_2); IR (neat) 3372 (br s), 2930 (s), 2862 (s), 1471 (s), 1444 (m), 1348 (w), 1265 (w), 1161 (w), 1076 (m), 1032 (m), 736 (m) cm^{-1}; HRMS (EI) *m/z* 280.1360 [(M^+) calcd. for $C_{14}H_{26}O^{35}Cl_2$: 280.1361].



150

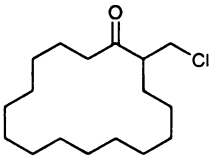
2-methylene-cyclohexadecanone (150).

Following general procedure V, the reaction of 0.35 g (1.4 mmol) of starting carbinol **136** and afforded 0.16 g (45%) of **150**, 16.1 mg (4%) **151** and 18.1 mg (4%) **152** after purification *via* flash silica chromatography (3 g; 3% Et_3N/hexanes).

150: R_f = 0.53 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.92 (s, 1 H), 5.69 (s, 1 H), 2.72 (ddd, *J* = 18.6, 10.2, 3.0 Hz, 1 H), 2.62 (m, 1 H), 2.32 (m, 1 H), 1.92 (m, 1

H), 1.65 (series of m, 3 H), 1.51 (series of m, 3 H), 1.25 (series of m, 18 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 204.2 (C), 149.4 (C), 125.3 (CH_2), 42.7 (CH_2), 37.1 (CH_2), 30.9 (CH_2), 25.8 (CH_2), 25.3 (CH_2), 24.8 (CH_2), 24.7 (CH_2), 24.5 (CH_2), 24.4 (CH_2), 24.1 (CH_2), 24.0 (CH_2), 23.8 (CH_2), 23.4 (CH_2), 21.6 (CH_2); IR (neat) 3056 (w), 2943 (s), 2868 (s), 1720 (s), 1675 (w), 1478 (s), 1442 (s), 1364 (m), 1262 (m), 1105 (m), 1072 (m), 928 (w), 744 (s) cm^{-1}; LRMS (EI) m/z 250.1 (M^+).

For previous syntheses see: (a) Muehlstaedt, M.; Koehler, H. J.; Porzig, D.; Scholz, M. *J. Prakt. Chem.* **1970**, *312*, 292-299. (b) Marshall, J. A.; Audia, v. H. *J. Org. Chem.* **1985**, *50*, 1607-1611



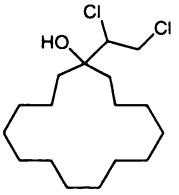
151

2-methylene-cyclohexadecanone (151).

Following general procedure V, the reaction of 0.35 g (1.4 mmol) of starting carbinol **136** and afforded 0.16 g (45%) of **150**, 16.1 mg (4%) **151** and 18.1 mg (4%) **152** after purification *via* flash silica chromatography (3 g; 3% Et_3N/hexanes).

151: R_f = 0.43 (95:5 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.66 (d, *J* = 10.5 Hz, 1 H), 3.43 (dd, *J* = 11.0, 6.0 Hz, 1 H), 2.90 (m, 1 H), 2.55 (m, 1 H), 2.41 (m, 1 H), 1.74 (m, 1 H), 1.63 (m, 2 H), 1.47 (m, 4 H), 1.26 (series of m, 19 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 211.9 (C), 53.8 (CH), 44.3 (CH_2), 43.0 (CH_2), 30.3 (CH_2), 27.8 (CH2), 27.5 (CH_2), 27.3 (CH2), 27.0 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 26.2 (CH_2), 26.1 (CH_2), 26.1 (CH_2), 25.6 (CH_2), 21.8 (CH_2); IR (neat) 2928 (s), 2855 (s), 1716 (s),

1458 (s), 1369 (w), 1284 (w), 1091 (w), 908 (m), 733 (s) cm^{-1}; HRMS (EI) *m/z* 287.2145 [(M^+) calcd. for $C_{17}H_{31}O^{35}Cl$: 286.2063].

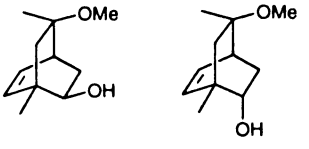


152

1-(1,2-dichloro-ethyl)-cyclopentadecanol (152).

Following general procedure V, the reaction of 0.35 g (1.4 mmol) of starting carbinol **136** and afforded 0.16 g (45%) of **150**, 16.1 mg (4%) **151** and 18.1 mg (4%) **152** after purification *via* flash silica chromatography (3 g; 3% Et_3N/hexanes).

152: R_f = 0.26 (95:5 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.03 (m, 2 H), 3.70 (t, *J* = 10.0 Hz, 1 H), 1.78 (br s, 1 H), 1.65 (m, 2 H), 1.62 (m, 1 H), 1.50 (m, 1 H), 1.34 (m, 24H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 223.8 (C), 76.4 (C), 71.2 (CH), 46.0 (CH_2), 37.3 (CH_2), 34.8 (CH_2), 27.5 (CH_2), 27.4 (CH_2), 26.8 (CH_2), 26.5 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 21.7 (2 CH_2); IR (neat) 3464 (br w), 2934 (s), 2858 (s), 1460 (m), 1350 (w), 1259 (w), 1151 (w), 1091 (w), 1047 (w), 908 (s), 734 (s) cm^{-1}; HRMS (EI) *m/z* 322.1855 [(M^+) calcd. for $C_{17}H_{32}O^{35}Cl_2$: 322.1830].



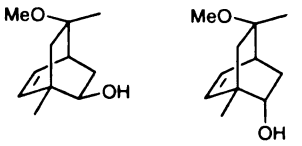
153 154

(1*S, 2*R**, 4*S**, 8*R**)-8-methoxy-1,8-dimethylbicyclo[2.2.2]oct-5-en-2-ol (153) and (1*S**, 2*S**, 4*S**, 8*R**)-8-methoxy-1,8-dimethylbicyclo[2.2.2]oct-5-en-2-ol (154).**

Following general procedure IV, the reaction of 2.02 g (11.2 mmol) of starting ketone **27**, afforded 1.16 g (57%) of **153:154**, as a 1:1 diastereomeric mixture, with no purification necessary.

153: R_f = 0.45 (5:1 hexanes/EtOAc); $[\alpha]_{D}^{20}$ = -26.2 (*c* 0.36, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.11 (t, *J* = 8.1 Hz, 1 H), 5.69 (d, *J* = 7.8 Hz, 1 H), 3.33 (dm, *J* = 9.3 Hz, 1 H), 3.09 (s, 3 H), 2.43 (m, 1 H), 2.09 (br s, 1 H), 1.79 (d, *J* = 13.8 Hz, 1 H), 1.61 (dd, *J* = 13.5, 2.7 Hz, 1 H), 1.21 (d, *J* = 13.5 Hz, 1 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 0.80 (dt, *J* = 13.5, 3.0 Hz, 1 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 134.9 (CH), 134.0 (CH), 78.8 (C), 71.4 (CH), 49.3 (CH_3), 42.3 (CH_2), 40.5 (C), 39.2 (CH), 32.9 (CH_2), 24.5 (CH_3), 21.2 (CH_3); IR (neat) 3439 (br s), 3040 (m), 2930 (s), 2828 (m), 1579 (w), 1516 (w), 1456 (s), 1365 (s) 1323 (m), 1259 (m), 1194 (m), 1165 (m), 1089 (s), 1070 (s), 995 (w), 922 (w), 846 (w), 723 (m), 704 (s) cm^{-1}; LRMS (EI) *m/z* 150.0 (M^+ -MeOH); HRMS (EI) *m/z* 182.1303 [(M^+); calcd. for $C_{11}H_{18}O_2$: 182.1307].

154: R_f = 0.36 (5:1 hexanes/EtOAc); $[\alpha]_{D}^{20}$ = -98.0 (*c* 0.14, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.25 (t, *J* = 8.1 Hz, 1 H), 5.76 (d, *J* = 8.1 Hz, 1 H), 3.54 (dm, *J* = 8.4 Hz, 1 H), 3.05 (s, 3 H), 2.45 (m, 1 H), 2.09 (br s, 1 H), 1.79 (d, *J* = 13.8 Hz, 1 H), 1.53 (dt, *J* = 13.8, 2.7 Hz, 1 H), 1.21 (d, *J* = 13.5 Hz, 1 H), 1.04 (s, 3 H), 1.00 (s, 3 H), 0.88 (dd, *J* = 13.5, 1.5 Hz, 1 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 138.6 (CH), 133.9 (CH), 78.7 (C), 73.4 (CH), 49.3 (CH_3), 46.6 (CH_2), 40.7 (C), 39.4 (CH), 33.9 (CH_2), 24.2 (CH_3), 21.0 (CH_3); IR (neat) 3441 (br s), 3042 (m), 2934 (s), 2826 (m), 1579 (w), 1516 (w), 1460 (m), 1367 (m), 1325 (w), 1246 (w), 1196 (w), 1159 (w), 1101 (m), 1066 (s), 995 (w), 902 (w), 843 (w), 727 (m), 704 (w), 677 (w) cm^{-1}; LRMS (EI) *m/z* 149.8 (M^+ -MeOH); HRMS (EI) *m/z* 182.1312 [(M^+); calcd. for $C_{11}H_{18}O_2$: 182.1307].



155 156

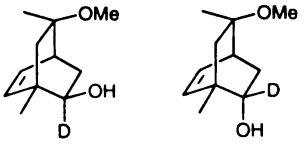
(1*S, 2*R**, 4*S**, 8*S**)-8-methoxy-1,8-dimethylbicyclo[2.2.2]oct-5-en-2-ol (155) and (1*S**, 2*S**, 4*S**, 8*S**)-8-methoxy-1,8-dimethylbicyclo[2.2.2]oct-5-en-2-ol (156).**

Following general procedure IV, the reaction of 2.07 g (11.4 mmol) of starting ketone **28**, afforded 1.66 g (79%) of **155:156**, as a 1:1 diastereomeric mixture, with no purification necessary.

155: R_f = 0.12 (25:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.21 (AB_q, *J* = 6.3, 2.1 Hz, 1 H), 5.88 (d, *J* = 8.1 Hz, 1 H), 3.45 (dt, *J* = 9.9, 2.4 Hz, 1 H), 3.10 (s, 3 H), 2.56 (m, 1 H), 2.00 (s, 1 H), 1.83 (d, *J* = 13.2 Hz, 1 H), 1.79 (d, *J* = 13.2 Hz, 1 H), 1.37 (s, 3 H), 1.30 (dt, *J* = 14.1, 2.7Hz, 1 H), 1.13 (dd, *J* = 13.5Hz, *J* = 1.5 Hz, 1 H), 1.09 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 136.0 (CH), 133.9 (CH), 79.5 (C), 48.9 (CH_3), 41.5 (CH_2), 40.3 (C), 39.4 (CH), 32.8 (CH_2), 25.5 (CH_2), 21.9 (CH_3), 21.1 (CH_3); IR (neat) 3445 (br s), 3040 (m), 2970 (s), 2824 (m), 1550 (m), 1460 (s), 1371 (s) 1325 (m), 1259 (m), 1190 (m), 1126 (s), 1099 (s), 1074 (s), 997 (m), 968 (m), 918 (s), 897 (m), 702 (s), 677 (m) cm^{-1}; HRMS (EI) *m/z* 182.1302 [(M^+); calcd. for $C_{11}H_{18}O_2$: 182.1307].

156: R_f = 0.22 (25:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.38 (AB_q, *J* = 6.6, 1.8 Hz, 1 H), 5.88 (d, *J* = 5.1 Hz, 1 H), 3.49 (m, 1 H), 3.09 (s, 3 H), 2.62 (m, 1 H), 2.17 (ddd, *J* = 4.94, 3.29, 1.09 Hz,, 1 H), 1.39 (d, *J* = 13.5 Hz, 1 H), 1.26 (s, 1 H), 1.25 (s, 3 H), 1.19 (s, 3 H), 1.07 (d, *J* = 13.8 Hz, 1 H), 0.98 (dt, *J* = 14.7, 3.3 Hz, 1 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 134.2 (CH), 133.4 (CH), 78.9 (C), 74.2 (CH), 49.3 (CH_3), 47.2 (CH_2), 40.9 (C), 39.3 (CH), 35.9 (CH_2), 22.8 (CH_3), 21.2 (CH_3); IR (neat) 3437 (br s),

3034 (s), 2932 (s), 2831 (s), 1610 (w), 1454 (s), 1369 (s), 1344 (s), 1307 (s), 1273 (s), 1192 (s), 1136 (s), 1076 (s), 955 (s), 881 (m), 850 (s), 819 (m), 756 (s), 731 (s), 657 (w) cm^{-1}; HRMS (EI) *m/z* 182.1301 [(M^+); calcd. for $C_{11}H_{18}O_2$: 182.1307].



157 158

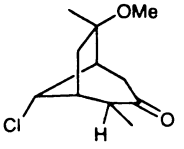
(1*S, 2*R**, 4*S**, 8*R**)-8-methoxy-1,8-dimethylbicyclo[2.2.2]oct-5-en-2-ol (157) and (1*S**, 2*S**, 4*S**, 8*R**)-8-methoxy-1,8-dimethylbicyclo[2.2.2]oct-5-en-2-ol (158).**

Following general procedure IV, the reaction of 2.00 g (11.1 mmol) of starting ketone **27**, afforded 1.00 g (49%) of **157:158** as a 1:1 diastereomeric mixture, with no purification necessary.

157: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (AB_q, *J* = 8.1 Hz, *J* = 1.2 Hz, 1 H), 5.77 (d, *J* = 8.1 Hz, 1 H), 3.17 (s, 3 H), 2.53 (m, 1 H), 2.48 (d, *J* = 14.4 Hz, 1 H), 1.87 (s, 1 H), 1.67 (m, 1 H), 1.61 (dd, *J* = 13.5, 2.7 Hz, 1 H), 1.16 (s, 3 H), 1.10 (s, 3 H), 0.86 (dd, *J* = 13.5, 2.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.9 (CH), 134.5 (CH), 78.9 (C), 77.5 (CD), 49.4 (CH_3), 42.7 (CH_2), 40.5 (C), 39.4 (CH), 33.5 (CH_2), 24.6 (CH_3), 21.2 (CH_3); IR (neat) 3433 (br s), 3040 (m), 2934 (s), 2870 (s), 2826 (m), 1458 (s), 1385 (s), 1325 (m), 1280 (m), 1221 (m), 1145 (s), 1109 (s), 1076 (s), 947 (m), 920 (m), 890 (m), 723 (s), 700 (m), 673 (m) cm^{-1}; HRMS (EI) *m/z* 183.1342 [(M^+); calcd. for $C_{11}H_{17}DO_2$: 183.1369].

158: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.33 (t, *J* = 7.2 Hz, 1 H), 5.85 (d, *J* = 7.8 Hz, 1 H), 3.13 (s, 3 H), 2.53 (m, 1 H), 1.83 (s, 1 H), 1.72 (m, 1 H), 1.61 (dd, *J* = 13.5, 2.7 Hz, 1 H), 1.29 (d, *J* = 13.5 Hz, 1 H), 1.12 (s, 3 H), 1.08 (s, 3 H), 0.97 (d, *J* = 13.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8 (CH), 134.3 (CH), 78.8 (C), 76.4 (CD), 49.5 (CH_3), 46.6

(CH_2), 40.8 (C), 39.5 (CH), 34.0 (CH_2), 24.3 (CH_3), 21.1 (CH_3); HRMS (EI) *m/z* 183.1378 [(M^+); calcd. for $C_{11}H_{17}DO_2$: 183.1369].

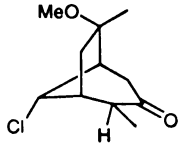


163

(1*R, 2*S**, 5*S**, 6*S**, 8*R**)-2-8-chloro-6-methoxy-2,6-dimethyl-bicyclo[3.2.1]octan-3-one (163).**

Following general procedure V, the reaction of 0.93 g (5.1 mmol) of **153:154**, as a 1:1 diastereomeric mixture, afforded 0.49 g (45%) of **158** after purification *via* flash silica chromatography (15 g, 1% Et_3N/hexanes).

163: R_f = 0.31 (4:1 hexanes/EOtAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.37 (td, *J* = 4.5, 1.2 Hz, 1 H), 3.08 (s, 3 H), 2.93 (m, 1 H), 2.68 (ddd, *J* = 16.2, 3.6, 0.9 Hz, 1 H), 2.46 (ddd, *J* = 15.9, 2.7, 1.2 Hz, 1 H), 2.39 (m, 1 H), 2.28 (m, 1 H), 1.77 (d, *J* = 14.7 Hz, 1 H), 1.60 (ddd, *J* = 9.3, 6.9, 1.5 Hz, 1 H), 1.29 (s, 3 H), 0.97 (d, *J* = 6.9 Hz, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 209.5 (C), 80.6 (C), 61.1 (CH), 51.0 (CH), 50.8 (CH_3), 45.5 (CH), 43.8 (CH), 38.4 (CH_2), 37.5 (CH_2), 25.7 (CH_3), 11.8 (CH_3); IR (neat) 2974 (s), 2939 (s), 2874 (m), 2829 (m), 1714 (s), 1690 (w), 1450 (m), 1412 (m), 1379 (s), 1323 (m), 1215 (m), 1161 (s), 1149 (s), 1086 (s), 1053 (s), 912 (s), 819 (m), 805 (m), 785 (m), 733 (s) cm^{-1}; HRMS (EI) *m/z* 216.0913 [(M^+); calcd. for $C_{11}H_{17}ClO_2$: 216.0917].

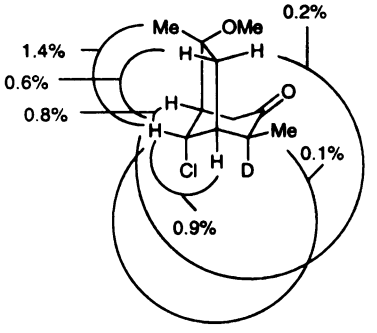


165

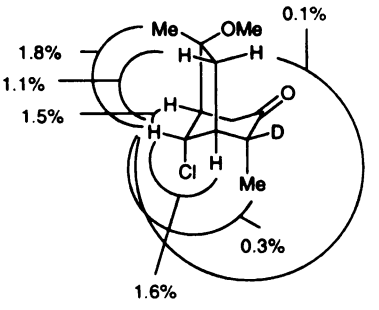
(1*R, 2*S**, 5*S**, 6*R**, 8*R**)-8-chloro-6-methoxy-2,6-dimethyl-bicyclo[3.2.1]octan-3-one (165).**

Following general procedure V, the reaction of 1.00 g (5.4 mmol) of **155:156**, as a 1:1 diastereomeric mixture, afforded 0.38 g (33%) of **165** after purification *via* flash silica chromatography (13 g, 1% Et_3N/hexanes).

165: R_f = 0.36 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.74 (td, *J* = 6.3, 1.5 Hz, 1 H), 3.11 (s, 3 H), 3.08 (m, 1 H), 2.89 (ddd, *J* = 15.0, 4.2, 1.2 Hz, 1 H), 2.50 (m, 1 H), 2.32 (m, 1 H), 2.22 (dq, *J* = 15.9, 1.5 Hz, 1 H), 1.95 (dd, *J* = 14.4, 6.9 Hz, 1 H), 1.46 (d, *J* = 14.7 Hz, 1 H), 1.17 (s, 3 H), 0.96 (d, *J* = 6.6 Hz, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 210.9 (C), 82.1 (C), 62.0 (CH), 49.6 (CH_3), 49.4 (CH), 45.5 (CH), 44.2 (CH), 39.7 (CH_2), 38.1 (CH_2), 20.0 (CH_3), 11.8 (CH_3); IR (neat) 2970 (s), 2941 (s), 2750 (m), 1710 (s), 1462 (m), 1421 (m), 1379 (s), 1325 (m), 1209 (m), 1147 (m), 1095 (s), 1086 (s), 1053 (m), 908 (s), 890 (s), 829 (m), 788 (m), 760 (m), 733 (s) cm^{-1}; LRMS (EI) *m/z* 216.0 (M^+), 218.0 (M^{+2}); HRMS (EI) *m/z* 216.0918 [(M^+); calcd. for $C_{11}H_{17}ClO_2$: 216.0917].



167



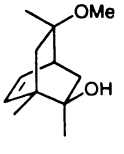
168

(1*R, 2*S**, 5*S**, 6*S**, 8*R**)-2-deutero-8-chloro-6-methoxy-2,6-dimethyl-bicyclo[3.2.1]octan-3-one (167) and (1*R**, 2*R**, 5*S**, 6*S**, 8*R**)-2-deutero-8-chloro-6-methoxy-2,6-dimethyl-bicyclo[3.2.1]octan-3-one (168).**

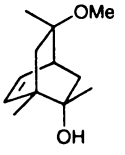
Following general procedure V, the reaction of 0.18 g (0.98 mmol) of **157:158**, as a 1:1 diastereomeric mixture, afforded 0.12 g (60%) of **167:168**, as a 2:1 diastereomeric mixture, after purification *via* flash silica chromatography (5 g, 10:1 hexanes/EtOAc).

167: R_f = 0.56 (4:1 hexanes/EtOAc); $[\alpha]_{546}^{20}$ = +40.0 (*c* 0.23, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.40 (dt, *J* = 4.5, 1.5 Hz, 1 H), 3.12 (s, 3 H), 2.71 (dd, *J* = 15.9, 3.9 Hz, 1 H), 2.51 (ddd, *J* = 16.2, 3.0, 1.5 Hz, 1 H), 2.43 (m, 1 H), 2.31 (m, 1 H), 1.81 (d, *J* = 14.4 Hz, 1 H), 1.64 (dd, *J* = 14.4, 6.6 Hz, 1 H), 1.32 (s, 3 H), 1.00 (s, 3 H); For 1-D NOE correlations see figure shown above; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 209.7 (C), 80.7 (C), 61.2 (CH), 51.1 (CH), 50.9 (CH_3), 48.5 (CD), 45.5 (CH), 38.6 (CH_2), 37.6 (CH_2), 25.8 (CH_3), 11.8 (CH_3); IR (neat) 2974 (s), 2937 (s), 1714 (s), 1450 (s), 1412 (m), 1379 (s), 1323 (m), 1226 (s), 1153 (s), 1078 (s), 918 (s), 852 (m), 798 (m), 733 (s) cm^{-1}; HRMS (EI) *m/z* 217.7186 [(M^+); calcd. for $C_{11}H_{16}DO_2{}^{35}Cl$: 217.7192].

168: R_f = 0.31 (5:1 hexanes/EtOAc); $[\alpha]_{546}^{20}$ = +18.0 (*c* 0.08, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.26 (t, *J* = 3.3 Hz, 1 H), 3.14 (s,3H), 2.78 (dd, *J* = 10.8, 2.7 Hz, 1 H), 2.68 (ddd, *J* = 10.8, 1.5, 0.6 Hz, 1 H), 2.45 (m, 1 H), 2.39 (m, 1 H), 1.83 (m, 2 H), 1.34 (s, 3 H), 1.32 (s, 3 H); For 1-D NOE correlations see figure shown above; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 208.5 (C), 80.0 (C), 59.4 (CH), 50.9 (CH_3), 50.4 (CH), 49.3 (CD), 45.0 (CH_2), 44.6 (CH), 37.1 (CH_2), 26.0 (CH_3), 19.8 (CH_3); IR (neat) 2970 (s), 2937 (s), 1709 (s), 1454 (m), 1377 (m), 1325 (m), 1226 (m), 1167 (m), 1084 (m), 1064 (s), 929 (m), 790 (m) cm^{-1}; HRMS (EI) *m/z* 217.7190 [(M^+); calcd. for $C_{11}H_{16}DO_2{}^{35}Cl$: 217.7192].



159



160

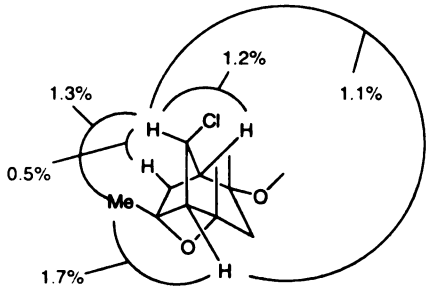
(1*S, 2*R**, 4*S**, 8*R**)-8-methoxy-1,2,8-trimethyl-bicyclo[2.2.2]oct-5-en-2-ol (159) and (1*S**, 2*S**, 4*S**, 8*R**)-8-methoxy-1,2,8-trimethyl-bicyclo[2.2.2]oct-5-en-2-ol (160).**

To 5.3 mL (27.7 mmol, 5.00 eq) of a chilled (0 °C) 3.0 M methyl magnesium bromide/THF solution was added, 0.99 g (5.2 mmol, 1.00 eq) **27** in 5 ml THF dropwise. After complete addition, the reaction was stirred at 0 °C for 2 hrs and then at room temperature for 5 hrs. Upon cooling back to 0 °C, the reaction was quenched with an aqueous solution of $NH_4Cl_{(sat)}$, warmed to room temperature and then stirred for 2 hrs. After separation the ethereal layer was washed two times with an aqueous solution of $NH_4Cl_{(sat)}$, afterwhich the combined aqueous layers were extracted once with 20 ml Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated to afford a yellow oil. The residual was purified *via* flash alumina chromatography (30 g; basic, Activity III; 50:1 Hex/EtOAc) to 0.74 g (73%) of **159:160** as a 1:1 mixture.

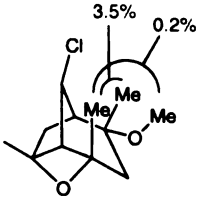
159: R_f = 0.26 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.17 (t, *J* = 8.1 Hz, 1 H), 5.92 (d, *J* = 7.8 Hz, 1 H), 3.23 (s, 3 H), 2.78 (br s, 1 H), 2.63 (m, 1 H), 1.93 (dd, *J* = 13.9, 3.0 Hz, 2 H), 1.32 (dd, *J* = 13.5, 2.1 Hz, 1 H), 1.15 (s, 3 H), 1.09 (s, 3 H), 1.08 (s, 3 H), 1.02 (d, *J* = 14.1 Hz, 1 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 140.1 (CH), 133.1 (CH), 78.7 (C), 72.5 (C), 49.6 (CH_3), 46.2 (CH_2), 43.5 (C), 41.6 (CH_2), 40.2 (CH), 26.9 (CH_3), 24.5 (CH_3), 18.1 (CH_3); IR (neat) 3512 (br s), 3043 (m), 2970 (s), 2936 (s), 2874 (s), 2828 (m), 1610 (w), 1452 (s), 1363 (s), 1286 (s), 1159 (s), 1109 (s), 1093 (s), 1086 (s), 906 (m), 885 (s), 744 (s), 680 (s) cm^{-1}; LRMS (EI) *m/z* 196.1 (M_+), 197.2 (M_{+1}); HRMS (EI) *m/z* 196.1462 [(M^+); calcd. for $C_{12}H_{20}O_2$: 196.2860].

160: R_f = 0.10 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.32 (t, *J* = 7.0 Hz, 1 H), 5.84 (d, *J* = 8.0 Hz, 1 H), 3.11 (s, 3 H), 2.49 (m, 1 H), 2.19 (s, 1 H), 2.15 (dd, *J* =

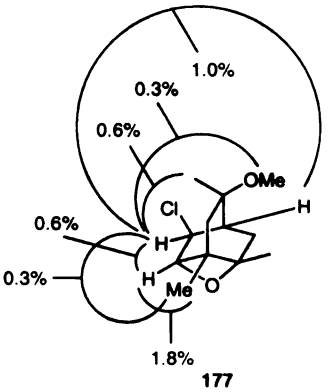
14.0, 2.0 Hz, 1 H), 1.58 (d, J = 14.5 Hz, 1 H), 1.23 (dd, J = 13.5, 2.5 Hz, 1 H), 1.22 (s, 3 H), 1.09 (s, 3 H), 1.07 (s, 3 H), 1.04 (d, J = 14.0 Hz, 1 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 138.0 (CH), 134.6 (CH), 79.2 (C), 74.7 (C), 49.3 (CH_3), 44.8 (CH_3), 43.6 (C), 40.8 (CH_2), 40.4 (CH), 24.6 (CH_3), 22.3 (CH_3), 18.2 (CH_3); IR (neat) 3445 (br s), 3095 (m), 2964 (s), 2934 (s), 2874 (m), 1512 (w), 1460 (s), 1365 (s), 1251 (m), 1147 (s), 1099 (s), 1070 (s), 925 (m), 841 (m), 744 (s), 680 (m) cm^{-1}.



176



176



177

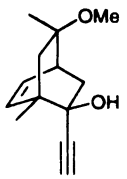
(1*R, 3*S**, 5*R**, 6*R**, 7*R**, 8*S**)-7-chloro-5-methoxy-1,3,5-trimethyl-1-oxa-tricyclo[4.2.1.0^{1,2}]nonane (176) and 6-chloro-4-methoxy-1,2,4-trimethyl-8-oxa-tricyclo[3.3.1.0^{2,7}]nonane (177).**

Following general procedure V, the reaction of 98.5 mg (0.50 mmol) of **159**, afforded 39.3 mg (34%) of **177** and 32.3 mg (28%) of **176** after purification *via* flash silica chromatography (5 g, 10:1 hexanes/EtOAc).

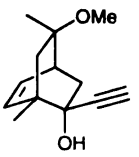
176: R_f = 0.33 (5:1 hexanes/EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.15 (t, J = 4.4 Hz, 1 H), 3.18 (s, 3 H), 2.38 (m, 1 H), 2.35 (d, J = 15.3 Hz, 1 H), 2.24 (d, J = 13.7 Hz, 1 H), 1.96 (t, J = 4.9 Hz, 1 H), 1.81 (dd, J = 15.3, 6.5 Hz, 1 H), 1.38 (dd, J = 13.7, 7.1 Hz, 1 H), 1.31 (s, 3 H), 1.30 (s, 3 H), 1.22 (s, 3 H); For 1-D NOE correlations see figure shown above; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 78.9 (C), 62.8 (C), 60.8 (CH), 58.6 (C), 50.7 (CH_2), 48.5 (CH_3), 46.0 (CH), 36.3 (CH), 27.7 (CH_2), 27.1 (CH_3), 21.6 (CH_3), 19.9

(CH_3); IR (neat) 2930 (s), 2855 (m), 1458 (m), 1379 (m), 1321 (w), 1234 (w), 1132 (w), 1066 (m), 910 (w), 893 (m), 787 (m) cm^{-1}; HRMS (EI) *m/z* 231.1152 [(M^{+1}); calcd. for $C_{12}H_{19}O_2{}^{35}Cl$: 230.1074].

177: R_f = 0.12 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.93 (d, *J* = 1.1 Hz, 1 H), 4.22 (s, 1 H), 3.91 (d, *J* = 4.4 Hz, 1 H), 3.25 (s, 3 H), 2.74 (m, 1 H), 2.03 (d, *J* = 15.4 Hz, 1 H), 1.89 (t, *J* = 1.65 Hz, 1 H), 1.81 (d, *J* = 14.8 Hz, 1 H), 1.41 (s, 3 H), 1.13 (d, *J* = 1.1 Hz, 3 H), 0.90 (s, 3 H); For 1-D NOE correlations see figure shown above; ^{13}C-NMR (125 MHz, $CDCl_3$) δ 77.6 (C), 75.0 (C), 63.0 (CH), 60.0 (CH), 49.3 (CH_3), 47.6 (C), 44.8 (CH_2), 44.7 (CH), 41.6 (CH_2), 27.8 (CH_3), 25.1 (CH_3), 19.0 (CH_3); IR (neat) 3424 (br s), 2987 (s), 2934 (s), 2874 (s), 1608 (m), 1462 (s), 1379 (s), 1257 (ms), 1230 (ms), 1172 (s), 1115 (s), 1066 (s), 952 (ms), 925 (s), 893 (s), 871 (ms), 781 (ms) cm^{-1}; HRMS (EI) *m/z* 231.1163 [(M^+ +H); calcd. for $C_{12}H_{19}O_2{}^{35}Cl$: 230.1074].



161



162

(1*S, 2*S**, 4*S**, 8*S**)-1,8-dimethyl-2-ethynyl-8-methoxybicyclo[2.2.2]oct-5-en-2-ol (161) and (1*S**, 2*R**, 4*S**, 8*S**)-1,8-dimethyl-2-ethynyl-8-methoxybicyclo[2.2.2]oct-5-en-2-ol (162).**

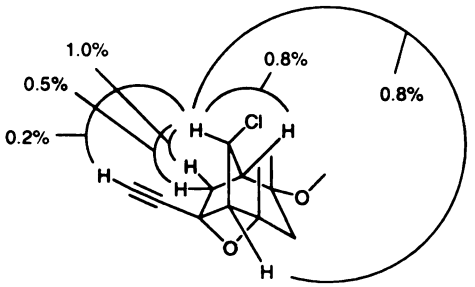
To 55.5 mL (27.7 mmol, 5.00 eq) of a chilled (0 °C) 0.5 M ethynyl magnesium bromide/THF solution, was added 1.00 g **27** (5.54 mmol, 1.00 eq) in 10 mL THF dropwise *via* syringe. The reaction was kept at 0 °C for 10 min and then heated to reflux (80 °C), which was maintained for 2.5 hrs The reaction was cooled to 0 °C and quenched with an aqueous solution of $NH_4Cl_{(sat)}$ and then partitioned with 30 mL Et_2O. After

separation the ethereal layer was washed two times with 30 mL of an aqueous solution of $NH_4Cl_{(sat)}$. The combined aqueous layers were extracted three times with 20 mL Et_2O. The combined ethereal layers were washed once with 30 mL brine, dried over $MgSO_4$, filtered, and concentrated to afford a yellow oil. The oil was purified *via* flash alumina chromatography (30 g; basic, Activity III; 30:1 hexanes/EtOAc) to afford 0.77 g (68%) of **161:162** in a 2.8:1.0 mixture.

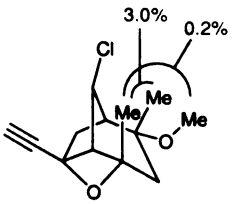
161: R_f = 0.33 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.23 (t, *J* = 7.5 Hz, 1 H), 5.90 (d, *J* = 8.1 Hz, 1 H), 3.14 (s, 3 H), 2.74 (s, 1 H), 2.57 (m, 1 H), 2.34 (s, 1 H), 2.12 (dd, *J* = 13.8, 2.7 Hz, 1 H), 1.90 (d, *J* = 13.8 Hz, 1 H), 1.88 (dd, *J* = 13.5, 2.7 Hz, 1 H), 1.22 (s, 3 H), 1.09 (s, 3 H), 0.99 (d, *J* = 14.1 Hz, 1 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 138.5 (CH), 133.8 (CH), 88.2 (C), 78.4 (C), 72.7 (C), 71.0 (CH), 49.5 (CH_3), 43.8 (CH), 43.2 (CH_2), 41.6 (CH_2), 40.9 (C), 24.5 (CH_3), 19.0 (CH_3); HRMS (EI) *m/z* 206.1308 [(M^+), calcd. for $C_{13}H_{18}O_2$: 206.1307].

162: R_f = 0.29 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.30 (t, *J* = 7.2 Hz, 1 H), 5.78 (d, *J* = 7.8 Hz, 1 H), 3.13 (s, 3 H), 2.69 (dd, *J* = 13.8, 2.4 Hz, 1 H), 2.51 (m, 1 H), 2.44 (s, 1 H), 2.07 (s, 1 H), 1.40 (dd, *J* = 13.8, 3.3 Hz, 1 H), 1.23 (s, 3 H), 1.15 (d, *J* = 14.1 Hz, 1 H), 1.07 (s, 3 H), 1.02 (d, *J* = 13.8 Hz, 1 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 135.4 (CH), 134.2 (CH), 85.9 (C), 78.7 (C), 72.7 (C), 71.1 (CH) 49.3 (CH_3), 41.0 (CH), 40.8 (C), 40.2 (CH_2), 39.6 (CH_2), 24.5 (CH_3), 18.9 (CH_3); HRMS (EI) *m/z* 206.1306 [(M^+), calcd. for $C_{13}H_{18}O_2$: 206.1307].

161:162: IR (KBr) 3400 (br s), 3300 (s), 3090 (m), 2998 (s), 2990 (s), 2975 (s), 2670 (m), 2620 (m), 2030 (w), 1699 (w), 1420 (m), 1345 (s), 1110 (m), 1080 (s), 1015 (m), 920 (m), 910 (m), 850 (m), 760 (s) cm^{-1}.



183

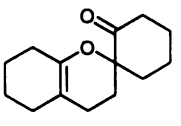


183

(1*R, 3*R**, 4*R**, 6*S**, 7*R**, 8*S**)-6-chloro-1-ethynyl-4-methoxy-2,4-dimethyl-8-oxa-tricyclo[3.3.1.0^{1,2}]nonane (183).**

Following general procedure V, the reaction of 0.30 g (1.4 mmol) of **156**, afforded 0.14 (39%) of **183** after purification *via* flash silica chromatography (3.5 g, 1% Et_3N/hexanes).

140: R_f = 0.44 (4:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.15 (t, *J* = 4.8 Hz, 1 H), 3.16 (s, 3 H), 2.65 (d, *J* = 15.6 Hz, 1 H), 2.50 (t, *J* = 5.7 Hz, 1 H), 2.18 (dd, *J* = 15.6, 6.6 Hz, 1 H), 2.16 (d, *J* = 13.8 Hz, 1 H), 2.01 (t, *J* = 5.1 Hz, 1 H), 1.49 (s, 3 H), 1.37 (dd, *J* = 13.5, 7.2 Hz, 1 H), 1.26 (d, *J* = 15.9 Hz, 1 H), 1.22 (s, 3 H); For 1-D NOE correlations see figure shown above; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 82.5 (C), 78.6 (C), 71.8 (C), 64.2 (C), 59.4 (CH), 52.8 (C), 50.6 (CH_3), 48.1 (CH), 45.2 (CH), 36.1 (CH_2), 27.1 (CH_3), 27.0 (CH_2), 22.8 (CH_3); IR (neat) 3300 (m), 3090 (w), 3966 (s), 2939 (s), 2810 (m), 2100 (w), 1498 (m), 1379 (m), 1319 (m), 1234 (m), 1188 (m), 1159 (m), 1136 (s), 1064 (s), 895 (s), 814 (m), 738 (s), 679 (m) cm^{-1}; HRMS (EI) *m/z* 240.0919 [(M^+); calcd. for $C_{13}H_{17}{}^{35}ClO_2$: 240.7256].



217

Preparation of Diels-Alder Adduct (217).

A typical ring expansion/*exo*-olefin insertion procedure, reaction time shortened to 1 hr, was performed on 0.50 g (4.5 mmol) **84** and afforded 0.19 g (40%) of **90**. Enone **90** was immediately dissolved in 6.5 ml (0.28 M) PhH. To this solution was added 0.85 g (9.1 mmol, 5.00 eq) norbornylene. The reaction was refluxed (80 °C) for 12 hrs, cooled to room temperature and concentrated. The oil was purified *via* flash silica chromatography (4 g, 20:1 hexanes/EtOAc) to afford 0.32 g (82%) **217**.

217: R_f = 0.57 (5:1 hexanes/EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.70 (td, *J* = 12.0, 5.4 Hz, 1 H), 2.22 (dt, *J* = 12.6, 5.4 Hz, 1 H), 2.09 (m, 2 H), 1.98 (series of m, 5 H), 1.80 (m, 3 H), 1.58 (series of m, 8 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 211.9 (C), 144.5 (C), 104.7 (C), 80.4 (CH_2), 39.5 (CH_2), 38.7 (CH_2), 28.8 (CH_2), 28.3 (CH_2), 27.6 (CH_2), 27.4 (CH_2), 23.0 (CH_2), 22.7 (CH_2), 22.7 (CH_2), 20.7 (CH_2); IR (neat) 2960 (s), 2949 (s), 1710 (s), 1555 (m), 1498 (m), 1322 (m), 1244 (m), 1180 (m), 1161 (m), 1136 (s), 1068 (s), 895(m), 758 (s), cm^{-1}; HRMS (EI) *m/z* 220.2156 [(M^+); calcd. for $C_{14}H_{20}O_2$: 220.1463].

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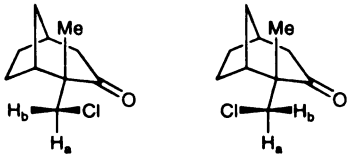
65 This analysis also supports Johnson's conclusion of a preferred CH_2Cl rotomer present in [3.2.1]-ketone **10**. The methyl substituent appears as a doublet (J = 0.6 Hz), resultant from W-coupling with the CH_2Cl protons making two conformers possible. Johnson used aromatic solvent induced shifts of **10** to deduce the preferred conformer shown below. NOE data is consistent with this model. (For aromatic solvent induced shifts see Bhacca, N. S., Williams, D. H. In *Applications of NMR Spectroscopy in Organic Chemistry*, Holden-Day: San Francisco, CA, **1964**, Chapter 7.)



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