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Approaches to the Synthesis of Bicyclo(5.3.0)decane
Containing Natural Products *via*
Furan-Terminated Cationic Cyclizations

presented by

Gary Michael Johnson

has been accepted towards fulfillment
of the requirements for

Masters degree in Chemistry

Steven P. Tanis
Major professor

Date July 1, 1987

APPROACHES TO THE SYNTHESIS OF BICYCLO(5.3.0)DECANE CONTAINING NATURAL PRODUCTS VIA FURAN TERMINATED CATIONIC CYCLIZATIONS

By

Gary Michael Johnson

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ABSTRACT

APPROACHES TO THE SYNTHESIS OF BICYCLO(5.3.0)DECANE CONTAINING NATURAL PRODUCTS VIA FURAN TERMINATED CATIONIC CYCLIZATIONS

by

Gary Michael Johnson

The guaianolides and pseudoguaianolides are members of a class of natural products which possess a bicyclo(5.3.0)decane skeleton. These functionally and stereochemically complex natural products have exhibited a broad and potent spectrum of biological activities; and as a result have been the targets of extensive synthetic studies.

As part of a general program in furan chemistry, we have examined and demonstrated the utility of furans as dianions in annulation sequences. When coupled with the ability of the furan nucleus to serve as the operational equivelent of a variety of acyclic, carbocyclic, and heterocyclic systems, this methodology should serve well in the synthesis of complex systems such as those represented by the guaianolides and pseudoguaianolides.

We will describe general and flexible approaches to guaianolide precursors utilizing furan terminated cationic cyclizations to form the crucial bicyclo(5.3.0)decane ring system. Pseudoguaianolides might also be obtainable through simple modification of these precursors.

Para mi bella esposa Linda

Te Amo

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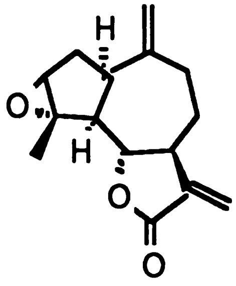
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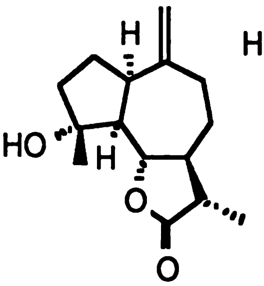
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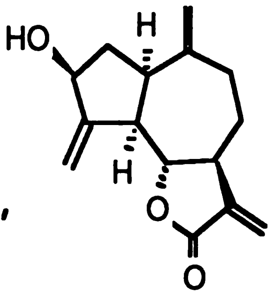
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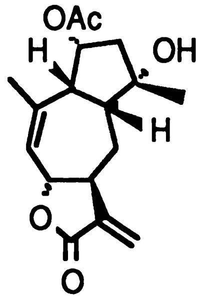
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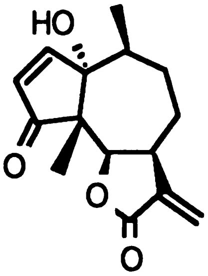
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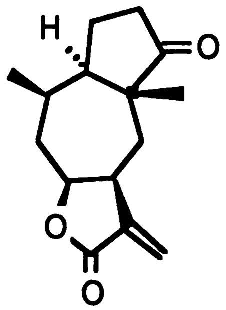
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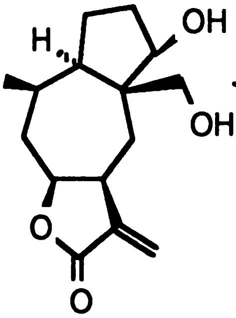
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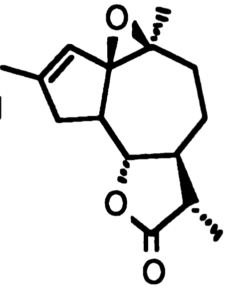
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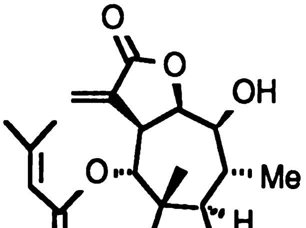
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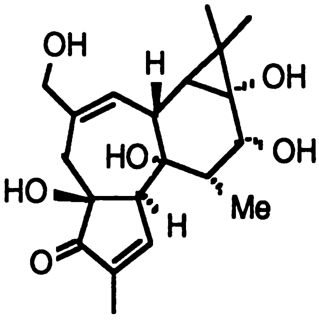
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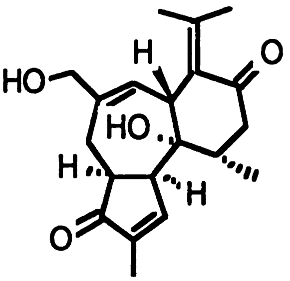
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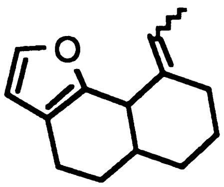
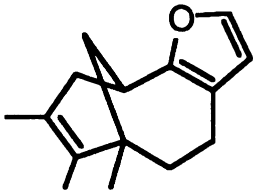
An abundance of bioactive molecules that exist in nature, are found to contain within their framework, 5-membered, oxygenated, heterocyclic rings in various states of oxidation[1]. These include guaianolides[2a] (**1**-**4**), pseudoguaianolides[2a-c] (**5**-**9**), tiglanes[3] (**10**, **11**), daphnanes[3], and ingenanes[3]. A common feature of compounds **1-11**, in addition to a butyrolactone moiety, is the bicyclo(5.3.0) decane skeleton. Because of the challenges associated with the synthesis of highly substituted and/or oxygenated bicyclo(5.3.0) decanes, and the diverse biological activities associated with compounds like **1-11**, which include allergenic[4], contraceptive[5] (**8**), cocarcinogenic[3a,b, 6] (**10, 11**), cytotoxic[7] (**3, 5**), antitumor[3], antineoplastic[8] (**9**), antihelmenthic[9], antifeedant[10], and antileukemic[11] (**7**) properties, extensive efforts have been expended in the syntheses of **1-11** and related compounds.[12]

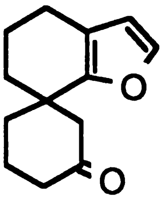
In keeping with our current program in furan terminated cationic cyclizations, which have resulted in the construction of fused-, bridged-, and spirocyclic- ring systems[12], we have extended our efforts towards the synthesis of bicyclo(5.3.0)-decane precursers of **1-11**. Of particular initial interest is the demonstration that a suitable intermediate for the synthesis of the relatively simple bicyclo(5.3.0) decane containing compounds[2] **1**, **2**, **3**, and **5**, can be readily prepared. We envision the furyl-ketone **12**, as a particularily attractive precursor to both the guaianolide (**1-3**) and pseudoguaianolide (**5**) families of sesquiterpenes.



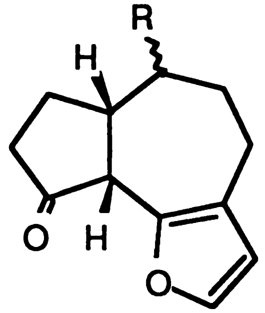
FUSED



BRIDGED



SPIRO



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We have previously demonstrated the ability of the furyl moiety to successfully participate in annulation processes, culminating with a regio-controlled, furan terminated cyclization[12]. These considerations,along with the plethora of useful functionalities which can be derived from the product furans *(figure 1)* have led us to approach compounds **1-11** via such a pathway.

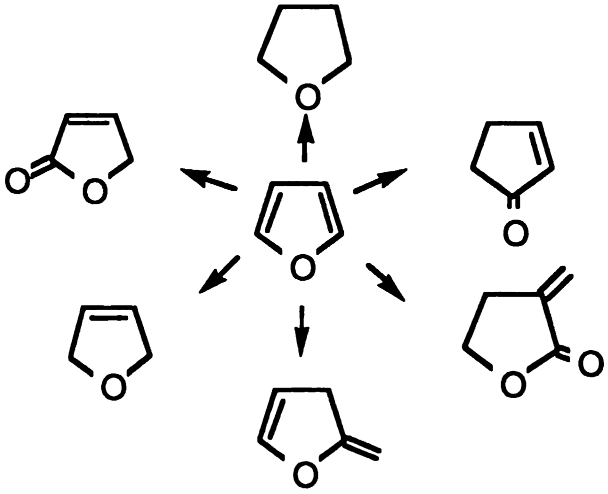
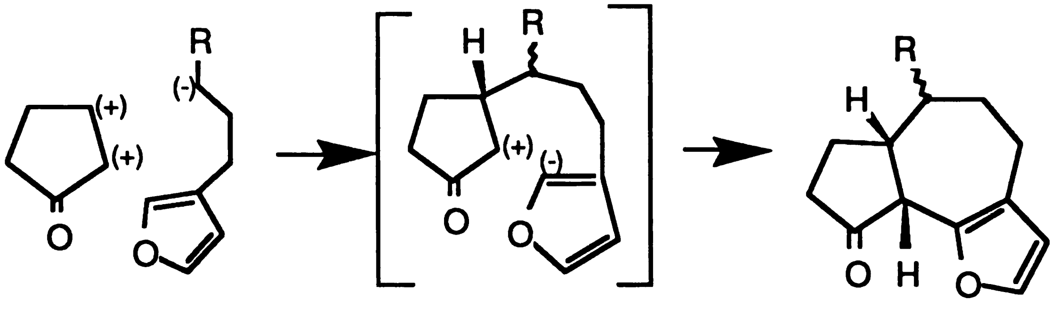


FIGURE 1

As illustrated in *scheme 1*, the coupling of a hypothetical cyclopentane dication equivelent, selectively at the ß- position with a furyl anion equivalent would lead to the substituted cyclopentane **15**, which after, cyclization by a Friedel-Crafts type process would afford **12**. For this sequence to succeed, the

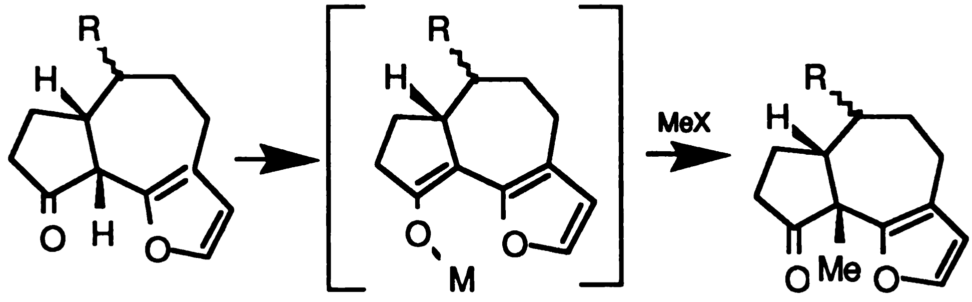


13 **14** **15** **12**

SCHEME 1

reactivities of the di-anion and di-cation equivelents must be adjusted such that only one regioisomer results from the initial C-C bond formation. With respect to the furyl moiety, selectivity can be guaranteed by relying on the vastly different levels of reactivity displayed by a side chain organometallic and the neutral furan with respect to an electrophilic center. In order to assure regiochemical integrity in the initial carbon-carbon bond forming sequence, we anticipate utilizing a cyclopentane di-cation equivelent in which the second site of electron deficiency is developed as a result of the chemistry employed in the first carbon-carbon bond formation. In such a fashion **12** could be produced possessing a variety of R functions, eventually leading to Estafiatin **1**[9, 13], Compressanolide **2**[14], and Zaluzanin **3**[15]. The development of synthetic methodology which will allow facile construction of compound **12** will be the subject of this thesis.

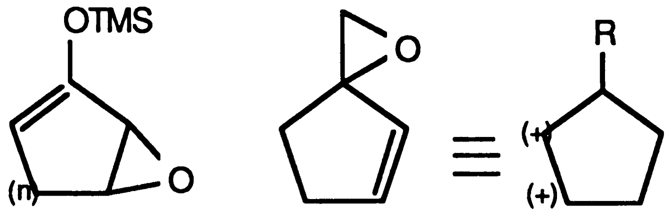
An additional consideration, which heightens our interest in the preparation of **12**, is that the alkylation of the putative thermodynamic enolate of **12** (*scheme 2*) should place a methyl at the desired ring fusion carbon, perhaps affording eventually a pseudoguaianolide such as **5**. Alteration of the nature of the di-anion and di-cation equivelents should also provide access to more highly oxygenated compounds and yield products of annulation sequences with alternate furan placement; thus furnishing assorted ambrosanolides, helenanolides, and tiglanes.



SCHEME 2

RESULTS & DISCUSSION

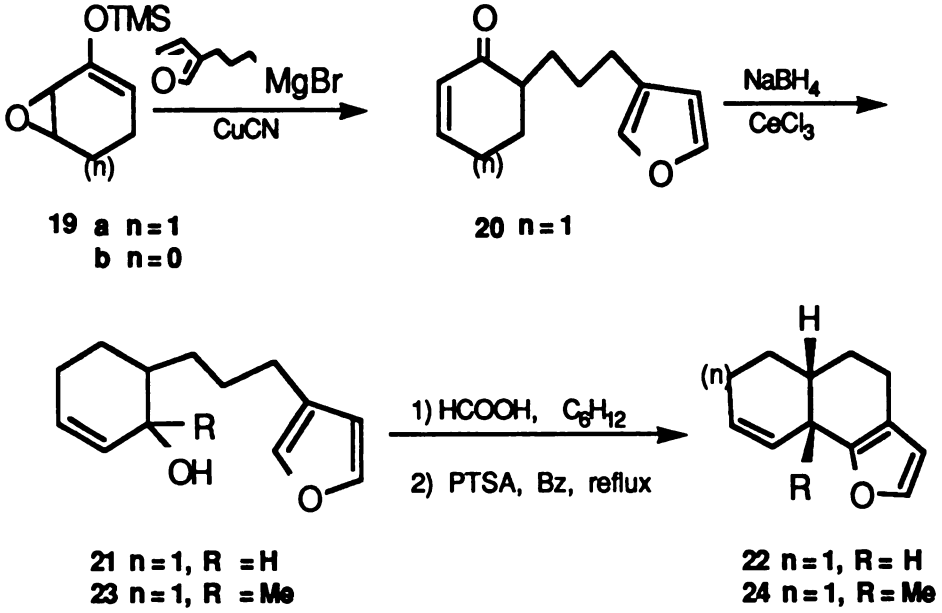
We planned to construct the bicyclo(5.3.0)decane ring system, present in **1-11**, utilizing a furan terminated cationic cyclization. As described previously, this synthetic approach will couple a furyl di-anionic equivelent with a cyclopentenoid di-cation equivelent. The chemistry of Marino[16], and Wender[16], and results from our own laboratories[12] suggested employing epoxy-cyclopentene enol ether **16**[12], 16 (n=1), and vinyl spiroepoxide **17**[12] as bis-elecrophiles. To determine



16 **17**

FIGURE 2

the utility of such a construction, we examined the model system outlined in *scheme 3.* The enol silyl ether **19**, prepared from 7-oxo-bicyclo(4.1.0)heptane, was treated with the Grignard reagent derived from 3-(3-furyl)propyl bromide **18**[17] and CuCN, which after Sn_2' addition, hydrolysis and dehydration, provided the enone **20**[12h] (70%). $NaBH_4$ reduction of enone **20** according to Luche[18] ($CeCl_3$), afforded the allylic alcohol **21** (70%). Exposure of **21** to our previously described cyclization conditions[12] (HCOOH, C_6H_{12}), led to the corresponding formate; none of the desired cyclized material was obtained. However, cyclization to **22** (25% unoptimised) was observed when either i) the initially formed formate was treated with pTsOH in refluxing benzene; or ii) pTsOH was added catalytically to the HCOOH/C_6H_{12} reaction mixture. The bicyclo(4.4.0)decane system **24**[12h], corresponding to **22** with a methyl group in a ring fusion position can also be prepared from **20** (*scheme 3).* Addition of



SCHEME 3

MeLi to enone **20**, affords the tertiary allylic alcohol **23**. Treatment of **23** with HCOOH/C_6H_{12} followed by pTsOH as described above gave a fine yield (72%) of cyclized product **24**[12h] (n=1). These results suggested that a variety of linearly fused carbocyclic adducts related to **22** and **24** might be routinely prepared by variation of the ring size of bis electrophile **19**, or via the chain length of the furyl organometallic.

To obtain the bicyclo(5.3.0)decane system present in the target (**1-3,5**) guaianolide and pseudoguaianolide natural products, we wished to employ the same technology; however with **19b** (n=0) in place of the cyclohexanone derived epoxy enol silyl ether. Unfortunately, despite the numerous attempts utilizing a wide variety of reaction conditions, we were unable to prepare and isolate **19b**. We also examined the preparation and utilization of **19b** in situ; to no avail.

Therefore, we reluctantly concluded that the epoxy enol silyl ether constructed from cyclopentenone was too labile to be of any utility in this synthetic endeavor.

The projected construction of the guaianolide and pseudoguaianolide bicyclo(5.3.0) ring system might yet be realized if we could replace **19b** (n=0) with an alternative cyclopentenoid 1,2-bis-electrophile. We have previously employed enone derived vinyl spiroepoxides in this context[12], suggesting application of this class of bis-electrophile equivelents to the problem at hand. Thus, methyl-thio-methyllithium (*figure 3*) addition to cyclopentenone **25** gave the MTM alcohol **26** in 94% distilled yield. Exposure of **26** to 30 equivelents of MeI led to a quantitative crude yield of the sulfonium salt **27**, which could be recrystallized from ethanol. Salt **27** could be conviently converted in situ to spiroepoxide **28** as shown below (*figure 3).* With the requisite spiroepoxide

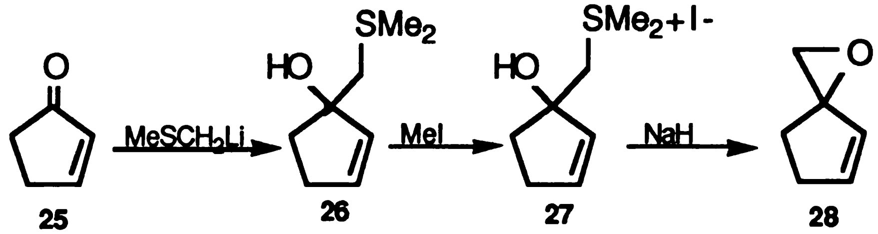
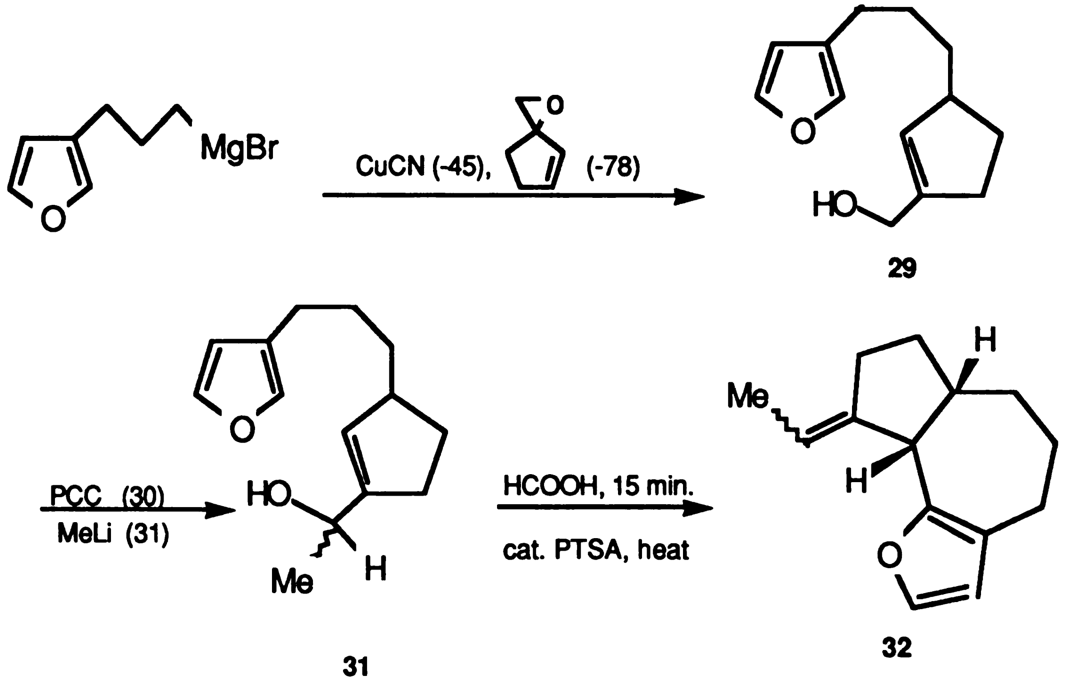


FIGURE 3

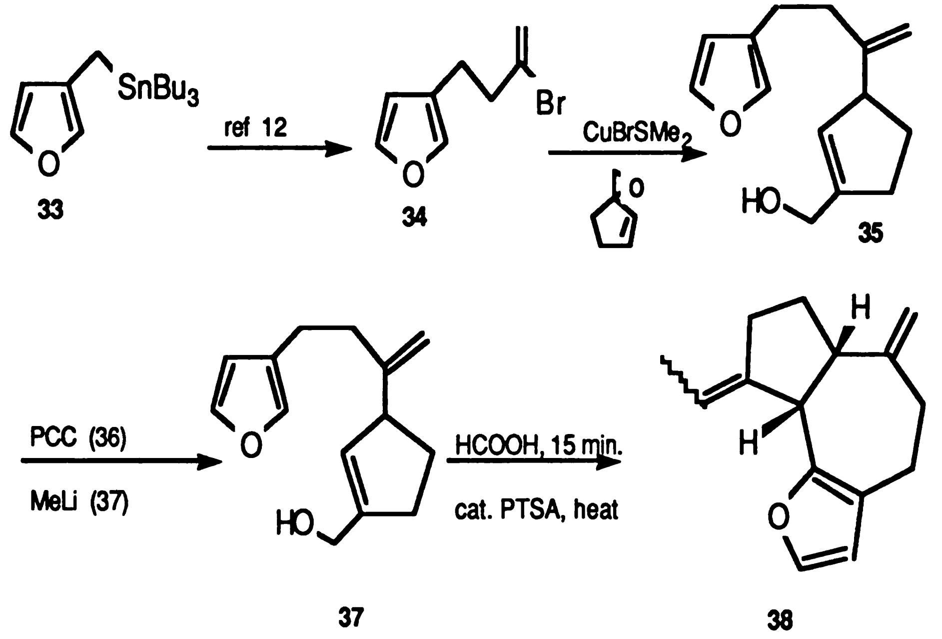
prepared, if not in hand, we turned our attention to the synthesis of the cyclization substrate, and the crucial annulation sequence *(scheme 4).* Assisted (CuCN) SN_2' addition of the Grignard reagent prepared from 3- (3-furyl)propyl bromide **18**[17] to **28** gave allylic alcohol **29** in 70-90% yield. Based upon earlier experience[12], we expected the primary allylic alcohol initiated cyclization to fail; therefore we prepared the secondary allylic alcohol as outlined in *scheme 4.* Thus allylic alcohol **29** was oxidized (PCC, 80-95%), and the crude product aldehyde was treated with methyllithium to provide the secondary allylic alcohol



SCHEME 4

31 in 90-95% yield. Alcohol **31** underwent smooth cyclization when reacted with HCOOH/C_6H_{12}, followed by pTsOH in refluxing benzene, leading to **32** as a mixture of olefin isomers (54%). A slight modification of the cyclization conditions to include a catalytic amount of pTsOH fifteen minutes after introduction of HCOOH was found to lead almost exclusively to **32** in yields of 85-95%. This method allowed the routine preparation of several grams of furan **32**.

Having successfully constructed the model (5.3.0)decane skeleton, we turned our efforts to the synthesis of a suitably functionalized guaianolide precursor as illustrated in *scheme 5.* Copper catalyzed addition of the vinyl anion of **34** to the



SCHEME 5

spiroepoxide **28** provided allylic alcohol **35** in 69% yield. Utilization of CuBr·SMe$_2$^{19} in the sequence was found to be crucial to its success; with CuCN leading to dimerization of the vinyl Grignard. Moreover, the use of the vinyl Grignard (MgBr$_2$·Et$_2$O)^{23}, rather than the initally produced vinyl lithium, was found to be important as the lithium derivatives afforded less than 20% of the desired alcohol **35**. By analogy to the observation reported in *scheme 2* , **35** was smoothly converted (PCC, 85% crude, MeLi, 81%) to the secondary allylic alcohol **37**. Cyclization with HCOOH/C$_6$H$_{12}$, and a catalytic amount of pTsOH, afforded adduct **38** in 72% yield as a mixture of olefin isomers. The somewhat lower yield might to be due to the increased fragility of the system. This assumption is based upon a rather simplistic examination (^{1}H-NMR) of the effects of extended reaction time, heat, and amount of pTsOH added. However, consistent yields are readily obtained with careful monitering via TLC.

With cyclized substrates now in hand (**32**, **38**), we needed to remove the two carbons of the alkylidine moiety to arrive at our desired intermediate ketone **12**. Quite a few methods have been reported in the literature[25-29] for the cleavage of C-C double bonds to afford the corresponding ketone. In selecting some of them for the parent substrate, we had to consider their compatability with the relatively acid, and oxygen, sensitive disubstituted furan present in **32**. With these considerations in mind we elected to examine the ability of **a)** i) OsO_4[25], ii) $NaIO_4$[26]; **b)** $KMnO_4$[27]; **c)** RuO_4[28]; **d)** O_3[29]; and **e)** i) MCPBA, ii) H_3O^+, iii) $NaIO_4$; to perform this transformation. Reaction conditions **a-c** were examined in detail; to no avail. We observed either no reaction, or fruitless consumption and destruction of the substrate **32**. Similiarly, ozone failed to afford the desired ketone **12**. However, epoxidation (**e**), did provide variable yields of a mixture of epoxides. Unfortunately, the conversion of these epoxides to ketone **12** (HCOOH, K_2CO_3, $NaIO_4$) was inefficient; providing **12** in but 3% overall yield from **32**.

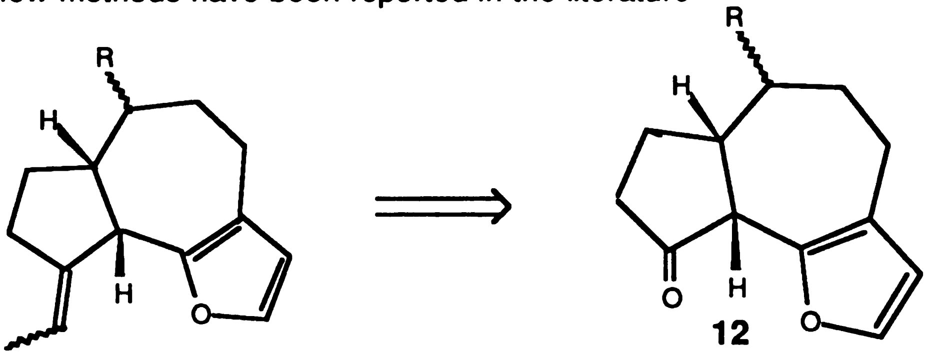
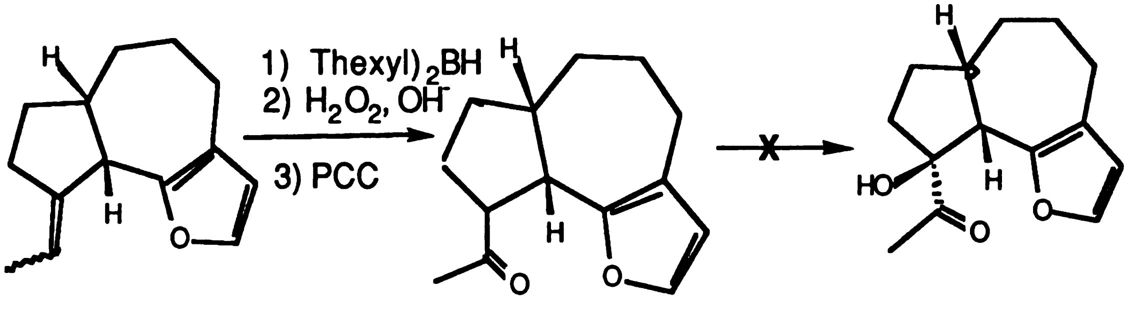


FIGURE 4

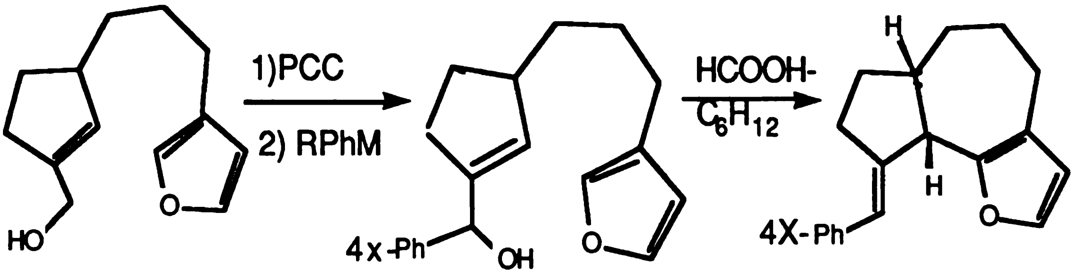
Given the difficulties encountered in the "direct" C-C double bond cleavage, we elected to investigate a multi-step approach via the corrresponding ketone **39** (figure 5). Hydroboration of **32** followed by oxidation of the organoborane, and

PCC oxidation of the product alcohol gave ketone **39** in 42% yield from **32**. The design concept from this point was "simple", to effect the hydroxylation of the putative thermodynamic enolate, providing **40**. This could then be followed by cleavage to **12**. Unfortunately, despite a number of attempts, we were unable to secure **40**. We were also unable to demonstrate the production of the desired enolate precurser to **40**. Therefore we modified our route to remove this problem as described in *scheme 6*.



32 **39** **40**

FIGURE 5



29

41a X= H
b X=OMe

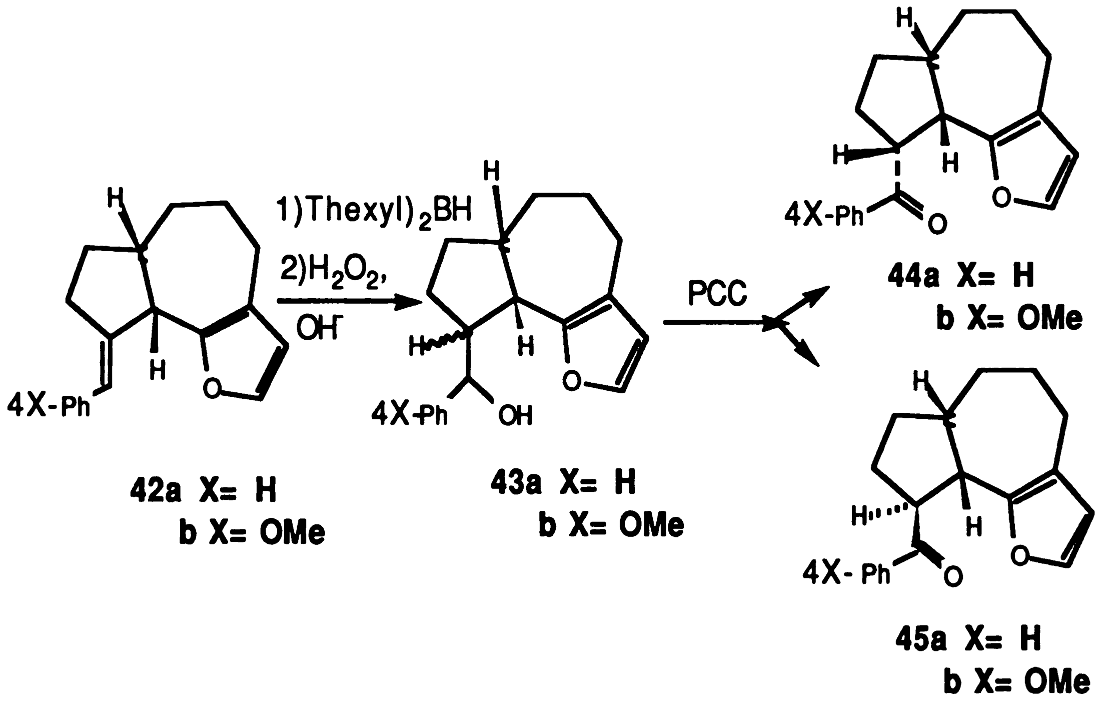
42a X= H
b X= OMe

SCHEME 6

The addition of phenyl-lithium or (4-methoxy)phenylMgBr to the aldehyde prepared from **29** gave **41a** and **41b** in 71% and 70% yield, respectively.

Exposure of **41a** and **41b** to HCOOH-C_6H_{12} furnished the desired cyclized compounds **42a** (87%) and **42b** (74%) as single olefin isomers. With **42a** and **42b** in hand, we next examined the conversion of these compounds to ketone **12**.

Hydroboration of **42a** and **42b** (*scheme 7*) provided alcohols **43a** (55%, with 35% recd. S.M.) and **43b** (60%, with 8% recd. S.M.) as a mixture of stereoisomers. Oxidation with PCC afforded ketones **44a, 45a** (55%) and **44b, 45b** (59%) as 5:1, and (6-8):1 mixtures, respectively. These epimeric mixtures could be separated into major and minor components, which were initially assigned as α- and ß-benzoyl isomers respectively. At this point, the assignment



42a X= H
b X= OMe

43a X= H
b X= OMe

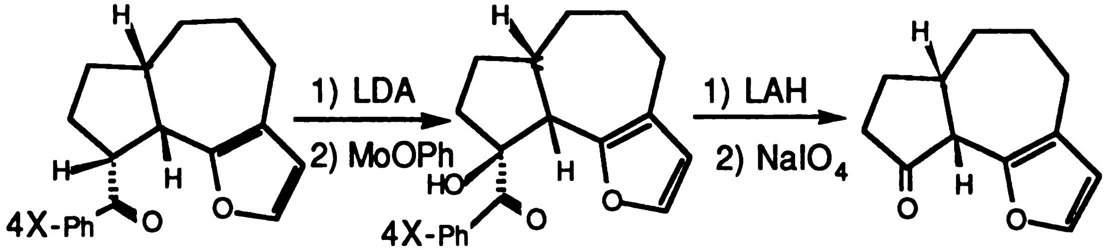
44a X= H
b X= OMe

45a X= H
b X= OMe

SCHEME 7

was based only on the mode of synthesis; the presumed conformation of the precurser olefins, and the previously demonstrated difficulty to effect proton removal at the tertiary position. Should this analysis be correct, we then have in hand, a preponderance of an epimer which is less stable than the alternative one having benzoyl placement on the convex face of the molecule. To examine this possibility, ketones **44b**, and **45b** were separately exposed to NaOMe (6 equiv.) in refluxing methanol. In each of these cases, only the minor isomer **45b** was isolated; this was previously presumed to be the more stable ß-benzoyl compound, thus providing support for the assumption listed above. In one additional experiment, we observed that separate treatment of the major α-ketone **44b**, and the ß-ketone **45b**, with NaOMe in CH_3OD afforded mono-deuterated **45b** from **44b** at room temperature and mono-deuterated **45b** from **45b** only after prolonged reflux. This result suggested that the ketones did not enolize with equal facility and that the next stage of this study, namely the enolate hydroxylation, should be performed with purified ketones **44a**, and **44b**.

Therefore, treatment of **44b** with LDA (1.1 eq., -78°C, -45°C) followed by MoOPH-HMPA-Pyr[30] (-78°C to RT) yielded a single α-hydroxy ketone **46** (72%, with 24% recd. S.M.) as seen in *scheme 8*. The stereochemistry depicted



44b R= OMe **46 R= OMe** **12**

SCHEME 8

is based on the assumption that hydroxylation will occur from the more accessible convex face of the molecule. Reduction of **46** with LAH gave a single diol **47** (83%) which was immediately cleaved with $NaIO_4$ (aq. t- BuOH) to give 49% of a mixture of **12** and anisaldehyde, and 51% of an unknown compound with molecular weight 310. Removal of anisaldehyde as a bisulfite complex provided pure **12** in 35% yield from the diol.

Although **12** was only isolated in 35% yield, the conditions have not yet been optimised in terms of the solvent choice, amount of $NaIO_4$, or reaction time employed. Initial attempts at cleavage in aq. ether, or aq. acetone, resulted in no reaction over a twenty four hour period with up to three equivelents of $NaIO_4$. Optimium quantities of peroidate, reaction time, and solvent may very well raise the yield of **12**, and these endeavours are in progress. The unknown material (M.W. 310, CI/MS) presently obtained was thought possibly to be a dehydration product based on the 250 NMR spectrum. Structural studies are continuing with the hope that the structure of the unknown compound will provide insight for the choice of the proper reaction conditions.

CONCLUSIONS

The approach described for the syntheses of the bicyclo(5.3.0) decane ring systems, which utilizes a furan terminated cationic cyclization sequence has proved to be useful and flexible; affording the desired guaianolide precursor **12**. With this information in hand, we will examine the conversion of the more judiciously functionalized **38**, or an equivelent, to an analog of **12**. Additional studies will be directed toward the production of methyl and oxygen functionalized congeners of **38**. Although there were some difficulties in the C-C bond cleavage steps, the matter did not prove to be impossible; only tedious. The adducts in question can be manipulated albeit with difficulty. Optimization of the final sequence, especially the $NaIO_4$ cleavage should raise the overall yield to a more palatable level.

An interesting point noted during the course of this work was the cyclization of adduct **21** in the model (4.4.0) decane ring system to provide **22**. In general, we have found that secondary allylic alcohols were not inclined to directly provide high yields of cyclized products. The fact that this system did cyclize is worthy of note. The modified cyclization procedure (cat. PTSA, heat) developed in this work should lead to a general increase in the product bicyclo(5.3.0)decane yield regardless of the nature of the secondary allylic alcohol. The bicyclo(4.4.0)decane system produced in this study is also of interest as the precursor of a variety of terpenoids. Time permitting, this avenue of research will also be examined.

In order to prepare a guaianolide with the chemistry described above, we anticipate preparing analogs of **12** (R=H) in which R= (=CH_2), (=O), (OR').

Manipulation of these functionalities should afford the methylene moiety present in a number of target guaianolides. Furan manipulation to target butenolides is well precedented in the literature[31] and has been examined in our laboratories. Manipulation of the ketone functionality should readily provide the desired structural features on the second pendant 5 membered ring.

Additionally, the placement of a methyl moiety in the ring junction of **12** on related compounds should lead to the synthesis of the pseudoguaianolide family of natural products. In the current study, we believe that the 5-7 ring system is cis fused. However, molecular mechanics (MM2) calculations on both cis and trans epimers of **12** have indicated that trans is favored by 2.0 Kcal. Should this be the case, then trans fused pseudoguaianolides could be readily constructed.

In summary, this work has demonstrated that systems such as 12 can be readily prepared; and that the chemistry is sufficiently flexible to allow incorporation of modifications that lead to the desired products. Therefore, we plan to utulize this methodology for the synthesis of a number of biologically significant guaianolides.

EXPERIMENTAL

General: Tetrahydrofuran, ethyl ether, benzene, and hexane were dried by distillation under argon from sodium benzophenone ketyl. Di-isopropyl amine, collidine, and methylene chloride were dried by distillation from calcium hydride. N,N dimethyl formamide was dried by distillation from phosphorous pentoxide. N-butyl-, sec-butyl-, and t-butyl lithium in hexane were purchased from Aldrich Chemical Co., Milwaukee, Wis., and were titrated by the method of Watson and Eastham.[21] Magnesium metal was activated by successive washings with 0.1N aq. HCl, distilled water, acetone, and anhydrous ether respectively, and then dried in a dessicator over phosphorous pentoxide at reduced pressure.

Chromatography was performed using the flash technique of Still et. al.[22], using the silica gel and solvents mentioned. The column outer diameter (o.d.) is listed in millimeters. Thin layer chromatography used Merck SIL G/UV precoated glass plates. Spots were visualized by dipping into one of the following: 1) a solution of vanillin (1.5 g) in absolute ethanol100. ml) and conc. sulfuric acid (0.5 ml), or 2) a solution of phosphomolybdic acid (5.0 g) in absolute ethanol (100. ml); and then heating the plate.

Proton magnetic resonance spectra were recorded at 60 MHz (Varian T-60), 80 MHz (Varian FT-80), and 250 MHz (Bruker WM-250) as solutions in deuteriochloroform unless otherwise indicated. Chemical shifts are reported in parts per million on the δ scale relative to a tetramethylsilane internal standard. Data are reported as follows: chemical shift(multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, brs=broad singlet), coupling constant (Hz), integration). ^{13}C magnetic resonance spectra were recorded on a Bruker WM-

250 spectrometer (68.9 MHz) and are reported in parts per million from tetramethylsilane on the δ scale.

High resolution mass spectra were performed by the M. S. U. Regional Mass Spectroscopy Facility; Dept. of Biochemistry, East Lansing, Michigan 48824. Electron impact (EI/MS) and chemical ionization (CI/MS) mass spectra were recorded on a Finnigan 4000 utilizing an INCOS 4021 data system. A Pye-Unicam SP-1000 infrared spectrophotometer was used to record infrared spectra using polystyrene as a standard. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

All reactions, unless otherwise stated, were carried out under a blanket of argon in flame dried glassware, with the rigid exclusion of moisture from all reagents. Base washed glassware was prepared as follows: washing in an KOH/EtOH base bath, followed by distilled water, ammonium hydroxide, distilled water, absolute ethanol, and flame drying. Syringes, cannulas, needles, and spin bars employed with base washed glassware were also prepared in the same manner.

3-(3-furyl)-propyl-1-bromide[17] **(18)** - To a solution of triphenyl-phosphine (25.99 g, 99.2 mmol) in CH_2Cl_2 (600. ml), cooled in an ice water bath, was added 3-(2-furyl)-propan-1-ol[12h] (10.0 g, 79.4 mmol), followed by addition of NBS (17.66 g, 99.2 mmol) in 4 portions over ten minutes. After stirring at 0°C for four hours, the solution was warmed to RT and stirred one hour further. The solution was concentrated in vacuo; cast into hexane (350. ml), and stored overnight in a freezer. The precipitated Ph_3PO was removed by filtration through a pad of celite, the filter cake washed with hexane, and the combined filtrates were washed with $NaHCO_3$, and brine (250. ml ea.), dried ($MgSO_4$), and concentrated in vacuo to provide the crude product as a pleasant smelling pale yellow liquid.

Distillation (BP_{24} 93-97°C) provided 11.0 g, (73.3%) of **18**. Rf=0.68 in hex/ether (1/1).

6-(3-(3-furyl)-propyl)-cyclohex-2-en-1-ol (21) - To a solution of the enone (**20**)[12] (0.42 g, 2.10 mmol) in anhydrous MeOH (20. ml), cooled to 0°C in an ice water bath, was added $CeCl_3 \cdot 7H_2O$ (0.786 g, 2.10 mmol) in one portion. After five minutes, $NaBH_4$ (0.159 g, 4.20 mmol) was added in two portions, and the reaction stirred for one half hour. The solution was quenched with sat. aq. NH_4Cl (20. ml), cast into hexane /ether (150 ml, 1/2), and then washed with sat. aq. NH_4Cl, sat. aq. $NaHCO_3$, and brine (150 ml ea.), followed by drying ($MgSO_4$) and concentration in vacuo. Purification by chromatography on a column of silica gel (50 mm o.d., 100. g, 230-400 mesh, hexane/ether (4/1), 25 ml fractions) using the flash technique provided 0.30 g (69%) of the alcohol **21** from fractions 24-49. Rf=0.24 in (1/1) hexane/ether.

EI/MS (70 eV): 206(M^+,3.6), 188(1.5), 170(1.5), 159(5.4), 143(7.7), 124(6.7),108(31.9), 95(29.2), 81(66.1), 70(59.1) 53(59.5), 41(base)

^{1}H-NMR(250 MHz): δ :7.30(brs, 1), 7.18(brs, 1), 6.24(brs, 1), 5.84(d, j=2.1Hz, 1), 5.70(m, 1), 4.00(brs, 1), 2.41(m, 2), 2.01(m,2),1.80-1.00(m, 8)

IR (Neat): 3600-3100, 2980-2820, 1570, 1500, 1250, 1015, 780 cm^{-1}

Attempted Cyclization of Allylic Alcohol (21) - To a solution of the allylic alcohol (0.20 g, 0.97 mmol) in cyclohexane (4. ml) at RT was added in one portion formic acid (1. ml). The mixture stirred for ten minutes, and then was cast into ether/ water (40 ml, 1/1) and the organic phase separated. The aqueous phase was extracted with ether (3 x 25.ml), and the combined organic layers washed with $NaHCO_3$, and brine (100 ml ea.), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (30 mm o.d., 40.0 g, 230-400 mesh, hexane/ether (4/1), 15 ml fractions) using the flash technique. Fractions 9-15 provided 0.110 g, (49%) of the formate esters of allylic alcohol **21**. Rf=0.6 in (10/1) hexane/ether.

EI/MS (70 eV): 234(M^+, 1.9), 188(12.8), 171(2.0), 159(2.4), 147(8.8), 131(6.9), 117(4.6), 104(25.1), 94(73.4), 81(base), 67(26.5)

^{1}H-MR(250 MHz): δ :7.87(s, 1), 7.84(s, 1), 7.33(d, J=1 Hz, 1), 7.18(brs, 1), 6.25(brs, 1), 6.0-5.12(m, 4), 2.24(m, 2), 2.05(m, 2), 1.95-1.10(m, 6)

IR (Neat): 3015, 2980-2860, 1720, 1500, 1450-1430, 1220-1130(w),1020, 870, 780 cm^{-1}

Cyclization of Formate Ester to (22) - To a solution of the formate esters, (0.036 g, 0.152 mmol) in benzene (10. ml) was added pTsOH (0.066 g, 0.69 mmol), and the mixture was refluxed gently for one half hour. The clear solution which had turned blue in color, was diluted with ether (40 ml), and carefully quenched with sat. aq. $NaHCO_3$ (40 ml). This was followed by solid $NaHCO_3$ until one obtained a pH of 9.0. The organic phase was separated, and the aqueous phase extracted with ether (3 x 40 ml). The combined organic layers were washed with brine (100 ml), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by chromatography on a column of silica gel (20 mm o.d., 20. g, 230-400 mesh, packed in (300/1) hexane/ether run in (100/1) hexane/ether, 10.0 ml fractions) using the flash technique, provided 0.0071g, (25%) of the cyclized product **22**, from fractions 7-16. Rf=0.36 in (99/1) hexane/ether.

EI/MS (70 ev): 188(M^+, 47.0), 173(3.5), 160(base), 145(22.9), 131(34.9),117(20.6), 105(10.6), 91(28.7), 77(13.3), 65(5.85), 53(3.31)

^{1}H-MR(250 MHz): δ : 7.22(d, J=1.5 Hz, 1), 6.18(d, J=2.5 Hz, 1), 5.82(d of t, J=14, 4 Hz, 1), 5.5(d of t, J=13, 1 Hz, 1), 2.42(t, J=8.4 Hz,2), 2.20-1.55(m, 1)

IR (Neat): 3010-2840, 1510, 1450, 1210, 1170-1030, 970, 895, 800,730 cm^-

<u>1-(1-hydroxymethyl)-3-(3-(3-furyl)-propyl)-1-cyclopentene (29)</u> - (A) To a solution of 1-((dimethylsulfonio)methyl)cyclopent-2-en-1-ol[12h] **(27)**, (3.78 g, 13.23 mmol) in THF (150 ml) in a 250 ml base washed round bottom flask, was added NaH (0.480 g, 15.87 mmol) in one portion. The mixture stirred for five and one half hours and was then cooled in a dry ice-isopropanol bath (-78°C). (B) To activated Mg metal (0.50 g, 20.6 mmol), in a 500 ml base washed round bottom flask with condenser, is added 10% of a solution of 3-(3 furyl)-propyl bromide[17] **18** (3.00 g, 15.87 mmol) in THF (10. ml). After reaction began, the remaining 90% of the bromide solution was diluted with THF (85. ml) and added over one half hour, followed by gentle refluxing for two hours. The mixture was cooled in a dry ice-isopropanol bath, and CuCN (1.42 g, 15.87 mmol) was added in one portion. After stirring at -78°C for one hour, the mixture was warmed to -45°C (dry ice-acetonitrile) for one half hour, then cooled to -78°C for one quarter hour. The spiroepoxide (A) at -78°C, was then added <u>via cannula</u> over one half hour. After stirring at -78°C for three hours, the mixture was warmed to RT over one and one half hours. The solution was then quenched with sat. aq. NH_4Cl (100 ml) and NH_4OH/H_2O (220 ml, 1:1). The mixture was saturated with NaCl, separated, and the aqueous phase was extracted with ether (3 x 100. ml). The combined organic layers were washed with $NaHCO_3$, and brine (200 ml ea.), dried ($MgSO_4$), and concentrated <u>in vacuo</u>. The crude product was purified by chromatography on a column of silica gel (50 mm o.d., 200. g, 230-400 mesh, packed hexane/ether (4/1), run hexane/ether (2/1), 100 ml fractions) using the flash technique. Fractions 11-23 provided 2.089 g (76.6%) of **29**. Rf=.28 in (1/1) hexane/ether) as a pale yellow viscous liquid.

EI/MS (70 eV): 206(M^+, 8.8), 188(14.9), 175(19.3), 159(5.5), 147(3.5),131(6.6), 123(8.6), 106(14.8), 95(47.3), 79(base), 67(83.3),53(56.3), 41(86.7)

^{1}H-NMR(250 MHz): δ : 7.31(t, J=1 Hz, 1), 7.18(brs, 1), 6.26(brs, 1), 5.06(m, 1), 4.16(s, 2), 2.67(m, 1), 2.40(t, J=7.5 Hz, 2),2.30(m, 2), 2.10(m, 1), 1.65-1.20(m, 5)

IR (Neat): 3640-3100, 2980-2880, 2860, 1500, 1450, 1430, 1380, 1160, 1020(w), 875, 775, 720 cm^{-1}

3-(3-(3-furyl)-propyl)-cyclopent-1-ene-1-carboxaldehyde(30) -To a solution of alcohol **29** (1.00 g, 4.854 mmol) in CH_2Cl_2 (400. ml), in a 1L base washed round bottom flask, was added celite (25. g), followed by PCC (1.57 g, 7.28 mmol). After stirring two hours at room temperature, ice cold hexane (200 ml) was added and the mixture was filtered through a plug of celite/silica gel. The filtrate was dried ($MgSO_4$), and concentrated in vacuo, to give the crude aldehyde as a viscous yellow liquid. The crude product was purified by chromatography on a column of silica gel (50 mm o.d., 100. g, 230-400 mesh, hexane/ether (5/1), 30 ml fractions) using the flash technique. Fractions 10-16 afforded 0.667 g. (67.4%) of **30**. Rf=0.48 in (1/1) hexane/ether.

EI/MS (70 eV): 204(M^+, 30.2), 186(3.2), 175(7.7), 147(13.1), 133(5.0), 122(base), 109(13.2), 95(34.0), 81(74.1), 67(55.5), 53(45.6)

^{1}H-NMR(250 MHz): δ : 9.73(s, 1), 7.31(m, 1), 7.20(brs, 1), 6.75(m, 1), 6.26(brs, 1), 2.89(m, 1), 2.55(m, 2), 2.45(t, J=6.3 Hz, 2),2.18(m, 1), 2.00-1.35(m, 5)

IR (Neat): 2980-2880, 2860, 2710, 1675, 1610, 1500, 1430, 1350, 1255, 1160, 1020, 870, 770, 720 cm^{-1}

1-(1-hydroxyethyl)-3-(3-(3-furyl)-propyl)-1-cyclopentene (31) -

To a solution of the aldehyde **30** (1.151 g, 5.642 mmol) in ether (500. ml), in a 1L base washed round bottom flask cooled in a dry ice-isopropanol bath to -78°C, is added MeLi(1.4M, 7.6 ml, 10.64 mmol), and the mixture stirred for one hour.

Additional MeLi (0.33 equiv.) was then added and the mixture stirred for one additional half hour until no starting material was observed by TLC. The solution was warmed to room temperature over one half hour, and was quenched with sat. aq. NH_4Cl (200 ml). After separation, the aqueous phase was extracted with ether (3 x 150 ml). The combined organic layers were dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (50 mm o.d., 125. g, 230-400 mesh, hexane/ether (2.5/1), 40 ml fractions) using the flash technique. Fractions 14-35 afforded 1.161 g (94%) of **31**. Rf=0.20 in (1/1) hexane/ether.

EI/MS (70eV): 220(M^+, 3.0), 202(7.4), 187(1.1), 175(3.0), 159(2.5), 147(2.4), 133(2.4), 120(9.9), 111(4.4), 95(15.4), 81(18.5), 67(15.3) 53(12.8), 43(base)

^{1}H-NMR(250 MHz): δ : 7.34(t, J=1.5 Hz, 1), 7.19(brs, 1), 6.23(brs, 1), 5.51 (brs, 1), 4.39(q, J=6.3 Hz, 1), 2.64(m, 1), 2.40(t, J=8.4 Hz,2), 2.28(m, 2), 2.09(m, 1), 1.66-1.30(m, 6), 1.27(d of d, J=5.4, 1 Hz, 3)

IR (Neat): 3700-3100, 3000-2820, 1500, 1450-1430, 1370, 1160, 1060, 1020, 870, 840, 770 cm^{-1}

Cyclization of Alcohol (31) - To a solution of the alcohol **31** (0.100 g, 0.4545 mmol) in cyclohexane (40. ml), in a 100 ml base washed round bottom, was added formic acid (10. ml) in one portion. After stirring twenty minutes, pTsOH (two crystals) was added and the mixture was heated gently (50°) for five minutes. After stirring twenty five minutes, the mixture was diluted with cyclohexane (25 ml) and carefully quenched with sat. aq. $NaHCO_3$ (60 ml). This was followed by solid NaHCO3 until pH 9.0 was obtained. The aqueous phase was extracted with ether (3 x 50 ml), and the combined organic layers were washed with brine (75 ml), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (40 mm o.d., 30. g, 230-400 mesh, hexane/ether (15/1), 10 ml fractions) using the flash technique. Fractions, 5-10 afforded 0.089 g (96.7%) of **32**. Rf=0.64 in (10/1) hexane/ether.

EI/MS (70eV): 202(M^+, base), 187(47.3), 173(62.8) 159(19.4), 145(16.3),131(23.8), 117(16.8), 105(14.9), 91(37.5), 77(28.8), 65(24.9)

^{1}H-NMR(250 MHz): δ : 7.20(d, J=1.5 Hz, 1), 7.17(d, J=1.5 Hz, .33), 6.19(d, J=1.5 Hz, .33), 6.15(d, J= 1.5 Hz, 1), 5.26(t, J=1 Hz, .33), 4.88 (d of q, J=6, 4 Hz, 1), 3.78(m, 1), 2.8-1.2(m, 13)

IR (Neat): 3000-2800, 1505, 1460-1420,1150, 890, 830, 790, 725, 690 cm^{-1}

2-bromo-4-(3-furyl)-but-1-ene (34) - To a solution of **33**[12] (12.0 g, 32.42 mmol) in THF (75. ml), in a 250 ml base washed round bottom flask, cooled in a dry ice-isopropanol bath, was added n-BuLi (2.4M, 17.6 ml, 1.3 eq.) over fifteen minutes. After stirring for one hour at -78°C, CuCN (3.78 g, 42.2 mmol, 1.3 eq.) was added in one portion and the reaction stirred one hour further. The mixture was warmed (-45°) in a dry ice-acetonitrile bath for one half hour, and then cooled again to -78°C. To the cuprate was added a solution of 2,3-dibromopropene[24] (8.43 g, 42.2 mmol) in THF (15. ml) by cannula over one half hour. After stirring at -78°C for three hours, the reaction was quenched with sat. aq. NH_4Cl (100 ml) and the organic phase separated. The aqueous phase was extracted with ether (3 x 250 ml), and the combined organic layers were then dried ($MgSO_4$) and concentrated in vacuo **(NO HEAT)**. The crude product was purified by chromatography on a column of silica gel (60 mm o.d., 500. g.,230-400 mesh, (99/1) hex./ether, 250 ml fractions) using the flash technique. Fractions 23-40 gave 5.15 g. (79%) of the pure product **34**. Rf=0.19 in hexane.

EI/MS (70 eV): 202(M^++1, 4.9), 200(5.11), 121(66.9), 103(5.59), 91(15.2), 81(base), 53(57.6), 39(42.7)

^{1}H-NMR (250MHz): δ : 7.28 (m, 2), 6.28 (m,2), 5.58 (m, 1), 5.42 (m, 1), 2.70(s, 4)

IR (Neat): 3000-2860, 1630, 1570, 1500, 1450, 1430, 1385, 1190, 1160, 1115, 1070, 1035, 890, 875, 780, 725 cm^{-1}

1-(1-hydroxymethyl)-3-(4-(3-furyl)-but-1-en)-1-cyclopentene (35) - (A) To a solution of 1-((dimethylsulfonio)methyl)-cyclopent-2-en-1-ol[12] (0.10 g, 0.350 mmol) in THF (4.0 ml), in a 25 ml base washed round bottom flask, was added NaH (0.01 g, 0.420 mmol, 85%) in one portion. After stirring at room temperature for three hours, the mixture was cooled to -78°C, in a dry ice-isopropanol bath. (B) To a solution of 2-bromo-4-(3-furyl)-butene (0.211 g, 1.05 mmol) in ether (4.0 ml) in a 25 ml base washed round bottom flask cooled in a dry ice-isopropanol bath was added n-BuLi (1.3M, 1.05 mmol, 0.81 ml). After stirring for one hour at -78°C, the mixture was warmed to -45°C (dry ice-acetonitrile bath) and the reaction stirred for one hour. The solution was then cooled to -78°C once more, and was added via cannula to 1.10 mmol of $MgBr_2$ at -78°C; prepared in situ from 1.10 mmol of ethylene dibromide and 1.25 mmol of magnesium metal in 5.0 ml of ether.

After addition was complete, the mixture was warmed to -45°C for one half hour, and then cooled back to -78°C, and copper bromide dimethyl sulfide (0.108 g, 0.525 mmol) was added in one portion. After stirring one half hour at -78°C, the in situ generated spiroepoxide (A), at -78°C, was added via cannula over fifteen minutes. The reaction stirred at -78°C for three hours and was then allowed to warm to room temperature and quenched with $NaHCO_3$ (10 ml). This solution was diluted with ether (200 ml), and cast into $NaHCO_3$/sat. aq. NH_4Cl/H_2O (90/60/40 ml). After separation, the aqueous phase was extracted with ether (3 x 100 ml), and the combined etheral layers were washed with $NaHCO_3$, brine, (200 ml ea.), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromotography on a column of silica gel (30. mm o.d., 30. g., 230-400 mesh, packed in hexane/ether (6/1), run in hexane/ether

(3/1),10 ml fractions) using the flash technique. Fractions 20-72, gave 0.0525 g (68.9%) of pure **35**. Rf=0.25 in (1/1) hexane/ether.

EI/MS (70eV): 218(M^+, 3.7), 200(2.4), 187(2.6), 171(1.5), 162(2.8), 149(5.5), 137(base), 119(19.9), 105(22.2), 96(41.9), 81(88.6), 67(84.9)

^{1}H-NMR (250MHz): δ :7.33(t, J=2 Hz, 1), 7.21(m, 1), 6.28(m, 1), 5.56(m,1), 4.81(m, 1), 4.73(m, 1), 4.21(brs, 2), 3.35(m, 1), 2.59 (t, J=7.4 Hz, 2), 2.27(m, 5), 1.76-1.35(m, 2)

IR (Neat): 3640-3100, 3000-2800, 1630, 1500, 1450, 1430, 1380, 1150,1020(w), 890, 870, 780, 720 cm^{-1}

3-(4-(3-furyl)-but-1-en)-cyclopent-1-ene-1-carboxaldehyde (36) - To a solution of the alcohol **35** (0.375 g, 1.72 mmol) in CH_2Cl_2 (150. ml), in a 500 ml base washed round bottom flask, is added celite (10. g) followed by PCC (0.593 g, 2.75 mmol) in one portion. After stirring for one and one half hours, ice cold hexane (75 ml) was added and the mixture filtered through a plug of celite/silica gel. The solution was dried ($MgSO_4$), and concentrated in vacuo to provide the aldehyde as a viscous yellow liquid. The crude product was purified by chromatography on a column of silica gel (30 mm o.d., 30. g, 230-400 mesh, hexane/ether (5/1), 10 ml fractions) using the flash technique. Fractions12-27 afforded 0.240 g (65%) of **36**. Rf=0.51 in (1/1) hexane/ether.

EI/MS (70 eV): 217(M^++1, 2.3), 216(M^+, 15.6), 201(2.1), 187(12.7), 172(1.94), 145(3.9), 135(24.9), 122(12.9), 107(16.1), 95(11.8), 81(base), 67(21.6), 53(36.6), 41(25.6)

^{1}H-NMR(250MHz): δ : 9.71(s, 1), 7.34(t, J=2.1 Hz, 1), 7.21(m, 1), 6.73(m, 1), 6.28(brs, 1), 4.85(brs, 1), 4.81(brs, 1), 3.53(m, 1), 2.71-2.0(m, 7), 1.79(m, 1)

IR (Neat): 3000-2880, 2850, 2700, 1720, 1670, 1620, 1500, 1450, 1430,1380, 1350, 1300-1250(w), 1160-1100(w), 1015, 890, 780 cm^{-1}

1-(1-hydroxyethyl)-3-(4-(3-furyl)-but-1-en)-1-cyclopentene (37) - To a solution of the aldehyde, **36**, (0.0438 g, 0.203 mmol) in ether (25. ml) in a 50 ml base washed round bottom cooled in a dry ice-isopropanol bath, was added MeLi (1.1M, 0.304 mmol, 0.19 ml), and the mixture stirred for one half hour. Additional MeLi (0.5 equiv.) was added, and the mixture stirred one half hour further until no starting material was seen by TLC. The solution was slowly warmed to 0°C, quenched with sat. aq. NH_4Cl (35 ml), and extracted with ether (3 x 50 ml). The ether layers were combined, washed with brine (75 ml), dried ($MgSO_4$), , and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (10 mm o.d., 10.0 g, 230-400 mesh, packed hexane/ether (4/1), run hexane/ether (2/1), 6 ml fractions) using the flash technique. Fractions 8-18 provided 0.042 g (89%) of **37**. Rf=0.18 in (1/1) hexane/ether.

EI/MS (70eV): 232(M^+, 2.8), 214(1.6), 189(2.7), 171(1.2), 162(3.0) 151(23.6), 133(4.14), 121(4.9), 107(24.2), 93(18.3), 81(51.1), 67(12.5), 43(BASE)

^{1}H-NMR(250MHz): § : 7.12(t, J=2 Hz, 1), 7.06(brs, 1), 6.09(brs, 1), 5.45(m, 1), 4.90(brs, 1), 4.77(brs, 1), 4.15(m, 1), 3.25(m,1), 2.49(t, J=8.5 Hz, 2), 2.20(m, 2), 2.02(m, 1), 1.57(m, 1), 1.4-1.15(m, 3), 1.13(d of d, J=6.3 Hz, 1 Hz, 3)

IR (Neat): 3660-3100, 3000-2840, 1630, 1500, 1450, 1430, 1370, 1160, 1065, 1020, 890, 870, 780 cm^{-1}

Cyclization Of Alcohol (37) - To a solution of the alcohol **37** (0.058 g, 0.250 mmol) in cyclohexane(10. ml) in a 25 ml base washed round bottom was added formic acid (2.5 ml, 98%) in one portion . After one half hour the mixture was cast into cyclohexane (50.0 ml), and carefully quenched with sat. aq. $NaHCO_3$ (50 ml). After separation, the aqueous phase was extracted with ether (3 x 40 ml), and the combined organic layers were washed with brine (75 ml), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (30 mm o.d., 30. g, 230-400 mesh, packed hexane/ether (15/1), run in hexane/ether (10/1), 8-10 ml fractions) using the flash technique.

Fractions 5-9 and 11-22, respectively, resulted in 0.0271 g (51%) of the cyclized product **38**, and 0.0355 g (49%) of the formate ester **37**. Rf=0.7 (**38**),and 0.21 (**37**) in (10/1) hexane/ether.

EI/MS (70eV): **(cyclized)**: 214(M^+, base), 199(43.7), 185(48.0), 171(19.2), 157(24.7), 143(13.0), 129(17.7), 115(15.1), 105(9.1), 91(24.1), 77(14.9), 65(10.5), 55(8.3)

^{1}H-NMR (250 MHz): δ : **(cyclized)**: 7.23 (d, J=1 Hz, 1), 6.14(d, J=2 Hz, 1), 5.01(d of q, J=6.4, 2.1 Hz, 1), 4.86(brs, 1), 4.78(m, 1), 3.83(m, 1), 2.98(q, J=6 Hz, 1), 2.52(t, 2), 2.54-2.16(m, 5), 1.92(m, 1), 1.58(d of d, J=8.3, 1 Hz, 3)

IR (Neat): **(cyclized)**: 3000-2820, 1630, 1505, 1460-1420, 1260, 1180-1000(w), 890, 830-790(w), 725 cm^{-1}

EI/MS (70eV): **(formate)**: 260(M^+, 12.8), 214(37.4), 199(10.8), 185(14.9), 172(35.7), 157(13.6), 145(8.81), 133(base), 119(23.4), 105(22.3), 91(39.8), 81(55.6), 65(10.3), 53(19.2)

^{1}H-NMR(250 MHz): δ : **(formate)**: 7.76(brs, 1), 7.70(s, .57), 7.22(m, 1), 7.18 (m, 1), 6.2(m, 1), 5.65(m, 1), 5.58(m, 1), 4.98(s, .58), 4.95(s,1), 4.85(t, J=1 Hz, 1), 4.55(brs, .57), 3.25(m, 1), 2.49(m, 2), 2.20(m, 2), 2.02(m, 1), 1.57(m, 1), 1.14s, 3), 1.15(d of d, J=6.3, 2.4 Hz, 1.57)

IR (Neat): **(formate)**: 3000-2820, 1720, 1630, 1500, 1450, 1380, 1200-1150(w), 1050(w), 890, 870, 830, 780, 730 cm^{-1}

MODIFIED CYCLIZATION: The combined reagents were allowed to stir at RT for twenty minutes. PTSA (2 crystals) was then added and the solution heated gently (50°) for two minutes, and after stirring for twenty minutes further, the reaction was diluted with cyclohexane (20 ml). The aqueous phase was separated, diluted with cyclohexane (20 ml), quenched with $NaHCO_3$ (20 ml sat. aq. and then solid), saturated with NaCl, and extracted with ether (3 x 50 ml). The combined organic layers were washed with $NaHCO_3$ and brine (50 ml ea.), dried ($MgSO_4$), and concentrated in vacuo. The cyclized product **38** was obtained in 72% yield after purification by flash chromatography.

__1-(1-hydroxybenzyl)-3-(4-(3-furyl)-but-1-en)-1-cyclopentene (41a)__ - To a solution of the aldehyde, (36), (0.460 g, 2.256 mmol) in ether (150. ml) cooled in a dry-ice isopropanol bath (-78°) was added phenyl-lithium (2M, 1.73 ml, 1.5 eq.) dropwise, and the mixture stirred for three hours. Additional phenyl-lithium (0.75 ml) was added and the mixture stirred for three hours further. The mixture was allowed to warm to RT and stirred overnight. The mixture was quenched with NH_4Cl (50 ml), separated, and the aqueous phase was extracted with ether (3 x 50 ml). The combined organic layers were dried $MgSO_4$, and concentrated _in vacuo_. The crude product was purified by chromatography on a column of silica gel (50 mm o.d.,100 g., 230-400 mesh, 300 ml forerun, hexane/ether(2.5/1), 30 ml fractions) using the flash technique. Fractions 8-25 provided 0.4469 g. (70.3%) of **41a**. Rf=0.35 in (1/1) hexane/ether.

EI/MS (70eV): 282(M^+, 0.51), 264(8.4), 182(19.5), 175(4.31), 145(4.82), 128(7.87), 115(9.39), 105(BASE), 91(28.9), 77(50.0), 67(18.8)

^{1}H-NMR (250MHz): δ : 7.30(m, 6), 7.18(s, 1), 6.23(s, 1), 5.65(m, 1), 5.28(brs, 1), 2.66(brs, 1), 2.40(t, J=13.2 Hz, 2), 2.15(m, 3), 1.90t, J=8.5 Hz, 1), 1.4(m, 5)

IR (neat): 3640-3140, 3030, 2930, 2860, 1600, 1495, 1455, 1380, 1300, 1200, 1160, 1070, 1025, 875, 775, 705 cm^{-1}

__Cyclization of Alcohol (41a)__ - To a solution of the alcohol **41a** (0.4118 g, 1.460 mmol) in cyclohexane (175. ml) was added formic acid (35. ml, 98%) in one portion. After stirring one half hour, the mixture was separated and the organic phase washed twice with sat. aq. $NaHCO_3$ (50 ml). The solution was dried ($MgSO_4$), and concentrated _in vacuo_. The crude product was purified by chromatography on a column of silica gel (40 mm o.d., 50. g., 230-400 mesh, (20/1) hexane/ether, 25 ml fractions) using the flash technique. Fractions 5-15 gave 0.3343 g. 87% of **42a**. Rf=0.66 in (1/1) hexane/ether.

EI/MS (70eV): 264(M+ BASE), 235(2.2), 207(2.2), 191(2.2), 173(97.8), 165 (14.4), 147(20.0), 128(22.2), 115(40.0), 91(63.3), 77(17.7)

^{1}H-NMR (250 MHz): δ : 7.25(m, 6), 6.22(d, J= 2Hz, 1), 5.84(q, J=7.8 Hz, 1) 4.0(brs, 1), 2.85(m, 2), 2.62-1.44(m, 9)

IR (Neat): 3020, 2920, 2840, 1650, 1600, 1560, 1540, 1440, 1150, 1060, 910, 900, 860, 790, 760, 730, 690 cm^{-1}

1-(1-hydroxy-p-methoxybenzyl)-3-(4-(3-furyl)-but-1-en)-1-cyclopentene (41b) - To Mg metal (0.233 g, 9.59 mmol) was added ten percent of a solution of p-bromoanisole (1.570 g, 8.400 mmol) in THF (10. ml). After the reaction began the remaining bromide was diluted with THF (90. ml) and then added over one quarter hour. After two hour of gentle reflux, the solution was cooled in a dry-ice isopropanol bath (-78°), and a solution of the aldehyde **36**, (0.979 g, 4.799 mmol) in THF (25. ml) was added over one half hour. After stirring for three hours at -78°, the mixture was warmed to RT and stirred overnight until no further starting material could be seen by TLC. The mixture was quenched with sat. aq. NH_4Cl (25 ml), separated, and the aqueous phase was extracted with ether (3 x 50 ml). The combined organic layers were dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (50. mm o.d., 100. g, 230-400 mesh, 200. ml forerun, hexane/ether(2.5/1), 50 ml fractions) using the flash technique. Fractions 8-18 provided 1.305 g. (87.%) of **41b**. Rf=0.21 in (1/1) hexane/ether.

EI/MS (70 eV): 312(M$^+$, 1.1), 241(1.1), 171(12.2), 161(1.1), 147(2.2), 129(BASE), 111(18.9), 101(8.9), 83(20.0), 71(34.4), 55(94.4)

^{1}H-NMR (250 MHz): δ : 7.34(brs, 1), 7.24(d, J=8.4 Hz, 2), 7.18(brs, 1), 6.85(d,J=8.4 Hz, 2), 6.75(d, J=1 Hz, 1), 6.24(brs, 1), 5.63(m, 1), 5.22(brs, 1), 3.8(s, 3), 3.75(s, 1), 2.66(brs, 1), 2.4(t, J=10.5 Hz, 2), 2.1(m, 3), 1.83(brs, 1), 1.64-1.22 (m, 5)

IR (NEAT): 3640-3080, 2930, 2850, 1610, 1585, 1510, 1460, 1440, 1305, 1250, 1175, 1105, 1025, 875, 830, 780, 735 cm^{-1}

High Res./MS: calculated for $C_{20}H_{24}O_3$: 312.1725; observed: 312.1724

Cyclization of Alcohol (41b) - To a solution of the alcohol **41b** (1.300 g, 4.17 mmol) in cyclohexane (500. ml) was added formic acid (35. ml, 98%) in one portion. After stirring ten minutes, the mixture was separated and the organic phase washed twice with sat. aq. $NaHCO_3$ (150 ml). The solution was dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (50 mm o.d., 50. g., 230-400 mesh, (8/1) hexane/ether, 25 ml fractions) using the flash technique. Fractions 5-8 gave 0.9063 g. 74% of **42b**. Rf=0.77 in (1/1) hexane/ether.

EI/MS (70eV): 294(M^+ BASE), 264(8.4), 251(3.6), 235(5.0), 186(15.4), 173(59.1), 147(44.9), 121(34.9), 105(14.1), 91(30.6), 77(18.9)

^{1}H-NMR (250 MHz): δ : 7.26(d, J=1 Hz, 1), 7.2(d, J= 8.4 Hz, 2), 6.81(d, J=8.4 Hz, 1), 6.19(d, J=1 Hz, 1), 5.73(m, 1), 3.94(m, 1), 3.78 (s, 3), 2.65(m, 2), 2.58-1.18(m, 9)

IR (Neat): 2920, 2840, 1740(w), 1605, 1510, 1460, 1440, 1295, 1245, 1175,1150, 1125, 1060, 1035, 900, 860, 820, 735, 690 cm^{-1}

High Res./MS: calculated for $C_{20}H_{22}O_3$: 294.1620; observed: 294.1614

Compound 43a: To a THF solution of borane-dimethyl sulfide[23] (1.8 M, 1.36 ml, 2.44 mmol) cooled to -10°C in a ice-salt water bath, was added 2,3-dimethyl-2-butene (0.290 ml, 2.44 mmol) dropwise. The mixture was warmed to 0°C, stirred one hour, warmed to room temperature, and stirred two hours further. A solution of cyclized product **42a** (0.258 g, 0.975 mmol) in THF (3. ml) was added dropwise and the mixture stirred 21 hours at room temperature. The mixture was cooled to 0°C, quenched carefully with water (2.0 ml), followed by 3N NaOH (3.0

ml), and 30% hydrogen peroxide (5.0 ml). The solution stirred at 0°C for one hour, warmed to room temperature over one hour, and was then cast into sat. aq. NH_4Cl (30 ml) and ether (50 ml). The organic layer was separated and washed with 10% sodium bisulfite, and sat. aq. $NaHCO_3$ (30 ml ea.). The aqueous phases were combined, saturated with sodium chloride, and extracted with ether (3 x 50 ml). The combined organic phases were washed with brine (50 ml), dried ($MgSO_4$), and concentrated in vacuo. The crude alcohols were purified by chromatagrophy on a column of silica gel (20 mm o.d., 15.0 g., 230-400 mesh, hexane/ether (15/1), 5-7 ml fractions) using the flash technique. Fractions 6-14 gave 88.8 mg. (34.5%) recovered starting material **42a**. Fractions 16-23 gave 0.1524 g. (55.4%) of **43a**.

EI/MS (70 eV): 282(M^+,3.5), 264 (8.0), 173(8.8), 149(25.2), 134 (19.5),119(55.4), 105(BASE), 91(62.8), 77(33.2), 71(18.5), 55(30.9)

^{1}H-NMR (250 MHz): δ : 7.22(m, 6H), 6.12(d, J=1.2 Hz, 1), 6.04(d, J=1.2 Hz, 0.2), 4.59(d, J=8.9 Hz, 0.2), 4.39(d, J=8.9 Hz, 1), 3.57(t, J=15.6 Hz, 1), 2.71-1.09(m, 13)

IR (Neat): 3580, 3500-3200, 3010(w), 2990-2800, 1820(w), 1600(w), 1510, 1490, 1450, 1370(w), 1270(w), 1150, 1070-1000, 895, 875, 760, 730, 695 cm-1

Compound 43b: To a THF solution of borane-dimethyl sulfide[23] (2.0 M, 0.272 ml, 0.544 mmol) cooled to -10°C in a ice-salt water bath, was added 2,3-dimethyl-2-butene (64.7 ul, 0.544 mmol) dropwise. The mixture was warmed to 0°C, stirred one hour, warmed to room temperature, and stirred one hour further. A solution of cyclized product **42b** (64.0 mg., 0.218 mmol) in THF (1.0 ml) was added dropwise and the mixture stirred 20 hours at room temperature. The mixture was cooled to 0°C, quenched with water (1.0 ml), followed by 3N NaOH (2.0 ml), and 30% hydrogen peroxide (3.0 ml). The solution stirred at 0°C for one hour, warmed to RT over one hour, and was cast into sat. aq. NH_4Cl (30 ml) and ether (50 ml). The organic layer was separated and washed with 10% sodium bisulfite, and sat. aq. $NaHCO_3$ (30 ml ea.). The aqueous phases were combined, saturated with sodium chloride, and extracted with ether (3 x 50 ml). The combined organic phases were washed with brine (50 ml), dried ($MgSO_4$), and concentrated in vacuo.

The crude alcohols were purified by chromotagrophy on a column of silica gel (10 mm o.d., 1.5 g., 230-400 mesh, hexane/ether (2/1), 2 ml fractions) using the flash technique. Fractions 2,3 gave 5.4 mg. (8.%) recovered starting material **42b**. Fractions 8-14 gave 40.6 mg. (59.8%) of **43b**.

EI/MS (70 eV): 312(M^+, 6.5), 294(24.4), 186(3.9), 176(17.0), 147(36.7),137(BASE), 121(26.6), 109(12.7), 91(22.3), 77(20.9), 55(10.0)

^{1}H-NMR (250 MHz): δ : 7.28(d, J=1.2 Hz, 1), 7.21(d, J=8.9 Hz, 1.3), 6.83(d, J=1.2 Hz, 1.3), 6.19(d, J=8.9 Hz, 1), 4.39(d, J=10.1 Hz, 1), 3.78, 3.79(s, s, 3.7), 3.58(t, J=15.6 Hz, 1), 2.62(m,4), 2.30(m, 2), 2.15-1.15(m, 7)

IR (Neat): 3600-3320, 3080-2800, 1730(w), 1610, 1580, 1510, 1465, 1450, 1380, 1305, 1250, 1175, 1105, 1025, 895, 830, 735, 690 cm^{-1}

High Res./MS: calculated for $C_{20}H_{24}O_3$: 312.1725; observed: 312.1728

Compound 44a, 45a: To the alcohol **43a** (0.1493 g, 0.5294 mmol) in CH_2Cl_2 (50. ml) was added celite (3.0 g), followed by PCC (0.228 g, 1.06 mmol) in one portion. After stirring 2.5 hours another 50 mgs. (0.25 mmol) of PCC was added, and the mixture stirred one half hour further. The mixture was then diluted with ice cold hexane (50 ml), and filtered through a plug of celite/silica gel. The filter cake was rinsed with hexane/ether (400 ml, 95/5), and the combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (20. mm o.d., 25. g., 230-400 mesh, hexane/ether (8/1), 8 ml fractions) using the flash technique. Fractions 7-16 gave 0.0798 g (54%) of the products **44a**, and **45a** as a 5:1 mixture (alpha/beta) which could be separated by flash chromatography. Fractions 18-23 gave 0.010 g (6.7%) recovered starting material **43a**.

EI/MS (70eV): (44a, 45a): 280(M+, 33.3), 264(2.8), 152(1.89), 203(3.78), 175(6.8),160(31.9), 147(73.0), 133(48.6), 119(17.5), 105(BASE), 91(44.3), 77(81.0), 65(8.1)

^{1}H-NMR (250MHz): δ : (44a, 45a):7.67(d, J=8.5 Hz, 0.2), 7.60(d, J=8.5 Hz, 2), 7.23(d, J=8.5Hz, 0.2), 7.20(d, J=8.5 Hz, 2), 7.12(s, 1.2), 6.82(d, J=1 Hz, 0.2), 6.58(d, J=1 Hz, 1), 5.91(d, J=1 Hz, 0.2), 5.60(d,J=1 Hz, 1), 4.19(m, 1.2), 3.6(m, 1), 2.27-1.08(m, 11)

IR (Neat): (44a, 45a): 3020(w), 2960-2800, 1665, 1585, 1570, 1500, 1438, 1360, 1205,1150, 990, 885, 860, 755, 720, 675 cm^{-1}

Compound 44b, 45b: To the alcohol **43b** (0.038 g, 0.1218 mmol) in CH_2Cl_2 (10. ml) was added celite (0.5 g), followed by PCC (0.066 g, 0.305 mmol) in one portion. After stirring 2.5 hours another 15 mg. (0.075 mmol) of PCC was added, and the mixture stirred one half hour further. The mixture was then diluted with ice cold hexane (30 ml), and filtered through a plug of celite/silica gel. The filter cake was rinsed with hexane/ether (200 ml, 95/5), and the combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (10. mm o.d., 2. g., 230-400 mesh, hexane/ether (2/1), 1 ml fractions) using the flash technique. Fractions 2-5 gave 0.0221 g (58.5%) of the products **44b**, and **45b** as a (6-8):1 mixture (alpha/beta) which could be further separated by flash chromatography. Mp (major isomer): 93-94°, Mp(mixture):78-81°, Minor isomer: oil.

EI/MS (70eV): (**44b**): 310(M+, 47.1), 174(13.3), 163(74.8), 149(43.2), 135(BASE), 119(16.3), 105(18.4), 91(37.7), 77(37.9), 55(60.4)

^{1}H-NMR (250MHz): δ : (**44b**) :7.79(dd, J=8.9, 1 Hz, 2), 6.80(dd, J=8.9, 1 Hz, 2), 6.74(d, J=1 Hz, 1) 5.74(d, J=1 Hz, 1), 4.24(m, 1), 3.82(s,1), 3.71(m, 1), 2.60-1.21(m, 11)

<u>IR (neat)</u>: (**44b**): 3010-2860, 1760(w), 1670, 1605, 1580, 1515, 1460, 1450, 1420, 1375, 1260, 1235, 1190-1170, 1118, 1070, 1030, 920, 850, 820,790, 750, 700, 690 cm^{-1}

<u>High Res./MS (44b)</u>: calculated for $C_{20}H_{22}O_3$: 310.1569; observed: 310.1566

<u>EI/MS (70eV)</u>: (**45b**): 310(M^+, 24.0), 293(4.89), 202(5.01), 174(16.6), 163(46.7), 148(17.3), 135(BASE), 107(8.81), 91(19.8), 77(25.2)

<u>^{1}H-NMR (250MHz)</u>: δ :(**45b**): 7.80(dd, J=8.9, 1 Hz, 2), 6.96(d, 1 Hz, 1), 6.86(dd, J= 8.9, 1 Hz, 2), 6.03(d, J=1 Hz, 1), 3.92(m, 1), 3.84(s, 1), 3.80(m,1), 2.60-1.40(m, 11)

<u>IR (Neat)</u>: (**45b**): 3010-2820, 1725(w), 1670, 1600, 1580, 1510, 1455, 1420, 1365, 1310, 1260, 1215, 1170, 1070, 1030, 900, 840, 740, 695 cm^{-1}

<u>**Alpha Hydroxy Ketone 46**</u>: To a solution of the major ketone **44b**, (0.1467 g, 0.4732 mmol) in THF (6. ml) at -78°C was added LDA (1.5 M, 1.5 eq., 0.47 ml) dropwise. The mixture stirred for one half hour, was warmed to -45°C (dry-ice/acetonitrile) for one half hour, and then cooled back to -78°C . MoOPh·HMPA·PYR[30] (0.410 g, 0.710 mmol, 2 eq.) was then added in one portion, and the mixture was allowed to warm from -78° to RT over 2.5 hours. The mixture was diluted with ether (50 ml), and washed with sodium sulfite (20 ml) and citric acid (30 ml). The aqueous layers were salted and extracted with ether (3 x 50 ml), and the combined organic layers were dried ($MgSO_4$) and concentrated <u>in vacuo</u>. The crude was purified via chromatography on a column of silica gel (30 mmm o.d., 20. g. 230-400 mesh, (10/1) hexane/ether for fract. 1-36, (3/1) hexane/ether for fract. 37-72, 8 ml fractions, 30 ml forerun) using the flash technique. Fractions 2-15 gave 35.2 mgs (24%) recovered **44b**, and fractions 30-68 gave 111. mgs (72%) of the product **46**. Rf = 0.32 in (1/1) hexane/ether.

<u>EI/MS (25eV)</u>: 308(M-18, BASE), 191(4.1), 179(53.4), 148(22.5), 135(71.2), 119(13.9), 105(11.5), 91(8.4), 84(27.4)

CI/MS (25eV): 367(M+41, .98), 355(M+29, 1.97), 327(M+1, 17.3), 309(79.7), 191(22.4), 163(2.95), 147(22.4), 135(BASE), 121(13.4)

^{1}H-NMR (250MHz): δ : (C_6D_6): 8.24, 8.2,(d, J=8.9 Hz, 2), 6.79 (d, J=1 Hz, 1), 6.65, 6.61(d, J=8.9 Hz, 2), 5.80(d, J=1 Hz, 1), 3.65(d, J=8.9 Hz, 1), 3.25(d, J= 6.5 Hz,1), 3.18(s, 3), 2.88(brs, 1), 2.72(d of t, 13.4, 8. Hz, 1), 2.6-1.2(m, 9)

IR (neat): 3620-3200, 3080-2800, 1710(w), 1670, 1600, 1510, 1450, 1420, 1370, 1300, 1245, 1170, 1030, 860-780, 735, 685 cm^{-1}.

High Res./MS: calculated for $C_{20}H_{22}O_4$: 326.1518; observed: 326.1546

Diol 47: To a solution of LAH (12.4 mg., 0.326 mmol) in ether (1.5 ml) at 0°C was added a solution of compound **46** (0.1061 g., 0.3255 mmol) in ether (1.5 ml). The mixture was stirred for one half hour at 0°C, and then warmed to RT over 1.5 hours. LAH (6.2 mgs, 0.5 eq.) was added and the mixture stirred one hour further. The mixture was quenched with water (1 ml), diluted with ether (50 ml), and washed with 15% NaOH (25 ml). The aqueous layers were saturated with salt and extracted with ether (3 x 50.ml), and the combined organic layers were dried ($MgSO_4$), and concentrated in vacuo to give 88.6 mgs. (83%) of the crude diol **47**, which was used without further purification.

EI/MS (25eV): 310(M-18, 2.65), 190(25.2), 163(35.9), 147(BASE), 137(52.1), 121(15.1), 109(8.13), 91(27.1), 77(26.7), 55(45.7)

CI/MS (25eV): 369(M+41, .50), 355(M+29, 3.65), 339(M+11, 4.92), 329(M+1, 11.7), 311(M-18, BASE), 293(11.3), 190(13.3), 175(21.2), 147(43.4), 137(29.3), 121(12.0), 85(25.6)

^{1}H-NMR (250MHz): δ : (C_6H_6): 7.29, 7.26,(d, J=8.9 Hz, 2), 7.10 (d, J=1 Hz, 1), 6.74, 6.70(d, J=8.9 Hz, 2), 5.93(d, J=1 Hz, 1), 4.31(d, J=4.4 Hz, 1), 3.82(d, J= 6.7 Hz,1), 3.31(s, 3), 2.55-0.90(m, 13)

IR (neat): 3700-3100, 3020-2810, 1735(w), 1620, 1520, 1460, 1300, 1250,1190, 1100-1000, 970, 910, 840, 810, 750 cm^{-1}

High Res./MS: calculated for $C_{20}H_{24}O_4$: 328.1675; observed: 328.1671

Ketone 12: To diol **47** (0.0886 g., 0.2701 mmol) in t-BuOH (3.5 ml) was added $NaIO_4$ (0.145 g., 0.675 mmol) in H_2O (3.5 ml). The mixture was stirred for 1.5 hours, diluted with ether (50 ml), and separated. The aqueous layer was diluted with brine (6.5 ml), and extracted with ether (3 x 50 ml). The combined organic layers were dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography (30 mm o.d., 40. g 230-400 mesh, 50 ml fractions, fract. 1-20 (10/1) Hexane/ether, fract. 21-40 (8/1) hexane/ether, fract. 41-60 (5/1) hexane/ether, fract. 61-80 (2/1) hexane/ether, fract. 81-100 (ether), 200. ml forerun) using the flash technique. Fractions 7-40 gave 25.8 mg. (49%) of a 3/1 mixture of compound **12** and anisaldehyde. Fractions 41-70 gave 62.0 mg. of a compound M.W. 310 (CI/MS). The anisaldehyde/product mixture was taken up in ethanol (50 ml) and washed with cold sat. aq. $NaHCO_3$. The aqueous was extracted with ether (3 x 10 ml), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to provide 17.7 mg. (35%) of ketone **12**.

EI/MS (25eV): 190(M^+,13.6), 163(7.14), 149(37.1), 134(BASE), 119(18.6), 105(7.14), 96(10.0), 91(20.0), 77(10.0), 69(7.14), 55(25.7)

^{1}H-NMR (250MHz): δ : 7.28(d, J=1 Hz, 1), 6.15(d, J=1 Hz, 1), 3.66(d, J=6.6 Hz, 1), 2.6-1.0(m, 11)

^{1}IR (neat): 3080-2800, 1730, 1600, 1515, 1460, 1385, 1340-1230, 1125, 1075, 905, 880, 840, 740, 700 cm^{-1}

High Res./MS: calculated for $C_{12}H_{14}O_2$: 190.0999; observed: 190.0979

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