AN ABSTRACT OF THE THESIS OF

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Title: Total Synthesis of (+)-Bourgeanic Acid and Conformational Analysis of its Dilactone

Abstract approved: Redacted for Privacy
James D. White

The total synthesis of (+)-bourgeanic acid (**1**), a secondary metabolite isolated from several *Ramalina* species of lichen is described. An interesting property exhibited by **1** is the facile cyclization under mild dehydrating conditions to give the eight-membered dilactone **15** in high yield.

The synthesis of **1** began with the asymmetric alkylation of the enolate derived from **94** with (*R*)-2-methyl-1-iodobutane (**101**) to give **109**. Conversion of **109** to aldehyde **16** was followed by the reaction of **16** with (*E*)-crotylboronate **153**, prepared from (-)-diisopropyl tartrate, to give alcohol **112**. When several attempts to esterify carboxylic acid **161** with **112** using established methods met with failure, an alternative esterification employing β-lactone **164** in a reaction with the lithium alkoxide of **112** was exploited to prepare ester **113**. Completion of the synthesis of **1** from **113** was achieved by oxidative cleavage of the double bond in **113** with ozone, followed by an oxidative workup. Synthetic **1** was found to be identical in all respects with a sample of natural bourgeanic acid, thus confirming that this substance is the self-esterification product of (2*S*, 3*S*, 4*R*, 6*R*)-3-hydroxy-2,4,6-trimethyloctanoic acid (**2**).

Examination of dilactone **15** using the MMX87 force field led to the discovery of a low-energy *syn* conformation (*syn*-**15**) and a higher energy *anti* conformer (*anti*-**15**). A C_2-axis of symmetry present in the low-energy conformer (*syn*-**15**) is in agreement with a conclusion drawn from the ^{13}C NMR spectrum of **15** which shows only one half the number of resonance lines expected from a non-symmetrical structure. The calculated energy difference (8.5 kcal/mol) between *syn*-**15** and *anti*-**15** leads to an equilibrium concentration for the *anti* conformer below the detection limit of the NMR method and thus supports the experimental findings. The cyclization of **1** to **15** was also studied using force field calculations. Starting from a low-energy conformation of **1** calculated using the MMX87 force field, models (**186** and **187**) of the intermediate expected in the cyclization of **1** to **15** were evaluated with respect to intramolecular alcohol oxygen and carbonyl carbon distances and the associated conformational energy. This analysis is discussed within the framework of the Menger hypothesis governing the rate of intramolecular reactions and offers insight into why the observed cyclization takes place in such an efficient and expeditious manner.

Total Synthesis of (+)-Bourgeanic Acid and Conformational Analysis of its Dilactone

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Finally, I thank my wife Carol. Her love, understanding, and constant support were of immeasurable help in keeping life in the proper perspective.

to Carol

Life is infinitely more strange than

anything the mind of man can invent. . ."

- Sherlock Holmes -

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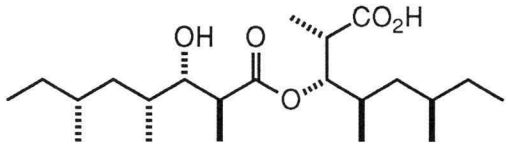
TOTAL SYNTHESIS OF (+)-BOURGEANIC ACID AND CONFORMATIONAL ANALYSIS OF ITS DILACTONE

I. INTRODUCTION

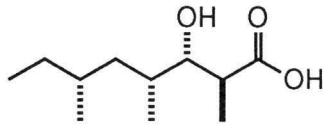
"The progress in synthetic chemistry over the past twenty years has been so marvelous that the artificial production of the vital principles composing living organisms seems possible in the relatively near future".[1] Written in 1873, this statement by Emile Jungfleisch was at the heart of a controversy among scientists concerned with the stereochemistry of life processes. While some such as Pasteur argued that "all artificial products of the laboratory . . . are superposable on their images", others such as Jungfleisch believed that "optical activity can be created without the intervention of life".[1] Today, 117 years later, advances in synthetic organic chemistry over the previous two decades can still be viewed as marvelous. Further, the belief of Jungfleisch has been realized, and is considered well established in several important areas of contemporary synthesis. The account which follows serves to illustrate the use of some of the synthetic methods whereby "optical activity can be created." In this exercise they have been applied to a stereoselective synthesis of (+)-bourgeanic acid.

In 1973 Bodo and co-workers reported[2] the isolation of (+)-bourgeanic acid (**1**) from several *Ramalina* species of lichen. Degradation and spectroscopic analysis established the relative stereochemistry of this novel lichen metabolite.[3] More recently, the absolute configuration of **1** was announced[4] after an X-ray crystallographic study was completed on a derivative of (-)-hemibourgeanic acid (**2**). Although **1** has no reported biological activity, bourgeanic acid is unique among lichen metabolites in

being the first member of a new class of naturally occurring compounds, the "aliphatic depsides".



(+) - Bourgeanic Acid **1**

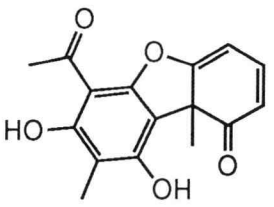


(-) - Hemibourgeanic Acid **2**

Lichens can be considered nature's prime example of symbiosis. Composed of an alga and a fungus, the success of the partnership may be measured by the fact that over 20,000 species are known.[5] The alga provides the photosynthetic machinery required to drive primary metabolism, while the fungal partner utilizes the products from this chemistry as starting materials for the synthesis of secondary metabolites. Although it is clear how the fungal component benefits from this relationship, it remains to be discovered of what value, if any, this symbiosis is to the alga.

The interest in these plants by mankind results primarily from their use as traditional medicines. Medicinal uses of dried lichen, or the corresponding extracts, dates back to the records found in ancient Egypt, Greece, and China.[6] Widespread use of lichen substances in Europe for the treatment of ailments such as pulmonary tuberculosis, jaundice, and edema, began in the 15th century and has continued up to the present day.[7] Of the lichen species tested thus far, more than half have been found to exhibit antibiotic properties. A compound which has received considerable attention is usnic acid (**3**). Active against Gram positive bacteria, strains of tuberculosis, and certain fungi,[6] usnic acid also possesses anti-cancer properties.[8,9] Possessing these qualities, **3** would appear to be of considerable medicinal value. However,

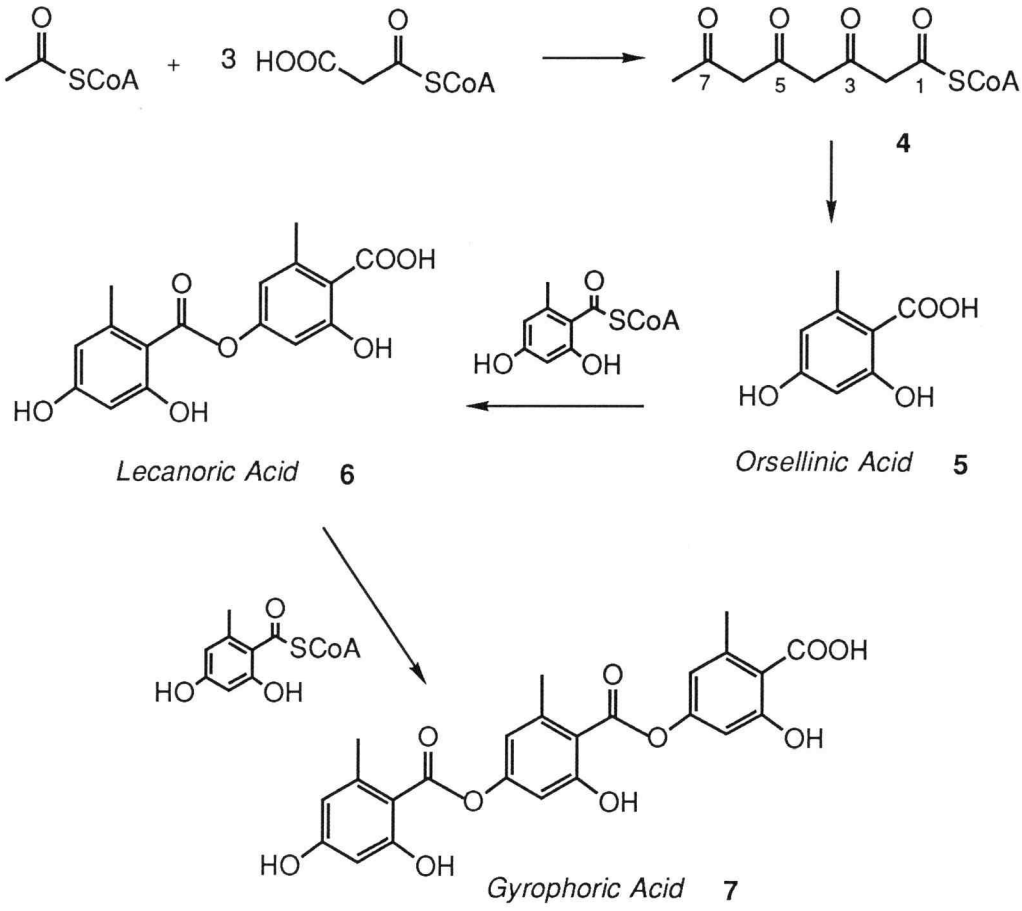
due to poor solubility characteristics under conditions required for *in vivo* use, neither usnic acid nor hundreds of derivatives prepared thus far have found clinical application except in the treatment of skin disorders.[6]



Usnic Acid **3**

Under the influence of sunlight the algal partner generates the products of primary metabolism. These compounds, mainly simple carbohydrates and amino acids, are used by the fungus in the secondary metabolic pathways.[10] The majority of secondary metabolites isolated from lichens have been found to be derived via the acetate-malonate pathway. The largest group is comprised of aromatic compounds, the depsides being the most common. Precursor incorporation studies have shown that these compounds arise by the condensation of one acetyl-CoA unit with three malonyl-CoA units to give an eight-carbon polyketide **4** (Scheme I).[11] Cyclization between carbons 2 and 7 of **4** followed by dehydration leads in the simplest case to orsellinic acid (**5**). Condensation with a second molecule of orsellinic acid affords lecanoric acid (**6**), a commonly occurring depside. Further reaction with orsellinyl-CoA leads to the tridepside gyrophoric acid (**7**). An interesting aspect of this process is that while the isolated fungal component has been found to produce free orsellinic acid, this metabolite has not been observed in the composite organism, the lichen. This result suggests that the algal partner

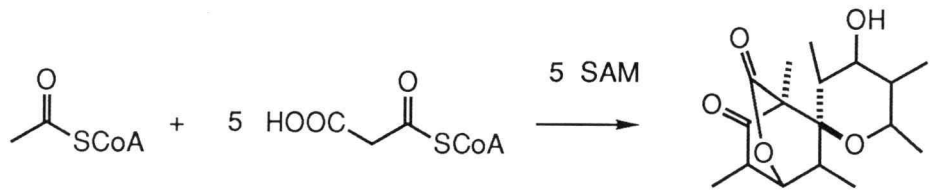
Scheme I



participates in the formation of lecanoric acid (**6**) and other derivatives of orsellinic acid.[12] The interesting spirolactone portenol (**8**), isolated from a *Roccella* species of lichen,[13] has also been shown by labeling studies to be the product of the acetate-malonate pathway (Scheme II). One acetyl-CoA, five malonyl-CoA plus five C1-units originating from *S*-adenosylmethionine (SAM) are incorporated into **8**.

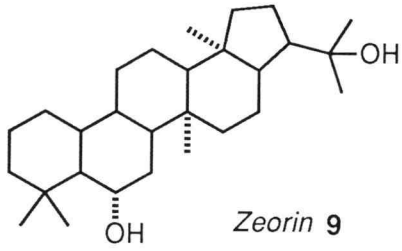
Lichen substances that can be identified as products of the mevalonate pathway are less common. Those most frequently encountered are

Scheme II

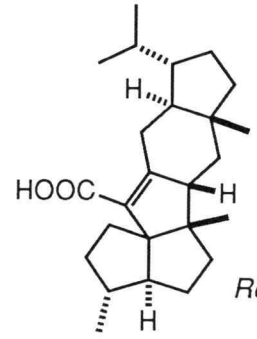


Portenol **8**

triterpenes,[10] a representative example being zeorin **9**. Several steroids and carotenoids have also been isolated. Perhaps the most interesting compound characterized thus far is retigeranic acid **10**. It is the only known member of a class of pentacyclic sesterterpenes.

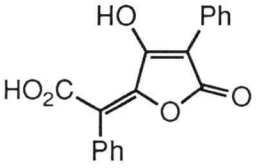


Zeorin **9**

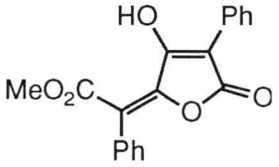


Retigeranic Acid **10**

Products of the shikimate pathway form the smallest group of secondary metabolites found in lichens. The most common substances in this family are derivatives of pulvic acid **11**. Evidence of their shikimate origin comes from the results of feeding experiments using [1-^{14}C]phenylalanine.[14] In this case, the methyl ester of **11**, vulpinic acid **12**, was isolated with the label distributed equally among four carbon atoms in accord with prediction based on the shikimate pathway.



Pulvic Acid **11**



Vulpinic Acid **12**

Biosynthetic studies regarding the origin of bourgeanic acid have been carried out by Bodo.[3] On the premise that bourgeanic acid is derived from a polyketide intermediate, Bodo sought to determine the source of the branching methyl groups. A series of feeding experiments using [1-^{14}C]acetate, [1-^{14}C]propionate and [methyl-^{14}C]*S*-adenosylmethionine clearly showed that the methyl groups of **1** originate from methionine (Table I). Bodo went on to

Table I: Percent incorporation of radiolabeled materials into bourgeanic acid.

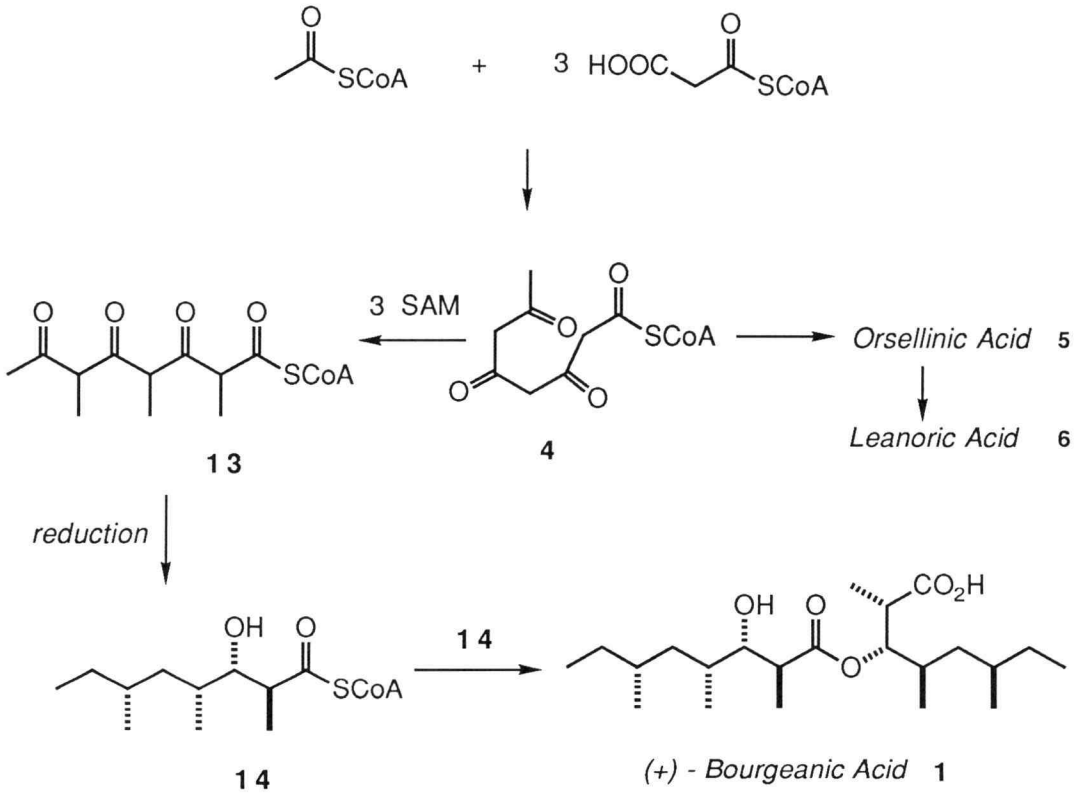
Precursor	% Incorporation
[1-^{14}C]CH_3CO_2Na	1.17
[1-^{14}C]$CH_3CH_2CO_2Na$	0.03
[CH_3-^{14}C]methionine	11.33

suggest a pathway to **1** (Scheme III) that drew a comparison with the proposed formation of the depside lecanoric acid (**6**). Starting with acetyl-CoA and three malonyl-CoA precursors, sequential condensation and decarboxylation affords the previously postulated C_8-polyketide **4**. Interception of **4** by three equivalents of S-adenosylmethionine results in the formation of the methylated

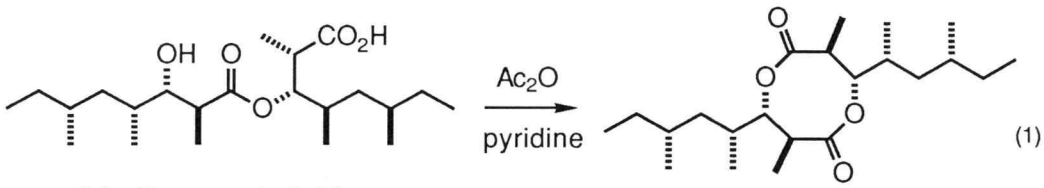
polyketide **13**. Reduction of **13** to hemibourgeanyl-CoA **14**, self esterification, and hydrolysis would lead directly to bourgeanic acid (**1**).

The chemistry of bourgeanic acid was explored during degradation studies carried out by Bodo.[3] Of particular interest was the discovery of the eight-membered ring dilactone **15**. First isolated as a side product (16%) in

Scheme III



the dehydration of **1** with acetic anhydride in refluxing pyridine (eq 1), milder conditions, 0 °C for 24 h, afforded a 53% yield of **15**. In view of the difficulty usually associated with the synthesis of eight-membered ring compounds, this finding is quite surprising.



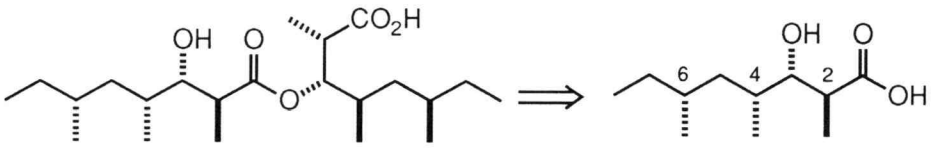
(+) - Bourgeanic Acid **1** **15** (1)

Historically, the synthesis of natural products has been carried out to prove the structure and stereochemistry of substances found in nature.[15] The synthesis of **1** described below, continues in this tradition, providing independent proof of the absolute configuration of (+)-bourgeanic acid (**1**). A further impetus for embarking on this synthetic endeavor was an opportunity to measure the present "condition and power of the science."[16]

II. TOTAL SYNTHESIS OF (+)-BOURGEANIC ACID

Bourgeanic acid (**1**) may be viewed in a retrosynthetic sense as the condensation product of two molecules of hemibourgeanic acid (**2**) (Scheme IV). A strategy for the synthesis of **1** based on this analysis leads to **2** as the initial target. Implicit in this approach is the need for a method of achieving the self esterification of **2** to give **1**. Close inspection of the stereochemical features of **2** from a synthetic standpoint brings into focus two areas of immediate interest.

Scheme IV



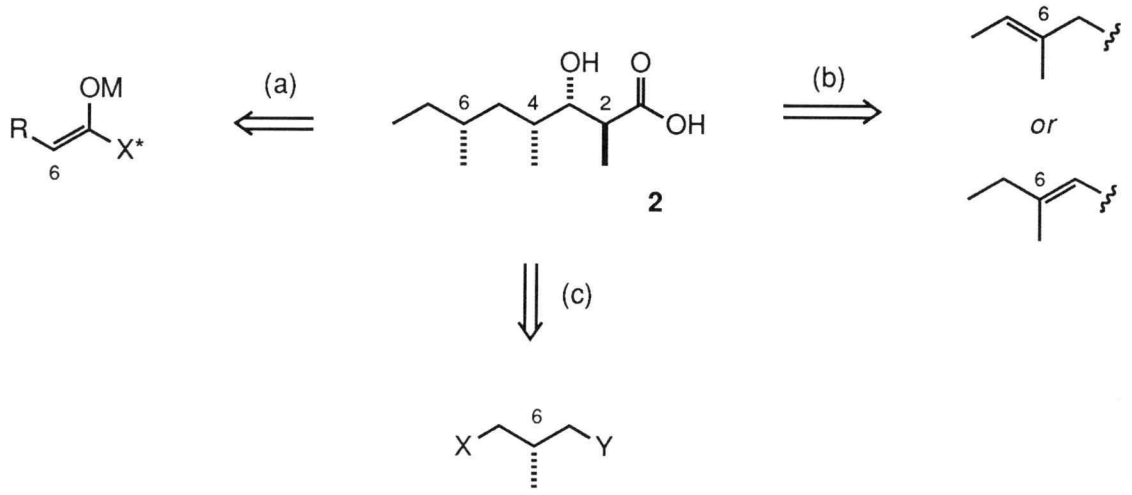
(+) - Bourgeanic Acid **1** *(-) - Hemibourgeanic Acid* **2**

Consider first the stereogenicity present at C-6 of **2**. The absence of adjacent functional groups places limits on the methods which can be used to introduce this asymmetric center without extensive manipulation. Possible approaches (Scheme V) include: a) reaction of a chiral enolate,[17] the α-carbon becoming the C-6 center; b) stereocontrolled addition of hydrogen to an sp^2-hybridized center at C-6; or c) use of a compound possessing the desired chirality and which is available from a commercial source.

The remaining stereocenters at C-2, C-3, and C-4 have a 2,3-*anti*-3,4-*syn* relationship and, as such, resemble polypropionate subunits present in

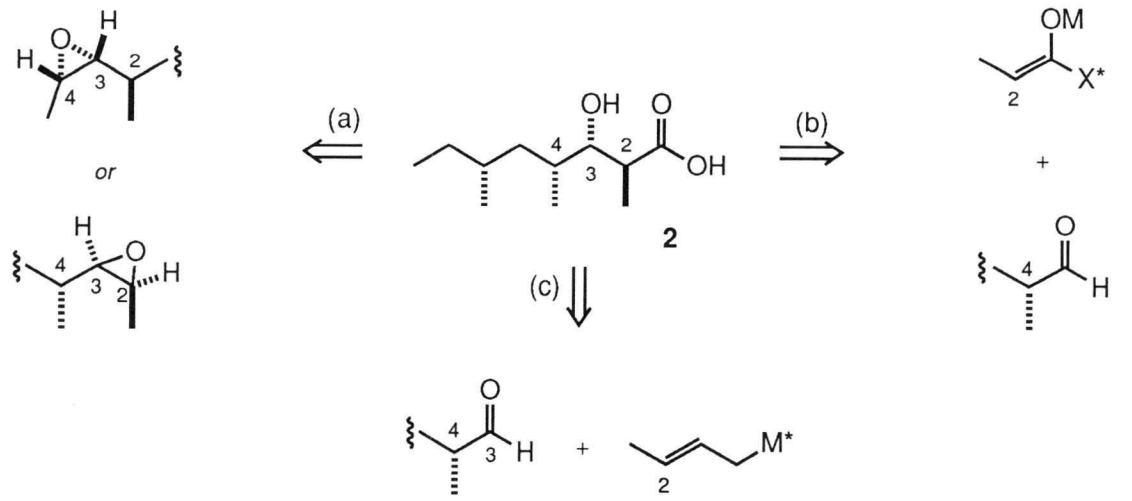
many natural products. Current approaches to the synthesis of compounds containing adjacent stereocenters (Scheme VI) have relied primarily on the

Scheme V



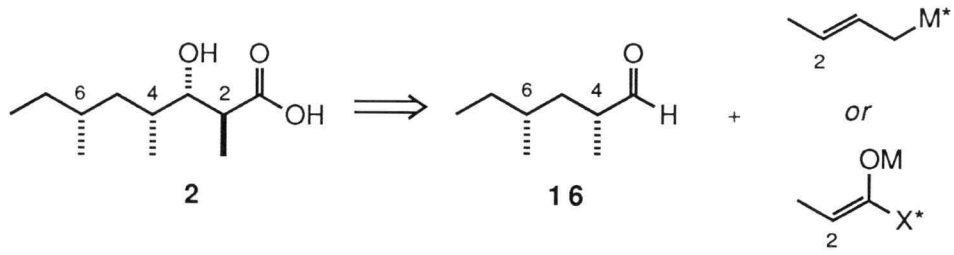
use of a) chiral epoxides;[18] b) diastereoselective aldol reactions,[19] and c) crotylation methods[20] to introduce relative and absolute stereochemistry.

Scheme VI



The use of a chiral epoxide in the preparation of **2** (Scheme VI) would require the synthesis of a chiral molecule containing at least two stereogenic centers. Ring opening at a specific end of the epoxide subunit will generate needed stereochemistry by an inversion process. The remaining approaches to **2** are similar in two respects. Both must proceed with selective *si*-face addition to an aldehyde, generating the 3,4-*syn* configuration, and, at the same time, they must produce the required 2,3-*anti* relationship between the carbon atoms involved in bond formation.

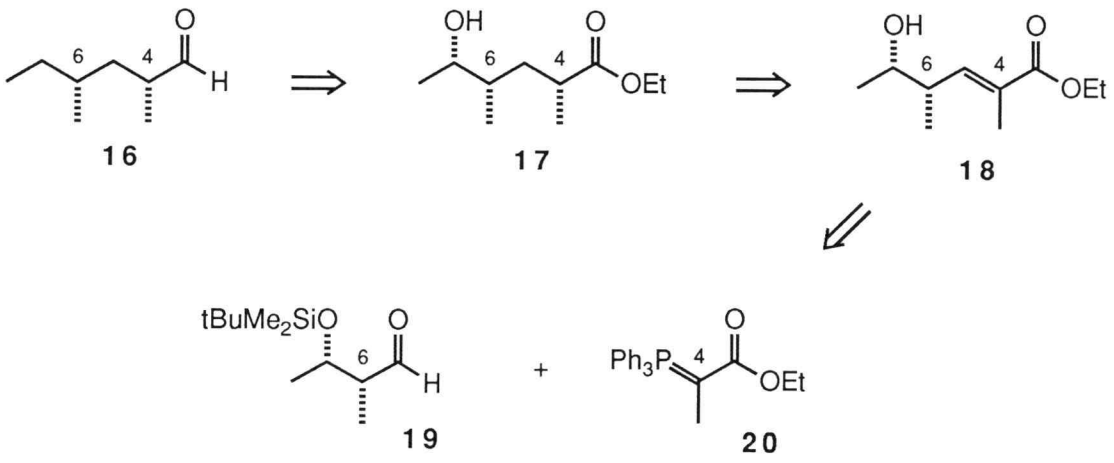
Scheme VII



An aldol strategy appears more attractive than a crotylation approach to **2** because the product would have the C-1 carbon atom at the correct oxidation level. In contrast, the addition of crotyl anion to the appropriate aldehyde affords a product which requires oxidative cleavage of the terminal double bond to produce the carboxylic acid function found in hemibourgeanic acid (**2**). Although stereoselective aldol reactions have been quite successful as a general approach to 2,3-*syn* selectivity in acyclic systems, a 2,3-*anti* relationship between the newly formed stereogenic centers has proven more difficult to obtain.[19] However, the construction of 2,3-*anti* stereochemistry

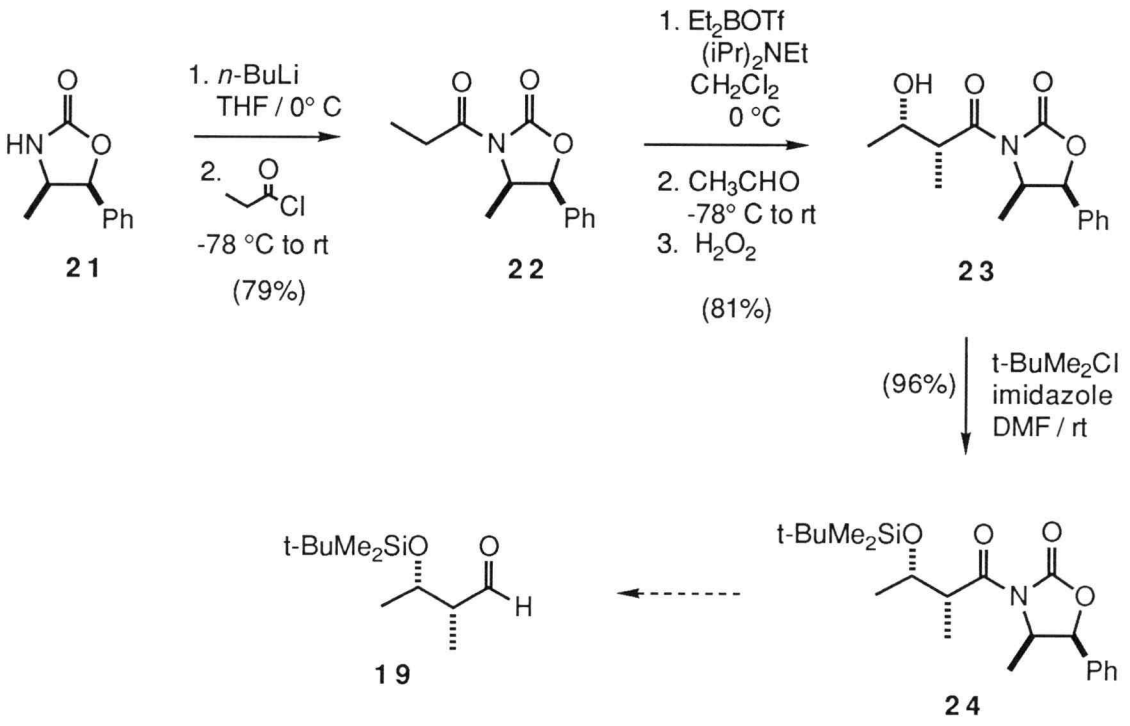
using chiral crotylating agents is usually no more difficult than the introduction of 2,3-*syn* stereochemistry.[20] Given the extensive literature precedent for each of these transformations, a route to **2** based upon either of these methods (Scheme VII) relies on the availability of aldehyde **16**. A substantial effort was therefore invested in finding an efficient, stereospecific route to this 2,4-dimethylhexanal. In the discussion which follows reference to carbon atoms by number is based upon the numbering scheme used for hemibourgeanic acid (**2**).

Scheme VIII

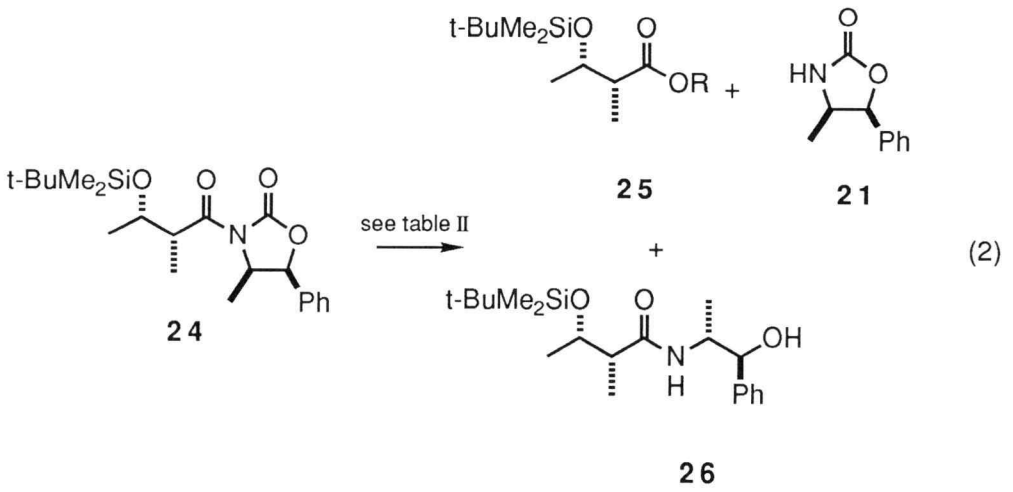


Embodied in **16** are the 4*R* and 6*R* stereocenters of **2**. These configurations therefore defined the parameters of the initial synthetic task. The first approach to **16** was patterned after the preparation of an intermediate (**17**) previously used in the synthesis of premonensin by Evans and DiMare[21] (Scheme VIII). In this scheme, conversion of **17** to aldehyde **16** requires stereoselective hydrogenation of the double bond in **18**, deoxygenation at C-7, and reduction of the ester to the aldehyde oxidation level.

Scheme IX



Accordingly, the boron enolate of **22** reacted with acetaldehyde to give the secondary alcohol **23** as a single diastereomer (Scheme IX). Conversion



of **23** to silyl ether **24** was accomplished using the standard procedure[22] involving treatment with t-butyldimethylsilyl chloride and imidazole in DMF. With the C-6 stereocenter in place, it remained to remove the chiral directing group (auxiliary) and transform the resulting product into aldehyde **19**. In **24** the chiral auxiliary is represented by the oxazolidinone portion of the molecule. Unfortunately, all attempts to remove the chiral auxiliary in **24** (eq 2) by hydrolysis, transesterification, or reduction resulted in mixtures of oxazolidinone **21**, amide **26**, and low yields of the desired product (Table II).

Table II: Reaction conditions and outcome from the attempted removal of the chiral auxilary in **24** (equation 2).

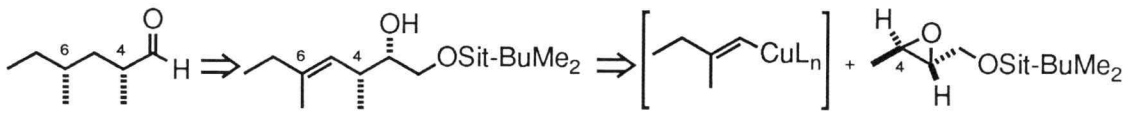
Entry	Rxn Conditions	**25**	**21**	**26**
1	$PhCH_2OLi$ THF / 0° C	40%	30%	28%
2	$PhCH_2OLi$ THF / -78° C	0%	0%	only product
3	$NaBH_4$ MeOH / 0° C	complex mixture	28%	0%
4	1M LiOH THF / H_2O / rt	0%	10%	55%
5	1. LiOH H_2O_2 / dioxane 0° C 4 hr 2. CH_2N_2	complex mixture	22%	0%

The difficulty encountered with this transformation was surprising in view of the fact that Evans and DiMare reported a 75% yield for the transesterification

represented by entry 1 of Table 2. The only apparent difference between the two cases is in the chiral auxiliary involved. The present experiment used the 2-oxazolidinone derived from norephedrine whereas the literature precedent employed the oxazolidinone derived from phenylalanine as a starting material. The size and nature of the alcohol protecting group may also have contributed to this problem. Walba[23] recently reported similar difficulties in removing a related chiral auxiliary from a molecule having a β-hydroxy group protected as a *t*-butyldimethylsilyl ether.

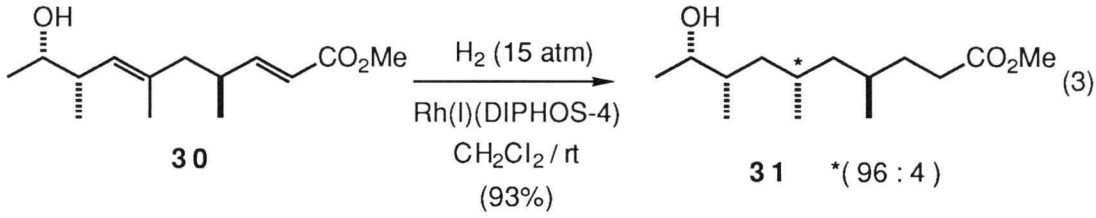
These results prompted consideration of a second synthetic route to aldehyde **16**. The strategy shown in Scheme X was based upon the use of the chiral epoxide **29** containing the latent configuration required at C-4 of **16**. Stereoselective hydrogenation of olefin **27**, prepared by the addition of a

Scheme X



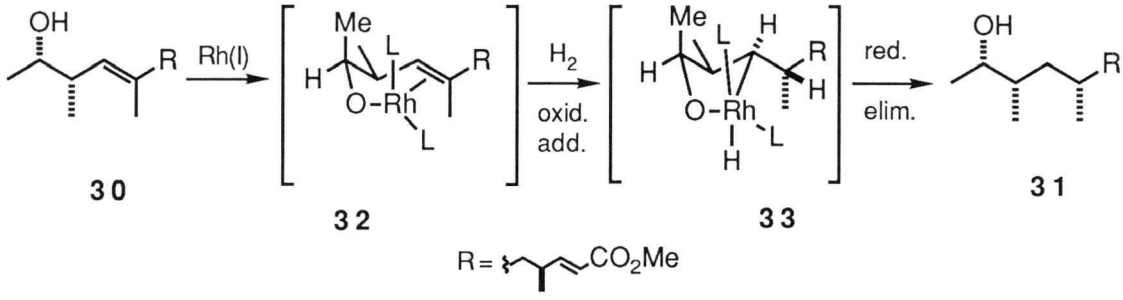
16 **27** **28** **29**

vinyl cuprate (**28**) to epoxide **29**, was envisioned for the introduction of the stereocenter at C-6. The choice of the latter step was based upon the success of heteroatom directed homogeneous hydrogenation of carbon-carbon double bonds involving transition metal catalysts.[24] For example, the rhodium(I) catalyst used[25] in the stereoselective reduction of **30** to give **31** (eq 3) appeared particularly well suited to the reduction of **27** as planned. The

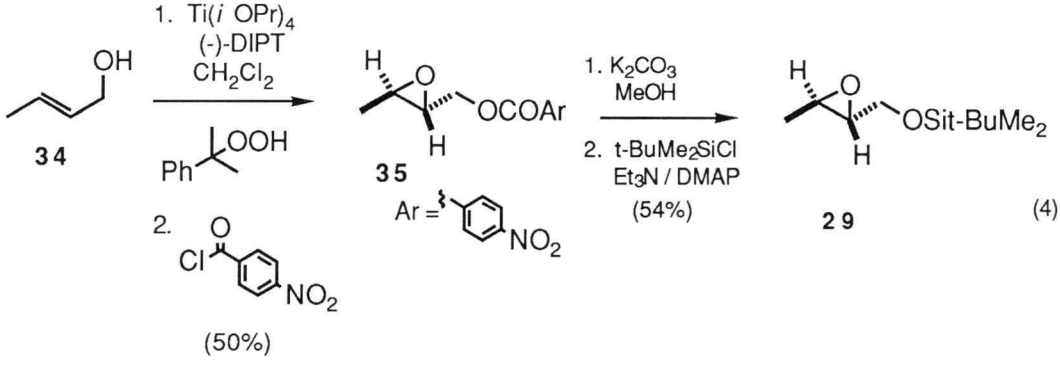


selectivity observed in this reaction is explained by using the hydroxyl group in **30** as a ligand for the cationic transition metal (Scheme XI). Oxidative addition of hydrogen to complex **32**, followed by hydride migration to give **33** and reductive elimination, affords **31** by the selective addition of hydrogen to one face of the double bond in **30**.

Scheme XI

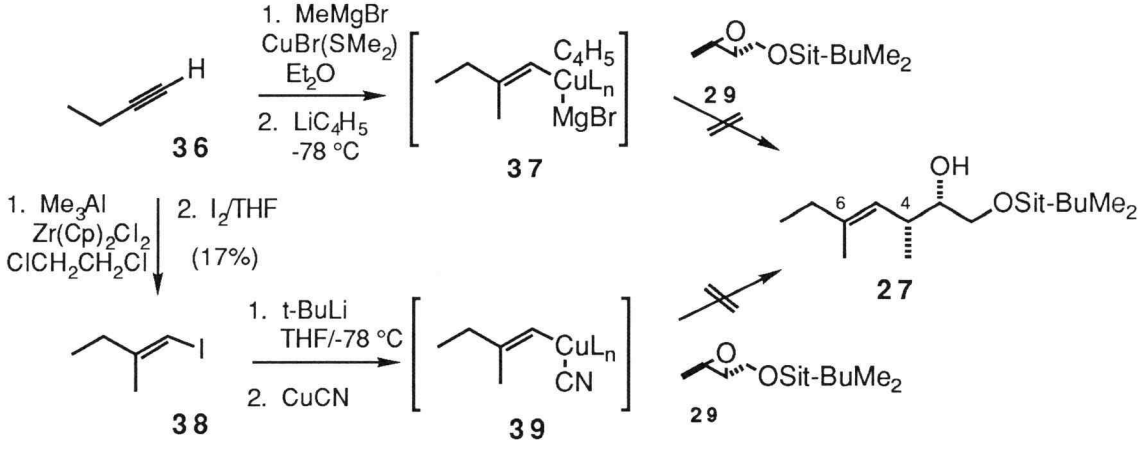


The synthesis of **27** was expected to be straightforward by the addition of a vinyl cuprate to epoxide **29**. Helquist and co-workers[26] have introduced



this methodology for the preparation of trisubstituted olefins and homoallylic alcohols. The required epoxide **29** was readily prepared from crotyl alcohol (**34**) (eq 4) using the asymmetric epoxidation chemistry developed by Sharpless and co-workers.[27] The asymmetric epoxidation of **34** was carried out using catalytic amounts of (-)-diisopropyl tartrate and titanium(IV)-isopropoxide in the presence of excess cumene hydroperoxide. Protection of the alcohol *in situ* as a *p*-nitrobenzoate ester afforded epoxide **35** in 50% yield and 98% ee as a crystalline solid. Due to the nature of the conditions anticipated in the succeeding reaction sequence, the base labile *p*-nitrobenzoate group in **35** was replaced with the more stable silyl protecting group. Treatment of **35** with a catalytic amount of potassium carbonate in methanol, followed by exposure of the crude epoxyalcohol to *t*-butyl-dimethylsilyl chloride and a catalytic amount of 4-N,N-dimethylaminopyridine

Scheme XII



in dichloromethane, afforded **29** in a modest 54% yield. Vinyl cuprate **37** was obtained by treatment of 1-butyne (**36**) with the organocopper reagent

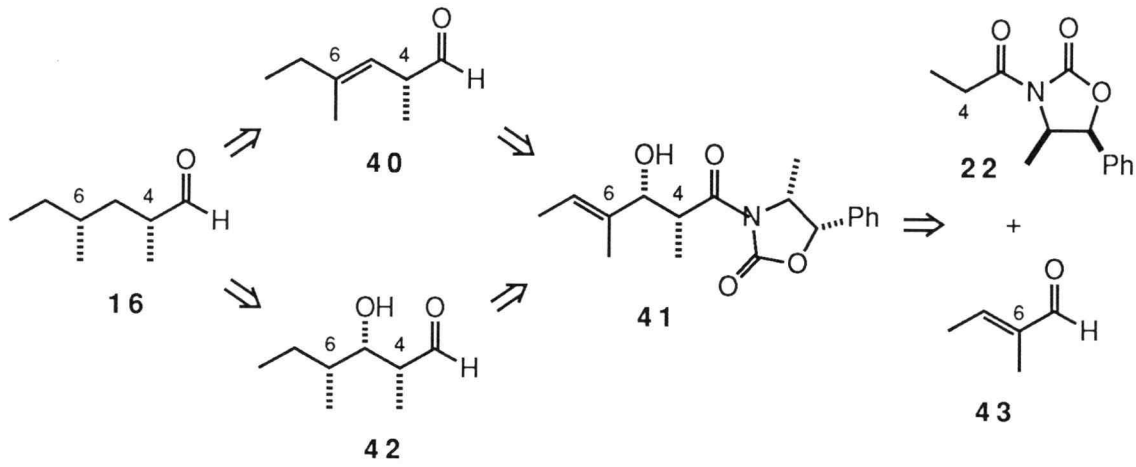
prepared from methylmagnesium bromide and copper(I) bromide (Scheme XII) followed by the addition of 1-lithio-1-butyne at -78 °C. The latter reagent was prepared in ether from *n*-butyllithium and 1-butyne. Addition of epoxide **29** to **37** at -78 °C, followed by stirring at -20 °C for 24 hours, returned 22% of the starting epoxide **29** and several minor components, none of which contained olefinic protons when examined by ^{1}H NMR spectroscopy.

The technical difficulty enountered in preparation of **37** (3 days ≤ -20 °C; warming above -20 °C led to decomposition of the copper species) is reported to be characteristic of the methyl Grignard reagent.[26] The corresponding reaction with higher homologs requires only two hours at -20 °C to prepare the analogous copper species. Faced with this fact, an alternative route to the required vinyl cuprate was developed using chemistry introduced by Negishi and co-workers.[28]

Reaction of 1-butyne (**36**) with trimethylaluminum in the presence of zirconocene dichloride (Scheme XII) followed by treatment of the intermediate organometallic species with iodine gave the volatile vinyl iodide **38**. Preparation of the vinyl lithium species from **38** by halogen-metal exchange with *t*-butyllithium, followed by reaction with copper(I) cyanide as described by Lipshutz,[29] presumably gave the desired higher-order cyano cuprate **39**. Addition of **29** to this reagent at -78 °C gave a minor amount of a less polar product (relative to **29** by TLC), trace amounts of more polar compounds, and unreacted **29**. Warming of the reaction mixture to -20 °C and finally to 0 °C gave a complex mixture of products. Analysis of this mixture by ^{1}H NMR spectroscopy provided no evidence for the presence of the desired alcohol **27**. The failure of this reaction may be due in part to the much lower reactivity of 1,2-disubstituted epoxides with organocuprates relative to the terminal epoxides used in the examples cited above. It should be pointed out that

subsequent to this work, Baker[30] demonstrated the successful use of this strategy by conducting a similar reaction in the presence of borontrifluoride etherate.

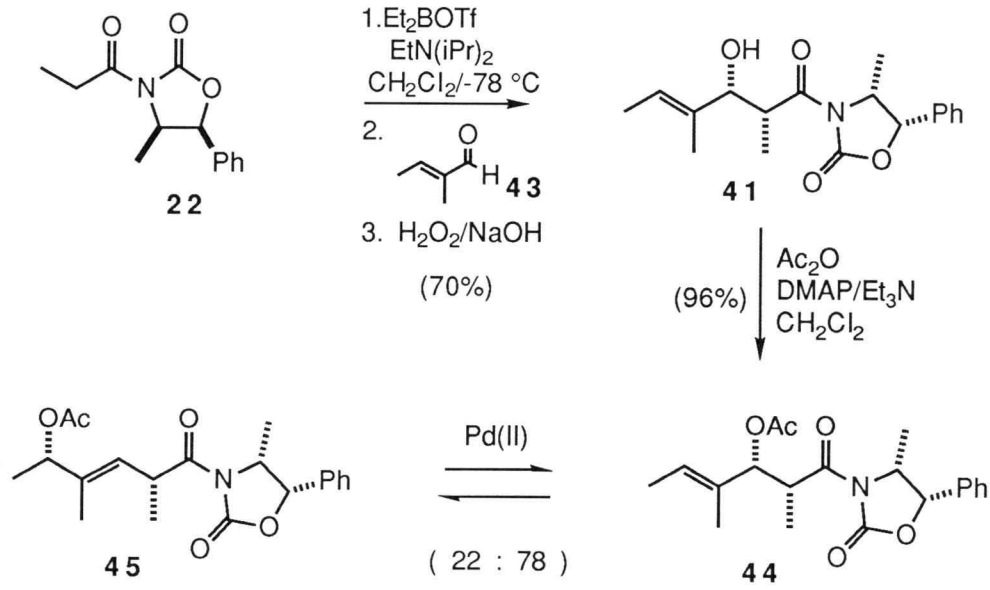
Scheme XIII



A third approach to **16** (Scheme XIII) couples an aldol reaction to introduce the stereocenter at C-4 with a subsequent stereocontrolled alkene hydrogenation to furnish the desired configuration at C-6. An attractive feature of this scheme was the possibility of pursuing two avenues to **16** from the common intermediate **41**. The known allylic alcohol **41** was readily prepared via the aldol reaction (Scheme XIV) of commercially available tiglaldhyde (**43**) with the previously used N-propionyl-2-oxazolidinone **22**. The first reaction sequence explored was an attempt to transpose the allylic alcohol function in **41** such that the product could be converted to aldehyde **40**. The ability of palladium(II) salts to mediate rearrangement of allylic acetates is well established[32] and was considered ideal for the task at hand. Allylic alcohol **41** was therefore converted to the corresponding acetate **44** and treated with

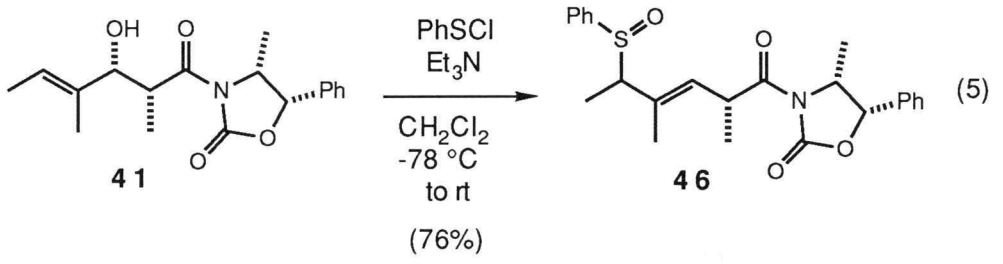
bisacetonitrile palladium(II) chloride in THF at room temperature.[32c] The progress of the reaction was then followed by thin layer chromatography (TLC). A second, slightly more polar component was present in the mixture after a few hours. Analysis by TLC after 18 h suggested that the ratio of the two components was unchanged from the ratio seen after 7 hours. Isolation of each component by chromatography and analysis by ^{1}H NMR spectroscopy indicated that the new compound was the desired rearrangement product **45**. Unfortunately, **45** was the minor component of the mixture, being present in a 22:78 ratio with the starting acetate **44**.

Scheme XIV



In view of the unsatisfactory equilibrium in this allylic acetate rearrangement, a second rearrangement process was investigated. Allylic sulfenylates have been shown to undergo rapid [2.3]-sigmatropic rearrangement to the corresponding allylic sulfoxides,[33] the reaction being

irreversible in the absence of thiophiles. Accordingly, alcohol **41**, upon exposure to phenylsulfenyl chloride in dichloromethane at -78 °C and subsequent warming to room temperature, afforded allylic sulfoxide **46** as a mixture of four diastereomers (eq 5). However, all attempts to reductively



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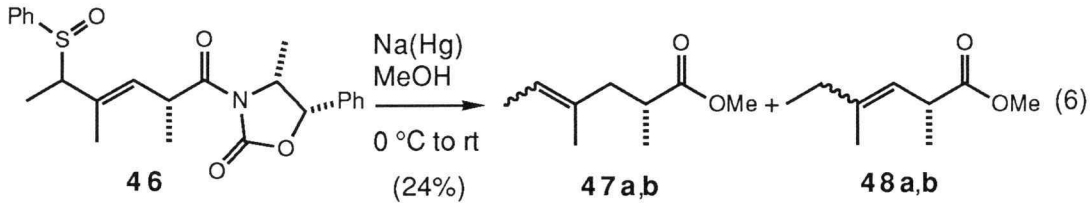
cleave the C-S bond in **46** met with disappointment, giving a mixture of four isomeric olefins **47a,b** and **48a,b** (eq 6) in 24% yield with sodium amalgam in methanol,[34] and a complex mixture of products (eq 7) when **46** was treated with lithium triethylborohydride in the presence of a palladium(II) complex.[35]



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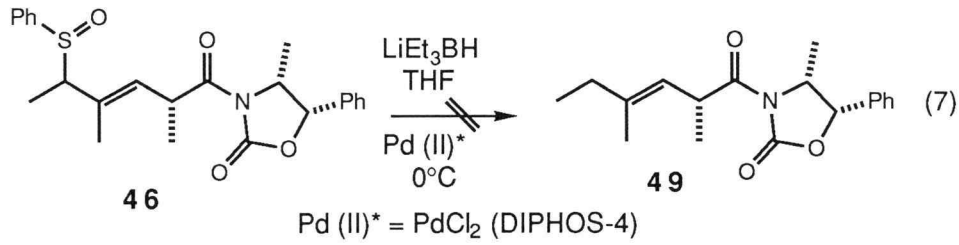
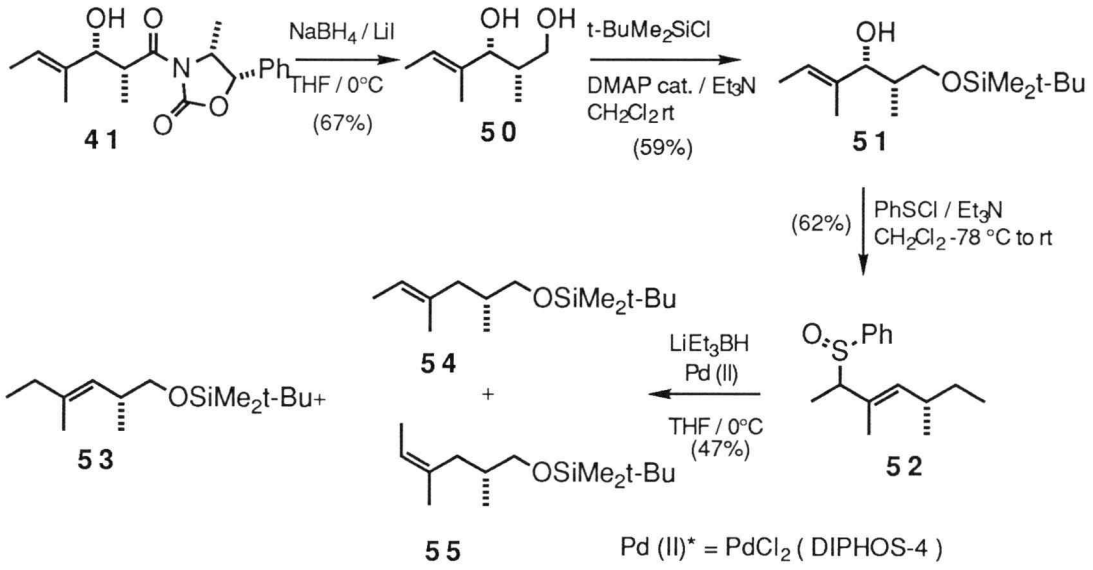


(7)

Reasoning that the chiral auxiliary, was a possible source of difficulty, **41** was converted to the corresponding diol **50** with lithium borohydride (Scheme XV). The primary alcohol was selectively silylated with *t*-butyldimethylsilyl chloride in the presence of a catalytic amount of 4-N,N-dimethylaminopyridine[36] in dichloromethane to give alcohol **51**. Conversion of **51** to the rearranged allylic sulfoxide **52** with benzenesulfonyl chloride was followed by reduction

Scheme XV

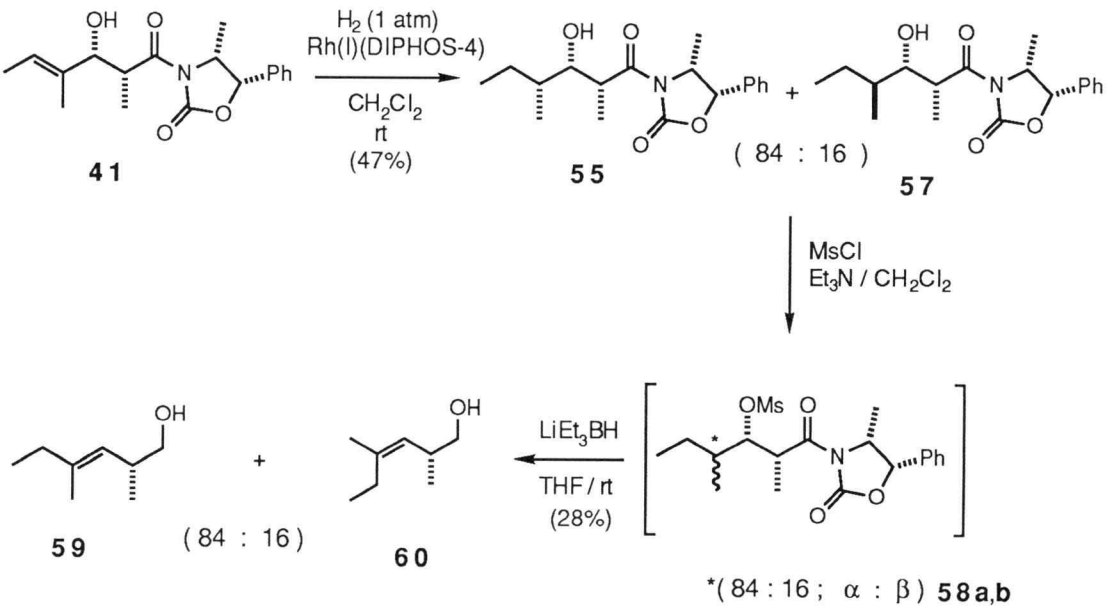


with lithium triethylborohydride in the presence of a palladium(II) catalyst.[35] Although reductive cleavage of the C-S bond was observed, the reaction proceeded in only moderate yield and with complete loss of alkene stereochemistry, affording a 1:1:1 mixture of the desired product **53** and the E and Z isomers **54** and **55**.

Returning to **41** (Scheme XVI), the alternate pathway to **16** via **42** previously illustrated in Scheme XIII was briefly explored. Reduction of **41** using hydrogen in the presence of a rhodium(I) catalyst was reported[31] to give

a mixture of the two possible diastereomers expected from the addition of hydrogen to either face of the carbon-carbon double bond. In accord with this report, exposure of **41** to hydrogen at one atmosphere in the presence of rhodium(I) (NBD) (DIPHOS-4), where NBD = norbornadiene and DIPHOS-4 =1,4 (bisdiphenylphoshino)butane, led to an 84:16 mixture of **56** and **57,** where **56** has *R* configuration at C-6 as required for the synthesis of **16**. Attempted removal of the secondary alcohol from this mixture of **56** and **57** by exposure to methanesulfonyl chloride and treatment of the crude mesylates **58a,b** with lithium triethylborohydride[37] provided instead the corresponding elimination products **59** and **60**.

Scheme XVI

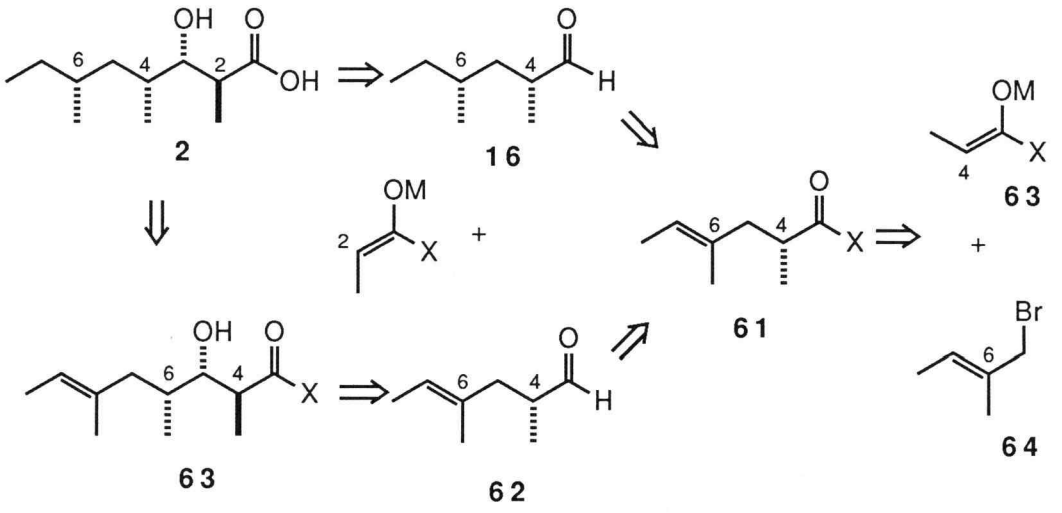


Since the geometry of the double bond is crucial in determining the stereochemistry of the product derived from allylic alcohols in directed hydrogenation reactions, the consistent loss of alkene stereochemistry

demonstrated in the results given above suggested that further studies based on a strategy involving reductive cleavage of a carbon heteroatom bond en route to **16** would be futile.

In view of this shortcoming, a fourth approach to hemibourgeanic acid (**2**) was examined (Scheme XVII). Deviating slightly from the previous routes, an asymmetric alkylation involving a chiral enolate **63** and allylic bromide

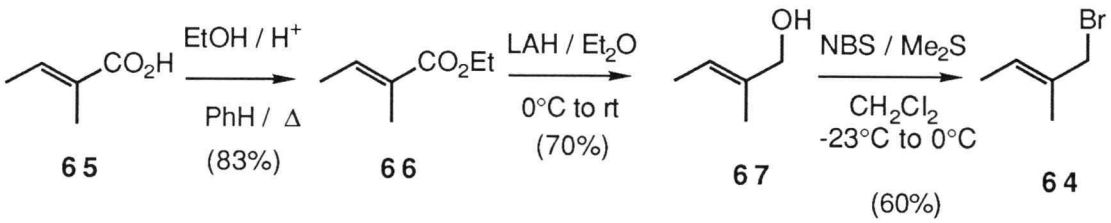
Scheme XVII



64 was envisioned as a way of introducing the absolute stereochemistry at C-4. The product of this alkylation, alkene **61**, would contain eight of the eleven carbons present in **2**. In principle, conversion of **61** to **2** via **16** or **62** requires only face-selective reduction of the carbon-carbon double bond to generate the stereocenter at C-6, followed by a stereoselective aldol reaction to introduce the remaining stereocenters at C-2 and C-3 in **2**. Furthermore, the order in which these steps are conducted, via **16** or **62**, appeared to be of little consequence and thus provided valuable flexibility to the synthetic plan.

In 1982, Evans and co-workers[38] described the use of chiral N-acyl-2-oxazolidinones as reagents for asymmetric alkylation reactions. Although high enantioselectivities (ee's > 98%) are attainable by this method, a limiting factor to its general use is the need for highly reactive alkylating agents in excess to achieve good overall yields. Allylic bromide **64** was chosen as the alkylating agent for this sequence and was prepared in three steps (Scheme XVIII) from commercially available tiglic acid (**65**). The first two steps in the sequence, involving Fischer esterification and reduction of the resulting ethyl ester

Scheme XVIII

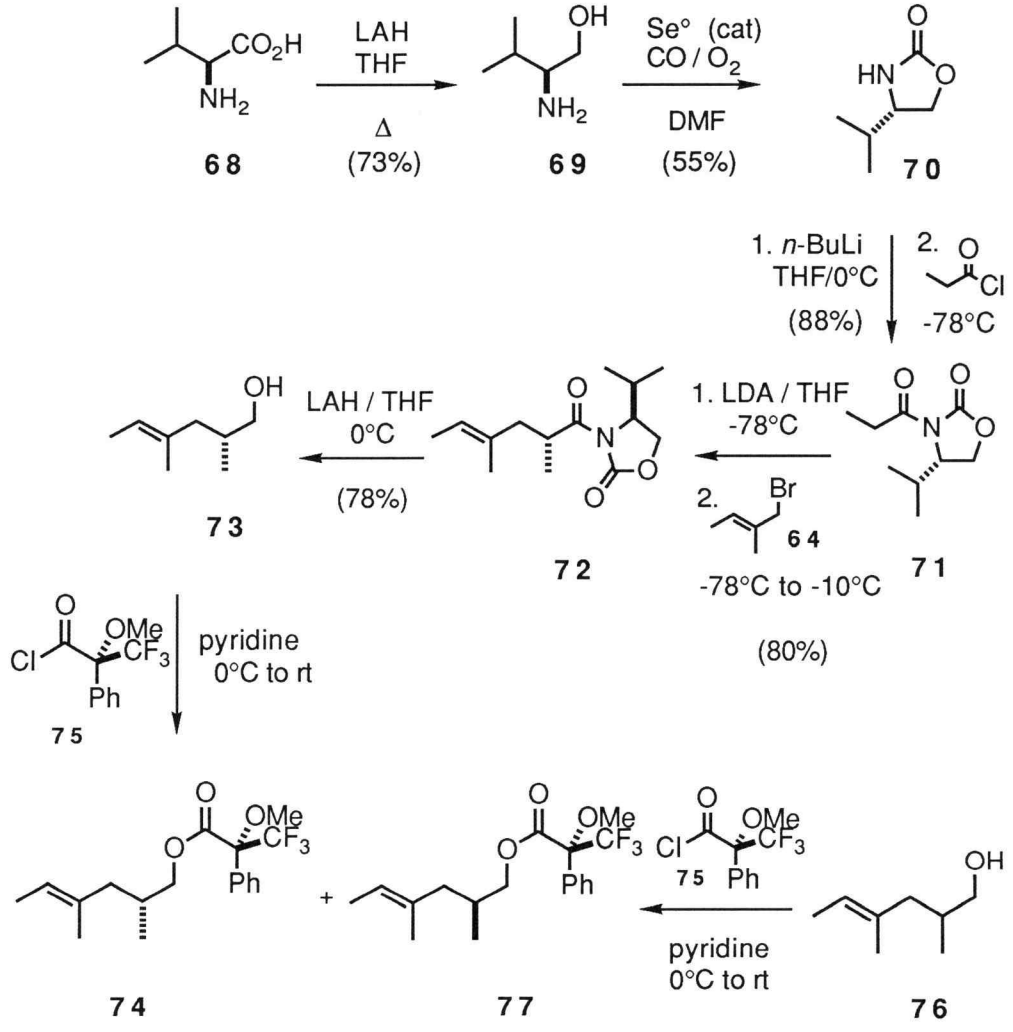


66[39] with lithium aluminum hydride in ether, afforded allylic alcohol **67**[40] in a reproducible 58% overall yield. Unfortunately, the conversion[41] of **67** to **64** proved less reliable, giving **64** in yields ranging from 15-60%. The carbonyl component **71** required for this sequence (Scheme XIX) was prepared[38] by N-acylation of the 2-oxazolidinone **70** with propionyl chloride, the latter being derived from (*S*)-valinol **69** via a selenium catalyzed carbonylation reaction.[42]

Reaction of **64** with the lithium enolate prepared from **71** afforded good yields (73-80%) of the desired alkylation product **72**. Alcohol **73** was prepared by treatment of **72** with lithium aluminum hydride in tetrahydrofuran. ^{1}H NMR analysis of the corresponding methoxytrifluoromethylphenyl acetate (MTPA-ester) **74**, prepared from **73** by reaction with (+)-acid chloride **75**,[42]

suggested that the alkylation reaction proceeded with excellent enantioselectivity. This conclusion was reached after a comparison ^1H NMR

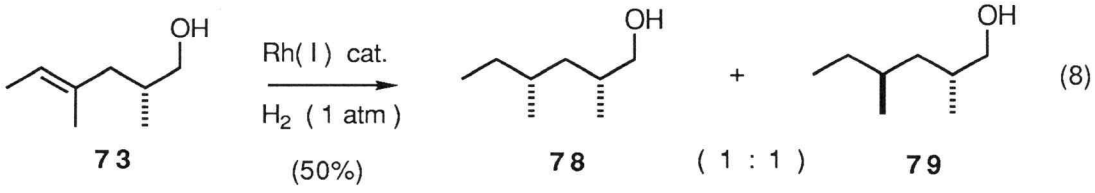
Scheme XIX



analysis was made of the same derivative prepared from the racemic alcohol **76**. Diastereomers **74** and **77**, prepared from **76**, each showed a unique chemical shift and multiplicity for the carbinol methylene protons. While one diastereomer exhibited a pair of one proton doublet-of-doublets at 4.24 and

4.02 ppm, the other displayed a two proton doublet at 4.13 ppm. The ^{1}H NMR spectrum of the MTPA-ester **74** prepared from **73** contained only the pair of one proton doublet-of-doublets at 4.24 and 4.02 ppm, indicating that a single alkylation product was obtained in this experiment. The assignment of absolute stereochemistry as depicted in **73** rested upon the literature precedent for this reaction.[38]

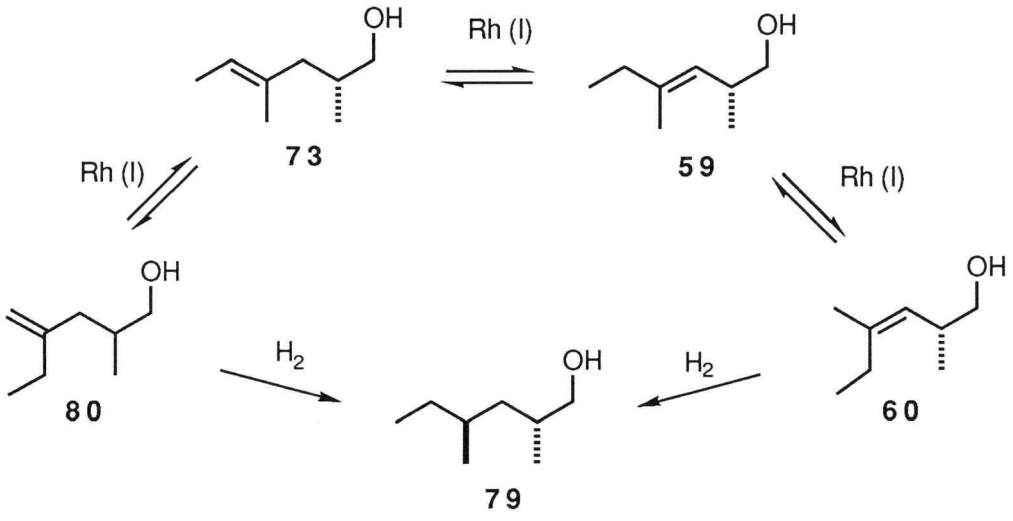
Having successfully constructed the C-4 stereocenter as described above, alcohol **73** served as the starting material for two lines of investigation depicted earlier in Scheme XVII. The initial plan employing a Rh(I) catalyzed stereoselective hydrogenation to introduce the C-6 stereogenic center remained enticing and it was decided to explore this approach with bishomoallylic alcohol **73**. Although this catalyst has proven to be extremely selective for hydrogenation of homoallylic alcohols possessing an intervening chiral center,[21] its use with higher homologs similar in structure to **73** has not been reported. When **73** was stirred under an atmosphere of hydrogen in the presence of rhodium(I)(NBD)(DIPHOS-4) as a catalyst, a 1:1 mixture of diastereomers **78** and **79** was produced in a 50% yield (eq 8). By comparison, the heterogeneous catalytic hydrogenation of **73** with 10% Pd-C



afforded the same isomers in a 1.3:1 ratio. A possible explanation for this curious result was found by examination of the recovered alkene. Analysis of this material by ^{1}H NMR spectroscopy indicated that isomerization of the

double bond in **73** had taken place.[44] Thus, assuming the rate of isomerization **73** (Scheme XX) competes with the reduction step and the stereochemical outcome is defined by the previously discussed reaction mechanism (Scheme XI), addition of hydrogen to **60** or **80** will produce **79** in

Scheme XX

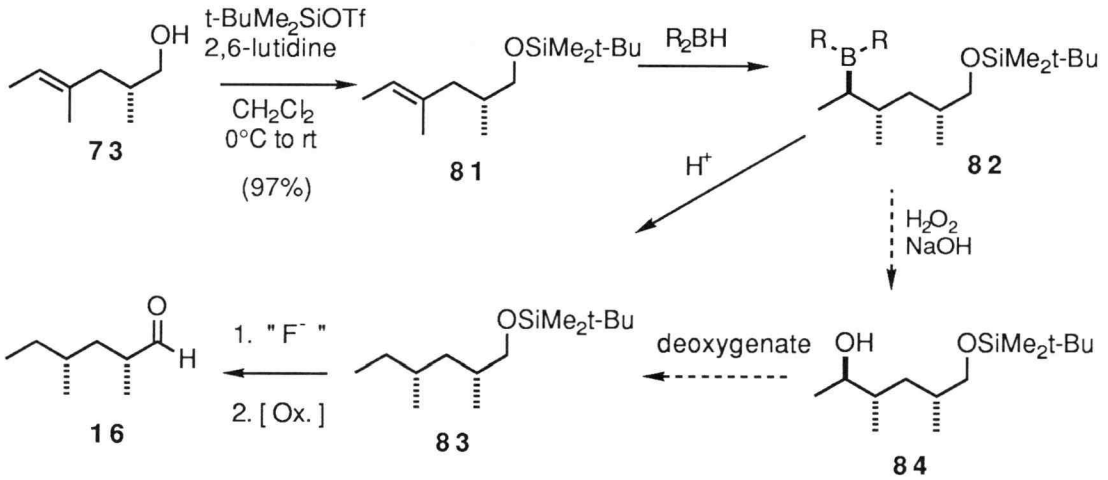


preference to the desired diastereomer **78**. Further work on this route was halted when attempts to separate **78** and **79** by chromatography (TLC, HPLC) as the free alcohols, *p*-nitrobenzoate esters, or α-naphthyl carbamates proved unsuccessful.

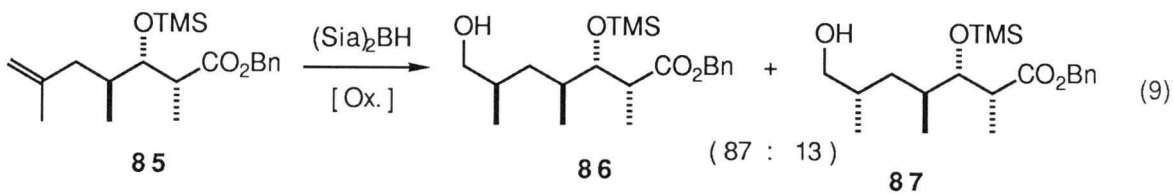
The disappointing results with directed catalytic hydrogenation led to the abandonment of this tactic for setting the C-6 configuration. In its place, a hydroboration strategy was considered as a means of achieving the same overall result (Scheme XXI). Stereoselective hydroboration of **81**, prepared from alcohol **73** and subsequent protonolysis of the intermediate organoborane **82,** would be expected to give silyl ether **83**. Removal of the

silyl protecting group in **83** and oxidation of the intermediate alcohol should then afford aldehyde **16**. Alternatively, hydroboration of **81** with oxidative work-up to give **84**, followed by reductive removal of the C-7 hydroxyl function to yield **83**, was also deemed possible though obviously a less desirable option in view of the extra steps involved.

Scheme XXI

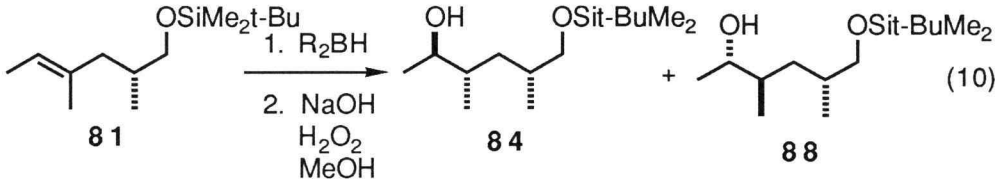


Hydroboration of olefins containing chiral centers has been shown to proceed with good levels of stereoselection.[45] For example, alkene **85** reacts with disiamylborane in dichloromethane at 0°C to give a 87:13 ratio of alcohols **86** and **87** after oxidative workup[46] (eq 9). The initial series of experiments designed to test this approach to **2** involved the hydroboration of



(9)

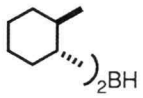
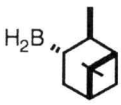
silyl ether **81** with an oxidative workup to give **84** and **88** (eq 10). The decision to oxidize the intermediate organoboranes during the search for a selective hydroborating agent was based upon the premise that a proton bonded to the C-7 carbinol carbon would be easily identified in the ^1H NMR spectrum of the mixture, thereby allowing simple assessment of stereoselectivity (**84**:**88**) in the reaction. The results of experiments involving **81**



and several hydroborating agents are collected in Table III. The isomer ratios were determined by integration of the methine proton assigned to the secondary carbinol carbon in the ^1H NMR spectrum of each isomer. The assignment of stereochemistry to **84** and **88** as shown was based upon literature precedent[47] and the currently accepted mechanism[45] of this reaction. The use of achiral hydroborating agents (entries 1-3) afforded in each case a 1:1 mixture of **84** and **88**. Encouraged by the recent success of Brown and co-workers[47] in their asymmetric hydroboration studies of olefins with chiral organoboranes, monoisopinylcampheylborane ($IpcBH_2$) was prepared[47] from (-)-α-pinene for use with alkene **81**. Exposure of **81** to this reagent, followed by oxidative workup (entry 4), gave an inseparable 5.5:1 mixture of **84** and **88**. Although the observed selectivity (**84**:**88**) was lower than hoped, the 5.5:1 ratio conforms to results reported[47] for simple trisubstituted olefins. The inability to separate the diastereomeric alcohols **84** and **88** suggested that any hope of obtaining pure **83** by protonolysis of **82**

(Scheme XXI) was unlikely. Therefore, further experiments based upon this chemistry were not conducted.

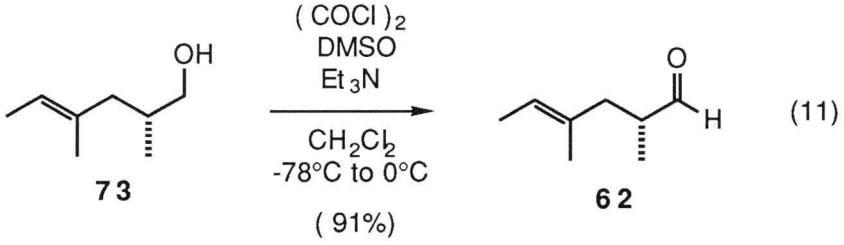
Table III: Hydroboration studies with alkene **81** followed by oxidative workup (eq 10).

Entry	Rxn Conditions	Ratio[a] **84** / **88**	Yield (**8 4**+ **88**)
1	BH_3•SMe_3 CH_2Cl_2 / 0°C	1 / 1	(67%)
2		1 / 1	(15%)
3	Thexyl borane THF / 0° C to rt	1 / 1	(77%)
4		5.5/1[b]	(76%)

[a] Product ratios determined by ^{1}H-NMR

[b] Stereochemical assignment based upon literature precedent.[47]

While the above studies concerning the introduction of the C-6 stereogenic center were in progress, an investigation addressing the construction of the remaining stereocenters in **2** at C-2, C-3, and C-4 was initiated. A stereoselective aldol reaction with aldehyde **62** (Scheme XVII), readily available via oxidation of alcohol **73** (eq 11), would provide **63**, an obvious precursor to **2**. Enolate anions derived from arylpropionate esters have been shown by Heathcock[48] to undergo highly *anti*-selective aldol reactions with a wide variety of aldehydes. However, a limitation



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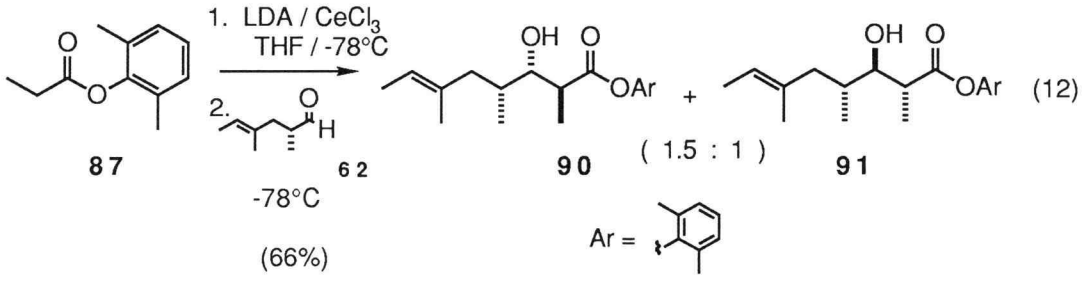
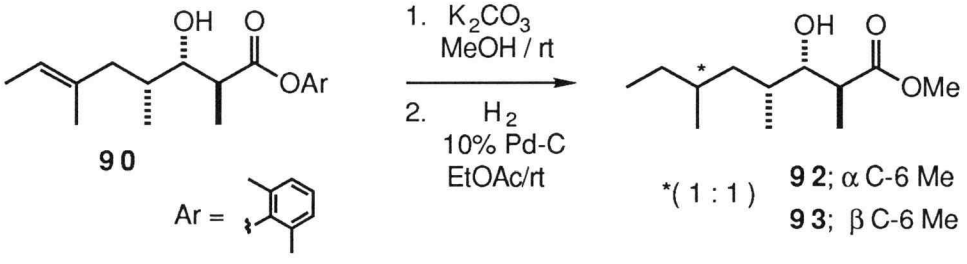
accompanying the use of this class of enolate is the moderate to poor face selectivity observed with aldehydes bearing an α-chiral center.[19a,c] This fact notwithstanding, the lithium enolate prepared from **87** (eq 12) was allowed to



(12)

react with aldehyde **62** in the presence of cerium(III) chloride[49] to give **90** and **91** in a 1.5:1.0 ratio and 66% yield. The utility of the added cerium(III) salt in this reaction was demonstrated by the fact that, in its absence, the identical ratio of aldol products was produced but in only 40% yield. Separation of **90** and **91** was possible by HPLC. Analysis of each isomer by ^{1}H NMR showed the methine proton on the carbon bearing hydroxyl group in the major aldol product as a doublet-of-doublets (J = 2.9, 9.0 Hz) at 3.75 ppm, while the same proton in the minor isomer resembled a triplet (J = 6.0 Hz) at 3.52 ppm. The fact that the same methine proton in **2** is reported[3] as a doublet-of-doublets (J = 2.5, 8.5 Hz) at 3.72 ppm suggested that the major component of the aldol reaction was **90** having the desired 2,3-*anti* and 3,4-*syn* relationship between the three contiguous asymmetric centers. Although the means to introduce

three of the four stereogenic centers in **2** had been discovered, the poor selectivity encountered thus far in attempting to introduce the C-6 stereocenter in **2** via an sp^2 hybridized carbon atom was cause for concern. The question at this point was whether a mixture of C-6 epimers derived from **90** could be separated to allow the preparation of pure **2**. To investigate this problem a 1:1 mixture of methyl hemibourgeanate **92** and its C-6 epimer **93** was prepared from **90** via transesterification using potassium carbonate in methanol (eq 13), followed by catalytic hydrogenation at one atmosphere using 10% palladium on charcoal. All attempts to separate **92** from **93** via chromatography or recrystallization of their *p*-bromophenacyl esters proved unsuccessful.

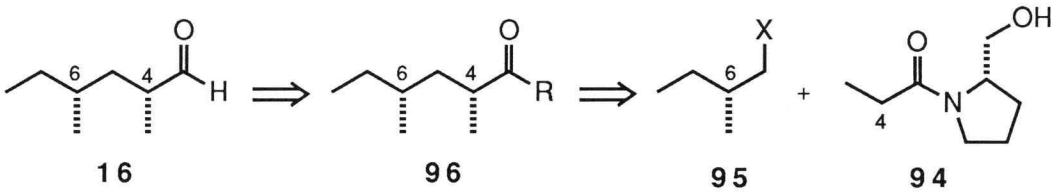


(13)

At this point it became clear that any approach to the synthesis of **2** incorporating a sp^2 hybridized carbon at C-6 was likely to fail or at best be inefficient if it would require the separation of diastereomers. In view of this conclusion, this general approach to bourgeanic acid was abandoned.

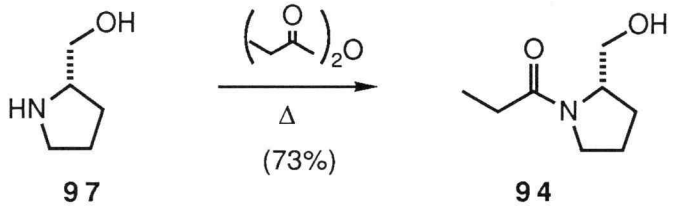
Attention was then directed to the remaining route initially discussed in scheme V, in which a starting material containing the C-6 stereocenter in place is used. The results from two groups[50] investigating the use of chiral enolates derived from N-propionylprolinol (**94**) in asymmetric alkylation reactions suggested a route to aldehyde **16** that was finally successful (Scheme XXII). In this approach, the stereocenter located at C-6 is incorporated into the

Scheme XXII



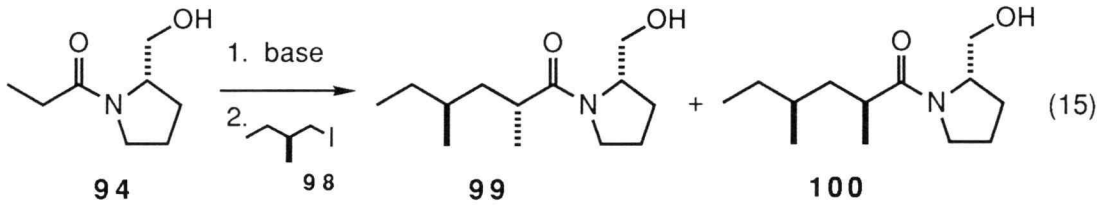
16 **96** **95** **94**

alkylating agent **95** (X=Cl, Br, I), with the C-4 center of **16** generated during C-C bond formation. Adjustment in the oxidation state of the carbonyl carbon of **96** would then give **16**. Amide **94** was prepared[50a] from (*S*)-prolinol (**97**) and propionic anhydride by heating the neat reagents to 70 °C for 3 h (eq 14) followed by distillation of **94** from the reaction mixture under reduced pressure.



97 **94** (14)

An initial series of asymmetric alkylation experiments (Table IV) employing the dianion of **94** and the commercially available (*S*)-2-methyl-1-iodobutane **98** (eq 15) were conducted to determine the optimum conditions for this reaction. In each case the molar concentration of the enolate prepared from **94** and the alkyl iodide **98** was held constant. In the first experiment, the enolate was prepared in THF at room temperature and the resulting heterogeneous mixture cooled to -78 °C. The alkyl iodide **98** was then



94 **98** **99** **100** (15)

(see Table IV)

added as a solution in THF and the mixture was allowed to slowly warm to room temperature (entry 1). Aqueous work-up and analysis of the product mixture by ^{13}C NMR spectroscopy indicated a 7:1 mixture of diastereomers **99** and **100** based upon an average ratio of line intensities of selected carbon signals. The assignment of *R* configuration to the new stereogenic center of

Table IV: Asymmetric alkylation of the dianion of **94** with iodide **98**.

Entry	Reaction Conditions	Product Ratio[a] **99** / **100**	Yield (**99** + **100**)
1	1. 2 LDA / THF /rt 2. **98**, -78°C to rt	7.0 / 1	(65%)
2	1. 2 LDA / THF /rt 2. **98** / HMPA -78°C to rt	12.2 / 1	(54%)
3	1. 2 LDA / THF /rt 2. HMPA / rt to -78°C 3. **98**, -78°C / 2 h	16.8 / 1	(24%)

[a] Product ratios determined by ^{13}C-NMR. Assignment of stereochemistry to major diastereomer based upon literature precident.[50]

the major isomer (**99**) in this mixture was based upon literature precedent[50] and the proposed[51] structure of the enolate as depicted in Figure 1. Assuming exclusive formation of the (*Z*)-enolate from **94**, preferential approach of the alkyl iodide **98** from the *re*-face and opposite the alkoxymethyl group of the pyrrolidine ring would provide **99** as the major product of this reaction. The result shown in entry 2 was obtained by following the previous procedure up to the point of iodide addition. In this instance, **98** was added as a solution in THF containing 2.0 equivalents of hexamethylphosphoramide (HMPA). The course of the reaction was followed by TLC during stepwise warming of the reaction to room temperature. At -40 °C the reaction had proceeded only to a small extent. Further warming to -20 °C appeared to have little or no influence

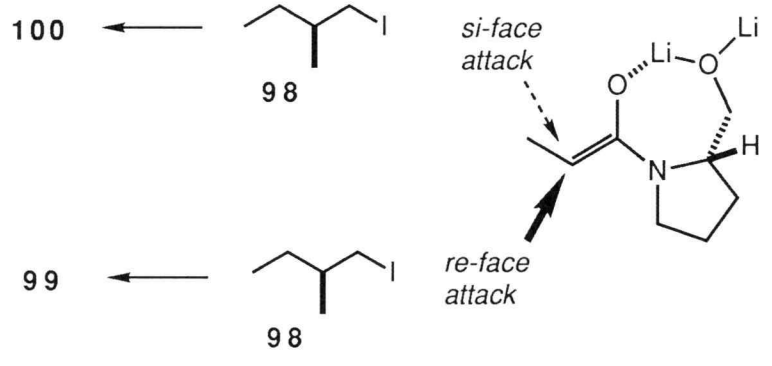


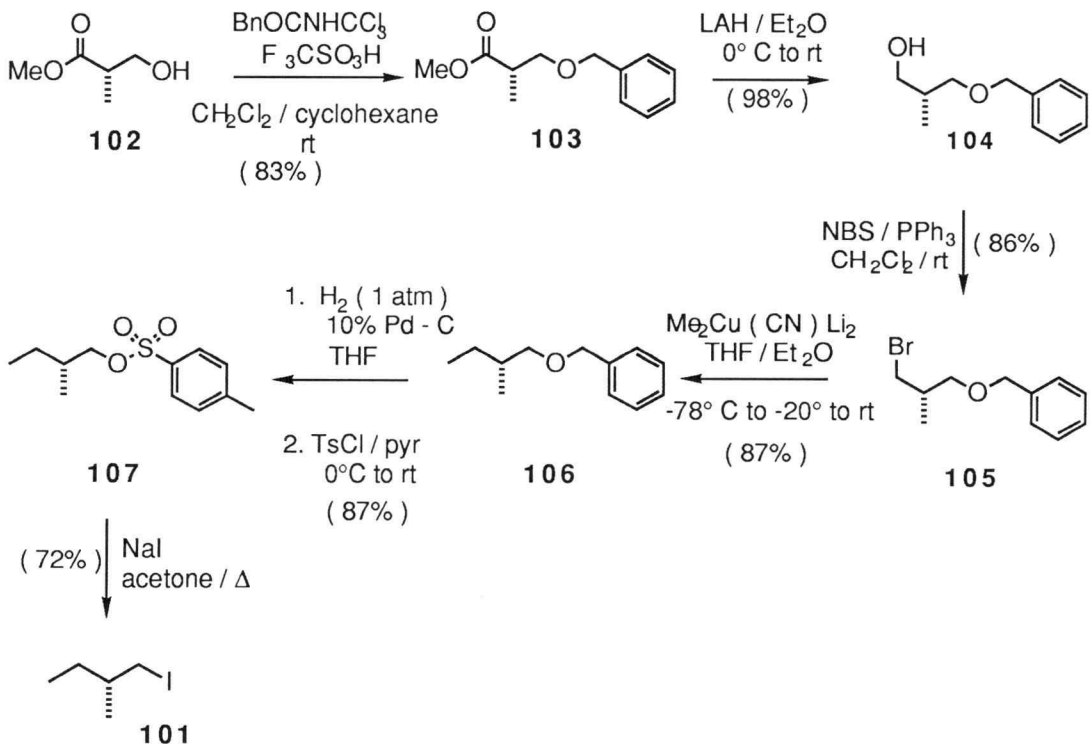
Figure 1: Proposed structure for the enolate of **94** leading to the formation of **99** and **100.**

on the overall conversion. The mixture was then slowly warmed to room temperature. Work-up and analysis as before showed an increase in stereoselectivity (12.2:1) but a slightly reduced yield under these conditions. In the final experiment of this series (entry 3), 2.0 equivalents of HMPA were added to the enolate mixture at room temperature followed by cooling of the resulting solution to -78 °C. Addition of **98**, followed by quenching of the

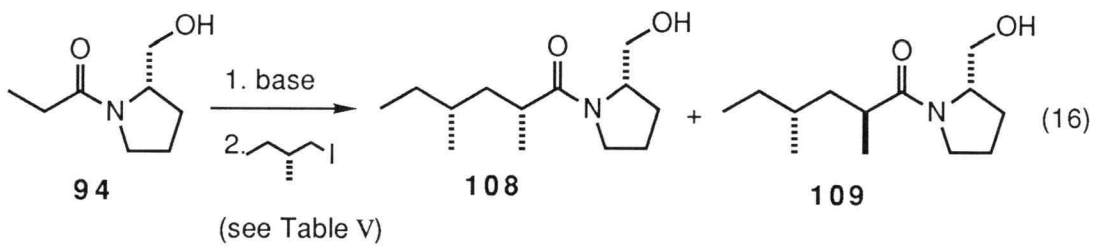
reaction at -78 °C after two hours, resulted in an increase in selectivity (16.8:1) but at the expense of overall yield (24%). Clearly, the results of these exploratory studies indicate that low temperature is advantageous in achieving a high level of stereoselectivity in this reaction. Also apparent from these experiments is that a homogeneous reaction medium is necessary for an effective reaction at reduced temperatures.

Having established conditions favorable for this alkylation, the reaction was repeated with (*R*)-iodide **101** as the alkylating agent. (*R*)-2-Methyl-1-iodobutane[52] (**101**) was prepared from commercially available methyl (2*S*)-3-hydroxy-2-methylpropionate (**102**) as outlined in Scheme XXIII. Conversion of **102** to benzyl ether **103** with benzyl 2,2,2-trichloroacetimidate under acid catalysis[53] was followed by reduction of **103** to alcohol **104** with lithium

Scheme XXIII



aluminum hydride in ether. Treatment of **104** with N-bromosuccinimide in the presence of triphenylphosphine afforded bromide **105**.[54] Coupling of **105** with the higher order cyanocuprate prepared from copper(I) cyanide and 2 equivalents of methyllithium[55] afforded benzyl ether **106** in 87% yield. Removal of the benzyl group by hydrogenolysis and treatment of the crude product mixture with *p*-toluenesulfonyl chloride in pyridine gave tosylate **107** in 87% yield from benyl ether **106**. Reaction of **107** with sodium iodide in refluxing acetone[56] afforded the desired alkyl iodide **101** in seven steps and 38% overall yield from ester **102**. Using the optimum conditions determined from model studies, alkylation reaction of the dianion of **94** with **101** (eq 16) showed a high level of selectivity (entry 1; Table V) for **108** in preference to



109 (17:1), but proceeded in only 34% yield. However, using the same conditions and allowing the reaction to stand for three days at -78 °C afforded 49% of the alkylation products **108** and **109** with similar stereoselectivity (entry 2).

A brief investigation employing modifications to the procedure used above was undertaken in an effort to increase the overall yield of this reaction (Table V). The use of two equivalents of potassium hexamethyldisilazide (entry 3) in THF to generate the dianion of **94**, followed by addition of **101** at -78 °C showed only a trace of the alkylation product. Following the conditions

used in entry 1, and substituting potassium hexamethyldisilazide for lithium diisopropylamide (LDA) also provided no more than a trace of the product (entry 4). An attempt (entry 5) at using the same potassium base in conjunction with *n*-butyllithium to generate the mixed potassio-lithio salt also resulted in failure. A final modification to this reaction (entry 6) was the use of

Table V: Asymmetric alkylation of the dianion of **94** with iodide **101**

Entry	Reaction Conditions	Product Ratio[a] **108** / **109**	Yield (**108**+ **109**)
1	1. 2 LDA / THF /rt 2. HMPA / rt to -78°C 3. **101** -78°C / 5 h	17.0 / 1	(34%)
2	1. 2 LDA / THF /rt 2. HMPA / rt to -78°C 3. **101** -78°C / 65 h	19.0 / 1	(49%)
3	1. 2KN($SiMe_3$)$_2$ THF / rt 2. **101** -78°C / 5 h	(trace amount by TLC)	
4	1. 2KN($SiMe_3$)$_2$ THF / rt 2. HMPA / rt to -78°C 3. **101** -78°C / 5 h	(trace amount by TLC)	
5	1. 2 KN($SiMe_3$)$_2$ THF / 0°C 2. n-BuLi / 0° to rt 3. **101**-78°C / 5 h	(trace amount by TLC)	
6	1. 2 LDA / THF /rt 2. TMEDA / rt to -78°C 3. **101** -78°C / 65 h	11.5 / 1	(17%)

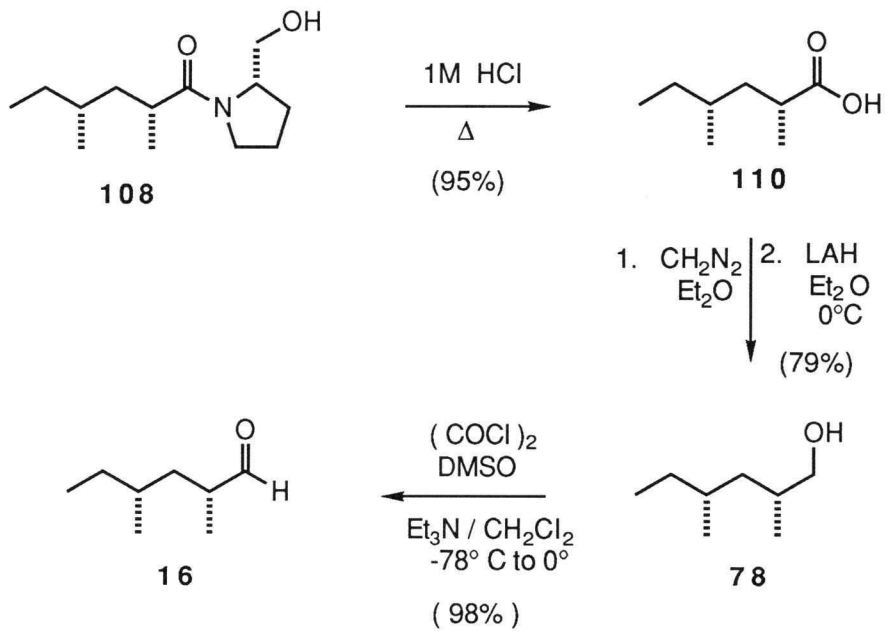
[a] Product ratios determined by ^{13}C-NMR. Assignment of stereochemistry to major diastereomer based upon literature precident .[50]

tetramethylethylenediamine (TMEDA) in place of HMPA under the conditions specified in entry 2. The ability of TMEDA to chelate lithium atoms[57] suggested that it would function like HMPA in its capacity to solubilize the enolate and thus provide the homogeneous conditions found necessary for reaction to take place at low temperatures. Interest in this modification was based upon the difference in structure between HMPA and TMEDA and the known association[58] of these reagents with alkali metal enolates. The principal question to be addressed was whether this change would affect the stereoselectivity of this reaction by changing the ligands which may be associated with the cation of the active enolate species. In this case, the desired alkyaltion took place with lower selectivity (11.5:1) and in lower yield (17%) when compared to the analogous reaction using HMPA. Although no general conclusion regarding the effect of this change could be made on the basis of this single experiment, the overall result was less satisfactory than the conditions involving HMPA. Thus, the procedure outlined in entry 2 proved to be optimal among the modifications studied and was used to continue the synthesis. On a 1.0 g (6.4 mmol) scale, the reaction consistently afforded a 49-55% yield of **108** and **109** in a 17.0-19.0 : 1 ratio. However, when conducted on a 25.0 mmol scale, the overall conversion remained essentially the same but the level of diastereoselectivity fell to 8.5-10 : 1.

With the C-6 and C-4 configurations now in place, all that remained for the synthesis of aldehyde **16** was an adjustment in the carbonyl oxidation level of **108**. Hydrolysis of amide **105** in refluxing aqueous acid[50a] (Scheme XXIV) afforded the corresponding carboxylic acid **110** in excellent yield. Optically pure **110** was obtained via fractional crystallization of the cinchonidine salt of this carboxylic acid from aqueous acetone. Treatment of

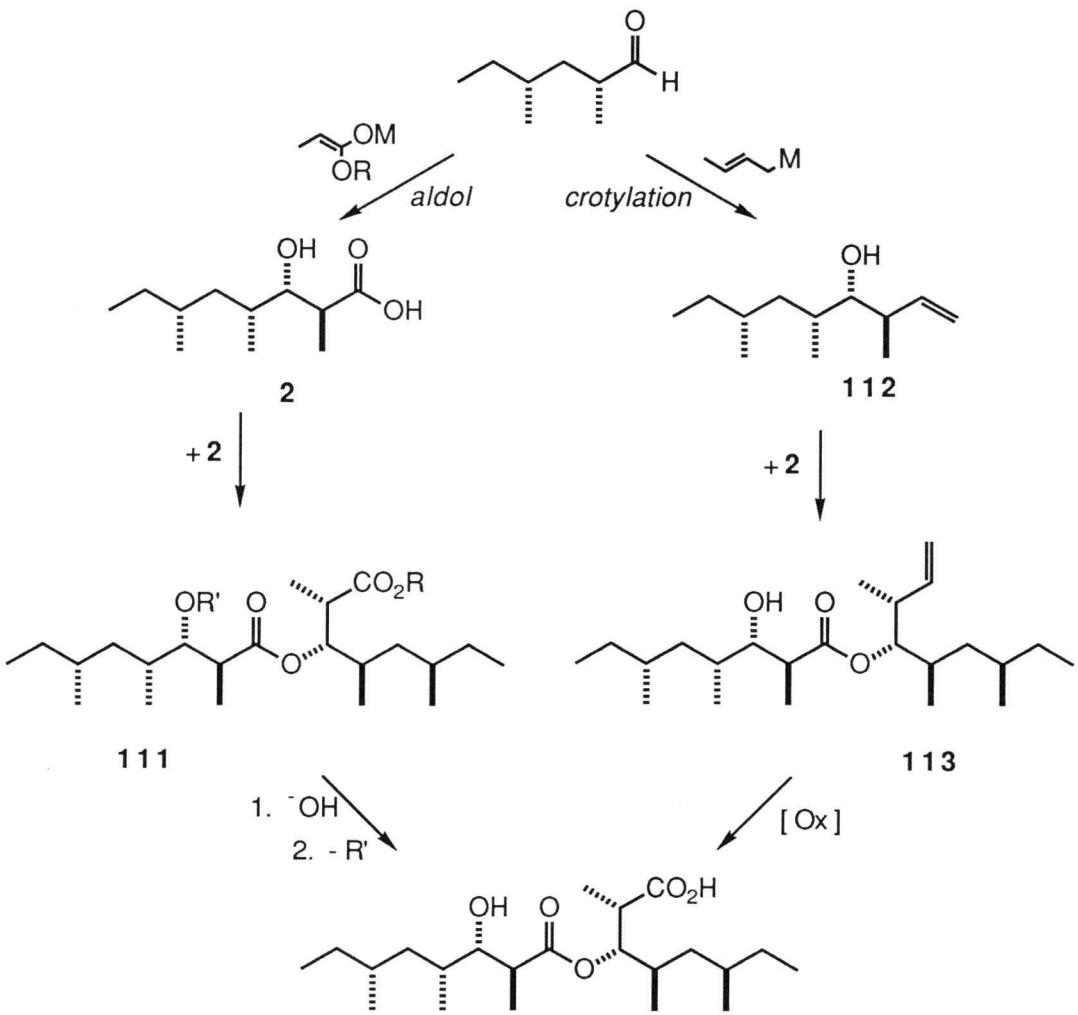
110 with diazomethane and reduction of the resulting methyl ester with lithium aluminum hydride in ether provided the previously seen alcohol **78**. Finally, oxidation of **78** using the Swern[59] conditions yielded aldehyde **16**, a pivotal substance in the projected route to (+)-bourgeanic acid (**1**). It should be noted that aldehyde **16** was an unstable compound prone to epimerization during column chromatography and trimerization (carbon resonance observed at 112 ppm in ^{13}C NMR) upon standing at 0°C.

Scheme XXIV



At this juncture, two strategies were evaluated as possible routes to **1**. The introduction of the remaining stereocenters present in **2** via **16** required the implementation of an *anti*-selective aldol or crotylation reaction (Scheme XXV).

Scheme XXV



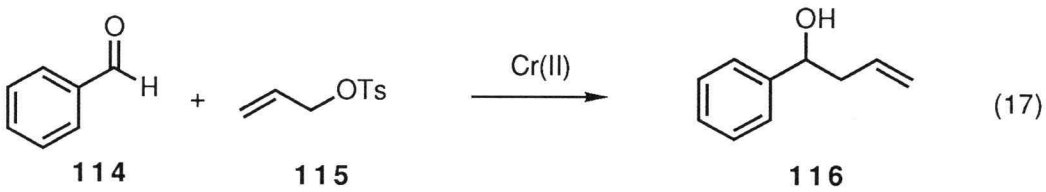
(+)-Bourgeanic Acid **1**

Examination of the aldol route indicated that execution of an *anti*-selective aldol reaction would afford hemibourgeanic acid (**2**). Completion of the synthesis of bourgeanic acid (**1**) would then require the self condensation of **2** to give **1**. A synthetic scheme based upon this strategy necessarily involves the intermediacy of **111**, the coupling product of two suitable derivatives of **2**. While deprotection of the hydroxyl function (R') in **111**

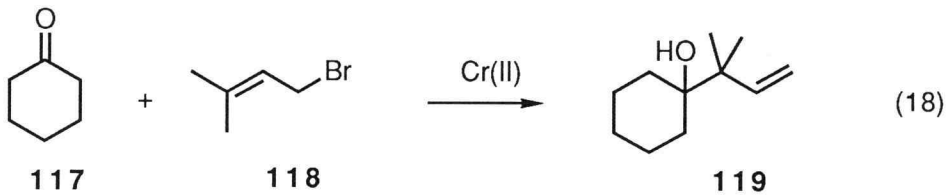
presents little problem conceptually, selective hydrolysis of the terminal ester in the presence of the internal ester linkage was deemed more problematic.

The alternative route via alkene **112** appeared more attractive in two respects. Compound **112** could serve as a precursor to hemibourgeanic acid (**2**), and subsequent coupling of **112** with **2** to give **113** would avoid the requirement of a selective ester hydrolysis. The terminal carboxylic acid function in **1** could then be introduced via oxidative cleavage of the carbon-carbon double bond in **113**. Adopting this approach, the search began for a selective crotylation procedure.

In 1977, Hiyama and co-workers[60] described the reaction of allylic halides and tosylates with chromium(II) chloride to produce as yet undefined organochromium species. These reagents were found to react with aldehydes (eq 17) and ketones (eq 18) to give the corresponding homoallylic alcohols. A notable feature of this reaction was observed with aldehydes and crotyl

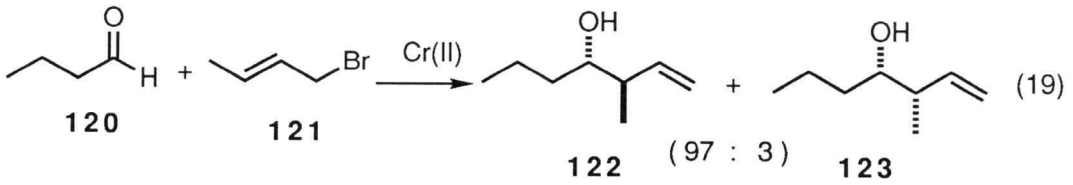


114 **115** **116** (17)



117 **118** **119** (18)

halides as reactants. For example, in the reaction of *n*-butyraldehyde **120** with the low valent organochromium species prepared from crotyl bromide



(**121**), a high preference for the formation of the *anti* stereoisomer**122** is observed in preference to the *syn* stereoisomer**123** is observed (eq 19). The rationale for the *anti* selectivity in these reactions has been explained[60,61] invoking a chair transition state (Figure 2) composed of the reactive organochromium species and the aldehyde. In this view the *trans* geometry

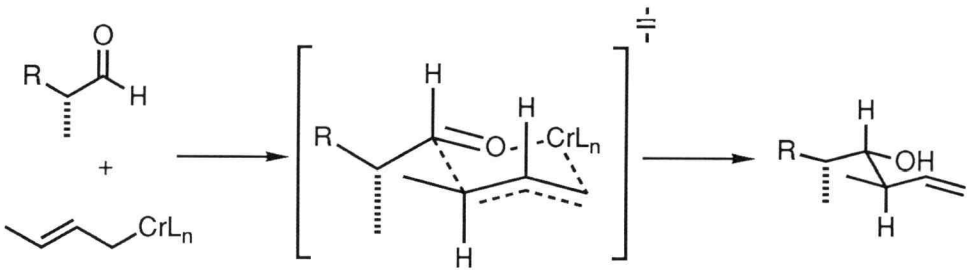
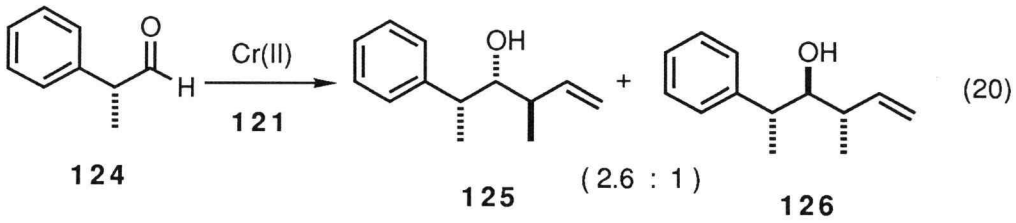
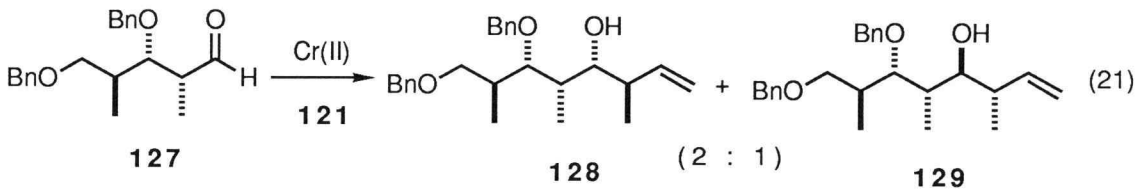
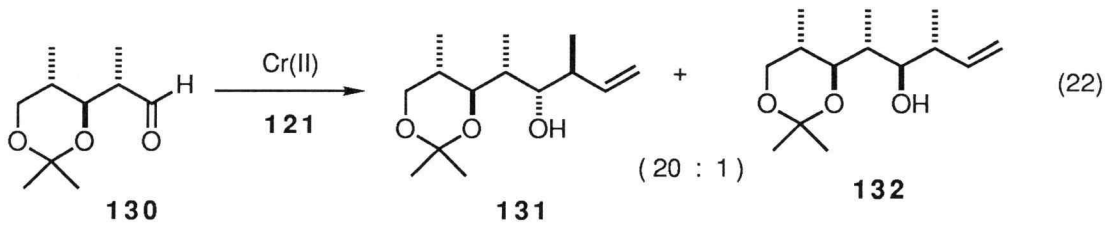


Figure 2: Chair transition state leading to *anti* selectivity in the reaction of aldehydes with crotylchromium reagents.

of the crotyl subunit gives rise to the *anti* relationship observed in the product. The scope of this reaction was further investigated[61] using chiral aldehydes as substrates (eq 20-22). While moderate selectivity was found with aldehydes **124** and **127**, others such as **130** (eq 22) combined with the crotylchromium reagent derived from **121** in a highly stereoselective manner to give **131** as the major product.

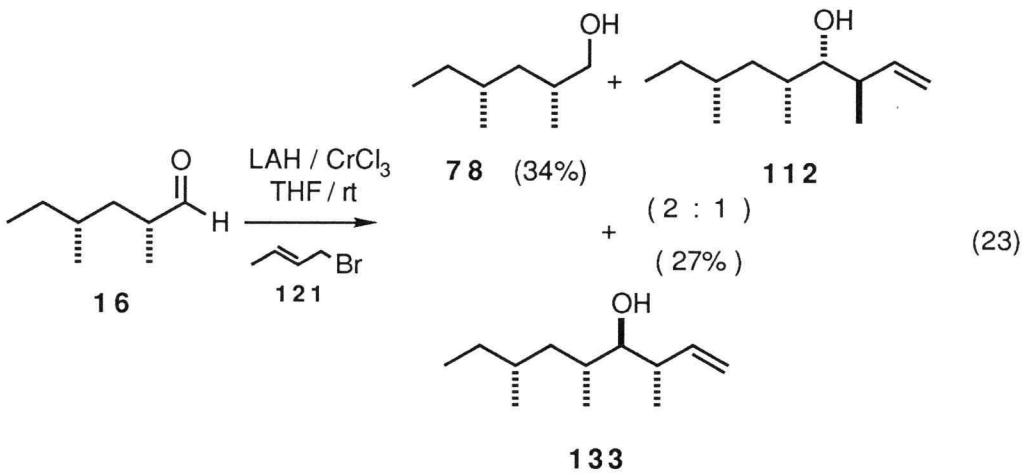






In the present work, aldehyde **16** was added to the organochromium reagent prepared from crotyl bromide (**121**) and chromium(II) chloride in THF (eq 23). The latter was prepared *in situ* by the action of lithium aluminum hydride on anhydrous chromium(III) chloride.[60] Surprisingly, the major product of the reaction was alcohol **78** formed in 34% yield by reduction of aldehyde **16**. The addition product was found as a 2:1 mixture of diastereomers **112** and **133**. The major product was assigned structure **112** based upon the proposed mechanism (Figure 2) and the literature results cited above. Several modifications to the reaction conditions were tried in an effort to increase the ratio of **112** to **133** and suppress the formation of alcohol **78**. Unfortunately, changing the reaction temperature, order of reagent addition,

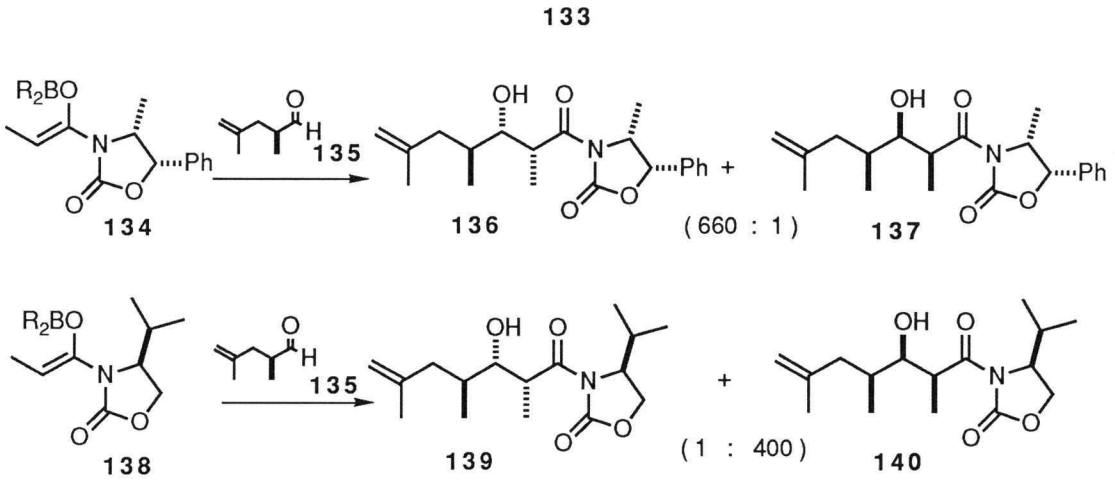
use of the more soluble tris(tetrahydrofuran)chromium(III) chloride[62] as the chromium(III) source, or a solution of lithium aluminum hydride in THF had no beneficial effect on the outcome of this reaction. In each case the same poor selectivity of **112**:**133** was observed accompanied by the reduction product **78**.



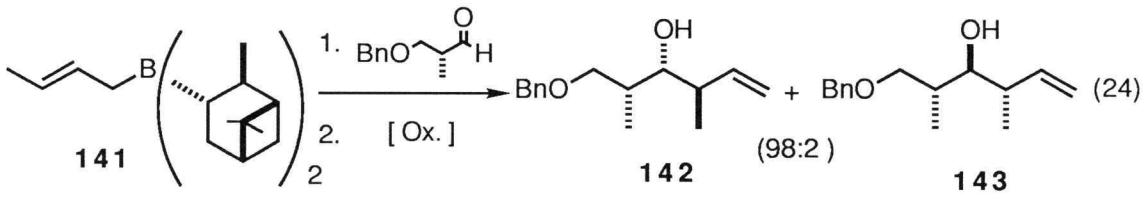
16 121 133 (23)

The difficulty encountered above in the selective addition of a nucleophile to a single face of a chiral aldehyde exemplifies a long-standing problem in organic synthesis.[63] In the area of aldol reactions, the asymmetric induction afforded by a chiral auxiliary incorporated into the enolate has been shown to be the overriding factor in determining which face (*si* or *re*) of the aldehyde carbonyl system is approached in the reaction. For example, boron enolate **134** reacts with aldehyde **135** to give **136** and **137** in a ratio of 660:1[64] (Scheme XXVI). In contrast, boron enolate **138** of opposite chirality condenses with **135** to give **139** and **140** in a 1:400 ratio.

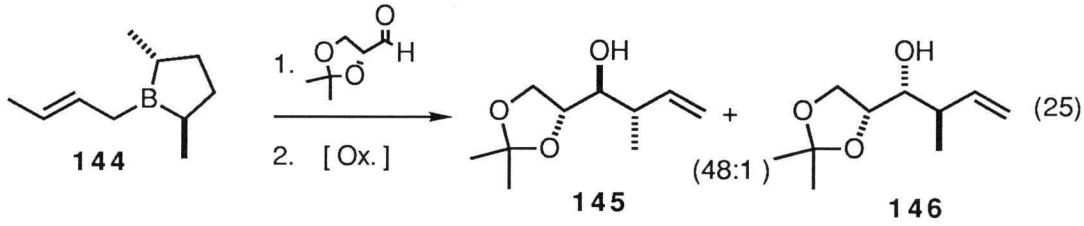
Scheme XXVI



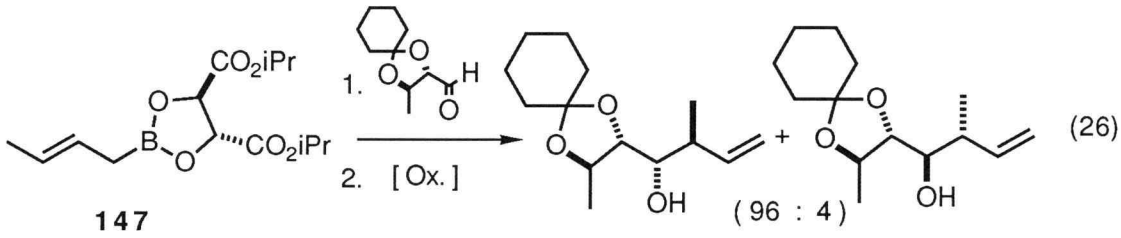
This principle has been extended by several groups to include the delivery of allyl and crotyl anions in the form of chiral boranes[20a,65] (eq 24 and 25) and boronates[66,67] (eq 26 and 27). The crotyl boronate chemistry developed by Roush[66] (eq 26) was considered for the initial series of experiments. The asymmetric induction exhibited by these reagents originates in the chirality of the tartrate ester coordinated to boron. The stereoselectivity observed with this reagent is attributed[68] to an unfavorable interaction of the non-bonding electron pairs associated with the ester and aldehyde carbonyl groups (Figure 3). Thus, coordination of the aldehyde to the boron atom affords complexes **A** and **B**, interchangeable by rotation of the aldehyde around the O-B bond. The unfavorable interaction depicted in **B** leads to preferential delivery of the crotyl unit to the *si*-face of the aldehyde via complex **A**. Using this mechanism and results cited in the literature, it was determined that the boronate prepared from the (*S,S*)-tartrate would be required for reaction with aldehyde **16** to give **112**.



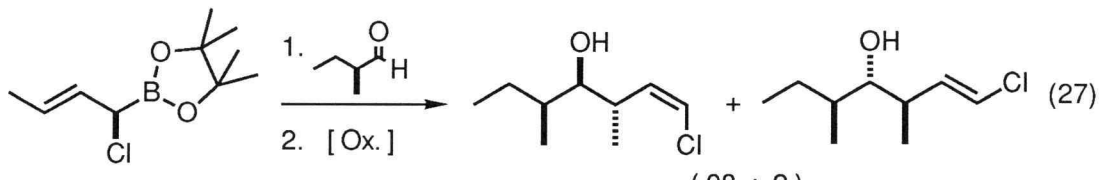
141 142 143



144 145 146

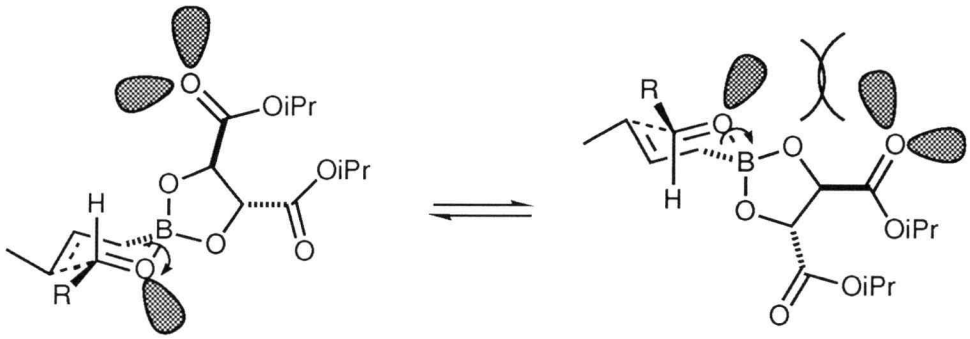


147 148 149



150 151 152

The crotyl boronate **153** could be prepared (Scheme XXVII) from *trans*-2-butene (**154**) and (-)-diisopropyl tartrate (DIPT) (**155**) in either of two ways. A one step procedure involved preparation of the (*E*)-crotylpotassium species from **154** using modified Schlosser conditions,[69] trapping with dimethoxy fluoroborate, hydrolysis of the intermediate dimethoxy boronate, and subsequent treatment with an excess of (-)-DIPT to give **153**. Following this



si - face attack favored

re - face attack disfavored

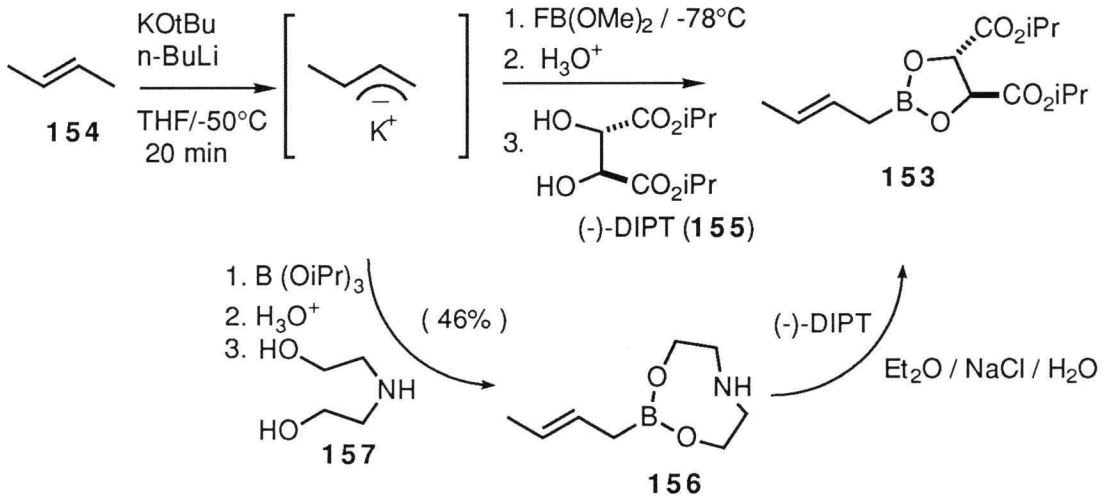
Figure 3: The role of non-bonding electron pair interactions in the face selective addition of chiral crotylboronates to aldehydes.

procedure boronate **153** was isolated as a mixture with unreacted (-)-DIPT (**155**). Although the crude **153** could be used without further purification, the lack of a convenient method to assess the percent composition of **153** in the mixture and the sensitivity of this reagent to moisture led to the use of the alternate route[20b] shown in Scheme XXVII. Aminoboronate **156**, prepared in moderate yield from **154** and diethanolamine, is an air stable solid which can be purified by recrystallization from ether and dichloromethane. More important, however, is that **156** is easily converted to the moisture sensitive crotyl boronate **153** on any scale simply by stirring a two phase-mixture of **156** with (-)-DIPT (**155**) in ether with saturated aqueous sodium chloride, followed by extractive work-up with ether, drying over magnesium sulfate, and concentration under reduced pressure.

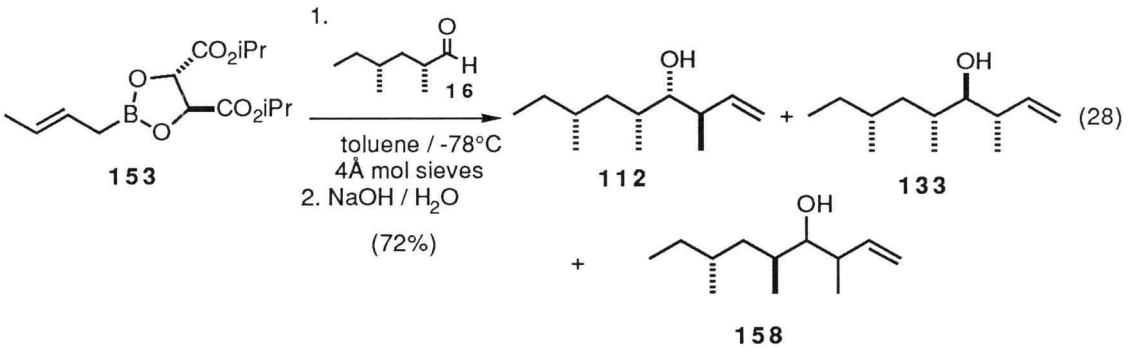
Reaction of aldehyde **16** with **153** in toluene at -78 °C afforded **112**, **133**, and **158** as a mixture of diastereomers (eq 28) in 56-71% yield. The product ratio (**112** + **133** : **158**) was determined by ^{13}C NMR spectroscopy and found to reflect the ratio of C-4 epimers present in the starting aldehyde.

Significantly, the **112**:**133** ratio was consistently in excess of 95 to 5, indicating that a high level of facial selectivity occurs in this reaction. Although this mixture was inseparable by column chromatography, pure **112** was obtained by preparative gas chromatography.

Scheme XXVII



Inspection of **112** reveals that all of the stereogenic centers of hemibourgeanic acid (**2**) are present. The synthesis of **2** from **112** requires only the conversion of a terminal double bond to a carboxylic acid function (Scheme XXVIII). Towards this end, treatment of **112** with *t*-butyldimethylsilyl triflate in the presence of 2,6-lutidine afforded silyl ether **159** in 83% yield. Exposure of **159** to ozone at -78 °C in dichloromethane, followed by decomposition of the intermediate ozonide with dimethyl sulfide in refluxing dichloromethane, provided aldehyde **160** in good yield. Oxidation of aldehyde **160** to the corresponding carboxylic acid **161** was accomplished in 97% yield using sodium chlorite in the presence of excess 2-methyl-2-butene.[70] Synthetic hemibourgeanic acid (**2**) prepared by the flouride

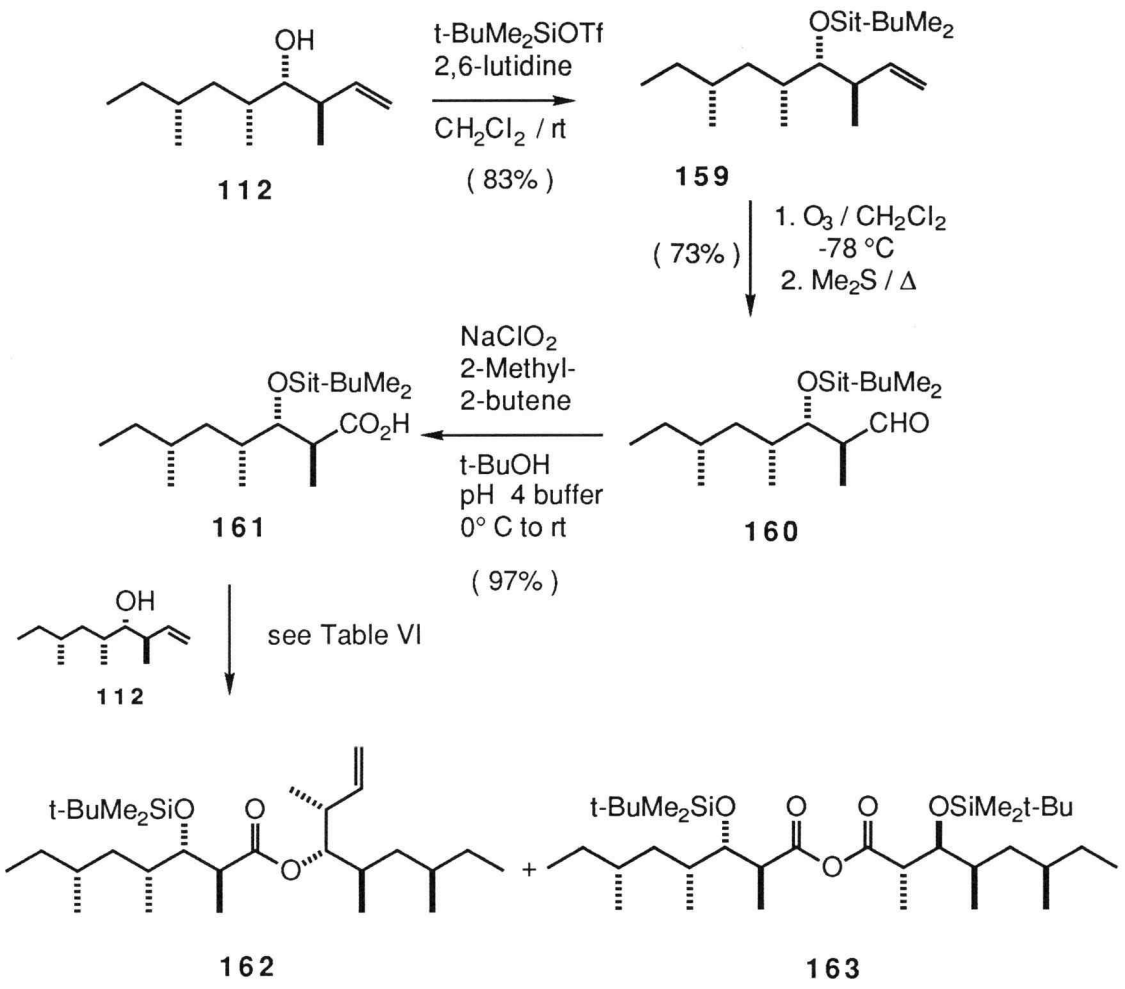


mediated desilylation of **161** (Scheme XXIX) was identical with the compound obtained by hydrolysis[3] of a sample of authentic (+)-bourgeanic acid. Thus, the initial goal of synthesizing **2** had been realized. Perhaps of equal importance, the successful synthesis of (-)-hemibourgeanic acid confirmed the absolute configuration of **1** deduced previously by Bodo on the basis of his X-ray crystallographic study.[4]

The stage was now set to execute the final synthetic sequence to bourgeanic acid (**1**). With the β-siloxy acid **161** in hand, it remained to couple this material to alcohol **112** to give **162**. Oxidative cleavage of the vinyl group in **162**, followed by deprotection of the hydroxyl function, would then afford bourgeanic acid (**1**).

The importance of the ester linkage in natural product synthesis has led to the development of numerous methods for the construction of the acyl-oxygen bond. The sterically hindered secondary alcohol **112** presents a significant problem in this respect and suggested that the acyl component in this reaction would require substantial activation. A series of experiments designed to explore the acylation of **112** were conducted (Table VI) using **112** and **161** and well established esterification methods.[71-76]

Scheme XXVIII



The first method examined conditions developed by Mukaiyama and co-workers[71] (entry 1). Unexpectedly, the only product from this reaction was the anhydride of hemibourgeanic acid **163** (Scheme XXVIII). The identity of this material was revealed upon examination of the IR spectrum where strong absorptions at 1819 and 1751 cm^{-1}, characteristic of anhydrides,[77] were observed. Although the formation of anhydrides is known to take place under Mukaiyama's esterification conditions, the extent to which it occurred in this case (60%) was surprising. Several other methods involving carboxylate

activation (entries 2-5) gave similar results - formation of anhydride **163** and the return of alcohol **112**. In the one case where the desired product **162** was formed (entry 6), it was obtained as an inseparable mixture with anhydride

Table VI: Esterification of carboxylic acid **161** with alcohol **112**.

Table VI: Esterification reactions ionvolving carboxylic acid **161** and alcohol **112** .

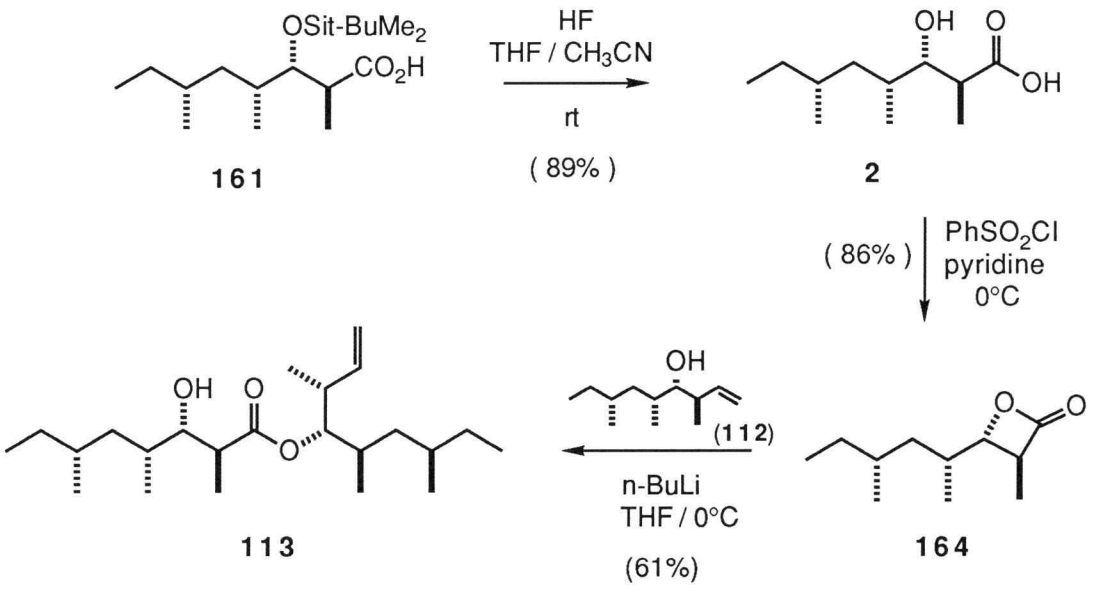
Entry	Reagents / Conditions	Products[a] (%yield)	Reference
1	**112** + **161** $(iPr)_2NEt$ / tol / Δ 	**163** (60%)	71
2	1. **161** + $(COCl)_2$ / DMF 2. 2,6-lutidine / CH_3CN / 0°C 3. **112**	**163** (68%)	72
3	1. **161** + $(Cl_3CCO)_2O$ $(iPr)_2NEt$ / CH_2Cl_2 2. **112**	**163** (TLC)[b]	73
4	1. **161** + n-BuLi / toluene /0°C 2. $(COCl)_2$ 3. **112** / Δ	**163** (46%)	74
5	1. **161** + n-BuLi / THF / 0°C 2. $(EtO)_2POCl$ 3. Li salt of **112** / DMAP 0°C to rt	**163** (59%)	75
6	1. **161** + $(EtO)_2POCl$ Et_3N / THF / 0°C 2. Li salt of **112** / DMAP 0°C to rt	**163** (35%) + **162** (22%) as a1:1 mixture by ^{1}H-NMR; inseparable by LC and HPLC	75
7	**163** +**112** DMAP / rt	NR	76

[a] Products identified by ^{1}H-NMR after isolation by Flash chromatography.

[b] Product identified by Thin Layer Chromatography (TLC).

163. A final attempt to effect preparation of **162** (entry 7) made use of undesired anhydride **163** and the acylation catalyst 4-*N*,*N*-dimethylaminopyridine (DMAP). While Hassuer[76] described the successful use of DMAP in the acylation of tertiary alcohols with acetic anhydride, none of the desired ester **162** was produced when these conditions were applied to **112** and **163**.

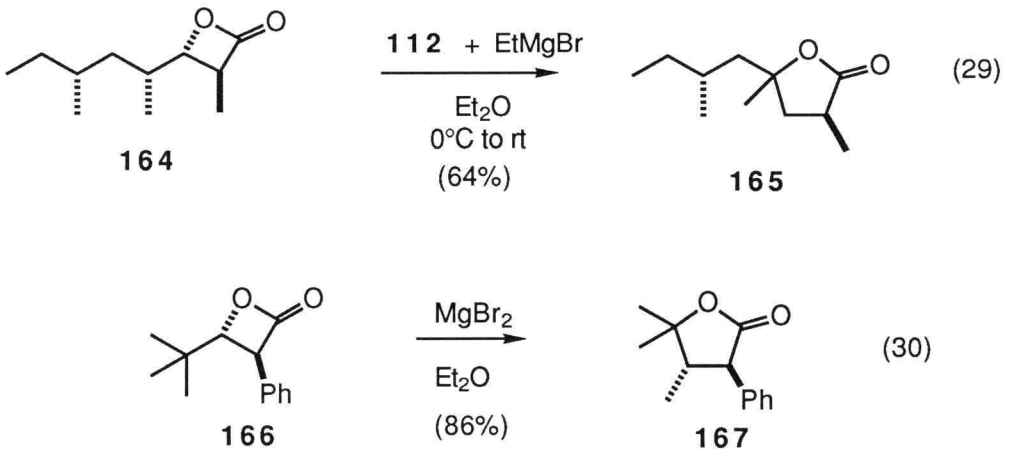
Scheme XXIX



The disappointing results displayed in Table VI made it clear that the desired esterification was unlikely to succeed using **112** and **161** as the components. The decision to retain **112** in the synthetic scheme demanded that a substitute for **161** be found. Attention turned to β-lactone **164** as a potential acylating agent (Scheme XXIX). Support for this choice was found in a report by Vederas and co-workers[78] which showed that "hard" nucleophiles

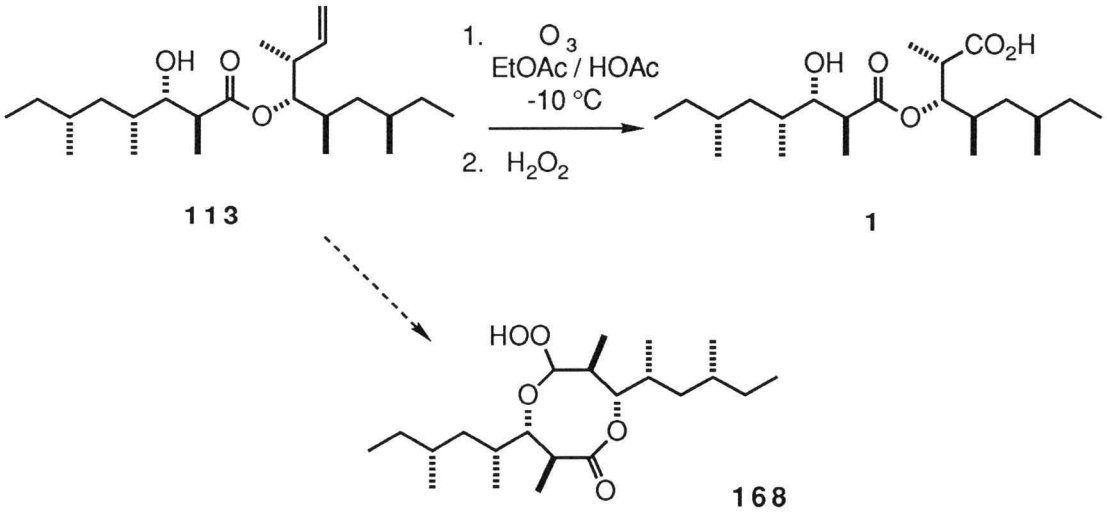
such as the methoxide anion react with β-lactones via acyl-oxygen bond cleavage to give the corresponding methyl ester. Interestingly, the required β-lactone **164** had been prepared by Bodo[3] from hemibourgeanic acid (**2**) during the determination of the relative stereochemistry of **1**. In the present case, lactone **164** was readily available (Scheme XXIX) by exposure of β-siloxy acid **161** to aqueous hydrofluoric acid in 1:1 acetonitrile/THF to give hemibourgeanic acid (**2**), followed by treatment of **2** with phenylsulfonyl chloride in anhydrous pyridine at 0 °C.[79]

The crucial test in this approach to **113** via **164** came when alcohol **112** was treated with *n*-butyllithium in THF at 0 °C, followed by the addition of lactone **164**. The desired ester **113** was isolated from this reaction in a modest 44% yield. Optimization of the reaction subsequently allowed the preparation of **113** in a 58-61% yield based upon the starting β-lactone **164**. A noteworthy observation was that the use of the lithium alkoxide of **112** was found to be of particular importance in securing ample quantities of **113**. The corresponding sodium salt of **112**, for example, afforded a low yield of **113**, with decomposition of **164** being the major reaction pathway. Interestingly, the bromomagnesio salt, generated by the action of ethylmagnesium bromide on **112** in ether (eq 29), reacted with **164** to give the γ-lactone **165** in 64% yield. Support for the structure of **165** came from the observation of a three proton singlet at 1.36 ppm in the ^{1}H NMR spectrum of the product which was assigned to the tertiary methyl group in **165**. Also supportive of **165** was a strong band at 1769 cm^{-1} in the IR spectrum of this material which is characteristic of γ-lactones. This type of rearrangement is not without precedent. The β-lactone **166** (eq 30) was reported[80] to undergo rearrangement to **167** in 86% yield upon treatment with magnesium bromide in ether.



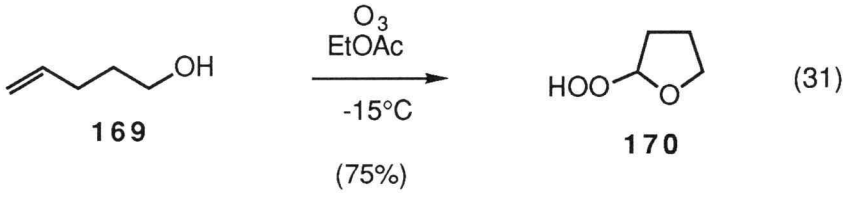
The successful preparation of **113** left only a single task to complete the synthesis of bourgeanic acid (**1**). This was the transformation of the vinyl group in **113** to a carboxylic acid function. The direct conversion of **113** to **1** was attempted by ozonolysis with an oxidative work-up (Scheme XXX).

Scheme XXX

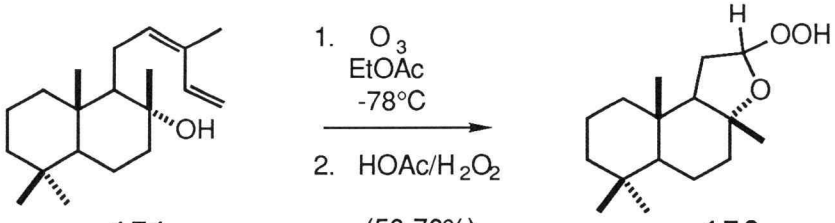


Thus, treatment of **113** at -10 °C with an excess of ozone in a 1:1 mixture of ethyl acetate and glacial acetic acid was followed by warming to

room temperature, addition of 30% aqueous hydrogen peroxide, and stirring overnight at room temperature.[81] A trace amount of **1** was isolated after column chromatography together with a major component similar in appearance to **1** by ^{1}H NMR spectroscopy. Examination of the latter material by IR spectroscopy indicated that the compound contained an OH group, displaying a band at 3409 cm^{-1}, while the remaining bands in the spectrum were very similar in position and appearance to the starting alkene **113**. Consideration of these data and the literature describing the mechanism and synthetic applications of ozonolysis in organic chemistry,[82,83] led to the hypothesis that the major product from **113** under these conditions was the cyclic α-alkoxyhydroperoxide **168**. In support of this conclusion were reports[84,85] of the formation of cyclic α-alkoxyhydroperoxides **170** and **172** upon ozonolysis of alkenes **169** (eq 31) and **171** (eq 32) respectively.



169 **170** (31)

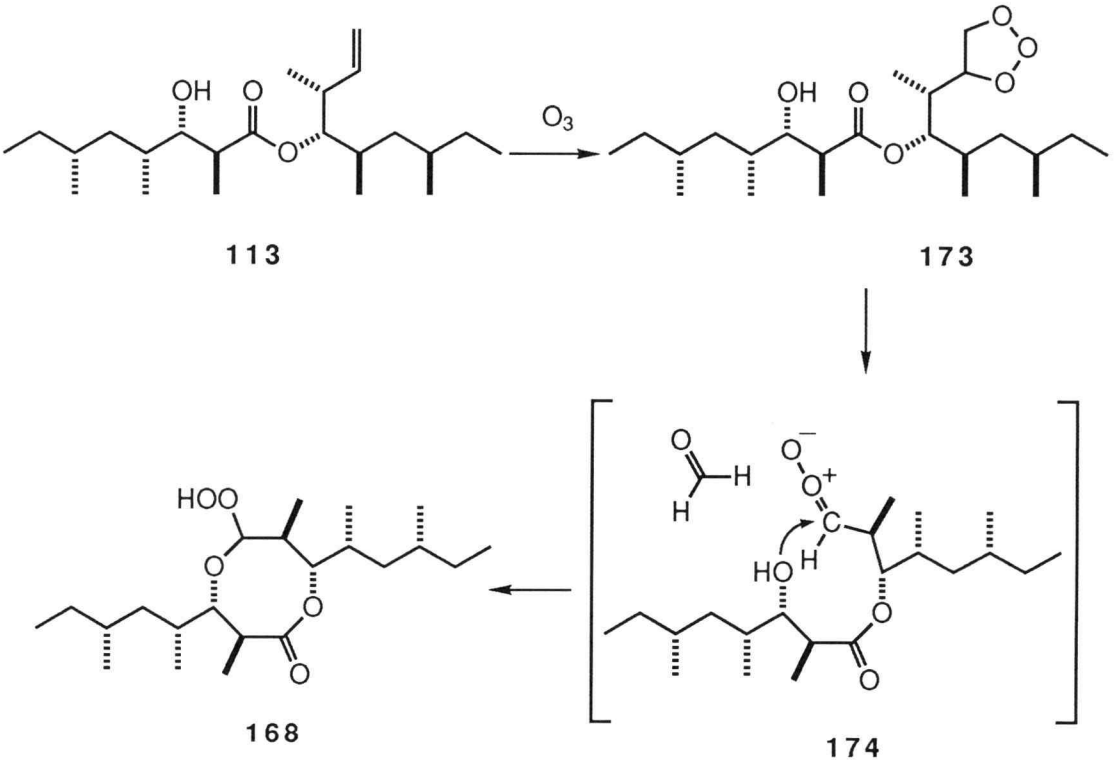


171 (50-70%) **172** (32)

Also in favor of **168** was the previously mentioned report by Bodo[3] of the isolation of the eight-membered ring dilactone **15** during the degradation of **1**. Presumably the factors governing the unexpected cyclization of **1** to **15** could

also allow for the production of **168**. The formation of hydroperoxide **168** by ozonolysis of **113** can be envisioned (Scheme XXXI) to take place via interception of the carbonyl oxide **174**, generated upon initial decomposition of ozonide **173**, by the internal hydroxyl group.

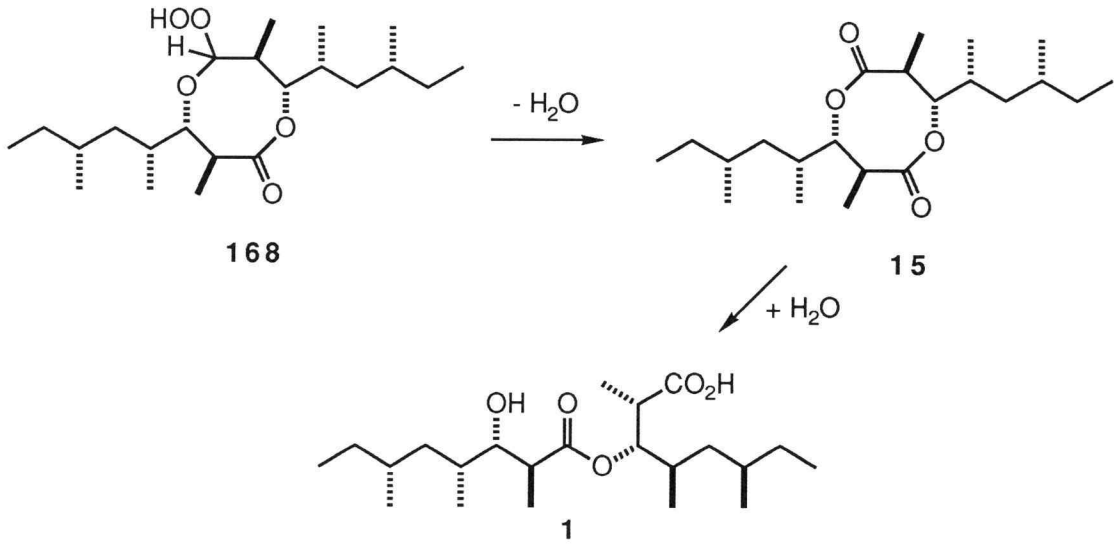
Scheme XXXI



The possibility that **168** had indeed been produced suggested the use of dilactone **15** as a precursor to bourgeanic acid (Scheme XXXII). In a formal sense, this sequence involves simply the loss of water from **168** to give dilactone **15**, followed by the addition of the elements of water across one ester bond in **15** to give bourgeanic acid (**1**). Since the final step in this sequence would require the selective hydrolysis of a single ester linkage in

15, a study of this reaction was conducted with the dilactone prepared from **1**. Treatment of **1** with three equivalents of benzenesulfonyl chloride in pyridine at 0 °C (eq 33) afforded crystalline **15** in 96% yield, identical in optical rotation and melting point with the natural material isolated by Bodo.[3] Analysis of this compound by ^{1}H NMR indicated that **15** possessed a C_2-axis of symmetry since only one-half the expected number of protons for **15** were observed (Figure 4). The ^{13}C NMR spectrum of **15** fully supported this conclusion displaying only eleven carbon signals for this C_{22}-compound (Figure 5).

Scheme XXXII



While a C_2-axis of symmetry is evident in a two-dimensional representation of **15** (C_2-axis perpendicular to the plane of the paper), an examination of Dreiding models revealed that the molecular symmetry of **15** was dependent on conformation. Two distinct conformations of **15** are possible depending upon the relative orientation of the ester carbonyl dipoles (Figure 6). In *syn*- **15** the dipoles are arranged roughly parallel, whereas in

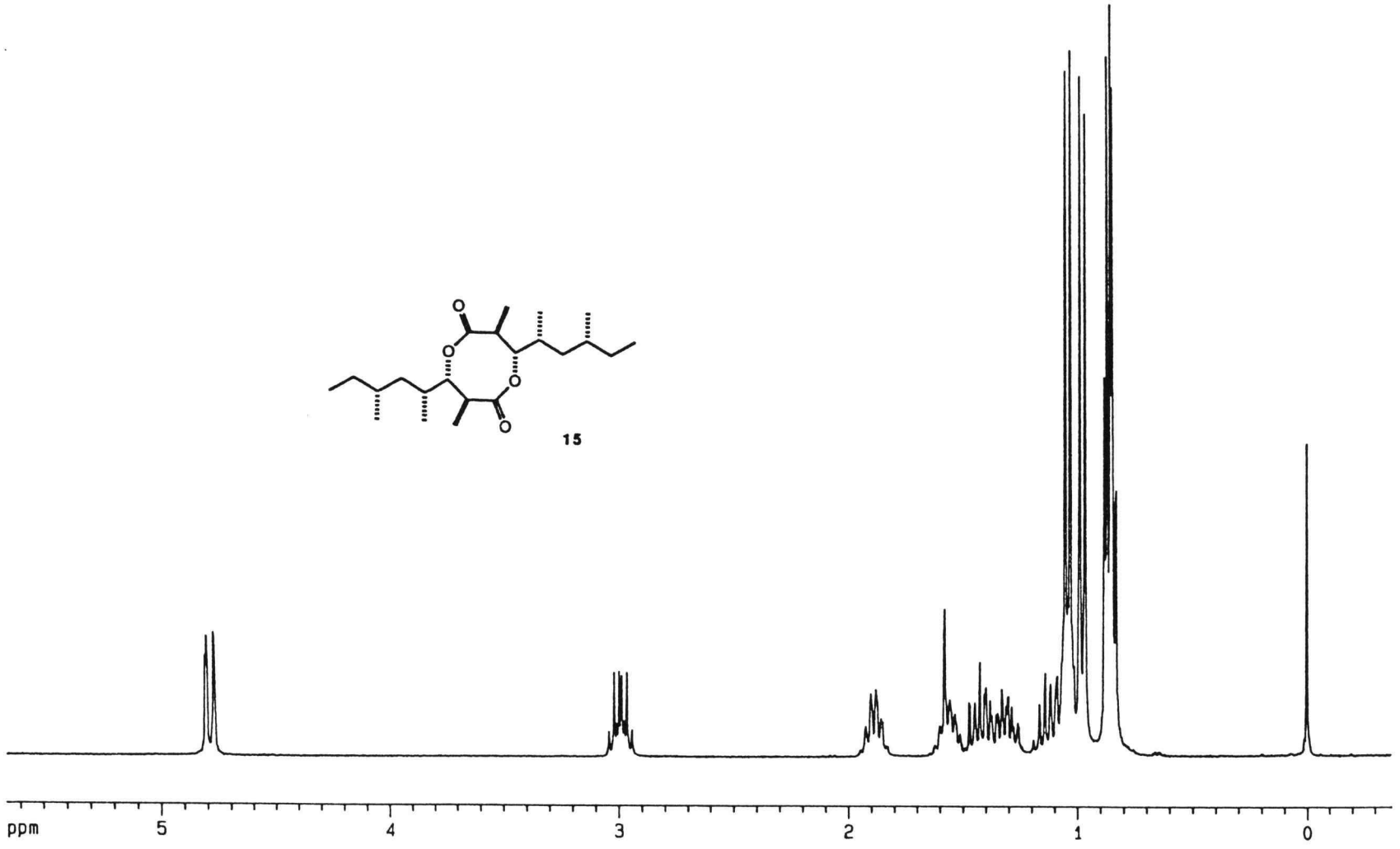


Figure 4: ^{1}H NMR spectrum of dilactone **15**.

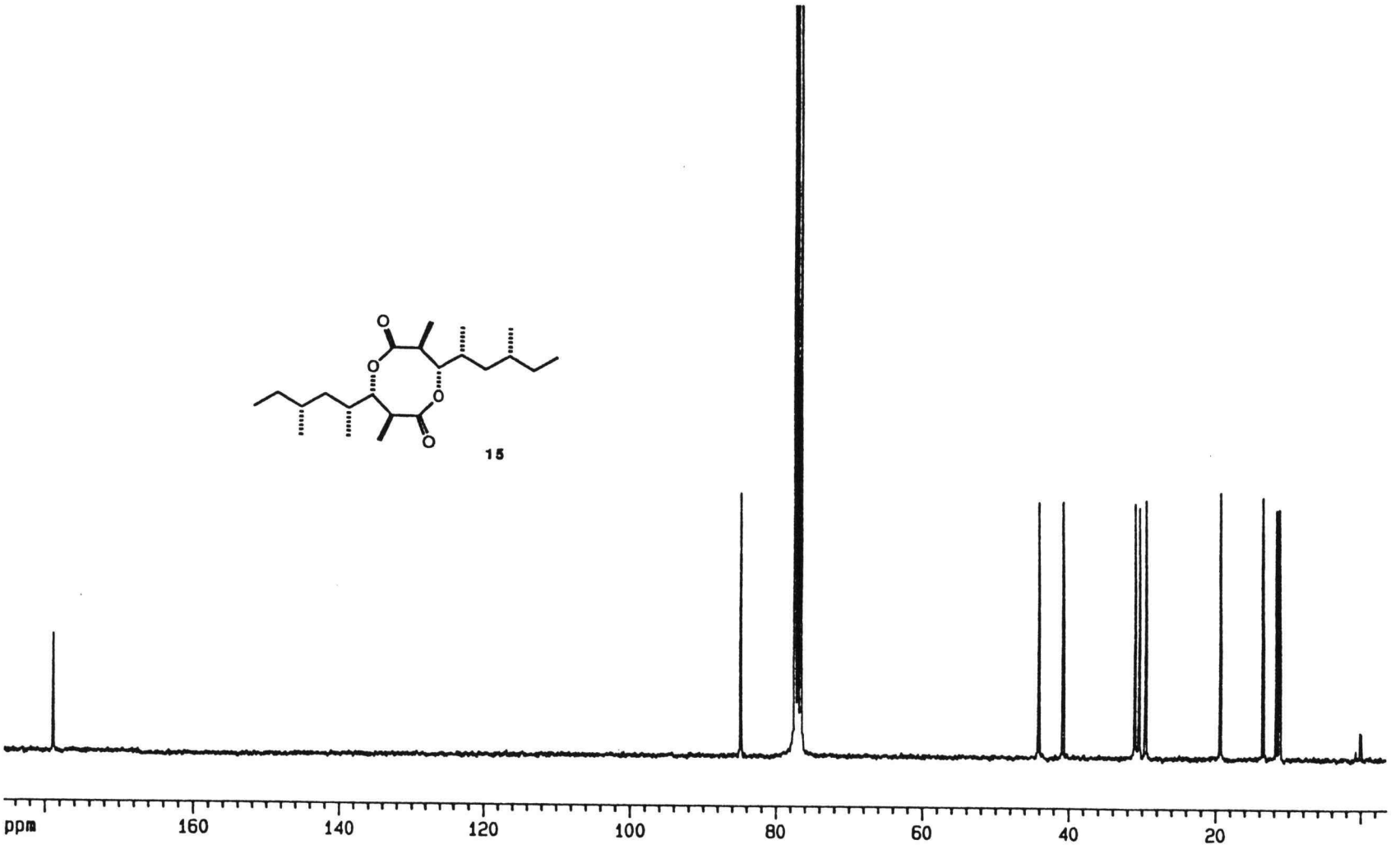
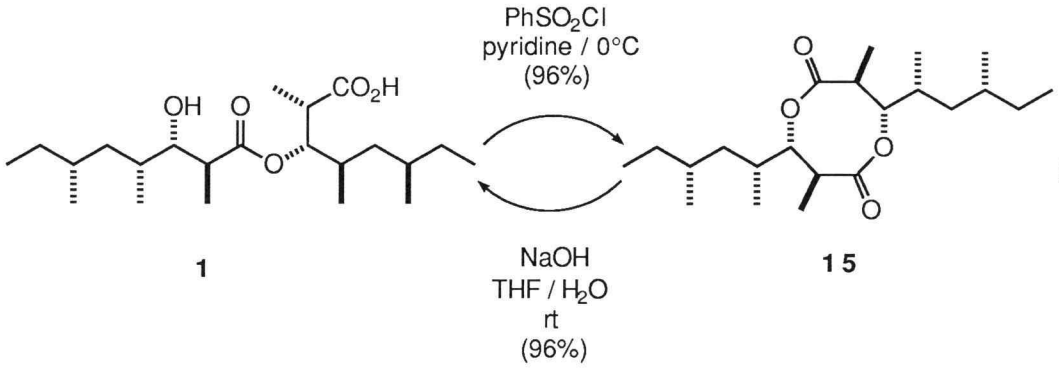


Figure 5: ^{13}C NMR of dilactone **15**.



(33)

anti-**15** they have an *anti*-parallel relationship. It is only in the *syn* conformation, however, that the C_2-axis of symmetry is present. Further discussion of the stereochemistry of this interesting compound is deferred to a later chapter in this account.

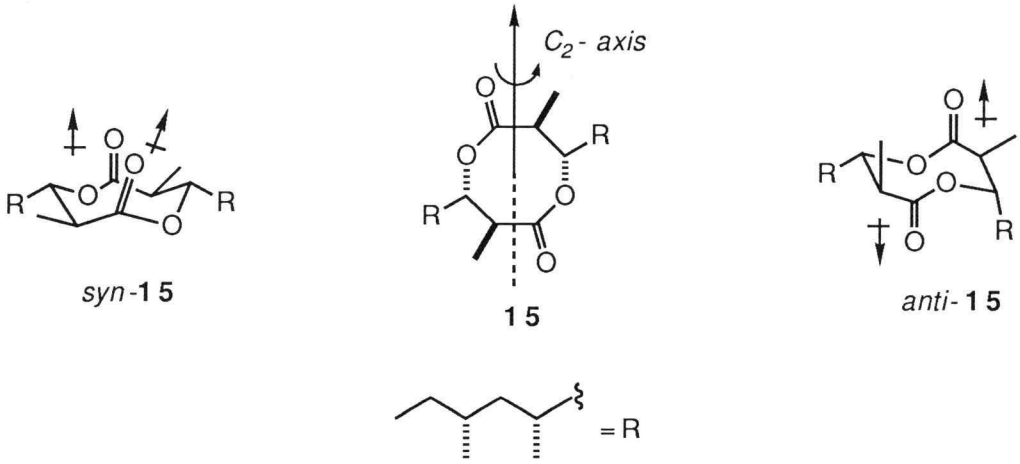
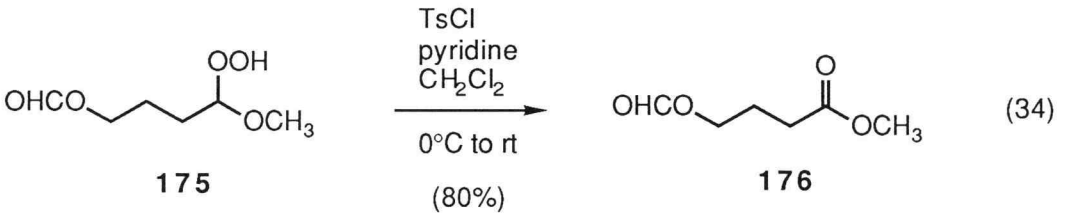


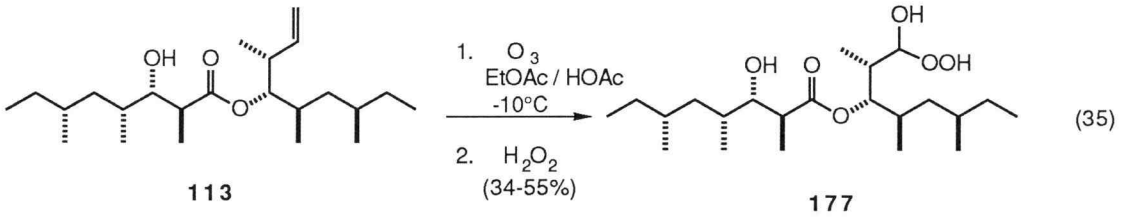
Figure 6: Orientation of carbonyl dipoles in *syn* -**15** and *anti* -**15**.

Exposure of **15** to aqueous sodium hydroxide at room temperature (eq 33) resulted in rapid conversion of the dilactone to **1** in excellent yield. Since the conversion of α-alkoxyhydroperoxides such as **175** to the corresponding ester **176** proceeds in an efficient manner upon treatment with *p*-toluensulfonyl chloride in pyridine (eq 34),[86] the completion of this synthetic



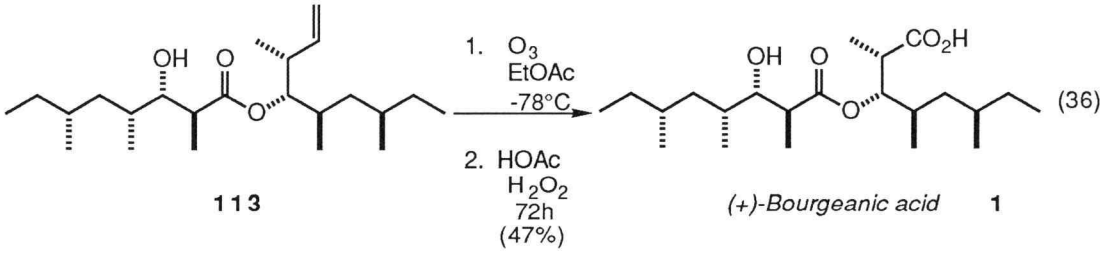
(34)

endeavor appeared close at hand. However, repitition of the ozonolysis of **113** as described above (Scheme XXX) afforded a product which, upon inspection by ^1H NMR, displayed four additional one proton signals at 10.55



(35)

(bs), 9.82 (bs), 2.93 (d), and 1.79 ppm (bs), each exchangeable with D_2O. The ^{13}C NMR spectrum of this material revealed twenty-two carbon signals with a methine carbon resonance at 112.3 ppm, a result consistent with the proposed



(36)

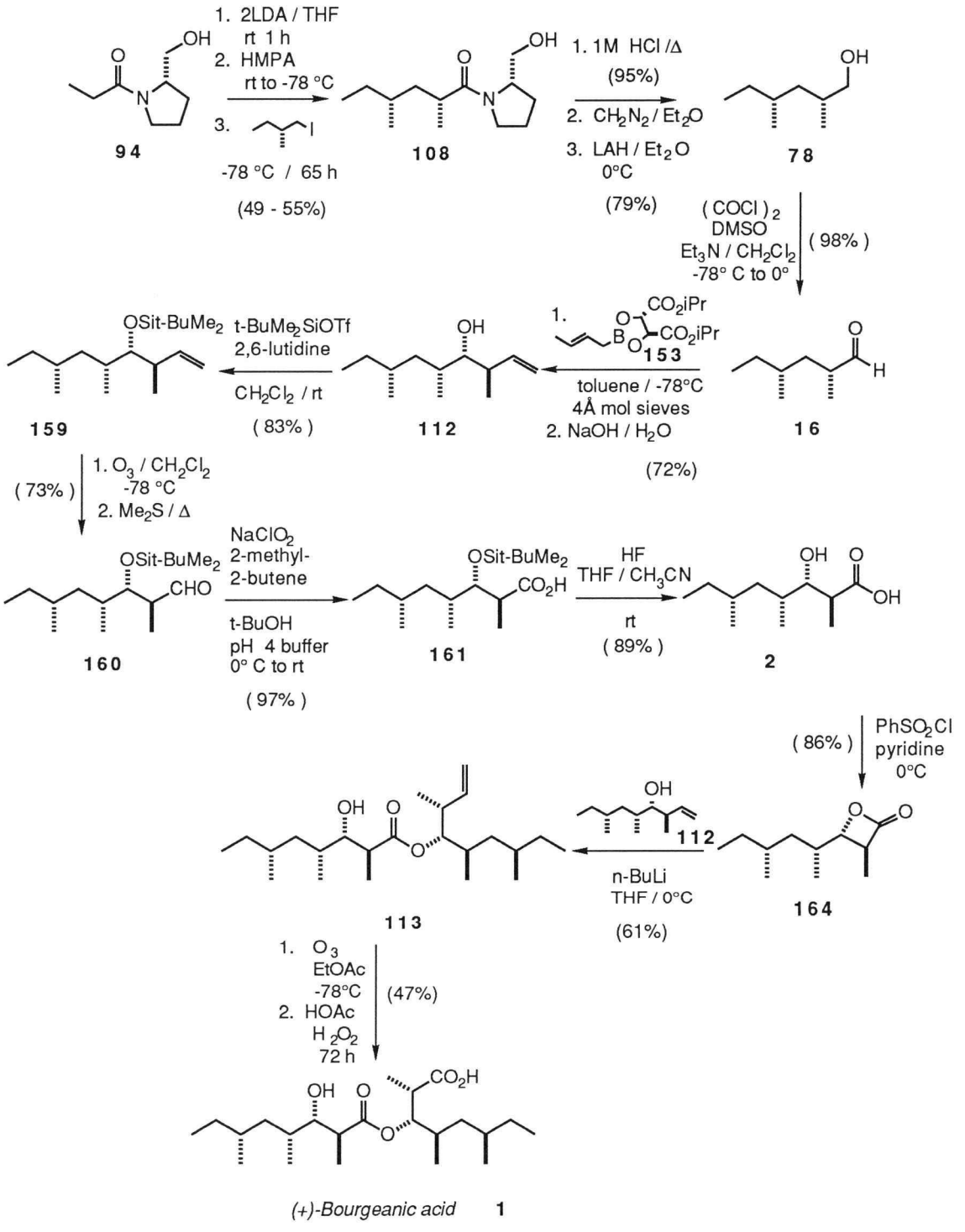
structure **168**. Exposure of this material to *p*-toluenesulfonyl chloride in pyridine afforded none of the desired dilactone **15** but returned instead a mixture of compounds that included a minor amount of **1**. The presence of **1** in this mixture provided chemical evidence that was deemed inconsistent with the generation of **168** in the ozonolysis of **113**, and advocated instead the open chain hydroxyhydroperoxide **177** (eq 35). Although these results

indicated that bourgeanic acid could be prepared via **177**, the inefficiency of the dehydration reaction and the low yields (34-55%) observed in the preparation of **177** prompted further study of the ozonolysis of **113**.

The synthesis of bourgeanic acid was finally completed by using a modification of the ozonolysis conditions desribed above. Thus, exposure of **113** to ozone at -78 °C in ethyl acetate (eq 36), followed by replacement of the solvent with a mixture of glacial acetic acid and 30% aqueous hydrogen peroxide and then stirring the intermediate ozonide for three days at room temperature, afforded (+)-bourgeanic acid (**1**) in 47% yield as a white solid. The material was identical in all respects with an authentic sample of **1**.[3] The ^{1}H NMR and ^{13}C NMR spectra of this novel lichen metabolite are given in Figures 7 and 8 respectively.

In summary, the total synthesis of bourgeanic acid was accomplished in 12 steps and in 3.4% overall yield from the readily available (*R*)-2-methyl-1-iodobutane **101** (scheme XXXIII). The use of an asymmetric alkylation reaction and a diastereoselective crotylation reaction as key steps in the synthesis allowed the efficient introduction of the remaining stereocenters in (-)-hemibourgeanic acid (**2**) and also confirmed its absolute configuration as 2*S*, 3*S*, 4*R*,6*R*. The obstacle encountered in the formation of the ester linkage in **1** via condensation of carboxylic acid **161** with alcohol **112** was overcome by using β-lactone **164** in place of an activated derivative of **161**. Coupling of **112** with **164** furnished **113** which, upon ozonolysis and oxidative workup, afforded **1**. In this manner, (+)-bourgeanic acid (**1**) has been shown by total synthesis to be the self condensation product of (2*S*, 3*S*, 4*R*, 6*R*)-3-hydroxy-2,4,6-trimethyloctanoic acid as previously proposed.[4]

Scheme XXXIII



(+)-Bourgeanic acid **1**

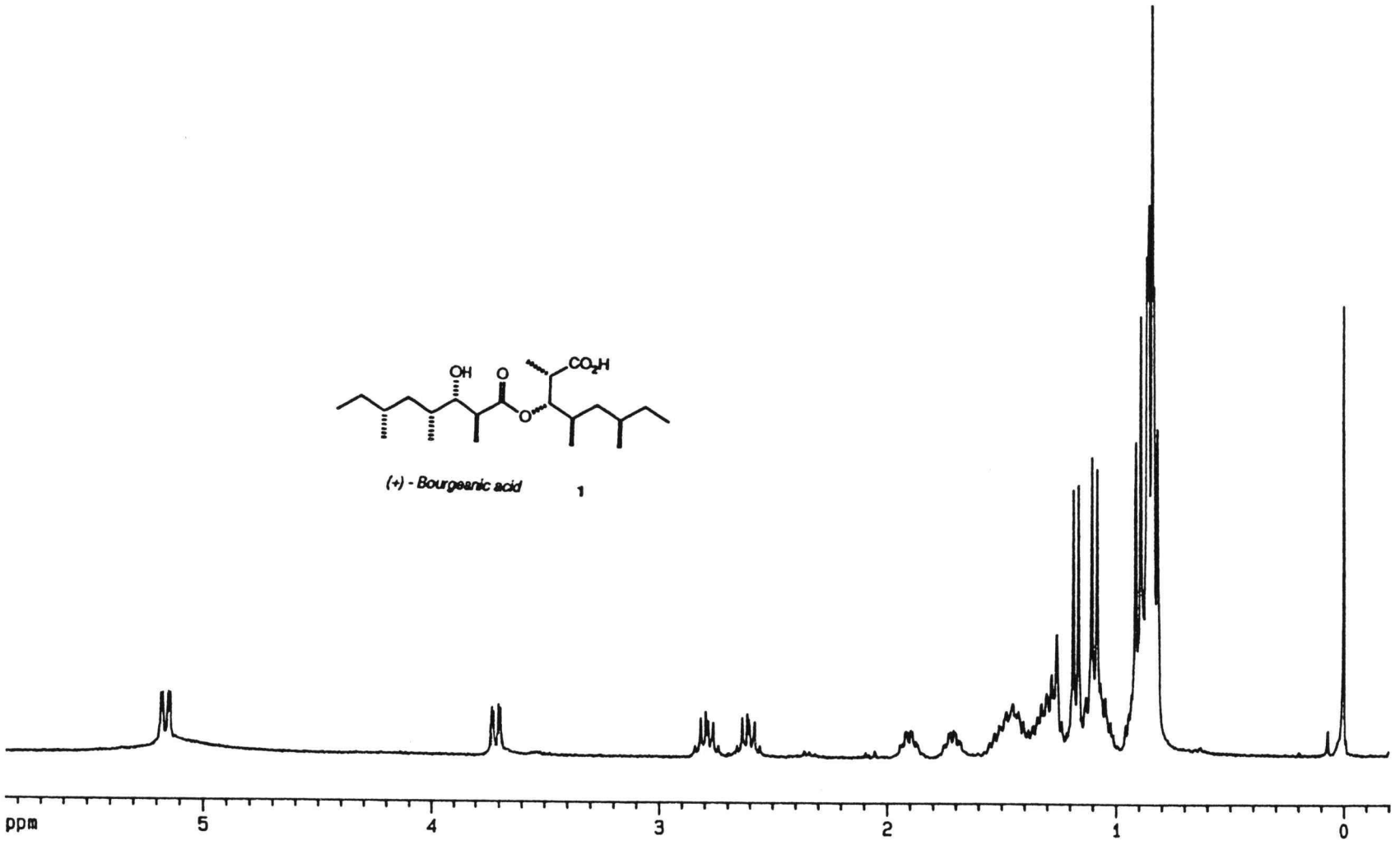


Figure 7: ^{1}H NMR spectrum of bourgeanic acid.

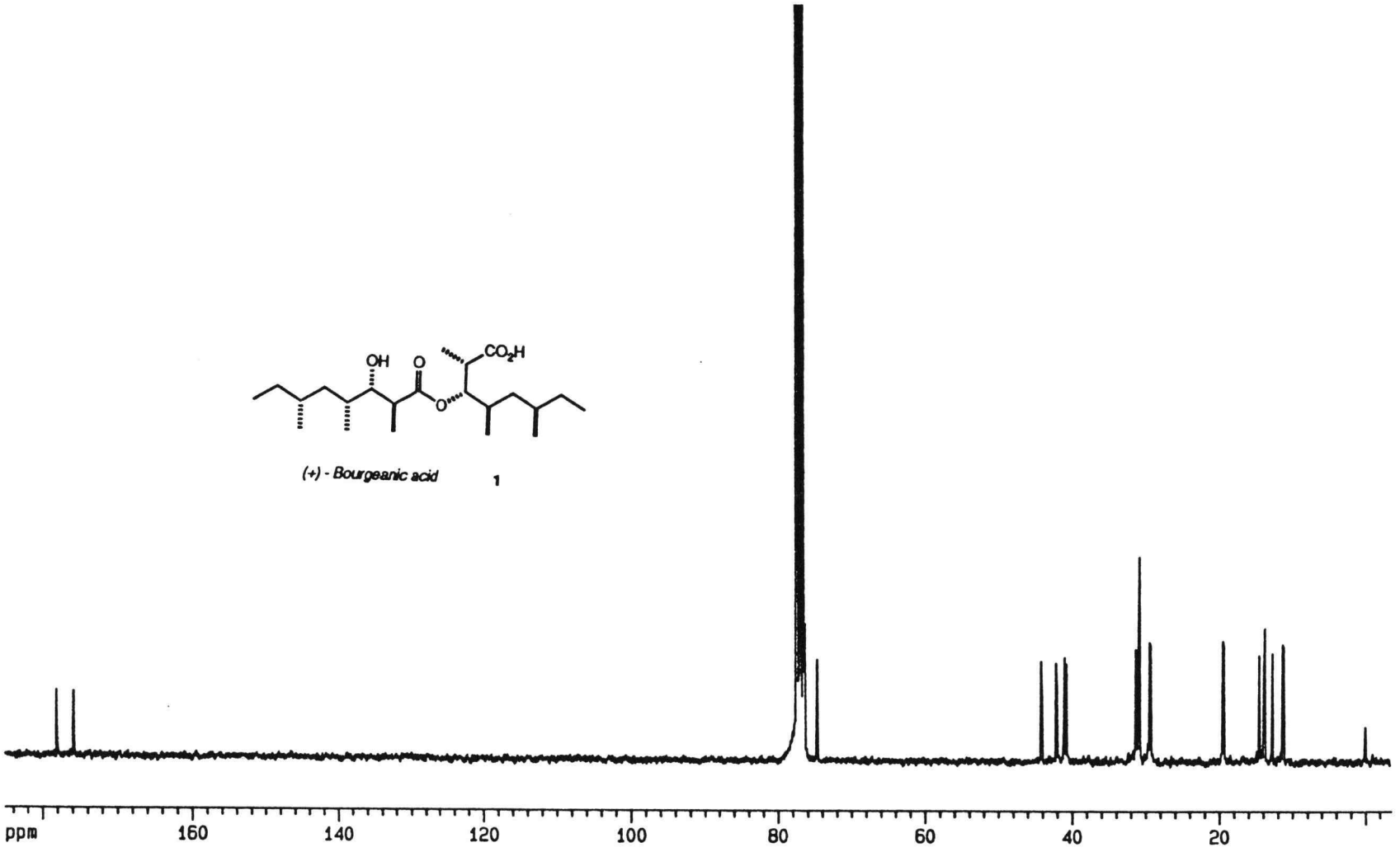


Figure 8: ^{13}C NMR spectrum of bourgeanic acid.

III. CONFORMATIONAL ANALYSIS OF BOURGEANIC ACID DILACTONE

Occasionally, the researcher engaged in the total synthesis of natural products encounters a compound which is exceptional in character and which merits further examination in its own right. In the present study, **15** is just such a compound. Dilactone **15** contains an eight-membered ring formed by facile cyclization of an acyclic precursor, in this instance bourgeanic acid (**1**). The synthesis of medium-sized rings in this manner is usually fraught with difficulty, affording only low yields of the cyclized product. In marked contrast to this generalization is the fact that **1** readily gives dilactone **15** in 96% yield. Of further interest is the observation that, of the two conformations available to **15** (Figure 9), spectroscopic data support the presence of only *syn*-**15**. In view of these observations, **1** and **15** were examined by molecular mechanics techniques with the goal of understanding the energetics of these compounds and the unexpected physical properties exhibited by **15**.

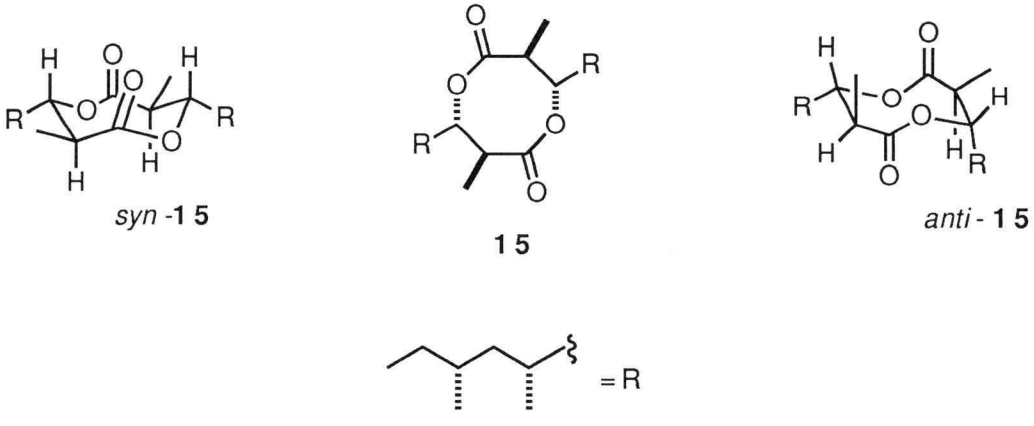


Figure 9: The *syn* and *anti* conformations of dilactone **15**.

The molecular mechanics or force field method of evaluating the physical properties of organic molecules is based upon concepts of classical mechanics.[87] Corrections to this ball and spring approach to determining the energy of a model structure rely on the use of empirically derived force field parameters. In each calculation, the total energy (E_{tot}) of a structure is defined (eq 37) as the sum of the individual energies associated with bond stretching (E_s), bending (E_b), out-of-plane bending (E_{sb}), van der Waals (E_{vw}), torsional

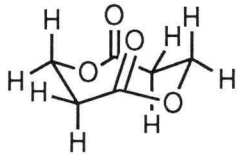
$$E_{tot} = E_s + E_b + E_{sb} + E_{vw} + E_\phi + E_\mu \qquad (37)$$

strain (E_f), and dipole-dipole interactions (E_m). Since the force field parameters used in estimating molecular energies are based upon a limited amount of experimental data, this method is most reliable for the comparison of structural and conformational isomers in the ground state. Transition state calculations are also possible but require a determination of the individual force field parameters specific to the reaction under study. An advantage of the molecular mechanics approach to studying the physical properties of molecules, as opposed to semi-empirical or *ab initio* methods, is the number of atoms which may be accomodated in the model structure. Calculations involving models of **15** or **1** using the latter techniques are not practical at present due to the amount of computer time which would be required and the associated cost.

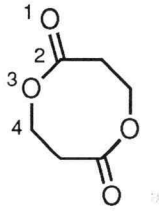
The programs employed in the current study are based on the Allinger MM2 empirical force field.[87] Generation of model structures and preliminary calculations were carried out using MODEL[88] on a VAX 11/750 computer or PCMODEL[89] running on an IBM PS/2 Model 50 Z equipped with a 80287 math co-processor. The final energy minimization of each model structure was

accomplished using the MMX87[90] force field. Data used in the discussion below was available in the output files generated by the MMX87 program. Included in these files are the values to the individual energy terms given in equation 37, along with bond distances, bond angles, torsional angles, atom cartesian coordinates, and calculated heat of formation data. The ball and stick figures shown below were generated in ATOMS[91] using the atom coordinates of the minimized structure.

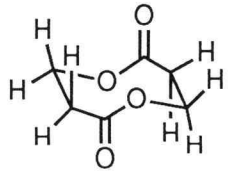
A starting point for this analysis was the inspection of Dreiding molecular models of **15**. This exercise revealed that two distinct conformations, each having all the ring alkyl groups equatorially disposed, are open to **15** (Figure 9). Physical evidence in agreement with this point of departure was found in the ^{1}H NMR spectrum of **15** (Figure 4), where vicinal methine protons located on the ring carbons (4.79 and 2.99 ppm) exhibit a 10.2 Hz coupling. This value is consistent with a trans diaxial relationship suggested in these conformations.



syn-**178**



178



anti-**178**

The first observation from this analysis was that the ring atoms adopt a crown conformation in *syn*-**15** and a chair or twist-chair conformation in *anti*-**15**. The absence of information regarding the conformational preferences of the unsubstituted analog of **15**, dilactone **178**, suggested that recourse should be made to available data on cyclooctane. A computational study by

Hendrickson[92] indicated that several conformational minima are available to the flexible cyclooctane ring. The conformations relevant to the present study are shown in Figure 10 where the energies have been normalized to the boat-chair form **179**. The crown conformation **180** is found to be 2 kcal/mol higher in energy than **179**, while the two chair forms **181** and **182** are approximately

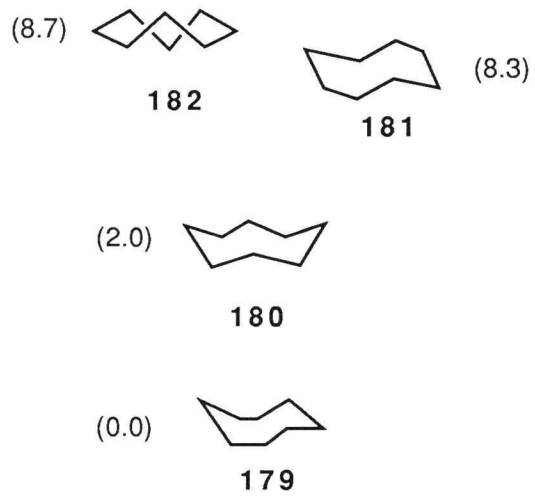


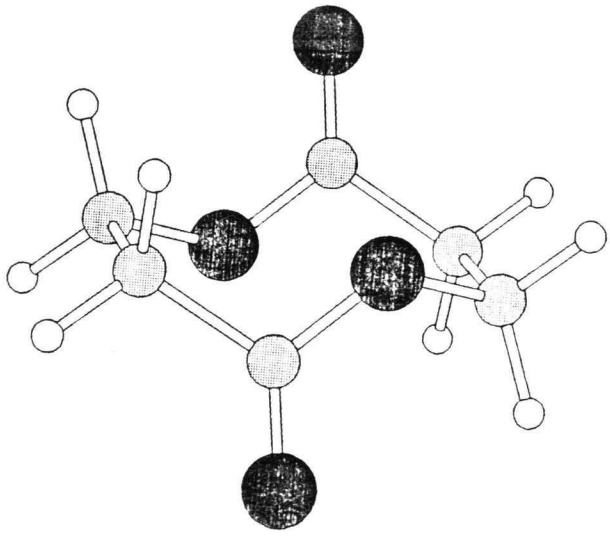
Figure 10: Selected conformations of cyclooctane and associated energy values relative to **179**.

8.5 kcal/mol higher in energy than **179**. These data suggested that an inherent energy difference of 6.5 kcal/mol was possible for the same conformations available to the unsubstituted dilactones *syn*-**178** and *anti*-**178**. An unknown factor in this analysis is the effect of replacing two $-CH_2CH_2-$ units present in cyclooctane with two -O-CO- units in dilactone **178**. While replacement of a methylene group by a heteroatom would not be expected to have a significant impact on the stability of the eight-membered ring conformations discussed above, the effect of substituting two sp^3 hybridized carbons of cyclooctane with two sp^2 hybridized carbons (-CO-) in

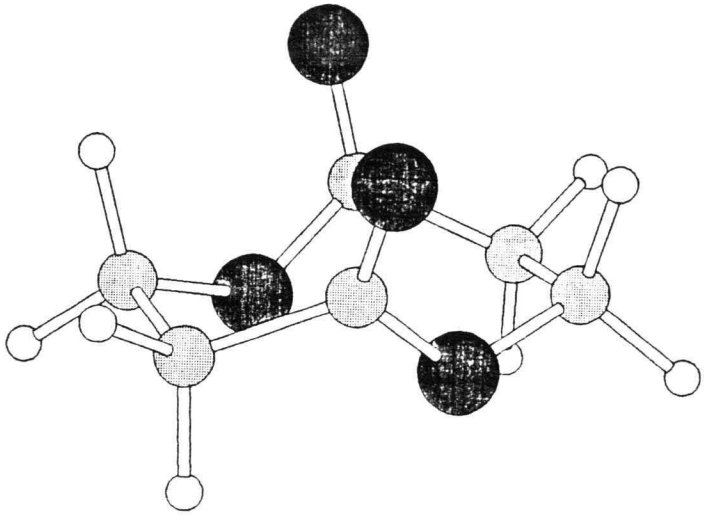
178 could not be predicted. The conceivable risk in extrapolating from cyclooctane to dilactone **178** suggested that a molecular mechanics study of *syn*-**178** and *anti*-**178** would be of value in appraising the accuracy of the starting models.

In 1982 Allinger reported the application of his MM2 force field to the conformational analysis of four-to-eight-membered ring lactones.[93] Comparison of moments of inertia and dipole moments for the model structures calulated using the MM2 force field with experimental values obtained by microwave spectroscopy were in good agreement. This result suggests that the existing force field parameters for the ester functional group accurately represent the lactone subunit in molecules containing this functionality.

Input of models representing *syn*-**178** and *anti*-**178** into the MMX87 force field minimization routine provided the relative energy data given in Table VII and the corresponding structures represented in Figure 11. Comparison of total energy values (E_{tot}) for *syn*-**178** and *anti*-**178** indicates that although the two conformations display the same relative order of stability as cyclooctane with *syn*-**178** (crown) being more stable than *anti*-**178** (chair), the difference in energy (2.9 kcal/mol) is much less than the 6.5 kcal/mol implied by the cyclooctane model. The data in Table VII also show that the energy difference between *syn*-**178** and *anti*-**178** is largely a result of torsional strain (1.8 kcal/mol) and van der Waals interactions (1.7 kcal/mol). The largest contributor to the torsional strain in *syn*-**178** and *anti*-**178** is associated with the atoms composing the ester linkage (1-4 in **178**). In *syn*-**178** the torsional angle formed by atoms 1 to 4 is 38°, while the corresponding value in *anti*-**178** is 36°.



anti-**178**



syn-**178**

Figure 11: Calculated (MMX) minimum energy conformations for *syn*-**178** and *anti*-**178**.

Table VII: Calculated (MMX) total energy and individual energy contributions for *syn*-**178** and *anti*-**178** in kcal/mol.

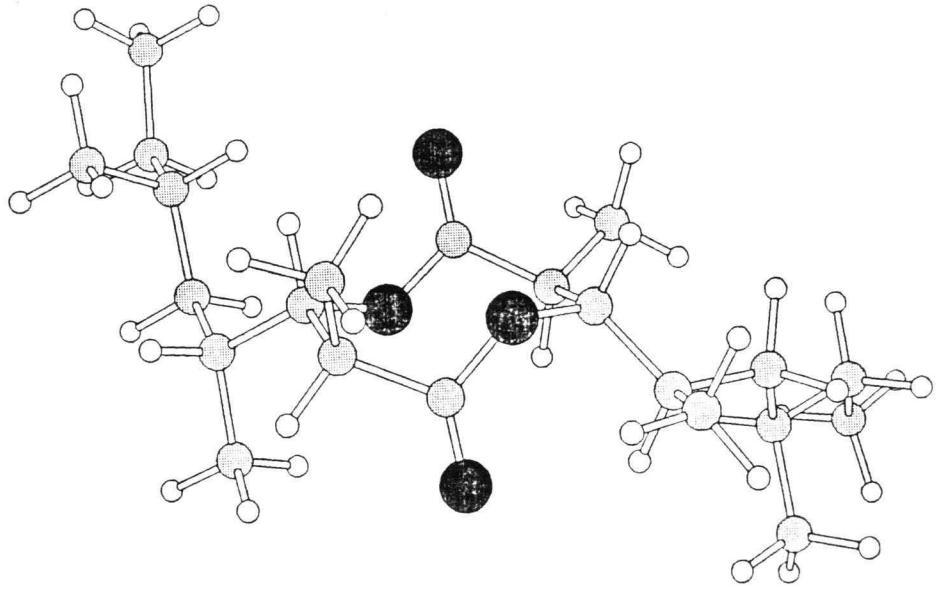
Conformation	E_{tot}	E_s	E_b	E_{sb}	E_{vw}	E_ϕ	E_μ
syn-**178**	18.07	0.63	1.91	0.18	6.36	6.86	2.79
anti-**178**	20.95	0.69	2.30	0.21	8.05	8.69	2.19
/ ΔE /=	2.88	0.06	0.39	0.03	1.69	1.83	0.60

Expanding each of the starting models *syn*-**178** and *anti*-**178**, to include the remaining atoms of dilactone **15**, followed by minimization in the MMX87 force field, afforded the relative energy data presented in Table VIII for *syn*-**15** and *anti*-**15**. The final geometries depicting these conformations are given in Figure 12. These data indicate that the addition of alkyl groups to *syn*-

Table VIII: Calculated (MMX) total energy and individual energy contributions for *syn*-**15** and *anti*-**15** in kcal/mol.

Conformation	E_{tot}	E_s	E_b	E_{sb}	E_{vw}	E_ϕ	E_μ
syn-**15**	34.56	2.86	7.27	0.88	17.67	9.66	2.67
anti-**15**	43.10	3.15	8.54	0.99	19.50	15.41	2.28
/ ΔE /=	8.54	0.29	1.27	0.11	1.91	5.75	0.39

178 and *anti*-**178** results in an energy difference between the *syn*-**15** and *anti*-**15** conformations of 8.5 kcal/mol. Examination of the individual energy contributions (Table VIII) reveals that the predominant factor in this energy difference is torsional strain (5.8 kcal/mol). Note also that the difference in energy between *syn*- **15** and *anti*- **15** due to van der Waals interactions



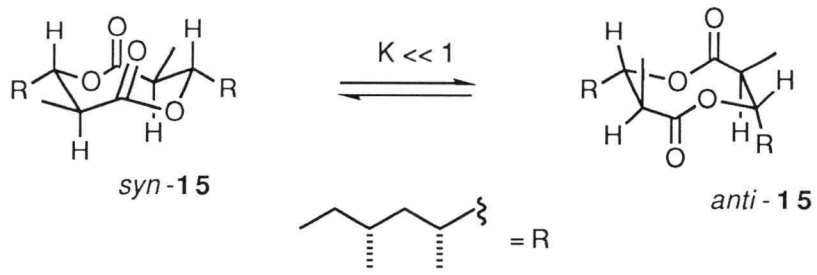
anti-**15**

syn-**15**

Figure 12: Calculated (MMX) minimum energy conformations for *syn*-**15** and *anti*-**15**.

(1.9 kcal/mol) has remained essentially the same as found between the unsubstituted dilactone conformations *syn*- **178** and *anti*- **178**. One source of increased torsional strain in *anti*-**15** can be seen in Figure 12 as eclipsing interactions between the ring alkyl groups and adjacent hydrogen atoms. One set of ring substitutents are eclipsed (ϕ Me-H = 7°, ϕ alkyl-H = 2°) while in the remaining set the groups are positioned between an eclipsed and a staggered arrangement (ϕ Me-H = 37°, ϕ alkyl-H = 38°). In contrast, the equivalent set of dihedral angles associated with *syn*-**15** are all near the ideal value of 60 degrees (60 ± 7°).

An important consequence of this study is that the difference in total energy between *syn*-**15** and *anti*-**15** can explain why only the *syn* conformer is observed spectroscopically. Assuming a conformational equilibrium between *syn*-**15** and *anti*-**15** (Figure 13) and that $\Delta S=0$, the calculated difference in conformational energy of 8.5 kcal/mol yields an equilibrium constant (K) of 5.8 X 10^{-7} for this system at room temperature. Thus, the concentration of *anti*-**15** implied by this value is below the limit of detection by NMR spectroscopy.



syn - **15**

anti - **15**

Figure 13: Conformational equilibrium between *syn*-**15** and *anti*-**15**.

A second issue addressed by this analysis was the facile cyclization of **1** to **15**. The ease of ring closure via reaction at the ends of an open chain molecule may be evaluated in a qualitative manner by considering two independent parameters: the probability of the reacting centers meeting one another and the strain encountered in closing the ring.[94] While the probability of cyclization taking place is expected to decrease as the number of intervening atoms linking the two reactive sites increases, the strain energy component involved with ring closure will vary with ring size. The rate and feasibility of intramolecular reactions, especially as they relate to enzymatic systems, has been the subject of considerable research and debate. While Menger[95] argues "that the rate of reaction between functionalities A and B is proportional to the *time* that A and B reside within a critical *distance*," Houk[96] considers the strain energy present in the transition state of the rate determining step to be the dominant factor. The use of molecular mechanics calculations to model the transition states of organic reactions has been demonstrated, but the method is limited at present by the lack of force field parameters for all but a few reactions.[96,97] The absence of transition state parameters for the conversion of **1** to **15** did not allow analysis of this reaction by the Houk approach. However, the time and distance criteria considered important by Menger appeared amenable to investigation by molecular mechanics techniques.

The starting point for this analysis was a conformational study of bourgeanic acid (**1**). Minimization of a model of **1** using the MMX87 force field led to a group of conformers with energies within 2 kcal/mol of each other. It should be noted that an exhaustive search for a global minimum was not conducted. Instead structures found in local minima were modified by rotation of selected dihedral angles and subjected to the minimization procedure until

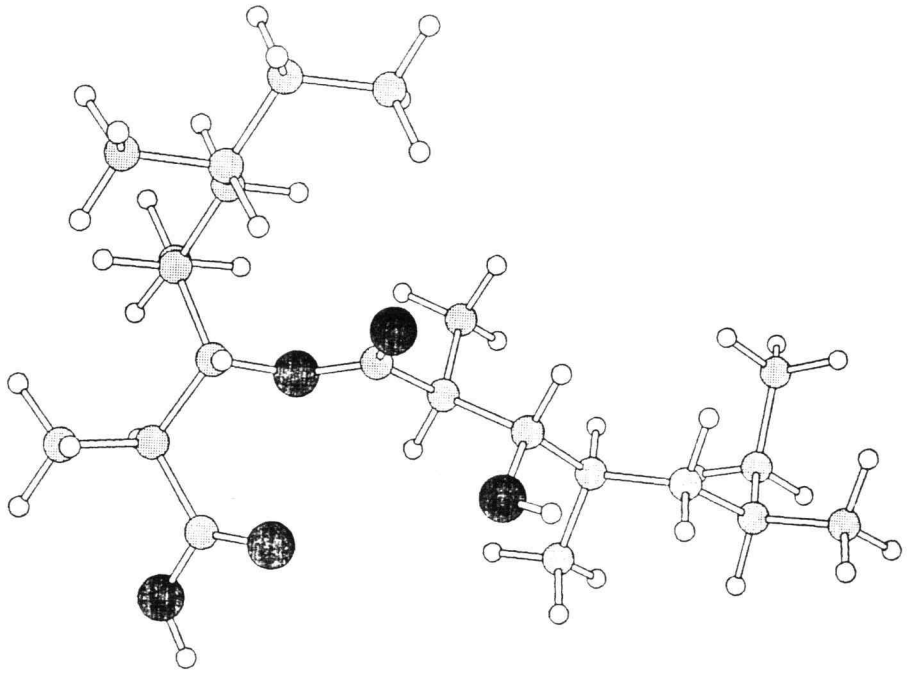
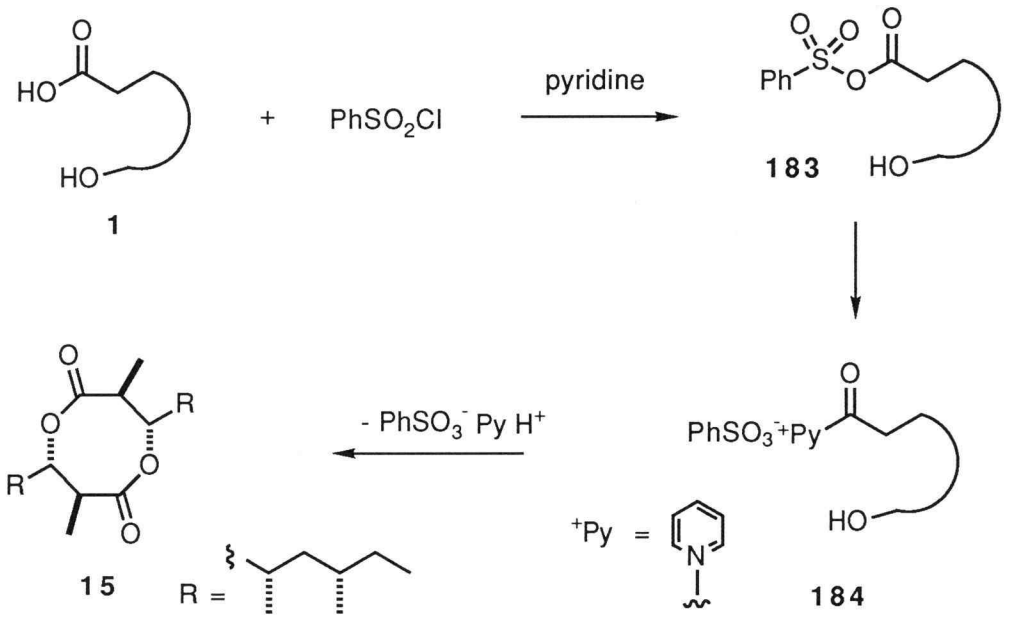


Figure 14: Calculated (MMX) minimum energy conformation for bourgeanic acid.

the lowest energy conformer in each series was located. A representative of this group is shown in Figure 14. Conspicuous in this view of **1** is the perpendicular arrangement of the carboxylic acid and ester chains. Also noteworthy is that the hydrogen atoms connected to carbons which become ring atoms upon cyclization to **15** are in an *anti* relationship, a fact in agreement with the 9.6 Hz coupling observed for the protons in the carboxylic acid subunit (5.16 and 2.79 ppm), and 9.4 Hz coupling observed for the protons of the ester chain (3.71 and 2.60 ppm) in the ^{1}H NMR spectrum of **1** (Figure 7). A distinctive feature of this particular conformation is the short distance (4.6Å) separating the oxygen of the alcohol function and the carbon of the carboxylic acid group. Although the stability of the conformation implied in this ground state representation of **1** cannot be used in a discussion of the

transition state energetics for ring closure to **15**, the O···CO distance in this model is less than that expected for an unsubstituted ω-hydroxy carboxylic acid.

Scheme XXXIV



The influence of alkyl groups on the rate of intramolecular reactions is often discussed in terms of the "*gem*-dialkyl effect." According to this theory, the rate of cyclization of a bifunctional molecule is enhanced relative to the unsubstituted analog due to favorable enthalpy and entropy changes upon ring closure.[98] Experimental evidence supports this effect in reactions involving the formation of three to six-membered rings.[99] Unfortunately, this theory has not been tested sufficiently in the area of medium-ring cyclizations[100] to allow direct application of its principles to the present study with any confidence. Therefore, this analysis was continued using the guidelines specified in the Menger hypothesis.[95] The model employed in this

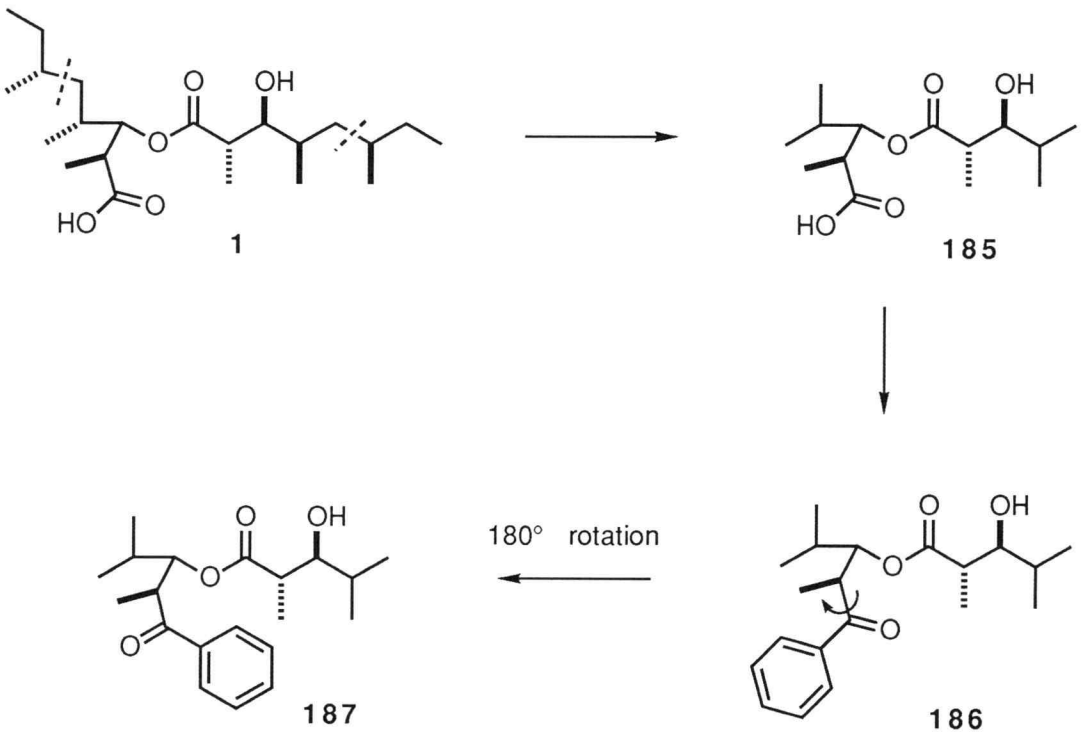
approach was considered representative of the reactive intermediate involved in the cyclization of **1** to **15**.

In a series of articles describing the reaction of nucleophiles with acetic anhydride in pyridine, Fesht and Jenks[101] concluded that an acylpyridinium species is the reactive intermediate under these conditions. Based on this work it is reasonable to assume that conversion of **1** to **15** by treatment with phenylsulfonyl chloride (Scheme XXXIV) proceeds via initial formation of a mixed acyl-sulfonyl anhydride **183**, followed by reaction with pyridine, to give the acylpyridinium intermediate **184**. Intramolecular addition of the alcohol oxygen in **184** to the carbonyl carbon of the acylpyridinium group and collapse of the resulting tetrahedral intermediate gives **15**.

The absence of force field parameters capable of describing the acylpyridinium moiety depicted in **184** required the use of an alternate model. As a result, a phenyl ketone group was chosen as a substitute for the acylpyridinium subunit. The model studied was derived from **1** as outlined in Scheme XXXV. Removal of the isobutyl groups at the end of each chain in **1** afforded the diisopropyl analog **185**. Deletion of these atoms was carried out to shorten the calculation times for each model using the MMX87 force field. This modification was justified by assuming that the steric effects of the isopropyl groups in **185** will be similar in magnitude to the C_7H_{15} substituents in **1**. Replacement of the carboxylic acid function in **185** by a phenyl ketone afforded **186** with the carbonyl dipoles in a *syn* orientation. Assuming that ring closure to give **15** can take place by addition of the alcohol oxygen to either face of the carbonyl system, rotation of the phenylketo moiety in **186** by 180° provided a second model **187** for study. In this model the dipoles of the carbonyl groups have an *anti* relationship.

Close inspection of **186** and **187** revealed that the distance between the reacting centers, the alcohol oxygen and the ketone carbonyl carbon, could be varied simply by rotating the bond connecting the ester carbonyl carbon and the carbon bearing the methyl group. It should be noted that this

Scheme XXXV



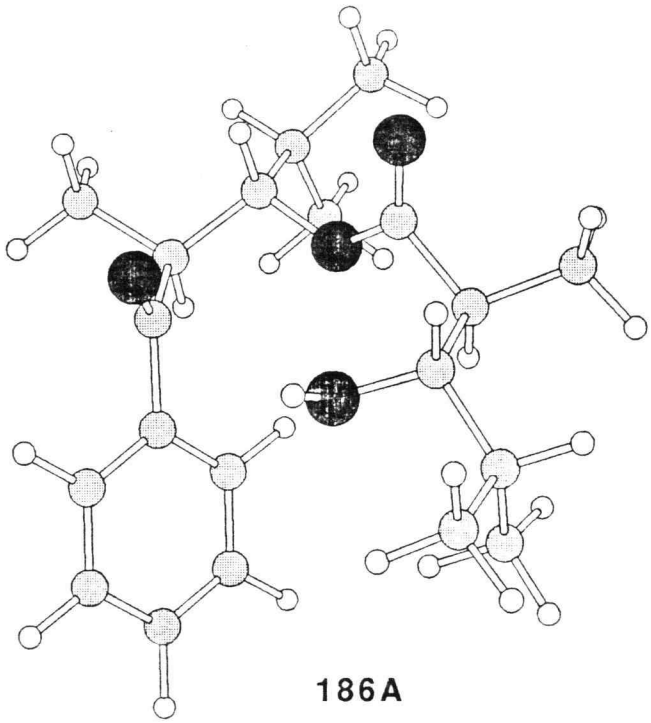
rotation preserves the *anti* relationship between the C-2 and C-3 hydrogen atoms in **1**, as suggested by the coupling constant for these protons. Following this protocol, three minimum energy conformations were located for both **186** and **187**. The total energy and intramolecular O···CO distances are listed for each conformer in Table IX. Examination of the atom distances indicates that the conformer **186A** and **187A** (Figure 15) have intramolecular O···CO distances significantly shorter than those in the remaining models.

Table IX: Calculated (MMX) total energy, heat of formation, and intramolecular O···CO distances for **186A-C** and **187A-C.**

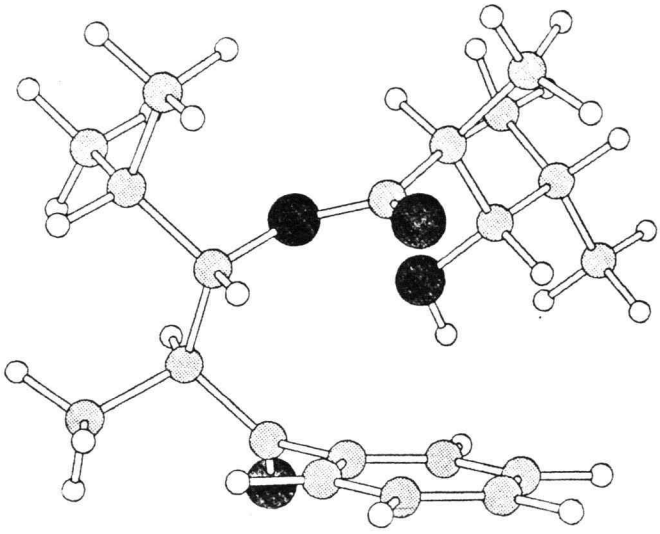
Conformer	E_{tot} (kcal/mol)	ΔH_f (kcal/mol)	Distance$_{(O...CO)}$ (Å)
186A	25.844	-95.837	3.10
186B	27.152	-94.529	5.15
186C	27.624	-94.057	5.55
187A	27.349	-94.332	3.48
187B	28.519	-93.162	5.98
187C	26.443	-95.239	5.46

The O.....CO distance in **186A** is very near what Menger terms the "critical distance" (3.0 Å) for a reaction of this type. His choice of this value is based upon an analysis of X-ray structures by Burgi[102] in which non-bonding O···CO interactions were observed as deviations of the carbonyl group carbon from planarity when O···CO distances were approximately 3.0 Å or less. By this argument, the hydroxyl function in **186A** and **187A** is ideally positioned to react and give dilactone **15**. Thus, the distance criterion in the Menger hypothesis appears to be satisfied by conformations **186A** and **187A**.

It should be emphasized that in this theory the rate of an intramolecular reaction is dependent on the *distance* and the *residence time* of a reactive conformation. Although the total energy values given in Table IX allow a qualitative assessment of conformational preferences, a relative *time* factor is not obvious from the raw data. However, if the *residence time* may be equated to the effective concentration of a reactive conformer, then the mole fraction associated with this conformation will provide a quantitative estimate of this



186A



187A

Figure 15: Calculated (MMX) minimum energy conformations for **186A** and **187A**.

value. The mole fractions of any number of conformations available to a molecule may be determined[103] using the Boltzman equation (eq 38) where

$$\frac{N_i}{N_j} = e^{-(E_i - E_j) / RT} \qquad (38)$$

N_i and N_j are the mole fractions of conformers (i) and (j), E_i and E_j are expressed in units of cal deg^{-1} mol^{-1} and degrees Kelvin respectively. If the difference in entropy between conformations is considered to be insignificant,

$$N_1 + N_2 + \cdots N_i = 1 \qquad (39)$$

then the energy values required for use in equation 38 are simply the enthalpies associated with each conformer. In the present analysis, the DH_f values available in the MMX87 output files of each conformer studied were used to generate the mole fraction ratios defined by equation 38. The mole

Table X: Calculated (MMX) heat of formation, mol fractions, and intramolecular O···CO distances for **186A-C** and **187A-C**.

Conformer	ΔH_f (kcal/mol)	N_i	Distance$_{(O...CO)}$(Å)
186A	-95.837	0.654	3.10
186B	-94.529	0.059	5.15
186C	-94.057	0.025	5.55
187A	-94.332	0.041	3.48
187B	-93.162	0.005	5.98
187C	-95.239	0.217	5.46

fraction (N_i) of each conformation listed in Table X was extracted from these ratios by using equation 39. These data indicate that the two model conformations with favorable intramolecular O···CO distances, **186A** and **187A**, are occupied by 70% of the conformers originating from the minimum energy conformation of **1**. Thus, the *residence time* estimated by this approach also appears to favor the cyclization of **1** to **15**.

In summary, the conformational analysis of dilactone **15** has provided an explanation of why only a single conformation of **15** is observed by ^1H and ^{13}C NMR spectroscopy. In this instance, the relative energy difference calculated for the *syn* and *anti* dilactone conformations (8.5 kcal/mol) places the population of *anti* conformer below the detection limit of the NMR method. Also the facile cyclization of **1** to **15** has been shown to be amenable to study with molecular mechanics techniques. Within the framework of the Menger hypothesis[95] this analysis supports the unexpectedly facile formation of **15** from **1**. In particular, it suggests why this cyclization is more probable than would have been predicted based upon current knowledge related to the synthesis of eight-to-eleven-membered rings.

IV. EXPERIMENTAL

General

Starting materials and reagents purchased from commercial suppliers were generally used without further purification. When necessary, liquids were distilled under argon and solids were recrystallized from the appropriate solvent. Solvents were dried by distillation from the appropriate drying agent immediately prior to use. Toluene, tetrahydrofuran (THF), and ether were distilled from potassium and benzophenone under an argon atmosphere. Diisopropylamine, triethylamine, diisopropylethylamine, 2,6-lutidine, dimethylsulfoxide (DMSO), hexamethylphosphoramide (HMPA), tetramethylethylene diamine (TMEDA), and dichloromethane were distilled from calcium hydride under argon. Pyridine was distilled from barium oxide under argon. All solvents used for routine isolation of products and chromatography were reagent grade and glass distilled. Moisture and air sensitive reactions were carried out under an atmosphere of argon.

Concentration under reduced pressure refers to the use of a rotary evaporator at water aspirator pressures. Residual solvent was removed by vacuum pump at pressures less than 2 torr. Reaction flasks were flame dried under a stream of argon. Syringes were oven dried at 160 °C and cooled to room temperature in a desiccator over anhydrous calcium sulfate.

Analytical thin layer chromatography (TLC) was conducted using 1.5 x 5.0 cm precoated aluminum E. Merck TLC plates (0.2 mm layer thickness of silica gel 60 F-254). Spots were visualized by ultraviolet light, exposure to iodine vapors, or by heating the plate after dipping in a 3-5% solution of phosphomolybdic acid in ethanol, or a 1% solution of vanillin in 0.1M H_2SO_4

in methanol. Flash chromatography was carried out using E. Merck silica gel 60 (230-400 mesh ASTM).

Melting points were measured using a Büchi melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 243 polarimeter at ambient temperature using a 1 decimeter cell of 1 mL capacity. Infared (IR) spectra were recorded with a Nicolet 5DXB FT-IR spectrometer. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained using either an IBM NR-80F, Bruker AC-300, or Bruker AM-400 spectrometer. All chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane using the δ scale. ^{1}H NMR spectral data are reported in the order of: chemical shift, number of protons, multiplicity, (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and b = broad), and coupling constant (J) in Hertz. Mass spectra (MS) were obtained using either a Varian MAT CH-7 or a Finnigan 4500 spectrometer and an ionization potential of 70 eV. High resolution mass spectra were recorded using a Kratos MS-50 TC spectrometer. Elemental analyses were performed by Desert Analytics, Tucson, Arizona.

(4*R*,5*S*)-3-(Propionyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (**22**). To a solution of oxazolidinone **21** (890 mg, 5.02 mmol) in 16.5 mL of THF at 0 °C was added a solution of *n*-butyllithium (2.0 mL, 5.0 mmol; 2.5 M solution) in hexane. The resulting solution was stirred for 10 min before being cooled to -78 °C and propionyl chloride (465 mg, 5.02 mmol) added as a solution in 1 mL of THF. After 2 h the reaction was warmed to room temperature and quenched with 10% aqueous NH_4Cl. Extraction with CH_2Cl_2 and drying of the organic layers (Na_2SO_4) was followed by concentration under reduced pressure to a viscous oil. Column chromatography (30% EtOAc/hexane) afforded 917 mg (79%) of **22** as a

colorless oil: R_f 0.54 (EtOAc/hexane, 1:1); $[\alpha]_D$ +41.9° (c 2.00, CH_2Cl_2), [lit[38] $[\alpha]_D$ +43.8° (c 2.00, CH_2Cl_2)]; IR (neat) 2984, 1785, 1705, 1247, 768, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.30 (5H, m), 5.67 (1H, d, J=7.3 Hz), 4.77 (1H, m, J=6.7 Hz), 3.00 (2H, m), 1.19 (3H, t, J=7.4 Hz), 0.90 (3H, d, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 153.1, 133.4, 128.8, 128.7, 125.7, 79.0, 54.8, 29.3, 14.6, 8.3.

(2'*R*,3'*S*,4*R*,5*S*)-3-(2'-Methyl-3'-hydroxybutanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (**23**). To a solution of triethylborane (0.56 g, 5.7 mmol) in 4.0 mL of CH_2Cl_2 at 0 °C was added trifluoromethanesulfonic acid (0.86 g, 5.7 mmol) neat with stirring. The solution was stirred at room temperature for 1 h, cooled to 0 °C, and oxazolidinone **22** (1.2 g, 5.2 mmol) was added as a solution in 8.0 mL of CH_2Cl_2 followed by diisopropylethyl amine (0.80 g, 6.2 mmol). The resulting solution was stirred at 0°C for 30 min, cooled to -78 °C, and acetaldehyde (0.25 g, 5.7 mmol) was added using a precooled syringe. After 30 min at -78 °C the solution was warmed to room temperature and stirred for 1.5 h. The reaction was quenched by pouring the solution into a rapidly stirred solution of 25 mL of MeOH and 12 mL of an aqueous pH 7 phosphate buffer at 0 °C. Addition of 14 mL of 30% aqueous H_2O_2 to the mixture and stirring at 0 °C for 1 h was followed by extraction with Et_2O, washing of the combined organic layers with H_2O, saturated aqueous NaCl, and drying over $MgSO_4$. Concentration of the solution under reduced pressure afforded a pale yellow tar which solidified upon standing. Crystallization of the solid from EtOAc/hexane provided 1.16 g (81%) of **23** as colorless prisms: R_f 0.37 (EtOAc/hexane, 1:1); mp 115-116 °C (EtOAc/hexane); $[\alpha]_D$ +19.7° (c 2.00, CH_2Cl_2); IR (KBr) 3470, 2977, 1774, 1664, 1457, 1203, 768, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.27 (5H, m), 5.69 (1H, d, J=7.3 Hz), 4.81 (1H, m, J=6.8 Hz), 4.19 (1H, m), 3.76 (1H, m),

2.97 (1H, s, exchangeable w/D_2O), 1.25 (3H, d, J=6.8 Hz), 1.22 (3H, d, J=6.2 Hz), 0.89 (3H, d, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 152.8, 133.1, 128.9, 128.8, 125.6, 78.9, 67.7, 54.7, 43.2, 19.7, 14.4, 10.4; MS m/z (rel intensity) 277 (M^+, 1), 259 (10), 233 (100).

(2'*R*,3'*S*,4*R*,5*S*)-3-[(1,1-Dimethylethyl)dimethylsiloxy]-2'-methylbutanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (**24**). To a solution of **23** (1.00 g., 3.61 mmol) in 5.0 mL of DMF was added *t*-butyldimethylsilyl chloride (652 mg, 4.33 mmol) and imidazole (614 mg, 9.02 mmol) with stirring. After 24 h at room temperature the solution was poured into water and extracted with Et_2O. Concentration of the dry ($MgSO_4$) solution and column chromatography (10% EtOAc-hexane) afforded 1.36 g (96%) of **24** as a crystalline solid: R_f 0.55 (30% EtOAc/hexane); mp 46-47 °C (EtOAc/hexane); $[\alpha]_D$ - 1.6° (c 1.61, CH_2Cl_2); IR (KBr) 2964, 1774, 1693, 1352, 835, 771, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.30 (5H, m), 5.62 (1H, d, J=7.0 Hz), 4.73 (1H, m), 4.10 (1H, m), 3.84 (1H, m), 1.20 (3H, d, J=6.0 Hz), 1.19 (3H, d, J=6.7 Hz), 0.90 (3H, d), 0.89 (9H, s), 0.07 (3H, s), 0.05 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 152.8, 133.3, 128.7, 125.6, 78.8, 69.8, 55.3, 45.2, 25.8, 21.7, 18.0, 14.3, 12.4, -4.4, -4.9.

(2*R*)-(E)-3-Methyloxiranemethanol 4-Nitrobenzoate (**35**). Into a flame dried 500 mL three-necked flask was placed powdered 3Å molecular sieves and 100 mL of CH_2Cl_2. The resulting slurry was cooled to -20 °C and (-)-diisopropyl tartrate (1.36 g, 5.81 mmol) was added, followed by (*E*)-2-buten-1-ol (**34**) (7.00 g, 97.0 mmol) and titanium(IV)isopropoxide (1.37g, 4.82 mmol). After stirring the mixture for 15 min cumene hydroperoxide (36.9 g, 194.0 mmol) was added over 1.5 h via cannula. The resulting mixture was stirred for 2 h before the excess hydroperoxide was destroyed by the slow addition (1.5 h) of trimethylphosphite (18.1 g, 146 mmol) at a rate which did not let the

reaction temperature rise above -20 °C. Triethylamine (11.8 g, 116 mmol) was then added, followed by *p*-nitrobenzoyl chloride (18.0 g, 97.0 mmol) as a solution in 30 mL of CH_2Cl_2. The yellow mixture was warmed to 0 °C, stirred for 1 h, and filtered through a pad of Celite. The filtrate was washed with 10% aqueous tartaric acid (3x35 mL), saturated aqueous $NaHCO_3$ (3x30 mL), and saturated aqueous NaCl before being dried over Na_2SO_4. The mixture was filtered through a short pad of silica gel and concentrated under reduced pressure to give a viscous yellow oil. Further concentration under reduced pressure (2 mm) and at 60 °C for 7 h, followed by standing overnight at 5 °C, afforded a solid. Crystallization from Et_2O provided 11.5 g (50%) of **35** as pale yellow needles: R_f 0.27 (30% EtOAc/hexane); mp 103-104 °C (Et_2O) [lit[27] 103.5-104 °C (Et_2O)]; $[\alpha]_D$ +48.0° (c 3.78, $CHCl_3$) [lit[27] $[\alpha]_D$ - 48.5° (c 3.77, $CHCl_3$) for 2*S* isomer > 98% ee]; IR (KBr) 2987, 1727, 1526, 1286, 871, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32-8.23 (4H, m), 4.71 (1H, dd, J=3.0, 12.1 Hz), 4.20 (1H, dd, J=6.9, 12.1 Hz), 3.10 (1H, m), 3.04 (1H, m), 1.39 (3H, d, J=5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 150.7, 135.1, 130.9, 123.6, 66.1, 56.1, 52.6, 17.21.

(2*R*)-(E)-3-Methyloxiranemethanol *t*-Butyldimethylsilyl ether (**29**). To a suspension of epoxide **35** (119 mg, 0.50 mmol) in 5.0 mL of MeOH was added solid K_2CO_3 (6.9 mg, 0.05 mmol) with stirring. After 5 min the clear colorless solution was concentrated under reduced pressure and the residue was dissolved in 5.0 mL of CH_2Cl_2. To this solution was added *t*-butyldimethylsilyl chloride (181 mg, 1.20 mmol), triethylamine (121 mg, 1.20 mmol), and 4-N,N-dimethylaminopyridine (DMAP) (12 mg, 0.10 mmol). Stirring for 10.5 h at room temperature was followed by washing the organic layer with water and saturated aqueous NaCl before drying over Na_2SO_4. Concentration under reduced pressure and column chromatography (10%

EtOAc/hexane) afforded 54.6 mg (54%) of **29** as a colorless oil: R_f 0.60 (30% EtOAc/hexane); $[\alpha]_D$ +13.4° (c 4.49, $CHCl_3$), [lit[27] $[\alpha]_D$ +13.1° (c 7.33, $CHCl_3$) 92% ee); IR (neat) 2958, 1472, 1255, 1087, 837, 778 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 3.72 (2H, m), 2.85 (2H, m), 1.31 (3H, d, J=5 Hz), 0.90 (9H, s), 0.07 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.5, 59.6, 52.2, 25.9, 18.3, 17.3, -5.3.

(*E*)-2-Methyl-1-iodo-1-butene (**38**). To a solution of zirconocene dichloride (1.46 g, 5.00 mmol) in 12.5 mL of 1,2-dichloroethane was added trimethylaluminum (0.72 g, 10.0 mmol) via cannula. Stirring for 10 min at room temperature gave a clear yellow solution. Cooling of this solution to 0 °C was followed by the addition of 1-butyne (**36**) (0.27 g, 5.00 mmol) via cannula. Warming to room temperature with stirring overnight (24 h) gave a deep yellow solution which was cooled to 0 °C and treated with iodine (1.52 g, 6.00 mmol) as a solution in 8.0 mL of THF. Stirring for 30 min at 0 °C was followed by warming to room temperature where the reaction was quenched by the careful addition (a vigorous effervesence occurred) of H_2O. Extraction with ether was followed by washing with saturated aqueous NaS_2O_3, water, and saturated aqueous NaCl. Drying of the organic layer over $MgSO_4$, concentration under reduced pressure, and column chromatography using pentane as an eluant afforded 166 mg (17%) of **38** as a pale orange liquid: IR (neat) 3057, 2968, 1619, 1458, 802, 766, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (1H, m, J=1.3 Hz), 2.22 (2H, q, J=6.4 Hz), 1.84 (3H, s), 1.04 (3H, t, J=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 73.6, 32.5, 23.9, 12.6.

(2*R*',3*R*',4*R*,5*S*)-(*E*)-3-(2,4-Dimethyl-3-hydroxy-4-hexenoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (**41**). To a solution of triethylborane (231 mg, 2.36 mmol) in 1.5 mL of CH_2Cl_2 at 0 °C was slowly added neat trifluoromethanesulfonic acid (354 mg, 2.36 mmol). After stirring for 1 h at room temperature oxazolidinone **22** (500 mg, 2.14 mmol) was added

as a solution in 3.0 mL of CH_2Cl_2 followed by the addition of ethyldiisopropylamine (333 mg, 2.58 mmol) in 0.5 mL of CH_2Cl_2. The solution was stirred at 0 °C for 30 min, cooled to -78 °C, and (*E*)-2-methyl-2-butenal (**43**) (200 mg, 2.38 mmol) was added as a solution in 0.5 mL of CH_2Cl_2. Stirring for 30 min at -78 °C was followed by 2 h at room temperature, at which time the reaction was quenched by pouring the solution into 10 mL of MeOH and 4 mL of an aqueous pH 7 phosphate buffer at 0 °C. Addition of 6 mL of 30% aqueous H_2O_2 to this mixture and stirring for 1 h at 0 °C was followed by extraction with CH_2Cl_2, washing of the combined organic layers with saturated aqueous NaCl and drying over $MgSO_4$. Concentration of the dried solution under reduced pressure and column chromatography (2-5% EtOAc/CH_2Cl_2) afforded 477 mg (70%) of **41** as a viscous oil. Crystallization from Et_2O/hexane provided colorless needles: R_f 0.28 (2% EtOAc/CH_2Cl_2); mp 86-87 °C (Et_2O/hexane); $[\alpha]_D$ + 35.5° (c 1.70, $CHCl_3$); IR (neat) 3490, 2984, 1779, 1699, 1364, 1196, 989, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.30 (5H, m), 5.68 (1H, d, J=7.2 Hz), 5.64 (1H, m, J=1.3, 6.6 Hz), 4.78 (1H, m, J=6.7 Hz), 4.38 (1H, m), 3.98 (1H, dq, J=3.8, 7.0 Hz), 1.65 (6H, m), 1.16 (3H, d, J=7.0 Hz), 0.91 (3H, d, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 152.6, 134.3, 133.1, 128.8, 128.7, 125.6, 120.5, 78.9, 75.5, 54.9, 40.7, 14.3, 13.04, 13.02, 10.4; MS m/z (rel intensity) 317 (M^+,8), 233 (44), 134 (33), 118 (64), 57 (100).

(2'*R*,3'*R*,4*R*,5*S*)-(*E*)-3-(3'-Acetoxy-2',4'-dimethyl-4-hexenoyl) -4-methyl-5-phenyl-1,3-oxazolidin-2-one (**44**). A solution of **41** (71 mg, 0.22 mmol), acetic anhydride (46 mg,0.45 mmol), Et_3N (45 mg, 0.45 mmol), and 4-N,N-dimethylaminopyridine (7 mg, 0.06 mmol) in 0.5 mL of CH_2Cl_2 was stirred for 11 h at room temperature. Dilution with CH_2Cl_2 was followed by washing with 5% aqueous HCl, saturated aqueous $NaHCO_3$,

H_2O, and drying over $MgSO_4$. Concentration under reduced pressure gave a viscous oil which on trituration with 20% EtOAc-hexane afforded 78 mg (96%) of **44** as a colorless solid: R_f 0.45 (30% EtOAc/hexane); needles, mp 107.5-108 °C (Et_2O/hexane); $[\alpha]_D$ +9.0° (c 1.20, $CHCl_3$); IR (KBr) 2977, 1782, 1720, 1700, 1235, 1195, 957, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (3H, m), 7.32 (2H, m), 5.70 (1H, d, J=7.1 Hz), 5.59 (1H, m, J=6.8 Hz), 5.57 (1H, d, J=5.2 Hz), 4.62 (1H, m, J=6.6 Hz), 4.23 (1H, dq, J=5.2, 6.9 Hz), 2.09 (3H, s), 1.68 (3H, d, J=0.8 Hz), 1.64 (3H, m, J=6.7 Hz), 1.13 (3H, d, J=6.8 Hz), 0.88 (3H, d, J=6.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.8, 170.3, 153.1, 133.2, 131.5, 128.68, 128.66, 125.6, 122.1, 79.0, 55.4, 40.2, 21.0, 14.4, 13.1, 12.8, 10.8; MS m/z (rel intensity) 359 (M^+, 0.6), 299 (54), 240 (72), 134 (65), 118 (100).

(5'*S*,2'*R*,4*R*,5*S*)-(*E*)-3-(2',4'-Dimethyl-5-acetoxy-3-hexenoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (**45**). A solution of **44** (47 mg, 0.13 mmol) and $PdCl_2(CH_3CN)_2$[104] (22 mg, 0.08 mmol) in 2.0 mL of THF was stirred at room temperature for 18 h. The brown solution was filtered through a short plug of silica gel, concentrated under reduced pressure, and the residue chromatographed on silica gel (hexane-EtOAc-CH_2Cl_2, 16:3:1) to give 24.7 mg (53%) of recovered **44**, 3.7 mg (9%) of **45**, and 13 mg of a 1:1 mixture of **44** and **45**. Compound **45**: R_f 0.27 (hexane-EtOAc-CH_2Cl_2, 8:2:1); $[\alpha]_D$ -30.3° (c 0.37, $CHCl_3$); IR (neat) 2984, 1783, 1734, 1701, 1238, 1196 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.30 (5H, m), 5.65 (2H, dd, J=7.3 Hz), 5.26 (1H, q, J=6.4 Hz), 4.75 (1H, m, J=6.7 Hz), 4.68 (1H, dq, J=6.9, 9.4 Hz), 2.06 (3H, s), 1.72 (3H, d, J=1.3 Hz), 1.31 (3H, d, J=6.5 Hz), 1.27 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 170.2, 152.6, 136.9, 133.3, 128.8, 128.7, 125.6, 125.2, 78.9, 74.6, 55.1, 36.9, 21.4, 19.1, 18.2, 14.4, 12.7; MS m/z (rel intensity) 299 (48), 240 (M^+ - CH_3CH=CHPh, 100), 134 (33), 118 (57).

(2'*R*,4*R*,5*S*)-(E)-3-[2',4'-Dimethyl-5'-(phenylsulfinyl)-3'-hexenoyl]-4-methyl-5-phenyl-1,3-oxazolidin-2-one. Sulfoxide (46). To a solution of **41** (215 mg, 0.68 mmol) in 3.4 mL of CH_2Cl_2 was added Et_3N (137 mg, 1.35 mmol). The solution was cooled to -78 °C and phenylsulfenyl chloride[105] (157mg,1.07 mmol) added as a solution in 0.2 mL of CH_2Cl_2. Stirring at -78 °C for 15 min was followed by warming to room temperature. The reaction was quenched after 30 min by the addition of 3 mL of an aqueous pH 7 phosphate buffer. Extraction with CH_2Cl_2, drying of the organic phase over $MgSO_4$, and concentration under reduced pressure gave a clear viscous oil. Column chromatography (10% EtOAc/ CH_2Cl_2) afforded 220 mg (76%) of **46** as an inseparable 9:5:2:1 mixture of diastereomers: R_f 0.17 (5% EtOAc/CH_2Cl_2); IR (neat) 2977, 1781, 1701, 1137, 1041 cm^{-1}; major diastereomer ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.28 (5H, m), 5.67 (1H, d, J=6.7 Hz), 5.28 (1H, d, J=9.6 Hz), 4.72 (1H, m, J=6.7 Hz), 4.61 (1H, m, J=2.5, 7.0 Hz), 3.38 (1H, q, J=7.0 Hz), 1.75 (3H, d, J=1.3 Hz), 1.44 (3H, d, J=7.0 Hz), 1.32 (3H, d, J=7.0 Hz), 1.08 (3H, d, J=6.8 Hz), 0.88 (3H, d, J=6.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.8, 152.5, 143.1, 134.0, 133.1, 131.0 , 130.1, 129.7, 128.8, 128.7, 125.5, 125.1, 78.8, 70.7, 55.03, 37.13, 17.9, 15.4, 14.4, 12.1; MS m/z (rel intensity) 300 (M^+ - PhSO, 62), 218 (43), 125 (65), 109 (100).

(2*S*,3*R*)-(*E*)-2,4-Dimethyl-3-hydroxy-4-hexen-1-ol (50). To a solution of **41** (125 mg, 0.39 mmol) in 4.0 mL of THF at 0 °C was added anhydrous LiI (116 mg, 0.87 mmol) followed by $NaBH_4$ (33 mg, 0.87 mmol). Stirring for 1 h at 0 °C was followed by quenching with H_2O and addition of NaCl to give two layers. Extraction of the aqueous phase with EtOAc, drying of the combined organic layers over $MgSO_4$, concentration under reduced pressure, and column chromatography (30-50% EtOAc-CH_2Cl_2) of the residual oil afforded 38 mg (67%) of **50** as a colorless oil: R_f 0.26 (EtOAc-

CH_2Cl_2, 1:1); $[\alpha]_D$ +15.0° (c 1.82, $CHCl_3$); IR (neat) 3363, 2967, 1422, 1032, 991 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.51 (1H, m, J=1.2, 6.7 Hz), 4.09 (1H, d, J=3.7 Hz), 3.26 (2H, d, J=4.3 Hz), 2.31 (1H, bs), 2.16 (1H, bs), 1.88 (1H, m, J=1.9, 5.2 Hz), 1.64 (3H, m, J=1.1, 6.7 Hz), 1.60 (3H, s), 0.91 (3H, d, J=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 119.8, 78.9, 66.6, 37.7, 12.9, 12.7, 10.8; MS m/z (rel intensity) 144 (M^+, 7), 126 (14), 111 (15), 85 (100).

(4*R*,5*R*)-(*E*)-3,5-Dimethyl-6-[(1,1dimethylethyl)dimethylsiloxy]-2-hexene-4-ol (**51**). A solution of **50** (94 mg, 0.65 mmol), *t*-butyldimethylsilyl chloride (108 mg, 0.72 mmol), Et_3N (79 mg, 0.78 mmol), and DMAP (3 mg, 0.03 mmol) in 6.5 mL of CH_2Cl_2 was stirred overnight (18 h) at room temperature. The solution was washed with 10% aqueous NH_4Cl, and saturated aqueous NaCl, and was dried over $MgSO_4$. Concentration under reduced pressure and column chromatography (15% EtOAc-hexane) of the residual oil afforded 99 mg (59%) of **51** as a colorless oil: R_f 0.70 (10% EtOAc-CH_2Cl_2); $[\alpha]_D$ +9.9° (c 1.41, $CHCl_3$); IR (neat) 3436, 2957, 1254, 1099, 836, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.22 (1H, m, J=1.3, 6.8 Hz), 4.13 (1H, bs), 3.64 (2H, dq, J=5.4, 10.0 Hz), 2.74 (1H, d, J=2.9 Hz), 1.81 (1H, m, J=2.6, 7.0 Hz), 1.63 (3H, m, J=1.1, 6.8 Hz), 1.57 (3H, s), 0.90 (9H, s), 0.87 (3H, d, J=6.9 Hz), 0.06 (6H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 135.9, 119.3, 78.6, 67.5, 37.6, 25.8, 18.2, 13.0, 10.5, -5.6; MS m/z (rel intensity) 258 (M^+, 5), 201 (31), 109 (77), 75(100).

(5*S*)-(*E*)-6-[(1,1-Dimethylethyl)dimethylsiloxy]-2-(phenylsulfinyl)-3,5-dimethyl-3-hexene. Sulfoxide (**52**). To a solution of **51** (32 mg, 0.12 mmol), and Et_3N (63 mg, 0.62 mmol) in 1 mL of CH_2Cl_2 at -78 °C was added phenylsulfenyl chloride[105] (27 mg, 0.19 mmol) as a solution in 0.05 mL of CH_2Cl_2. The solution was warmed to room temperature after 15 min and the reaction was quenched by the addition of 1 mL of an aqueous pH

7 phosphate buffer. Extraction with CH_2Cl_2 and drying of the organic layers over $MgSO_4$ was followed by concentration under reduced pressure to a viscous oil. Column chromatography (10% EtOAc/CH_2Cl_2) afforded 28 mg (62%) of **52** as an inseparable 9:6:2:1 mixture of diastereomers: R_f 0.13 (2% EtOAc/CH_2Cl_2); IR (neat) 2956, 1254, 1087, 1046, 837, 776 cm^{-1}; major diastereomer; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.44 (5H, m), 4.87 (1H, d, J=9.5 Hz), 3.32 (2H, m), 3.17 (1H, m), 2.47 (1H, m), 1.70 (3H, d, J-1.4 Hz), 1.45 (3H, d, J=7.0 Hz), 0.87 (9H, s), 0.80 (3H, d, J=6.7 Hz), 0.02 (6H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 143.3, 135.1, 130.9, 130.4, 128.6, 125.5 , 124.8, 71.2, 67.5, 35.5, 25.8, 18.3, 16.7, 12.6, -5.36, -5.40; MS m/z (rel intensity) 241 (M^+ - PhSO, 42), 109 (26), 89 (100), 73 (71).

Ethyl (*E*)-2-Methyl-2-butenoate (**66**). A flask equipped with a Dean-Stark trap and charged with (*E*)-2-methyl-2-butenoic acid (**65**) (29.4 g, 0.294 mol), 50 mL of benzene, 60 mL of absolute EtOH, and 6 mL of concentrated H_2SO_4 was heated to reflux for 24 h. The resulting solution was concentrated under reduced pressure to approximately one-half the original volume, diluted with 125 mL of Et_2O, and washed with water, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl before being dried over $MgSO_4$. Concentration under reduced pressure and distillation using a 10 cm Vigreaux column afforded 31.3 g (83%) of **66** as a colorless oil: bp 154-157 °C /760 mm, [lit[39] bp 152-157 °C /760 mm; IR (neat) 2983, 1711, 1653, 1250, 1139, 735 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 6.84 (1H, m), 4.20 (2H, q), 1.78 (6H, m), 1.29 (3H, t).

(*E*)-2-Methyl-2-buten-1-ol (**67**). To a suspension of lithium aluminum hydride (4.7 g, 0.12 mol) in 100 mL of Et_2O at 0 °C was added dropwise over 30 min ester **66** (15.0 g, 0.117 mol) as a solution in 130 mL of anhydrous Et_2O. Stirring for 2 h at room temperature was followed by the

careful addition of 5 mL of H_2O, 5 mL of 15% aqueous NaOH, and finally 15 mL of H_2O. The resulting mixture was filtered, the filter cake washed with Et_2O, and the filtrate concentrated under reduced pressure to give a yellow oil. Distillation under reduced pressure afforded 7.1 g (70%) of **67** as a colorless oil: bp 58-59 °C /20 mm, [lit[40] bp 57-58 °C/23 mm]; IR (neat) 3331, 2977, 1674, 1447, 1007, 830, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.48 (1H, m, J=6.3 Hz), 3.97 (2H, s), 2.07 (1H, s), 1.66 (3H, s), 1.62 (3H, d, J=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 120.4, 68.8, 13.2, 12.9.

(*E*)-1-Bromo-2-methyl-2-butene (**64**). To a suspension of *N*-bromosuccinimide (7.38 g, 41.5 mmol) in 100 mL of CH_2Cl_2 at 0 °C was added neat dimethyl sufide (2.97 g, 47.9 mmol). Stirring for 30 min at 0 °C was followed by cooling of the yellow heterogeneous mixture to -23 °C and the addition of (*E*)-2-methyl-2-buten-1-ol (**67**) (2.75 g, 31.9 mmol) as a solution in 3.0 mL of CH_2Cl_2. After 30 min the mixture was warmed to 0 °C and stirred for an additional 4 h. The mixture was poured over ice, the organic layer separated and washed with saturated aqueous NaCl and dried over $MgSO_4$. Concentration under reduced pressure and column chromatography (100% pentane) afforded 2.8 g (60%) of **64** as a colorless oil: IR (neat) 2918, 1664, 1202, 776, 607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.69 (1H, m, J=6.7 Hz), 3.98 (2H, bs), 1.75 (3H, d, J=1.7 Hz), 1.63 (3H, d, J=7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.9, 115.8, 41.7, 14.3, 13.8.

(*S*)-(+)- Valinol (**69**). To a suspension of $LiAlH_4$ (14.6 g, 0.384 mol) in 330 mL of THF at 0 °C was added in small portions (*S*)-valine (**68**) (30.0 g, 0.256 mol). The mixture was refluxed for 17 h, cooled to room temperature, and diluted with 250 mL of Et_2O. The excess $LiAlH_4$ was destroyed by the careful addition of 15 mL of H_2O followed by 15 mL of 15% aqueous NaOH, and 45 mL of H_2O. Filtration of the mixture and drying of the solution over

K_2CO_3 was followed by concentration under reduced pressure to give a yellow oil. Distillation under reduced pressure using a 15 cm Vigreaux column afforded 19.4 g (73%) of (*S*)-valinol (**69**) as a colorless oil: bp 86-88 °C/6mm [lit[106] 62-67 °C/2.5 mm]; IR (neat) 3288, 2960, 1468, 1386, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.63 (1H, dd, J=3.7, 10.4 Hz), 3.31 (1H, dd, J=8.6, 10.4 Hz), 2.57 (1H, m), 1.69 (1H, septet, J=6.7 Hz), 0.95 (3H, d, J=6.7 Hz), 0.90 (3H, d, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$ δ 64.5, 58.4, 31.7, 19.2, 18.3.

(4*S*)-4-Isopropyl-1,3-oxazolidin-2-one (**70**). To a solution of **69** (15.0 g, 0.145 mol) and Et_3N (14.7 g, 0.145 mol) in 100 mL of DMF was added powdered selenium metal (0.57 g, 7.3 mmol). The resulting mixture was stirred at room temperature while carbon monoxide was bubbled through at a rate of 60 mL/min. After 10 min the selenium had dissolved giving a dark red solution. Oxygen was then bubbled through this solution at a rate of 10 mL/min for 7 h at which time the flow of CO was stopped. The continued flow of O_2 for 15 min resulted in the precipitation of the selenium. Filtration and concentration of the yellow solution under reduced pressure afforded a yellow solid. Crystallization from Et_2O/hexane afforded 10.3 g (55%) of **70** as hygroscopic colorless needles: R_f 0.19 (CH_2Cl_2/EtOAc/CH_3OH, 9:1:1); mp 71-72 °C (Et_2O/hexane) [lit[38] 71-72 °C]; $[\alpha]_D$ +16.8° (c 7.00, $CHCl_3$), [lit[38] $[\alpha]_D$ +14.8° (c 7.00, $CHCl_3$)]; IR (KBr) 3276, 2964, 1752, 1725, 1247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 (1H, bs), 4.45 (1H, t, J=8.7 Hz), 4.10 (1H, dd, J=6.5, 8.7 Hz), 3.61 (1H, q, J=8.7 Hz), 1.73 (1H, septet, J=6.7 Hz), 0.96 (3H, d, J=6.7 Hz), 0.90 (3H, d, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 68.6, 58.4, 32.7, 17.9, 17.6.

(4*S*)-3-(Propionyl)-4-isopropyl-1,3-oxazolidin-2-one (**71**). To a solution of oxazolidinone **70** (5.00 g, 38.7 mmol) in 110 mL of THF at 0 °C was added a solution of *n*-butyllithium (16.1 mL, 38.7 mmol; 2.4 M solution) in

hexane. The resulting solution was stirred for 10 min, cooled to -78 °C, and propionyl chloride (3.76 g, 40.6 mmol) was added as a solution in 5.0 mL of THF. After 2 h at -78 °C the reaction was warmed to room temperature and quenched with 10% aqueous NH_4Cl. Extraction with Et_2O and washing the combined organic layers with saturated aqueous NaCl was followed by drying ($MgSO_4$) and concentration under reduced pressure to give a yellow oil. Column chromatography (30% EtOAc/hexane) afforded 6.4 g, (88%) of **71** as a colorless oil: R_f 0.45 (EtOAc/hexane, 1:1); $[\alpha]_D$ +94.8° (c 8.66, CH_2Cl_2), [lit[38] $[\alpha]_D$ +96.8° (c 8.7, CH_2Cl_2)]; IR (neat) 2967, 1780, 1703, 1247, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.44 (1H, m), 4.25 (2H, m), 2.94 (2H, m), 2.37 (1H, m), 1.17 (3H, t, J=7.5 Hz), 0.92 (3H, d, J=7.0 Hz), 0.88 (3H, d, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 154.1, 63.3, 58.4, 29.1, 28.4, 17.9, 14.6, 8.4.

(2'*S*,4*S*)-(*E*)-3-(2,4-Dimethyl-4-hexenoyl)-4-isopropyl-1,3-oxazolidin-2-one (**72**). A solution of LDA was prepared at 0 °C by the addition of *n*-BuLi (4.3 mL, 6.9 mmol; 1.6 M in hexanes) to a solution of diisopropylamine (0.70 g, 6.9 mmol) in 10.0 mL of THF. Cooling to -78 °C was followed by the addition of **71** (1.20 g, 6.47 mmol) as a solution in 2.0 mL of THF. After 30 min **64** (2.80 g, 18.8 mmol) was added as a solution in 2.0 mL of THF. Stirring for 15 min at -78 °C was followed by stirring for an additional 2 h at -10 °C. The reaction was quenched with 10% aqueous NH_4Cl, extracted with Et_2O, and the combined extracts washed with saturated aqueous NaCl before being dried over $MgSO_4$. Concentration under reduced pressure and column chromatography (25% EtOAc-hexane) of the residual oil afforded 1.27 g (80%) of **72** as a clear colorless oil: R_f 0.40 (30% EtOAc-hexane); $[\alpha]_D$ +64.8° (c 2.11, CH_2Cl_2); IR (neat) 2968, 1781, 1702, 1388, 1238, 1205 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$); δ 5.24 (1H, m, J=1.3, 6.4 Hz), 4.46 (1H, m), 4.22 (2H, m), 4.03 (1H, dd, J=7.1 Hz), 2.50 (1H, dd, J=6.9, 13.3 Hz), 2.29 (1H, m),

1.98 (1H, dd, J=7.6, 13.3 Hz), 1.64 (3H, s), 1.55 (3H, d, J=6.6 Hz), 1.08 (3H, d, J=6.7 (Hz), 0.90 (3H, d, J=7.3 Hz), 0.84 (3H, d, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 153.8, 132.9, 121.2, 63.0, 58.4, 44.2, 35.7, 28.4, 17.9, 16.3, 15.3, 14.5, 13.4; MS m/z (rel intensity) 253 (M^+, 36), 124 (100), 109 (43), 96 (97), 81 (55).

(2*S*)-(*E*)-2,4-Dimethyl-4-hexen-1-ol (**73**). To a solution of **72** (1.00 g, 3.95 mmol) in 22 mL of THF at 0 °C was added $LiAlH_4$ (0.45 g, 11.8 mmol). Stirring at 0 °C for 30 min was followed by the careful addition of 1.0 mL of H_2O at 0 °C, warming to room temperature, and drying over $MgSO_4$. Filtration through a pad of Celite, concentration under reduced pressure, and column chromatography using 5-10% EtOAc-CH_2Cl_2, afforded 398 mg (74%) of **73** as a colorless oil: R_f 0.45 (10% EtOAc-CH_2Cl_2); $[\alpha]_D$ +4.8° (c 2.64, CH_2Cl_2); IR (neat) 3345, 2957, 1668, 1453, 1038, 806 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.23 (1H, dd, J=6.0, 6.6 Hz), 3.44 (2H, m), 2.06 (1H, m), 1.82 (2H, m), 1.58 (6H, m), 0.86 (3H, d, J=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 120.2, 68.5, 44.2, 33.7, 16.7, 15.6, 13.3; MS m/z (rel intensity) 128 (M^+, 43), 97 (45), 95 (64), 81 (26), 70 (63), 58 (100).

The enantiomeric excess of **73** was assessed by ^1H and ^{13}C NMR analysis of the α-methoxy-α-trifluoromethylphenyl acetate (MTPA-ester)[43] prepared by stirring **73** in pyridine with an excess of the (*S*)-MTPA acid chloride (**75**) at room temperature. Aqueous workup and purification by column chromatography afforded **74** as a colorless oil: $[\alpha]_D$ +36.1° (c 2.38, CH_2Cl_2); IR (neat) 2964, 1749, 1273, 1170, 1024, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (2H, m), 7.41 (3H, m), 5.18 (1H, m, J=5.7 Hz), 4.24 (1H, dd, J=4.5, 10.6 Hz), 4.02 (1H, dd, J=6.0, 10.6 Hz), 3.55 (3H, s), 2.02 (2H, m), 1.83 (1H, m), 1.56 (6H, d, J=6.0 Hz), 0.86 (3H, d, J=6.1 Hz) ^{13}C NMR (100

MHz, $CDCl_3$) δ 166.7, 133.0, 128.6, 128.4, 127.4, 124.4 (q, CF_3), 121.9, 121.0, 70.9, 55.4, 43.7, 30.5, 16.7, 15.4, 13.3.

(2*S*)-(*E*)-2,4-Dimethyl-4-hexenal (62). To a solution of $(COCl)_2$ (236 mg, 1.86 mmol) in 2.0 mL of CH_2Cl_2 at -78 °C was added a solution of DMSO (290 mg, 3.71 mmol) in 2.0 mL of CH_2Cl_2. After 5 min **73** (119 mg, 0.93 mmol) was added as a solution in 3.0 mL of CH_2Cl_2. After an additional 10 min Et_3N (564 mg, 5.57 mmol) was added in 2.0 mL of CH_2Cl_2. Stirring for 20 min at -78 °C was followed by stirring at 0 °C for 30 min. The reaction was quenched by the addition of an aqueous pH 7 phosphate buffer followed warming to room temperature. The mixture was filtered and the solid was washed with pentane. The filtrate was washed with H_2O, saturated aqueous NaCl, and dried over $MgSO_4$. Concentration under reduced pressure and column chromatography (20% Et_2O-pentane) of the residual oil afforded 107 mg (91%) of **62** as a pale yellow oil: R_f 0.46 (20% EtOAc-hexane); $[\alpha]_D$ -9.5° (c 5.61, $CHCl_3$); IR (neat) 2975, 2716, 1729, 1455, 1383 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.62 (1H, d, J=2.2 Hz), 5.26 (1H, m), 2.50 (1H, m), 2.43 (1H, dd), 1.98 (1H, m, J=2.2), 1.58 (6H, m), 1.03 (3H, d, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 132.2, 121.5, 44.4, 40.8, 15.5, 13.4, 13.2; MS m/z (rel intensity) 126 (M^+, 7), 111 (22), 84 (47), 69 (100).

(2*S*,3*S*,4*R*)-(*E*)-(2',6'-Dimethylphenyl)-3-hydroxy-2,4,6-trimethyl-6-octenoate (90), and (2*R*,3*R*,4*R*)-(*E*)-(2',6'-Dimethylphenyl)-3-hydroxy-2,4,6-trimethyl-6-octenoate (91). A solution of LDA was prepared at 0 °C by the addition of *n*-BuLi (0.92 mL, 1.47 mmol) to a solution of diisopropylamine (148 mg, 1.47 mmol), in 4.0 mL of THF. The solution was cooled to -78 °C and 2,6-dimethylphenyl propionate[48b] (**87**) (250 mg, 1.40 mmol) added as a solution in 1.0 mL of THF. After 1 h a slurry of anhydrous $CeCl_3$ (618 mg, 1.66 mmol) in 3.0 mL of

THF was added to the enolate and the resulting mixture was stirred for 30 min at -78 °C. A solution of **62** (161 mg, 1.27 mmol) in 1.0 mL of THF was added and after 45 min the reaction was quenched with 2 mL of 10% aqueous NH_4Cl. Extraction with Et_2O, drying of the organic phase ($MgSO_4$), concentration under reduced pressure, and column chromatography of the residue using CH_2Cl_2 afforded 255 mg (66%) of the aldol product as a 1.5:1.0 mixture of diastereomers. Separation of the diastereomers was achieved by HPLC using two 7.8mm x 30 cm μ-Porosil columns in tandem and 5% EtOAc-hexane as eluant (flow rate 3.4 mL/min, chart speed 5 mm/min, UV detection at 295 nm). Major diastereomer (**90**): t_R = 18.0 min; $[\alpha]_D$ - 14.6° (c 2.15, $CHCl_3$); IR (neat) 3529, 1741, 1142, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (3H, m), 5.28 (1H, m, J=5.3 Hz), 3.75 (1H, dd, J=2.9, 9.0 Hz), 2.94 (1H, dq, J=1.7, 7.0 Hz), 2.17 (7H, m), 2.00 (1H, dd, J=7.8, 12.9 Hz), 1.91 (1H, m, J=2.8, 6.9 Hz), 1.59 (6H, m), 1.34 (3H, d, J=7.2 Hz), 0.88 (3H, d, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 148.0, 133.6, 130.0, 128.6, 125.8, 120.1, 74.9, 44.4, 43.7, 32.0, 16.4, 15.4, 14.5, 13.3, 12.1; MS m/z 305 (M^+, 3), 286 (M^+-H_2O, 1.4), 234 (18), 178 (9), 127 (38), 122 (100), 69 (90).

Minor diastereomer (**91**): t_R = 18.7 min; $[\alpha]_D$ -6.6° (c 1.20, $CHCl_3$); IR (neat) 3535, 2973, 2928, 1741, 1456, 1151, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (3H, m), 5.25 (1H, m, J=5.5 Hz), 3.52 (1H, t, J=6.0 Hz), 3.07 (1H, dq, J=1.4, 7.2 Hz), 2.43 (1H, d, J=13.1 Hz), 2.17 (6H, s), 1.18 (1H, m, J=3.6, 6.8, 10.5 Hz), 1.77 (1H, dd, J=10.5, 13.1 Hz), 1.58 (6H, m), 1.47 (3H, d, J=7.2 Hz), 0.93 (3H, d, J=6.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.3, 147.9, 134.0, 130.0, 128.7, 126.0, 120.6, 78.2, 42.3, 41.5, 34.3, 16.43, 16.36, 15.5, 15.4, 13.4.

(5*R*)-(*E*)-3,5-Dimethyl-6-[(1,1-dimethylethyl)dimethylsiloxy]-2-hexene (**81**). To a solution of **73** (200 mg, 1.56 mmol) and 2,6-lutidine

(334 mg, 3.12 mmol) in 6.2 mL of CH_2Cl_2 at 0 °C was added *t*-butyldimethylsilyl triflate (619 mg, 2.34 mmol). The solution was warmed to room temperature and after 20 min was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous NaCl and dried ($MgSO_4$) before being concentrated under reduced pressure. Column chromatography (2% Et_2O-hexane) of the residual oil afforded 366 mg (97%) of **81** as a colorless oil: R_f 0.64 (10% EtOAc-hexane); $[\alpha]_D$ -1.1° (c 3.58, $CHCl_3$); IR (neat) 2960, 2887, 1670, 1470, 1254, 1090, 837, 776, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.17 (1H, m, J=5.7 Hz), 3.38 (2H, m, J=5.4, 10.6 Hz), 2.10 (1H, dd, J=5.2, 12.4 Hz), 1.73 (1H, m), 1.65 (1H, dd, J=8.7, 12.4 Hz), 1.56 (6H, m), 0.89 (9H, s), 0.80 (3H, d, J=6.5 Hz), 0.03 (6H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 134.3, 119.8, 68.2, 43.8, 33.8, 25.7, 18.3, 16.5, 15.5, 13.3, -3.0; MS m/z (rel intensity)185 (M^+, - *t*-Bu', 0.2), 109 (65), 75 (100), 69 (32).

Methyl (2*S*)-3-(Benzyloxy)-2-methylpropionate (**103**). To a solution of (*S*)-(+)-methyl 3-hydroxy-2-methylpropionate (18.8 g , 0.158 mol) in 370 mL of cyclohexane and 190 mL of CH_2Cl_2 (2:1 v/v) was added benzyl 2,2,2-trichloroacetimidate (50.0 g, 0.198 mol) followed by triflormethanesulfonic acid (2.40 g, 0.016 mol). The resulting solution was stirred overnight at room temperature. After 24 hours the mixture was filtered, and the solid was washed with CH_2Cl_2. The combined filtrates were washed with H_2O, saturated aqueous $NaHCO_3$, H_2O, and finally saturated NaCl before being dried over $MgSO_4$. Column chromatography (15% EtOAc-hexane) afforded 27.4 g (83%) of **103** as a clear colorless oil: R_f 0.38 (20% EtOAc-hexane) $[\alpha]_D$ + 11.3° (c 3.80, $CHCl_3$), [lit[53] $[\alpha]_D$ +9.7° (c 3.40, $CHCl_3$); IR (neat) 2979, 1742, 1455, 1201, 1097, 739, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.27 (5H, m), 4.52 (2H, s), 3.69 (3H, s), 3.65 (1H, dd, J=1.7, 9.3

Hz), 3.49 (1H, dd, J=4.9, 9.3 Hz), 2.79 (1H, m, J=7.1 Hz), 1.18 (3H, d, J=7.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.3, 138.1, 128.3, 127.55, 127.52, 73.0, 71.9, 51.7, 40.1, 13.9; MS m/z (rel intensity) 208 (M^+, 12), 122 (12), 107 (60), 91 (100), 77 (35).

(2*R*)-3-(Benzyloxy)-2-methyl-1-propanol (104). To a suspension of $LiAlH_4$ (5.0 g, 0.132 mol) in 130 mL of Et_2O at 0 °C was added a solution of **103** (27.4 g, 0.132 mol) in 130 mL of Et_2O dropwise with stirring. The mixture was warmed to room temperature and after 30 min the excess $LiAlH_4$ was quenched by the careful addition of 5.0 mL of H_2O, 5.0 mL of 15% aqueous NaOH and 15 mL of H_2O. After 15 min anhydrous $MgSO_4$ was added and stirring was continued for 15 min. The mixture was filtered, the solid washed with Et_2O, and the combined filtrates concentrated under reduced pressure to give 23.9 g (98%) of **104** as a clear yellow oil of sufficient purity for the subsequent experiment. An analytical sample was obtained by column chromatography (30% EtOAc-hexane) as a clear colorless oil: R_f 0.15 (20% EtOAc/hexane); $[\alpha]_D$ + 16.8° (c 4.31, $CHCl_3$) [lit[107] $[\alpha]_D$ + 16.4° (c 4.50, $CHCl_3$)]; IR (neat) 3396, 3030, 2873, 1095, 737, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.27 (5H, m), 4.52 (2H, s), 3.64-3.53 (3H, m, J=4.7, 9.1 Hz), 3.42 (1H, dd, J=8.2, 9.1 Hz), 2.62 (1H, dd, J=4.7, 6.7 Hz), 2.03 (1H, m, J=7.0 Hz), 0.88 (3H, d, J=7.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.9, 128.4, 127.7, 127.6, 75.4, 73.3, 67.8, 35.5, 13.4; MS m/z (rel intensity) 180 (M^+, 100), 165 (25), 107 (22), 91 (51).

(2*S*)-3-(Benzyloxy)-2-methyl-1-bromopropane (105). To a solution of **104** (23.7 g, 0.131 mol) in 260 mL of CH_2Cl_2 was added triphenylphospine (PPh_3) (36.2 g, 0.138 mol). The solution was cooled to 0 °C and N-bromosuccinimide (NBS) (24.6 g, 0.138 mol) added in four 6.15 g portions over 10 minutes (note: a vigorous effervescence was observed with

each addition). The clear yellow solution was then warmed to room temperature and stirred overnight. After 20 hours at room temperature an additional 0.1 equivalents of PPh_3 (3.4 g) and NBS (2.3 g) were added and the solution was stirred for 3 h. The solution was washed with 5% aqueous $NaHCO_3$ and the organic layer concentrated under reduced pressure to a dark blue oil. Treatment of the oil with 150 mL of hexane and 150 mL of H_2O gave a mixture containing a blue solid. This mixture was stirred at room temperature for 20 min, filtered, and the solid washed with hexane. The organic layer was separated from the aqueous layer and dried over $MgSO_4$. Concentration of the dry solution under reduced pressure and column chromatography of the residual oil (10% EtOAc-hexane) afforded 27.7 g (86%) of **105** as a clear colorless oil; R_f 0.53 (30% EtOAc-hexane); $[\alpha]_D$ +12.7° (c 5.44, EtOH) [lit[54] $[\alpha]_D$ + 13° (c 1, EtOH)]; IR (neat) 3030, 2965, 1454, 1099, 736, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.28 (5H, m), 4.51 (2H, s), 3.50 (2H, m, J=1.2, 5.1 Hz), 3.40 (2H, m, J=2.1, 5.6 Hz), 2.13 (1H, m, J=1.2, 5.6, 6.9 Hz), 1.02 (3H, d, J=6.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.3, 128.3, 127.6, 127.5, 73.1, 72.7, 38.2, 35.6, 15.8; MS m/z (rel intensity) 243 (M^+, 0.7), 180 (100) 165 (21), 91 (60).

(2*R*)-1-(Benzyloxy)-2-methylbutane (**106**). A flame-dried flask was charged with 4.79 g (53.5 mmol) of CuCN. The solid was gently heated with a flame under argon driving off any moisture through the top of the flask. Upon coming to room temperature under argon, the solid was suspended in 100 mL of THF and the mixture was cooled to -78 °C. To this suspension was added via cannula MeLi (1.4M solution in Et_2O) (76.4 mL, 106.9 mmol) from a 100 mL graduated cylinder using a positive pressure of argon. After completing the addition the opaque mixture was warmed to 0 °C and stirred for 5 min. The slightly opaque solution was then cooled to -78 °C and **105** (10.0

g, 41.6 mmol) added via cannula as a solution in 50 mL of THF. The resulting yellow solution was warmed to -20 °C, stirred for 4 h and then left to come to room temperature overnight. After a total time of 20 h the reaction was quenched by the addition of 50 mL of 10% NH_4OH in saturated aqueous NH_4Cl, (CAUTION: Addition of the first few mL was accompanied by a vigorous reaction), followed by 50 mL of H_2O. The layers were separated, the aqueous layer was extracted with Et_2O, and the combined organic layers were washed with saturated aqueous NaCl and dried over $MgSO_4$. Removal of the solvent under reduced pressure followed by column chromatography using 2% EtOAc-hexane afforded 6.43 g (87%) of **106** as a clear colorless oil: R_f 0.38 (5% EtOAc-hexane); $[\alpha]_D$ -4.5° (c 3.23; $CHCl_3$); IR (neat) 2961, 1455, 1099, 734, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.27 (5H, m), 4.50 (2H, s), 3.29 (2H, ddd, J= 5.1, 6.3, 15.5 Hz), 1.69 (1H, m, J=1.2, 6.6 Hz), 1.49 (1H, m, J=5.4, 7.5 Hz), 1.15 (1H, m, J=5.4, 7.5 Hz), 0.91 (3H, d, J=6.7 Hz), 0.88 (3H, t, J=7.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.8, 128.3, 127.5, 127.4, 75.7, 72.9, 35.0, 26.3, 16.6, 11.3; MS m/z (rel intensity) 178 (M^+, 1.3), 91 (100). Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.73; H, 10.30.

(*R*)-2-Methyl-1-butanol 4-Methylbenzenesulfonate (107). To a solution of **106** (12.2 g, 68.4 mmol) in 70 mL of THF was added 4 drops of 10% HCl and 610 mg of 10% Pd-C. The mixture was stirred for 3 h under H_2 (1 atm) and then filtered through a plug of $MgSO_4$ using pentane as a wash. The resulting solution was concentrated by fractional distillation using a 25 cm Vigreaux column and a gradual increase in the oil bath temperature to 115 °C. The resulting solution, a 1:1:1 mixture of (*R*)-2-methyl-1-butanol, toluene, and THF, as shown by ^1H NMR (300 MHz, $CDCl_3$), was used directly in the next experiment.

The alcohol solution was combined with 100 mL of pyridine and cooled to 0 °C. To this solution was added *p*-toluensulfonyl chloride (16.9 g, 88.4 mmol) in small portions. The resulting solution was stirred at 0 °C for 10 min before being warmed to room temperature and stirred for 15 h. The reaction was diluted with one volume of Et_2O and the resulting mixture filtered, the solid being washed with Et_2O. The filtrate was washed with 0.1 M aqueous HCl, H_2O and finally saturated aqueous NaCl before being dried over $MgSO_4$. The dry solution was concentrated under reduced pressure and the residual oil chromatographed using 15% EtOAc-hexane to afford 14.4 g (87%) of **107** as a colorless oil: R_f 0.43 (20% EtOAc-hexane); $[\alpha]_D$ -4.7° (c 1.06, $CHCl_3$) [lit[108] $[\alpha]_D$ -3.4° (neat) ≤ 96% ee); IR (neat) 2966, 1359, 1176, 963, 843, 665, 555 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (2H, m, J=8.3 Hz); 7.35 (2H, m, J=7.8 Hz), 3.84 (2H, m, J=5.7, 9.3 Hz), 2.46 (3H, s), 1.70 (1H, m, J=6.5 Hz), 1.38 (1H, m, J=7.5 Hz), 1.14 (1H, m, J=7.5 Hz), 0.88 (3H, d, J=6.7 Hz), 0.83 (3H, t, J=7.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.6, 133.0, 129.7, 127.8, 74.8, 34.2, 25.3, 21.6, 15.9, 10.9; MS m/z (rel intensity) 242 (M^+, 0.9), 155 (15), 91 (48), 70 (100).

(2*R*)-2-Methyl-1-iodobutane (**101**). A solution of **107** (14.3 g, 59.0 mmol) and NaI (18.6 g, 123.9 mmol; dried 24 h at 70 °C at <1 mm Hg) in 295 mL of acetone was heated at reflux for 5 h. Upon cooling to room temperature the mixture was diluted with 300 mL pentane, filtered, and the solid was washed with 100 mL of pentane. The combined organic layers were washed with H_2O (1 L), saturated aqueous $Na_2S_2O_3$ and dried over $MgSO_4$. The solution was concentrated at atmospheric pressure by distillation using a 25 cm Vigreaux column and a maximum bath temperature of 120 °C. The still pot residue was further distilled at reduced pressure to give 8.4 g (72%) of **101** as a pale yellow oil: bp 105 °C/130 mm [lit[52] bp 59-60 °C/38mm]; $[\alpha]_D$ - 6.0° (c

8.55, $CHCl_3$) [lit[52] $[\alpha]_D$ - 5.6° (neat)]; IR (neat) 2966, 1456, 1193, 601, 580, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.20 (2H, m, J=4.5, 9.5, 14.1 Hz), 1.39 (2H, m), 1.26 (1H, m, J=7.5 Hz), 0.97 (3H, d, J=6.4 Hz), 0.89 (3H, t, J=7.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 36.3, 29.1, 20.1, 17.5, 11.3; MS m/z (rel intensity) 198 (M^+, 7), 70 (100).

(2*S*)-2-(Hydroxymethyl)-1-propionylpyrrolidine (**94**). A mixture of **97** (4.8 g, 48.3 mmol) and propionic anhydride (6.29 g, 48.3 mmol) was heated to 65-70 °C for 3 hours. The dark orange solution was cooled to room temperature, diluted with toluene and concentrated under reduced pressure. The residual oil was distilled under reduced pressure, collecting the fraction boiling between 161-164 °C (2.8 mm). A second distillation afforded 5.56 g (73%) of **94** as a clear colorless oil: bp 145-146 °C/1.55 mm [lit[51] bp 110 °C, < 0.001 mm]; $[\alpha]_D$ -73.7° (c 3.80, $CHCl_3$) [lit[51] $[\alpha]_D$ -65.3° (c 21.6, CH_2Cl_2); IR (neat) 3392, 2975, 1619, 1466, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.23 (1H, m, J=2.7), 3.60 (2H, m, J=2.7, 11.1 Hz), 3.49 (2H, m), 3.33 (2H, q, J=7.4 Hz), 2.11-1.82 (2H, m), 1.59 (1H, m), 1.16 (3H, t, J=7.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.0, 67.2, 61.0, 47.8, 28.1, 24.2, 8.7; MS m/z (rel intensity) 157 (M^+, 1.7), 126 (26), 70 (100).

(2*S*,2'*R*,4'*R*)-2-(Hydroxymethyl)-1-(2',4'-dimethylhexanoyl)-pyrrolidine (**108**). A solution of LDA was prepared in 5.0 mL of THF at 0 °C from diisopropylamine (1.42 g,14.0 mmol) and *n*-BuLi (8.40 mL ,13.4 mmol; 1.6 M in hexanes). After 10 min a solution of **94** (1.00 g, 6.36 mmol) in 8.0 mL of THF was added and the resulting solution warmed to room temperature. Stirring for 1 h gave a heavy white precipitate. To this mixture was added hexamethylphosphoramide (HMPA) (2.20 mL, 12.7 mmol). The resulting clear yellow solution was cooled to -78 °C and iodide **101** (1.38 g, 6.97 mmol) added as a solution in 3.0 mL of THF. The flask was fitted with a

second septum and placed into a pre-cooled jar containing Drierite and allowed to stand at -78 °C (freezer) for 3 days. The reaction was quenched at -78 °C by the addition of a saturated aqueous solution of NH_4Cl. Upon coming to room temperature, the mixture was extracted with Et_2O, the combined organic layers were washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residual oil was chromatographed using MeOH:EtOAc:Hexane (1:3:6) to give 706 mg (49%) of the product as a 19:1 mixture of diastereomers: R_f 0.27 (MeOH: EtOAc: Hexane; 1:3:6); major diastereomer: IR (neat) 3396, 2962, 1618, 1464, 1435, 1055, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.26 (1H, dd, J=2.4, 7.6 Hz), 4.26 (1H, m), 3.70-3.47 (4H, m), 2.67 (1H, m, J=6.4 Hz), 2.04 (1H, m), 1.91 (2H, m), 1.73 (1H, m), 1.60 (1H, m), 1.36 (2H, m), 1.14 (3H, d, J=6.8 Hz), 1.09 (2H, m), 0.87 (3H, t, J=7.2 Hz), 0.86 (3H, d, J=6.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.5, 67.8, 60.9, 47.8, 40.7, 35.6, 32.1, 29.4, 28.2, 24.4, 19.4, 18.2, 11.2; MS m/z (rel intensity) 227 (M^+, 2), 196 (8), 70 (100); HRMS Calcd. for $C_{13}H_{25}NO_2$: 227.1885. Found: 227.1885.

(2*R*, 4*R*)-2,4-Dimethylhexanoic Acid (110). A suspension of **108** (632 mg, 2.78 mmol) in 16.5 mL of 1.0 M aqueous HCl was heated to reflux (bath temperature 110 °C) for 2 h. The mixture was cooled to room temperature and extracted with Et_2O, and the combined extracts dried ($MgSO_4$) before being concentrated under reduced pressure to give 379 mg (95%) of **110** as a pale yellow oil. Bulb-to-bulb distillation (125 °C/20 mm) afforded an analytical sample as a clear colorless oil: IR (neat) 3475-2353 (br s), 2986, 1708, 1465, 1241, 942 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.57 (1H, m, J=6.1, 7.1 Hz), 1.74 (1H, m, J=5.2, 9.0, 13.7 Hz), 1.36 (2H, m), 1.18 (3H, d, J=7.1 Hz), 1.15 (2H, m), 0.89 (3H, d, J=6.5 Hz), 0.87 (3H, t, J=7.3Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 183.8, 40.8, 37.3, 32.2, 29.4, 18.9, 17.8, 11.1; MS m/z

(rel intensity) 145 (M^+, 7), 127 (1), 74 (100), 71 (80). Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.32; H, 11.26.

An optically pure sample of **110** was obtained via recrystallization of its cinchonidine salt. Thus, a mixture of **110** (56.0 mg, 0.39 mmol) and cinchonidine (114.0 mg, 0.39 mmol) was dissolved with heating in 50% aqueous acetone. Standing at 0 °C afforded 93.6 mg of a crystalline solid. Recrystallization of the salt (mp 78-82 °C) to a constant specific rotation $[\alpha]_D$ - 86.8° (c 1.12, $CHCl_3$) was followed by decomposition with 2M aqueous HCl, and extraction with Et_2O. Concentration of the dry solution ($MgSO_4$) under reduced pressure afforded 31.5 mg (56%) of **110** as a clear colorless oil: $[\alpha]_D$ - 30.6° (c 3.01, $CHCl_3$).

(2*R*,4*R*)-2,4-Dimethylhexan-1-ol (78). A solution of **110** (3.40 g, 23.6 mmol) in 50 mL of Et_2O was treated with an excess of CH_2N_2 at room temperature. The solution was concentrated under reduced pressure to half the original volume and added dropwise to a slurry of $LiAlH_4$ (0.94 g, 23.6 mmol) in 50 mL of Et_2O at 0 °C. The reaction was quenched after 1.5 h by the careful addition of 0.95 mL of H_2O at 0 °C, followed by 0.95 mL of 15% aqueous NaOH at room temperature, and finally 3 mL of H_2O. The resulting mixture was stirred with $MgSO_4$, filtered, and concentrated to an oil. Column chromatography using 15% Et_2O-pentane, afforded 2.43 g (79%) of **78** as a clear colorless oil: R_f 0.28 (20% EtOAc-hexane); $[\alpha]_D$ + 3.7° (c 1.67, $CHCl_3$); IR (neat) 3334, 2961, 1462, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.52 (1H, m, J=5.5, 10.4 Hz), 3.39 (1H, m, J=5.5, 10.4 Hz), 1.72 (1H, m, J=1.5, 6.7 Hz), 1.62-1.27 (4H, m), 1.07 (1H, m, J=1.2 Hz) 0.98-0.83 (10H, m); ^{13}C NMR (75.5 MH, $CDCl_3$) δ 68.4, 40.5, 33.1, 31.5, 28.9, 19.8, 17.3, 11.1; MS m/z 112 ($M^+ - H_2O$, 1.1), 83 (69), 70 (100); HRMS Calcd. for C_8H_{17} ($M^+ - H_2O$): 113.1330. Found: 113.1330.

(2*R*,4*R*)-2,4-Dimethylhexanal (16). To a solution of $(COCl)_2$ (0.974 g, 7.68 mmol) in 5.0 mL of CH_2Cl_2 at -78 °C was added a solution of DMSO (1.20g, 15.4 mmol) in 5.0 mL of CH_2Cl_2. Stirring for 5 min was followed by the addition of **78** (500 mg, 3.84 mmol) as a solution in 5.0 mL of CH_2Cl_2. After 10 min Et_3N (2.33 g, 23.0 mmol) was added as a solution in 5.0 mL of CH_2Cl_2. Stirring for 20 min was followed by warming to 0 °C. After 30 min at 0 °C the mixture was diluted with pentane, filtered, and the filtrate concentrated under reduced pressure. Purification of the residue by column chromatography (10% Et_2O-pentane) afforded 484 mg (98%) of **16** as a pale yellow oil: R_f 0.49 (10% EtOAc-hexane); IR (neat) 2964, 2705, 1728, 1461, 1379 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.57 (1H, d, J=2.5 Hz), 2.43 (1H, m, J=2.5, 6.8 Hz), 1.72 (1H, m), 1.39 (2H, m) 1.18-1.07 (2H, m), 1.08 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=7.0Hz), 0.88 (3H, t, J=7.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 205.5, 44.1, 37.8, 31.9, 29.1, 19.2, 14.1, 11.1. 2,4-Dinitrophenylhydrazone: mp 112-113°C (EtOH) [lit[3] mp 96-96.5 °C (EtOH); $[\alpha]_D$ -37.6° (c 0.25, $CHCl_3$) [lit[3] $[\alpha]_D$ -16.1° (c 0.70. $CHCl_3$)]; MS m/z (rel intensity) 308 (M^+, 7), 238 (8), 220 (22), 203 (44), 117 (30), 69 (100).

(*E*)-Crotylboronate Diethanolamine Complex (156). A suspension of KOtBu (903 mg, 8.05 mmol) in 3.8 mL of THF was cooled to -78 °C and *trans*-2-butene (**154**) (0.6 g, 1.0 mL, 11mmol) added via a double ended needle from a cooled graduated centrifuge tube. To this mixture was added *n*-BuLi (5.1 mL, 8.1 mmol) as a 1.6 M solution in hexanes. The resulting orange mixture was carefully warmed to -50° ± 3 °C and stirred for 20 min. The dark orange mixture was recooled to -78 °C and triisopropylborate (1.51 g, 8.05 mmol) added dropwise causing a gradual discharge of the orange color. The reaction was quenched after 30 min by the addition of 15 mL of 1N aqueous HCl. The mixture was warmed to room temperature, the

organic layer removed, and the aqueous phase extracted with EtOAc (2x10 mL). The combined organic layers were transferred to a flask containing diethanolamine (677 mg, 6.44 mmol). The resulting mixture was stirred for 3 h under argon with a large excess of powdered 4 Å molecular sieves. Filtration and concentration under reduced pressure provided a white solid. Crystallization of the solid from CH_2Cl_2-Et_2O afforded 625 mg (46%) of **156** as fine white needles; mp 117-118 °C, [lit[20b] 119-120 °C (CH_2Cl_2-Et_2O)]; IR (KBr) 3092, 2929, 1665, 1214, 1063, 966, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.67 (1H, m, J=1.7, 7.6, 15.3 Hz), 5.30 (1H, m, J=1.7, 7.6, 15.3 Hz), 4.54 (1H, bs), 4.01 (2H, m), 3.88 (2H, m), 3.22 (2H, bd, J=7.7 Hz), 2.81 (2H, m), 1.64 (3H, dd, J=1.1, 6.4 Hz), 1.36 (2H, d, J=7.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 132.9, 121.7, 62.8, 51.4, 23.8 (vb), 18.1; MS m/z (rel intensity) 114 (100).

(3*R*,4*S*,5*R*,7*R*)-3,5,7-Trimethyl-1-nonen-4-ol (112). A suspension of **156** (1.01 g, 6.00 mmol) in a solution of (-)-diisopropyl tartrate (DIPT) (1.41 g, 6.00 mmol) and 7.5 mL of Et_2O was rapidly stirred at room temperature while 7.5 mL of saturated aqueous NaCl was added. After five min the layers were separated, and the aqueous layer was extracted with Et_2O. The combined extracts were dried over $MgSO_4$, filtered under argon, and concentrated under reduced pressure to give **153** as a clear viscous oil. This material was used without further purification in the next step.

A solution of **153** in 25.0 mL of toluene was stirred with 900 mg of powdered 4Å molecular sieves at -78 °C and **16** (481 mg, 3.74 mmol) was added as a solution in 6.0 mL of toluene. After stirring for 4 h at -78 °C the reaction was quenched by the addition of 15 mL of 2N aqueous NaOH. The resulting mixture was warmed to 0 °C and stirred for 20 min before being filtered through a pad of Celite. The organic layer was separated and the

aqueous layer was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and the Et_2O removed under reduced pressure. The toluene solution was placed on a short oversized column of silica gel packed in hexane. Elution with hexane removed the toluene and further elution with 5% EtOAc-hexane afforded 491 g (71%) of the product as a clear colorless oil. Pure **112** was obtained by preparative gas chromatography (20m 4% Carbowax column, He carrier gas and a flow rate of 75 mL/min, chart speed 2 cm/min) under isothermal conditions (120°C): t_R = 6.4 min; R_f 0.32 (10% EtOAc-hexane); $[\alpha]_D$ - 4.31° (c 1.02, $CHCl_3$); IR (neat) 3481, 3077, 2963, 1639, 997, 912 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (1H, m, J=8.4, 10.5, 16.3 Hz), 5.13 (2H, m, J=2.0, 10.5, 16.3 Hz), 3.18 (1H, m, J=3.2, 6.7 Hz), 2.28 (1H, m, J=8.1 Hz), 1.74 (1H, m, J=3.4, 6.9 Hz), 1.49 (1H, d, J=3.4 Hz), 1.46-1.34 (3H, m), 1.13-1.00 (2H, m), 0.98 (3H, d, J=6.6 Hz), 0.83 (3H, t, J=7.4 Hz), 0.86 (6H, overlapping d, J=6.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 141.7, 116.3, 76.3, 42.4, 41.4, 31.4, 31.3, 29.2, 19.6, 16.6, 13.1, 11.2; MS m/z (rel intensity) 184 (M^+, 2), 167 (14), 111 (100), 97 (89), 69 (65). Anal. Calcd. for $C_{12}H_{24}O$: C, 78.20; H, 13.12. Found: C, 78.03; H, 13.30.

(3*R*,4*S*,5*R*,7*R*)-4-[(1,1-Dimethylethyl)dimethylsiloxy]-3,5,7-trimethylnon-1-ene (**159**). To a 0.1 M solution of **112** (934 mg, 5.06 mmol) in CH_2Cl_2 containing 2,6-lutidine (1.09 g, 10.12 mmol) at 0 °C was added (1.47 g, 5.57 mmol) of *t*-butyldimethylsilyl triflate (TBDMSOTf). The solution was warmed to room temperature and stirred for 4.5 h before being quenched by the addition of saturated aqueous $NaHCO_3$. Separation of the layers, extraction of the aqueous layer with CH_2Cl_2, drying ($MgSO_4$) and concentration under reduced pressure afforded a viscous oil. Column chromatography (2% Et_2O-hexane) afforded 1.26 g (83%) of **159** as a clear colorless oil: R_f 0.63 (5% EtOAc-hexane); $[\alpha]_D$ + 13.0° (c 1.47, $CHCl_3$) ; IR

(neat) 3077, 2961, 1642, 1254, 910, 836, 813, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (1H, m, J=7.7, 10.4, 17.0 Hz), 4.97 (2H, m, J=7.7, 17.0 Hz), 3.36 (1H, dd, J=3.6, 4.8 Hz), 2.34 (1H, m, J=4.8, 7.1 Hz), 1.67 (1H, m), 1.37 (2H, m), 1.24 (1H, m, J=5.0, 7.1 Hz), 0.99 (3H, d, J=6.9 Hz), 0.90 (9H, s), 0.89-0.78 (9H, m), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 142.3, 113.7, 79.3, 42.8, 42.0, 33.8, 31.7, 28.7, 26.2, 19.8, 18.5, 17.6, 15.5, 11.2, -3.6, -3.7; MS m/z (rel intensity) 242 (M^+- *t*-Bu•, 14), 167 (22), 136 (25), 112 (19), 73 (100). Anal. Calcd. for $C_{18}H_{38}OSi$: C, 72.41; H, 12.83. Found: C, 72.38; H, 12.86.

(2*S*,3*S*,4*R*,6*R*)-3-[(1,1,-Dimethylethyl)dimethylsiloxy]-2,4,6-trimethyloctanal (**160**). A solution of **159** (1.26 g, 4.22 mmol) in 60 mL of CH_2Cl_2 was cooled to -78 °C and treated with O_3 until a faint blue color presisted. The solution was sparged with argon while warming to room temperature, treated with a large excess of Me_2S, and the resulting solution refluxed for 8 h (bath temperature 60-65 °C). Upon coming to room temperature, additional Me_2S was added and stirring continued overnight. Concentration of the solution under reduced pressure and column chromatography of the residual oil (2-4% EtOAc-hexane) afforded 0.865 g of **160** and 122 mg of the unreacted ozonide, each as a colorless oil. Resubjecting the ozonide to the reduction conditions, followed by column chromatography as above, afforded an additional 66 mg of **160** for a total of 931 mg (73%): R_f 0.33 (5% EtOAc-hexane); $[\alpha]_D$ + 53.0° (c 1.00; $CHCl_3$); IR (neat) 2960, 2712, 1728, 1463, 1036, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.78 (1H, d, J=2.8 Hz), 3.74 (1H, dd, J=3.7, 4.7 Hz), 2.55 (1H, m, J=2.8, 4.7, 7.3 Hz), 1.74 (1H, m, J=4.9, 6.9 Hz), 1.44-1.28 (3, m, J=4.9, 8.9 Hz), 1.07 (3H, d, J=7.1 Hz), 0.99 (2H, m), 0.89 (9H, s), 0.88 (3H, d, J=7.0 Hz), 0.85 (6H, m), 0.07 (3H, s), 0.05 (3H, s); ^{13} C NMR (75.5 MHz, $CDCl_3$) δ 205.4, 78.1, 50.0, 40.5,

35.0, 31.7, 28.3, 25.9, 19.9, 18.3, 15.2, 12.4, 11.1, -3.9, -4.3; MS m/z (rel intensity) 301 (M^+, 2), 259 (61), 243 (4), 217 (12), 131 (31), 75 (100). Attempts at exact mass determination or elemental analysis met with failure.

(2*S*,3*S*,4*R*,6*R*)-3-[(1,1-Dimethylethyl)dimethylsiloxy]-2,4,6-trimethyloctanoic acid (**161**). To a solution of **160** (845 mg, 2.81 mmol) in 23 mL of *t*-BuOH and 17.5 mL of an aqueous pH 4 phosphate buffer cooled to 0 °C was added 2-methyl-2-butene (1.97 g, 28.1 mmol). The resulting solution was stirred at 0 °C while a 1 M aqueous solution of $NaClO_2$ (540 mg, 4.78 mmol) was added dropwise. Stirring for 15 min at 0 °C was followed by 2.5 h at room temperature. The reaction was diluted with saturated aqueous NH_4Cl, extracted wtih CH_2Cl_2, and the combined organic layers dried ($MgSO_4$) before being concentrated under reduced pressure. The residual oil was chromatographed using 10% EtOAc-hexane to give 866 mg (97%) of **161** as a clear colorless oil; R_f 0.12 (5% EtOAc-hexane); $[\alpha]_D$ +15.6° (c 0.93, $CHCl_3$); IR (neat) 3382-2347 (broad) 2960, 1711, 1073, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.75 (1H, dd, J=3.3, 5.1 Hz), 2.66 (1H, dq, J=5.1, 7.2 Hz), 1.75 (1H, m), 1.38 (3H, m), 1.21 (3H, d, J=7.4 Hz), 1.00 (2H, m), 0.91 (9H, s), 0.92-0.83 (9H, m), 0.12 (3H, s), 0.09 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 179.3, 78.3, 43.3, 39.9, 34.3, 31.5, 28.3, 25.9, 19.9, 18.3, 15.8, 14.9, 11.1, -4.0, -4.4; MS m/z (rel intensity) 317 (M^+, 0.4), 259 (100), 217 (26), 75 (29). Anal. Calcd. for $C_{17}H_{36}O_3Si$: C, 64.50; H, 11.46. Found: C, 64.60; H, 11.45.

(-)-Hemibourgeanic acid (**2**). To a solution of **161** (849 mg, 2.68 mmol) in 26 mL of THF-CH_3CN (1:1) at room temperature was added 2.4 mL of 48% aqueous HF. After 48 hours the reaction was diluted with 0.1 M aqueous HCl (40 mL) and extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to a pale yellow oil. This material was dissolved in Et_2O and extracted with 5% $NaHCO_3$. The

combined aqueous layers were acidified with 10% aqueous HCl to pH 1, extracted with CH_2Cl_2, and dried over $MgSO_4$. Concentration under reduced pressure afforded 484 mg (89%) of **2** as a clear colorless oil: R_f 0.22 (MeOH/EtOAc/hexane 1:3:6); $[\alpha]_D$ -4.4° (c 0.22, $CHCl_3$) [lit[3] $[\alpha]_D$ = -3.2° (c 1.08; $CHCl_3$)]; 3660-2400, 3436, 3964, 1714, 1464, 981 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.64 (1H, dd, J=3.2, 8.6 Hz), 2.66 (1H, m, J=1.0, 7.2 Hz), 1.75 (1H, m, J=3.2, 6.8 Hz), 1.48-1.30 (4H, m), 1.19 (3H, d, J=7.2 Hz) 1.09 (3H, m), 0.87 (3H, d, J=6.9 Hz), 0.87 (3H, t, J=7.2Hz), 0.86 (3H, d, J=6.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.6, 75.2, 43.3, 40.9, 31.5, 31.2, 29.2, 19.4, 14.1, 12.9, 11.2; MS m/z (rel intensity) 202 (M^+, 0.5), 129 (8), 111 (11), 103 (100), 85 (64), 74 (43), 69 (33).

(1'*R*,3*R*,3'*R*)-3-Methyl-4-(1',3'-dimethylpentyl)-2-oxetanone. β-lactone (164). To a solution of **2** (109 mg, 0.54 mmol) in 5.4 mL of pyridine at 0 °C was added benzenesulfonyl chloride (285 mg, 1.61 mmol). The reaction was allowed to stand at 0 °C overnight (22 h) before being quenched with ice-cold H_2O. Extraction with Et_2O was followed by washing the combined organic layers with ice-cold saturated aqueous $NaHCO_3$, saturated aqueous NaCl, and drying over $MgSO_4$. Concentration under reduced pressure and column chromatography of the residual oil (5% EtOAc-hexane) afforded 85 mg (86%) of **164** as a clear colorless oil: R_f 0.33 (10% EtOAc-hexane); $[\alpha]_D$ -32.6° (c 1.08, $CHcl_3$) [lit[3] $[\alpha]_D$ -32.2° (c 0.70, $CHCl_3$)]; IR (neat) 2963, 1827, 1461, 1123, 867 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.87 (1H, dd, J=4.1, 8.3 Hz), 3.24 (1H, dq, J=4.1, 7.5 Hz), 1.86 (1H, m), 1.45 (1H, m), 1.39 (3H, d, J=7.5 Hz), 1.22 (1H, m), 1.05 (2H, m), 1.01 (3H, d, J=6.6 Hz), 0.95 (3H, d, J=6.7 Hz), 0.87 (3H, t, J=7.1 Hz), 0.85 (1H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.1, 83.8, 48.9, 38.7, 34.9, 31.2, 28.1, 20.0, 15.6, 12.9, 10.9; M/S m/z (rel intensity) 184 (M^+, 12), 167 (24), 112 (11), 84 (38), 69 (100).

Ester 113. To a solution of **112** (975 mg, 0.407 mmol) in 2.5 mL of THF at 0 °C was added *n*-BuLi (0.26 mL, 0.41 mmol) in hexane. Stirring for 10 min at 0 °C was followed by the addition of **164** (75.0 mg, 0.407 mmol) as a solution in 2.0 mL of THF. The reaction was quenched after 5.5 h at 0 °C by the addition of saturated aqueous NH_4Cl. Extraction with Et_2O, concentration of the dried ($MgSO_4$) organic layers under reduced pressure, and column chromatography of the residual oil (7% EtOAc-hexane) afforded 91.2 mg (61%) of **113** as a clear colorless oil: R_f 0.35 (10% EtOAc-hexane); $[\alpha]_D$ -11.8° (c 0.45, $CHCl_3$); IR (neat) 3535, 2964, 1717, 1461, 1179, 916 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (1H, m, J=8.8, 10.3, 16.9 Hz), 4.99 (2H, m, J=1.5, 14.5, 16.9 Hz), 4.80 (1H, dd, J=4.0, 7.7 Hz); 3.59 (1H, m, J=3.3, 4.8 Hz), 2.58 (1H, m, J=7.2 Hz), 2.49 (1H, d, J=4.8 Hz, exchanges with D_2O), 2.47 (1H, m), 1.88 (1H, m, J=4.1 Hz), 1.71 (1H, m, J=3.3, 6.9 Hz), 1.43 (3H, m), 1.27 (3H, m), 1.14 (3H, d, J=7.2), 1.10-1.02 (4H, m), 0.99 (3H, d, J=7.0 Hz), 0.96-0.81 (18H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.2, 140.7, 115.3, 78.9, 74.9, 43.8, 41.2, 40.8, 40.4, 31.6, 31.4, 31.3, 31.1, 29.3, 28.9, 19.7, 19.5, 17.2, 14.4, 14.3, 13.0, 11.3, 11.1; MS m/z (rel intensity) 369 (M^+, 28), 357 (M^+-H_2O, 0.4), 287 (11), 203 (2), 185 (100), 167 (39), 97 (26), 69 (42). Anal. Calcd. for $C_{23}H_{44}O_3$: C, 74.95; H, 12.03. Found: C, 74.55; H, 11.86.

Dilactone 15. Benzenesulfonyl chloride (8.2 mg, 0.047 mmol) was added to a solution of **1** (6.0 mg, 0.016 mmol) in 0.3 mL of pyridine at 0 °C. The resulting solution was allowed to stand overnight (22.5 h) at 0 °C before being diluted with H_2O and extracted with Et_2O. Concentration of the dry ($MgSO_4$) solution under reduced pressure and column chromatography (10% EtOAc-hexane) afforded 5.4 mg (96%) of **15** as a crystalline solid: R_f 0.53 (10% EtOAc/hexane); mp 74.5-75 °C (Et_2O-hexane) [lit[3] 77 °C (EtOH/H_2O)]; $[\alpha]_D$ + 59.3° (c 0.54, $CHCl_3$), [lit[3] $[\alpha]_D$ +56 ° (c 1.21, $CHCl_3$)]; IR (KBr) 2962,

1744, 1731 (shoulder), 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.79 (1H, dd, J=1.9, 10.2 Hz), 2.99 (1H, dq, J=6.8, 10.2 Hz), 1.88 (1H, dq, J=1.5, 6.4 Hz), 1.56 (1H, m, J=6.7 Hz), 1.42 (1H, m, J=6.1, 7.8, 13.5 Hz), 1.33 (1 H, m, J=4.9, 7.2, 13.5 Hz), 1.09 (2H, m, J=7.3 Hz), 1.04 (3H, d, J=6.9 Hz), 0.98 (3H, d, J=6.8 Hz), 0.86 (3H, d, J=6.5 Hz), 0.85 (3H, t, J=7.4 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.9, 84.9, 44.1, 40.7, 30.9, 30.4, 29.5, 19.2, 13.5, 11.6, 11.2; MS m/z (rel intensity) 369 (M^+, 2), 240 (100), 185 (75), 128 (15), 85 (69), 70 (65).

Hydroperoxide 177. A solution of **113** (10.6 mg, 0.029 mmol) in 1 mL of EtOAc-HOAc (1:1 v/v) was cooled to -10 °C and treated with O_3 until all of the starting material had been consumed. The solution was sparged with argon while warming to room temperature and then 1 ml of 30% aqueous H_2O_2 was added. After stirring for 1 h at room temperature the solution was diluted with 1 mL of 10% aqueous HCl and extracted with EtOAc. Concentration of the dry ($MgSO_4$) solution and column chromatography (10-30% EtOAc-hexane) afforded 5.5 mg (46%) of **177** as a colorless oil: R_f 0.64 (MeOH-EtOAc-hexane, 1:3:6); IR (neat) 3409, 2963, 1713, 1460, 1183, 984 cm^{-1}; $[\alpha]_D$ -15.0° (c 0.42, $CHCl_3$) δ 10.55 (1H, bs, exchanges with D_2O), 9.82 (1H, bs, exchanges with D_2O), 5.23 (1H, d, J=5.9 Hz), 4.94 (1H, dd, J=1.9, 10.3 Hz), 3.91 (1H, dd, J=2.2, 10.3 Hz), 2.93 (1H, d, J=4.6 Hz, exchanges with D_2O), 2.71 (1H, dq, J=2.8, 7.2 Hz), 2.27 (1H, dq, J=6.1, 7.0 Hz), 1.90 (1H, m, J=6.6 Hz), 1.79 (2H, bs + m, singlet exchanges with D_2O), 1.46 (3H, m), 1.26 (3H, m), 1.12 (3H, d, J=7.2 Hz), 1.09 (3H, m), 0.99 (3H, d, J=7.0 Hz), 0.94-0.81 (19H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.4, 112.3, 75.9, 75.1, 43.9, 41.0, 40.8, 36.8, 31.3, 31.0, 30.9, 30.4, 29.6, 29.5, 19.31, 19.29, 14.5, 13.4, 12.4, 11.3, 11.2, 11.1; MS m/z (rel intensity) 387 (M^+ - H_2O, 2), 287 (3), 185 (43), 111 (36), 83 (58), 69 (100).

(+)-Bourgeanic acid (**1**). A solution of **113** (8.3 mg, 0.023 mmol) in 1 mL of EtOAc was cooled to -78 °C and O_3 was bubbled through the solution until the starting material had been consumed as shown by TLC. The solution was sparged with argon while warming to room temperature and then concentrated under reduced pressure to give 12.0 mg of a viscous oil. The oil was dissolved in 0.5 mL of glacial acetic acid and 0.5 mL of 30% aqueous H_2O_2 and was stirred for 72 h at room temperature. The solution was diluted with 1 mL of 10% aqueous HCl, extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (MeOH-EtOAc-hexane, 1:3:6) afforded 7.2 mg of an amorphous solid. Analysis of this material by ^1H NMR (300 MHz, $CDCl_3$) showed the peaks to be broadened, suggesting that the product was a metal complex (metal ion extracted from the silica gel) of the desired hydroxy-acid. This material was dissolved in HOAc, diluted with 0.1M aqueous HCL, and extracted with EtOAc. Concentration of the dry solution ($MgSO_4$) under reduced pressure afforded 4.2 mg (47%) of **1** as a white crystalline solid: mp 124.5-125 °C (hexane), [lit[3] mp 125-126 °C (hexane)]; $[\alpha]_D$ +7.3° (c 0.40, $CHCl_3$), [lit[3] $[\alpha]_D$ + 7.0° (c 1.00, $CHCl_3$)]; IR (KBr) 3418, 2963, 1745, 1720, 1462, 1265, 1195 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.16 (1H, dd, J=2.6, 9.6 Hz), 3.71 (1H, dd, J=2.5, 9.4 Hz), 2.79 (1H, m, J=7.1, 9.6 Hz), 2.60 (1H, m, J=7.2, 9.4 Hz), 1.90 (1H, m, J=2.6, 7.1 Hz), 1.71 (1H, m, J=2.3, 6.8 Hz), 1.45 (3H, m), 1.29 (4H, m), 1.17 (3H, d, J=7.1 Hz), 1.09 (3H, d, J=7.2 Hz), 1.08 (3H, m), 0.96-0.81 (20H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.0, 175.8, 76.4, 74.7, 44.1, 42.1, 41.0, 40.7, 31.2, 30.9, 30.8, 29.4, 29.2, 19.4, 19.3, 14.4, 13.8, 13.7, 12.7, 11.3, 11.1; MS m/z (rel intensity) 387 (M^+, 0.7), 287 (9), 185 (100), 167 (51), 111 (18), 83 (39), 69 (42).

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