exchangeable), 1.8-2.1 (5 H, complex m), 2.1-2.6 (4 H, complex m), 3.15-3.3 (4 H, m), 3.4 (4 H, t, J = 1.5 Hz), 4.0 (1 H, t), 4.58 (1 H, d, J = 3 Hz); MS, exact mass calcd for $C_{12}H_{21}OS_4$ (M^+ + 1) 309.048, found 309.047.

Keto Thiolactol 27. To a solution of oxa-tricyclic ketone **13** (50 mg, 0.36 mmol) and 1,2-ethanedithiol (30 μL, 0.36 mmol) in THF (1 mL) was added at -78 °C 1 M $ZnCl_2$ in THF (2% equiv). The mixture was slowly warmed to -10 °C, the reaction was quenched with 25% aqueous ammonium acetate, and the solution was extracted with Et_2O. The organic layer was dried and evaporated. The residue was flash chromatographed on silica gel, eluting with 20% EtOAc/hexane to afford **27** (53 mg, 64%) as an oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.65-1.8 (3 H, complex m), 2.1-2.25 (1 H, m), 2.3-2.42 (1 H, m), 2.6 (1 H, dd, J = 14, 2 Hz), 2.7-3.1 (8 H, complex m), 4.25 (1 H, s(b)), 5.4 (1 H, s(b)).

Ketone 28. To a solution of **27** (23 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) was added, at room temperature, boron trifluoride etherate (2% equiv) and the solution was stirred for 10 min. The mixture was quenched with 25% aqueous ammonium acetate, extracted with CH_2Cl_2, dried, and evaporated to afford **28** (20 mg, 87%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.6 (1 H, s(b), exchangeable), 1.65-1.9 (4 H, complex m), 2.0-2.15 (1 H, m), 3.5 (1 H, dd, J = 12, 9 Hz), 3.65 (1 H, dd, J = 12, 3 Hz), 3.7-3.85 (2 H, m), 3.15 (4 H, s(b)), 4.2 (1 H, t), 4.52 (1 H, d, J = 4 Hz); MS, exact mass calcd for $C_{10}H_{17}O_2S_2$ (M^+ + 1) 233.067, found 233.067.

Ketone 29a. A solution of oxa-tricyclic ketone **14** (358 mg, 2.18 mmol) and 1,2-ethanedithiol (0.21 mL, 2.18 mmol) in THF (6 mL) was cooled to -78 °C and $TiCl_4$ (5 μL, 0.044 mmol) added. The mixture was warmed to room temperature for 30 min and finally heated to 50 °C for 48 h. The reaction mixture was quenched with 25% aqueous ammonium acetate, extracted with ether, dried, and evaporated. The residue was flash chromatographed on silica gel, eluting with 40% EtOAc/hexane to afford **29a** (460 mg, 82%) (substantial amount of hemiacetal **29b**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.35 (3 H, s), 1.4-2.3 (11 H, complex m), 3.0 (1 H, s, exchangeable), 3.15-3.25 (4 H, m), 4.52 (1 H, d, J = 4 Hz); MS, exact mass calcd for $C_{12}H_{19}OS_2$ (M^+ + 1 - H_2O) 243.088, found 243.088.

Registry No. 1, 103668-91-3; **2**, 103668-90-2; **3**, 109390-69-4; **4a**, 100-73-2; **4b**, 26334-42-9; **5a**, 109390-83-2; **5b**, 109390-98-9; **6a**, 109390-85-4; **6b**, 109390-99-0; **7**, 109390-72-9; **8a**, 109390-93-4; **8b**, 109391-02-8; **9a**, 109390-94-5; **9b**, 109391-03-9; **10**, 109390-74-1; **11**, 109390-75-2; **12**, 109390-76-3; **13**, 109390-77-4; **14**, 109390-78-5; (*R*,*R*)-**15**, 109390-79-6; (*R*,*S*)-**15**, 109390-95-6; (*R*,*R*)-**16**, 109390-80-9; (*R*,*S*)-**16**, 109391-04-0; **18**, 109390-81-0; **19**, 109390-82-1; **21**, 70260-40-1; **22**, 109390-84-3; **24**, 109390-86-5; **25**, 109390-87-6; **26**, 109390-88-7; **27**, 109390-89-8; **28**, 109390-90-1; **29a**, 109391-05-1; **29b**, 109391-06-2; $[Rh(OAc)_2]_2$, 15956-28-2; $EtOC(O)CH{=}PPh_3$, 1099-45-2; $HS(CH_2)_2SH$, 540-63-6; methyl 3,4-dihydro-2*H*-pyran-2-acetate, 109390-70-7; sodium 3,4-dihydro-2*H*-pyran-2-acetate, 109390-71-8; ethyl *trans*-3-(3,4-dihydro-2*H*-pyran-2-yl)acrylate, 76919-60-3; ethyl *cis*-3-(3,4-dihydro-2*H*-pyran-2-yl)acrylate, 109390-73-0; 3-(3,4-dihydro-2*H*-pyran-2-yl)propanal, 109390-91-2; ethyl *trans*-5-(3,4-dihydro-2*H*-pyran-2-yl)-2-pentenoate, 109390-92-3; ethyl *trans*-5-(3,4-dihydro-2-methyl-2*H*-pyran-2-yl)-2-pentenoate, 109391-01-7; ethyl *trans*-3-(3,4-dihydro-2-methyl-2*H*-pyran-2-yl)acrylate, 109390-96-7; ethyl *cis*-3-(3,4-dihydro-2-methyl-2*H*-pyran-2-yl)acrylate, 109390-97-8; methyl 4-(3,4-dihydro-2-methyl-2*H*-pyran-2-yl)butanoate, 109391-00-6.

Supplementary Material Available: X-ray crystal structure analysis of **25** and tables of functional coordinates and temperature factors, bond distances, and bond angles for **25** (4 pages). Ordering information is given on any current masthead page.

Local Conformer Effects in Unsaturated Lactones

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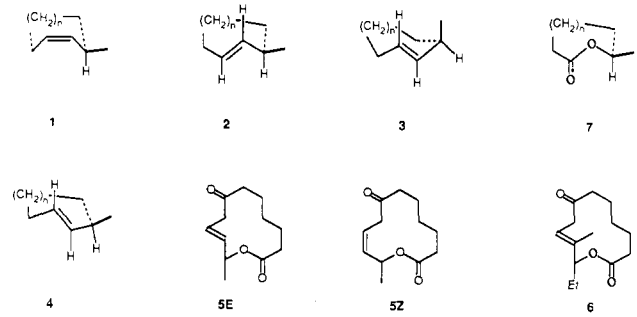
Contribution from S. M. McElvain Laboratory of Organic Chemistry, Chemistry Department, University of Wisconsin, Madison, Wisconsin 53706. *Received February 2, 1987*

Abstract: Allylic unsaturated lactones **5E** and **5Z** can be epoxidized and osmylated with useful stereocontrol. The epoxidations follow the pattern predicted from evaluation of local conformer effects, and epoxides **8** and **14** are favored. These products correspond to peripheral attack on the exposed olefin face of conformers similar to **1** (*Z*-alkene) or **2** (*E*-alkene). As in the case of simple carbocyclic alkenes, osmylation of the *Z*-isomer (**5Z**) follows the same selectivity pattern as the epoxidation, and **16** is the major diol. However, the isomeric **5E** is osmylated from the opposite olefin face compared to the epoxidation and gives **13** as the major diol. The analysis of epoxidations by the local conformer approach is compared with the results of molecular mechanics (MACROMODEL) evaluations of the favored conformers of **5E** and **5Z** and of the derived epoxides.

In a previous report from this laboratory, the selective epoxidation of 3-methylcycloalkenes in 8-15-membered rings was described.[1] Olefin face preferences were interpreted on the basis of local conformer effects due to the inherent geometric requirements of the ring segment -C=C-C(CH_3)- and its neighboring substituents. Transition-state geometry for the highly selective electrophilic additions to *Z*-alkenes was approximated by the tub-like local conformer **1** having pseudoequatorial methyl. The less selective reactions of disubstituted *E*-alkenes were attributed to transition states resembling the crownlike local geometry **2** with a pseudoequatorial methyl group. The extrapolation from local olefin geometry to transition-state geometry is intuitively simple for cis addition reactions because the bicyclic transition states differ from olefin conformers **1** and **2** by relatively small changes in bond angles and hybridization. As long as the electrophile is compact and does not introduce major new steric interactions, the same factors which favor **1** and **2** (minimized transannular, gauche, and eclipsed interactions) should favor similar transition-state geometries. In the case of MCPBA epoxidations, these conditions are satisfied and even the final epoxide can be expected to prefer a similar local geometry as in **1** or **2**.

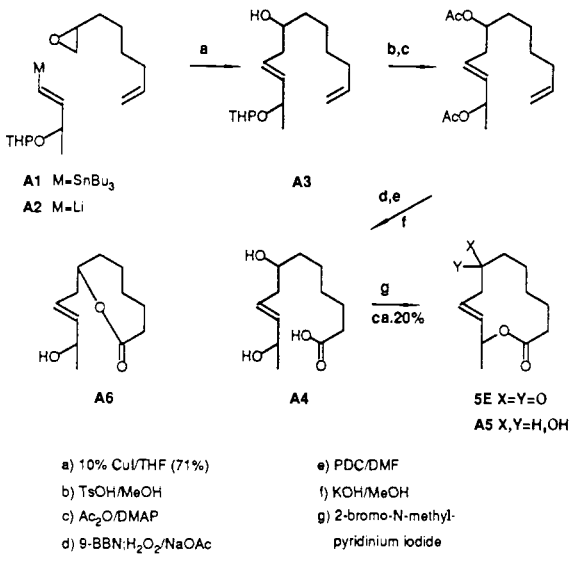
Osmylations are significantly less selective then are epoxidations in the medium ring alkenes.[1] Useful selectivity is observed with the *Z*-alkenes, but not in the case of the disubstituted *E*-isomers. This trend was attributed to the steric bulk of the reactive electrophile (OsO_4·L) which might be tolerated better in transition-state geometries with pseudoaxial methyl, derived from olefin local conformer **3**, or in non-crownlike local geometries such as **4**.



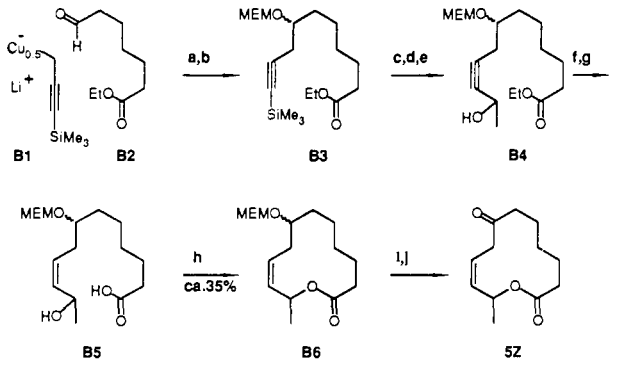
(1) Vedejs, E.; Gapinski, D. M. *J. Am. Chem. Soc.* **1983**, *105*, 5058.

0002-7863/87/1509-5437$01.50/0

Scheme I

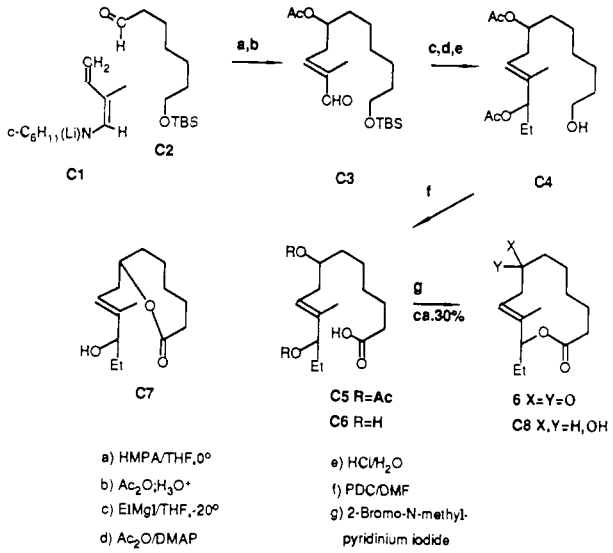


Scheme II



Additional insights can be gleaned from a comparison of medium ring alkene reactions in substrates such as **5** which incorporate allylic lactone oxygen. The olefin face selectivity of analogous acyclic systems has been extensively studied,[2a] but the transition-state geometry in these unconstrained substrates is still uncertain.[2b] There are fewer options in the medium rings because alkyl-substituted lactones are predicted to adopt a transoid geometry **7** which closely resembles an *E*-alkene in its local conformational preferences.[3] Trends toward increased or decreased selectivity should therefore clarify transition-state preferences. We were also interested in lactones **5** and **6** because the derived epoxides and diols are related to several of the macrolide antibiotics (for example, methynolide).[4] This paper describes the epoxidations and osmylations of **5** and **6** together with detailed comparisons of alkene and epoxide conformational preferences with the MACROMODEL program of Still et al.[5]

Scheme III



Preparation of Starting Materials

Syntheses of **5E,Z** and **6** have been designed to depend on the presence of a C_7 oxygen substituent. This group simplifies the stereochemical correlation of epoxidation and osmylation products as will be shown later. Also the C_7 oxygen function is important for maintaining a close structural similarity to the corresponding segments in macrolide aglycons. The individual routes (Schemes I–III) are not optimized, but they have been developed sufficiently to provide necessary starting materials for the stereochemical studies. Only the key steps will be described.

In Scheme I, the precedented use of an organotin reagent **A1** for epoxide opening via an alkenyl cuprate **A2**[6] afforded **A3** in 70% yield. After conversion to hydroxy acid **A4**, macrolactonization by the Mukaiyama method[7] gave a mixture of the desired **A5** together with byproducts, one of which could be separated. Since a parent ion was not observed for this byproduct, structure **A6** cannot be distinguished from the alternative possibility of a 16-membered diolide.[7b] Unfortunately, **A5** could not be obtained in pure form due to the presence of diastereomers and byproducts. This mixture was therefore treated with Jones reagent to effect conversion into ketone **5E** which could then be separated.

A different route was explored for preparation of the cis alkene **5Z**. As shown in Scheme II, the silylated propargyl cuprate **B1**[8] added efficiently to aldehyde ester **B2**. Desilylation of the resulting **B3** with Bu_4NF followed by lithium acetylide condensation with acetaldehyde then gave **B4** (57% from **B3**) and conventional steps afforded the lactonization substrate **B5**. As before, the Mukaiyama procedure was reasonably effective (ca. 40%), but separation of the lactone was only possible after cleavage of the MEM ether (Me_2BBr)[9] and Swern oxidation to **5Z**.

Scheme III describes a similar route to the trisubstituted alkene **6**. Reaction of aldimine anion **C1** with aldehyde **C2** under equilibrating conditions (THF–HMPA, 0 °C)[10] gave a 53% yield of the γ-substitution product **C3**. After functional group manipulations, the diastereomer mixture **C4** was oxidized to **C5** and the derived diol **C6** was cyclized. As in Scheme I, a byproduct (8%) was isolated from the lactonization step which was isomeric with the desired **C8** according to mass spectroscopic evidence. The 8-membered lactone structure **C7** fits the data, but exact mass

(2) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247 and references therein. (b) Vedejs, E.; McClure, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 1094.

(3) Typical recent examples: Schomburg, D.; Hopkins, P. A.; Lipscomb, W. N.; Corey, E. J. *J. Org. Chem.* **1980**, *45*, 1544. Thang, T. T.; Lukacs, G.; Omura, S.; Bartner, P.; Boxler, D. L.; Brambilla, R.; Mallams, A. K.; Morton, J. B.; Reichert, P.; Sancilio, F. D.; Surprenant, H.; Tomalesky, G. *J. Am. Chem. Soc.* **1978**, *100*, 663.

(4) Review: Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569.

(5) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981. For information regarding the modified MACROMODEL MM2 force field, see: Goldsmith, D. J.; Bowen, J. P.; Qamhiyeh, E.; Still, W. C. *J. Org. Chem.* **1987**, *52*, 951. Footnote 10.

(6) Corey, E. J.; Wollenberg, R. H. *J. Org. Chem.* **1975**, *40*, 2265.

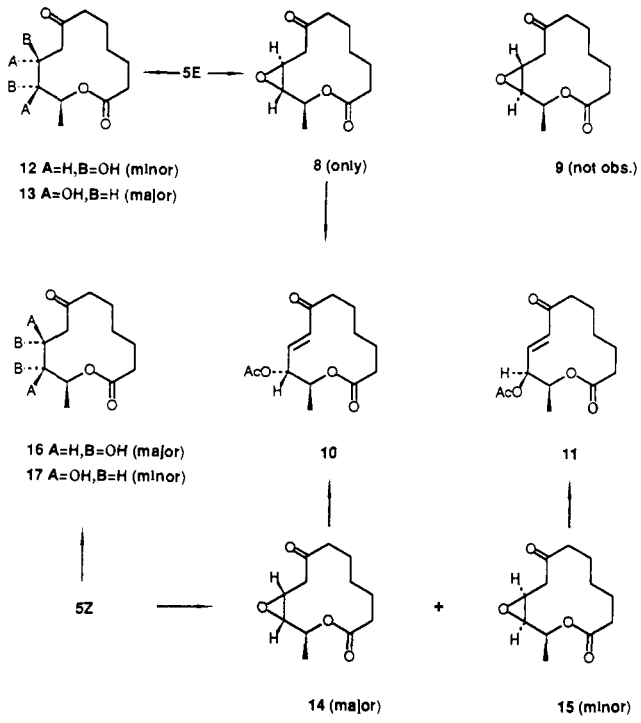
(7) (a) Mukaiyama, T.; Usui, K.; Saigo, K. *Chem. Lett.* **1976**, 49. (b) For a recent sample of diolide formation, see: Fox, C. M. J.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J., *J. Chem. Soc., Chem. Commun.* **1985**, 1805.

(8) (a) The lithium or bromomagnesium acetylides gave substantial amounts of allenic products. (b) Corey, E. J.; Kirst, H. A. *Tetrahedron Lett.* **1968**, 5041.

(9) Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3914.

(10) Vedejs, E.; Gapinski, D. M. *Tetrahedron Lett.* **1981**, *22*, 4913.

Scheme IV



determination cannot be regarded as conclusive proof because C7 did not crystallize and could have contained traces of C8. Separation of C8 was not possible, but **6** could be isolated in modest yield after oxidation of the lactone mixture with pyridinium dichromate.[11]

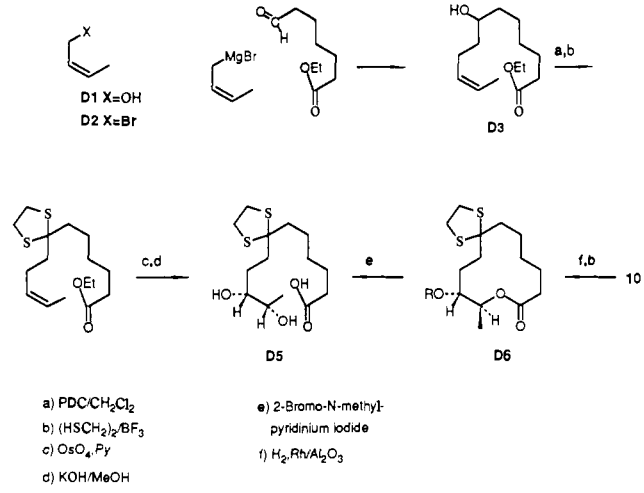
Osmylations and Epoxidations

To evaluate olefin face reactivity preferences, the *Z*- and *E*-alkene lactones **5Z** and **5E** were treated with MCPBA and with catalytic OsO_4 in the presence of *N*-methylmorpholine *N*-oxide.[12] The epoxides proved unstable on silica gel and were therefore converted directly into correlation compounds. Thus, **5E** was epoxidized, the crude product was treated with DBU to induce elimination, and the resulting hydroxy enone was acylated to give the acetoxy enone **10** as the sole isomer detected. The isomeric **11** was not found, nor was any indication of diastereomer **9** detected at the epoxide stage. Similarly, the osmylation products from **5E** were acylated (Ac_2O, dimethylaminopyridine) and treated with DBU. In this case, a 1:3 ratio of diols **12** + **13** and the corresponding acetoxy enones **10** and **11** was produced.

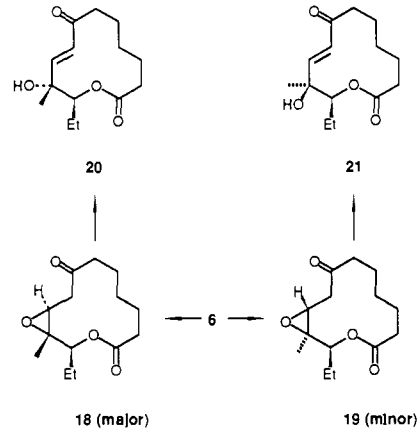
In the case of lactone **5Z**, both the osmylation and epoxidation gave a mixture of diastereomers with similar selectivity. As in the *E*-alkene study, the stereochemistry of products was established by conversion into acetoxy enones **10** and **11**. Epoxides **14** + **15** gave a 3:1 ratio of **10**:**11** after DBU treatment and acylation, and the same result was obtained from diols **16** + **17** after acylation and DBU-induced elimination.

The stereochemical assignments were established by chemical correlation of **10** with a saturated lactone of known stereochemistry (Scheme V). Grignard adduct **D3**, derived from the alcohol **D1** and bromide **D2**, was converted via conventional steps into **D4**. Stereochemistry was established by osmylation to a thioketal diol, and the corresponding hydroxy acid **D5** was cyclized by the

Scheme V



Scheme VI



Mukaiyama method[7] to lactone **D6**. The same isomer was then prepared from acetoxy lactone **10** by hydrogenation (Rh/Al_2O_3) and thioketalization. Similar treatment of the isomeric **11** cleanly gave the diastereomer of **D6** and established that stereochemical integrity had not been lost in the correlation sequence.

Lower olefin face selectivity was found for epoxidation of the trisubstituted *E*-alkene **6**. As before, the mixture of epoxides **18** + **19** was converted into hydroxy enones **20** + **21** (1.5:1) for identification. The major isomer **20** was identical with material prepared earlier by Yamaguchi et al.[13] Osmylation followed by acylation and DBU-induced elimination gave a 1:1.5 ratio of **20**:**21**. Thus, neither the epoxidation nor the osmylation occurred with useful selectivity in the case of **6**. This behavior contrasts with the highly selective reactions of trisubstituted alkenes where the vinylic methyl group is remote from the allylic methyl (for example, (*E*)-1,3-dimethylcyclododecene).[1]

Discussion

1. Osmylations. The major diol from **5E** + catalytic OsO_4 is **13** (75% of the product). This result was not anticipated because analogous carbocyclic alkenes react without significant selectivity[1] and because the acyclic model compound **22** is osmylated with a modest 3:2 preference for the *opposite* olefin face. Peripheral attack of (OsO_4·ligand) on a local conformer **23** would correspond to the model system **22** in selectivity, but this pathway leads to the *minor* product **12**. Formation of **13** requires a transition state derived from a conformer having a pseudoaxial methyl group (as

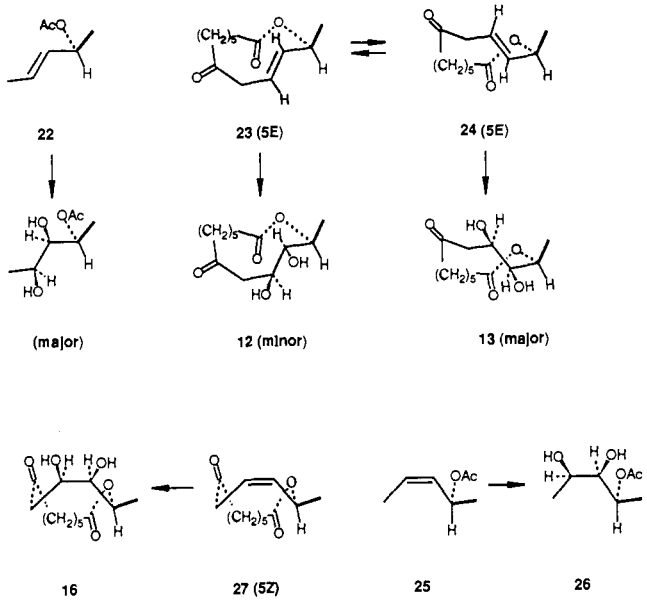
(11) Separation problems due to diastereomers and byproducts precluded a detailed investigation of the lactonization step. Especially bothersome was the presence of byproducts in Schemes I–III which had incorporated an additional oxygen atom relative to **5** or **6**. In the case of **5Z**, pure samples were observed to slowly undergo the conversion into the unknown oxidation products (diastereomer mixture) upon storage in the freezer. Crude products appeared to undergo this transformation more rapidly during attempted purification.

(12) Van Rheenen, V.; Kelly, R. C.; Chan, D. Y. *Tetrahedron Lett.* **1976**, 1973.

(13) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Soc. Chem. Jpn.* **1979**, *52*, 1989. We thank Prof. Yamaguchi for spectra and a sample of authentic **20**.

(14) (a) Schröder, M. *Chem. Rev.* **1980**, *80*, 187. (b) Sharpless, K. B.; Teranishi, A. Y.; Backvall, J.-E. *J. Am. Chem. Soc.* **1977**, *99*, 3120; **1980**, *102*, 4263.

Scheme VII



in **3**) or from a non-crown olefin environment (as in **4**). A transition state related to the local conformer **24** (similar to **3**) is most likely. Formation of the osmate ester by peripheral (front face) bonding to the olefinic carbons keeps the osmate ligands far from the sterically congested interior of the 12-membered ring and avoids serious ligand–methyl interactions.

There would be similar steric advantages for peripheral attack on the local geometry **23** with the added benefit of a pseudoequatorial methyl orientation in the crownlike olefin environment. However, there are also some disadvantages, especially for cis-addition reactions with a relatively late transition state. Extensive rehybridization[2b] from **23** + OsO_4·L results in substantial transannular interactions due to the proximity of the alkene and $-(CH_2)_n$—C(=O)—O– segments. The nearly parallel arrangement of C=C and lactone C—O in **23** may also reduce alkene HOMO reactivity. Electronic effects of this sort are not apparent in the osmylations of acyclic alkenes,[2b] but conformationally unrestricted substrates such as **22** are free to point the ester carbonyl group away from the alkene and can therefore avoid unfavorable electronic effects.

Osmylation of the trisubstituted *E*-alkene **6** occurs with a similar but lower olefin face preference compared to the reaction of **5E**. This result (1.5:1) is too marginal for a detailed rationale, but decreased selectivity indicates that *adjacent* vinylic and allylic methyl groups reduce the advantages of any one particular conformation over others.

Osmylations are more predictable in the *Z*-olefin series. Isomer **5Z** reacts with the same olefin face preference as does the acyclic model compound **25** (3:1 in favor of **16** from **5Z**; 2.3:1 in favor of **26** from **25**[2b]). Analogous selectivity was seen with carbocyclic *Z*-alkenes in our earlier study.[1] These results are easily understood by using essentially the same late-transition-state geometry for osmylation of all of the *Z*-alkenes, including the acyclic systems. In the medium ring lactone **5Z**, front face attack of OsO_4 on **27** (similar to olefin local conformer **1**) is proposed. Even though the transition state will have considerable rehybridization relative to **27**, the preferred local geometry will not change significantly along the reaction coordinate. A cis-fused bicyclic transition state derived from **27** will prefer a pseudoequatorial "exo" methyl group adjacent to the "bridgehead" (original olefinic) carbons. This geometry requires some changes in ring bond angles, but otherwise it resembles **27**.

2. Epoxidations. The reaction of MCPBA with medium ring *E*-alkenes is highly consistent, and more predictable than the corresponding osmylations.[15,16] Thus, **5E** gives a single major product **8** corresponding to peripheral attack on conformers similar to **23**. The isomeric **5Z** reacts with lower selectivity (3:1 in favor of **14**), but the usual preference for a transition state having a pseudoequatorial substituent (as in **27**) is observed. As in the osmylations, the trisubstituted derivative **6** is epoxidized with marginal selectivity, but the reaction does favor the expected major product **18**. Overall, the epoxidations of *E* and *Z* medium ring alkenes are well-behaved and the same trends are observed in rings of varying complexity.[1,15,16]

The local conformer approach for predicting epoxidation selectivity considers only the immediate environment of the alkene. A detailed understanding of ring conformations is not required, but there are some implicit assumptions which must be evaluated with care. In general, the transition-state geometry for medium ring cis additions is deduced by extrapolation from a reference compound having known conformational preferences. Reactions with early transition states can be approximated by extrapolation from the alkene, provided that the *relative* stability of different local conformers does not change as new bonds begin to form. For late-transition states, extrapolation from the product is preferred and is subject to similar qualifications as above. Either extrapolation for epoxidations leads to the same predictions because medium ring alkenes and epoxides prefer similar local geometry. The most important difference is the reluctance of the epoxide to adopt conformations with oxygen on the "inside" of the ring. This restricts the epoxide to those conformations which correspond to the most plausible transition-state geometries via peripheral attack on various alkene conformers. Since there are few added steric effects in the transition state (peracid perpendicular to the olefin plane), it is not surprising that epoxidation of medium ring alkenes occurs with consistent olefin face selectivity.

Information derived from molecular mechanics methods clarifies some of the trends in selectivity and also helps to confirm the generalizations regarding local conformer preferences. In principle, the comparison of varied transition-state geometries by suitable force-field methods would be most revealing if reliable transition-state parameters were available. In the absence of this information, molecular mechanics methods can be used to interface with the local conformer approach by providing energy estimates for various conformers of reference structures. The unsaturated lactones **5E** and **5Z** were selected for study because they contain groups with potentially conflicting preferences (alkene vs. lactone) which are not easily compared by an intuitive approach. Both lactones **5E** and **5Z**, the corresponding epoxides, and several simpler model compounds have therefore been evaluated with the MACROMODEL program of Still et al.[5b] No attempt has been made to extend the comparison to osmylations because the nature of the transition state is controversial,[14] and reliable parameters for the osmate esters are not available.

Results with the *Z*-alkenes and their epoxides are especially revealing. In all cases, the lowest energy conformer found contains the predicted local geometry **1**. There are no deviations from this local geometry for the simple carbocycle (*Z*)-3-methylcyclododecene among any of the conformers within 1.5 kcal of the best one found. Similarly, all conformations of the corresponding major epoxide[1] up to 2 kcal above the best one found are derived from local conformer **1** + oxygen attached from the peripheral direction (attack away from transannular steric bulk). Since both the alkene and the epoxide have similar conformational preferences, it is safe to extrapolate this geometry to the transition state for epoxidation.[1]

The same alkene geometry is also found for the best conformer of lactone **5Z**, but in this case, a conflict between the local preference of the *Z*-alkene and the (presumably) transoid lactone subunit is apparent. The lowest energy conformer (Figure 1A) does not have the idealized crownlike (carbonyl eclipsed with O–C–H hydrogen) environment for the secondary ester –C(O)–O–CH(CH_3)– segment shown in structure **7** which is ex-

(15) For a survey of earlier literature, see ref 2b and 16.

(16) Recent examples of related epoxidations: Still, W. C.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105. Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *Ibid.* **1986**, *108*, 2106.

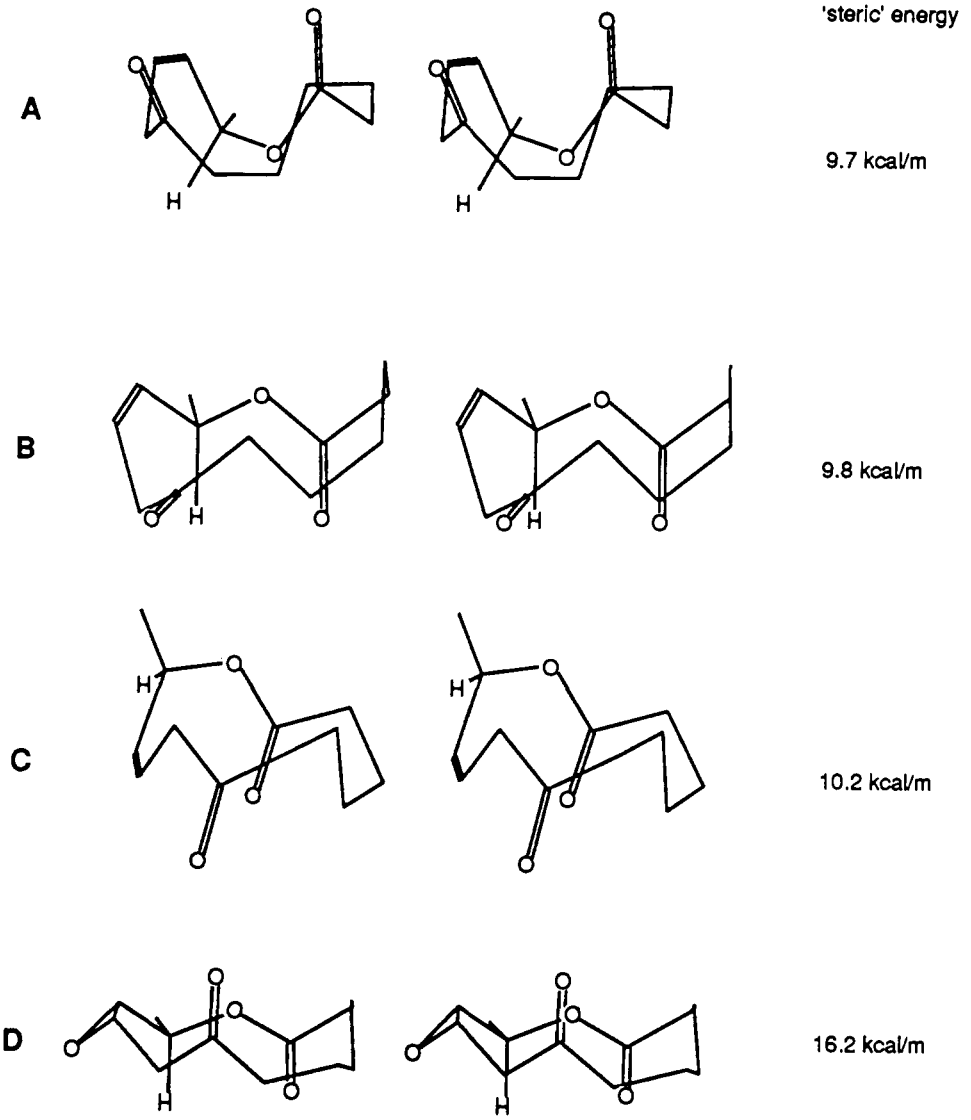


Figure 1. *Z*-Lactone (**5Z**) and the major epoxide (**14**). The three-dimensional images can be visualized with a simple stereo viewer (such as the "Stereoscope", Hubbard Scientific Co., Northbrook, IL) or by focusing the eyes on a point ca. 50 cm away, inserting the printed images ca. 35 cm away and refocusing the eyes slightly until the two images coincide.

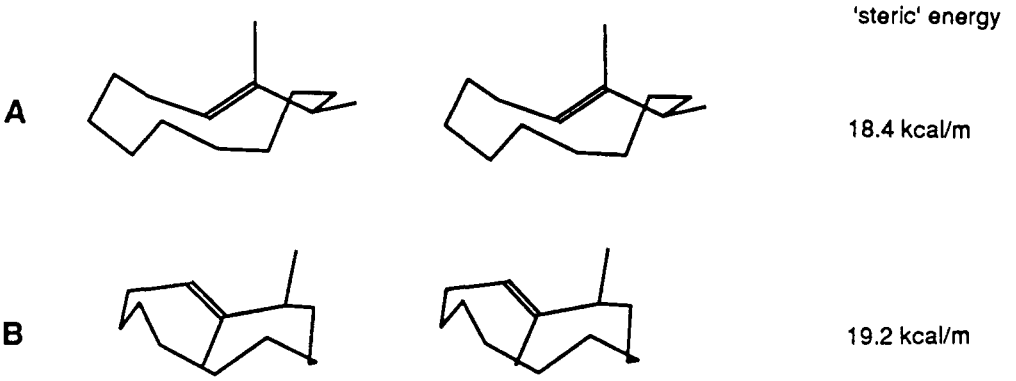


Figure 2. 2,3-Dimethylcyclododecene.

pected in a typical medium ring lactone according to X-ray data.[3] This local geometry does appear in the second best conformer (Figure 1B), but the third best (Fig. 1, C, 0.5 kcal above A) deviates from "ideal" ester geometry and also adopts the "nonideal" pseudoaxial methyl geometry. Such deviations are less apparent in the corresponding major epoxide, and the best conformer found (Figure 1D) has the idealized local geometry for both epoxide and lactone. However, there is a significant decrease in epoxidation face selectivity in **5Z** compared to (*Z*)-3-methylcyclododecene (3:1 vs. 6:1), and the conflicting preferences of *Z*-alkene and *E*-lactone subunits are likely responsible for compressing the $\Delta\Delta G^*$ of competing transition states leading to **14** vs. **15**.

As expected,[1] the lowest energy conformers of (*E*)-3-methylcyclododecene contain the crownlike, pseudoequatorial segment C—CH=CH—C(CH_3)—C as in local conformer **2**. Deviations are more common than in the *Z*-isomer, and the first non-crown conformation is encountered 0.9 kcal above the best one. The situation with the major epoxide (**2** + oxygen from the peripheral direction) is very similar and the best conformers correspond to idealized crownlike local geometry. The (*E*)-2,3-dimethylcyclo-

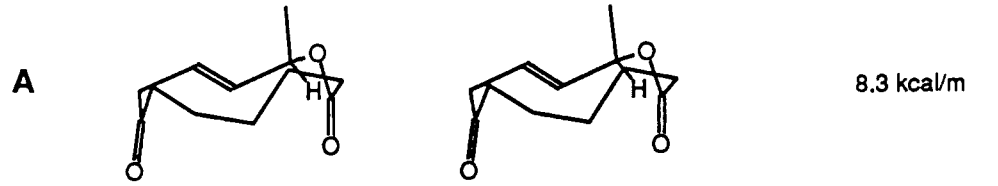


Figure 3. *E*-Lactone (**5E**).

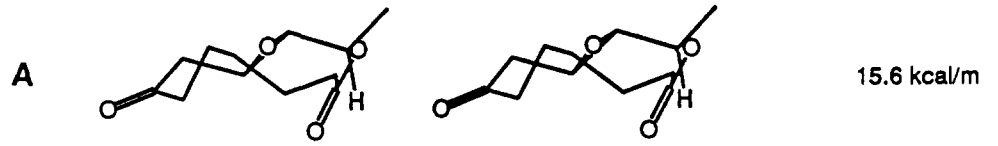


Figure 4. Epoxide **8**.

dodecene system has been studied briefly as a model for lactone **6**. The best conformer (by 0.7 kcal, Figure 2A) corresponds to the idealized geometry **2**, a result which is somewhat surprising in view of the poor selectivity encountered with the related trisubstituted lactone **6** in epoxidation as well as in osmylation. However, the continuum of next best conformers in the hydrocarbon case shows little preference between local conformer **2** and non-crown structures (for example B, Figure 2, 0.8 kcal above A). Apparently, the transition states in MCPBA or OsO_4·L addition to **6** discriminate poorly between variants of these geometries.

Not surprisingly, the *E*-lactone **5E** is the most delicately balanced system of all those compared by the computational method. The lowest energy conformer (Figure 3A) has a non-crown olefin environment as well as a non-crown ester linkage, and none of the other conformers within 1 kcal of A really corresponds to idealized olefin geometry. This situation undoubtedly results from the demanding geometric requirements of *E*-alkene and transoid ester subunits in the same vicinity. However, the transition state appears not to be perturbed by these ground-state conflicts, judging from the high epoxidation selectivity of **5E**. This system behaves at least as well as does the corresponding carbocycle ((*E*)-3-methylcyclododecene[1]), and the local conformer prediction is consistent with the observed epoxide stereochemistry.

The results of MACROMODEL conformer evaluation of epoxide **8** provide important insight into the origin of high epoxidation selectivity with **5E**. The four best conformers found (within 0.6 kcal of the lowest one, A, Figure 4) correspond to the local geometry **2** + "peripheral" oxygen. Both the ester and trans epoxide subunits have the crownlike environment with a pseudoequatorial adjacent methyl group, and the ester carbonyl is within ca. 20° of the "ideal" eclipsed arrangement relative to pseudoaxial allylic hydrogen. In this case, extrapolation from product geometry to the transition state is most appropriate. The product epoxide fits the local conformer approximation well, and by implication, the transition state must be sufficiently advanced to feel this preference. The conflicting preferences of the starting alkene, on the other hand, are not important in the transition state.

In summary, the local conformer approximation for epoxidation stereochemistry survives the presence of allylic ester functionality. The favored ground state and product geometries computed with the method of Still et al.[5] compare well with the qualitative analysis of the epoxidations. As in our earlier study,[1] osmylations obey different rules in the case of *E*-alkenes, but the *Z* alkenes, including lactone **5Z**, react as predicted by local conformer analysis.

Experimental Section

Alcohol A3. To a solution of stannane **A1** (11.6 g, 26.25 mmol)[6] in dry THF (50 mL), at −78 °C, was added *n*-BuLi (18 mL, 1.57 M, 28.3 mmol). The mixture was stirred for 1 h at −78 °C. CuI (685.8 mg, 3.6 mmol, purified by extraction with THF and drying under high vacuum) was added in one portion. Stirring was continued for 15 min more, at which time 1,7-octadiene monoxide (2.2 g, 17.5 mmol) was added. The mixture was stirred for 1.5 h at −78 °C and 12 h at −25 °C and was then quenched by the addition of acetic acid (2.3 mL). The reaction mixture was partitioned between ether and water. The organic layer was washed with NH_4Cl (saturated, aqueous, 50 mL) and brine (50 mL) followed by drying over $MgSO_4$. The solvent was evaporated and the residue applied to a silica gel column (70 × 4 cm). Elution with hexane removed all of the tetrabutylstannane. The elution solvent was changed to 30% ethyl acetate–hexane. Fractions were collected every 20 mL. In this way, pure **A3** was isolated (3.68 g, 71%, R_f 0.18, 30% ethyl acetate–hexane): NMR (100 MHz, $CDCl_3$) δ 5.96–5.24 (m, 3 H), 5.05–4.84 (m, 2 H, terminal methylene), 4.60 (br s, 1 H, OTHP), 4.20 (quintet, J = 6 Hz, 1 H, allylic methine), 4.0–3.3 (m, 3 H), 2.4–1.2 (m, 16 H), 1.28 (d, J = 6 Hz, 3 H); IR (neat) 3420, 2940, 2870, 1450, 1375, 1210 cm^{-1}.

Acylation of A3. Protected alcohol **A3** (494 mg, 1.66 mmol) was dissolved in methanol (25 mL). A small amount (ca. 20 mg) of *p*-toluenesulfonic acid was added. After 1.5 h triethylamine (2 mL) was added and the solvent evaporated. The residue was dissolved in ether and washed once with 10% HCl (10 mL) and once with brine. The solution was dried ($MgSO_4$) and evaporated and the residue taken up in ether (25 mL). Triethylamine (1.84 mL, 13.28 mmol) was added along with a catalytic amount (ca. 100 mg) of dimethylaminopyridine. Acetic anhydride (1.30 mL, 13.82 mmol) was then added and the mixture stirred for 1 h at 25 °C. Routine aqueous workup gave a residue which was purified by passing through a short (15 g) silica gel plug with 30% ethyl acetate to remove polar impurities. The diacetate was sufficiently pure for the next step.

Acid A4. The diacetate prepared as above (1.0 g, 3.5 mmol) was dissolved in dry THF (20 mL) at 0 °C. To this solution was added 9-**BBN** in THF (7.4 mL, 0.5 M, 3.7 mmol, Aldrich). The mixture was then warmed to 25 °C and stirred overnight. The trialkylborane was oxidized by the addition of 3 M NaOAc (30 mL) followed by dropwise addition of 30% H_2O_2 (5.8 mL), again at 0 °C. The mixture was stirred at 25 °C for 5 h. The layers were separated and the organic layer washed twice with brine (20 mL). After drying $MgSO_4$) and solvent evaporation, the residue was applied to a short silica gel column. Elution with 30% ethyl acetate:hexane gave first some nonpolar impurities, followed by the desired primary alcohol (822 mg, 78%). The alcohol (185 mg, 0.61 mmol) was dissolved in DMF (20 mL). Pyridinium dichromate (1.53 g, 4.06 mmol) was added in one portion. The reaction mixture was stirred for 20 h at 25 °C, at which time TLC analysis indicated the reaction to be complete. The reaction mixture was poured into an equal volume of water and extracted with ether (2 × 20 mL). The water layer was salt saturated and extracted again with ether. The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was evacuated overnight under high vacuum to remove residual DMF. The diacetoxy acid (146 mg, 76%) was used without further purification.

Diacetoxy acid prepared as above 77 mg, 0.25 mmol) was dissolved in methanolic KOH (2.6 mL, 1.25 M) and stirred at 25 °C for 30 min. The solvent was evaporated (aspirator) and the residue dissolved in water (2 mL). The aqueous layer was extracted with ether to remove nonacidic contaminants. The water layer was then acidified with HCl to pH 2 and extracted (6 × 1 mL) with ethyl acetate. The water layer was salt saturated and extracted again with ethyl acetate (2 × 2 mL). After drying over $MgSO_4$ and solvent evaporation, the residue was evacuated under high vacuum overnight to give **A4** (40 mg, 71%): NMR (200 MHz, $CDCl_3$) δ 6.00 (br s, 3 H), 5.60 (m, 2 H), 4.20 (br m, 1 H), 3.65 (br m, 1 H), 2.37 (t, J = 7.4 Hz, 2 H), 2.10 (m, 2 H), 1.80–1.20 (m, 8 H), 1.23 (d, J = 6.0 Hz, 3 H); IR (neat) 3400 (br), 2960, 1710 cm^{-1}; m/e, calcd for $C_{12}H_{22}O_4$ 230.15179, found 230.1517.

Lactonization of A4. 2-Bromo-*N*-methylpyridinium iodide (515 mg, 1.73 mmol) was dissolved in dry CH_3CN (70 mL) and heated to reflux. To this solution was added, via motor-driven syringe, a solution of acid **A4** (101 mg, 0.44 mmol) and triethylamine (1.02 mL, 7.4 mmol) in CH_3CN (10 mL). The addition was performed at a rate of 1.25 mL/h. When addition was complete, the reaction mixture was stirred for 1 h at 90 °C, solvent was then removed (aspirator), and the tarry, black

residue was applied to a short silica gel column (15 g). After elution with 40% ethyl acetate (80 mL) a pale yellow oil was isolated. The residue was purified further by PLC (40% ethyl acetate:hexane). A minor band (10 mg, 11%) was isolated (R_f 0.2) and assigned structure **A6**: NMR (270 MHz, $CDCl_3$) δ 5.65 (m, 2 H), 4.59 (pentet, J = 7.0 Hz, 1 H), 4.29 (m, 1 H), 2.62–2.36 (m, 2 H), 2.49 (t, J = 8.0 Hz, 2 H), 1.80–1.50 (m, 8 H), 1.26 (d, J = 6.5 Hz, 3 H); IR ($CHCl_3$) 3400, 2940, 1720, 1460, 1265 cm^{-1}; m/e, no parent ion, base 135 amu. The major band (R_f 0.4) was isolated (36 mg, 41%) as a mixture (1:1) of lactone **A5** (mixture of diastereomers) and byproducts. To an ether solution of the hydroxy lactone **A5** (96 mg, 45 mmol, contaminated with byproducts) was added Jones' reagent (0.25 mL, 2 M, 0.5 mmol). After 15 min, the mixture was poured into ether/water and the aqueous layer extracted twice with ether. The combined organic layers were washed with $NaHCO_3$ brine and dried ($MgSO_4$) and evaporated. The oxidation products were separated by HPLC with use of a μ-Partisil (Whatman M-9) column (60:20:20 hexane–CH_2Cl_2–Et_2O, 5 mL/min). The fast-moving band (27 mg) proved to be a mixture of products of overoxidation: m/e 226.1206 (calcd for $C_{12}H_{18}O_4$); partial NMR ($CDCl_3$) δ 5.92 (td, J = 7.7, 15.4 Hz) 5.71 (dd, J = 15.4, 8.1 Hz), and 4.38 (dd, J = 6.1, 5.9 Hz).

The slower moving band proved to be the desired keto lactone **5E** (29 mg, 31%, R_f 0.31): mp 45–46 °C (from hexane); NMR (270 MHz, $CDCl_3$) δ 5.29 (m, 2 H), 5.00 (pentet, J = 6.5 Hz, 1 H), 2.79 (dd, J = 7.2, 10.8 Hz, 1 H), 2.71 (dd, J = 10.6, 5.1 Hz, 1 H), 2.46 (ddd, J = 4.3, 9.3, 13.6 Hz, 1 H), 2.15 (ddd, J = 2.8, 6.3, 11.3 Hz, 1 H), 1.94 (m, 2 H), 1.68 (m, 1 H), 1.47 (m, 2 H), 1.24 (d, J = 5.8 Hz, 3 H), 1.09 (m, 3 H), IR (neat) 2950, 1720, 1705 cm^{-1}; m/e, calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1256.

MEM Ether B3. To a solution of 1-(trimethylsilyl)propyne[8b] (0.561 g, 5.0 mmol) in THF (10 mL) at −78 °C was added *tert*-butyllithium (1.9 mL, 4.12 mmol, 2.18 M in pentane) dropwise via syringe. The solution turned bright yellow and as the reaction progressed, the color dissipated until it was a very light yellow. After 2 hs, solid copper(1) iodide (0.413 g, 2.17 mmol) was added in one portion. The cooling bath was changed to a 0 °C ice–water bath and the reaction was allowed to warm up. After about 1 min, the mixture turned brown and the solids dissolved. The mixture was recooled to −78 °C after 30 min, and 6-carbethoxyhexanal,[17] **B2** (0.25 g, 1.44 mmol), in THF (2 mL) was added dropwise via syringe over a 10-min period. TLC analysis after 20 min indicated the absence of any aldehyde. The reaction mixture was poured into cold saturated aqueous NH_4Cl (20 mL) and ether (20 mL). The aqueous layer turned a bright blue. The organic layer was washed once more with saturated aqueous NH_4Cl (25 mL) and with brine (1 × 20 mL). The aqueous layers were combined and washed with ether (1 × 10 mL) and ethyl acetate (1 × 20 mL). The organic layers were combined and dried ($MgSO_4$) and solvent removed (aspirator) to yield 0.423 g of an orange oil which was used without purification. To a solution of the crude alcohol (0.10 g, 0.35 mmol) in CH_2Cl_2 (3 mL) was added *N,N*-diisopropylethylamine (0.19 mL, 1.05 mmol) and MEM chloride (Aldrich, 0.12 mL, 1.05 mmol) at room temperature. After 15 h the reaction mixture was washed with 1 N aqueous HCl (2 × 7 mL) and 5% aqueous $NaHCO_3$ (1 × 7 mL). The aqueous layers were each extracted with methylene chloride (2 × 5 mL) and the organic layers were combined and dried ($MgSO_4$) and solvent removed (aspirator) to give 0.13 g of an oil. Purification yielded 96 mg of a clear oil (74%, R_f 0.21, 15% ethyl acetate/hexane), **B3**: IR (neat) ALKYNE 2160, C=O 1730 cm^{-1}; 270-MHz NMR ($CDCl_3$) δ 4.78 (d, J = 7.3 Hz, 1 H), 4.69 (d, J = 7.3 Hz, 1 H), 4.07 (q, J = 7 Hz, 2 H), 3.73–3.57 (m, 3 H), 3.52–3.47 (m, 2 H), 3.34 (s, 3 H), 2.4 (dd, J = 5.7, 2 Hz, 2 H), 2.24 (t, J = 7.4 Hz, 2 H), 1.65–1.45 (m, 4 H), 1.4–1.2 (m, 4 H), 1.2 (t, J = 7 Hz, 3 H), 0.08 (s, 9 H).

Desilylation of B3 Ethyl 7-((2-Methoxyethoxy)methoxy)dec-9-ynoate. The silyl compound, **B3** (0.70 g, 1.81 mmol), was dissolved in THF (20 mL) and tetrabutylammonium fluoride (TBAF) (0.57 g, 2.17 mmol) in THF (5 mL) was added dropwise. After all the TBAF had been added, the dark reaction mixture was allowed to stir for 10 min and was then poured into saturated aqueous NH_4Cl (20 mL). Ether (20 mL) was added and the organic layer washed once more with saturated aqueous NH_4Cl (25 mL) and with brine (1 × 25 mL). The combined aqueous layers were extracted with ether (1 × 20 mL) and ethyl acetate (1 × 20 mL). The organic layers were combined and dried ($MgSO_4$) and solvent removed (aspirator) to yield 0.59 g of a dark brown oil. Purification yielded 0.458 g (84%) of an oil (R_f 0.22, 20% ethyl acetate/hexane): IR (neat) ALKYNE 2130, C=O 1735 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 4.83 (d, J = 7 Hz, 1 H), 4.76 (d, J = 7 Hz, 1 H), 4.13 (q, J = 7 Hz, 2 H), 3.82–3.64 (m, 3 H), 3.6–3.54 (m, 2 H), 3.4 (s, 3 H), 2.45 (dt, J = 5, 2.5 Hz, 2 H), 2.3 (t, J = 7.4 Hz, 2 H), 1.99 (t, J = 2.6 Hz, 1 H), 1.73–1.55 (m, 4 H), 1.45–1.3 (m, 4 H), 1.26 (t, J = 7 Hz, 3 H).

Ethyl 7-((2-Methoxyethoxy)methoxy)-11-hydroxyundec-9-ynoate (B4). To a solution of the alkyne from above (98 mg, 0.326 mmol) in THF (2 mL) at −78 °C was added *n*-BuLi (0.23 mL, 0.39 mmol, 1.72 M in hexane) dropwise via syringe over 2 min. After 50 min, freshly distilled acetaldehyde (0.10 mL, 1.79 mmol) was added. The reaction was quenched after 20 min by pouring it into cold saturated aqueous NH_4Cl (5 mL). Ether (5 mL) was added and the mixture extracted. The organic layer was then washed with brine (1 × 5 mL), and the aqueous layers were combined and extracted with ether (2 × 7 mL). The organic layers were combined and dried ($MgSO_4$) and solvent removed (aspirator). Purification of the crude oil on an HPLC Magnum 9 column (1% MeOH/$CHCl_3$, 4.4 mL/min) gave 75 mg (68%) of **B4** as a clear oil: IR (neat) ALKYNE 2240, OH 3450, C=O 1735 cm^{-1}; 270-MHz NMR ($CDCl_3$) δ 4.8 (d, J = 7.1 Hz, 1 H), 4.75 (d, J = 7.1 Hz, 1 H), 4.5 (q, J = 6.5 Hz, 1 H), 4.13 (q, J = 7.2 Hz, 2 H), 3.9–3.81 (m, 1 H), 3.75–3.65 (m, 2 H), 3.61–3.56 (m, 2 H), 3.4 (s, 3 H), 2.45 (dd, J = 5.7, 1.8 Hz, 2 H), 2.4 (br s, 1 H), 2.3 (t, J = 7.5 Hz, 2 H), 1.73–1.55 (m, 4 H), 1.42 (d, J = 6.6 Hz, 3 H), 1.42–1.3 (m, 4 H), 1.26 (t, J = 7.2 Hz, 3 H).

Hydrogenation of B4; Conversion to B5. A suspension of the catalyst Pd on $CaCO_3$ with $Pb(OAc)_4$[18] (100 mg) in ethyl acetate (10 mL) was allowed to equilibrate for 50 min under a slight positive pressure of hydrogen. The alkyne **B4** (0.15 g, 0.44 mmol) in ethyl acetate (2 mL) was then added via the sidearm, and the reaction was stirred for 1.5 h under a slight positive pressure of hydrogen. Filtration through a plug of Celite and removal of the solvent (aspirator) yielded 0.166 g of an oil. NMR spectral analysis showed the oil to be a 9:1 mixture of the *Z:E* olefin isomers. This crude oil was dissolved in methanol (5 mL) and a solution of KOH in ethanol (5 mL, 6.2 mmol, 1.25 M) was added. The reaction was allowed to stir for 24 h, and then the solvent was removed (aspirator). The residue was dissolved in water (5 mL) and washed with ether (1 × 5 mL). The aqueous layer was carefully acidified to pH 2 with 6 N HCl and extracted with ethyl acetate (2 × 7 mL). The aqueous layer was then acidified to pH 1, saturated with solid NaCl, and extracted again with ethyl acetate (3 × 7 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed (aspirator) to give **B5** (0.163 g) as a clear oil: IR (neat) OH 3420, C=O 1710 cm^{-1}; 270-MHz NMR ($CDCl_3$) δ 5.64–5.4 (m, 3 H), 4.79–4.7 (m, 2 H), 4.65–4.55 (m, 1 H), 3.75–3.6 (m, 3 H), 3.58–3.54 (m, 2 H), 3.39 (s, 3 H), 2.52–2.3 (m, 1 H), 2.34 (t, J = 7.3 Hz, 2 H), 2.3–2.15 (m, 1 H), 1.7–1.6 (m, 3 H), 1.58–1.47 (m, 2 H), 1.43–1.3 (m, 4 H), 1.25 (d, J = 6.3 Hz, 3 H).

Lactonization of B5. MEM Lactone B6. To a refluxing solution of 2-bromo-*N*-methylpyridinium iodide (0.416 g, 1.4 mmol) in CH_3CN (50 mL) was added via motor-driven syringe a solution of the acid **B5** (0.11 g, 0.35 mmol) and triethylamine (0.78 mL, 5.6 mmol) in CH_3CN (10 mL). The addition was performed at a rate of 1.25 mL/h. When the addition was complete, the reaction mixture was heated at reflux for 1 h. The solvent was then removed (aspirator) and the tarry black-green residue applied to a plug of silica gel (40 g). Elution with 40% ethyl acetate/hexane (150 mL) and solvent removal yielded a yellow oil (67 mg) that was further purified via HPLC to give 40 mg of the lactone **B6** as a mixture of diastereomers (R_f 0.20, 25% ethyl acetate/hexane) contaminated by ca. 20–30% of byproducts which could not be separated. IR (neat) C=O 1722 cm^{-1}; 270-MHz NMR ($CDCl_3$) δ 5.85–5.35 (m, 2 H), 4.83–4.65 (m, 2 H), 3.9–3.77 (m, 1 H), 3.77–3.6 (m, 2 H), 3.6–3.5 (m, 2 H), 3.39 (s, 3 H), 2.6–2.5 (m, 1 H), 2.5–2 (m, 4 H), 1.9–1.1 (m, 8 H), 1.38–1.32 (m, 3 H).

Lactone 5Z. The MEM-protected lactone **B6** (33.5 mg, 0.112 mmol) was dissolved in CH_2Cl_2 (1 mL) and cooled to −78 °C. A solution of $BrBMe_2$[9] in CH_2Cl_2 (0.22 mL, 0.336 mmol, 1.5 M) was added dropwise via syringe. After 15 min, the cold solution was transferred quickly via cannula into a vigorously stirring mixture of THF (2 mL) and saturated aqueous $NaHCO_3$ (1.5 mL). The mixture was stirred for 15 min and then partitioned between water (5 mL) and CH_2Cl_2 (5 mL). The organic layer was then washed with water (5 mL), 10% aqueous $NaHSO_4$ (5 mL), and brine (5 mL). All the aqueous layers were extracted with ethyl acetate (2 × 5 mL). The organic layers were combined and dried ($MgSO_4$) and solvent removed to give 34 mg of an oil consisting of the deprotected hydroxy lactone. Dimethyl sulfoxide (DMSO) (178 μL, 2.50 mmol) was added to a cold (−78 °C) solution of oxalyl chloride (73 μL, 0.83 mmol) in CH_2Cl_2 (1 mL). After 1 min, a solution of the hydroxy lactone prepared as above (59 mg, 0.28 mmol) in CH_2Cl_2 (0.5 mL) was added via cannula. The solution was stirred at −23 °C for 1 h, and triethylamine (0.35 mL, 2.50 mmol) was added, producing a yellow precipitate. The ice bath was removed and the mixture allowed to warm to room temperature. After 20 min, the reaction mixture was washed

(17) Gapinski, D. M. Ph.D. Dissertation, University of Wisconsin, 1982.

(18) Lindlar, H.; Dubuis, R. *Org. Synth.* **1966**, *46*, 89.

with 1 N aqueous HCl (1 × 5 mL), water (1 × 5 mL), and brine (1 × 5 mL). The aqueous layers were extracted with CH_2Cl_2 (2 × 5 mL), and the organic layers were combined and dried ($MgSO_4$) and solvent removed (aspirator), to give 50 mg of a foul-smelling oil. Elution through a plug of silica gel gave 20 mg of product and final purification by HPLC (Magnum 9 column, 5:1:1 hexane–ether–Ch_2Cl_2) gave **5Z** as an oil; only 9 mg were obtained due to mechanical and volatility losses: *m/e*, exact mass for $C_{12}H_{18}O_3$ 210.1251, found 210.1256; error = 2.4 ppm; IR (neat) C=O 1730, C=O 1715 cm^{-1}; 270-MHz NMR ($CDCl_3$) δ 5.8–5.68 (m, 2 H), 5.6 (quintet J | 6.3 Hz, 1 H), 3.34 (dd, J = 15.5, 7.9 Hz, 1 H), 3.23 (dd, J = 15.5, 5.5 Hz, 1 H), 2.63 (dt, J = 12.5, 7.3 Hz, 1 H), 2.42 (ddd, J = 14, 8.5, 3.9 Hz, 1 H), 2.27 (ddd, J = 14.3, 8.6, 3.6 Hz, 1 H), 2.17 (dt, J = 12.5, 7 Hz, 1 H), 1.8–1.5 (m, 4 H), 1.48–1.25 (m, 2 H), 1.37 (d, J = 6.3 Hz, 3 H). The material was contaminated by ca. 10% **5E** and **5Z** could not be purified further.

Aldehyde C3. To a solution of diisopropylamine (5.4 mmol) in dry THF (20 mL) was added *n*-BuLi (5.4 mmol) at −78 °C. The mixture was stirred for 20 min and warmed to 0 °C. *N*-Cyclohexyltiglaldimine **C1** (4.9 mmol)[10] was added neat over 1–2 min. The solution immediately developed a bright yellow color. After the mixture was stirred for 20 min, HMPA (4.9 mmol) was added and the mixture was cooled to −78 °C. The aldehyde **C2**[17] (3 mmol in 3 mL hexane) was added dropwise over 15 min and the mixture was stirred for 1 h at −78 °C and then for 2 h at 0 °C under nitrogen. The reaction was quenched with acetic anhydride (22 mmol). After 1 h of stirring at 0 °C, the mixture was poured into an equal volume of pH 4.5 buffer (CH_3CO_2H/CH_3CO_2Na) and stirred for 1 h at 25 °C. Product isolation involved partitioning between water–hexane, extraction with saturated $NaHCO_3$, and drying over $MgSO_4$. After solvent removal, the product was isolated by preparative TLC over silica gel to yield 0.59 g (53%) of **C3** (R_f 0.27, 70:15:15 hexane–ether–CH_2Cl_2): NMR (270 MHz, $CDCl_3$) δ 9.66 (s, 1 H), 6.48 (q, J = 7.5 Hz, 1 H), 5.04 (qt, 6.6 Hz, 1 H), 3.59 (t, J = 6.4 Hz, 2 H), 2.62 (t, J = 6.8 Hz, 2 H), 2.05 (s, 3 H), 1.76 (s, 3 H), 1.32 (m, 10 H), 0.89 (s, 9 H), 0.04 (s, 6 H); IR (neat) 2940, 2865, 2720 (w), 1790, 1695 cm^{-1}; *m/e*, calcd 370.25389, found 370.2540.

Alcohol C4. Aldehyde **C3** (590 mg, 1.60 mmol) was dissolved in dry THF (25 mL). The mixture was then cooled to −20 °C. A stock solution of ethylmagnesium iodide (2.36 mL, 0.74 M, 1.75 mmol) was added dropwise with good stirring. The mixture was stirred for 1 h at −20 °C. The reaction mixture was then poured into an equal volume of NH_4Cl (saturated) at 0 °C and stirred for 5 min. Routine aqueous workup followed. The residue was applied to a 40-g silica gel column and eluted with 60:20:20 hexane:CH_2Cl_2:ether. Fractions were collected every 20 mL. Combining appropriate fractions gave pure Grignard adduct (378 mg, 60%).

A total of 837 mg of material prepared in this way was dissolved in ether (15 mL). Triethylamine (0.7 mL, 5.11 mmol) and dimethylaminopyridine (25.6 mg, 0.21 mmol) were added. The mixture was cooled to 0 °C. Acetic anhydride (0.79 mL, 8.36 mmol) was added via syringe, and the mixture was then stirred for 30 min at 0 °C. The reaction mixture was warmed to 0 °C and submitted to routine aqueous workup. The reaction residue was purified by passage through a short (15 g) silica plug with 70:15:15 hexane:ether:methylene chloride to yield a diacetate OTBS ether (826 mg, 89%): R_f 0.42, 60:20:20 hexane–ether–CH_2Cl_2.

The silyl ether diacetate (50 mg, 0.11 mmol) was dissolved in THF (4 mL) and treated with 4 drops of 10% aqueous HCl. After 1 h at 25 °C, the reaction mixture was partitioned between ether and water. The organic layer was washed with saturated $NaHCO_3$ (aqueous) and brine. After drying over $MgSO_4$ and solvent evaporation (aspirator followed by high vacuum), diacetate **C4** was isolated (34.9 mg, 95%): NMR (100 MHz, $CDCl_3$) δ 5.36 (t, J = 7 Hz, 1 H), 5.00 (t, J = 6 Hz, 2 H), 2.28 (t, J = 7 Hz, 2 H), 2.08 ns, 3 H), 2.05 (s, 3 H), 1.90–1.00 (m, 12 H), 1.62 ns, 3 H), 0.84 (t, J = 8 Hz, 3 H); IR (neat) 3450, 2940, 2870, 1740 cm^{-1}.

Acid C6. Diacetate **C4** (2.02 g, 6.16 mmol) was dissolved in dry DMF (30 mL). Pyridinium dichromate (8.08 g, 21.5 mmol) was added in one portion. The reaction mixture was stirred overnight at 25 °C and then poured into an equal volume of water and extracted (4 × 50 mL) with ether. The organic layer was then washed with brine and dried over $MgSO_4$, solvent was removed (aspirator), and residual DMF was pumped off under high vacuum. The residue was applied to a silica gel column (15 g) and eluted with 1:1 ethyl acetate–hexane to remove nonpolar impurities, allowing **C5** (1.5 g, 72%) to be isolated after elution with ethyl acetate. To a methanol solution of **C5** (206 mg, 0.6 mmol) was added methanolic KOH (3 mL, 1.25 M). The mixture was stirred at 25 °C for 1.5 h and solvent was then evaporated, the residue was dissolved in water and extracted (1 × 10 mL) with ether to remove nonacidic contaminants. The aqueous layer was then acidified to pH 3 with 6 N HCl and extracted (3 × 10 mL) with ethyl acetate, the pH of the aqueous solution was lowered to 1, and the solution was extracted again with ethyl acetate. The combined organic layers were dried, filtered, evaporated, and evacuated under high vacuum overnight giving **C6** (120 mg, 76%), which was used directly for all lactonizations: NMR (270 MHz, $CDCl_3$) δ 5.42 (br m, 4 H), 3.94 (t, J = 6.8 Hz, 1 H), 3.65 (m, 1 H), 2.33 (t, J = 7.2 Hz, 2 H), 2.18 (m, 2 H), 1.60 (s, 3 H), 1.60–1.35 (m, 10 H), 0.84 (t, J = 7.2 Hz, 3 H, methyl diastereomer), 0.83 (t, J = 7.3 Hz, 3 H, methyl diastereomer); IR (neat) 3400 (br), 2970, 1715 cm^{-1}.

Lactonization of Acid C6. 1-Methyl-2-bromopyridinium iodide (298 mg, 1.0 mmol) was dissolved in dry CH_3CN (70 mL) and heated to 90 °C. Acid **C6** (67 mg, 0.25 mmol) and triethylamine (0.26 mL, 1.9 mmol) were dissolved in dry CH_3CN (10 mL). The solution was loaded into a 10-mL syringe and added to the pyridinium salt solution at the rate of 1.25 mL/h (via motor-driven syringe pump). After addition was complete, the reaction mixture was stirred for 1 h at 90 °C. The solvent was then removed (aspirator) and the tarry residue applied to a short silica gel column (15 g). Elution with 1:1 ethyl acetate–hexane (100 mL) gave a pale yellow residue (ca. 40 mg). This residue was further purified by HPLC (2 ft porasil A, 1:1 ethyl acetate–hexane, 10 mL/min) giving a fast-moving band (24 mg **C8** as 1:1 mixture of diastereomers) contaminated with a small amount of a third component: NMR (270 MHz, $CDCl_3$) δ 5.55 (t, J = 7.7 Hz, 2 H), 5.11 (t, J = 7.2 Hz, 1 H), 5.04 (t, J = 7.0 Hz, 1 H), 3.87 (m, 1 H), 3.54 (m, 1 H), 2.37–2.19 (m, 8 H), 1.73 (s, 6 H), 1.70–1.27 (m, 20 H), 0.92 (t, J = 7.3 H, 3 H), 0.90 (t, J = 7.4 Hz, 3 H). Lactone **C7** (6 mg, 10%) was isolated from a slower moving band. Only one diastereomer of **C7** was isolated: NMR (270 MHz, $CDCl_3$) δ 5.43 (t, J = 6.8 Hz, 1 H), 4.59 (quintet, J = 6.6 Hz, 1 H), 3.94 nt, J = 6.8 Hz, 1 H), 2.4–2.35 (m, 4 H), 1.82–1.51 (m, 10 H), 1.62 (s, 3 H), 0.84 (t, J = 7.0 Hz, 3 H); IR (neat) 3400, 2930, 2860, 1720 cm^{-1}; *m/e*, calcd for $C_{14}H_{24}O_3$ 240.17253, found 240.1726.

Oxidation of Hydroxy Lactone C8. To a stirred solution of hydroxy lactone **C8** (58.5 mg, 0.24 mmol, contaminated with a second compound) in CH_2Cl_2 (15 mL) was added pyridinium dichromate (210 mg, 0.46 mmol). The reaction mixture was stirred for 18 h at 25 °C and then filtered through a Celite mat and the solvent evaporated. The residue was passed through a very short SiO_2 plug to remove nonpolar impurities and then submitted to HPLC. The two components could only be separated with use of an analytical μ-porasil column (2:1:1 hexane–CH_2Cl_2–Et_2O, 2 mL/min) and small injection volumes (less than 4 mg of mixture per injection). After repeated injections, pure keto lactone **6** was isolated (3.5 column volumes, 23 mg, 39%): NMR (270 MHz, $CDCl_3$) δ 5.68 (t, J = 8.3 Hz, 1 H), 5.08 (t, J = 7.0 Hz, 1 H), 3.10 (m, 2 H), 2.67 (ddd, J = 4.5, 12.0, 16.0 Hz, 1 H), 2.46 (ddd, J = 3.0, 6.0, 10.0 Hz, 1 H), 2.11 (m, 2 H), 1.79 ns, 3 H), 1.69 (quintet, J = 7.2 Hz, 2 H), 1.75–1.32 (m, 6 H), 0.93 nt, J = 7.9 Hz, 3 H); IR (neat) 2960, 1720, 1710 cm^{-1}; *m/e*, calcd for $C_{14}H_{22}O_3$ 238.1568, found 238.1556.

Grignard Adduct D3. Neat *cis*-5-bromo-2-pentene[19] (164 mg, 1.11 mmol) was added slowly to magnesium powder (32 mg, 1.33 mmol) in dry THF (2 mL). The reaction initiated rapidly after ca. 40 mg of bromide was added. The mixture was stirred for 20 min after addition was complete. The Grignard reagent was then added, via cannula, to a THF solution (5 mL) of 6-carboethoxyhexanal[17] (191 mg, 1.11 mmol) at −20 °C. The reaction mixture was stirred at −20 °C for 1 h and then warmed to 25 °C for 15 min and quenched with NH_4Cl (saturated, aqueous, 3 mL). Routine aqueous workup gave a colorless oil which was further purified by PLC. A band centered at R_f 0.32 (30% ethyl acetate–hexane) gave **D3** (79 mg, 30%): NMR (200 MHz, $CDCl_3$) δ 5.44 (m, 2 H), 4.14 (quartet, J = 7 Hz, 2 H), 3.54 (m, 1 H), 2.28 (m, 4 H), 1.60 (d, J = 6 Hz, 3 H), 1.2–1.6 (m, 8 H), 1.21 (t, J = 7 Hz, 3 H); IR (neat) 3450, 2930, 1725 cm^{-1}; *m/e*, calcd for $C_{14}H_{26}O_3$ 242.18818, found 242.1882.

Oxidation of D3. Alcohol **D3** (117 mg, 0.48 mmol) was dissolved in CH_2Cl_2 (10 mL). Pyridinium dichromate (Aldrich, 272 mg, 0.73 mmol) was added in one portion. The mixture was stirred for 36 h at 25 °C, at which time TLC analysis showed reaction to be complete. The reaction mixture was filtered and the solvent evaporated. The residue was applied to a preparative TLC plate and eluted with 2:1:1 hexane–ether–CH_2Cl_2. A band centered at R_f 0.36 was isolated as the desired ketone (57 mg, 50%): NMR (270 MHz, $CDCl_3$) δ 5.44 (m, 1 H), 5.34 (m, 1 H), 4.11 (quartet, J = 7.0 Hz, 2 H), 2.45 (t, J = 7.7 Hz, 2 H), 2.41 (t, J = 7.2 Hz, 2 H), 2.29 (t, J = 7.5 Hz, 4 H), 1.62 (m, 6 H), 1.25 (t, J = 7.0 Hz, 3 H); IR (neat) 2920, 1720 (br) cm^{-1}; *m/e*, calcd for $C_{14}H_{24}O_3$ 240.1725, found 240.1726.

Lactone D6. The ketone as prepared above (84 mg, 0.35 mmol) was dissolved in ethanedithiol (0.5 mL) and cooled to 0 °C. $BF_3{\cdot}Et_2O$ (49

(19) From the alcohol[20] + PBr_3.

(20) Method of: Crombie, L.; Harper, S. H. *J. Chem. Soc.* **1950**, 873. See also: Coxon, J. M.; Hartshorn, M. P.; Swallow, W. H. *J. Org. Chem.* **1974**, *39*, 1142.

μL, 0.40 mmol) was carefully added by syringe. The cold bath was removed, and the reaction was allowed to stir at 25 °C for 10 min. The reaction mixture was diluted with ether and partitioned between hexane and water. The organic layer was washed with 15% NaOH (2 × 10 mL), H_2O (1 × 10 mL), and brine (1 × 10 mL), dried ($MgSO_4$), and evaporated. The residue was purified by PLC (R_f 0.68, 3:1:1 hexane–ether–CH_2Cl_2) to give a single major product as a colorless oil (81 mg, 74%). The thioketal from above (62 mg, 0.2 mmol) in ether (3 mL) was added to OsO_4 (75 mg, 0.25 mmol) in ether (10 mL) plus pyridine (52 μL). The mixture was stirred overnight at 25 °C, $NaHSO_3$ (10 mL of 2.9 M aqueous solution) was added, and stirring was maintained for 1 h. The mixture was then diluted with ether, layers were separated, and the water layer was washed with ether (3 × 10 mL). The combined organic layers were washed with brine, dried, and evaporated, and the residue was passed through a short silica gel plug with 70% ethyl acetate–hexane to remove polar osmium residues. The resulting colorless oil was purified by PLC, eluting with 70% ethyl acetate–hexane. The sole mobile band was isolated (R_f 0.15, 50% ethyl acetate–hexane) as the desired diol (41 mg, 59%): NMR ($CDCl_3$, 270 MHz) δ 4.12 (quartet, J = 7.0 Hz, 2 H), 3.81 (m, 1 H), 3.60 (m, 1 H), 3.27 (s, 4 H), 2.30 (t, J = 8.0 Hz, 2 H), 2.30–2.18 (m, 2 H), 1.91 (m, 4 H), 1.67–1.29 (m, 8 H), 1.25 (t, J = 7.0 Hz, 3 H), 1.18 (d, J = 6.6 Hz, 3 H); IR (neat) 3490 (br), 2940, 1730 cm^{-1}.

A portion of the diol (33 mg, 0.095 mmol) was dissolved in methanol (5 mL). KOH in methanol (1.0 mL, 1.25 M) was added at 25 °C, and the mixture was stirred for 15 min. The solvent was evaporated and water added (3 mL) to dissolve the residue. The aqueous solution was extracted once with ether and then carefully acidified to pH 5 with 10% HCl. The water layer was thoroughly extracted with ethyl acetate (3 × 10 mL), salted out (NaCl), and extracted again (2 × 10 mL). The organic layers were combined, dried, and evaporated, and the residue was kept overnight under high vacuum to give acid **D5**. The crude acid was dissolved in dry CH_3CN (10 mL), along with triethylamine (0.24 mL, 1.69 mmol). This mixture was added over 6 h (via motor-driven syringe) to refluxing CH_3CN (60 mL) in which 2-bromo-*N*-methylpyridinium iodide (110 mg, 0.37 mmol) had been dissolved. The reaction mixture was heated at reflux 1 h after addition was complete at which time solvent was evaporated, and the residue was applied to a silica gel column (15 g) and eluted with 40% ethyl acetate–hexane (100 mL). The yellow residue obtained was further purified by PLC with the same solvent system. The major band (R_f 0.46) was isolated as the desired twelve-membered lactone **D6** (5 mg, 17%): NMR (270 MHz, $CDCl_3$) δ 4.72 (dq, J = 9.5, 6.1 Hz, 1 H), 3.81 (m, 1 H), 3.28 (s, 4 H), 2.38–1.83 (m, 15 H), 1.34 (d, J = 6.6 Hz, 3 H). The lactone was further characterized by conversion to acetate **D7** (TEA/Ac_2O).

Acetoxy Lactone D7. Hydroxy lactone **D6** (5 mg, 0.016 mmol) was dissolved in ether (2 mL). One crystal of 4-(dimethylamino)pyridine was added, followed by the addition of triethylamine (10 μL, 0.072 mmol) and acetic anhydride (10 μL, 0.10 mmol). The mixture was stirred at 25 °C for 30 min and then was poured into ether–water and washed with 10% HCl and brine. After drying over $MgSO_4$ and solvent evaporation, the residue was applied to an analytical TLC plate (20 × 20 cm) and eluted with 2:1:1 hexane–ether–CH_2Cl_2. The sole mobile band (R_f 0.48) was collected as **D7** (2.5 mg, 45%): NMR (270 MHz, $CDCl_3$) δ 4.98 (ddd, J = 10.1, 4.1, 2.1 Hz, 1 H), 4.88 (dq, J = 10.1, 5.5 Hz, 1 H), 3.27 (m, 4 H), 2.42 (ddd, J = 15, 8, 4 Hz, 1 H), 2.26 (ddd, J = 15, 10.5, 5 Hz, 1 H), 2.08 (s, 3 H), 1.92, 1.43 (m, 12 H), 1.22 (d, J = 5.5 Hz, 3 H); IR (CCl_4) 2920, 2840, 1740 cm^{-1}; m/e, calcd for $C_{16}H_{26}O_4S_2$ 346.1272, found 346.1271. A small sample was recrystallized from hexane (−25 °C) giving white needles, mp 84–86 °C.

10 and 11 via Osmylation of 5E. Osmium tetroxide (5 mg, 0.008 mmol) and *N*-methylmorpholine *N*-oxide[12] (10.5 mg, 0.078 mmol) were dissolved in acetone (3 mL) containing 3 drops of water. Keto lactone **5E** (15 mg, 0.071 mmol) was dissolved in acetone (3 mL) and added via cannula to the oxidizing solution. The mixture was stirred for 1.5 h at 25 °C. After this time, aqueous $NaHSO_3$ (3 mL) was added to destroy the OsO_4 and the reaction mixture was poured into an ether–water mixture. The aqueous layer was extracted twice with ether, and the organic layers were combined, washed with brine, and dried. After evaporation of solvent, the residue was dissolved in ether. A small crystal of dimethylaminopyridine was added, followed by triethylamine (98 μL, 0.9 mmol) and acetic anhydride (70 μL, 0.9 mmol). The resulting mixture was stirred for 0.5 h at 25 °C and submitted to routine aqueous workup. The residue was dissolved in dry CH_3CN (3 mL), DBU (21 μL, 0.14 mmol) was added, and the mixture was stirred for 1 h at 25 °C. The reaction mixture was partitioned between ether and water, dried ($MgSO_4$), and evaporated. TLC analysis (50:25:25 hexane–ether–CH_2Cl_2; 2 elutions) of the residue showed a major (R_f 0.27) and a minor (R_f = 0.40) product. The residue was applied to an analytical TLC plate (20 cm × 20 cm) eluted twice with 50:25:25 hexane–ether–CH_2Cl_2. The minor, fast-moving product was isolated as **10** (R_f 0.36, 3.2 mg, 17%): m/e, base = 111 amu; exact mass for $C_{14}H_{20}L_5$ 268.1305, found 268.1311; error = 2.3 ppm; IR (neat) C=O 1730, C=O 1690 cm^{-1}; 270-MHz NMR ($CDCl_3$) δ 6.49 (d, J = 15.3 Hz, 1 H), 6.33 (dd, J = 15.8, 7.5 Hz, 1 H), 5.13 (dd, J = 9.5, 8 Hz, 1 H), 5.01 (dq, J = 9.5, 6.3 Hz, 1 H), 2.68 (ddd, J = 13.4, 7.1, 4.5 Hz, 1 H), 2.49 (ddd, J = 14.3, 10.1, 4.2 Hz, 1 H), 2.35–2.2 (m, 2 H), 2.08 (s, 3 H), 1.9–1.5 (m, 4 H), 1.45–1.3 (m, 1 H), 1.29 (d, J = 6.3 Hz, 3 H), 1–0.8 (m, 1 H). The major, more polar product (R_f 0.23) was **11** (9.6 mg, 51%): m/e, base = 111 amu; exact mass for $C_{14}H_{20}O_5$ 268.1305, found 268.1311; error = 2.3 ppm; IR (neat) C=O 1730, C=O 1690 cm^{-1}; 270-MHz NMR ($CDCl_3$) δ 6.49 (s, 2 H), 5.53 (t, J = 1.8 Hz, 1 H), 5.25 (qd, J = 6.6, 2.1 Hz, 1 H), 2.68 (ddd, J = 13.4, 7.1, 4.5 Hz, 1 H), 2.49 (ddd, J = 14.3, 10.1, 4.2 Hz, 1 H), 2.35–2.2 (m, 2 H), 2.19 (s, 3 H), 1.9–1.5 (m, 4 H), 1.45–1.3 (m, 1 H), 1.24 (d, J = 6.8 Hz, 3 H), 1–0.8 (m, 1 H). Osmylation of **5Z**: the same procedure described above for **5E** on 1.2 mg of **5Z** gave a crude acetoxyenone mixture with a 3:1 ratio of **10–11** by NMR analysis. After purification, the two isomers were obtained in a combined yield of 0.9 mg with the isomer ratio unchanged.

Epoxidation/Rearrangement of 5Z. A solution of the keto lactone **5Z** (2 mg, 0.0095 mmol) in CH_2Cl_2 (0.2 mL) was added to solid mCPBA (5.8 mg, 0.0285 mmol) and stirred at ambient temperature. After 18 h, 10% aqueous Na_2SO_3 (0.2 mL) was added and the mixture stirred for 10 min. The layers were separated and the organic layer was washed with 1 M Na_2CO_3 (2 × 0.2 mL) and brine (1 × 0.2 mL). The aqueous layers were washed with CH_2Cl_2 (3 × 0.2 mL), and the organic layers were dried ($MgSO_4$) and combined and solvent removed under a stream of nitrogen. The crude residue (2.4 mg) was then dissolved in ether (0.2 mL) and DBU (3 μL, 0.02 mmol) was added. The reaction was stirred at ambient temperature for 30 min and then washed with 0.5 N HCl (2 × 0.2 mL) and brine (1 × 0.2 mL). The aqueous layers were extracted with ether (3 × 0.2 mL) and the organic layers were dried ($MgSO_4$) and combined and the solvent removed under a stream of nitrogen. The NMR spectrum of the crude product revealed the presence of two hydroxy enones, in a ratio of 3:1 (integration). The crude oil was purified via TLC (10 × 20 cm plate, 50% ethyl acetate–hexane, eluted 2×) to give pure samples (1.9 mg combined). Major hydroxy enone (R_f 0.25): exact mass for $C_{12}H_{18}O_4$ 226.12, found 226.1206; error = 2.7 ppm; IR (neat) OH 3420, C=O 1740, C=O 1690 cm^{-1}; 270-MHz NMR ($CDCl_3$) δ 6.5 (d, J = 2.7 Hz, 2 H), 4.87 (quintet, J = 6.6 Hz, 1 H), 4.16–4.08 (m, 1 H), 2.7 nbr s, 1 H), 2.63 (dt, J = 12.2, 6.5 Hz, 1 H), 2.44 (ddd, J = 14, 9.8, 3.9 Hz, 1 H), 2.38–2.3 (m, 1 H), 2.24 (ddd, J = 14, 7.5, 3.6 Hz, 1 H), 1.8–1.55 (m, 4 H), 1.5–1.35 (m, 1 H), 1.4 (d, J = 6.3 Hz, 3 H), 1.05 (dt, J = 14.9, 7.5 Hz, 1 H). Minor hydroxy enone (R_f 0.13): IR (neat) OH 3480, C=O 1720 C=O 1675 cm^{-1}; 270-MHz NMR ($CDCl_3$) δ 6.7 (dd, J = 15.8, 1.6 Hz, 1 H), 6.47 (dd, J = 15.8, 3.3 Hz, 1 H), 5.15 (qd, J = 6.8, 1.1 Hz, 1 H), 4.4–4.3 (m, 1 H), 2.66 (ddd, J = 13.3, 6.7, 3.2 Hz, 1 H), 1.82–1.5 (m, 4 H), 1.4–1.15 (m, 1 H), 1.39 (d, J = 6.8 Hz, 3 H), 1–0.78 (m, 1 H).

For correlation, the minor hydroxy enone prepared as above (1 mg, 0.004 mmol) was dissolved in CH_2Cl_2 (0.1 mL) and DMAP (one crystal), triethylamine (3 μL, 0.022 mmol), and acetic anhydride (1 μL, 0.011 mmol) were added. The reaction was washed after 30 min with 0.5 N HCl (2 × 0.2 mL) and brine (1 × 0.2 mL). The aqueous layers were extracted with CH_2Cl_2 (3 × 0.2 mL), the organic layers were dried ($MgSO_4$) and combined, and solvent was removed under a stream of nitrogen. The NMR spectrum shows the presence of only the acetoxy enone **11**.

Epoxidation of 5E. The same procedure as described for **5Z** was used with 48 h reaction time. Thus, **5E** (14 mg) gave a single major hydroxy enone (7.1 mg, 47%) which proved to be identical with the *major* hydroxyenone from **5Z**. Acylation as before gave only **10**. Traces of material were obtained at R_f corresponding to the diastereomer, but the quantity was too small (<0.1 mg) for meaningful yield estimates.

Correlation with D7. Acetoxy enones **10** and **11** (15.6 mg, 0.058 mmol) from osmylation of **5E** were dissolved in ethyl acetate (5 mL). The hydrogenation catalyst, Rh/Al_2O_3 (ca. 10 mg), was added and the reaction mixture was stirred under a slightly positive hydrogen atmosphere. After 4 h the mixture was filtered through a Celite mat and the solvent was evaporated. The residue was applied to an analytical TLC plate (20 × 20 cm) and eluted twice with 2:1:1 hexane–ether–CH_2Cl_2. The sole mobile band (R_f 0.39) was isolated as the corresponding saturated ketone mixture (9.6 mg, 68%).

The saturated keto lactone from above (9.2 mg, 0.034 mmol) was dissolved in ethanedithiol (0.2 mL). The mixture was cooled to 0 °C, and $BF_3{\cdot}Et_2O$ (5 μL, 0.04 mmol) was added via microliter syringe. After the mixture was stirred for 15 min at 0 °C, TLC showed the reaction to be complete. The mixture was diluted with ether and partitioned between hexane and water. After the organic layer was washed three times with 15% NaOH and once with brine, the solution was dried ($MgSO_4$) and

the solvent evaporated. The residue was applied to half of an analytical TLC plate (20 × 20 cm) and eluted twice with 2:1:1 hexane-CH_2Cl_2-ether. The minor, fast-moving band (R_f 0.47, 1 mg) corresponded to independently synthesized keto lactone **D7**. The major band (4.9 mg, 44%) was isolated as the diastereomeric dithioketal: NMR (270 MHz, $CDCl_3$) δ 5.05 (d of quartets, J = 6.2, 2.3 Hz, 1 H), 4.90 (ddd, J = 10.1, 4.5, 2.3 Hz, 1 H), 3.27 (m, 4 H), 2.50 (ddd, J = 14.4, 6.4, 4.1 Hz, 1 H), 2.24 (ddd, J = 4.0, 11.3, 14.4 Hz, 1 H), 2.13 (s, 3 H), 1.89-1.76 (m, 12 H), 1.22 (d, J = 6 Hz, 2 H); IR (CCl_4) 2970, 1745 cm^{-1}; m/e, calcd for $C_{16}H_{26}O_4S_2$ 346.12723, found 346.1271. The sample was recrystallized from hexane at -25 °C, mp 136-139 °C.

Epoxidation; Elimination of 6. The epoxidation, DBU sequence as described for **5E** starting with 17 mg of **6** gave a mixture of two products, separable by TLC (50% ethyl acetate-hexane). The more polar band (R_f 0.1) was **21** (3.4 mg, 18%): IR (neat) 3580 (w), 2930, 1730, 1690, 1640 cm^{-1}; NMR (270 MHz, $CDCl_3$) δ 6.56 (d, J = 15.8 Hz, 1 H), 6.42 (d, J = 15.8 Hz, 1 H), 4.90 (dd, J = 9.5, 4.0 Hz, 1 H), 2.66 (ddd, J = 12.5, 7.0, 6.3 Hz, 1 H), 2.50 (ddd, J = 3.0, 11.5, 14.5 Hz, 1 H), 2.33 (m, 2 H), 2.00-1.40 (m, 11 H), 1.34 (s, 3 H), 0.92 (t, J = 7.3 Hz, 3 H); m/e, calcd for $C_{14}H_{22}O_4$ 254.2247, found 254.2247. The sample crystallized on standing and was recrystallized (hexane/CH_2Cl_2) giving white needles, mp 141-143 °C. The faster moving band (R_f 0.15) proved to be the diastereomeric lactone **20**[13] (5.5 mg, 29%), identical with an authentic sample provided by Prof. M. Yamaguchi.

Osmylation of 6. The same procedure used for **5E** converted **6** (24 mg) into a crude hydroxy enone mixture. The less polar product (6.4 mg, 23%) again corresponded to the Yamaguchi lactone **20** while the more polar isomer was **21** (9.7 mg, 36%).

Appendix

MACROMODEL Parameters. The structures found in Figures 1-4 were minimized with use of the Multiconformer routine in MACROMODEL using the default values of 60° dihedral angle resolution and 10° bond angle resolution. The closure bond for each molecule was chosen according to the guidelines set forth in the MACROMODEL documentation. In each case, the closure bond was chosen to be the bond between the third and fourth atoms away from the lactone carbonyl carbon. In the case of 2,3-dimethylcyclododecene, the bond between the fourth and fifth atoms away from the unsubstituted alkene carbon was chosen. The closure distance was varied between 1.0 and 2.0 Å to generate between 500 and 800 conformations as suggested by the MACROMODEL documentation. These values were highly dependent on the structure of the molecule. For example, for structure **5Z** 822 starting conformations were generated with a minimum closure distance of 1.0 Å and a maximum closure distance of 1.85 Å. The torsional angle defined by the lactone subunit was constrained to be 180° in all cases. In the case of the cycloalkenes, the angle defined by the double bond was contrained to be 0° or 180°, depending upon its cis or trans nature. For the epoxides studied, the torsional angle defined by the epoxide was allowed to assume four angles. For the epoxides derived from the cis alkenes, the angles were -40, -20, 0, and 20°; for the trans epoxides the angles were 140, 160, 180, and 200°. All other torsional angles were permitted to freely rotate within the 60° resolution constraints. Default values were used for all other parameters in the Multiconformer routine.

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An Asymmetric Synthesis of (-)-Steganone. Further Application of Chiral Biaryl Syntheses

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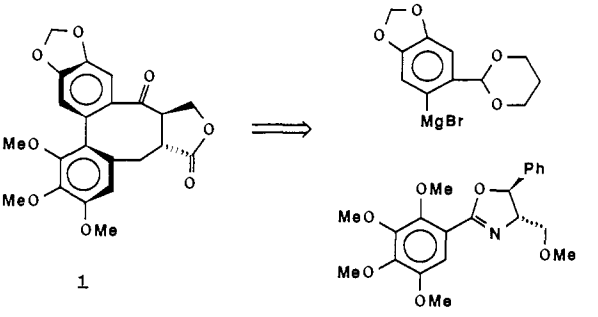
Abstract: An asymmetric synthesis of the title compound has been achieved by initially forming an axially chiral biphenyl precursor **11a** mediated by a chiral aromatic oxazoline (+)-**10**. The eight-membered ring was constructed around the biphenyl with particular attention addressing the rotational barrier for biphenyls to avoid racemization. The efficiency of this total synthesis was quite good until the last step, which incorporates the lactone moiety. Furthermore, approximately 10% racemization occurred in one of the latter steps (**17-18**) which was not evident until the final target was reached.

We have shown in previous reports that an aromatic system containing a chiral oxazoline is capable of being coupled with aromatic Grignard or lithium reagents furnishing chiral biphenyls,[1] binaphthyls,[2] and related systems.[3] We now describe the total synthesis of (-)-steganone (**1**) which originates from a diastereoselective coupling of two aryl moieties furnishing the axially chiral biphenyl required to construct the target compound (Scheme I).

(-)-Steganone (**1**), an antileukemic bisbenzocyclooctadiene lignan lactone, one of four isolated from *Steganotaenia araliacea* by Kupchan in 1973,[4] has attracted considerable synthetic interest. These lignans have demonstrated significant in vivo activity against P-388 leukemia in mice and have displayed significant in vitro activity against cells derived from human carcinoma of the nasopharynx (KB). The natural product contains three stereochemical elements, two of which are on the lactone ring and the

Scheme I



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