nitrile in 25 mL of MeOH containing 1 mL of concentrated hydrochloric acid was heated at reflux for 48 h. The cooled solution was diluted with water, thoroughly extracted with Et_2O, and worked up. Chromatography (15% Et_2O/hexane) and distillation (Kugelrohr, 145 °C, 0.1 mm) gave 510 mg (49%) of lactone **40**: IR ($CHCl_3$) 1783 cm^{-1}; ^1H NMR (250 MHz) δ 0.96 (3 H, d, J = 7.0 Hz), 1.14 (3 H, d, J = 6.6 Hz), 2.06 (1 H, m), 2.20 (1 H, dd, J = 17.0, 9.1 Hz, C_2-H), 2.44 (1 H, m), 2.69 (1 H, dd, J = 17.0, 8.3 Hz, C_2-H), 3.47 (2 H, m, $C_{2'}$-H), 4.27 (1 H, dd, J = 7.6, 3.4 Hz, C_5-H), 4.50 (1 H, d, J = 12.0 Hz, $PhCH_2$), 4.55 (1 H, d, J = 12.0 Hz, $PhCH_2$), 7.40 (5 H, m); $[\alpha]_D$ +46.9° (c 1.7, $CHCl_3$). Anal. ($C_{15}H_{20}O_3$) C, H.

4(*R*)-Methyl-5(*R*)-(1(*S*),4-dimethyl-2(*E*)-pentenyl)dihydro-2(3*H*)-furanone (43). Via the homologation technique described above, 990 mg (4.8 mmol) of diol **42** was converted into lactone **43** in 81% yield: IR ($CHCl_3$) 1765 cm^{-1}; ^1H NMR (250 MHz) δ 0.97 (6 H, d, J = 6.7 Hz), 1.11 (3 H, d, J = 6.6 Hz), 1.12 (3 H, d, J = 7.0 Hz), 2.14 (1 H, dd, J = 17.2, 8.2 Hz), 2.35 (3 H, m), 2.64 (1 H, dd, J = 17.2, 8.5 Hz), 3.98 (1 H, dd, J = 6.9, 3.4 Hz), 5.26 (1 H, dd, J = 15.5, 8.3 Hz), 5.48 (1 H, dd, J = 15.5, 6.5 Hz); $[\alpha]_D$ -20.4° (c 2.4, $CHCl_3$). Anal. ($C_{12}H_{20}O_2$) C, H.

3(*R*)-Carbomethoxy-4(*R*)-methyldihydro-2(3*H*)-furanone (1b). To a solution of 1.22 g (12.0 mmol) of diisopropylamine in 25 mL of THF at -10 °C was added 7.8 mL (1.54 M in hexane, 12.0 mmol) of n-butyllithium by using syringe techniques. After the solution had been stirred for 45 min, it was cooled to -78 °C. A solution of 600 mg (6.0 mmol) of R lactone **1** in 3 mL of THF was added dropwise followed by stirring of the reaction mixture for 1.5 h. The mixture was treated with 1.96 g (12.0 mmol) of HMPA followed by 1.02 g (12.0 mmol) of methyl cyanoformate and then stirred at -78 °C for 3 h. Dilution of the reaction mixture with brine, extraction with $CHCl_3$, workup, chromatography (50% Et_2O/hexane), and crystallization (Et_2O/pentane) gave 868 mg (91%) of lactonic ester **1b**: mp 46 °C; IR ($CHCl_3$) 1739, 1780 cm^{-1}; ^1H NMR (250 MHz) δ 1.21 (3 H, d, J = 6.6 Hz), 3.05 (1 H, m), 3.21 (1 H, d, J = 9.0 Hz), 3.83 (3 H, s), 3.86 (1 H, m), 4.52 (1 H, dd, J = 8.5, 7.0 Hz). The enantiomer provided the following data: $[\alpha]_D$ -44.1° (c 2.6, $CHCl_3$). Anal. ($C_7H_{10}O_4$) C, H.

Diethyl 2-Methyl-4(*E*)-hexen-3(*R*)-yl Phosphate (49a). To a 0 °C solution of 500 mg (4.4 mmol) of (*R*)-2-methyl-4-hexen-3-ol (**14b**) in 10 mL of Et_2O was added dropwise via syringe 1.77 mL (2.6 M/hexane, 4.6 mmol) of n-butyllithium. After the solution had been stirred for 1 h, 794 mg (4.6 mmol) of diethyl phosphorochloridate was added dropwise. The solution was stirred for 45 min at 0 °C and for 3 h at 25 °C, poured into water, and worked up. Distillation (Kugelrohr, 100 °C, 0.5 mm) provided the phosphate in quantitative yield: IR (CCl_4) 1260, 1034 cm^{-1}; ^1H NMR (250 MHz) δ 0.91 (3 H, d, J = 7.3 Hz), 0.93 (3 H, d, J = 7.7 Hz), 1.31 (6 H, m), 1.72 (3 H, dd, J = 6.3, 1.0 Hz), 1.88 (1 H, m), 4.07 (4 H, m), 4.46 (1 H, q, J = 7.2 Hz), 5.46 (1 H, dd, J = 15.3, 8.3 Hz), 5.76 (1 H, m).

Alkylation of Lactonic Ester 1b with Allylic Phosphate 49a. To a solution of 40 mg (0.26 mmol) of lactonic ester **1b** in 2 mL of THF was added 10.4 mg (0.26 mmol, 60% suspension) of NaH at 25 °C. After the mixture had been stirred for 1.5 h, 30.4 mg (0.026 mmol) of $(Ph_3P)_4Pd(0)$ and 7 mg (0.026 mmol) of Ph_3P were added followed by 128 mg (0.52 mmol) of phosphate **49a** in 0.5 mL of THF. After the mixture had been stirred for 2 h, it was diluted with water, extracted with ether, and worked up to give the crude alkylation product: ^1H NMR (250 MHz, partial for the major diastereomer) δ 0.97 (6 H, d, J = 7.0 Hz), 1.05 (3 H, d, J = 7.0 Hz), 1.24 (3 H, d, J = 7.0 Hz), 3.75 (3 H, s), 5.48 (1 H, dd, J = 15.0, 6.3 Hz), 5.59 (1 H, dd, J = 15.0, 6.3 Hz). The crude material was dissolved in 0.7 mL of DMSO containing 5 μL of water and 22.0 mg (0.52 mmol) of LiCl. The mixture was heated to 190 °C for 3 h followed by cooling to room temperature, dilution with water, extraction with ether, and workup. Distillation (Kugelrohr, 1 mm) of all material boiling below 200 °C gave 75 mg of distillate. Capillary GC analysis (method B) showed lactone *ent*-**16b** (C_t, t_R 16.8 min, 3.4%), *ent*-**26b** (B_t, t_R 17.2 min, 79.3%), *ent*-**22b** (B_c, t_R 16.4 min, 0.9%), and *ent*-**28b** (C_c, t_R 22.8 min, 16.4%).

Acknowledgment. This work was supported by the National Institutes of Health Grants AI-15617 and GM-33180. R.T.W. and A.K. express their gratitude for the receipt of Dox Fellowships. We are indebted to Kanegafuchi (Japan) for generous gifts of materials used in this work. We are indebted to Professor Jack Faller for informing us of the NMR integration technique for α-phenethylamine.

Applications of the 3-Methyl-γ-butyrolactone Strategy to the Synthesis of Polypropionates: The Prelog–Djerassi Lactonic Ester, *ent*-Invictolide, and the C_{19}–C_{27} Fragment of Rifamycin S[1]

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Contribution from the Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut 06511-8118. *Received November 23, 1987*

Abstract: Applications of the 3-methyl-γ-butyrolactone strategy for the synthesis of polypropionates are discussed. The preferred mode of hemiacetalization upon ozonolysis of bis(olefin) **8c** was determined by conversion of the products to the methyl ester of the Prelog–Djerassi lactone acid **1**. Similarly, lactone **2**, the enantiomer of invictolide, was prepared as a proof of the absolute stereochemistry of the pheromone. The bis(acetonide) **3**, an intermediate in the synthesis of the antibiotic rifamycin S, was synthesized. The transformation of lactones into β-hydroxy ketones and the thermodynamic stability of lactone intermediates are discussed.

In the preceding paper,[2] the basic strategy for the synthesis of enantiomerically pure polypropionate starter units from 3-methyl-γ-butyrolactone was discussed. In this paper, the details of the applicability of this approach to the synthesis of the Prelog–Djerassi lactonic ester **1**; lactone **2**, the enantiomer of the pheromone invictolide; and the C_{19}–C_{27} fragment **3** of the macrolide antibiotic rifamycin S, are discussed.

Our first task was to investigate the palladium-mediated alkylation of transposed lactone **4a**.[3,4] Carbomethoxylation of

(1) Taken in part from the Ph.D. theses of R.T.W. (Yale, 1986) and A.K. (Yale, 1987).

(2) Ziegler, F. E.; Kneisley, A.; Thottathil, J. K.; Wester, R. T. *J. Am. Chem. Soc.*, preceding paper in this issue.

(3) All structures are the enantiomers shown, unless designated otherwise.

(4) For a preliminary account, see: Ziegler, F. E.; Wester, R. T. *Tetrahedron Lett.* **1986**, *27*, 1225.

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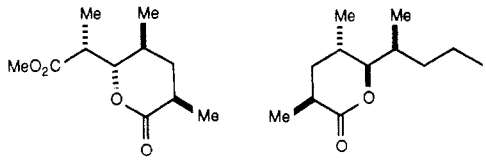
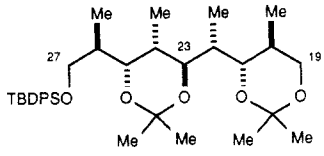
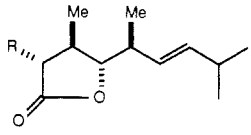


1 2

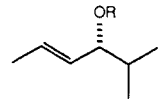


3

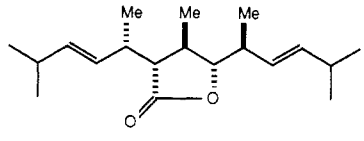
lactone **4a** via the Mander procedure[5] (2.0 equiv of LDA/$NCCO_2Me$) provided a 13:1 ratio of lactonic esters in 92% yield. The appearance of a doublet (J = 11.4 Hz) at δ 3.25 in the ^1H NMR spectrum of the mixture indicated that the major component had a trans relationship between the ester and the vicinal methyl group. The palladium-mediated alkylation of the THF-soluble sodium salt of ester **4b** with phosphate **5** gave rise to a 2:1 ratio (^1H NMR) of alkylated esters. The mixture was inconsequential as Krapcho decarbomethoxylation[6] provided trans lactone **6** and cis lactone **7** (23:1) in 91 and 4% yield, respectively. When a chromatographic fraction of the two lactones (**6**:**7**, 25:1) was subjected to equilibration (t-BuOH, t-BuOK), a 9:1 ratio of lactones **6**:**7** was obtained. This equilibrium position differed from the 97:3 (trans:cis) ratio obtained in the prototypical lactones bearing no C_4 substituent.[4]



4a, R = H
b, R = CO_2Me



5a, R = H
b, R = $PO(OEt)_2$



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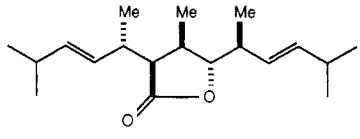
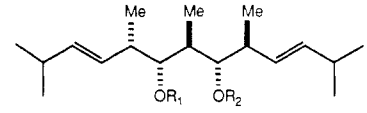


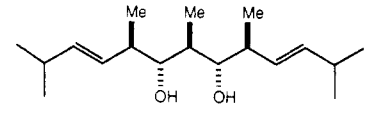
7

The conversion of lactone **6** to diol **8c** was met with several difficulties. While the Criegee rearrangement occurred without incident, the $LiAlH_4$ reduction of the hydroxy acetates **8a** gave a mixture of the desired diol **8c** (48%), acetaldehyde acetals **8b** (28%), and meso diol **9** (5%). The source of the meso diol was traced to a sample of R alcohol precursor of phosphate **5** that was less than 100% enantiomerically pure (~80% ee). The acetal **8b** was characterized by the appearance in its ^1H NMR spectrum of eight methyl doublets, one of which appeared at δ 1.28 and was coupled (J = 5.0 Hz) to a one-proton quartet at δ 4.62. The acetal is presumed to arise by hydroxyl (or alkoxy aluminate) addition to the intermediate derived from hydride addition to the ester followed by elimination of aluminate. While the diol **8c** could be liberated from the acetal with some difficulty with aqueous HCl (80% yield overall), subsequent experiments (vide infra) demonstrated that Dibal reduction was a viable alternative to $LiAlH_4$ reduction; saponification of the acetates proved capricious.

The shortcoming of diol **8c** as an intermediate for unidirectional chain iteration is the presence of two chemically indistinguishable olefins. Nonetheless, the diol, by virtue of its lack of symmetry, presented an interesting case with which to study the preferred mode of hemiacetalization of the putative dialdehyde derived from ozonolysis in methanol. Collapse of the primary ozonide would give a mixture of dialdehyde/aldehydo zwitterions/bis(zwitterion) in a presumed ratio of 1:2:1. The hydroxyl groups could intramolecularly trap the aldehyde as a hemiacetal, or the zwitterion as an alkoxyhydroperoxide. Reduction with dimethyl sulfide and exposure to acidic methanol would produce the four possible anomers represented by structures **10a,b** and **11a,b**. Clearly, several intermediates can lead to two modes of cyclization and a pair of anomers for each pathway.



8a, R_1, R_2 = H, Ac
b, R_1, R_2 = $CHCH_3$
c, R_1 = R_2 = H



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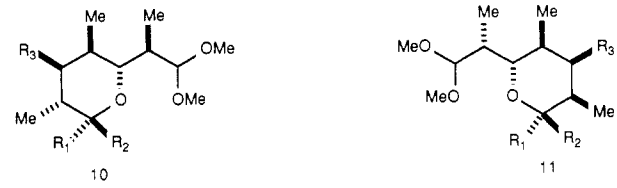


10 11

a, R_1 = OMe, R_2 = H, R_3 = OH
b, R_1 = H, R_2 = OMe, R_3 = OH
c, R_1 = OMe, R_2 = R_3 = H
d, R_1 = R_3 = H, R_2 = OMe
e, R_1, R_2 = O, R_3 = H

In the event, ozonolysis of bis(olefin) **8c** followed by reductive workup and acetalization afforded two products, which, after chromatography, gave a less polar (33%) and a more polar acetal (30%). All four possible stereoisomers may be considered to exist in a chair conformation having the alkyl chain and the vicinal methyl group equatorial and the hydroxyl group axial. The anomers **10a** and **10b** have the C_3 methyl group axial, and **11a** and **11b** have the same methyl group equatorially disposed. The more polar component displayed the ring acetal methine hydrogen as a doublet (J = 8.7 Hz, δ 4.41). Only anomer **11a** has a large dihedral angle between the acetal hydrogen and its vicinal hydrogen. The less polar component revealed the same hydrogen as a doublet (J = 2.9 Hz, δ 4.56) and the hydroxyl proton as a doublet (J = 10.4 Hz, δ 2.99), strongly hydrogen bonded to the anomeric methoxyl group. To a first approximation, both anomers **10b** and **11b** can accommodate these data. Although the two isomers were readily interconverted in acidic methanol, it is not necessarily true that they are anomeric because structural isomerization can be operative. To exclude the latter possibility, both isomers were deoxygenated.

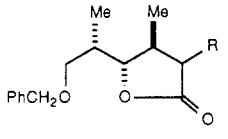
Radical deoxygenation[7] appeared to be the method of choice, but traditional derivatization proved troublesome. The more polar isomer reacted sluggishly with thiocarbonyldiimidazole in refluxing dichloroethane while the less polar, hydrogen-bonded isomer was inert. The xanthate of the more polar isomer was readily prepared via the sodium alkoxide; however, the tri-*n*-butyltin hydride promoted deoxygenation provided low yields of the deoxygenation

(5) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425. For a study on the mechanism of this reaction, see: Ziegler, F. E.; Wang, T.-F. *Tetrahedron Lett.* **1985**, *26*, 2291.
(6) Krapcho, A. P. *Synthesis* **1982**, 805.
(7) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. I* **1975**, 1574. (b) Barton, D. H. R.; Motherwell, W. B. *Pure Appl. Chem.* **1981**, *53*, 15. (c) Barton, D. H. R.; Motherwell, W. B.; Stange, A. *Synthesis* **1981**, 743.

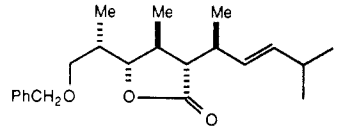
product. A satisfactory solution required conversion of the hydroxyl groups of both isomers to their lithium alkoxides followed by acylation with phenyl chlorothionocarbonate.[8] Deoxygenation was achieved with tri-*n*-butyltin hydride/AIBN in refluxing toluene. When either deoxygenation product was treated with *p*-TsOH/$CH(OMe)_3$/MeOH, a 1:1 mixture of the deoxygenation products was obtained. Consequently, the two cyclization products from ozonolysis are anomers, the more polar being acetal **11a**, the less polar, **11b**. The deoxygenation products are respectively **11c** and **11d**.

The equatorial methoxy acetal **11c** proved to be susceptible to ozonolysis at −78 °C, while its anomer was unreactive.[9] The hydroxy ester formed during ozonolysis was converted to the lactone **11e** upon exposure to CF_3CO_2H/THF. Oxidation of the acetal group of **11e** required ozonolysis in acetic acid at room temperature for 30 h, providing a 2:1 mixture of the methyl ester of the Prelog–Djerassi lactone **1**[10] and recovered acetal. Prolonged ozonolysis to consume **11e** led to substantial amounts of unidentified products. In a similar fashion, the axial anomer **11d** could be equilibrated to the equatorial anomer **11e** with acid during ozonolysis and brought through the sequence leading ultimately to **1**.

The five centers of asymmetry present in lactone **6** were generated via the Claisen rearrangement of (*S*)-3-methyl-γ-butyrolactone with *R* alcohol **5a**, inversion of the element of "CO_2" in the resultant C_t lactone to provide lactone **4a**, and alkylation with *R* phosphate **5b**. These centers of asymmetry may be established in an alternative manner. Lactone **12a**, derived from (*R*)-3-methyl-γ-butyrolactone and *R* alcohol **5a** followed by equilibration and "CO_2" transposition,[2] undergoes alkylation with phosphate **5b** via the lactonic ester **12b** followed by decarboxylation. The difference between these experiments is that the carbon chains, although homochiral, have been introduced in inverse order; the enantiomeric (*R*)-3-methyl-γ-butyrolactone has been employed; and the initially introduced chain in the second example has had its olefin functionality converted to a protected alcohol function prior to introduction of the second olefin chain. This process generates at the centers of chirality in lactone **13** the same absolute stereochemistry present in lactone **6**, but has the termini of the developing chain differentially functionalized. This approach would permit continued iteration toward the olefin end of the chain.



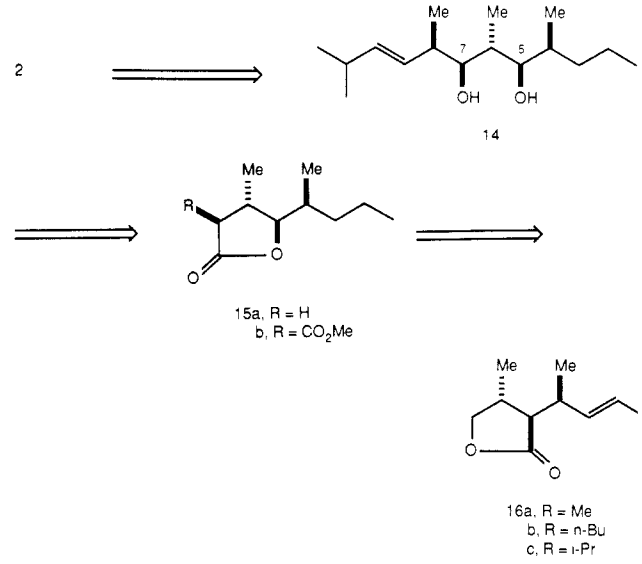
12a, R = H
b, R = CO_2Me



13

Invictolide (*ent*-**2**), isolated by Tumlinson and co-workers,[11] is one component of a mixture of three compounds that function as the aggregation pheromone of the red fire ant, *Solenopsis invicta* (Buren). The stereochemistry of invictolide was demonstrated by synthesis and spectroscopic analysis.[12,13] No determination had been made as to whether invictolide was a single enantiomer, or perhaps, racemic. The methodology at hand lent itself to the preparation of invictolide of high enantiomeric purity; arbitrarily, enantiomer **2** was chosen.

Scheme I



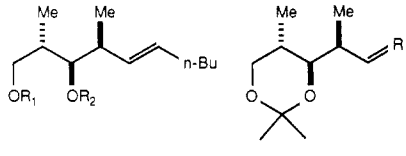
The retrosynthesis (Scheme I) of *ent*-invictolide requires the diol **14** having C_7 of the *S* configuration (β) to satisfy the C_5,C_6-anti, C_6,C_7-anti arrangement that would occur upon alkylation of lactone **15**. Clearly, hemiacetalization can occur in only one way upon ozonolysis of diol **14**. Lactone **15** is most ideally derived by transposition of B_t lactone **16a**. While the Claisen rearrangement of the ortholactone of (*R*)-3-methyl-γ-butyrolactone and (*R*)-3(*e*)-penten-2-ol could be conducted without incident, the Sharpless kinetic resolution of the alcohol occasionally gave enantiomeric excesses less than were deemed desirable for biological assay, and the high water solubility of the alcohol made isolation difficult. Accordingly, the more highly enriched and more readily attainable (*R*)-2(*E*)-octen-4-ol was used to produce lactone **16b**, or *R* alcohol **5a** was employed to form lactone **16c** as starting material.[2]

The Criegee sequence and ketalization efficiently transformed lactone **16b** into the acetonide **17b** in 89% yield. The installation of the proper hydrocarbon side chain was accomplished in 46% overall yield. Ozonolysis of the double bond of acetonide **17b** provided the aldehyde **18a** as an intermediate. Direct Wittig olefination gave rise to a 2:1 mixture of olefins that was not separated nor was the stereochemistry of the olefins assigned. Reduction of the double bond was required; Raney nickel was used to avoid the possibility of isomerization at the stereogenic allylic site.[14] The ^{13}C NMR spectrum of acetonide **19a** indicated the presence of a single diastereomer while capillary gas chromatography revealed a %ds = 96.5. Conversion of diol **19b** into transposed lactone **15a** was accomplished in 78% yield by the established procedure of monotosylation, cyanide displacement, and methanolysis.

The chirality at C_8 of diol **14** is opposite that present at C_4, the latter having been introduced via the *R* phosphate **5b**. Accordingly, *S* phosphate *ent*-**5b** was required to establish the C_8 chirality. Lactone **15a** was carbomethoxylated, alkylated with the *S* phosphate (96% ee) under the influence of palladium(0) catalysis, and decarbomethoxylated to give pure lactone **20** (52% overall) and a 2:1 mixture of lactone **20** and its C_3 epimer (11%) after chromatography. The Criegee sequence readily converted the lactone into the target diol **14**, itself undergoing ozonolysis and acetalization to a mixture of acetals **21a** (44%) and **21b** (32%). The major, less polar component was identified as the axial anomer **21a** because the C_2-H appeared as a singlet at δ 4.54. The minor

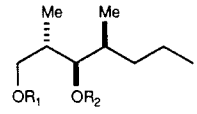
(8) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932.
(9) Deslongchamps, P.; Atlanti, P.; Frehel, D.; Malaval, A.; Moreau, C. *Can. J. Chem.* **1974**, *52*, 3651.
(10) (a) Midland, M. M.; Tsai, D. J.-S. *J. Am. Chem. Soc.* **1985**, *107*, 3915. (b) Nakai, E.; Kitahara, E.; Sayo, N.; Ueno, Y.; Nakai, T. *Chem. Lett.* **1985**, 1725. (c) Chow, H.-F.; Fleming, I. *Tetrahedron Lett.* **1985**, *26*, 397 and references cited therein.
(11) Rocca, J. R.; Tumlinson, J. H.; Glancey, B. M.; Lofgren, C. S. *Tetrahedron Lett.* **1983**, *24*, 1889.
(12) Rocca, J. R.; Tumlinson, J. H.; Glancey, B. M.; Lofgren, C. S. *Tetrahedron Lett.* **1983**, *24*, 1893.
(13) For syntheses of racemic invictolide, see: (a) Hoye, T. R.; Peck, D. R.; Swanson, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 2738. (b) Schreiber, S. L.; Wang, Z. *Ibid.* **1985**, *107*, 5303. (c) Yamamoto, Y.; Taniguchi, K.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1429. For a preliminary account of this work, see: (d) Ziegler, F. E.; Stirchak, E. P.; Wester, R. T. *Tetrahedron Lett.* **1986**, *27*, 1229.
(14) (a) Chan, K.-K.; Cohen, N.; De Noble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497. (b) Gould, T. J.; Balestra, M.; Wittman, M. D.; Gary, J. A.; Rossano, L. T.; Kallmerten, J. *J. Org. Chem.* **1987**, *52*, 3889.

component displayed the same signal at δ 4.68 as a doublet with J = 2.3 Hz. The equatorial anomer **21b** was subjected to the deoxygenation and ozonolysis employed above (**11a** → **1**) to provide the volatile "pheromone", (+)-invictolide (**2**).

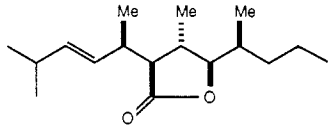


17a, $R_1 = R_2 = H$
b, $R_1, R_2 = CMe_2$

18a, R = O
b, R = CHMe



19a, $R_1, R_2 = CMe_2$
b, $R_1 = R_2 = H$



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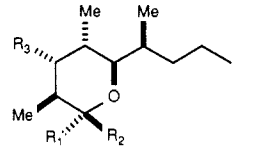
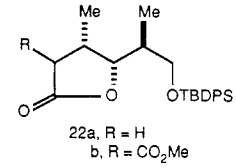


21a, R_1 = OMe, R_2 = H, R_3 = OH
b, R_1 = H, R_2 = OMe, R_3 = OH
c, R_1 = OMe, $R_2 = R_3$ = H

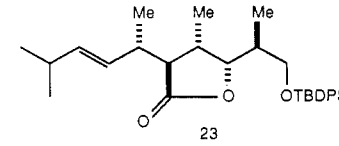
At this time, Schreiber and Wang[13b] in this Laboratory had completed a synthesis of racemic invictolide. Field tests were performed by Dr. Tumlinson (USDA, Gainesville) on the two synthetic substances in admixture with their copheromones. The racemate displayed activity while the dextrorotatory enantiomer was inactive. In the interim, Mori has reported the synthesis of both enantiomers and has found the levorotatory form, *ent*-**2**, to be active.[15]

A third challenge for the polypropionate strategy was the construction of the bis(acetonide) **3**,[16] an intermediate in the formation of the C_{19}–C_{27} ansa chain in Kishi's synthesis of the macrocyclic antibiotic rifamycin S.[17,18] In designing an approach to this compound, a right-to-left construction appears in order as the terminating olefin could be transformed into the oxygenated C_{27} site. At issue is the question of whether iteration should be linear, wherein C_{19}, C_{20}, and C_{21} of **3** are derived from C_4, C_3, and C_2, respectively, of (*R*)-3-methyl-γ-butyrolactone with iteration proceeding only to the left, or whether iteration should be transpositional, requiring C_4, C_3, and C_2 of (*R*)-3-methyl-γ-butyrolactone to become C_{23}, C_{22}, and C_{21}, respectively, of **3** with iteration proceeding once to the right and then continuing to the left. Arguing against the latter approach is the necessity to begin with a C_c starter unit (C_{21},C_{22}-cis) that requires the use of the iodolactonization procedure early in the synthesis. Alternatively, the linear approach begins with the more readily accessible B_t isomer. The anti relationship between the C_{22}-α-Me and C_{23}-β-OH translates into a trans relationship in the corresponding lactone. The cis relationship of the C_{24}-α-Me and the C_{25}-α-OH coupled with the β-configuration of the C_{26}-Me requires the iodolactonization procedure to attain the proper stereochemistry at the left-hand terminus of the chain.

Lactone **22a** of near 100% ee,[2] representing the C_{20}–C_{22} stereogenic centers of the ansa chain, was carbomethoxylated in 98% yield to give a single lactonic ester **22b** of undefined stereochemistry at the newly created stereogenic center. Palladium-mediated alkylation of the lactonic ester gave a single product of alkylation as witnessed by the presence of a singlet at δ 3.79 for the methyl ester. Ostensibly, alkylation occurs from the β-face, distal to the two substituents. Krapcho decarboxylation provided a kinetic mixture of C_2–C_3 trans lactone **23** (71%) and cis lactone **24** (21%).[19] The trans/cis selectivity (3.4:1) is significantly lower when the C_3 and C_4 substituents are cis than in the formation of lactones **6** and **7** (23:1) where the C_3 and C_4 substituents are trans. The equilibration of lactones **23** and **24** with *t*-BuOK/*t*-BuOH gave a 1:1 mixture of the two lactones, distinctly different from the 9:1 ratio obtained with lactones **6** and **7**. Rewardingly, kinetic protonation of the LDA-generated enolate from lactone **23** or **24** gave a 19:1 ratio of cis lactone **24** to trans lactone **23**, respectively. Thus, the creation of a butyrolactone having all cis substituents, unattainable by either Claisen rearrangement or in useful yield by palladium-mediated alkylation, was now accessible in highly substituted systems by kinetic protonation.



22a, R = H
b, R = CO_2Me



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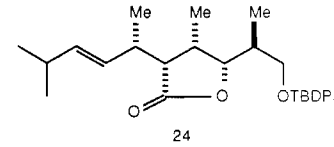

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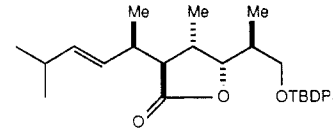

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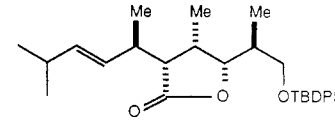


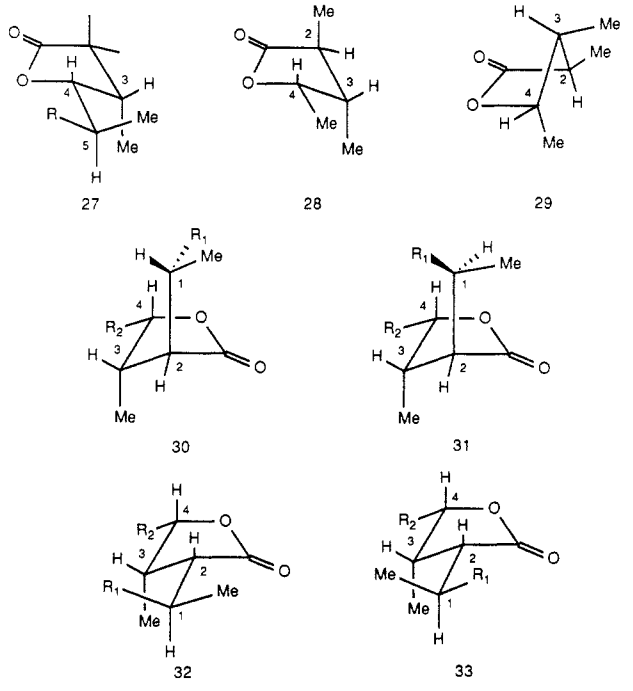
26

To assist in the understanding of the energetics involved in the equilibration of lactones **23** and **24**, lactonic ester **22b** was alkylated with *S* phosphate *ent*-**5b** to provide trans lactone **25** and cis lactone **26**. The pairs of trans lactones **23** and **25** and cis lactones **24** and **26** differ only in the stereogenicity of the newly incorporated side chain. However, equilibration of lactones **25** and **26** showed a 3:1 preference in favor of the trans isomer **25**. Kinetic protonation of their enolates gave the same selectivity in favor of the cis isomer (19:1). The ^1H NMR spectra ($CDCl_3$ and C_6D_6) of these lactones provided insight regarding their preferred conformations.

Lactones **22**–**26** can be assigned the preferred conformation **27** for the chain attached to C_4 of the butyrolactone. The C_4-H/C_5-H coupling constant was ~10 Hz while the C_3-H/C_4-H value was in the range of 3–5 Hz. These values require C_3 to be the flap of the envelope conformation of the butyrolactone ring while the side chain adopts a staggered C_4–C_5 and eclipsed C_3-Me, C_5-H rotameric conformation that minimizes syn pentane interactions.[20] Calculations performed on 2,3-*trans*,4-*cis*-trimethyl-γ-butyrolactone have shown that conformation **28** ($J_{2,3}$ = 0.66 Hz; $J_{3,4}$ = 5.69 Hz) is preferred over **29** ($J_{2,3}$ = 11.33 Hz; $J_{3,4}$ = 6.93 Hz).[21] These results are supported by the presence of $J_{2,3}$ = 1.9 Hz and $J_{3,4}$ = 5.6 Hz for lactone **23** and $J_{2,3}$ = 0.7 Hz and $J_{3,4}$ = 5.1 Hz for lactone **25**. The preferred rotamers about

(15) Mori, K.; Nakazono, Y. *Tetrahedron* **1986**, *42*, 6459.
(16) For a preliminary report, see: (a) Ziegler, F. E.; Kneisley, A. *Tetrahedron Lett.* **1987**, *28*, 1725. (b) Ziegler, F. E.; Kneisley, A. *Heterocycles* **1987**, *25*, 105.
(17) (a) Kishi, Y. *Pure Appl. Chem.* **1981**, *53*, 1163. (b) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (c) Lewis, M. D.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2343.
(18) For other synthetic efforts directed toward the ansa-chain of rifamycin S, see: (a) Roush, W. R.; Palkowitz, A. D. *J. Am. Chem. Soc.* **1987**, *109*, 953. (b) Danishefsky, S. D.; Myles, D. C.; Harvey, D. F. *J. Am. Chem. Soc.* **1987**, *109*, 862. (c) Tschamber, T.; Waespe-Sarcevic, N.; Tamm, C. *Helv. Chim. Acta* **1986**, *69*, 621. (d) Hanessian, S.; Pougny, J.-R.; Boessenkool, I. K. *Tetrahedron* **1984**, *40*, 1289. (e) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1984**, *105*, 2487. (f) Masamune, S.; Imperiali, B.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5528. (g) Nakata, M.; Takao, H.; Ikeyama, Y.; Sakai, T.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1749.
(19) The numbering system in this discussion is arbitrary, reflecting, in part, the numbering used for butyrolactones. The Experimental Section utilizes IUPAC numbering.
(20) Kishi, Y.; Lewis, M. D. *Tetrahedron Lett.* **1982**, *23*, 2343. See also ref 13a.
(21) Jaime, C.; Ortuno, R. M.; Font, J. *J. Org. Chem.* **1986**, *51*, 3946.

the C_1–C_2 bond of diastereomers **23** and **25** are best represented by structures **30** and **31**, respectively. The C_1-H/C_2-H coupling in the former diastereomer is 5.6 Hz while the latter is 8.3 Hz. In addition, the C_1-Me is at the same chemical shift in $CDCl_3$ (δ 1.15) and C_6D_6 (δ 1.10), suggesting the same average environment for each methyl group in the given solvent. The ^{1}H NMR spectra of the all-cis lactones **24** (conformation **32**) and **26** (conformation **33**) proved informative. The backbone coupling of C_1-H through C_4-H could be ascertained by recording the spectra in both $CDCl_3$ and C_6D_6. The anti C_1-H/C_2-H conformation was confirmed by a coupling constant of ~10 Hz, C_2-H/C_3-H had J = ~1–2 Hz and C_3-H/C_4-H revealed J = ~5 Hz. The C_1-Me group in conformation **32** was deshielded ($\Delta\delta$ = −0.25 ($CDCl_3$), $\Delta\delta$ = −0.52 (C_6D_6)) relative to **33**, while the vinyl proton vicinal to C_1 in conformation **33** was deshielded ($\Delta\delta$ = −0.54 ($CDCl_3$), $\Delta\delta$ = −0.64 (C_6D_6)) relative to **32**. The $\Delta\Delta G°$ for the difference in energy between K_{eq} **23**/**24** and K_{eq} **25**/**26** is small at ~0.6 kcal/mol. The effect may be due to a stabilization of conformation **31** over **30** for the trans isomers, the latter having interactions of R_1 with the ring, while cis conformer **33** is destabilized, but to a lesser degree, relative to **32**, owing to the interaction of the R_1 chain with the carbonyl.



27 28 29

30 31

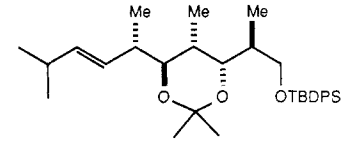
32 33

To this point in our studies, no Criegee rearrangement had been conducted on a pair of cis and trans lactones to verify the stereospecificity of the rearrangement. Cis lactone **24** gave the acetonide **35**, which bears five contiguous stereogenic centers that have the absolute stereochemistry present at C_2–C_6 of 6-deoxyerythronolide B.[22] However, the trans lactone **23** afforded 46% yield of the cis lactone **24** and the desired acetonide **34** in 31% yield. The Criegee sequences were stereospecific; each lactone provided a unique acetonide. The addition of methyllithium to the lactone carbonyl of **23** is hindered (conformation **30**) on the top face by the C_2 chain and on the bottom face by the ring methyl group. Deprotonation by methyllithium was competitive with addition, the cis lactone arising from kinetic protonation of the enolate. Enolization was also observed for trans lactone **25**; cis lactone **26** underwent carbonyl addition. Efforts to overcome enolization through the use of cerium[23] or titanium-based[24] forms of methyl anion were unsuccessful.

The ^{1}H NMR spectra of acetonides **34** and **35** corroborated the correctness of the stereochemical assignments of the lactones **23** and **24**. Acetonide **35**, derived from the cis lactone, revealed the methine ether protons at δ 3.45 (J = 9.9, 1.9 Hz) and δ 3.82 (J = 10.0, 1.9 Hz). The small couplings are to the cis, ring methine proton and the large coupling to the vicinal protons on the equatorially disposed chains. On the other hand, acetonide **34** showed a more complex, first-order coupling pattern for the same protons.

Formation of a new lactone template was achieved by the cyanide homologation procedure, which converted acetonide **34** into lactone **37a** in 64% overall yield. Alcohol **36a**, an intermediate in this process, had been reported by Kishi as its enantiomer, *ent*-**36a**. The ^{1}H NMR spectrum and specific rotation of the enantiomers were in accord with one another.[17b]

Introduction of the last methyl-bearing stereogenic center was accomplished in standard fashion. Carbomethoxylation of lactone **37a** produced lactonic ester **37b** in 93% yield. Alkylation was achieved with *S* phosphate **5b** followed by decarboxylation to provide trans lactone **38** in 87% yield with greater than 95% diastereoselectivity.



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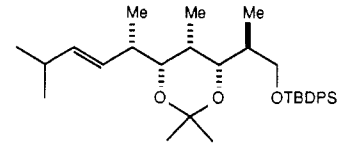

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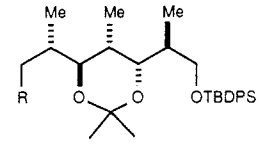
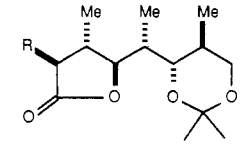
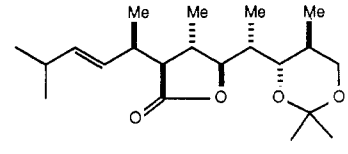


36a, R = OH
b, R = OTs
c, R = CN
d, R = CO_2H



37a, R = H
b, R = CO_2Me

Lactone **38** bears the correct stereochemistry for all the stereogenic centers present in the target fragment **3**, except for the epimerizable stereogenic center (C_{25} in **3**) of the lactone. While this stereochemistry could be corrected by the iodolactonization procedure, a different approach was explored to test the utility of the lactone ring as a source of ketones, which appear in polypropionate-derived natural products in the guise of hemiketals (e.g., elaiophylin[25]) and spiroketals (e.g., calcimycin[26]).



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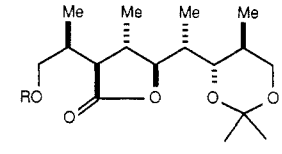
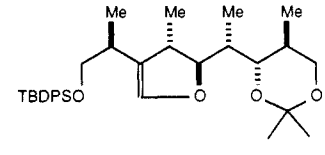


39a, R = OH
b, R = TBDPS



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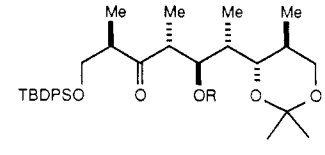


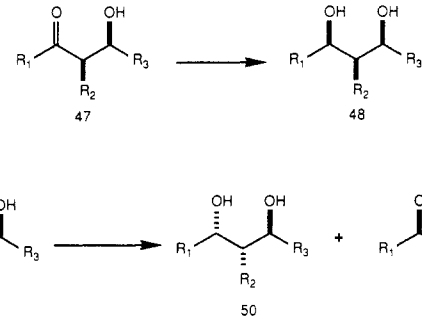
41a, R = CHO
b, R = H

(22) For recent synthetic accomplishments in the erythronolide field, see: Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1565 and references cited therein.

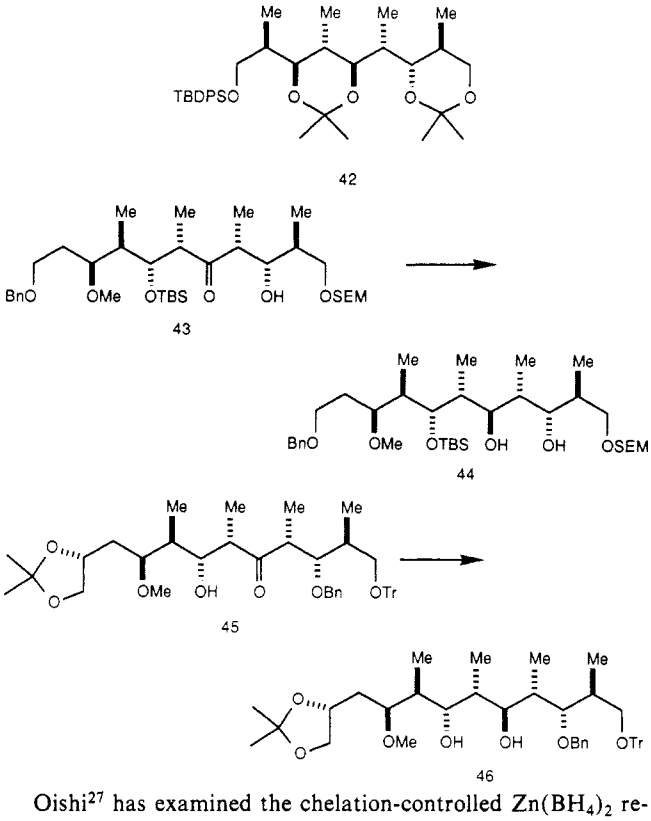
(23) (a) Imamoto, T.; Sugiura, Y.; Takayama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904.

(24) Reetz, M. T.; Kyung, S. H.; Huellmann, M. *Tetrahedron* **1986**, *42*, 2931.

Scheme II

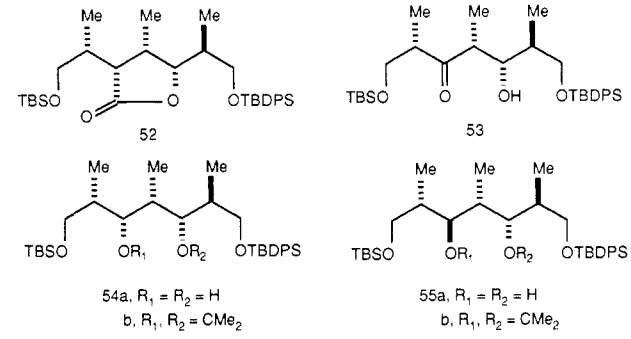


Ozonolysis of the double bond of lactone **38** followed by $NaBH_4$ reduction produced alcohol **39a**, which was protected as its *tert*-butyldiphenylsilyl ether. Reduction of the lactone with diisobutylaluminum hydride gave a mixture of hemiacetals that were successfully converted to the enol ether **40** with methanesulfonyl chloride/triethylamine. The hemiacetals underwent elimination at different rates. The elimination most likely proceeds via an E2 process as acidic conditions rapidly gave acetals by participation of the silyloxy group with the oxygen-stabilized carbocation derived from the hemiacetal. Ozonolysis of the enol ether followed by ammonolysis of the formate ester gave the desired β-hydroxy ketone **41b** (79% from lactone **39b**). Reduction of the β-hydroxy ketone with Dibal/CH_2Cl_2 was nonselective, providing the desired bis(acetonide) **3** in 42% yield and its stereoisomer **42** in 46% yield upon ketalization. This result was unexpected as Masamune[18f] had observed 16:1 selectivity in the Dibal/ether reduction of β-hydroxy ketone **43** to diol **44**, and Hanessian[18d] had realized >10:1 selectivity in the Dibal/toluene reduction of β-hydroxy ketone **45** to diol **46**. Upon changing the solvent in the reduction of β-hydroxy ketone **41b**, no improvement in stereoselectivity was obtained.



Oishi[27] has examined the chelation-controlled $Zn(BH_4)_2$ reduction of β-hydroxy ketones (**47** → **48**; $R_1 = R_2$ = alkyl, R_3 = H), finding high selectivity for the formation of syn diols (Scheme II). Narasaka[28] has investigated the reduction of syn-substituted β-hydroxy ketones (**47** → **48**, $R_1 = R_2 = R_3$ = alkyl) as their di-*n*-butylboron complexes and has also found high syn selectivity. On the other hand, anti-substituted β-hydroxy ketones (**49** → **50** + **51**, $R_1 = R_2 = R_3$ = alkyl) gave syn,anti and anti,anti products, whose ratio varied as a function of alkyl substituents.

In light of these observations, β-hydroxy ketone **41b** was reduced with $Zn(BH_4)_2$ to give exclusive formation of the undesired, anti,anti reduction product **42**. However, *syn*-β-hydroxy ketone **53**, prepared from lactone **26**, followed a predictable course, giving the syn,syn diol **54a**.[29]



After the completion of this work, Evans[30] reported that tetramethylammonium triacetoxyborohydride reduces syn- and anti-substituted β-hydroxy ketones to trans diols while Davis[31] has made similar observations using dialkylchlorosilanes. These reagents show promise for the selective reduction of β-hydroxy ketone **41b** to give the desired syn,anti stereochemistry.

The use of 3-methyl-γ-butyrolactones as templates for the synthesis of polypropionate-derived natural products and synthons thereof has been demonstrated. The examples studied have provided insight into the scope of the strategy, have opened an entry into carbonyl containing substrates, and have produced products of virtual 100% enantiomeric purity.

Experimental Section

See the preceding paper in this issue for details.[2]

3(*S*)-Carbomethoxy-4(*R*)-methyl-5(*S*)-(1(*S*),4-dimethyl-2(*E*)-pentenyl)dihydro-2(3*H*)-furanone (4b). A solution of lactone **4a**[2] in 6 mL of THF was added dropwise to a solution of LDA [diisopropylamine (0.72 g, 7.14 mmol), *n*-BuLi (2.9 mL, 7.14 mmol, 2.45 M in hexane), 30 mL of THF; −20 °C, 1 h] at −78 °C. After having been stirred for 1.5 h, HMPA (0.64 g, 3.57 mmol) was added followed by methyl cyanoformate (0.61 g, 7.14 mmol). After having been stirred for 3 h, the reaction mixture was poured into brine, extracted with ether, and worked up. Chromatography (25% ether/hexanes) gave 830 mg (92%) of a 13:1 mixture of lactonic ester **4b** and its C_3 epimer: ^{1}H NMR (250 MHz, major) δ 0.98 (3 H, d, J = 6.8 Hz), 0.99 (3 H, t, J = 6.8 Hz), 1.15 (3 H, d, J = 6.6 Hz), 1.17 (3 H, d, J = 6.9 Hz), 2.31 (1 H, m), 2.45 (1 H, m), 2.81 (1 H, m), 3.25 (1 H, d, J = 11.4 Hz), 3.81 (3 H, s), 3.96 (1 H, dd, J = 9.4, 3.3 Hz), 5.28 (1 H, dd, J = 15.5, 7.8 Hz), 5.51 (1 H, dd, J = 15.5, 6.7 Hz). Anal. ($C_{14}H_{22}O_4$) C, H.

3(*R*),5(*S*)-Bis(1(*S*),4-dimethyl-2(*E*)-pentenyl)-4(*R*)-methyldihydro-2(3*H*)-furanone (6) and 3(*S*),5(*S*)-Bis(1(*S*),4-dimethyl-2(*E*)-pentenyl)-4(*R*)-methyldihydro-2(3*H*)-furanone (7). To a suspension of pentane-washed NaH (0.13 g, 3.21 mmol, 60% suspension) in 20 mL of THF at 25 °C was added dropwise (syringe/septum) a solution of lactonic ester **4b** (0.78 g, 3.06 mmol) in 6 mL of THF. After having been stirred for 2.5 h, $(Ph_3P)_4Pd$ (0.18 g, 0.15 mmol) and Ph_3P (39 mg, 0.15 mmol) were added, and the resulting yellow solution was cooled to 0 °C. A solution of allylic phosphate **5b**[2] in 7 mL of THF was added over 10 min. The reaction mixture was stirred for 1 h at 0 °C and then for 2 h at 25 °C. The solution was poured into water, extracted with ether, and

(25) Neuperts-Laves, K.; Dobler, M. *Helv. Chim. Acta* **1982**, *24*, 262 and references cited therein.
(26) Chaney, M. D.; Demarco, P. V.; Jones, N. D.; Occolowitz, J. I. *J. Am. Chem. Soc.* **1974**, *96*, 1932.
(27) Nakata, T.; Tani, Y.; Hatozaki, M.; Oishi, T. *Chem. Pharm. Bull. Jpn.* **1984**, *32*, 1411.
(28) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233.
(29) The stereochemistry was determined from the ^{1}H NMR spectrum of the acetonide **54b** as was described for acetonide **35**.
(30) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939.
(31) Anwar, S.; Davis, A. P. *J. Chem. Soc., Chem. Commun.* **1986**, 831.

worked up. Chromatography (7.5% ethyl acetate/hexanes) afforded 1.13 g of a 2:1 mixture of alkylation products: ^{1}H NMR (250 MHz, partial) δ 3.74 (6 H, s), 4.01 (2 H, dd, J = 10.0, 2.5 Hz, major), 4.02 (1 H, dd, J = 10.0, 2.5 Hz, minor); IR ($CHCl_3$) 1768, 1733 cm^{-1}. A solution of the crude alkylation products (1.04 g, 3.0 mmol), LiCl (0.25 g, 6.0 mmol), and water (54 mg) in 9.5 mL of DMSO was heated at 200 °C for 3 h. The cooled solution was poured into water, extracted with ether, washed with water, and worked up. Chromatography (7.5% ether/hexanes) gave 750 mg (91%) of trans lactone **6** and 37 mg (4%) of cis lactone **7**. Trans lactone **6**: ^{1}H NMR (250 MHz) δ 0.97 (6 H, d, J = 6.7 Hz), 0.98 (6 H, d, J = 6.8 Hz), 1.10 (3 H, d, J = 6.9 Hz), 1.12 (3 H, d, J = 6.9 Hz), 1.14 (3 H, d, J = 7.1 Hz), 2.25 (4 H, m), 2.40 (1 H, m), 2.67 (1 H, m), 3.79 (1 H, dd, J = 8.4, 3.6 Hz), 5.4 (4 H, m); ^{13}C NMR 17.3, 17.7 (2 Me), 22.2 (4 Me), 30.7, 34.7, 36.2, 38.8, 53.2, 87.6, 126.1, 128.3, 138.3, 139.7, 176.8 ppm; IR ($CHCl_3$) 1772 cm^{-1}; $[\alpha]_D$ −34.9° (c 3.3, $CHCl_3$). Anal. ($C_{19}H_{32}O_2$) C, H; *cis*-Lactone **7**: ^{1}H NMR (250 MHz) δ 0.96 (6 H, d, J = 6.7 Hz), 0.97 (6 H, d, J = 6.8 Hz), 1.07 (3 H, d, J = 6.6 Hz), 1.12 (3 H, d, J = 6.7 Hz), 1.21 (3 H, d, J = 6.9 Hz), 2.2–2.7 (6 H, m), 3.99 (1 H, dd, J = 8.3, 3.0 Hz), 5.4 (4 H, m); IR ($CHCl_3$) 1768 cm^{-1}; $[\alpha]_D$ −28.5° (c 0.7, $CHCl_3$).

2,5(*S*),7(*S*),9(*S*),12-Pentamethyl-3(*E*),10(*E*)-tridecadiene-6(*R*),8-(*S*)-diol (8c). To a solution of lactone **6** (0.18 g, 0.61 mmol) in 4 mL of ether at −18 °C was added methyllithium (0.45 mL, 1.5 M in ether, 0.68 mmol). After having been stirred for 15 min, the reaction mixture was poured into saturated aqueous $NaHCO_3$, extracted thoroughly with ether, and worked up (dried over anhydrous Na_2CO_3). The crude residue (190 mg) was dissolved in 8 mL of THF at 0 °C to which was added 4 mL of cold 30% H_2O_2 and 0.2 mL of HOAc. After having been stirred at 0 °C for 30 min and for 16 h at 25 °C, the mixture was poured into saturated aqueous $NaHCO_3$, extracted thoroughly with hexane, washed with water, and worked up to give 200 mg of crude hydroperoxides: ^{1}H NMR (250 MHz, partial) δ 7.80 (s, ROOH), 7.87 (s, ROOH). To a solution of the hydroperoxides in 5 mL of CH_2Cl_2 at 0 °C was added triethylamine (0.18 g, 1.83 mmol), 4-(dimethylamino)pyridine (2 mg), and acetic anhydride (0.18 g, 1.83 mmol). After having been stirred at 0 °C for 30 min and for 1 h at 25 °C, the solution was diluted with 5 mL of CH_2Cl_2 and was heated at reflux for 6 h. The cooled reaction mixture was poured into saturated aqueous $NaHCO_3$, extracted with ether, and worked up to give 200 mg of crude acetates. The acetates in 5 mL of ether were slowly added to a stirred suspension of $LiAlH_4$ (1.0 g) in 75 mL of ether at 0 °C. After having been stirred for 1 h at 0 °C and for 16 h at 25 °C, the reaction mixture was cautiously decomposed (1 mL H_2O; 1 mL 15% NaOH; 3 mL H_2O). Chromatography (15% ethyl acetate/hexanes) gave 83 mg of diol **8c**, 9 mg of *meso*-diol **9**, and 53 mg of acetal **8b**.[32] Diol **8c**: ^{1}H NMR (250 MHz) δ 0.82 (3 H, d, J = 6.8 Hz), 0.96 (3 H, d, J = 7.0 Hz), 0.99 (12 H, d, J = 6.7 Hz), 1.09 (3 H, d, J = 6.9 Hz), 1.69 (1 H, m), 2.30 (2 H, m), 2.43 (2 H, m), 3.43 (1 H, dd, J = 7.8, 2.9 Hz), 3.54 (1 H, dd, J = 8.6, 3.0 Hz), 5.45 (4 H, m); IR ($CHCl_3$) 3444 cm^{-1}; LRMS (CI, NH_3) (M + 1) 283, (M + NH_4^+) 300; $[\alpha]_D$ −1.7° (c 0.5, $CHCl_3$). Diol **9**: ^{1}H NMR (250 MHz) δ 0.81 (3 H, d, J = 6.9 Hz), 0.98 (12 H, d, J = 6.7 Hz), 1.08 (6 H, d, J = 6.9 Hz), 1.65 (1 H, m), 2.27 (2 H, m), 2.43 (2 H, m), 3.22 (2 H, br s), 3.43 (2 H, dd, J = 8.5, 3.1 Hz), 5.42 (4 H, m); IR ($CHCl_3$) 3447 cm^{-1}; LRMS (CI, NH_3) (M + 1) 283, (M + NH_4^+) 300; $[\alpha]_D$ 0° (c 0.4, $CHCl_3$). Acetals **8b**: ^{1}H NMR (250 MHz) δ 0.68 (3 H, d, J = 7.0 Hz), 0.97 (3 H, d, J = 7.0 Hz), 0.99 (12 H, d, J = 7.0 Hz), 1.05 (3 H, d, J = 6.8 Hz), 1.28 (3 H, d, J = 5.0 Hz, acetal Me), 1.55 (1 H, m), 2.30 (4 H, m), 3.07 (1 H, dd, J = 9.8, 2.3 Hz), 3.14 (1 H, dd, J = 10.0, 2.3 Hz), 4.62 (1 H, q, J = 5.0 Hz, acetal methine), 5.4 (4 H, m).

3(*R*),5(*S*)-Dimethyl-3(*R*)-hydroxy-2(*R*)-methoxy-6(*S*)-(1(*R*)-methyl-2,2-dimethoxyethyl)tetrahydro-2*H*-pyran (11a) and 3(*R*),5-(*S*)-Dimethyl-3(*R*)-hydroxy-2(*S*)-methoxy-6(*S*)-(1(*R*)-methyl-2,2-dimethoxyethyl)tetrahydro-2*H*-pyran (11b). Ozone was passed through a solution of diolefin **8c** (80 mg, 0.28 mmol) in 8 mL of CH_2Cl_2 at −78 °C until the blue color of ozone persisted. The solution was purged with N_2, and 4 mL of dimethyl sulfide was added. After the solution had been warmed to 25 °C and stirred for 2 h, it was diluted with ether, washed with water, and worked up to give 77 mg of crude product. The residue was dissolved in 4 mL of methanol to which was added 150 μL of trimethyl orthoformate and 8 mg of p-toluenesulfonic acid. After the mixture had been stirred for 1.5 h at 25 °C, it was poured into saturated aqueous $NaHCO_3$, extracted with ether, and worked up. Chromatography (30% ethyl acetate/hexanes) gave 24 mg (33%) of acetal **11b** (less polar) and 22 mg of acetal **11a** (more polar). Acetal **11a**: ^{1}H NMR (250 MHz) δ 0.88 (3 H, d, J = 7.0 Hz), 0.94 (3 H, d, J = 7.0 Hz), 1.02 (3 H, d, J = 6.9 Hz), 1.62 (1 H, m), 1.74 (1 H, m), 1.85 (1 H, m), 3.35 (3 H, s), 3.39 (3 H, s), 3.46 (3 H, s), 3.82 (1 H, dd, J = 10.6, 2.3 Hz), 4.33 (1 H, d, J = 8.8 Hz), 4.41 (1 H, d, J = 8.7 Hz); IR ($CHCl_3$) 3506 cm^{-1}; LRMS (CI, NH_3) (M + 1) 263, (M + NH_4^+) 280; $[\alpha]_D$ +94.9° (c 0.9, $CHCl_3$). Acetal **11b**: ^{1}H NMR (250 MHz) δ 0.92 (6 H, d, J = 7.0 Hz), 1.06 (3 H, d, J = 7.2 Hz), 1.66 (2 H, m), 1.85 (1 H, m), 1.97 (1 H, m), 2.99 (1 H, d, J = 10.4 Hz), 3.31 (3 H, s), 3.33 (3 H, s), 3.36 (3 H, s), 3.54 (1 H, d, J = 10.4 Hz), 3.85 (1 H, dd, J = 11.0, 1.9 Hz), 4.42 (1 H, d, J = 8.8 Hz), 4.56 (1 H, d, J = 2.9 Hz); IR ($CHCl_3$) 3493, 3624 cm^{-1}; LRMS (CI, NH_3) (M + 1) 263, (M + NH_4^+) 280; $[\alpha]_D$ −38.7° (c 1.05, $CHCl_3$).

3(*R*),5(*S*)-Dimethyl-6(*S*)-(1(*R*)-methyl-2,2-dimethoxyethyl)tetrahydro-4*H*-pyran-2(3*H*)-one (11e). To a solution of alcohol **11a** (21 mg, 0.08 mmol) in 1 mL of THF at −18 °C was added dropwise (syringe/septum) 98 μL of n-butyllithium (0.24 mmol, 2.4 M hexane). After the solution had been stirred for 1.5 h, phenyl chlorothionocarbonate (138 mg, 0.80 mmol) was added. The solution was warmed to 25 °C over 45 min and then stirred for an additional 2.5 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$, extracted with ether, and worked up. Chromatography (15% ethyl acetate/hexanes) gave 26 mg (82%) of the thionocarbonate derivative: ^{1}H NMR (250 MHz) δ 0.92 (3 H, d, J = 7.0 Hz), 0.95 (3 H, d, J = 7.0 Hz), 1.02 (3 H, d, J = 6.9 Hz), 1.90 (3 H, s), 3.35 (3 H, s), 3.40 (3 H, s), 3.46 (3 H, s), 3.75 (1 H, dd, J = 10.6, 2.2 Hz), 4.24 (1 H, d, J = 8.9 Hz), 4.41 (1 H, d, J = 8.7 Hz), 5.87 (1 H, t, J = 2.8 Hz), 7.10–7.50 (5 H, m). A solution of the thionocarbonate (25 mg, 0.069 mmol), n-Bu_3SnH (180 mg, 0.69 mmol), and azoisobutyronitrile (AIBN, 1.3 mg) in 0.5 mL of toluene was heated at 90 °C for 6 h. The cooled solution was poured into saturated aqueous $NaHCO_3$, extracted with ether, and worked up. Chromatography (10% ethyl acetate/hexanes) gave 17 mg of crude deoxy compound **11c**: ^{1}H NMR (250 MHz) δ 0.77 (3 H, d, J = 6.6 Hz), 0.89 (3 H, d, J = 6.6 Hz), 0.95 (3 H, d, J = 7.0 Hz), 1.60 (3 H, s), 1.75 (1 H, s), 1.97 (1 H, m), 3.25 (1 H, dd, J = 10.0, 2.2 Hz), 3.35 (3 H, s), 3.39 (3 H, s), 3.46 (3 H, s), 3.88 (1 H, d, J = 8.4 Hz), 4.42 (1 H, d, J = 1.0 Hz); LRMS (CI, NH_3) (M + 1) 247, (M + NH_4^+) 264. Ozone was passed through an ethyl acetate solution of deoxy acetal **11c** (11 mg) at −78 °C for 1.5 h. The solution was purged with N_2, diluted with ether, and worked up. The crude residue was dissolved in 0.5 mL of THF containing 4 μL of trifluoroacetic acid. After having been stirred for 3 h at 25 °C, the reaction mixture was poured into saturated aqueous $NaHCO_3$, extracted with ether, and worked up. Chromatography (30% ethyl acetate/hexanes) gave 6.4 mg of lactone **11e**: ^{1}H NMR (250 MHz) δ 0.94 (3 H, d, J = 6.9 Hz), 0.95 (3 H, d, J = 6.3 Hz), 1.28 (3 H, d, J = 7.0 Hz), 1.95 (4 H, m), 2.50 (1 H, m), 3.38 (3 H, s), 3.41 (3 H, s), 4.26 (1 H, dd, J = 9.6, 1.2 Hz), 4.44 (1 H, d, J = 8.7 Hz); IR ($CHCl_3$) 1718 cm^{-1}; $[\alpha]_D$ +45.2° (c 0.6, $CHCl_3$).

3(*R*),5(*S*)-Dimethyl-2(*S*)-methoxy-6(*S*)-(1(*R*)-methyl-2,2-dimethoxyethyl)tetrahydro-2*H*-pyran (11d). The above procedure was employed with the following quantities of reagents: alcohol **11b** (23 mg, 0.09 mmol), n-BuLi (108 μL, 2.45 M in hexane, 0.26 mmol), phenyl chlorothionocarbonate (150 mg, 0.88 mmol), THF (1 mL). Chromatography (15% ethyl acetate/hexane) gave 29 mg of phenyl thionocarbonate: ^{1}H NMR (250 MHz) δ 0.89 (3 H, d, J = 6.9 Hz), 0.90 (3 H, d, J = 7.0 Hz), 1.02 (3, H, d, J = 7.2 Hz), 1.92 (2 H, m), 2.10 (1 H, m), 3.27 (6 H, s), 3.33 (3 H, s), 3.85 (1 H, dd, J = 10.8, 1.8 Hz), 4.39 (1 H, d, J = 8.7 Hz), 4.46 (1 H, d, J = 2.9 Hz), 5.83 (1 H, t, J = 3.1 Hz), 7.10–7.50 (5 H, m). Deoxygenation was conducted as described (vide supra): phenyl thionocarbonate (28 mg, 0.07 mmol), n-Bu_3SnH (200 mg, 0.7 mmol), AIBN (1 mg), toluene (0.5 mL). Chromatography (10% ethyl acetate/hexane) afforded 12 mg of deoxyacetal **11d**: ^{1}H NMR (250 MHz) δ 0.82 (3 H, d, J = 7.1 Hz), 0.89 (3 H, d, J = 6.6 Hz), 0.91 (3 H, d, J = 7.0 Hz), 1.29 (1 H, m), 1.45 (1 H, m), 1.60 (1 H, m), 1.77 (1 H, m), 2.00 (1 H, m), 3.31 (3 H, s), 3.33 (3 H, s), 3.35 (3 H, s), 3.58 (1 H, dd, J = 10.3, 1.9 Hz), 4.41 (1 H, d, J = 8.9 Hz), 4.42 (1 H, d, J = 4.6 Hz); LRMS (CI, NH_3) (M + 1) 247; $[\alpha]_D$ + 111.4° (c 0.44, $CHCl_3$).

3(*R*),5(*S*)-Dimethyl-6(*S*)-(1(*R*)-methylcarbomethoxymethyl)tetrahydropyran-2(3*H*)-one (1). Ozone was rapidly passed through a glass frit into a solution of acetal **11e** (5 mg, 0.02 mmol) in 2 mL of acetic acid for 30 h at 25 °C. The solution was diluted with ether, washed to neutrality with aqueous $NaHCO_3$ solution, and worked up. Chromatography (30% ethyl acetate/hexane) gave 3.5 mg (75%) of a 2:1 mixture of the Prelog–Djerassi lactonic acid ester **1** and acetal **11e**. A pure sample of the lactonic ester **1** (1.3 mg, 27%) was obtained by HPLC (12.5% ethyl acetate/hexane; t_R 14 min; 3.0 mL/min): ^{1}H NMR (250 MHz) δ 1.01 (3 H, d, J = 6.6 Hz), 1.21 (3 H, d, J = 7.1 Hz), 1.29 (3 H, d, J = 7.0 Hz), 1.47 (1 H, q, J = 12.0 Hz), 1.95 (2 H, m), 2.53 (1 H, m), 2.73 (1 H, qd, J = 7.1, 2.5 Hz), 3.74 (3 H, s), 4.54 (1 H, dd, J = 10.3, 2.6 Hz); IR ($CHCl_3$) 1727 cm^{-1}; HRMS (EI) calcd 214.1205, found 214.1200; $[\alpha]_D$ +36.4° (c 0.06, $CHCl_3$) [lit.[33] $[\alpha]_D$ +38° (c 1.0, $CHCl_3$)].

2(*S*),4(*S*)-Dimethyl-5(*E*)-decene-1,3(*R*)-diol (17a). Lactone **16b**

(32) Some acetal of diol **9** may have been present but was not detected.

(33) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 479.

(5.86 g, 27.9 mmol) was converted to diol **17a** in 89% yield by using the procedure described for lactone **16c**.[2] Lactone **17a**: bp 150 °C (0.2 Torr, Kugelrohr); ^{1}H NMR (250 MHz, $CDCl_3$, D_2O) δ 0.89 (3 H, d, J = 7.0 Hz), 0.90 (3 H, t, J = 6.0 Hz), 1.00 (3 H, d, J = 6.9 Hz), 1.33 (4 H, m), 1.85 (1 H, m), 2.04 (2 H, m), 2.40 (1 H, m), 3.42 (1 H, dd, J = 8.0, 4.0 Hz), 3.62 (1 H, dd, J = 10.8, 7.1 Hz), 3.73 (1 H, dd, J = 10.8, 3.5 Hz), 5.42 (1 H, dd, J = 15.0, 7.0 Hz), 5.53 (1 H, td, J = 15.0, 5.5 Hz); IR (neat) 3350, 1440, 970 cm^{-1}; $[\alpha]_D$ +0.89° (*c* 1.8, $CHCl_3$). Anal. ($C_{12}H_{24}O_2$) C, H.

4(*R*)-(1(*S*)-Methyl-2(*E*)-heptenyl)-2,2,5(*S*)-trimethyl-1,3-dioxane (17b). A solution of diol **17a** (4.24 g, 21.0 mmol) and *p*-toluenesulfonic acid (95 mg, 0.46 mmol) in 2,2-dimethoxypropane (40 mL, 0.33 mol) was stirred at 25 °C for 18 h. The solution was diluted with ether, washed successively with aqueous $NaHCO_3$ and brine, and worked up. Distillation (120 °C, 0.2 Torr, Kugelrohr) gave 4.82 g (95%) of acetonide **17b**: ^{1}H NMR (250 MHz) δ 0.75 (3 H, d, J = 6.7 Hz), 0.89 (3 H, m), 0.97 (3 H, d, J = 6.9 Hz), 1.33 (4 H, m), 1.37 (3 H, s), 1.39 (3 H, s), 1.81 (1 H, m), 2.02 (2 H, m), 2.30 (1 H, pentuplet of doublets, J = 7.5, 2.5 Hz), 3.41 (1 H, dd, J = 10.0, 2.9 Hz), 3.48 (1 H, t, J = 10.9 Hz), 3.69 (1 H, dd, J = 10.0, 5.1 Hz), 5.40 (1 H, dd, J = 15.0, 5.5 Hz), 5.50 (1 H, dd, J = 15.0, 6.0 Hz); $[\alpha]_D$ +38.0° (*c* 1.8, $CHCl_3$). Anal. ($C_{15}H_{28}O_2$) C, H.

4(*R*)-(1(*S*)-Methylbutyl)-2,2,5(*S*)-trimethyl-1,3-dioxane (19a). A solution of acetonide **17b** (4.8 g, 19.9 mmol) in 110 mL of methanol was ozonized at −78 °C until the blue color of ozone persisted. The solution was purged of ozone with oxygen, dimethyl sulfide (6 mL) was added, and the solution was warmed to 25 °C and allowed to stand for 18 h. The solvent was removed in vacuo, and the residue taken up in ether, washed with brine, and worked up. Distillation (115 °C, 0.3 Torr, Kugelrohr) gave 3.5 g (93%) of aldehyde **18a**: ^{1}H NMR (250 MHz) δ 0.78 (3 H, d, J = 6.7 Hz), 1.18 (3 H, d, J = 7.1 Hz), 1.33 (3 H, s), 1.44 (3 H, s), 1.92 (1 H, m), 2.48 (1 H, qd, J = 6.8, 2.6 Hz), 3.59 (1 H, t, J = 11.2 Hz), 3.75 (1 H, dd, J = 11.6, 5.2 Hz), 4.12 (1 H, dd, J = 10.6, 2.6 Hz), 9.66 (1 H, s); IR (neat) 1725 cm^{-1}. To a suspension of ethyltriphenylphosphonium bromide (4.65 g, 12.5 mmol) in 150 mL of ether at −78 °C was added dropwise (syringe/septum) 5.22 mL of *n*-butyllithium (2.4 M in hexane, 12.5 mmol). The reaction flask was then placed in an ice–water bath as a solution of aldehyde **18a** (2.11 g, 11.4 mmol) in 8 mL of ether was added dropwise, after which the reaction mixture was allowed to stir at 25 °C for 20 h. The mixture was poured into water and the water was extracted thoroughly with ether. The ether extracts were washed with brine and worked up. Chromatography (20% EtOAc/hexanes) and distillation (110 °C, 0.5 Torr, Kugelrohr) gave 1.35 g (60%) as a mixture of olefin isomers **18b**. A solution of the crude olefins (2.75 g, 13.4 mmol, from two Wittig reactions) in 150 mL of ethanol containing 0.2 g of Raney nickel W-2 was hydrogenated under atmospheric pressure at 25 °C for 2 days. The mixture was filtered through Celite and washed with ether. The filtrate was concentrated in vacuo and distilled (85 °C, 1 Torr, Kugelrohr) to afford 2.3 g (83% from the olefins) of the desired acetonide **19a**: ^{1}H NMR (250 MHz) δ 0.69 (3 H, d, J = 6.6 Hz), 0.84 (3 H, d, J = 6.9 Hz), 0.89 (3 H, m), 1.29 (4 H, m), 1.34 (3 H, s), 1.39 (3 H, s), 1.64 (1 H, m), 1.85 (1 H, m), 3.46 (2 H, m), 3.67 (1 H, dd, J = 11.4, 5.1 Hz); ^{13}C NMR (63 MHz) 12.4, 12.7, 14.2, 19.1, 20.4, 29.6, 30.9, 33.0, 36.0, 66.4, 76.9, 98.0 ppm; $[\alpha]_D$ +34.7° (*c* 3.1, $CHCl_3$).

2(*S*),4(*S*)-Dimethylheptane-1,3(*R*)-diol (19b). Acetonide **19a** (2.3 g, 11.5 mmol) in 70 mL of THF and 25 mL of 1 N HCl was heated at gentle reflux until approximately 10 mL of solvent was removed. The cooled reaction mixture was poured into aqueous $NaHCO_3$, extracted with ether, and worked up. Distillation (135 °C, 1 Torr, Kugelrohr) gave 1.8 g (100%) of diol **19b**: ^{1}H NMR (250 MHz, $CDCl_3$, D_2O) δ 0.81 (3 H, d, J = 6.9 Hz), 0.87 (3 H, t, J = 6.8 Hz), 0.90 (3 H, t, J = 7.0 Hz), 1.34 (4 H, m), 1.87 (1 H, m), 1.44 (1 H, m), 3.47 (1 H, dd, J = 8.9, 2.7 Hz), 3.64 (1 H, dd, J = 10.6, 7.7 Hz), 3.72 (1 H, dd, J = 10.6, 3.7 Hz); IR (neat) 3350 cm^{-1}; $[\alpha]_D$ +19.8° (*c* 1.4, $CHCl_3$). Anal. ($C_9H_{20}O_2$) C, H.

4(*S*)-Methyl-5(*R*)-(1(*S*)-methylbutyl)dihydro-2(3*H*)-furanone (15a). To a pyridine solution (9 mL) of diol **19a** (304 mg, 1.9 mmol) at 0 °C was added *p*-toluenesulfonyl chloride (470 mg, 2.5 mmol). The mixture was stored in a freezer at −6 °C for 18 h. The reaction mixture was poured into excess 3 N HCl, and the solution was extracted thoroughly with ether. The combined extracts were successively washed with 3 N HCl, aqueous $NaHCO_3$, and brine. Workup gave 551 mg (93%) of crude tosylate: ^{1}H NMR (250 MHz, partial) δ 0.79 (3 H, d, J = 6.8 Hz), 0.91 (3 H, m), 0.91 (3 H, d, J = 6.9 Hz), 2.46 (3 H, s, Ar*Me*), 7.35 (2 H, d, J = 8.0 Hz), 7.81 (2 H, d, J = 8.2 Hz). A mixture of the tosylate and NaCN (570 mg, 8.8 mmol) in 10 mL of DMSO were heated at 80 °C for 24 h. The cooled reaction mixture was poured into water and extracted with ether. The extracts were washed with aqueous $NaHCO_3$, water, and brine and worked up. Chrommatography (25% EtOAc/hexanes) gave 180 mg (61%) of the nitrile: ^{1}H NMR (250 MHz) δ 0.85 (3 H, d, J = 6.7 Hz), 0.93 (3 H, m), 1.07 (3 H, d, J = 6.8 Hz), 1.35 (4 H, m), 1.69 (1 H, m), 1.98 (1 H, m), 2.54 (2 H, m), 3.33 (1 H, m); IR (neat) 3450, 2240 cm^{-1}. Anal. ($C_{10}H_{19}NO$). The nitrile was heated at reflux in 10 mL of 0.4 N aqueous methanolic HCl for 24 h. The cooled reaction mixture was poured into water, extracted with ether, worked up, and chromatographed to give lactone **15a** (78%): ^{1}H NMR (250 MHz) δ 0.93 (3 H, t, J = 6.6 Hz), 0.95 (3 H, d, J = 6.8 Hz), 1.15 (3 H, d, J = 6.6 Hz), 1.2–1.5 (4 H, m), 1.72 (1 H, m), 2.18 (1 H, dd, J = 17.3, 8.2 Hz), 2.39 (1 H, m), 2.70 (1 H, dd, J = 8.4, 7.2 Hz), 3.97 (1 H, dd, J = 6.8, 4.1 Hz); ^{13}C NMR 13.5, 13.8, 18.0, 19.0, 32.0, 35.3, 35.4, 36.0, 91.0, 176.0 ppm; IR (neat) 1775 cm^{-1}; $[\alpha]_D$ +36.2° (*c* 1.7, $CHCl_3$). Anal. ($C_{10}H_{18}O_2$) C, H.

3(*S*)-(1(*R*),4-Dimethyl-2(*E*)-pentenyl)-4(*S*)-methyl-5(*R*)-(1(*S*)-methylbutyl)dihydro-2(3*H*)-furanone (20). By use of the modified Mander procedure[5] as previously described, lactone **15a** (1.38 g, 8.11 mmol) gave 1.71 g (90%) of lactonic ester **15b** after chromatography (20% EtOAc/hexanes) and distillation (Kugelrohr, 135 °C, 1 Torr): ^{1}H NMR (250 MHz) δ 0.92 (3 H, m), 0.98 (3 H, d, J = 6.8 Hz), 1.18 (3 H, d, J = 6.6 Hz), 1.40 (4 H, m), 1.79 (1 H, m), 2.82 (1 H, m), 3.27 (1 H, d, J = 11.0 Hz, C_3-H), 3.83 (3 H, s), 3.99 (1 H, dd, J = 12.8, 3.6 Hz, C_5-H); IR (neat) 1780, 1740 cm^{-1}. To a suspension of NaH (162 mg, 5.1 mmol, 60% suspension) in 12 mL of THF at 25 °C was added dropwise lactonic ester **15b** (917 mg, 4.0 mmol) in 8 mL of THF. After having been stirred for 30 min, the reaction mixture was homogeneous. To the reaction vessel was added $(Ph_3P)_4Pd$ (92 mg, 2 mol %) and Ph_3P (23 mg, 2 mol %). After 5 min, *S* allylic phosphate *ent*-**5b**[2] (1.4 g, 5.6 mmol) in 8 mL of THF was added dropwise. After having been stirred for 3 h at 25 °C, the reaction mixture was poured into water, extracted with ether, and worked up. Chromatography (20% EtOAc/hexanes) gave 1.10 g (84%) of a 2:1 mixture of alkylation products: ^{1}H NMR (250 MHz, partial) δ 3.75 (s, minor), 3.78 (s, major). A mixture of the lactonic ester (964 mg, 2.98 mmol), LiCl (760 mg, 17.9 mmol), water (0.11 mL), and DMSO (25 mL) was heated at 150 °C for 19 h. The cooled reaction mixture was poured into water, and the aqueous solution was extracted thoroughly with ether. The combined extracts were washed with brine and worked up. Chromatography (10% EtOAc/hexanes) gave 120 mg (15%) of a 2:1 mixture of lactone **20** and its C_3 epimer and 546 mg (69%) of pure lactone **20**: ^{1}H NMR (250 MHz) δ 0.91 (3 H, d, J = 6.8 Hz), 0.91 (3 H, m), 0.97 (6 H, d, J = 6.9 Hz), 1.13 (3 H, d, J = 6.1 Hz), 1.16 (3 H, d, J = 6.9 Hz), 1.20–1.50 (4 H, m), 1.68 (1 H, m), 2.24 (3 H, m), 2.76 (1 H, m), 3.81 (1 H, dd, J = 7.5, 3.0 Hz), 5.33 (1 H, dd, J = 15.0, 6.0 Hz), 5.48 (1 H, dd, J = 15.0, 6.5 Hz).

(4*S*),6(*R*),8(*R*),11-Tetramethyl-9(*E*)-dodecene-5(*R*),7(*S*)-diol (14). By the employment of the procedure for the formation of diol **8c**, lactone **20** (390 mg, 1.5 mmol) gave, upon chromatography (15% ethyl acetate/hexane), diol **14** (196 mg, 0.7 mmol, 46%): ^{1}H NMR (250 MHz) δ 0.79 (3 H, d, J = 6.9 Hz), 0.87 (3 H, d, J = 6.7 Hz), 0.92 (3 H, m), 0.98 (3 H, d, J = 6.8 Hz), 1.00 (6 H, d, J = 6.6 Hz), 1.38 (4 H, m), 1.73 (2 H, m), 2.33 (1 H, m), 3.49 (1 H, m), 3.53 (1 H, m), 3.57 (1 H, m), 5.48 (2 H, m).

3(*S*),5(*S*)-Dimethyl-3(*R*)-hydroxy-6(*R*)-(1(*S*)-methylbutyl)-2(*S*)-methoxytetrahydro-2*H*-pyran (21a) and 3(*S*),5(*S*)-Dimethyl-3(*S*)-hydroxy-6(*R*)-(1(*S*)-methylbutyl)-2(*R*)-methoxytetrahydro-2*H*-pyran (21b). Conditions for the preparation of **11a** and **11b** were employed by using diol **14** (73 mg, 0.28 mmol), affording acetals **21a** (44%) and **21b** (32%). Acetal **21a**: ^{1}H NMR (250 MHz) δ 0.90 (6 H, d, J = 6.8 Hz), 0.92 (3 H, m), 1.02 (3 H, d, J = 7.4 Hz), 1.43 (4 H, m), 1.67 (1 H, m), 1.90 (1 H, m), 2.14 (1 H, m), 3.36 (3 H, s), 3.45 (2 H, m), 3.61 (1 H, dd, J = 10.9, 1.9 Hz), 4.54 (1 H, s, C_2-H). Acetal **21b**: ^{1}H NMR (250 MHz) δ 0.86 (3 H, d, J = 7.0 Hz), 0.91 (3 H, d, J = 6.7 Hz), 0.93 (3 H, m), 0.96 (3 H, d, J = 7.1 Hz), 1.37 (4 H, m), 1.60 (1 H, m), 1.95 (2 H, m), 3.47 (3 H, s), 3.49 (1 H, dd, J = 10.6, 2.3 Hz), 3.72 (1 H, m), 4.68 (1 H, d, J = 2.3 Hz, C_2-H); $[\alpha]_D$ −23.3° (*c* 1.03, $CHCl_3$).

3(*S*),5(*S*)-Dimethyl-6(*R*)-(1(*S*)-methylbutyl)tetrahydropyran-2-(3*H*)-one ((+)-Invictolide, 2). To a solution of acetal **21b** (19 mg, 0.08 mmol) in 0.75 mL of THF at −18 °C was added *n*-BuLi (0.15 mL, 1.6 M in hexane, 0.24 mmol). After the mixture was stirred for 1 h, phenyl chlorothionocarbonate (140 mg, 0.82 mmol) was added, and the reaction mixture was allowed to warm to 25 °C. The solution was poured into aqueous $NaHCO_3$ and worked up. Chromatography (2.5% ethyl acetate/hexane) provided 61 mg of impure phenyl thionocarbonate: ^{1}H NMR (250 MHz, partial) δ 3.41 (1 H, dd, J = 10.0, 2.0 Hz), 3.48 (3 H, s), 4.55 (1 H, t, J = 2.4 Hz), 7.10–7.40 (5 H, m). The crude phenyl thionocarbonate, *n*-Bu_3SnH (240 mg, 0.8 mmol), and AIBN (0.7 mg) in 0.6 mL of toluene were heated at 90 °C for 2 h. The cooled solution was poured into aqueous $NaHCO_3$ and worked up. The solvent was cautiously removed by aspirator with gentle warming. Chromatography (2% ethyl acetate/hexane) gave a crude residue contaminated with aromatic impurities: ^{1}H NMR (250 MHz, partial) δ 0.74 (3 H, d, J =

6.5 Hz), 0.92 (3 H, d, J = 6.8 Hz), 0.98 (3 H, d, J = 7.0 Hz), 2.93 (1 H, dd, J = 10.0, 2.3 Hz), 3.46 (3 H, s), 4.28 (1 H, d, J = 2.3 Hz). Ozone was passed through a solution of the crude acetal in 4 mL of ethyl acetate at 25 °C until the acetal was consumed (TLC, ~10 min). The excess ozone was removed with N_2, and the solvent was cautiously removed in vacuo. The residue was dissolved in 2 mL of CH_2Cl_2 containing p-TsOH (2 mg) and stirred at 25 °C for 1.5 h. The solution was diluted with ether, washed with aqueous $NaHCO_3$, and worked up. Chromatography (15% ethyl acetate/hexane) gave 8.3 mg of impure product that was distilled (Kugelrohr) to give (+)-invictolide (5.4 mg, 33%), whose ^1H NMR spectrum was in agreement with authentic, natural[11,12] and racemic, synthetic invictolide:[13b] ^1H NMR (250 MHz) δ 0.90 (3 H, m), 0.92 (3 H, d, J = 6.8 Hz), 0.97 (3 H, d, J = 6.7 Hz), 1.22 (3 H, d, J = 6.9 Hz), 1.40 (4 H, m), 1.65 (3 H, m), 1.99 (1 H, m), 2.65 (1 H, m), 3.90 (1 H, dd, J = 10.1, 1.9 Hz); $[\alpha]_D$ +77.4° (c 0.27, $CDCl_3$).[34]

3-Carbomethoxy-4(S)-methyl-5(R)-[1(S)-methyl-2-[($tert$-butyldiphenylsilyl)oxy]ethyl]dihydro-2(3H)-furanone (22b). Carbomethoxylation of lactone **22a** (164 mg, 0.41 mmol) was conducted by using the procedure described (vide supra), affording lactonic ester **22b** in 98% yield: ^1H NMR (250 MHz) δ 1.06 (3 H, d, J = 7.0 Hz), 1.07 (9 H, s), 1.08 (3 H, d, J = 7.1 Hz), 1.91 (1 H, m, C_1-H), 2.86 (1 H, m, C_4-H), 3.24 (1 H, d, J = 1.4 Hz, C_3-H), 3.78 (2 H, m, C_2-H), 3.79 (3 H, s, CH_3O), 4.61 (1 H, dd, J = 10.9, 4.9 Hz, C_5), 7.41 (6 H, m), 7.67 (4 H, m); IR (CCl_4) 1791, 1741 cm^{-1}; $[\alpha]_D$ −17.7° (c 2.43, $CHCl_3$). Anal. ($C_{26}H_{34}O_5Si$) C, H.

3(S)-(1(S),4-Dimethyl-2(E)-pentenyl)-4(S)-methyl-5(R)-[1(S)-methyl-2-[($tert$-butyldiphenylsilyl)oxy]ethyl]dihydro-2(3H)-furanone (23) and 3(R)-(1(S),4-Dimethyl-2(E)-pentenyl)-4(S)-methyl-5(R)-[1(S)-methyl-2-[($tert$-butyldiphenylsilyl)oxy]ethyl]dihydro-2(3H)-furanone (24). Lactonic ester **22b** (170 mg, 0.39 mmol) was alkylated with R phosphate **5b** as described to give an intermediate alkylated ester (215 mg, 100%) after chromatography (25% Et_2O/hexane): ^1H NMR (250 MHz) δ 0.94 (6 H, d, J = 7.2 Hz), 0.97 (3 H, d, J = 7.2 Hz), 0.99 (3 H, d, J = 6.5 Hz), 1.07 (9 H, s), 1.17 (3 H, d, J = 6.5 Hz), 1.89 (1 H, m), 2.24 (1 H, m), 2.59 (1 H, m), 2.90 (1 H, m), 3.74 (2 H, m), 3.75 (3 H, s), 4.33 (1 H, dd, J = 10.7, 5.7 Hz), 5.21 (1 H, dd, J = 15.0, 9.8 Hz), 5.57 (1 H, dd, J = 15.2, 7.2 Hz), 7.41 (6 H, m), 7.67 (4 H, m); IR (CCl_4) 1780, 1734 cm^{-1}. Decarbomethoxylation of the alkylation product (212 mg, 0.34 mmol) as described above and chromatography (10% Et_2O/hexane) afforded trans lactone **23** (71%) and cis lactone **24** (21%). Lactone **23**: mp 67–69 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (6 H, d, J = 6.7 Hz), 1.01 (3 H, d, J = 7.1 Hz), 1.02 (3 H, d, J = 6.7 Hz), 1.07 (9 H s), 1.15 (3 H, d, J = 6.9 Hz), 1.92 (1 H, m, $C_{2'(5)}$-H), 2.20 (1 H, dd, J = 5.6, 1.9 Hz, C_3-H), 2.25 (1 H, m, $C_{4'(3)}$-H), 2.36 (1 H, m, C_4-H), 2.56 (1 H, m, $C_{1'(3)}$-H), 3.87 (2 H, m, $C_{2'(5)}$-H), 4.35 (1 H, dd, J = 10.8, 5.6 Hz, C_5-H), 5.32 (1 H, dd, J = 15.3, 7.6 Hz, $C_{2'(3)}$-H), 5.46 (1 H, dd, J = 15.3, 6.4 Hz, $C_{3'(3)}$-H), 7.39 (6 H, m), 7.64 (4 H, m); ^1H NMR (250 MHz, C_6D_6) δ 0.51 (3 H, d, J = 7.1 Hz), 0.82 (3 H, d, J = 6.7 Hz), 0.91 (3 H, d, J = 6.8 Hz), 0.93 (3 H, d, J = 6.8 Hz), 1.10 (3 H, d, J = 6.8 Hz), 1.18 (9 H, s), 1.63 (1 H, m, $C_{1'(5)}$-H), 1.98 (2 H, m, C_3-H, C_4-H), 2.14 (1 H, m, $C_{4'(3)}$-H), 2.37 (1 H, m, $C_{1'(3)}$-H), 3.73 (1 H, dd, J = 9.8, 2.9 Hz, $C_{2'(5)}$-H), 3.88 (1 H, dd, J = 9.8, 5.0 Hz, $C_{2'(5)}$-H), 4.25 (1 H, dd, J = 10.4, 5.4 Hz, C_5-H), 5.33 (2 H, m, $C_{2'(3)}$-H, $C_{3'(3)}$-H), 7.24 (6 H, m), 7.82 (4 H, m); IR ($CHCl_3$) 1755 cm^{-1}; $[\alpha]_D$ −23.2° (c 1.04, $CHCl_3$). Anal. ($C_{31}H_{44}OSi$) C, H. Lactone **24**: mp 115–116 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 0.84 (3 H, d, J = 6.5 Hz), 0.99 (6 H, d, J = 6.7 Hz), 1.01 (3 H, d, J = 6.7 Hz), 1.07 (9 H, s), 1.30 (3 H, d, J = 5.6 Hz), 1.88 (1 H, m, $C_{1'(5)}$-H), 2.38 (1 H, m, $C_{4'(3)}$-H), 2.42 (3 H, m, C_3-H, $C_{1'(3)}$-H, C_4-H), 3.87 (1 H, dd, J = 9.9, 3.8 Hz, $C_{2'(5)}$-H), 3.86 (1 H, dd, J = 9.9, 4.9 Hz, $C_{2'(5)}$-H), 4.26 (1 H, dd, J = 10.7, 3.0 Hz, C_5-H), 5.23 (1 H, dd, J = 15.4, 6.8 Hz, $C_{2'(3)}$-H), 5.47 (1 H, dd, J = 15.4, 6.6 Hz, $C_{3'(3)}$-H), 7.39 (6 H, m), 7.65 (4 H, m); ^1H NMR (250 MHz, C_6D_6) δ 0.60 (3 H, d, J = 6.6 Hz), 0.76 (3 H, d, J = 6.7 Hz), 0.84 (3 H, d, J = 6.7 Hz), 0.91 (3 H, d, J = 6.8 Hz), 1.20 (9 H, s), 1.42 (3 H, d, J = 6.5 Hz), 1.63 (1 H, m, $C_{1'(5)}$-H), 1.95 (2 H, m, C_4-H), 2.11 (1 H, m, $C_{4'(3)}$-H), 2.32 (1 H, m, $C_{1'(3)}$-H), 3.75 (1 H, dd, J = 9.8, 2.7 Hz, $C_{2'(5)}$-H), 3.84 (1 H, dd, J = 10.8, 3.4 Hz, C_5-H), 3.93 (1 H, dd, J = 9.8, 4.9 Hz, $C_{2'(5)}$-H), 5.01 (1 H, dd, J = 15.4, 8.5 Hz, $C_{2'(3)}$-H), 5.23 (1 H, dd, J = 15.4, 6.6 Hz, $C_{3'(3)}$-H), 7.24 (6 H, m), 7.84 (4 H, m); IR ($CHCl_3$) 1760 cm^{-1}; $[\alpha]_D$ −10.6° (c 1.08, $CHCl_3$); HRMS (CI, M + H) calcd for $C_{31}H_{44}O_3Si$(H) 493.3140, found 493.3144.

3(S)-(1(R),4-Dimethyl-2(E)-pentenyl)-4(S)-methyl-5(R)-[1(S)-methyl-2-[($tert$-butyldiphenylsilyl)oxy]ethyl]dihydro-2(3H)-furanone (25) and 3(R)-(1(R),4-Dimethyl-2(E)-pentenyl)-4(S)-methyl-5(R)-[1(S)-methyl-2-[($tert$-butyldiphenylsilyl)oxy]ethyl]dihydro-2(3H)-furanone (26). Lactonic ester **22b** (342 mg, 0.62 mmol) was alkylated with S phosphate **5b** and decarbomethoxylated to give, after chromatography (5% ether/hexanes), trans lactone **25** (55%) and cis lactone **26** (34%). Trans lactone **25**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.97 (3 H, d, J = 7.0 Hz), 0.99 (6 H, d, J = 6.8 Hz), 1.00 (3 H, d, J = 6.8 Hz), 1.08 (9 H, s), 1.15 (3 H, d, J = 6.8 Hz), 1.90 (1 H, m), 2.03 (1 H, dd, J = 8.3, 0.7 Hz, C_3-H), 2.25 (1 H, m), 2.36 (1 H, m), 2.49 (1 H, m), 3.78 (2 H, m), 4.28 (1 H, d, J = 10.7, 5.1 Hz, C_5-H), 5.21 (1 H, ddd, J = 15.4, 8.0, 1.0 Hz), 5.45 (1 H, dd, J = 15.4, 6.6 Hz), 7.41 (6 H, m), 7.67 (4 H, m); ^1H NMR (250 MHz, C_6D_6) δ 0.60 (3 H, d, J = 7.0 Hz), 0.83 (3 H, d, J = 6.8 Hz), 0.87 (6 H, d, J = 6.8 Hz), 1.08 (9 H, s), 1.09 (3 H, d, J = 6.8 Hz), 1.65 (1 H, m), 1.85 (1 H, dd, J = 8.0, 0.8 Hz), 2.10 (2 H, m), 2.44 (1 H, m), 3.78 (1 H, dd, J = 10.0, 2.9 Hz), 3.89 (1 H, dd, J = 10.0, 5.0 Hz), 4.21 (1 H, dd, J = 10.7, 5.2 Hz), 5.12 (1 H, dd, J = 15.4, 7.9 Hz), 5.32 (1 H, dd, J = 15.4, 6.9 Hz), 7.41 (6 H, m), 7.67 (4 H, m). *cis*-Lactone **26**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.86 (3 H, d, J = 6.6 Hz), 0.99 (6 H, d, J = 6.7 Hz), 1.02 (3 H, d, J = 6.7 Hz), 1.05 (3 H, d, J = 6.7 Hz), 1.07 (9 H, s), 1.88 (1 H, m), 2.31 (1 H, m), 2.45 (3 H, m), 3.76 (1 H, dd, J = 9.9, 2.7 Hz), 3.85 (1 H, dd, J = 9.9, 4.8 Hz), 4.14 (1 H, dd, J = 10.8, 3.3 Hz), 5.46 (1 H, dd, J = 15.6, 6.7 Hz), 5.77 (1 H, dd, J = 15.6, 5.3 Hz), 7.41 (6 H, m), 7.67 (4 H, m); ^1H NMR (250 MHz, C_6D_6) δ 0.50 (3 H, d, J = 6.7 Hz), 0.80 (3 H, d, J = 6.7 Hz), 0.90 (3 H, d, J = 6.7 Hz), 1.05 (6 H, d, J = 6.7 Hz), 1.19 (9 H, s), 1.61 (1 H, m), 1.90 (1 H, m), 2.01 (1 H, dd, J = 9.4, 6.1 Hz), 2.33 (2 H, m), 3.78 (2 H, m), 3.91 (1 H, dd, J = 9.8, 4.9 Hz), 5.50 (1 H, ddd, J = 15.6, 6.6, 1.0 Hz), 5.97 (1 H, ddd, J = 15.6, 5.9, 1.0 Hz), 7.41 (6 H, m), 7.67 (4 H, m).[35]

6(R)-(1(S),4-Dimethyl-2(E)-pentenyl)-4(S)-[1(S)-methyl-2-[($tert$-butyldiphenylsilyl)oxy]ethyl]-2,2,5(S)-trimethyl-1,3-dioxane (35). Lactone **24** (80 mg, 0.16 mmol) was converted into a mixture (94 mg) of crude hydroperoxy hemiketals (vide supra): ^1H NMR (250 MHz, partial, major isomer) δ 1.07 (3 H, s), 3.90 (1 H, dd, J = 10.4, 3.4 Hz), 5.22 (1 H, dd), 5.44 (1 H, dd), 7.31 (6 H, m), 7.47 (1 H, s, OOH), 7.70 (4 H, m). Criegee rearrangement was accomplished as described to give 86 mg of a mixture of mono- and diacetates: ^1H NMR (250 MHz, partial) δ 1.87, 2.00, 2.01 (3 × 3 H, AcO). To a solution of the crude acetates in CH_2Cl_2 at −78 °C was added diisobutylaluminum hydride (Dibal) (0.6 mL, 0.6 mmol, 1 M in hexanes). The mixture was stirred at −78 °C for 2 h, quenched with MeOH, and warmed to 25 °C. The solution was diluted with ether, washed with saturated aqueous sodium potassium tartrate, and worked up to give crude diol: ^1H NMR (250 MHz, partial) δ 0.61 (3 H, d, J = 6.9 Hz), 0.91 (3 H, d, J = 7.0 Hz), 0.93 (3 H, d, J = 6.8 Hz), 0.95 (3 H, d, J = 6.7 Hz), 1.05 (9 H, s), 1.11 (3 H, d, J = 6.5 Hz), 4.4–4.8 (4 H, m), 5.13 (1 H, dd, J = 15.4, 8.9 Hz), 5.42 (1 H, dd, J = 15.4, 6.8 Hz), 7.44 (6 H, m), 7.67 (4 H, m). The crude diol was dissolved in 2,2-dimethoxypropane (2 mL) containing p-TsOH (2 mg) and was stirred for 4 h at 25 °C. The solution was diluted with ether, washed with aqueous $NaHCO_3$, and worked up. Chromatography (5% ether/hexanes) gave 74 mg (87%) of pure acetonide **35**: ^1H NMR (250 MHz) δ 0.83 (3 H, d, J = 7.0 Hz), 0.96 (3 H, d, J = 7.0 Hz), 1.00 (3 H, d, J = 6.9 Hz), 1.01 (3 H, d, J = 6.9 Hz), 1.03 (3 H, d, J = 7.0 Hz), 1.08 (9 H, s), 1.44 (6 H, s, C_2-Me), 1.55 (1 H, m, C_5-H), 1.85 (1 H, m, $C_{1'(4)}$-H), 2.27 (2 H, m, $C_{1'(6)}$-H, $C_{4'(6)}$-H), 3.45 (1 H, dd, J = 9.9, 1.9 Hz, C_6-H), 3.58 (1 H, dd, J = 9.6, 2.5 Hz, $C_{2'(4)}$-H), 3.82 (1 H, dd, J = 10.0, 1.9 Hz, C_4-H), 3.87 (1 H, dd, J = 9.6, 4.2 Hz, $C_{2'(4)}$-H), 5.14 (1 H, dd, J = 15.4, 8.8 Hz, vinyl H), 5.48 (1 H, dd, J = 15.4, 6.9 Hz, vinyl H), 7.29 (6 H, m), 7.41 (4 H, m); $[\alpha]_D$ +15.0° (c 1.8, $CHCl_3$); HRMS (CI, M + 1) calcd for $C_{33}H_{50}O_3Si$(H) 523.3609, found 523.3582.

6(S)-(1(S),4-Dimethyl-2(E)-pentenyl)-4(S)-[1(S)-methyl-2-[($tert$-butyldiphenylsilyl)oxy]ethyl]-2,2,5(S)-trimethyl-1,3-dioxane (34). Lactone **23** (292 mg, 0.59 mmol) was treated with methyllithium and subjected to the Criegee sequence giving 141 mg (46%) of cis lactone **24** in addition to 165 mg of a mixture of mono- and diacetates. The mixture was transformed into acetonide **34** (vide supra) in 31% (93 mg) overall yield: ^1H NMR (250 MHz) δ 0.84 (3 H, d, J = 6.7 Hz), 0.91 (3 H, d, J = 6.7 Hz), 0.98 (3 H, d, J = 6.8 Hz), 0.99 (3 H, d, J = 7.2 Hz), 1.05 (3 H, d, J = 6.8 Hz), 1.07 (9 H, s), 1.20 (3 H, s), 1.27 (3 H, s), 1.70 (1 H, m, $C_{1'(4)}$-H), 1.85 (1 H, m, C_5-H), 2.25 (2 H, m, $C_{4'(6)}$-H, $C_{1'(6)}$-H), 3.18 (1 H, dd, J = 6.6, 3.8 Hz, C_6-H), 3.60 (1 H, dd, J = 10.8, 3.9 Hz, C_4-H), 3.70 (2 H, m, $C_{2'(4)}$-H), 5.41 (2 H, m, vinyl H), 7.40 (6 H, m), 7.66 (4 H, m); $[\alpha]_D$ +31.7° (c 1.55, $CHCl_3$). Anal. ($C_{33}H_{50}O_3Si$) C, H.

6(S)-(1(S)-Methyl-2-hydroxyethyl)-4(S)-[1(S)-methyl-2-[($tert$-butyldiphenylsilyl)oxy]ethyl]-2,2,5(S)-trimethyl-1,3-dioxane (36a). Olefin

(34) Subsequent to our preliminary report,[13d] Mori[15] reported the synthesis of both enantiomers of invictolide: $[\alpha]^{22}_D$ +101° (c 0.615, $CHCl_3$); $[\alpha]^{25}_D$ −101° (c 0.450, $CHCl_3$). The direct comparison and identity of the ^1H NMR spectra of our sample, Tumlinson's, and Mori's have been established (personal communication, Tokyo, 1986, and ref 15).

(35) Lactones *ent*-**25** and *ent*-**26** were prepared and displayed the following data. *ent*-**25**: IR ($CHCl_3$) 1753 cm^{-1}; $[\alpha]_D$ −16.4° (c 2.43, $CHCl_3$). Anal. ($C_{31}H_{44}O_3Si$) C, H. *ent*-**26**: IR ($CHCl_3$) 1767 cm^{-1}; $[\alpha]_D$ +3.3° (c 1.01, $CHCl_3$). Anal. ($C_{31}H_{44}O_3Si$) C, H.

34 (22.4 mg, 0.04 mmol) was ozonized and reduced with $LiAlH_4$ (vide supra) to give 19.1 mg (98%) of alcohol **36a**: ^1H NMR (250 MHz) δ 0.89 (3 H, d, J = 6.7 Hz), 0.95 (3 H, d, J = 6.7 Hz), 1.00 (3 H, d, J = 7.1 Hz), 1.08 (9 H, s), 1.23 (3 H, s), 1.31 (3 H, s), 1.68 (1 H, m), 1.80 (2 H, m), 3.26 (1 H, t, J = 6.6 Hz), 3.57 (1 H, dd, J = 11.3, 6.1 Hz), 3.65–3.78 (4 H, m), 7.41 (6 H, m), 7.68 (4 H, m); IR (CCl_4) 3544 cm^{-1}; $[\alpha]_D$ +31.5° (c 1.0, $CHCl_3$) (lit.[19b] for *ent*-**36a**, $[\alpha]_D$ −30.8° (c 3.0, $CHCl_3$); HRMS (CI, M + 1) calcd for $C_{29}H_{44}O_4Si(H)$ 485.308, found 485.308.

6(*S*)-(1(*S*)-Methyl-2-cyanoethyl)-4(*S*)-[1(*S*)-methyl-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-2,2,5(*S*)-trimethyl-1,3-dioxane (36c). Alcohol **36a** (19 mg, 0.04 mmol) was converted to its tosylate and was displaced with sodium cyanide (vide supra) to afford 14 mg (68%) of nitrile **36c**: ^1H NMR (250 MHz) δ 0.91 (3 H, d, J = 6.9 Hz), 0.93 (3 H, d, J = 6.7 Hz), 1.08 (9 H, s), 1.15 (3 H, d, J = 6.9 Hz), 1.21 (3 H, s), 1.29 (3 H, s), 1.73 (2 H, m), 1.96 (1 H, m), 2.46 (2 H, m, $C_{2'(6)}$-H), 3.10 (1 H, t, J = 6.5 Hz), 3.52–3.70 (2 H, m), 3.73 (1 H, dd, J = 10.0, 4.8 Hz), 7.41 (6 H, m), 7.67 (4 H, m); IR (CCl_4) 2248 cm^{-1}.

4(*S*)-Methyl-5(*S*)-[1(*R*)-methyl-1-(2,2,5(*S*)-trimethyldioxan-4(*S*)-yl)methyl]dihydro-2(3*H*)-furanone (37a). A solution of nitrile **36c** (26 mg, 0.053 mmol) in 4 mL of diethylene glycol containing KOH (217 mg, 3.3 mmol) was heated at 200 °C for 40 h. The cooled solution was diluted with 15% aqueous NaOH and washed with ether. The aqueous phase was stirred vigorously with $CHCl_3$ as it was neutralized with 5% aqueous HCl. The aqueous phase was extracted with $CHCl_3$, and the combined organic phases were worked up to give 55 mg of crude acid **36d**. The acid in 2,2-dimethoxypropane (7 mL) containing *p*-TsOH (14 mg) was stirred at 25 °C for 48 h. The solution was diluted with ether, washed with aqueous $NaHCO_3$, and worked up. Chromatography (20% ethyl acetate/hexanes) gave lactone **37a** (13 mg, 95%): ^1H NMR (250 MHz) δ 0.71 (3 H, d, J = 6.2 Hz), 0.94 (3 H, d, J = 7.1 Hz), 1.20 (3 H, d, J = 6.7 Hz), 1.37 (3 H, s), 1.45 (3 H, s), 1.60 (1 H, m), 1.85 (1 H, m), 2.21 (1 H, dd, J = 17.7, 9.0 Hz, C_3-H), 2.42 (1 H, m), 2.75 (1 H, dd, J = 17.7, 9.0 Hz, C_3-H), 3.54 (1 H, t, J = 11.2 Hz), 3.71 (1 H, dd, J = 11.5, 5.9 Hz), 3.83 (1 H, dd, J = 10.7, 2.0 Hz), 4.11 (1 H, dd, J = 8.9, 5.5 Hz, C_5-H); IR (CCl_4) 1781 cm^{-1}; $[\alpha]_D$ +83.5° (c 0.2, $CHCl_3$); HRMS (CI, M + 1) calcd for $C_{14}H_{24}O_4(H)$ 257.1750, found 257.1756.

3(*R*)-Carbomethoxy-4(*S*)-methyl-5(*S*)-[1(*R*)-methyl-1-(2,2,5(*S*)-trimethyldioxan-4(*S*)-yl)methyl]dihydro-2(3*H*)-furanone (37b). Lactone **37a** (3.8 mg, 0.015 mmol) was converted into lactonic ester **37b** in 93% yield by the Mander procedure (vide supra) by using 8 equiv of both LDA and methyl cyanoformate. Lactone **37b**: ^1H NMR (250 MHz) δ 0.71 (3 H, d, J = 6.7 Hz), 0.96 (3 H, d, J = 7.0 Hz), 1.27 (3 H, d, J = 6.6 Hz), 1.37 (3 H, s), 1.44 (3 H, s), 1.85 (1 H, m), 1.96 (1 H, m), 2.76 (1 H, m), 3.31 (1 H, d, J = 9.6 Hz, C_3-H), 3.53 (1 H, t, J = 11.2 Hz), 3.71 (1 H, dd, J = 11.5, 5.0 Hz), 3.83 (3 H, s, OCH_3), 3.84 (1 H, dd, J = 10.5, 1.9 Hz), 4.13 (1 H, dd, J = 9.2, 7.7 Hz, C_5-H); IR (CCl_4) 1877, 1746 cm^{-1}; $[\alpha]_D$ +60.0° (c 0.15, $CHCl_3$); HRMS (CI, M + 1) calcd for $C_{16}H_{26}O_6(H)$ 315.1808, found 315.1790.

4(*S*)-Methyl-3(*S*)-(1(*R*),4-Dimethyl-2(*E*)-pentenyl)-5(*S*)-[1(*R*)-methyl-1-(2,2,5(*S*)-trimethyldioxan-4(*S*)-yl)methyl]dihydro-2(3*H*)-furanone (38). Lactonic ester **37b** was alkylated with *S* phosphate *ent*-**5b** as previously described. Decarboxylation by the Krapcho procedure and chromatography (20% ethyl acetate/hexanes) gave pure lactone **38** in 87% yield: ^1H NMR (250 MHz) δ 0.69 (3 H, d, J = 6.8 Hz), 0.91 (3 H, d, J = 7.0 Hz), 0.97 (6 H, d, J = 6.8 Hz), 1.14 (3 H, d, J = 6.9 Hz), 1.19 (3 H, d, J = 6.8 Hz), 1.36 (3 H, s), 1.44 (3 H, s), 1.73 (1 H, m), 1.84 (1 H, m), 2.10 (1 H, m), 2.27 (1 H, m), 2.28 (1 H, dd, J = 8.2, 4.6 Hz, C_3-H), 2.75 (1 H, m), 3.53 (1 H, t, J = 11.3 Hz), 3.70 (1 H, dd, J = 11.2, 4.7 Hz), 3.84 (1 H, dd, J = 10.6, 1.9 Hz), 3.96 (1 H, d, J = 9.6, 6.9 Hz, C_5-H), 5.30 (1 H, dd, J = 16.0, 7.1 Hz), 5.48 (1 H, dd, J = 16.0, 6.9 Hz); IR (CCl_4) 1773, 1190 cm^{-1}; $[\alpha]_D$ +89.7° (c 0.52, $CHCl_3$); HRMS calcd for $C_{21}H_{36}O_4$ 352.2615, found 352.2604.

4(*S*)-Methyl-3(*S*)-(1(*S*)-methyl-2-hydroxyethyl)-5(*S*)-[1(*R*)-methyl-1-(2,2,5(*S*)-trimethyldioxan-4(*S*)-yl)methyl]dihydro-2(3*H*)-furanone (39a). A solution of olefinic lactone **38** (5.0 mg, 0.014 mmol) in 3:1 $MeOH/CH_2Cl_2$ (2 mL) containing $NaHCO_3$ at −78 °C was ozonized until the blue color persisted. Excess ozone was purged with N_2. The solution was cannulated into a suspension of $NaBH_4$ (25.0 mg, 0.66 mmol) in 1 mL of MeOH at −78 °C. The mixture was stirred for 30 min at −78 °C and for 1 h at 25 °C, diluted with water, extracted with ether, and worked up. Chromatography (50% ethyl acetate/hexanes) gave hydroxy lactone **39a** (93%): ^1H NMR (250 MHz) δ 0.71 (3 H, d, J = 6.8 Hz), 0.95 (3 H, d, J = 7.1 Hz), 1.03 (3 H, d, J = 7.1 Hz), 1.22 (3 H, d, J = 6.4 Hz), 1.37 (3 H, s), 1.44 (3 H, s), 1.80–1.95 (2 H, m), 2.05–2.23 (2 H, m), 2.51 (1 H, dd, J = 10.3, 2.7 Hz, C_3-H), 3.53 (1 H, t, J = 11.6 Hz), 3.71 (1 H, dd, J = 11.6, 5.2 Hz), 3.77 (2 H, m), 3.85 (1 H, dd, J = 10.9, 1.9 Hz), 4.07 (1 H, t, J = 8.5 Hz); IR (CCl_4) 3478, 1765 cm^{-1}; $[\alpha]_D$ +36.1° (c 0.2, $CHCl_3$); HRMS (CI, M + 1) calcd for $C_{17}H_{30}O_5(H)$ 315.2172, found 315.2171.

4(*S*)-Methyl-3(*S*)-[1(*S*)-methyl-2-[(*tert*-butyldiphenylsilyl)oxy]-ethyl]-5(*S*)-[1(*R*)-methyl-1-(2,2,5(*S*)-trimethyldioxan-4(*S*)-yl)methyl]-dihydro-2(3*H*)-furanone (39b). A solution of alcohol **39a** (6.4 mg, 0.02 mmol), imidazole (6.9 mg, 0.10 mmol), *tert*-butyldiphenylsilyl chloride (13.6 mg, 0.05 mmol), and 4-(dimethylamino)pyridine (2.0 mg, 0.02 mmol) in 0.4 mL of DMF was stirred at 25 °C for 18 h. The solution was diluted with water, extracted with ether, and worked up. Chromatography (15% ether/hexanes) gave silyl ether **39b** (87%): ^1H NMR (250 MHz) δ 0.66 (3 H, d, J = 6.7 Hz), 0.94 (6 H, d, J = 7.1 Hz), 1.06 (9 H, s), 1.20 (3 H, d, J = 6.3 Hz), 1.37 (3 H, s), 1.45 (3 H, s), 1.84 (2 H, m), 2.00–2.25 (2 H, m), 2.63 (1 H, dd, J = 10.6, 2.9 Hz, C_3-H), 3.52 (1 H, m), 3.65 (1 H, dd, J = 10.3, 5.6 Hz), 3.70 (1 H, dd, J = 11.3, 4.9 Hz), 3.86 (1 H, dd, J = 10.4, 1.7 Hz), 3.90 (1 H, t, J = 9.0 Hz), 4.01 (1 H, t, J = 8.8 Hz, C_5-H), 7.42 (6 H, m), 7.66 (4 H, m); IR (CCl_4) 1772 cm^{-1}; $[\alpha]_D$ +26.7° (c 0.2, $CHCl_3$); HRMS (CI, M + 1) calcd for $C_{33}H_{48}O_5Si(H)$ 553.3351, found 553.3369.

4(*S*)-[6-[(*tert*-Butyldiphenylsilyl)oxy]-2(*R*)-hydroxy-4-oxo-1(*S*),3-(*R*),5(*R*)-trimethylhexanyl]-2,2,5(*S*)-trimethyl-1,3-dioxane (41b). To a CH_2Cl_2 solution (0.3 mL) of lactone **39b** at −78 °C was added dropwise diisobutylaluminum hydride (Dibal) (0.02 mL, 1 M in hexanes, 0.02 mmol). After having been stirred for 1 h, the mixture was quenched with MeOH, warmed to 25 °C, diluted with ether and shaken with saturated aqueous potassium sodium tartrate until the emulsion clarified. The aqueous phase was backwashed with ether, the combined organic extracts were dried (anhydrous Na_2CO_3), filtered, and concentrated to give 4.2 mg of crude hemiacetals: ^1H NMR (250 MHz, partial, major) δ 0.70 (3 H, d), 0.88 (3 H, d), 1.02 (3 H, d), 1.07 (9 H, s), 1.37 (3 H, s), 1.45 (3 H, s), 5.34 (1 H, t); (minor) δ 0.69 (3 H, d), 0.86 (3 H, d), 0.99 (3 H, d), 1.07 (9 H, s), 1.35 (3 H, s), 1.42 (3 H, s), 5.23 (1 H, br s). The crude hemiacetals were dissolved in CH_2Cl_2 (0.6 mL) and Et_3N (66 mg, 0.065 mmol) and cooled to 0 °C. After the dropwise addition of methanesulfonyl chloride (120 mg, 0.13 mmol) had been completed, the solution was stirred for 30 min and then at 25 °C for 30 min. The mixture was diluted with ether, washed with water, dried over anhydrous Na_2CO_3, filtered, and concentrated to give 6.5 mg of crude enol ether **40**: ^1H NMR (250 MHz, partial) δ 0.68 (3 H, d), 0.86 (3 H, d), 1.02 (3 H, d), 1.06 (9 H, s), 1.36 (3 H, s), 1.43 (3 H, s), 3.93 (1 H, dd, J = 8.8, 6.4 Hz), 5.96 (1 H, br s, vinyl). Ozonolysis of the crude enol ether was conducted as described for olefinic lactone **38**. The crude ozonolysis mixture was treated with dimethyl sulfide (0.5 mL) at −78 °C, warmed to 25 °C, and stirred for 45 min. The solution was concentrated in vacuo, diluted with ether washed with water, and worked up to give 6.5 mg of crude keto formate **41a**. ^1H NMR (250 MHz, partial) δ 5.34 (1 H, dd), 7.43 (6 H, m), 7.67 (4 H, m), 8.09 (1 H, s, CHO). The crude keto formate was dissolved in 3 mL of half-saturated NH_3/MeOH and was stirred for 3 h at 25 °C. Chromatography (30% ether/hexanes) gave 3.0 mg of hydroxy ketone **41b** (79%): ^1H NMR (250 MHz) δ 0.71 (3 H, d, J = 6.7 Hz), 1.02 (3 H, d, J = 6.9 Hz), 1.05 (3 H, d, J = 6.8 Hz), 1.08 (3 H, d, J = 6.9 Hz), 1.08 (9 H, s), 1.38 (3 H, s), 1.48 (3 H, s), 1.90 (2 H, m), 3.04 (2 H, m, $C_{4(3')}$-H, $C_{4(5')}$-H), 3.49 (1 H, t, J = 12.8 Hz), 3.56–3.68 (2 H, m), 3.73 (1 H, dd, J = 11.7, 5.1 Hz), 3.87 (1 H, d, J = 9.8, 7.8 Hz), 3.94 (1 H, dd, J = 7.3, 2.1 Hz), 7.42 (6 H, m), 7.65 (4 H, m); IR (CCl_4) 3503, 1711 cm^{-1}; $[\alpha]_D$ −22.1° (c 0.15, $CHCl_3$); HRMS (CI, M + 1) calcd for $C_{32}H_{48}O_5Si(H)$ 541.3351, found 541.3341.

6(*R*)-[1(*R*)-Methyl-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-4(*R*)-[1-(*R*)-methyl-1-(2,2,5(*S*)-trimethyldioxan-4(*S*)-yl)methyl]-2,2,5(*S*)-trimethyl-1,3-dioxane (3) and 6(*S*)-[1(*R*)-Methyl-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-4(*R*)-[1(*R*)-methyl-1-(2,2,5(*S*)-trimethyldioxan-4(*S*)-yl)methyl]-2,2,5(*S*)-trimethyl-1,3-dioxane (42). Hydroxy ketone **41b** (1.8 mg, 3.3 mmol) was reduced with Dibal as described for lactone **39b**. The ether extracts were worked up and chromatographed (30% ether/hexanes) to give two diols. More polar diol: ^1H NMR (250 MHz, partial) δ 0.73 (3 H, d), 0.76 (3 H, d), 0.97 (3 H, d), 1.01 (3 H, d), 1.07 (9 H, s), 1.37 (3 H, s), 1.47 (3 H, s); IR (CCl_4) 3445 cm^{-1}. Less polar diol: ^1H NMR (250 MHz, partial) δ 0.73 (3 H, d), 0.87 (3 H, d), 0.88 (3 H, d), 1.07 (9 H, s), 1.13 (3 H, d), 1.38 (3 H, s), 1.50 (3 H, s); IR (CCl_4) 3434 cm^{-1}. The more polar diol in 1 mL of 2,2-dimethoxypropane containing 1 mg of *p*-TsOH was stirred for 18 h at 25 °C. The solution was diluted with ether, washed with saturated aqueous $NaHCO_3$, and worked up. Chromatography (5% ether/hexanes) gave *bis*(acetonide) **3** in 42% yield, the ^1H NMR spectrum of which was identical with that of a sample prepared by Kishi:[17b] ^1H NMR (250 MHz) δ 0.71 (3 H, d, J = 6.7 Hz), 0.88 (3 H, d, J = 6.3 Hz), 0.90 (3 H, d, J = 6.6 Hz), 0.94 (3 H, d, J = 6.7 Hz), 1.08 (9 H, s), 1.21 (3 H, s), 1.26 (3 H, s), 1.34 (1 H, m), 1.35 (3 H, s), 1.39 (3 H, s), 1.70 (2 H, m), 2.04 (1 H, m), 3.26 (1 H, dd, J = 9.3, 6.3 Hz), 3.51 (1 H, t, J = 11.2 Hz), 3.70 (4 H, m), 3.86 (1 H, dd, J = 10.4, 1.8 Hz), 7.39 (6 H, m), 7.66 (4 H, m); HRMS (CI, M + 1) calcd for $C_{35}H_{54}O_5Si(H)$ 583.3821, found 583.3787. The less polar diol gave *bis*(acetonide) **42** upon ketalization (46%): ^1H NMR (250

MHz) δ 0.73 (3 H, d, J = 7.7 Hz), 0.78 (3 H, d, J = 6.9 Hz), 0.82 (3 H, d, J = 6.5 Hz), 1.00 (3 H, d, J = 7.2 Hz), 1.06 (9 H, s), 1.32 (3 H, s), 1.36 (3 H, s), 1.37 (3 H, s), 1.42 (3 H, s), 1.45-1.70 (2 H, m), 1.85 (1 H, m), 1.98 (1 H, m), 3.40-3.56 (3 H, m), 3.63-3.75 (2 H, m), 3.80 (1 H, dd, J = 6.3, 2.1 Hz), 3.84 (1 H, dd, J = 8.0, 1.8 Hz), 7.41 (6 H, m), 7.68 (4 H, m); HRMS (CI, M + 1) calcd for $C_{35}H_{54}O_5Si(H)$ 583.3821, found 583.3791.

3(*R*)-[1(*R*)-Methyl-2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4(*S*)-methyl-5(*R*)-[1(*S*)-methyl-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]dihydro-2(3*H*)-furanone (52). Olefinic lactone **24** (74.2 mg, 0.15 mmol) was ozonized, reduced, and silylated by using the procedure for the conversion of **38** to **39b** giving the *bis*(silyl ether) **52** in 89% yield: ^{1}H NMR (250 MHz) δ 0.06 (6 H, s), 0.89 (3 H, d, J = 6.7 Hz), 0.91 (9 H, s), 1.02 (3 H, d, J = 6.7 Hz), 1.08 (9 H, s), 1.27 (3 H, d, J = 6.6 Hz), 1.86 (2 H, m), 2.54 (2 H, m, C_3-H), 3.52 (2 H, m), 3.79 (2 H, m), 4.11 (1 H, dd, J = 10.7, 3.5 Hz, C_5-H), 7.41 (6 H, m), 7.67 (4 H, m); IR (CCl_4) 1781 cm^{-1}; $[\alpha]_D$ -4.2° (*c* 2.2, $CHCl_3$). Anal. ($C_{33}H_{52}O_4Si_2$) C, H.

7-[(*tert*-Butyldimethylsilyl)oxy]-1-[(*tert*-butyldiphenylsilyl)oxy]-5-oxo-2(*S*),4(*R*),6(*S*)-trimethylheptan-3(*S*)-ol (53). Lactone **52** (35 mg, 0.061 mmol) was converted to β-hydroxy ketone **53** in 82% yield by using the procedure described above: ^{1}H NMR (250 MHz) δ 0.02 (3 H, s), 0.03 (3 H, s), 0.86 (9 H, s), 0.93 (3 H, d, J = 6.9 Hz), 1.02 (3 H, d, J = 7.0 Hz), 1.06 (9 H, s), 1.13 (3 H, d, J = 7.1 Hz), 1.77 (1 H, m), 2.78 (1 H, m), 3.06 (1 H, m), 3.39 (1 H, d, J = 2.8 Hz), 3.58 (1 H, dd, J = 9.6, 5.3 Hz), 3.82 (3 H, m), 4.02 (1 H, m), 7.41 (6 H, m), 7.68 (4 H, m); IR (CCl_4) 3528, 1704 cm^{-1}; $[\alpha]_D$ +24.7° (*c* 2.4, $CHCl_3$). Anal. ($C_{32}H_{52}O_4Si_2$) C, H.

7-[(*tert*-Butyldimethylsilyl)oxy]-1-[(*tert*-butyldiphenylsilyl)oxy]-2(*S*),4(*S*),6(*S*)-trimethylheptane-3(*S*),5(*R*)-diol (54a) and 7-[(*tert*-Butyldimethylsilyl)oxy]-1-[(*tert*-butyldiphenylsilyl)oxy]-2(*S*),4(*S*),6(*S*)-trimethylheptane-3(*S*),5(*S*)-diol (55a). Ketone **53** (30.0 mg, 0.054 mmol) was reduced with Dibal as described above. Chromatography (20% ethyl acetate/hexanes) gave the less polar, *anti*-diol **55a** (44%) and the more polar, *syn*-diol **54a** (36%): Diol **55a**: ^{1}H NMR (250 MHz) δ 0.10 (6 H, s), 0.84 (6 H, d, J = 6.8 Hz), 0.91 (9 H, s), 1.07 (9 H, s), 1.07 (3 H, d, J = 6.9 Hz), 1.82 (2 H, m), 2.07 (1 H, m), 3.55 (1 H, m), 3.67-3.82 (4 H, m), 3.97 (1 H, d, J = 9.8 Hz), 4.23 (1 H, s), 4.52 (1 H, d, J = 3.9 Hz), 7.41 (6 H, m), 7.69 (4 H, m); IR (CCl_4) 3458 cm^{-1}; $[\alpha]_D$ +10.9° (*c* 0.5, $CHCl_3$); HRMS (CI, M + 1) calcd for $C_{32}H_{54}O_4Si_2(H)$ 559.3641, found 559.3642. Diol **54a**: ^{1}H NMR (250 MHz) δ 0.05 (3 H, s), 0.06 (3 H, s), 0.69 (3 H, d, J = 6.8 Hz), 0.90 (9 H, s), 0.99 (3 H, d, J = 6.7 Hz), 1.02 (3 H, d, J = 7.5 Hz), 1.07 (9 H, s), 1.84 (2 H, m), 1.93 (1 H, m), 3.56-3.82 (6 H, m), 3.83 (1 H, s), 4.23 (1 H, s), 7.44 (6 H, m), 7.68 (4 H, m); IR (CCl_4) 3479 cm^{-1}; $[\alpha]_D$ +15.8 (*c* 0.3, $CHCl_3$); HRMS (CI, M + 1) calcd for $C_{32}H_{54}O_4Si_2(H)$ 559.3641, found 559.3640.

6(*R*)-[1(*S*)-Methyl-2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4(*R*)-[1-(*S*)-methyl-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-2,2,5(*S*)-trimethyl-1,3-dioxane (54b). Diol **54a** (9.1 mg, 0.01 mmmol) was ketalized as previously described. Chromatography (3% ether/hexanes) gave 7.8 mg (82%) of the acetonide **54b**: ^{1}H NMR (250 MHz) δ 0.06 (6 H, s), 0.87 (3 H, d, J = 6.8 Hz), 0.92 (9 H, s), 0.97 (3 H, d, J = 6.9 Hz), 1.00 (3 H, d, J = 6.6 Hz), 1.06 (9 H, s), 1.37 (6 H, s), 1.60-1.80 (3 H, m), 3.47-3.62 (3 H, m), 3.68 (1 H, dd, J = 10.1, 1.7 Hz), 3.82-3.93 (2 H, m), 7.41 (6 H, m), 7.69 (4 H, m); $[\alpha]_D$ +15.1 (*c* 0.4, $CHCl_3$); HRMS (CI, M + 1) calcd for $C_{35}H_{58}O_4Si_2(H)$ 599.3954, found 599.3917.

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Diastereoselectivity in the Diels-Alder Reactions of Thioaldehydes

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Abstract: The Diels-Alder reaction of thioaldehydes with cyclopentadiene occurs with a preference for the endo isomer. The highest selectivity is observed for thioaldehydes RCHS where R is a bulky alkyl group such as *tert*-butyl or isopropyl. Thioaldehydes having α-alkoxy, acetoxy, or siloxy substituents also react with useful endo selectivity. Secondary orbital overlap is a small factor in these reactions since α-oxo thioaldehydes react with relatively low endo selectivity. Steric effects are primarily responsible for the endo preferences observed. The Diels-Alder reactions of chiral α-oxygen substituted thioaldehydes also occur with useful thioformyl face selectivity. A Cornforth transition state **5** is most likely for the selectivity observed for α-alkoxy or acetoxy thioaldehydes, but the α-hydroxy analogue **23** reacts with the opposite facial preference. The highest face selectivity is obtained with the acetonide of thioglyceraldehyde, generated by photolysis of the phenacyl sulfide **15b**.

We have been interested in synthetic applications of thioaldehyde Diels-Alder additions.[1-5] The high intrinsic reactivity and polarizability of the thioformyl group makes possible the formation of new carbon bonds with excellent control of regiochemistry (eq 1 vs 2, Scheme I).[2] An important additional requirement for exploring synthetic applications of this cycloaddition is to define the stereochemical aspects of the bond-forming step. As in any Diels-Alder process, the reaction may choose between "exo" and "endo" transition states **3** vs **4**, resulting in adducts **1** or **2**, respectively. If the thioaldehyde fragment is chiral, then there is the added feature of diastereomer excess to consider (eq 5 vs 6), and each of the endo or exo pathways may produce two isomeric products. For the endo approach in the cyclopentadiene example as illustrated, a chiral thioaldehyde can react at either thiocarbonyl face (**5** or **6**) to give the product diastereomers **7A** or **7B**. The corresponding exo approach (not shown) can produce **8A,B**. Given the many options for removal or modification of the sulfur substituent, useful methodology for control of remote stereochemistry would result if there is a strong bias for a single combination of the selectivity factors that con-

(1) Vedejs, E.; Eberlein, T. H.; Varie, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 1445.

(2) (a) Vedejs, E.; Eberlein, T. H.; Mazur, D. J.; McClure, C. K.; Perry, D. A.; Ruggeri, R.; Schwartz, E.; Stults, J. S.; Varie, D. L.; Wilde, R. G.; Wittenberger, S. *J. Org. Chem.* **1986**, *51*, 1556. (b) Vedejs, E.; Perry, D. A.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1983**, *105*, 6999.

(3) Vedejs, E.; Perry, D. A. *J. Am. Chem. Soc.* **1983**, *105*, 1683. Vedejs, E.; Perry, D. A.; Wilde, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 2985.

(4) Vedejs, E. *Acc. Chem. Res.* **1984**, *17*, 358. Vedejs, E.; Reid, J. G. *J. Am. Chem. Soc.* **1984**, *106*, 4617.

(5) (a) Vedejs, E.; Eberlein, T. H.; Wilde, R. G. *J. Org. Chem.* **1988**, *53*, 2220. (b) Vedejs, E.; Stults, J. S. *J. Org. Chem.* **1988**, *53*, 2226. (c) Vedejs, E.; Fields, S. *J. Org. Chem.*, in press. (d) Vedejs, E.; Fedde, C. L.; Schwartz, C. E. *J. Org. Chem.* **1987**, *52*, 4269. (e) Vedejs, E.f Wilde, R. G. *J. Org. Chem.* **1986**, *51*, 117. (f) Vedejs, E.; Perry, D. A. *J. Org. Chem.* **1984**, *49*, 573.

0002-7863/88/1510-5452$01.50/0