on silica gel afforded 289 mg (67%) of ether *ent*-**33** upon elution with hexane/60% ether–hexane gradient: IR (film) ν 3080, 3020, 2990, 2940, 2870, 1455, 1370, 1320, 1220, 1100, 1180, 910, 740, 690, 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (d, J = 9.7 Hz, 3 H, CH_3), 1.62 (s, 3 H, vinyl CH_3), 2.79 (m, 1 H), 3.30 (m, 2 H), 3.60 (m, 2 H), 3.94 (m, 1 H), 4.49 (m, 6 H, $PhCH_2O$), 5.30 (d, J = 9.3 Hz, 1 H, vinyl H), 7.31 (m, 15 H, phenyl H); $[\alpha]^{23}_D$ +29.3° (*c* 3.07, $CHCl_3$).[24] Anal. Calcd for $C_{29}H_{34}O_3$: C, 80.89; H, 7.96. Found: C, 80.81; H, 7.90.

(*S*)-3-(Benzyloxy)-2-methyl-1-propanol (36) A. From Olefin Ether 32. Ozone was bubbled through a stirred solution of 0.305 g (0.709 mmol) of (*E*)-alkene **32** in 18 mL of CH_2Cl_2 at −78 °C until a blue color persisted. Nitrogen was then bubbled through until the blue color disappeared and 0.27 mL (3.5 mmol) of methyl sulfide was added dropwise. The mixture was allowed to stir at −78 °C for 15 min and 0.780 mL (0.780 mmol) of 1 M lithium tris[1,1-diethylpropyloxy]aluminum hydride in THF was added dropwise. The solution was stirred for 0.5 h and 1.5 mL of water was added. The mixture was allowed to warm to room temperature and was filtered through Celite–$MgSO_4$. Concentration and chromatography on silica gel (elution with 25% EtOAc–hexanes) afforded 0.064 g (50%) of the alcohol **36** as an oil: IR (film) ν 3400, 2900, 1725, 1450, 1270, 1910, 1060, 1020, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, J = 6.9 Hz, 3 H, $CHCH_3$), 2.08 (m, 1 H, $CHCH_3$), 2.6 (br s, 1 H, OH), 3.3–3.6 (m, 4 H, H1, H3), 4.50 (s, 2 H, $PhCH_2O$), 7.3 (m, 5 H, phenyl H); $[\alpha]^{25}_D$ −10.7° (*c* 2.05, $CHCl_3$).

B. From Olefin Ether *ent*-33. The procedure described above was employed with 214 mg (0.49 mmol) of (*E*)-alkene *ent*-**33**[24] in 20 mL of dry CH_2Cl_2. Flash chromatography on silica gel afforded 57.4 mg (65%) of alcohol **36** upon elution with hexanes/50% ether–hexanes gradient: IR (film) ν 3400, 3090, 3070, 3040, 2970, 2930, 2870, 1495, 1455, 1370, 1220, 1095, 1040, 750, 700 cm^{-1}; ^1H NMR δ 0.87 (d, J = 7.0 Hz, 3 H, $CHCH_3$), 2.06 (m, 1 H, $CHCH_3$), 2.56 (m, 1 H, OH), 3.53 (m, 4 H), 4.51 (s, 2 H, $PhCH_2O$), 7.32 (m, 5 H, phenyl H); $[\alpha]^{24}_D$ −13.2° (*c* 2.27, $CHCl_3$).

(*R*)-3-(Benzyloxy)-2-methyl-1-propanol (37). A. From Olefin Ether 34. This alcohol was prepared from the (*Z*)-alkene **34** as described for the *S* isomer **36**: yield 38%; $[\alpha]^{25}_D$ +10.4° (*c* 1.45, $CHCl_3$) [lit.[8] $[\alpha]_D$ + 17.2° (*c* 3.24, $CHCl_3$)].

B. From Olefin Ether *ent*-32. The ozonolysis procedure employed for alcohol **36** was followed with 107 mg (0.248 mmol) of (*E*)-alkene *ent*-**32**[24] in 20 mL of dry CH_2Cl_2. Flash chromatography on silica gel afforded 31.3 mg (70%) of alcohol **37** upon elution with hexane/60% ether–hexane gradient: IR (film) ν 3400, 3100, 3070, 3040, 2970, 2920, 2870, 1495, 1460, 1375, 1220, 1095, 1040, 750, 700 cm^{-1}; ^1H NMR δ 0.90 (d, J = 7.1 Hz, 3 H, CH_3), 2.07 (m, 1 H), 2.60 (m, 1 H, OH), 3.55 (m, 4 H), 4.51 (s, 2 H, $PhCH_2$), 7.35 (m, 5 H, phenyl H); $[\alpha]^{23}_D$ +13.0° (*c* 1.56, $CHCl_3$) [lit.[8] $[\alpha]_D$ + 17.2° (*c* 3.24, $CHCl_3$)].

(2,*R*,5*S*)-2-[(Benzyloxy)methyl]-5,6-dihydro-3,5-dimethyl-2*H*-pyran (41). To a solution of 0.200 g (0.80 mmol) of diol **40** in 1.5 mL of dry CH_2Cl_2 at room temperature were added 0.167 g (0.88 mmol) of *p*-TsCl and 0.557 mL (4.0 mmol) of triethylamine. The mixture was allowed to stir for 1 week, 2 mL of water was added, and the layers were separated. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel. Elution with 1:1 ether–hexane afforded 0.125 g (62%) of pyran **41**: ^1H NMR δ 0.86 (d, J = 7.1 Hz, 3 H, $CHCH_3$), 1.58 (s, 3 H, vinyl CH_3), 2.41 (br s, 1 H, $CHCH_3$), 3.12 (B of ABX, J_{AB} = 10.8 Hz, J_{BX} = 9.1 Hz, 1 H, $ROCH_2$), 3.53 (A of ABX, J_{AB} = 10.5 Hz, J_{AX} = 6.0 Hz, 1 H, $ROCH_2$), 3.63 (B of ABX, J_{AB} = 10.5 Hz, J_{BX} = 2.8 Hz, 1 H, $ROCH_2$), 3.96 (A of ABX, J_{AB} = 10.8 Hz, J_{AX} = 4.4 Hz, 1 H, $ROCH_2$), 4.11 (br s, 1 H, ROCH), 4.59 (AB, J_{AB} = 12.3 Hz, $\Delta\nu$ = 10.9 Hz, 2 H, $PhCH_2O$), 5.45 (br s, 1 H, vinyl H), 7.33 (m, 5 H, phenyl H). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.34; H, 8.71.

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Supplementary Material Available: Experimental details for compounds **2–9**, **22–26**, **28**, **30–35**, **37**, **7TBS**, and **9TBS** (16 pages). Ordering information is given on any current masthead page.

Total Synthesis of Pseudomonic Acid C

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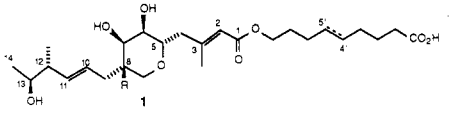
Two approaches to the synthesis of aldehyde **28**, a key intermediate in the total synthesis of pseudomonic acid C, were developed. One asymmetric route from the chiral hydroxy ester **11** proceeded in 13 steps via the hydroxy lactone **17**. A shorter approach involved the Lewis acid catalyzed cycloaddition of formaldehyde to the chiral diene **23a** to give **22a**, which was separated from its diastereomer and then converted into **28** in seven steps. The introduction of the C-8 side chain was initially accomplished by Julia coupling of **28** with the sulfone anion derived from **40** to give the olefin **34**. The stereoselective preparation of **34** was also carried out, via the ester **46a**, by a novel ester enolate Claisen rearrangement of the silyl-protected glycolate ester **44**. A third approach directed toward the synthesis of the side chain entailed controlling the C-10 stereochemistry of the benzyl-protected glycolate ester **48** by reduction of a precursor propargyl ketone **27** with Alpine borane. Ester enolate Claisen rearrangement then gave the ester **46b** with excellent stereocontrol.

The pseudomonic acids are structurally novel C-glycopyranoside antibacterials that have been isolated over the last 15 years.[1] The major constituent of the fermentation broth of *Pseudomonas fluorescens* is the epoxy triol pseudomonic acid A (mupirocin; **1a**), while the simplest member, pseudomonic acid C (**1c**), makes up only 2% of the culture medium. Although they are active mainly against Gram-positive bacteria,[2] the pseudomonic acids have generated a great deal of interest due to their ability



1

Pseudomonic Acid A : R=H; C10,11 epoxide
B : R=OH; C10,11 epoxide
C : R=H
D : R=H; C4',5' olefin

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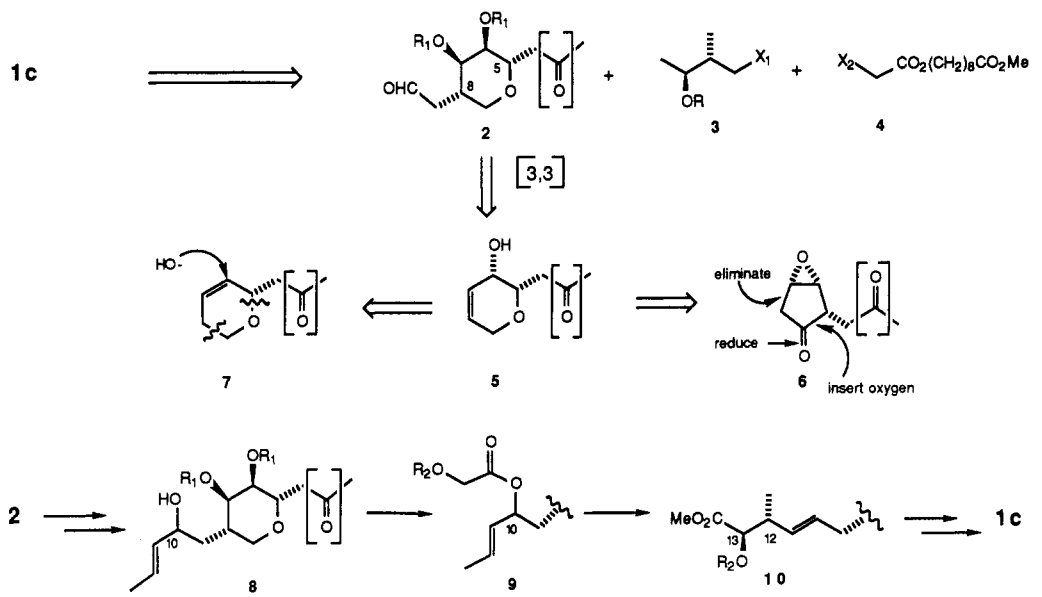
0022-3263/88/1953-4282$01.50/0

Scheme I



to function as competitive inhibitors, with respect to isoleucine, of bacterial isoleucyl t-RNA synthetase and therefore protein synthesis.[3] In addition, they have shown good activity against a variety of persistent skin pathogens such as *Staphylococcus aureus*.[4]

The synthetic community has also shown great interest in these stereochemically challenging molecules.[5] In most approaches to **1c**, a keto aldehyde related to **2** (Scheme I) is converted into the natural product by Wittig or Julia condensation of the methyl ketone with **4** (X_2 = PPh_3 or SO_2Ar) and coupling of the aldehyde group with the optically active fragment **3**. However, an alternative route for the introduction of the C-12 and C-13 stereochemistry could be based on the transfer of the chirality of **2** to these new stereocenters in a multistep process. Stereoselective addition of a vinyl nucleophile to **2** would give **8**, which could then be converted into **10** by Ireland ester enolate Claisen rearrangement of a suitable allylic glycolate ester **9**.[6]

Claisen rearrangement of an allylic alcohol[5f] such as **5** would introduce the C-8 side chain of **2** with the correct configuration and, in addition, produce an olefin that could be cis hydroxylated to give the proper C-6,7 stereochemistry. We then envisioned two possible routes to **5**. The first, from epoxy ketone **6**, required regiospecific insertion of the pyran oxygen, β-elimination of the epoxide, and finally, reductive removal of the carbonyl group. The intermediate **6** could be prepared by alkylation and asymmetric hydroboration of cyclopentadiene, analogous to a route used previously for the synthesis of daunosamine.[7] Alternatively, hydroxylation at the indicated position of **7** and olefin rearrangement would also produce **5**. Dihydropyran **7** could be prepared by the cycloaddition of formaldehyde with a functionalized diene.[8]

Results and Discussion

Synthesis of Tetrahydropyran Aldehyde 28. We began our first approach to **5** with optically active hydroxy ester **11** (Scheme II), prepared by the method of Partridge et al.[9] by alkylation of cyclopentadiene with methyl bromoacetate and subsequent asymmetric hydroboration (>95% ee). Mesylation followed by ester hydrolysis gave the crystalline lactone **12** in 80% yield. Addition of 1 equiv of methyllithium (THF, −78 °C, 80%) proceeded uneventfully, but the resulting hemiketal could not be selectively protected, either as its keto ether or hydroxy ketal, without significant decomposition. Elaboration to the C-5 methyl ketone side chain was postponed to a later time and the lactone was reduced to the diol instead. Selective protection of the primary alcohol as its *tert*-butyldiphenylsilyl ether[10] followed by hydroxyl-directed epoxidation[11] and oxidation[12] of the secondary alcohol gave the

(1) (a) Pseudomonic acid A: Banks, G. T.; Barrow, K.; Chain, E. B.; Fuller, A. T.; Mellows, G.; Woolford, M. *Nature (London)* **1971**, *234*, 416. (b) Pseudomonic acid B: Chain, E. B.; Mellow, G. *J. Chem. Soc., Chem. Commun.* **1977**, 318. (c) Pseudomonic acid C: Clayton, J. P.; O'Hanlon, P. J.; Rogers, N. H. *Tetrahedron Lett.* **1980**, *21*, 881. (d) Pseudomonic acid D: O'Hanlon, P. J.; Rogers, N. H.; Tyler, J. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2655.

(2) (a) White, A. R.; Masters, P. J.; Sutherland, R. *Proc. Int. Congr. Chemother., 13th* **1983**, *3*, 4.6/7-24. (b) Tasker, T. C. G.; Boon, R. J.; Masters, P. J.; King, J. D. *Ibid.* **1983**, *3*, 4.6/7-25.

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(5) (a) Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *J. Am. Chem. Soc.* **1980**, *102*, 6577. (b) Schonenberger, B.; Summermatter, W.; Ganter, C. *Helv. Chim. Acta* **1982**, *65*, 2333. (c) Snider, B. B.; Phillips, G. B.; Cordova, R. J. *J. Org. Chem.* **1983**, *48*, 3003. (d) Beau, J.-M.; Aburaki, S.; Pougny, J.-R.; Sinay, P. J. *J. Am. Chem. Soc.* **1983**, *105*, 621. (e) Fleet, G. W. J.; Shing, T. K. M. *Tetrahedron Lett.* **1983**, *24*, 3657. (f) Fleet, G. W. J.; Gough, M. J.; Shing, T. K. M. *Ibid.* **1983**, *24*, 3661. (g) Kozikowski, A. P.; Sorgi, K. L. *Ibid.* **1984**, *25*, 2085. (h) Jackson, R. F. W.; Raphael, R. A.; Stibbard, J. H. A.; Tidbury, R. C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2159. (i) Curran, D. P.; Suh, Y.-G. *Tetrahedron Lett.* **1984**, *25*, 4179. (j) Keck, G. E.; Kachensky, D. F.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 4317. (k) Kuroda, C.; Theramongkol, P.; Engebrecht, J. R.; White, J. D. *Ibid.* **1986**, *51*, 956. (l) Bates, H. A.; Farina, J.; Tong, M. J. *Ibid.* **1986**, *51*, 2637. (m) Williams, D. R.; Moore, J. L.; Yamada, M. *Ibid.* **1986**, *51*, 3916. (n) For a preliminary report of the work from this laboratory, see: Barrish, J. C.; Lee, H. L.; Baggiolini, E. G.; Uskoković, M. R. *J. Org. Chem.* **1987**, *52*, 1372.

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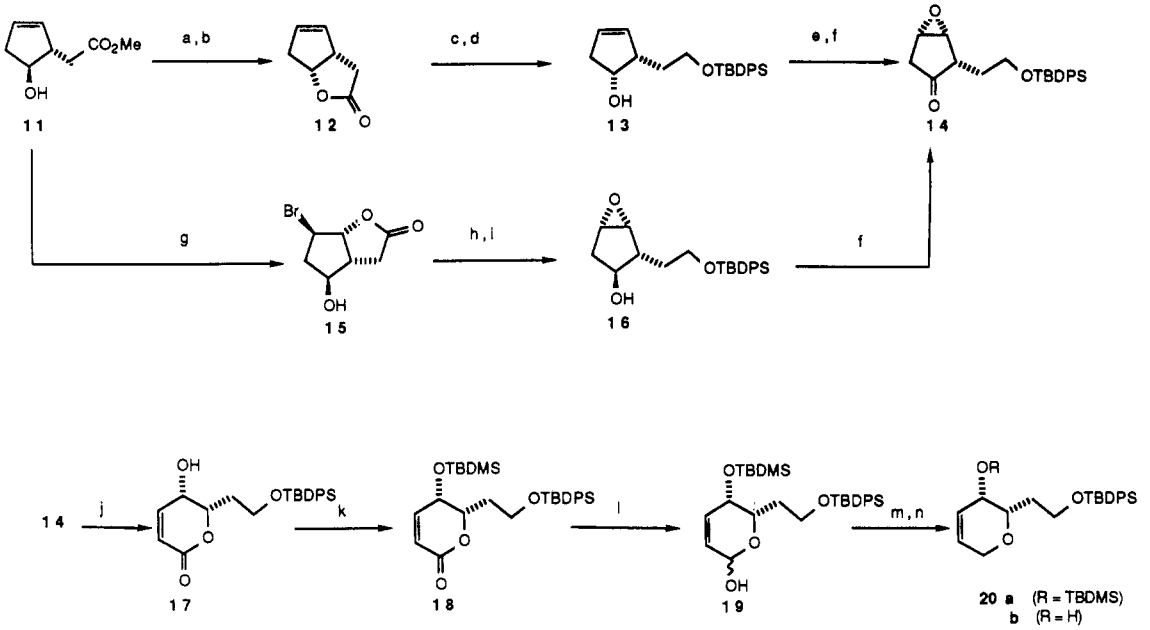
(8) Danishefsky, S.; Webb, R. R. *J. Org. Chem.* **1984**, *49*, 1955.

(9) (a) Partridge, J. J.; Chada, N. K.; Uskoković, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 7171. (b) Partridge, J. J.; Chada, N. K.; Uskoković, M. R. *Org. Synth.* **1984**, *63*, 44.

(10) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.

(11) (a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136. (b) Stork, G.; Patterson, I.; Lee, F. K. C. *Ibid.* **1982**, *104*, 4686.

Scheme II[a]

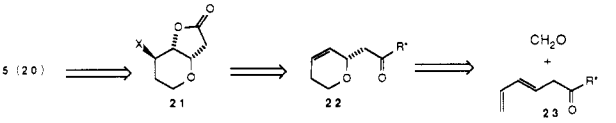


[a] (a) MsCl, pyridine; (b) NaOH, H_2O, THF (80% from 11); (c) $LiAlH_4$; (d) *t*-$BuPh_2SiCl$, pyridine (93% from 12); (e) *t*-BuOOH, $VO(acac)_2$; (f) PCC, NaOAc (92% from 13); (g) NaOH, H_2O; NBS, THF (73%); (h) $LiBH_4$, THF; 15% NaOH; (i) *t*-$BuPh_2SiCl$, pyridine (81% from 15); (j) (1) *m*-CPBA, CH_2Cl_2; (2) Et_3N (74%); (k) *t*-$BuMe_2SiOTf$ (83%); (l) Dibal-H (94%); (m) Et_3SiH, BF_3; (n) aqueous HOAc (44% from 19).

desired epoxy ketone **14**. A shorter route to **14** from **11** was also developed in which the ester group was first hydrolyzed with base and the resulting carboxylate salt then treated with *N*-bromosuccinimide to give the crystalline bromo lactone **15**. Reduction with lithium borohydride followed by quenching with aqueous base gave, after internal displacement of the bromide, the epoxy diol, which was protected and oxidized as before.

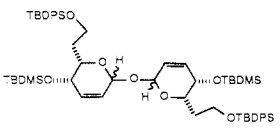
Epoxy ketone **14** was unstable toward β-elimination and was submitted immediately to Baeyer–Villiger oxidation. This reaction required more strenuous conditions than anticipated (refluxing methylene chloride, 1 day), but after treatment of the intermediate epoxy lactone with base, a 74% yield of the crystalline hydroxy lactone **17** was produced. Reduction of **17** with diisobutylaluminum hydride gave the rearranged and more stable five-membered ring hemiacetal as well as decomposition products. However, it was found that protection first as the *tert*-butyldimethylsilyl ether[13] followed by reduction with Dibal-H gave hemiacetal **19**. Further reduction according to the procedure of Kraus[14] with triethylsilane/boron trifluoride etherate gave **20a** as well as a dimeric product formed by attack of **19** on the intermediate oxonium ion (10–20%).[15] While **20a** could be purified by tedious chromatography, separation was usually postponed until after selective removal of the *tert*-butyldimethylsilyl ether[16] to give **20b** (44% overall from **19**).

An alternative approach to the synthesis of **20b**, which eliminates some of the problems associated with the above route, involves cycloaddition of formaldehyde onto a functionalized, chiral diene such as **23**. This strategy would provide the basic dihydropyran nucleus (**22**) and allow for the introduction of the hydroxyl group and the olefin of **20** via halo lactone **21**. Snider had shown in an analogous



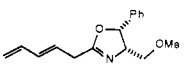
example[5c] that cycloaddition to generate a dihydropyran related to **22** occurred with very little asymmetric induction. We have attempted the cycloaddition of **23** and formaldehyde with the standard battery of chiral auxiliaries[17] and Lewis acids, as well as chiral Lewis acids[18] but, not unexpectedly, found only low levels of asymmetric induction. However, when R* = (*R*)-α-methylbenzylamine, the required *R* cycloadduct **22a** (45%) is easily separated from its *S* diastereomer **22b** (43%) by silica gel chromatography. Idolactonization of this olefinic secondary amide (I_2, aqueous THF; 72%) gave **24** without formation of the corresponding lactam. The iodide was eliminated by treatment with base (DBU, THF; 82%) to give the olefinic lactone **25** (also prepared in racemic form by Raphael[5h]), which in turn gave poor yields of the hemiketal on addition

(12) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(13) Corey, E. J.; Cho, H.; Rucker, C. Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.
(14) Kraus, G. A.; Frazier, K. A.; Roth, B. D.; Taschner, M. J.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 2417.
(15) ^1H NMR (200 MHz) 0.01 (s, 3 H), 0.03 (s, 3 H), 0.86 (s, 9 H), 1.05 (s, 9 H) 3.67 (m, 1 H), 4.21 (m, 1 H), 5.41 (br s, 1 H), 5.75 (dd, *J* = 3, 10 Hz, 1 H), 5.96 (m, 1 H).



(16) Nicolaou, K. C.; Magolda, *J. Org. Chem.* **1981**, *46*, 1506.

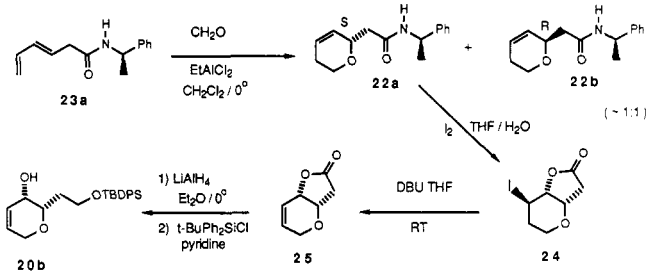
(17) The chiral auxiliaries used included (−)-8-phenylmenthol, (−)-*trans*-2-phenylcyclohexanol, and (−)-borneol. The oxazoline i



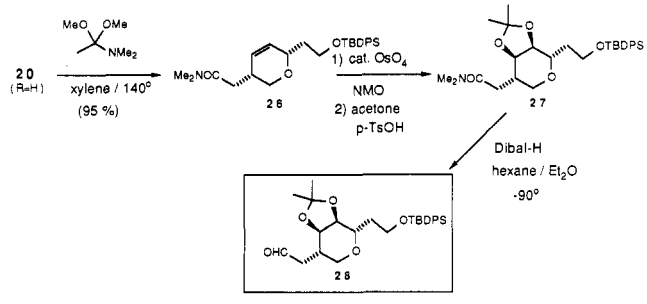
was also prepared and again gave a 1:1 diastereomeric mixture on reaction with formaldehyde. Lewis acids used included Me_2AlCl, Et_2AlCl, $EtAlCl_2$, $ZnCl_2$ (no reaction), $TiCl_4$, $Eu(hfbc)_3$ (no reaction), and (R-binaphth)-AlR.[18c]

(18) (a) Bednarski, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 3451. (b) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 6968. (c) See for example: Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310.

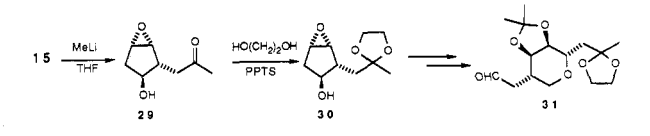
of 1 equiv of methyllithium. However, reduction ($LiAlH_4$) and monoprotection (t-$BuPh_2SiCl$) of **25** gave **20b**, identical with material made by the asymmetric route described above. While only one diastereomer could be used, the excellent yield of **22a** and its epimer, combined with the short sequence to **20b**, and the fact that no reduction adjacent to the pyran oxygen (vide supra) was required, made this approach very attractive.



Claisen rearrangement of the N,O ketal derived from **20b**[19] cleanly provided the amide **26** in excellent yield. This protocol was far superior to Claisen rearrangement of the vinyl ether to give the aldehyde directly, as well as the ester enolate or ortho ester Claisen variants. Oxidation with osmium tetraoxide[20] gave a crystalline diol, which was protected as its acetonide to give **27**. All four of the stereocenters around the tetrahydropyran ring were now in place, the C-6, -7, and -8 centers being introduced with complete stereocontrol. Finally, reduction of the dimethylamide with diisobutylaluminum hydride gave the critical aldehyde intermediate **28**.[21]



Recently, significant progress has been made in solving the problem of the preparation of a C-5 protected ketone side chain for **6**. Addition of 2 equiv of methyllithium to the bromo lactone **15** gave directly, upon warming from −78 °C to room temperature, the epoxy ketone **29** via internal displacement of the bromide. Ketalization of **29** gave **30**, which could be converted to **31** by using an analogous sequence to that from **16**.



Approaches to the C-8 Side Chain. With aldehyde **28** in hand, we next turned to methods for the convergent synthesis of the C-8 side chain. Attempts to couple **28** with the requisite phosphorane or phosphine oxide anion under a variety of conditions gave very low yields (<5%) of the desired olefin product, probably due to enolization adjacent to the aldehyde resulting in decomposition and/or recovery of starting material. Keck[5j] reported that the Julia coupling procedure using a sulfone anion derived from the tetrahydropyran aldehyde gave improved yields of the C-10,11 olefin. In our case, deprotonation of sulfone **32**, prepared in three steps from **28** (Scheme III), followed by addition of aldehyde **38** (prepared as shown from ester **36**[22,5j]) and trapping with methanesulfonyl chloride, gave **33** ($R_1 = SO_2Me$) as a mixture of diastereomers. Elimination using sodium amalgam gave **34** as a 2:1 mixture of E and Z isomers in 39% overall yield. The modification described recently by Williams,[5m] which entails trapping instead as the xanthate **33** (R_1 = C(S)SMe) followed by a free radical elimination, gave a 4:1 E:Z mixture in 46% overall yield. Williams has also shown that the aldehyde and sulfone partners can be reversed. Indeed, when aldehyde **28** was added to the sulfone anion derived from **40**, the initially formed hydroxy sulfone was trapped as the xanthate **35**. Elimination with tributyltin hydride gave a markedly improved 67% yield of **34** as a 6:1 E:Z mixture of isomers, which were separated by preparative HPLC. This approach is also applicable to the synthesis of a number of side-chain analogues.

The alternative approach to **34**, in which the primary focus was the "communication" of the stereochemical information[23] in **28** to the C-12 and C-13 centers, required, as the key step, the addition of a vinyl anion to **28** (Scheme IV). While not initially concerned with which isomer predominated, we did immediately realize that without an asymmetric center adjacent to the aldehyde, we would need to employ the chiral framework of **28** to induce the asymmetry at C-10. Chelation of the aldehyde carbonyl to either the pyran or the C-7 ether oxygen would reduce the inherent rotational flexibility of the acetaldehyde fragment, thereby making one face of the carbonyl group more accessible to attack by a nucleophile. In addition, Reetz has previously shown[24] that stereoselective addition to seven-membered ring chelates is possible.

Experimentally, we found that the addition of vinyl anions (M = Li, Mg, Cu) to **28** in the presence of chelating metals (Ti, Mg, Zn) uniformly gave poor stereoselectivity (<60:40). The one notable exception was when a vinyl Grignard was added to a mixture of the aldehyde and zinc bromide in THF. In the best case (R = H), a 79:21 ratio[25] of **41a**:**41b** was produced in 75% yield (85% based on recovered **28**). The isomers could be separated by HPLC and the stereochemical assignments made by comparison to material prepared from the corresponding propargyl ketones by asymmetric reduction with Alpine borane (vide infra). The major isomer presumably is derived from attack on the complex **42** involving the pyran oxygen and an axial acetaldehyde group (the perspective of the Newmann projection shown is from underneath the pyran ring of **28**). The minor diastereomer is derived from attack on the complex **43** involving the acetonide oxygen and an equatorial acetaldehyde group.[26] In the desired case (R

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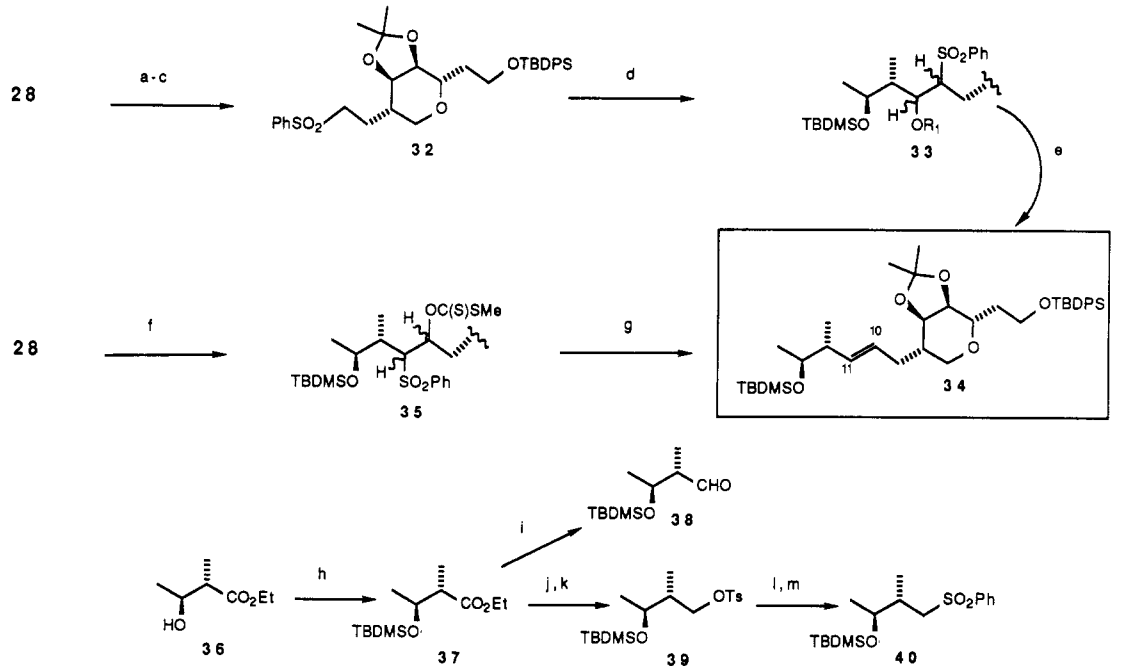
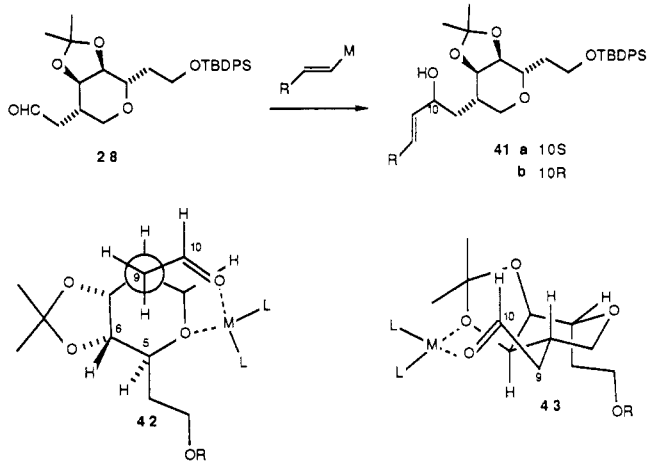
(21) Zakharkin, L. I.; Khorlina, I. M. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1959**, 2046.
(22) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825, 2829.
(23) Danishefsky, S.; Barbachyn, M. *J. Am. Chem. Soc.* **1985**, *107*, 7761.
(24) Reetz, M. T.; Kesseler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 989.
(25) Ratios were determined by HPLC and ^{13}C NMR analysis.
(26) Calculations performed on conformations **42** and **43** (without the complexed metal) using an appropriately parameterized Allinger MM2 program available at Roche show that **42** is more stable than **43** by ≥1.25 kcal. The effect of the metal and its attached ligands on the stability and reactivity of **42** and **43** is of course unknown. Rotation about the C-9,10 bond of **42** to expose the other aldehyde face (to produce the C-10 R alcohol) is prevented by steric interaction involving the aldehyde hydrogen and the C-6 hydrogen. The same rotation in **43**, to give the C-10 S alcohol, is possible and may account for some of this product.

Scheme III[a]



[a] (a) $LiAlH_4$ (95%); (b) CBr_4, Ph_3P (63%); (c) $PhSO_2Na$, HMPA (63%); (d) *n*-BuLi; **38**; (e) (1) MsCl; (2) Na(Hg) (39%); or (1) CS_2; MeI; (2) *n*-Bu_3SnH (46%); (f) **40**, LDA; CS_2; MeI; (g) *n*-Bu_3SnH, PhMe (67% from **28**); (h) *t*-$BuMe_2SiCl$ (86%); (i) Dibal-H (1 equiv); (j) Dibal-H (xs) (84%); (k) TsCl, pyridine (97%); (l) NaI, 2-butanone (90%); (m) $PhSO_2Na$, HMPA (81%).

Scheme IV



= Me) using propenylmagnesium bromide, we were disappointed to find a slightly lower selectivity (77:23 **41a**:**41b**) and yield (52%; 68% based on recovered **28**) and a more difficult HPLC separation which required multiple runs with reactions above a 100-mg scale. Stereochemical assignments were made as described above as well as by the eventual conversion to the natural product.

Direct application of the ester enolate Claisen rearrangement to the glycolate ester of **41a**, to give the C-12(*R*),13(*R*) anti unsaturated ester **46** (Scheme V), was prevented by the fact that deprotonation of such esters occurs by a chelation-controlled mechanism.[6] This gives predominantly the *E*[27] lithium enolate which, after trapping as the ketene silyl acetal and rearrangement, would result in the C-12(*R*),13(*S*) syn diastereomer epimeric to **46**. Changing the starting olefin geometry to *Z* would obviously give the incorrect (12*S*,13*S*) anti diastereomer. Two solutions to this problem were apparent. Inversion at C-10 to the *R* configuration, in combination with the *Z* olefin, would give **46** after the chelation-controlled rearrangement (vide infra). Another possibility, however, would be to develop conditions in which the *Z* lithium enolate, i.e. **45**, predominates. Trapping and rearrangement as usual would also then give **46**. Numerous workers have shown that Lewis acid complexation of the ether oxygen of a *tert*-butyldimethylsilyl ether is prevented or inhibited by both the steric bulk of the protecting group[28] and by the overlap of the oxygen lone pairs with a vacant orbital on silicon.[29] Indeed, we found, after work on an appropriate model system,[30] that when ester **44** (R_1 = TBDMS)[31] was added to a mixture of lithium diisopropylamide and trimethylsilyl chloride[33,34] in THF at −78 °C the resulting silyl ketene acetal gave, upon warming to room temperature,

(27) See enolate **49**, Scheme VI.

(28) (a) Frye, S. V.; Eliel, E. L. *Tetrahedron Lett.* **1986**, *27*, 3223. (b) Reetz, M. T.; Hullmann, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1600.

(29) (a) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265. (b) Keck, G. E.; Abbott, D. E. *Ibid.* **1984**, *25*, 1883. (c) Kahn, S. D.; Keck, G. E.; Hehre, W. J. *Ibid.* **1987**, *28*, 279. (d) Keck, G. E.; Castellino, S. *Ibid.* **1987**, *28*, 281.

(30) In work performed on the glycolate esters of *trans*-crotyl alcohol, we found that bulkier silyl ether protecting groups (e.g. triisopropylsilyl and *tert*-butyldiphenylsilyl) gave improved anti-syn selectivities (6:1) while a bulky alkyl protecting group (e.g. *tert*-butyl) still gave more of the syn diastereomer (3:1).

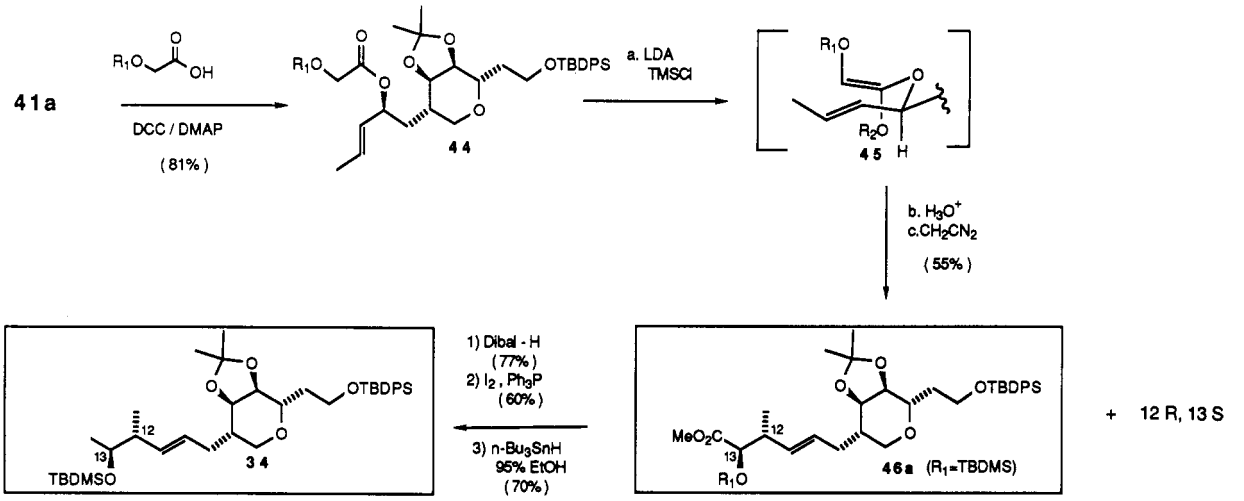
(31) Prepared in either of two ways from glycolic acid ((1) formation of the benzyl ester, (2) silylation, (3) debenzylation with H_2; see the Experimental Section; or (1) disilylation, (2) monodesilylation with K_2CO_3/MeOH).

(32) (a) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1979**, 4475. (b) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 552.

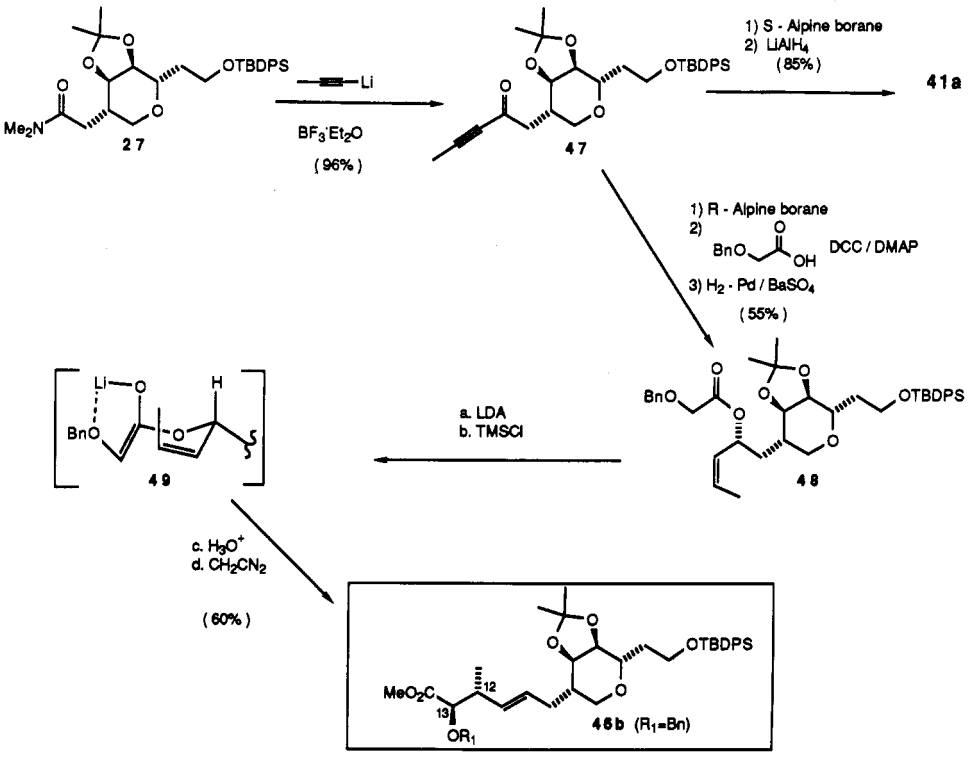
(33) (a) Ireland, R. E.; Mueller, R. H.; Williard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

(34) (a) Deprotonation conditions in which the Me_3SiCl was added after the base gave greatly reduced selectivity, indicating that some equilibration to the chelated enolate may be occuring. While Kallmerten has shown[6d] that, in the case of alkyl protected glycolate esters, equilibration is unlikely and the selectivity is derived from a chelation-directed deprotonation in a kinetic fashion, the inhibition of chelation with the silyl ethers and the probable slower deprotonation may allow for equilibration. We thank Professor Kallmerten (Syracuse University) for helpful discussions and for supplying data needed for the model studies.

Scheme V



Scheme VI



hydrolysis, and esterification, a 55% yield of **46a** combined with its C-13(*S*) diastereomer in a 4:1 ratio.[25] In addition, the starting ester **44** (R_1 = TBDMS) and C-trimethylsilylated **44** (formed by trapping of the enolate with TMSCl at carbon) were also recovered (27% combined). The latter two compounds were conveniently recycled by treatment of the reaction mixture with potassium carbonate in MeOH before chromatography to recover **41a** (R = Me). The diagnostic downfield chemical shift for the C-13 hydrogen[6d] of **46a** (δ 4.07) vs the syn diastereomer (δ 4.00) as well as the C-12 methyl group in the ^{13}C NMR (**46a**, δ 17.20; 12*R*,13*S*, δ 15.42) helped to prove the stereochemistry of the diastereomers. Sterically demanding dialkylamide bases such as lithium tetramethylpiperidide and lithium *tert*-octyl-*tert*-butylamide[35] gave slightly improved selectivities (6:1 and 7:1, respectively), but the conversion to product was much lower (<30%). However, even on a small scale (≤100 mg), separation of the two diastereomers required multiple HPLC runs.

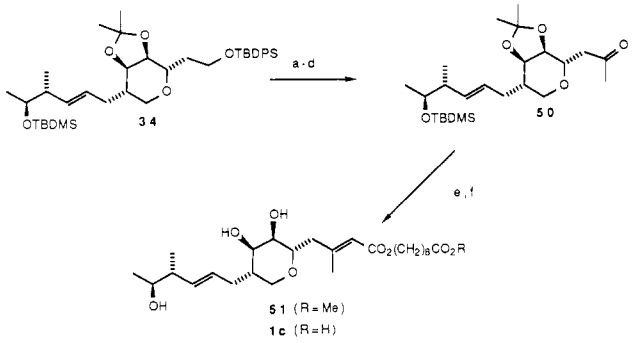
Reduction of the carboxymethoxy group of **46a** to the C-14 methyl group of **34** was carried out in three steps via the primary alcohol and iodide followed by radical reduction.[36] Reduction of the corresponding tosylate instead was accompanied by desilylation as well as decomposition. The olefin **34** prepared in this way was identical with the material prepared from the Julia coupling procedure described above.

The modest selectivities for both the Grignard addition to **28** and the Claisen rearrangement of **44** made a third approach to the C-8 side chain necessary. Asymmetric reduction of a C-10 carbonyl group using a chiral reducing agent (Scheme VI) would selectively introduce the C-10 hydroxyl stereochemistry. If the C-10 *R* diastereomer was

(35) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 491.

(36) Wuts, P. G. M.; D'Costa, R.; Butler, W. *J. Org. Chem.* **1984**, *49*, 2582.

Scheme VII[a]



[a] (a) *n*-Bu_4NF, THF (70%); (b) PCC, NaOAc (97%); (c) MeLi, THF (71%); (d) PCC, NaOAc (95%); (e) NaH, $(MeO)_2P(O)CH_2CO_2(CH_2)_8CO_2Me$, THF (88%); aqueous HOAc (80%); (f) KOH, $NaHCO_3$, THF, EtOH (77%).

prepared stereospecifically, application of the chelation-controlled glycolate ester enolate Claisen rearrangement would give **46** exclusively. An obvious C-10 carbonyl precursor was the propargyl ketone **47** (prepared by the addition of propynyllithium to the amide **27**[37]) since asymmetric reduction of this system is known to proceed with high selectivity and, in addition, the triple bond could be easily reduced to the *Z* olefin. Reduction of **47** with (*R*)-Alpine borane[38] (99%) ee; THF, 25 °C; 88%) gave the *R* propargyl alcohol (>20:1), which was esterified with the benzyl ether of glycolic acid[39] and then hydrogenated to give **48**. It was interesting to note that reduction of **47** with (*S*)-Alpine borane (92% optical purity; THF, 25 °C) gave, after reduction of the triple bond ($LiAlH_4$), **41a** (R = Me) (85%) in a 96(*S*):4(*R*) ratio. The chirality of **47** has no effect on the C-10 hydroxyl selectivity, which is completely determined by the asymmetric reagent. Deprotonation of **48** with lithium diisopropylamide (THF, −78 °C) gave, after trapping with trimethylsilyl chloride, hydrolysis, and esterification, **46b** (>20:1)[25] in 60% yield (along with 24% of the C-silylated **48**) via the chelated enolate **49**. While ester **46b** has not been carried further to **1c**, this route, of the three that have been described here, is conceivably the most stereochemically efficient one to the C-8 side chain of the pseudomonic acids. It has been used, with some modifications, for the synthesis of side-chain analogues.

Pseudomonic Acid C. The completion of the synthesis from **34** was straightforward (Scheme VII). Selective removal of the more accessible primary *tert*-butyldiphenylsilyl group was accomplished with 1.5 equiv of tetrabutylammonium fluoride. Oxidation of the primary alcohol gave an unstable aldehyde, which was immediately added to an excess of methyllithium. The resulting 1:1 mixture of diastereomeric secondary alcohols were, without separation, oxidized to the methyl ketone **50** (46% overall yield from **34**). The remainder of the C-5 side chain was attached by Horner–Emmons condensation to give, as expected, a 4:1 *E*:*Z* mixture[5j,24] of trisubstituted unsaturated esters, which were separated by HPLC. The protecting groups of the major isomer were removed in one step to give methyl pseudomonate C (**51**), the ^1H NMR, ^{13}C NMR, IR, and mass spectrum of which were identical with those reported.[1c] Selective hydrolysis of the methyl ester was first attempted with bakers' yeast at pH 7,[42] but yields of isolated **1c** ranged from 15 to 25%. Eventually saponification conditions were found (aqueous KOH, $NaHCO_3$)[5a] that consistently gave a 75% yield of the natural product, exhibiting the expected biological profile.

In conclusion, we have prepared the critical intermediate **28** required for the synthesis of the pseudomonic acids by two distinct routes from simple starting materials. In addition, a new approach for the introduction of the side-chain stereochemistry was developed by using the chirality of the central pyran fragment. While the silyl-based glycolate ester enolate Claisen rearrangement proceeded with only moderate levels of stereoselectivity, one can imagine applications of this enolate methodology to aldol, Michael, and alkylation reactions. In addition, extension of Bartlett's lactate enolate Claisen rearrangement[34b] to more complex systems has been accomplished and will be the subject of a future report.

Experimental Section

^1H nuclear magnetic resonance spectra were recorded at 100, 200, or 400 MHz in $CDCl_3$ unless otherwise indicated. ^{13}C NMR spectra were recorded at 50 MHz. Chemical shifts (δ) are reported downfiled from Me_4Si (δ 0.00). Optical rotations were determined on a Perkin-Elmer 241 polarimeter at the sodium D line. Melting points were determined on a Reichert hot stage apparatus and are uncorrected.

Purifications by flash chromatography[40] used Merck silica gel 60 (0.040–0.063 mm). Preparative HPLC was done on a Waters Prep LC 500. Thin-layer chromatography was performed on Merck 60 F-254 silica gel plates (visualization was accomplished by UV illumination and staining with a solution of 7% phosphomolibdic acid/ethanol followed by heating). Methylene chloride, dimethylformamide, hexamethylphosphoric triamide, pyridine, triethylamine, dimethyl sulfoxide, and toluene were all distilled from calcium hydride and stored over 4-Å molecular sieves. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Anhydrous ether was purchased from Fisher chemicals and used as is.

(1*S*,2*R*)-2-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-3-cyclopenten-1-ol (13). To a suspension of 11.57 g (306.71 mmol) of lithium aluminum hydride in 750 mL of anhydrous ether at 0 °C under argon was slowly added 19.0 g (152.20 mmol) of lactone **12** in 450 mL of anhydrous ether over a 1-h period. After 15 min at 0 °C the reaction was carefully quenched by adding 11.6 mL of H_2O followed by 11.6 mL of 15% NaOH and 34.8 mL of H_2O. After 1 h the resulting Al salts were filtered and washed with ethyl acetate. Evaporation gave 19.5 g of crude diol wich was dissolved in 65 mL of dry pyridine and cooled to 0 °C. A 43.8-mL (44.9 g, 163.5 mmol) portion of *tert*-butylchlorodiphenylsilane was added over 15 min and the resulting slurry stirred for 1 h at 0 °C and 1 h at room temperature. The mixture was diluted with 1 L of ether and washed with 4 × 400 mL of 1 N HCl and 200 mL of brine, and the ether layer was dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by medium-pressure chromatography with ethyl ether–petroleum ether (1:4) to give 52.14 g (93%) of **13** as a colorless oil: $[\alpha]^{25}_D$ +30.86° (*c* 0.4957, EtOH); ^1H NMR (200 MHz) δ 1.08 (s, 9 H), 3.27 (d, J = 4 Hz, 1 H, OH), 3.70 (m, 1 H), 3.80 (m, 1 H), 4.56 (m, 1 H), 5.53 (m, 1 H), 5.76 (m, 1 H); IR ($CHCl_3$) 3440, 822, 753 cm^{-1}; mass spectrum, *m/e* (relative intensity) 309 (4), 291 (3), 199 (70), 181 (7), 93 (100). Anal. Calcd for $C_{23}H_{30}O_2Si$: C, 75.36; H, 8.25. Found: C, 75.34; H, 8.42.

[1*S*-(1α,2β,5α)]-2-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-6-oxabicyclo[3.1.0]hexan-3-one (14). To a mixture of 52.14 g (142.33 mmol) of **13** and 753 mg (2.84 mmol) of vanadyl acetylacetonate in 160 mL of anhydrous methylene chloride at 0 °C was added dropwise, over a 30-min period, 61 mL of 4.65 M *tert*-butyl hydroperoxide in toluene (284.46 mmol). The reaction was stored at 0–5 °C overnight and then quenched by the addition of 50 mL of 10% $NaHSO_3$. After diluting with 1 L of

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(39) Manhas, M. S.; Amin, S. G.; Chawla, H. P. S.; Bose, A. K. *J. Heterocycl. Chem.* **1978**, *15*, 601.
(40) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(41) Martin, S. F.; Tu, C.; Chou, T. *J. Am. Chem. Soc.* **1980**, *102*, 5275.
(42) Clayton, J. P.; O'Hanlon, P. J.; Rogers, N. H.; King, T. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2827.

CH_2Cl_2 the organic layer was washed with 2 × 1 L of 10% $NaHSO_3$, and the combined aqueous washings were reextracted with 2 × 1 L of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and then evaporated, and the residue was purified by medium-pressure chromatography with methylene chloride–ether (95:5) to give 50.13 g (92%) of **14** as a white solid: mp 54–55 °C; $[\alpha]^{25}_D$ −0.69° (*c* 0.5830, EtOH); ^{1}H NMR (200 MHz) δ 1.06 (s, 9 H), 3.49 (br s, 1 H), 3.58 (br s, 1 H), 3.86 (m, 3 H); IR ($CHCl_3$) 3545, 845, 705 cm^{-1}; mass spectrum, *m/e* (relative intensity) 325 (2), 307 (5), 199 (100). Anal. Calcd for $C_{23}H_{30}O_3Si$: C, 72.21; H, 7.90. Found: C, 72.53; H, 8.14.

(−)-6-Bromohexahydro-4-hydroxy-2*H*-cyclopenta[*b*]furan-2-one (15). To a solution of 3.12 g (20 mmol) of **11** in 25 mL of anhydrous THF at 0 °C under argon was added, dropwise, 20 mL of 1 N KOH. The mixture was stirred at room temperature for 1 h at which point it was recooled to 0 °C and 4.72 g (20 mmol) of *N*-bromosuccinimide was added. After stirring for 4 h at room temperature, the reaction mixture was diluted with 25 mL of ethyl acetate and washed with 25 mL of 10% Na_2SO_3 and 25 mL of brine. The organic phase was dried (Na_2SO_4) and evaporated to give a crude residue, which was purified by flash chromatography with ethyl acetate–hexane (2:1) to give 3.2 g (73%) of **15** as an off-white solid: mp 63–64 °C (ether); $[\alpha]^{25}_D$ −41.02° (*c* 0.5265, $CHCl_3$); ^{1}H NMR (400 MHz) δ 2.26 (d, *J* = 9 Hz, 1 H, OH), 2.35 (dd, *J* = 2, 16 Hz, 1 H,), 2.50 (dd, *J* = 2, 18 Hz, 1 H), 2.69 (dd, *J* = 6, 16 Hz, 1 H), 2.95 (dd, *J* = 10, 18 Hz, 1 H), 3.20 (m, 1 H), 4.18 (m, 1 H), 4.41 (br s, 1 H) 5.25 (d, *J* = 7 Hz, 1 H); IR (KBr) 3515, 3420, 1762 cm^{-1}; mass spectrum, *m/e* (relative intensity) 141 (16), 123 (8), 113 (10), 81 (100). Anal. Calcd for $C_7H_9BrO_3$: C, 38.04; H, 4.10; Br, 36.15. Found: C, 37.58; H, 4.09; Br, 36.31.

[1*R*-(1β,2β,3β,5β)]-2-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-6-oxabicyclo[3.1.0]hexan-3-ol (16). To a suspension of 65 mg (3 mmol) of lithium borohydride and 2 mL of anhydrous THF at 0 °C under argon was added 221 mg (1 mmol) of **15** in 3 mL of THF. The mixture was warmed to room temperature and stirred for 1 h at which point 0.325 mL of 15% NaOH was added dropwise and the resulting mixture stirred an additional 15 min and then filtered through Celite (ethyl acetate wash). Evaporation gave a crude residue, which was purified by flash chromatography with methylene chloride–methanol (9:1) to give 137 mg (95%) of the diol as a colorless oil: $[\alpha]^{25}_D$ +105.92° (*c* 0.4050, EtOH); ^{1}H NMR (400 MHz) δ 1.70 (dd, *J* = 8, 18 Hz, 1 H), 2.57 (dd, *J* = 8, 14 Hz, 1 H), 3.15 (br s, 1 H, OH), 3.42 (br s, 1 H), 3.48 (br s, 1 H); IR ($CHCl_3$) 3510, 3410, 842 cm^{-1}; mass spectrum, *m/e* (relative intensity) 126 (4), 125 (5), 113 (18), 108 (11), 95 (48), 57 (100). Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 57.86; H, 8.51.

To a solution of 100 mg (0.694 mmol) of the above epoxy diol in 0.3 mL of dry pyridine under argon at 0 °C was added 229 mg (0.833 mmol) of *tert*-butylchlorodiphenylsilane. The mixture was stirred for 1 h at 0 °C and 1.5 h at room temperature at which point it was poured into 5 mL of 1 N HCl and extracted with 3 × 10 mL of ether. The combined ether extracts were dried ($MgSO_4$) and evaporated to give a crude residue, which was purified by flash chromatography with methylene chloride–ether (95:5) to give 225 mg (85%) of **16** as a colorless oil: $[\alpha]^{25}_D$ +44.10° (*c* 0.2789, EtOH); ^{1}H NMR (400 MHz) δ 1.06 (s, 9 H), 1.75 (dd, *J* = 8, 16 Hz, 1 H), 2.57 (dd, *J* = 7, 14 Hz, 1 H), 3.38 (br d, *J* = 13 Hz, 1 H), 3.43 (br d, *J* = 18 Hz, 1 H); IR ($CHCl_3$) 3620, 3450, 820, 702 cm^{-1}; mass spectrum, *m/e* (relative intensity) 325 (20), 307 (22), 28 (100). Anal. Calcd. for $C_{23}H_{30}O_3Si$: C, 72.21; H, 7.90. Found: C, 71.91; H, 8.12.

(5*R*-*cis*)-5,6-Dihydro-5-hydroxy-6-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-2*H*-pyran-2-one (17). A slurry containing 26.45 g (69.52 mmol) of **14** in 550 mL of anhydrous methylene chloride along with 55.8 g of sodium bicarbonate, 55.8 g (278.11 mmol) of 85% mCPBA, and 558 mg (1.55 mmol) of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide was stirred at reflux for 1 day. After cooling to room temperature, the mixture was diluted with 3.5 L of CH_2Cl_2 and washed with 3 × 1.5 L of 10% Na_2SO_3 and 1 × 750 mL of brine. The organic extracts were dried ($MgSO_4$) and evaporated to give the crude epoxy lactone. This material was dissolved in 330 mL of anhydrous methylene chloride and, after cooling to 0 °C, treated with 11.3 mL of dry triethylamine (8.14 g, 80.49 mmol) and stirred overnight at 0 °C. The reaction was quenched with 1.5 L of 1 N HCl, and after separation of the layers, the aqueous layer was extracted with 3 × 400 mL of methylene chloride. The combined organic extracts were washed with 250 mL of brine and dried ($MgSO_4$), and after evaporation to dryness, the residue was purified by flash chromatography with methylene chloride–ether (85:15) to give an off-white solid, which was recrystallized from ether–petroleum ether to give 20.4 g (74%) of **17**: mp 106–107 °C; $[\alpha]^{25}_D$ +56.66° (*c* 0.5242, EtOH); ^{1}H NMR (200 MHz) δ 1.06 (s, 9 H), 2.98 (d, *J* = 7 Hz, 1 H, OH), 3.85 (m, 2 H), 4.16 (m, 1 H), 4.57 (m, 1 H), 6.15 (d, *J* = 9 Hz, 1 H), 7.01 (dd, *J* = 6, 9 Hz, 1 H); IR ($CHCl_3$) 3580, 3400, 1732, 1632, 828, 702 cm^{-1}; mass spectrum, *m/e* (relative intensity) 339 (6), 321 (7), 261 (68), 255 (67), 234 (100), 199 (93); UV (EtOH) λ_{max} 220 nm (ε 26 238). Anal. Calcd for $C_{23}H_{28}O_4Si$: C, 69.66; H, 7.12. Found: C, 69.30; H, 6.88.

(5*S*-*cis*)-5,6-Dihydro-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-2*H*-pyran-2-one (18). To a solution of 7.50 g (18.90 mmol) of **17** and 4.3 mL (4.05 g, 37.8 mmol) of 2,6-lutidine in 20 mL of anhydrous methylene chloride at −15 °C was added dropwise, over a 30-min period, 5.1 mL (6.0 g, 22.70 mmol) of *tert*-butyldimethylsilyl trifluoromethanesulfonate. After 15 min, the reaction was quenched with saturated sodium bicarbonate and after warming to room temperature poured into 100 mL of saturated $NaHCO_3$. The aqueous phase was extracted with 3 × 250 mL of Et_2O, and the combined organic extracts washed with 2 × 200 mL of 1 N HCl and dried ($MgSO_4$). Evaporation to dryness gave a crude oil, which was purified by flash chromatography with petroleum ether–ethyl acetate (3:1) to give 8.04 g (83%) of a colorless oil along with 1.17 g of recovered **17**: $[\alpha]^{25}_D$ +80.67° (*c* 0.1562, EtOH); ^{1}H NMR (200 MHz) δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.85 (s, 9 H), 1.05 (s, 9 H), 3.80 (m, 1 H), 3.96 (m, 1 H), 4.06 (dd, *J* = 3, 4 Hz, 1 H), 4.63 (m, 1 H), 5.06 (d, *J* = 10 Hz, 1 H), 6.80 (dd, *J* = 5, 10 Hz, 1 H); IR ($CHCl_3$) 1728, 1632, 842, 828, 708 cm^{-1}; mass spectrum, *m/e* (relative intensity) 453 (33), 255 (100); UV (EtOH) λ_{max} 220 nm (ε 21 270). Anal. Calcd for $C_{29}H_{42}O_4Si_2$: C, 68.19; H, 8.29. Found: C, 68.49; H, 8.47.

(5*S*-*cis*)-5,6-Dihydro-6-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-2*H*-pyran-5-ol (20b). To a solution of 8.04 g (15.74 mmol) of **18** and 80 mL of anhydrous methylene chloride and 160 mL of hexanes cooled to −78 °C was added 19.7 mL of a 1 M solution of diisobutylaluminum hydride–hexane (19.7 mmol). After stirring for 15 min, the reaction mixture was quenched with 4.2 mL of methanol and warmed to room temperature. Brine (14.5 mL) was then added and the mixture poured into a stirring slurry of 600 mL of Et_2O and 30 g of $MgSO_4$. The mixture was stirred for 1 h, filtered, and evaporated to dryness and the resulting residue filtered through a pad of silica gel with petroleum ether–ethyl acetate (3:1) to give 7.60 g (94%) of a 3:1 mixture of lactols **19**: ^{1}H NMR (200 MHz) major, δ 0.04 (s, 6 H), 0.88 (s, 9 H), 1.06 (s, 9 H), 2.38 (d, *J* = 6 Hz, 1 H, OH), 3.72 (dd, *J* = 2, 4 Hz, 1 H), 3.86 (m, 2 H), 4.30 (m 1 H), 5.34 (br t, *J* = 3 Hz, 1 H), 5.88 (dd, *J* = 4, 10 Hz, 1 H), 6.02 (dd, *J* = 4, 10 Hz, 1 H), minor, δ 4.94 (m, 1 H), 5.12 (br d, *J* = 10 Hz, 1 H).

A 3.3-g (6.43 mmol) portion of the hemiacetal mixture was dissolved in 33 mL of anhydrous methylene chloride and cooled to −78 °C. A 3.1-mL (2.23 g, 19.3 mmol portion) of triethylsilane was added followed by 0.87 mL (1.0 g, 7.06 mmol) of boron trifluoride etherate. After 30 min, 1.6 g of solid sodium bicarbonate was added followed 15 min later by 10 mL of saturated sodium bicarbonate. The rapidly stirring solution was warmed up slowly to room temperature over 1 h and then poured into an additional 50 mL of saturated sodium bicarbonate. The aqueous layer was extracted with 3 × 200 mL of ether, and the combined organic extracts were dried ($MgSO_4$) and evaporated to give 2.7 g of a crude oil. A small sample of **20a** was purified by flash chromatography (petroleum ether–ether 96:4) for physical and analytical data: $[\alpha]^{25}_D$ +86.99° (*c* 0.4920, EtOH); ^{1}H NMR (200 MHz) δ 0.06 (s, 3 H), 0.07 (s, 3 H), 0.88 (s, 9 H), 1.05 (s, 9 H), 3.86 (m, 4 H), 4.04 d, *J* = 15 Hz, 1 H), 4.22 (d, *J* = 16 Hz, 1 H), 5.88 (br s, 2 H). Anal. Calcd for $C_{29}H_{4O3}Si_2$: C, 70.11; H, 8.93. Found: C, 70.16; H, 9.08.

A 5.82-g portion of the crude dihydropyran was dissolved in 80 mL of tetrahydrofuran and stirred with 80 mL of H_2O and 240 mL of acetic acid for 1 day at room temperature. The mixture was then diluted with 1.5 L of ethyl acetate and washed with 3 × 1 L of brine and 3 × 1 L of saturated sodium bicarbonate. The

organic extracts were dried (Na_2SO_4) and evaporated to dryness, and the resulting residue was purified by flash chromatography with petroleum ether–ethyl acetate (3:1) to give 2.43 g (44%) of **20b** as a colorless viscous oil: $[\alpha]^{25}_D$ +79.77° (*c* 0.3134, EtOH); ^{1}H NMR (200 MHz) δ 1.05 (s, 9 H), 3.80 (m, 4 H), 4.14 (m, 2 H), 6.00 (m, 2 H); IR ($CHCl_3$) 3585, 1115, 1088, 828, 708 cm^{-1}; mass spectrum, *m/e* (relative intensity) 325 (6), 307 (5), 255 (89), 199 (100). Anal. Calcd for $C_{23}H_{30}O_3Si$: C, 72.21; H, 7.90. Found: C, 72.05; H, 8.21.

[*R*-(*R,*R**)]-5,6-Dihydro-*N*-(1-phenylethyl)-2*H*-pyran-2-acetamide (22, *R** = (*R*)-HNCH(CH$_3$)Ph).** To a solution of 4.27 g (32.7 mmol) of 3,5-hexadienoyl chloride[41] in 150 mL of anhydrous ether at 0 °C under argon was added 9.9 g (82.0 mmol) of (*R*)-(+)-α-phenethylamine dissolved in 100 mL of ether. The resulting slurry was stirred for 2 h at room temperature and then quenched with 100 mL of 1 N HCl. The aqueous layer was extracted with 3 × 50 mL of ethyl acetate, and the combined organic extracts were washed with 1 × 50 mL of 1 N HCl, 1 × 50 mL of saturated $NaHCO_3$ and 2 × 50 mL of brine, dried ($MgSO_4$), and evaporated to solid residue. Recyrstallization from ether–petroleum ether gave 5.3 g (66%) of a white crystalline solid, **23**: mp 98–99 °C; $[\alpha]^{25}_D$ +9.41° (*c* 1.0100, $CHCl_3$); ^{1}H NMR (400 MHz) δ 1.49 (d, *J* = 7 Hz, 3 H), 3.05 (d, *J* = 8 Hz, 2 H), 5.10 (d, *J* = 10 Hz, 1 H), 5.15 (q, *J* = 8 Hz, 1 H), 5.20 (d, *J* = 17 Hz, 1 H), 5.75 (m, 1 H), 6.18 (dd, *J* = 12, 16 Hz, 1 H), 6.35 (dt, *J* = 8, 16 Hz, 1 H); IR ($CHCl_3$) 3430, 1668, 1650, 700 cm^{-1}; mass spectrum, *m/e* (relative intensity), 215 (M^+, 30), 172 (6), 120 (10), 105 (100); UV (MeOH) λ_{max} 211 nm (ε 28 850). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.27; H, 8.04; N, 6.51.

To a solution of 4.30 g (20.0 mmol) of the above amide in 300 mL of anhydrous methylene chloride at 0 °C under argon was added 0.96 g (32.0 mmol) of paraformaldehyde followed by 20 mL of 25% (1.97 M) ethylaluminum dichloride–hexane. The reaction mixture was stirred at room temperature overnight and was then quenched at 0 °C by adding 13 mL of methanol. The mixture was diluted to 1 L with ether and stirred with 60 mL of 10% HCl until the organic layer was clear. The solution was dried by stirring with $MgSO_4$ (~100 g) and was then filtered and evaporated to give a crude yellow oil, which was purified by repeated chromatography on a Waters PREP LC 500 with hexane–ethyl acetate (1:1) to give 2.20 g (45%) of crystalline **22(R)** as well as 2.10 g (43%) of the crystalline *S* diastereomer.

22(R): mp 93–94 °C (ether–petroleum ether); $[\alpha]^{25}_D$ +47.87° (*c* 0.1880, EtOH); ^{1}H NMR (400 MHz) δ 1.47 (d, *J* = 7 Hz, 3 H), 2.45 (m, 2 H), 3.70 (dt, *J* = 2, 10 Hz, 1 H), 4.02 (m, 1 H), 4.44 (br s, 1 H) 5.17 (m, 1 H), 5.67 (br d, *J* = 10 Hz, 1 H), 5.94 (br s, 1 H), 6.78 (br s, 1 H, NH); IR ($CHCl_3$) 3280, 1662, 1638, 1552, 707 cm^{-1}; mass spectrum, *m/e* (relative intensity) 245 (23), 230 (2), 162 (30), 140 (11), 105 (100). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.22; H, 7.76; N, 5.65.

22(S): mp 66–67 °C (ether–petroleum ether); $[\alpha]^{25}_D$ +73.48° (*c* 0.2055, EtOH); ^{1}H NMR (400 MHz) δ 1.48 (d, *J* = 7 Hz, 3 H), 2.42 (dd, *J* = 8, 16 Hz, 1 H), 2.51 (dd, *J* = 2, 16 Hz, 1 H), 3.69 (dt, *J* = 2, 10 Hz, 1 H), 4.00 (m, 1 H), 4.45 (br s, 1 H), 5.14 (m, 1 H), 5.61 (br d, *J* = 10 Hz, 1 H), 5.84 (m, 1 H), 6.72 (br s, 1 H, NH); IR ($CHCl_3$) 3305, 1640, 1550, 698 cm^{-1}; mass spectrum, *m/e* (relative intensity) 245 (M^+, 12), 230 (3), 162 (15), 140 (9), 120 (32), 106 (24), 105 (65), 83 (42), 20 (100). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N 5.71. Found: C, 73.30; H, 7.88; N, 5.72.

(3a*S*)-3,3a,5,7a-Tetrahydro-2*H*-furo[3,2-*b*]pyran-2-one (25). To a solution of 3.5 g (14.26 mmol) of **22** (R* = (*R*)-HNCH(CH$_3$)Ph) in 150 mL of THF and 150 mL of H_2O at 0 °C was added 7.9 g (31.37 mmol) of iodine. The mixture was stirred at 0 °C for 1 h and at room temperature for 3 h at which point ca. 50 g of ice was added along with 250 mL of ethyl acetate. The organic extracts were washed with 100 mL of 10% $Na_2S_2O_3$, dried (Na_2SO_4), and evaporated to give a crude oil, which was submitted to flash chromatography with hexane–ethyl acetate (7:3 then 1:1) to give 2.75 g (72%) of crystalline **24** (slightly impure) along with 0.41 g (12%) of recovered **22**: ^{1}H NMR (200 MHz) δ 2.84 (br d, *J* = 16 Hz, 1 H), 2.21 (m 1 H), 2.55 (d, *J* = 18 Hz, 1 H), 2.67 (dd, *J* = 4, 18 Hz, 1 H), 3.83 (d, *J* = 1 Hz, 1 H), 3.85 (dd, *J* = 1,4 Hz, 1 H), 4.56 (br s, 1 H), 4.65 (d, *J* = 2 Hz, 1 H), 4.79 (d, *J* = 2 Hz, 1 H). To the above iodo lactone (10.25 mmol) in 60 mL of anhydrous THF under argon at room temperature was added 2 mL (12.8 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene and the mixture stirred overnight. The reaction was evaporated and the residue dissolved in 100 mL of ethyl acetate and washed with 2 × 50 mL of 1 N HCl and 1 × 25 mL of brine. The organic extracts were dried (Na_2SO_4) and evaporated to give a crude oil, which was purified by flash chromatography with hexanes–ethyl acetate (1:1) to give 1.18 g (82%) of a crystalline solid: mp 93–94 °C (Et_2O); $[\alpha]^{25}_D$ +95.31° (*c* 0.1941, EtOH); ^{1}H NMR (400 MHz) δ 2.64 (d, *J* = 18 Hz, 1 H), 2.83 (dd, *J* = 6, 18 Hz, 1 H), 4.11 (dd, *J* = 1, 16 Hz, 1 H), 4.21 (dd, *J* = 3, 16 Hz, 1 H), 4.28 (m, 1 H), 4.56 (br s, 1 H), 6.10 (m, 1 H), 6.28 (dd, *J* = 2, 10 Hz, 1 H); IR ($CHCl_3$) 1768, 1651 cm^{-1}; mass spectrum, *m/e* (relative intensity) 140 (M^+, 17), 122 (2), 112 (4), 113 (4), 110 (5), 96 (57), 81 (30), 84 (62), 68 (39), 69 (60). Anal. Calcd for $C_7H_8O_3$: C, 60.00; H, 5.75. Found: C, 59.99; H, 5.85.

20 (R = H) from 25: To a suspension of 875 mg (23.26 mmol) of lithium aluminum hydride and 60 mL of anhydrous ether cooled to 0 °C under argon was added, dropwise, 1.63 g (11.63 mmol) of **25** dissolved in 40 mL of anhydrous THF. After stirring for 30 min, the reaction mixture was carefully quenched by sequentially adding 0.95 mL of H_2O, 0.95 mL of 15% NaOH, and 2.85 mL of H_2O. The slurry was stirred for 1 h at 0 °C, and the aluminum salts were filtered off and washed thoroughly with ethyl acetate. Evaporation gave a crude oil, which was purified by flash chromatography with methylene chloride–methanol (9:1) to give 1.53 g (91%) of a colorless oil: ^{1}H NMR (200 MHz) δ 1.76 (m, 1 H), 2.00 (m, 1 H), 2.28 (br s, 1 H, OH), 4.18 (br s, 2 H), 5.94 (m, 2 H). To the above diol (10.59 mmol) in 4.5 mL of dry pyridine at 0 °C under argon was added 3 mL (11.38 mmol) of *tert*-butylchlorodiphenylsilane. The mixture was stirred at 0 °C for 1 h and at room temperature for 1 h and was then diluted with 90 mL of ether and washed with 3 × 30 mL of 1 N HCl and 1 × 30 mL of brine. The ether layer was dried ($MgSO_4$) and evaporated to give a crude residue, which was purified by flash chromatography to give 3.71 g (92%) of **20**.

(2*S*-*cis*)-5,6-Dihydro-*N*,*N*-dimethyl-2-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-2*H*-pyran-5-acetamide (26). A solution of 2.43 g (6.35 mmol) of **20b** and 2.3 mL (2.11 g, 15.87 mmol) of *N*,*N*-dimethylacetamide dimethyl acetal in 13 mL of xylenes was stirred at reflux for 12 h. The solvent and excess reagents were evaporated under reduced pressure to give a crude oil, which was purified by flash chromatography with petroleum ether–ethyl acetate (3:2) to give 2.86 g (100%) of a colorless oil: $[\alpha]^{25}_D$ −38.99° (*c* 0.4514, EtOH); ^{1}H NMR (200 MHz) δ 1.05 (s, 9 H), 2.39 (d, *J* = 6 Hz, 1 H), 2.45 (d, *J* = 7 Hz, 1 H), 2.95 (s, 3 H), 3.75 (br s, 2 H), 3.80 (d, *J* = 6 Hz, 1 H), 3.87 (d, *J* = 6 Hz, 1 H), 4.30 (m, 1 H), 5.65 (br d, *J* = 11 Hz, 1 H), 5.84 (m, 1 H); IR ($CHCl_3$) 1635, 827, 708 cm^{-1}; mass spectrum, *m/e* (relative intensity) 451 (M^+, 1), 394 (77), 364 (59), 316 (3), 72 (100). Anal. Calcd for $C_{27}H_{37}NO_3Si$: C, 71.80; H, 8.26; N, 3.10. Found: C, 71.75; H, 8.49; N, 3.15.

[3a*R*-(3aα,4α,7α,7aα)]-Tetrahydro-*N*,*N*,2,2-tetramethyl-4-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-4*H*-1,3-dioxolo[4,5-*c*]pyran-7-acetamide (27). To a solution of 8.09 g (17.91 mmol) of **26** and 4.66 g (34.39 mmol) of *N*-methylmorpholine *N*-oxide in 185 mL of acetone was added a solution of 228 mg (0.89 mmol) of osmium tetraoxide in 65 mL of H_2O and the resulting mixture stirred at room temperature for 1 day. The solution was poured into 2 L of ethyl acetate and washed twice with 1 L of 15% $NaHSO_3$ and twice with 650 mL of 1 N HCl. The combined aqueous washings were extracted with 2 × 1 L of ethyl acetate, and the combined organic extracts were dried (Na_2SO_4) and evaporated to dryness to give a crude solid, which was recrystallized from ether–petroleum ether to give 7.85 g (90%) of a white crystalline solid: mp 98–100 °C; $[\alpha]^{25}_D$ +1.96° (*c* 0.5140, EtOH); ^{1}H NMR (200 MHz) δ 1.05 (s, 9 H), 2.95 (s, 3 H), 3.01 (s, 3 H); IR ($CHCl_3$) 3550, 3360, 1633, 1112, 835, 708 cm^{-1}; mass spectrum, *m/e* (relative intensity) 485 (M^+, 1), 428 (82), 410 (34), 199 (60), 87 (61), 72 (100). Anal. Calcd for $C_{27}H_{39}NO_5Si$: C, 66.77; H, 8.09, N, 2.88. Found: C, 66.88; H, 8.03; N, 2.78.

To a suspension of 7.85 g (16.16 mmol) of the above diol and 15.7 g of anhydrous cupric sulfate in 160 mL of acetone at room temperature was added 160 mg (0.81 mmol) of *p*-toluenesulfonic acid and the mixture stirred at room temperature for 1 day. The slurry was filtered through a pad of Celite and ~3.5 mL of a saturated sodium bicarbonate solution was carefully added.

$MgSO_4$ was then added followed by filtering through an additional pad of $MgSO_4$. Evaporation gave a crude residue, which was purified by flash chromatography with ethyl acetate–petroleum ether (9:1) to give 8.02 g (94%) of a colorless oil: $[\alpha]^{25}_D$ −13.92° (*c* 0.4958, EtOH); ^{1}H NMR (100 MHz) δ 1.06 (s, 9 H), 1.38 (s, 3 H), 1.53 (s, 3 H), 2.98 (s, 3 H), 3.02 (s, 3 H), 4.10 (m, 1 H); IR ($CHCl_3$) 1640, 705 cm^{-1}; mass spectrum, *m/e* (relative intensity) 510 (6), 468 (100), 410 (27). Anal. Calcd for $C_{30}H_{43}NO_5Si$: C, 68.53; H, 8.24, N, 2.66. Found: C, 68.35; H, 8.40; N, 2.72.

[3a*R*-(3aα,4α,7α,7aα)]-Tetrahydro-2,2-dimethyl-4-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-4*H*-1,3-dioxolo[4,5-*c*]pyran-7-acetaldehyde (28). To a solution of 4.0 g (7.60 mmol) of **27** in 120 mL of anhydrous ether cooled to −90 °C (MeOH–liquid N_2) under argon was added 9.5 mL of 1 M diisobutylaluminum hydride–hexane. After the mixture was stirred for 30 min, 3 mL of methanol was added rapidly and the reaction mixture allowed to warm to room temperature. After dilution with 500 mL of Et_2O, 15 mL of brine was added followed by 25 g of $MgSO_4$ and the slurry stirred for 1 h. Filtration and evaporation gave a crude residue, which was purified by flash chromatography with hexanes–ethyl acetate (3:1) to give 2.70 g (74%) of a colorless oil: $[\alpha]^{25}_D$ −25.48° (*c* 0.2865, EtOH); ^{1}H NMR (200 MHz) δ 1.05 (s, 9 H), 1.37 (s, 3 H), 1.52 (s, 3 H), 4.04 (br s, 1 H), 9.81 (s, 1 H); IR ($CHCl_3$) 2730, 1728, 705 cm^{-1}; mass spectrum, *m/e* (relative intensity) 467 (2), 425 (12), 367 (24), 255 (70), 199 (76), 69 (100). Anal. Calcd for $C_{28}H_{38}O_5Si$: C, 69.67; H, 7.94. Found: C, 69.39; H, 8.14.

(+)-1-(3-Hydroxy-6-oxabicyclo[3.1.0]hex-6-yl)-2-propanone (29). To a solution of 1.10 g (5 mmol) of **15** in 50 mL of anhydrous THF at −78 °C under argon was added 6.3 mL of 1.6 M methyllithium–ether and the resulting mixture stirred for 5 h at −78 °C and then warmed slowly to 0 °C. After the mixture was cooled back down to −78 °C, 3 mL of methanol (saturated with anhydrous Na_2CO_3) was slowly added and the reaction mixture then warmed up to room temperature. Brine (10 mL) was added the aqueous layer was extracted with 2 × 25 mL of ethyl acetate. The combined organic extracts were washed with 10 mL of brine, dried (Na_2SO_4), and evaporated to give a crude solid, which was crystallized (ether–hexanes) to give 0.476 g (61%) of a white solid: mp 69–70 °C; $[\alpha]^{25}_D$ +23.89° (*c* 0.5568, $CHCl_3$); ^{1}H NMR (400 MHz) δ 1.77 (dd, *J* = 7, 15 Hz, 1 H), 2.24 (s, 3 H), 2.57 (dd, *J* = 7, 15 Hz, 1 H), 2.81 (dd, *J* = 10, 17 Hz, 1 H), 3.04 (dd, *J* = 2, 17 Hz, 1 H), 3.38 (br s, 1 H), 3.49 (br s, 1 H), 3.61 (m, 1 H); IR (KBr) 3375, 1697 cm^{-1}; mass spectrum, *m/e* (relative intensity) 138 (6), 113 (12), 99 (53), 43 (100). Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.33; H, 7.92.

(+)-2-[(2-Methyl-1,3-dioxol-2-yl)methyl]-6-oxabicyclo-[3.1.0]hexan-3-ol (30). A mixture of 156 mg (1 mmol) of **29**, 248 mg (4 mmol) of ethylene glycol and 38 mg (0.15 mmol) of pyridinium tosylate in 10 mL of anhydrous benzene was refluxed with a Dean–Stark trap for 2 h under argon. After the mixture cooled to room temperature, the solvent was evaporated and the residue extracted into 10 mL of ether, which was then washed with 5 mL of saturated $NaHCO_3$ and 5 mL of brine, dried ($MgSO_4$), and evaporated. The crude residue was purified by HPLC chromatography with ethyl acetate–hexane (3:1) to give 91 mg (48%) of a colorless oil: $[\alpha]^{25}_D$ +52.47° (*c* 0.4040, $CHCl_3$); ^{1}H NMR ($CHCl_3$) δ 1.43 (s, 3 H), 1.72 (dd, *J* = 8, 14 Hz, 1 H), 2.13 (d, *J* = 12 Hz, 1 H), 2.54 (dd, *J* = 8, 12 Hz, 1 H), 3.35 (br s, 1 H, OH), 3.41 (br s, 1 H), 3.45 (br s, 1 H), 3.64 (m, 1 H), 4.02 (m 4 H); IR ($CHCl_3$) 3500 cm^{-1}; mass spectrum, *m/e* (relative intensity) 183 (12), 87 (100), 43 (62). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.60; H, 8.00.

[*S*-(*R,*S**)]-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-methylbutanoic Acid Ethyl Ester (37).** To a solution of 5.2 g (35.6 mmol) of **36** and 5.3 g (78.3 mmol) of imidazole in 25 mL of anhydrous dimethylformamide under argon at 0 °C was added, dropwise, a solution of 6.4 g (42.7 mmol) of *tert*-butyldimethylsilyl chloride in 20 mL of DMF. The reaction mixture was stirred overnight at room temperature at which point it was diluted with 200 mL of H_2O and extracted with 4 × 100 mL of ethyl acetate. The combined organic extracts were washed with 2 × 100 mL of 1 N HCl and 1 × 100 mL of brine and then dried ($MgSO_4$). Evaporation gave a crude oil, which was purified on a Waters Prep LC 500 with hexanes–ethyl acetate (99.5:0.5) to give 8.0 g (86%) of a clear, colorless liquid: $[\alpha]^{25}_D$ +29.43° (*c* 1.0055, $CHCl_3$); ^{1}H NMR (400 MHz) δ 0.03 (s, 3 H), 0.06 (s, 3 H), 0.85 (s, 9 H), 1.07 (d, *J* = 8 Hz, 3 H), 1.11 (d, *J* = 8 Hz, 3 H), 1.25 (t, *J* = 8 Hz, 3 H), 2.46 (m, 1 H), 4.00 (m, 1 H), 4.21 (q, *J* = 8 Hz, 2 H); IR ($CHCl_3$) 1728, 840 cm^{-1}; mass spectrum, *m/e* (relative intensity) 245 (2), 203 (50), 175 (17), 159 (20), 131 (8), 115 (22), 75 (100). Anal. Calcd for $C_{13}H_{28}O_3Si$: C, 59.95; H, 10.84. Found: C, 60.08; H, 10.83.

(*S*)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-methyl-1-butanol 4-Methylbenzenesulfonate (39). To a solution of 8.0 g (30.7 mmol) of **37** in 50 mL of hexanes and 25 mL of anhydrous methylene chloride at −78 °C under argon was added 93 mL of a 1 M solution of diisobutylaluminum hydride–hexane over a 30-min period. After 3 h at −78 °C, the mixture was warmed to −20 °C and stirred for an additional 2 h at which point the reaction mixture was cooled back down to −60 °C and quenched with 31 mL of MeOH. The solution was then allowed to warm to room temperature and was poured into 2 L of ether. Brine (140 mL) was added along with 280 g of $MgSO_4$ and the slurry was stirred for 1 h. Filtration and evaporation gave 5.6 g (84%) of the primary alcohol as a clear, colorless liquid: ^{1}H NMR (200 MHz) δ 0.08 (s, 6 H), 0.89 (s, 9 H), 0.96 (d, *J* = 7 Hz, 3 H), 1.21 (d, *J* = 7 Hz, 3 H), 3.54 (m, 1 H), 3.75 (d, *J* = 6 Hz, 1 H), 3.80 (d, *J* = 6 Hz, 1 H).

The above alcohol (25.7 mmol) was dissolved in 30 mL of dry pyridine and the solution cooled to 0 °C. A 8.9-g (46.5 mmol) portion of *p*-toluenesulfonyl chloride dissolved in 30 mL of pyridine was then added and the mixture stirred overnight at room temperature. The reaction was evaporated to dryness and the residue dissolved in 250 mL of ethyl acetate and washed with 3 × 100 mL of 1 N HCl. The combined aqueous washes were extracted with 250 mL of ethyl acetate and the combined organic extracts washed with 2 × 100 mL of brine, dried ($MgSO_4$), and evaporated. The resulting crude liquid was purified by chromatography on a Waters Prep LC 500 with hexanes–ethyl acetate (98.5:1.5) to give 8.5 g (97%) of **39** as a colorless oil: $[\alpha]^{25}_D$ +15.27° (*c* 1.0410, $CHCl_3$); ^{1}H NMR (400 MHz) δ 0.00 (s, 3 H), 0.04 (s, 3 H), 0.84 (s, 9 H), 0.89 (d, *J* = 8 Hz, 3 H), 1.09 (d, *J* = 8 Hz, 3 H), 2.48 (s, 3 H), 3.66 (m, 1 H), 3.89 (dd, *J* = 6, 8 Hz, 1 H), 4.08 (dd, *J* = 4, 8 Hz, 1 H), 7.35 (d, *J* = 8 Hz, 2 H), 7.80 (d, *J* = 8 Hz, 2 H); IR ($CHCl_3$) 850 cm^{-1}; mass spectrum, *m/e* (relative intensity) 229 (100). Anal. Calcd for $C_{18}H_{32}O_4SSi$: C, 58.02; H, 8.66. Found: C, 57.77; H, 8.75.

(2*S*,3*S*)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-methyl-1-(phenylsulfonyl)butane (40). A mixture of 8.5 g (24.9 mmol) of **39** and 5.6 g (37.4 mmol) of sodium iodide in 125 mL of dry 2-butanone was heated at reflux, under argon, for 1.5 h. After cooling to room temperature, the reaction mixture was evaporated to dryness and the residue dissolved in 100 mL of ether. This solution was washed with 2 × 25 mL of 10% $Na_2S_2O_3$ and 2 × 25 mL of brine, dried ($MgSO_4$), and evaporated to give 7.1 g (90%) of a colorless oil: ^{1}H NMR (200 MHz) δ 0.05 (s, 3 H), 0.07 (s, 3 H), 0.87 (s, 9 H), 0.95 (d, *J* = 6 Hz, 3 H), 1.11 (d, *J* = 6 Hz, 3 H), 3.26 (d, *J* = 6 Hz, 1 H), 3.28 (d, *J* = 4 Hz, 1 H), 3.65 (m, 1 H).

The above iodide (22.4 mmol) in 100 mL of dry hexamethylphosphoric triamide at room temperature under argon was treated with 10.9 g (66.6 mmol) of benzenesulfinic acid, sodium salt. After 30 min, the reaction mixture was diluted with 250 mL of ice–H_2O and extracted with 3 × 100 mL of ether. The combined organic extracts were washed with 2 × 50 mL of H_2O, dried ($MgSO_4$), and evaporated to give a yellow oil, which was purified by chromatography on a Waters Prep LC 500 with hexanes–ethyl acetate (94:6) to give 6.2 g (81%) of **40** as a colorless oil: $[\alpha]^{25}_D$ +15.27° (*c* 0.3930, $CHCl_3$); ^{1}H NMR (200 MHz) δ −0.02 (s, 3 H), 0.00 (s, 3 H), 0.82 (s, 9 H), 1.01 (d, *J* = 6 Hz, 3 H), 1.09 (d, *J* = 6 Hz, 3 H), 2.82 (dd, *J* = 9, 15 Hz, 1 H), 3.34 (dd, *J* = 2, 15 Hz, 1 H); IR ($CHCl_3$) 1320, 1150, 840 cm^{-1}; mass spectrum, *m/e* (relative intensity) 285 (71), 135 (100), 73 (62). Anal. Calcd for $C_{17}H_{30}O_3SSi$: C, 59.60; H, 8.85. Found: C, 59.70; H, 8.88.

[3a*S*-[3aα,4α,7aα,7α(2*E*,4*S,5*R**)]]-Tetrahydro-2,2-dimethyl-4-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-ethyl]-7-[5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-methyl-2-hexenyl]-4*H*-1,3-dioxolo[4,5-*c*]pyran (34).** To a solution of 1.3 mL (0.94 g, 8.76 mmol) of diisopropylamine in 16 mL of anhydrous THF under argon at 0 °C was added 3.4 mL of 2.35 M *n*-BuLi–hexane. The resulting LDA solution was stirred for 10 min and then cooled to −60 °C at which point 2.5 g (7.30

mmol) of sulfone **40** dissolved in 15 mL of THF was added dropwise. The yellow sulfone anion solution was stirred for 30 min and 3.5 g (7.30 mmol) of aldehyde **28** dissolved in 15 mL of THF was added dropwise. After the mixture was stirred at −60 °C for 1 h, 1.1 mL (1.4 g, 18.3 mmol) of neat carbon disulfide was added and the reaction mixture was warmed to 0 °C. After 10 min, 1.15 mL (2.6 g, 18.3 mmol) of neat methyl iodide was added and the mixture stirred an additional 20 min. The reaction was quenched wtih 50 mL of brine warmed to room temperature and extracted with 4 × 100 mL of ether. The combined organic extracts were washed with 2 × 50 mL of brine, dried ($MgSO_4$), and evaporated to an orange oil, which was purified by chromatography on a Waters Prep LC 500 with hexane–ethyl acetate (85:15) to give a mixture of four diastereomers of the xanthate sulfone (6.3 g) as a viscous yellow foam. This material, dissolved in 100 mL of dry toluene, was added to a stirring solution of 2.8 mL (3.0 g, 10.30 mmol) of tributyltin hydride in 100 mL of toluene at reflux. After 3.5 h, the reaction mixture was cooled to room temperature and evaporated to dryness. The crude residue was purified, and the *Z* and *E* isomers were separated by chromatography on a Waters Prep LC 500 with hexane–ethyl acetate (98.5:1.5) to give 3 g (61%) of the trans isomer **34** and 0.5 g (10%) of the 10,11-cis isomer.

34: $[\alpha]^{25}_D$ −16.88° (*c* 0.6517, $CHCl_3$); ^1H NMR (400 MHz) δ 0.02 (s, 6 H), 0.87 (s, 9 H), 0.94 (d, *J* = 7 Hz, 3 H), 1.01 (d, *J* = 7 Hz, 3 H), 1.06 (s, 9 H), 1.35 (s, 3 H), 1.50 (s, 3 H), 4.12 (br s, 1 H), 5.42 (m, 2 H); ^{13}C NMR (50 MHz) δ 15.83, 18.10, 19.21, 20.48, 25.87, 26.43, 26.81, 28.34, 34.15, 36.00, 37.04, 44.21, 59.67, 66.42, 71.79, 74.29, 74.69, 75.42, 108.42, 127.34, 127.55, 129.45, 133.96, 135.41, 135.54; IR ($CHCl_3$) 1110, 835 cm^{-1}; mass spectrum, *m/e* (relative intensity) 609 (8), 149 (100), 73 (48). Anal. Calcd for $C_{39}H_{62}O_5Si_2$: C, 70.22; H, 9.37. Found: C, 70.37; H, 9.64.

10,11-Cis isomer: $[\alpha]^{25}_D$ −22.72° (*c* 0.2112, $CHCl_3$); ^1H NMR (400 MHz) δ 0.02 (s, 6 H), 0.87 (s, 9 H), 0.88 (d, *J* = 7 Hz, 3 H), 0.90 (d, *J* = 7 Hz, 3 H), 1.03 (s, 9 H), 1.35 (s, 3 H), 1.50 (s, 3 H, 4.09 (br s, 1 H), 5.43 (m, 2 H); ^{13}C NMR (50 MHz) (only peaks different from trans compound are given) δ 16.9, 37.36, 39.09, 66.05, 71.65, 74.85, 75.68, 126.72, 134.64; IR ($CHCl_3$) 1110, 835 cm^{-1}; mass spectrum, *m/e* (relative intensity) 609 (10), 159 (100), 73 (46). Anal. Calcd for $C_{39}H_{62}O_5Si_2$: C, 70.22; H, 9.37. Found: C, 70.44; H, 9.63.

[3a*S*-[3aα,4α,7aα,7α(3*E*,2*S)]]-Tetrahydro-2,2-dimethyl-4-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-α-(1-propenyl)-4*H*-1,3-dioxolo[4,5-*c*]pyran-7-ethanol (41, R = Me) from 28.** The Grignard reagent was prepared by rapidly stirring a mixture of 40 mg (1.65 mmol) of magnesium turnings with 0.22 mL (2.58 mmol) of 1-bromopropene in 4 mL of anhydrous THF at room temperature under argon for 1.5 h. The resulting solution was added via syringe to a solution of 100 mg (0.207 mmol) of aldehyde **28** and 51 mg (0.21 mmol) of dry zinc bromide in 3.25 mL of anhydrous methylene chloride and 0.2. mL of THF at −100 °C. After stirring for 1 h, the reaction mixture was quenched with saturated NH_4Cl (5 mL), warmed to room temperature, and extracted with 3 × 10 mL of ether. The combined organic extracts were dried ($MgSO_4$) and evaporated to give a crude residue, which was purified by HPLC with hexanes–ethyl acetate (65:35) to give 43 mg (40%) of the *S* diastereomer **41a** (R = Me), 13 mg (12%) of the C-10 *R* diastereomer, **41b** (R = Me), and 25 mg of recovered **28** (68% based on recovered starting aldehyde).

41a (R = Me): $[\alpha]^{25}_D$ −17.41° (*c* 0.1550, EtOH); ^1H NMR (400 MHz) δ 1.00 (s, 9 H), 1.37 (s, 3 H), 1.50 (s, 3 H), 1.69 (d, *J* = 7 Hz, 3 H), 4.07 (m, 1 H), 4.20 (m, 1 H), 5.47 (dd, *J* = 7, 16 Hz, 1 H), 5.67 (m, 1 H); ^{13}C NMR (50 MHz) δ 17.64, 19.19, 26.36, 26.81, 28.21, 33.79, 35.90, 38.10, 59.70, 66.33, 71.05, 73.85, 74.92, 108.66, 127.44, 127.56, 129.48, 133.69, 133.91, 135.54; IR ($CHCl_3$) 3605, 1382, 1370, 820, 702 cm^{-1}; mass spectrum, *m/e* (relative intensity) 467 (8), 465 (15), 409 (10), 255 (20), 41 (100). Anal. Calcd for $C_{31}H_{44}O_5Si$: C, 70.95; H, 8.45. Found: C, 71.04; H, 8.68.

41b (R = Me): ^1H NMR (200 MHz) δ 1.04 (s, 9 H), 1.37 (s, 3 H), 1.51 (s, 3 H), 1.68 (d, *J* = 7 Hz, 3 H), 4.09 (m, 1 H), 4.13 (m, 1 H), 5.48 (dd, *J* = 7, 16 Hz, 1 H, 5.70 (m, 1 H); ^{13}C NMR (50 MHz) δ 17.62, 19.23, 26.36, 26.81, 28.23, 34.16, 35.96, 38.66, 59.66, 66.00, 77.55, 74.01, 75.01, 108.56, 126.79, 127.58, 129.49, 133.99 (2), 135.56.

[3a*S*-(3aα,4α,7aα,7α)]-1-[Tetrahydro-2,2-dimethyl-4-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-1,3-dioxolo-[4,5-*c*]pyran-7-yl]-3-pentyn-2-one (47). To a solution of 2 mL methyl acetylene (condensed at ca. −27 °C) in 20 mL of anhydrous THF at −78 °C was added, under argon, 3.6 mL of 2.5 M *n*-BuLi–hexane followed 10 min later by 1.2 mL (1.37 g, 9.68 mmol) of boron trifluoride etherate. After another 10 min, 1.59 g (3.03 mmol) of amide **27** dissolved in 8 mL of THF was added. The reaction was quenched 30 min later by adding 25 mL of saturated ammonium chloride and warming the mixture to room temperature. The aqueous layer was extracted with 3 × 25 mL of ether, and the combined organic extracts were dried ($MgSO_4$) and evaporated to give an oil, which was purified by flash chromatography with petroleum ether–ethyl acetate (85:15) to give 1.43 g (91%) of a white solid: mp 85–87 °C; $[\alpha]^{25}_D$ −20.12° (*c* 0.5218, EtOH); ^1H NMR (400 MHz) δ 1.05 (s, 9 H), 1.36 (s, 3 H), 1.49 (s, 3 H), 2.02 (s, 3 H), 4.06 (br s, 1 H); IR ($CHCl_3$) 2220, 1670, 1382, 1372, 702 cm^{-1}; mass spectrum, *m/e* (relative intensity) 520 (M^+, <1), 505 (2), 463 (20), 405 (15), 387 (3), 255 (40), 199 (50), 107 (100), 67 (50). Anal. Calcd for $C_{31}H_{40}O_5Si$: C, 71.50; H, 7.74. Found: C, 71.32; H, 7.78.

[3a*S*-[3aα,4α,7aα,7α(3*E*,2*S)]]-Tetrahydro-2,2-dimethyl-4-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-α-(1-propenyl)-4*H*-1,3-dioxolo[4,5-*c*]pyran-7-ethanol (41a, R = Me) from 47.** A sample of neat (-)-Alpine borane was prepared by stirring 0.74 g (6.12 mmol) of 9-BBN with 1.1 mL (0.91 g, 6.73 mmol) of (-)-α-pinene (92% ee) at 65 °C under argon for 5 h. The resulting solution was added to a solution of 640 mg (1.22 mmol) of **47** dissolved in 0.6 mL of anhydrous THF at room temperature under argon and the mixture stirred for 1 day. After the mixture was cooled to 0 °C, 0.7 mL of THF was added followed by excess acetaldehyde and the reaction mixture warmed to room temperature. The excess acetaldehyde was removed by a stream of argon and 1 mL of ether was added followed by, after cooling to 0 °C, 0.38 mL (0.37 g, 6.12 mmol) of ethanolamine. The resulting precipitate was filtered off and washed with ether and the filtrate evaporated to a crude oil, which was purified by flash chromatography with hexanes–ethyl acetate (3:1) to give 0.55 g (85%) of a colorless oil: $[\alpha]^{25}_D$ −19.85° (*c* 0.1511, EtOH); ^1H NMR (400 MHz) δ 1.04 (s, 9 H), 1.37 (s, 3 H), 1.52 (s, 3 H), 1.82 (s, 3 H), 4.10 (m, 1 H), 4.49 (m, 1 H); ^{13}C NMR (50 MHz) δ 3.49, 19.20, 26.33, 26.81, 28.14, 34.13, 35.80, 38.83, 59.73, 61.01, 65.85, 73.60, 75.01, 79.69, 81.78, 108.80, 127.56, 129.50, 133.94, 135.54; IR ($CHCl_3$) 3605, 1380, 1370, 702 cm^{-1}; mass spectrum, *m/e* (relative intensity) 465 (6), 425 (1), 407 (5), 255 (60), 199 (100).

To a slurry of 17 mg (0.455 mmol) of lithium aluminum hydride, 50 mg (0.91 mmol) of sodium methoxide, and 0.8 mL of anhydrous THF was added 0.12 g (0.227 mmol) of the above alcohol in 1.6 mL of THF and the mixture stirred at reflux for 4.5 h. The reaction mixture was cooled to room temperature and then 0 °C and quenched by the successive addition of 20 μL of H_2O, 20 μL of 15% NaOH, and 60 μL of H_2O. After the mixture was stirred at 0 °C for 1 h, filtration through a pad of Celite (ethyl acetate wash) followed by evaporation gave a crude residue, which was purified by flash chromatography with petroleum ether–ethyl acetate (3:1) to give 110 mg (92%) of pure **41a** as a viscous oil.

2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]acetic Acid. To a solution of 10 g (131.5 mmol) of glycolic acid in 130 mL of acetone under argon was added 1.15 equiv of triethylamine (151.2 mmol, 21 mL) followed by 1.05 equiv of benzyl bromide (138.1 mmol, 16.5 mL) and the mixture refluxed overnight (12 h). After the mixture cooled to room temperature, the solids were filtered off and washed with acetone, and the solution was evaporated. The resulting residue was dissolved in 300 mL of ethyl acetate and washed with 150 mL of H_2O. The aqueous layer was reextracted with 100 mL of ethyl acetate, dried ($MgSO_4$), and evaporated to give 17.20 g (78%) of the benzyl ester: ^1H NMR (200 MHz) δ 4.20 (s, 2 H), 5.24 (s, 2 H), 7.40 (s, 5 H).

To a solution of 14.20 g (85.45 mmol) of the above benzyl ester in 65 mL of dry pyridine at room temperature under argon was added 16.10 g (106.8 mmol) of *tert*-butyldimethylsilyl chloride. After 2 h, the mixture was poured into 250 mL of ether and washed with 150 mL of 1 N HCl and 100 mL of brine. The organic phase was dried ($MgSO_4$) and evaporated to give a crude product, which was purified by flash chromatography with hexanes–ethyl acetate (96:4) to give 20.02 g (83%) of the silyl ether–benzyl ester as a viscous oil: ^1H NMR (200 MHz) δ 0.08 (s, 6 H), 0.90 (s, 9 H), 4.28 (s, 2 H), 5.17 (s, 2 H), 7.35 (s, 5 H).

A 20.02-g (71.39 mmol) portion of the above silyl ether–benzyl ester in 270 mL of ethyl acetate was stirred with 2 g of 10% Pd/C under an atmosphere of hydrogen for ca. 3 h. The mixture was filtered through Celite and evaporated to give 13.10 g (96%) of the protected acid as a white solid: ^{1}H NMR (200 MHz) δ 0.09 (s, 3 H), 0.27 (s, 3 H), 0.92 (s, 9 H), 4.18 (s, 2 H).

[3a*S*-[3aα,4α,7aα,7α(3*E*,2*S)]]-Tetrahydro-2,2-dimethyl-4-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-α-(1-propenyl)-4*H*-1,3-dioxolo[4,5-*c*]pyran-7-ethanol [[(1,1-Dimethylethyl)dimethylsilyl]oxy]acetate (44, R_1 = TBDMS).** To a solution of 0.11 g (0.21 mmol) of alcohol **41a** in 0.32 mL of anhydrous methylene chloride at room temperature under argon was added 60 mg (0.31 mmol) of 2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]acetic acid followed by 65 mg (0.31 mmol) of dicyclohexylcarbodiimide and 4 mg (0.03 mmol) of (dimethylamino)pyridine. The slurry was stirred overnight at which point the solids were filtered off and washed with 50 mL of ether. The ether layer was washed with 25 mL of 1 N HCl, 25 mL of saturated $NaHCO_3$, and 25 mL of brine, dried ($MgSO_4$), and evaporated. The crude residue was purified by flash chromatography with petroleum ether–ethyl acetate (92.5:7.5) to give 118 mg (81%) of **44** as a colorless oil: $[\alpha]^{25}_D$ −21.02° (*c* 0.1760, EtOH); ^{1}H NMR (400 MHz) δ 0.06 (s, 6 H), 0.88 (s, 9 H), 1.01 (s, 9 H), 1.34 (s, 3 H), 1.47 (s, 3 H), 1.66 (d, J = 6 Hz, 1 H), 4.05 (br s, 1 H), 4.18 (s, 2 H), 5.34 (br d, J = 11 Hz, 1 H), 5.79 (m, 1 H); ^{13}C NMR (50 MHz) δ 17.74, 18.39, 19.22, 25.75, 26.48, 26.83, 28.30, 33.53, 35.33, 35.91, 59.58, 61.88, 66.33, 73.77, 74.21, 74.70, 75.81, 108.76, 127.58, 128.74, 129.53, 131.00, 133.85, 135.53, 170.92; IR ($CHCl_3$) 1751, 1672, 838, 702 cm^{-1}; mass spectrum, *m/e* (relative intensity) 681 (3), 639 (15), 581 (8), 255 (42), 75 (100). Anal. Calcd for $C_{39}H_{60}O_7Si_2$: C, 67.20; H, 8.68. Found: C, 67.00; H, 8.88.

[3a*S*-[3aα,4α,7aα,7α(3*E*,2*R)]]-6-[Tetrahydro-2,2-dimethyl-4-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-ethyl]-4*H*-1,3-dioxolo[4,5-*c*]pyran-7-yl]-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methyl-4-hexenoic Acid Methyl Ester (46a).** Lithium diisopropylamide was prepared by the addition of 0.072 mL of 2.5 M *n*-BuLi–hexane (0.18 mmol) to a solution of 0.027 mL (0.2 mmol) of diisopropylamine in 0.36 mL of dry THF at 0 °C. After 15 min at 0 °C the mixture was cooled to −78 °C and a mixture of 0.15 mL (1.2 mmol) of trimethylsilyl chloride, 0.105 mL (1.3 mmol) of dry pyridine, and 0.27 mL of THF were added, followed 5 min later by dropwise addition of 76 mg (0.11 mmol) of **44** (R_1 = TBDMS) in 0.6 mL of THF. After 15 min at −78 °C the mixture was warmed slowly to room temperature (1 h). The reaction mixture was quenched at 0 °C with 1 mL of 1 N HCl and extracted with 2 × 5 mL of ether. The organic layer was dried ($MgSO_4$) and evaporated and the residue esterified with CH_2N_2–Et_2O(0 °C). The mixture was then treated with 5 equiv of K_2CO_3 in 1 mL of MeOH at room temperature to hydrolyze the starting glycolate ester, and after acidification, extraction, and evaporation, the resulting crude oil was purified by flash chromatography with petroleum ether–ethyl acetate (92.5:7.5) to give 43 mg (55%) of **46** and the 12*R*,13*S* diastereomer followed by elution with petroleum ether–ethyl acetate (75:25) to give 15 mg of recovered **41a** (77% based on recovered **41a**). The two product diastereomers were separated by HPLC with hexanes–ethyl acetate (9:1) to give 30 mg of **46a** and 7 mg of the 12*R*,13*S* diastereomer.

46a: $[\alpha]^{25}_D$ −10.83° (*c* 0.84, EtOH); ^{1}H NMR (400 MHz) δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.09 (s, 9 H), 1.04 (d, J = 7 Hz, 3 H), 1.04 (s, 9 H), 1.36 (s, 3 H), 1.50 (s, 3 H), 3.66 (s, 3 H), 4.07 (d, J = 5 Hz, 1 H), 4.09 (m, 1 H), 5.45 (m, 2 H); ^{13}C NMR (50 MHz) δ 17.20, 18.31, 19.19, 25.72, 26.46, 26.80, 28.36, 33.89, 36.00, 36.98, 41.73, 51.47, 59.67, 65.97, 74.28, 74.69, 75.43, 76.39, 108.45, 127.55, 128.55, 129.45, 133.18, 133.94, 135.53, 173.31; IR ($CHCl_3$) 1748, 1380, 1368, 838, 702 cm^{-1}; mass spectrum, *m/e* (relative intensity) 696 (2), 653 (17), 595 (5), 255 (10), 239 (9), 135 (100). Anal. Calcd for $C_{40}H_{62}O_7Si_2$: C, 67.56; H, 8.79. Found: C, 67.52; H, 8.93.

12*R*,13*S* isomer: $[\alpha]^{25}_D$ −15.22° (*c* 0.44, EtOH); ^{1}H NMR (200 MHz) δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.89 (s, 9 H), 1.03 (s, 9 H), 1.36 (s, 3 H), 1.49 (s, 3 H), 3.66 (s, 3 H), 4.00 (d, J = 5 Hz, 1 H), 4.06 (br s, 1 H), 5.44 (m, 2 H); ^{13}C NMR (50 MHz) δ 15.42 (vs 17.20 for **46a**).

34 from 46a. To 37 mg (0.052 mmol) of **46a** in 0.3 mL of dry methylene chloride and 0.6 mL of hexanes at −78 °C was added 0.2 mL of a 1 M solution of diisobutylaluminum hydride and the resulting solution warmed to −20 °C. After 30 min, the reaction mixture was cooled back down to −78 °C and quenched with 0.04 mL of MeOH. After the mixture warmed to room temperature, 0.1 mL of brine was added, followed by 2 mL of ether and ca. 300 mg of $MgSO_4$. The slurry was stirred for 1 h, filtered (ether wash), and evaporated to 27 mg (77%) of a colorless oil: ^{1}H NMR (200 MHz) δ 0.08 (s, 6 H), 0.90 (s, 9 H), 1.00 (d, J = 7 Hz, 3 H), 1.03 (s, 9 H), 1.37 (s, 3 H), 1.50 (s, 3 H), 4.09 (m, 1 H), 5.46 (m, 2 H). To 17 mg (0.025 mmol) of the above alcohol in 0.15 mL of dry ether and 0.05 mL of acetonitrile under argon at room temperature was added 11 mg (0.043 mmol) of triphenylphosphine, 3 mg (0.043 mmol) of imidazole, 0.006 mL (0.043 mmol) of diisopropylamine, and 11 mg (0.043 mmol) of iodine. After 3 h, the triphenylphosphine oxide was filtered off (Et_2O wash) and the organic layer washed with 10% sodium thiosulfate, dried ($MgSO_4$), and evaporated to give a crude residue, which was purified by flash chromatography with petroleum ether–ethyl acetate (96:4) to give 12 mg (60%) of a colorless oil: ^{1}H NMR (200 MHz) δ 0.05 (s, 3 H), 0.08 (s, 3 H), 0.89 (s, 9 H), 0.99 (d, J = 7 Hz, 3 H), 1.04 (s, 9 H), 3.05 (d, J = 2 Hz, 1 H) 3.09 (br s, 1 H), 4.11 (m, 1 H), 5.48 (m, 2 H). Twelve milligrams (0.015 mmol) of the above iodide in 0.2 mL of 95% ethanol was stirred with a few crystals (catalytic amount) of azoisobutyronitrile and 0.012 mL (0.044 mmol) of tributyltin hydride under argon at room temperature overnight (12 h). One milliliter of 10% aqueous potassium fluoride was added and the resulting aqueous layer extracted with 3 × 5 mL of ether. The organic extracts were dried ($MgSO_4$) and evaporated to give a crude residue, which was purified by flash chromatography with petroleum ether–ethyl acetate to give 7 mg (70%) of **34** as a colorless liquid, identical by ^{1}H and ^{13}C NMR with the material prepared from Julia coupling of **28** and **40**.

[3a*S*-[3aα,4α,7aα,7α(3*Z*,2*R)]]-Tetrahydro-2,2-dimethyl-4-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-α-(1-propenyl)-4*H*-1,3-dioxolo[4,5-*c*]pyran-8-ethanol (Phenylmethoxy)acetate (48).** A sample of neat, optically pure (+)-Alpine borane was prepared by stirring 1.65 g (13.65 mmol) of 9-BBN with 2.40 mL (2.05 g, 15.01 mmol) of (+)-α-pinene (99% ee) at 65 °C under argon for 5 h. The resulting solution was added to a solution of 1.43 g (2.73 mmol) of **47** dissolved in 1.4 mL of anhydrous THF at room temperature under argon and the mixture stirred for 1 day. After the mixture was cooled to 0 °C, 1.5 mL of THF was added followed by excess acetaldehyde and the reaction mixture warmed to room temperature. The excess acetaldehyde was removed by a stream of argon and 2 mL of ether was added followed, after cooling to 0 °C, by 0.82 mL (0.83 g, 13.65 mmol) of ethanolamine. The resulting precipitate was filtered off and washed with ether and the filtrate evaporated to a crude oil, which was purified by flash chromatography with hexanes–ethyl acetate (3:1) to give 1.33 g (93%) of the alcohol as a colorless oil: $[\alpha]^{25}_D$ −22.27° (*c* 0.4400, EtOH); ^{1}H NMR (400 MHz) δ 1.04 (s, 9 H), 1.36 (s, 3 H), 1.50 (s, 3 H), 1.83 (s, 3 H), 4.09 (m, 1 H), 4.44 (m, 1 H); ^{13}C NMR (50 MHz) δ 3.54, 19.21, 26.41, 26.83, 28.27, 33.98, 35.95, 39.25, 59.64, 60.64, 66.01, 74.08, 74.94, 76.29, 80.14, 81.19, 108.70, 127.61, 129.51, 133.88, 135.54; IR ($CHCl_3$) 3605, 1380, 1370, 702 cm^{-1}; mass spectrum, *m/e* (relative intensity) 465 (3), 255 (50), 199 (100), 99 (15), 69 (58). Anal. Calcd for $C_{31}H_{42}O_5Si$: C, 71.23; H, 8.10. Found: C, 70.89; H, 8.16.

To a solution of 0.311 g (0.595 mmol) of the above alcohol in 3 mL of dry methylene under argon at room temperature were added 0.294 g (1.772 mmol) of 2-(phenylmethoxy)acetic acid, 0.183 g (0.886 mmol) of dicyclohexylcarbodiimide, and 10 mg (0.088 mmol) of (dimethylamino)pyridine. After stirring for 12 h, the mixture was filtered (ether wash) and the filtrate washed with 10 mL of 1 N HCl, 10 mL of saturated aqueous sodium bicarbonate, and 10 mL of brine. The organic layer was dried ($MgSO_4$) and evaporated to give a crude residue, which was purified by flash chromatography with petroleum ether–ethyl acetate (85:15) to give 0.339 g (85%) of the ester as a colorless oil: $[\alpha]^{25}_D$ +4.02° (*c* 0.4480, EtOH); ^{1}H NMR (400 MHz) δ 1.04 (s, 9 H), 1.37 (s, 3 H), 1.50 (s, 3 H), 1.84 (s, 3 H), 4.11 (d, J = 16 Hz, 1 H), 4.14 (d, J = 16 Hz, 1 H), 4.62 (s, 2 H), 5.58 (m, 1 H); IR ($CHCl_3$) 1752, 703 cm^{-1}; mass spectrum, *m/e* (relative intensity) 655 (1), 613 (2), 555 (4), 505 (1), 447 (10), 311 (9), 267 (8), 255 (26), 199 (25), 107 (22), 91 (100). Anal. Calcd for $C_{40}H_{50}O_7Si$: C, 71.61; H, 7.51. Found: C, 71.36; H, 7.72.

A 0.339-g (0.505 mmol) portion of the above ester was stirred with 34 mg of 5% Pd–$BaSO_4$ in 5 mL of dry pyridine at room temperature under an H_2 atmosphere. After 1 h, the mixture was filtered (methylene chloride wash) and evaporated to give a crude residue, which was purified by flash chromatography with petroleum ether–ethyl acetate (85:15) to give 251 mg (74%) of **48** as a colorless oil: $[\alpha]^{25}_D$ −21.15° (*c* 0.3451, EtOH); ^{1}H NMR (400 MHz) δ 1.04 (s, 9 H), 1.36 (s, 3 H), 1.50 (s, 3 H), 1.76 (d, *J* = 6 Hz, 3 H), 4.06 (s, 2 H), 4.09 (br s, 1 H), 4.61 (s, 2 H), 5.34 (dd, *J* = 10, 12 Hz, 1 H), 5.68 (m, 1 H), 5.80 (m, 1 H); ^{13}C NMR (50 MHz) δ 13.54, 19.19, 26.43, 26.83, 28.26, 33.44, 35.42, 36.02, 59.64, 65.95, 67.26, 68.59, 73.32, 74.49, 74.70, 76.13, 108.73, 127.54, 127.95, 127.99, 128.13, 128.45, 129.48, 133.90, 133.98, 135.52, 137.12, 169.69; IR ($cHCl_3$) 1748, 1635, 1380, 1370, 702 cm^{-1}; mass spectrum, *m/e* (relative intensity) 657 (2), 615 (20), 557 (5), 91 (100). Anal. Calcd for $C_{40}H_{52}O_7Si$: C, 71.39; H, 7.79. Found: C, 71.31; H, 7.97.

[3a*S*-[3aα,4α,7aα,7α(3*E*,2*R)]]-6-[Tetrahydro-2,2-dimethyl-4-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-4*H*-1,3-dioxolo[4,5-*c*]pyran-7-yl]-3-methyl-2-(phenylmethoxy)-4-hexanoic Acid Methyl Ester (46b).** Lithium diisopropylamide was prepared by the dropwise addition of 0.385 mL of 1.6 M *n*-BuLi–hexane (0.615 mmol) to a solution of 0.095 mL (0.675 mmol) of diisopropylamine in 1.2 mL of dry THF at 0 °C. After 15 min at 0 °C, the mixture was cooled to −78 °C and 250 mg (0.372 mmol) of glycolate ester **48** in 1.5 mL of THF was added followed 1 min later by a mixture of 0.14 mL (1.11 mmol) of trimethylsilyl chloride, 0.09 mL (1.11 mmol) of pyridine, and 1 mL of THF. After 15 min at −78 °C, the mixture was warmed slowly to room temperature (1 h). The reaction mixture was quenched at 0 °C with 5 mL of 1 N HCl and extracted with 3 × 10 mL of ether. The organic layer was dried ($MgSO_4$) and evaporated and the residue esterified with CH_2N_2–Et_2O (0 °C). The crude oil was purified by flash chromatography with petroleum ether–ethyl acetate (85:15) to give 155 mg (60%) of **46b** as well as 68 mg of the C-silylated **48**: $[\alpha]^{25}_D$ −7.42° (*c* 0.3365, EtOH); ^{1}H NMR (400 MHz) δ 1.04 (s, 9 H, 1.04 (d, 3 H, *J* = 7 Hz), 1.36 (s, 3 H), 1.50 (s, 3 H), 3.71 (s, 3 H), 3.81 (d, 1 H, *J* = 5 Hz), 4.08 (m, 1 H), 4.37 (d, 1 H, *J* = 12 Hz), 4.72 (d, 1 H, *J* = 12 Hz), 5.47 (m, 2 H); ^{13}C NMR (50 MHz) δ 17.02 (16.16),[43] 19.19, 26.40, 26.78, 28.31, 33.81, 35.98, 36.87, 40.35, 51.57, 59.68, 66.02, 72.56, 74.25, 74.64, 75.49, 82.14, 108.40, 127.51, 127.76, 127.96, 128.27, 128.79, 129.45, 133.11, 133.91, 133.95, 135.49, 137.40, 172.29; IR ($CHCl_3$) 1742, 1380, 1370, cm^{-1}; mass spectrum, *m/e* (relative intensity) 686 (M^+, 1), 255 (22), 199 (25), 91 (100). Anal. Calcd for $C_{41}H_{54}O_7Si$: C, 71.69; H, 7.92. Found: C, 71.54; H, 7.99.

[3a*S*-[3aα,4α,7aα,7α(2*E*,4*S,5*R**)]]-3-[Tetrahydro-2,2-dimethyl-7-[5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-methyl-2-hexenyl]-4*H*-1,3-dioxolopyran-4-yl]-2-propanone (50).** To a solution of 1.29 g (1.93 mmol) of **34** in 12 mL of anhydrous THF at room temperature under argon was added 2.90 mL of 1 M tetrabutylammonium fluoride–THF. After 2 h, the reaction mixture was poured into 25 mL of brine and the aqueous layer extracted with 3 × 50 mL of ether. The combined organic extracts were washed with 25 mL of brine, dried ($MgSO_4$), and evaporated to give a crude oil, which was purified by chromatography on a Waters Prep LC 500 with hexane–ethyl acetate (4:1) to give 0.58 g (70%) of a colorless oil: $[\alpha]^{25}_D$ −5.55° (*c* 0.9374, $CHCl_3$); ^{1}H NMR (400 MHz) δ 0.02 (s, 6 H), 0.87 (s, 9 H), 0.96 (d, *J* = 7 Hz, 3 H), 1.02 (d, *J* = Hz, 3 H), 1.35 (s, 3 H), 1.49 (s, 3 H), 4.11 (br s, 1 H), 5.43 (m, 2 H); ^{13}C NMR (50 MHz) δ 15.95, 18.06, 20.55, 25.84, 26.23, 28.23, 33.97, 35.71, 36.70, 44.18, 60.91, 66.40, 71.73, 74.27, 75.16, 78.30, 108.61, 127.04, 135.65; IR ($CHCl_3$) 3505, 1060, 835, cm^{-1}; mass spectrum, *m/e* (relative intensity) 159 (100), 73 (73). Anal. Calcd for $C_{23}H_{44}O_5Si$: C, 64.44; H, 10.35. Found: C, 64.25; H, 10.40.

A 639-mg (1.49 mmol) portion of the above alcohol dissolved in 7 mL of anhydrous methylene chloride was rapidly added to a slurry of 964 mg (4.47 mmol) of pyridinium chlorochromate, 964 mg of sodium acetate, 5.6 g of Celite, and 25 mL of methylene at room temperature under argon. The dark brown mixture was stirred for 1.5 h, diluted with 20 mL of ether, and stirred an additional 20 min. After the mixture was filtered through a pad of Florisil and washed with 200 mL of ether, the filtrate was washed with 100 mL of 1 N HCl and 100 mL of brine, dried ($MgSO_4$), and evaporated to give 619 mg (97%) of a light-yellow oil: ^{1}H NMR (200 MHz) δ 0.01 (s, 6 H), 0.87 (s, 9 H), 0.94 (d, *J* = 7 Hz, 3 H), 1.02 (d, *J* = 7 Hz, 3 H), 1.34 (s, 3 H), 1.49 (s, 3 H), 4.13 (br s, 1 H), 5.42 (m, 2 H), 9.78 (t, *J* = 1 Hz, 1 H). The above aldehyde (1.45 mmol) dissolved in 4 mL of anhydrous THF was added to a solution of 1.35 mL of 1.6 M methyllithium–ether and 7 mL of THF at −78 °C under argon. After 20 min, an additional 0.9 mL of 1.6 M methyllithium–ether was added and the mixture was warmed to 0 °C and stirred for 1.5 h. The reaction mixture was quenched with 10 mL of brine and warmed to room temperature, and the aqueous organic extracts were dried ($MgSO_4$) and evaporated to give a crude oil, which was purified by flash chromatography with petroleum ether–ethyl acetate (3:2) to give 456 mg (71%) of a colorless oil as a 1:1 mixture of diastereomers: $[\alpha]^{25}_D$ −8.41° (*c* 0.6775, $CHCl_3$); ^{1}H NMR (400 MHz) δ 0.02 (s, 6 H), 0.87 (s, 9 H), 0.95 (d, *J* = 7 Hz, 3 H), 1.01 (d, *J* = 7 Hz, 3 H), 1.19, 1.22 (d, *J* = 7 Hz, 3 H) 1.34 (s, 3 H), 1.49 (s, 3 H), 4.02, 4.12 (m, 1 H), 5.40 (m, 2 H); IR ($CHCl_3$) 3500, 1060, 835 cm^{-1}; mass spectrum, *m/e* (relative intensity) 385 (5), 310 (20), 295 (8), 252 (20), 235 (38), 159 (100), 73 (100). Anal. Calcd for $C_{24}H_{46}O_5Si$: C, 65.11; H, 10.47. Found: C, 64.69; H, 10.49.

To 456 mg (1.03 mmol) of 1:1 mixture of the above alcohols dissolved in 8 mL of anhydrous methylene chloride at room temperature under argon was added 1.11 g of sodium acetate followed by 1.11 g (5.15 mmol) of pyridinium chlorochromate. The dark brown slurry was stirred for 2 h and was then diluted with 10 mL of ether and stirred an additional 10 min. The mixture was filtered through a pad of florisil, washed with 200 mL of ether and evaporated to give a crude residue, which was purified by flash chromatography with petroleum ether–ethyl acetate (85:15) to give 433 mg (95%) of the ketone **50** as a colorless oil: $[\alpha]^{25}_D$ −2.05° (*c* 0.1463, EtOH); ^{1}H NMR (200 MHz) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 0.97 (d, *J* = 7 Hz, 3 H), 1.03 (d, *J* = 7 Hz, 3 H), 1.36 (s, 3 H), 1.52 (s, 3 H), 2.72 (s, 3 H), 4.15 (br s, 1 H), 5.41 (m, 2 H); IR ($CHCl_3$) 1718, 1380, 1370, 838 cm^{-1}; mass spectrum, *m/e* (relative intensity) 325 (5), 281 (2), 159 (100), 115 (34). Anal. Calcd for $C_{24}H_{44}O_5Si$: C, 65.41; H, 10.06. Found: C, 65.26; H, 9.80.

[2*S*-[2α(*E*),3β,4β,5α(2*E*,4*S,5*R**)]]-9-[[3-Methyl-1-oxo-4-[tetrahydro-3,4-dihydroxy-5-(5-hydroxy-4-methyl-2-hexenyl)-2*H*-pyran-2-yl]-2-butenyl]oxy]nonanoic Acid Methyl Ester (51).** To 97 mg of sodium hydride (60% by weight dispersion in mineral oil; 2.42 mmol, washed with hexanes) suspended in 1.5 mL of anhydrous THF at 0 °C was added 820 mg (2.42 mmol) of the phosphonate ester dissolved in 2 mL of THF. The resulting mixture was warmed to room temperature and stirred for 1 h. After the mixture was cooled back down to 0 °C, 356 mg (0.81 mmol) of ketone **50** dissolved in 2 mL of THF was added and the solution warmed to room temperature and stirred overnight. The reaction was then quenched with 5 mL of brine and the aqueous layer extracted with 2 × 10 mL of ether, dried ($MgSO_4$), and evaporated. The crude residue was purified by flash chromatography with petroleum ether–ethyl acetate (92:8) to give 470 mg (88%) of a colorless oil. Further separation by HPLC with hexane–ethyl acetate (9:1) gave 312 mg (59%) of the C-2 *E* isomer and 84 mg (16%) of the C-2 *Z* isomer.

***E* isomer**: $[\alpha]^{25}_D$ −10.10° (*c* 0.9410, $CHCl_3$); ^{1}H NMR (400 MHz) δ 0.00 (s, 3 H), 0.02 (s, 3 H), 0.87 (s, 9 H), 0.94 (d, *J* = 7 Hz, 3 H), 1.01 (d, *J* = 7 Hz, 3 H), 1.34 (s, 3 H), 1.49 (s, 3 H), 2.18 (s, 3 H), 2.28 (t, *J* = 8 Hz, 2 H), 3.66 (s, 3 H), 4.04 (t, *J* = 7 Hz, 2 H), 4.10 (br s, 1 H), 5.40 (m, 2 H), 5.74 (br s, 1 H); IR ($CHCl_3$) 1728, 1711, 1650, 838, cm^{-1}; mass spectrum, *m/e* (relative intensity) 637 (1), 608 (10), 159 (100); UV (EtOH) λ_{max} 218 nm (ε 10 600). Anal. Calcd for $C_{36}H_{64}O_8Si$: C, 66.22; H, 9.88. Found: C, 66.25; H, 9.79.

***Z* isomer**: $[\alpha]^{25}_D$ −17.47° (*c* 0.3435, $CHCl_3$); ^{1}H NMR (400 MHz) δ 0.01 (s, 3 H), 0.03 (s, 3 H), 0.89 (s, 9 H), 0.96 (d, *J* = 7 Hz, 3 H), 1.03 (d, *J* = 7 Hz, 3 H), 1.35 (s, 3 H), 1.51 (s, 3 H), 1.96 (s, 3 H), 2.31 (t, *J* = 7 Hz), 3.67 (s, 3 H), 4.06 (m, 2 H), 4.11 (m, 1 H), 5.43 (m, 2 H) 5.76 (br s, 1 H); IR ($CHCl_3$) 1725, 1710, 838, cm^{-1}; mass spectrum, *m/e* (relative intensity) 637 (1), 608 (10), 595 (8), 159 (100), 115 (13); UV (MeOH) λ_{max} 215 nm (ε 11 040). Anal. Calcd for $C_{36}H_{64}O_8Si$: C, 66.22; H, 9.88. Found: C, 66.28; H, 10.01.

(43) δ 16.16 is the value for the C-12 methyl carbon of the corresponding syn (12*R*,13*S*) diastereomer prepared by chelation-controlled Claisen rearrangement of the benzyl-protected glycolate ester of **41a** (R = Me).

A solution of 765 mg (1.17 mmol) of the above *E* ester in 30 mL of 80% aqueous acetic acid was stirred at room temperature overnight. The reaction was evaporated to dryness (high vacuum, room temperature) to give an oil, which was dissolved in 25 mL of ether. One milliliter of saturated sodium bicarbonate was added and the mixture stirred vigorously for 1 h. $MgSO_4$ was then added and the reaction mixture filtered and evaporated to give a crude residue, which was purified by flash chromatography with ethyl acetate–hexanes (3:1) to give 460 mg (80%) of **51** as a colorless oil: $[\alpha]^{25}_D$ +11.9° (*c* 0.27, $CHCl_3$); ^1H NMR (400 MHz) δ 0.99 (d, *J* = 7 Hz, 3 H), 1.15 (d, *J* = 7 Hz, 3 H), 2.23 (s, 3 H), 2.31 (t, *J* = 8 Hz, 2 H), 3.68 (s, 3 H), 4.08 (t, *J* = 8 Hz, 2 H), 5.47 (m, 2 H), 5.76 (br s, 1 H); ^{13}C NMR (50 MHz) δ 16.62 (C-17), 19.07 (C-15), 20.33 (C-14), 24.80 (C-3′), 25.91 (C-7′), 28.64 (C-8′), 29.04 (C-4′,5′,6′), 32.29 (C-9), 34.07 (C-2′), 41.86 (C-8), 43.08 (C-4), 44.67 (C-12), 51.46 (OMe), 63.78 (C-9′), 64.83 (C-16), 68.84 (C-6), 70.29 (C-7), 71.15 (C-13), 74.69 (C-5), 117.53 (C-2), 129.40 (C-10), 134.41 (C-11), 156.82 (C-3), 166.79 (C-1), 174.38 (C-1′); IR ($CHCl_3$) 3650, 3560, 1725, 1711, 1650 cm^{-1}; mass spectrum, *m/e* (relative intensity) 454 (10), 266 (75), 82 (100); UV (EtOH) λ_{max} 218 nm (ε 10620). Anal. Calcd for $C_{27}H_{46}O_8$: C, 65.03; H, 9.30. Found: C, 64.72; H, 9.20.

[2*S*-[2α(*E*),3β,4β,5α(2*E*,4*S,5*R**)]]-9-[[3-Methyl-1-oxo-4-[tetrahydro-3,4-dihydroxy-5-(5-hydroxy-4-methyl-2-hexenyl)-2*H*-pyran-2-yl]-2-butenyl]oxy]nonanoic Acid (Pseudomonic Acid C; 1c).** To a solution of 50 mg (0.1 mmol) of **51** in 1 mL of absolute ethanol and 1 mL of THF at 0 °C were added 1 mL of 1 N aqueous $NaHCO_3$ and 1 mL of 1 N aqueous KOH followed 5 min later by an additional 1 mL of 1 N KOH. After 4.5 h at 0 °C, the mixture was poured into 25 mL of rapidly stirring 1 N HCl at 0 °C, salted with solid NaCl, and extracted with 5 × 25 mL of ethyl acetate. The combined organic extracts were dried ($NaSO_4$) and evaporated to give a crude residue, which was purified by flash chromatography with methylene chloride–methanol (95:5 then 90:10) to give 37 mg (77%) of pseudomonic acid C as a colorless, viscous oil: $[\alpha]^{25}_D$ +7.64° (*c* 0.78, $CHCl_3$); ^1H NMR (200 MHz) δ 0.98 (d, *J* = 7 Hz, 3 H), 1.15 (d, *J* = 6 Hz, 3 H), 2.20 (s, 3 H), 2.29 (t, *J* = 7 Hz, 2 H), 4.08 (t, *J* = 6 Hz, 2 H), 5.45 (m, 2 H), 5.76 (br s, 1 H); ^{13}C NMR (50 MHz) δ 16.69, 19.12, 20.33, 24.62, 25.82, 28.46, 28.66, 28.75, 28.84, 32.29, 33.85, 41.83, 42.92, 44.73, 63.78, 64.83, 68.89, 70.34, 71.25, 74.75, 117.53, 129.54, 134.44, 156.77, 166.80, 178.10. Anal. Calcd for $C_{26}H_{44}O_8$: C, 64.44; H, 9.15. Found: C, 64.11; H, 9.29.

Registry No. **1c**, 71980-98-8; **11**, 49826-00-8; **12**, 54483-22-6; **13**, 115118-71-3; **14**, 107148-21-0; **19**, 107148-20-9; **16**, 115118-72-4; **16** (diol), 115183-63-6; **17**, 107148-22-1; **18**, 115118-73-5; **19** (epimer 1), 115118-74-6; **19** (epimer 2), 115118-75-7; **20a**, 115118-76-8; **20b**, 107148-23-2; **22a**, 115118-79-1; **22b**, 115118-78-0; **23a**, 115118-77-9; **24**, 115183-64-7; **25**, 115183-65-8; **26**, 115140-92-6; **27**, 107148-24-3; **27** (de-isopropylidinyl diol), 115118-80-4; **28**, 107148-25-4; **29**, 115118-81-5; **30**, 115118-82-6; (*E*)-**34**, 107148-28-7; (*Z*)-**34**, 115183-66-9; **34** (6-ol), 115118-88-2; **34** (6-iodo derivative), 115118-89-3; **34** (2-ol), 115118-90-6; **34** (2-al), 115118-91-7; **36**, 78088-28-5; **37**, 85576-58-5; **39**, 115118-83-7; **39** (1-ol), 85576-59-6; **40**, 115118-85-9; **41a**, 107148-26-5; **41b**, 107241-79-2; **44**, 115118-87-1; (12*R*,13*R*)-**46a**, 107148-27-6; (12*R*,13*S*)-**46a**, 115183-67-0; **46b**, 107148-32-3; **47**, 107148-29-8; **47** (reduced), 107148-30-1; **47** (reduced, phenylmethoxyacetate), 115140-93-7; **48**, 107148-31-2; **50**, 89726-74-9; **50** (reduced, diastereomer-1), 115118-92-8; **50** (reduced, diastereomer-2), 115183-68-1; **51**, 72042-22-9; (C-2*E*)-**51** (C-6,7-di-*O*-isopropylidene, C-13-*O*-TBDMS derivative), 89726-76-1; (C-2*Z*)-**51** (C-6,7-di-*O*-isopropylidene, C-13-*O*-TBDMS derivative), 115183-69-2; $CH_3C(OMe)_2NMe_2$, 18871-66-4; $CH_3C{\equiv}CH$, 74-99-7; $HOCH_2COOH$, 79-14-1; $HOCH_2COOCH_2Ph$, 30379-58-9; *t*-$BuMe_2SiOCH_2COOCH_2Ph$, 115118-86-0; *t*-$BuMe_2SiOCH_2COOH$, 105459-05-0; $(MeO)_2P(O)CH_2CO_2(CH_2)_8COOMe$, 92516-83-1; 3,5-hexadienoyl chloride, 108306-38-3; (*R*)-(+)-α-phenethylamine, 3886-69-9; (2*S*,3*S*)-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methyl-1-iodobutane, 115118-84-8.

Stereoselective Total Synthesis of (±)-Saframycin B

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A 20-step total synthesis of (±)-saframycin B (**2**) from (*Z*)-1-acetyl-3-arylidene-6-(arylmethyl)-2,5-piperazinedione **11** is described. Conversion of **11** to the imide **17a** was followed by 1,2-reduction with lithium tri-*tert*-butoxyaluminum hydride in a highly regioselective manner, and this was then cyclized to (*E*)-1,5-imino-3-benzazocine **19a** with isomerization of the double bond. The intermediate **19a** was efficiently converted to the *N*-methyl tricyclic lactam **26**, the structure of which was determined by X-ray crystallography. Conversion of **26** to the amine **13** and subsequent stereoselective intramolecular cyclization through its *O*,*N*-acetal **30** provided 9-*epi*-pentacyclic ester **31**. Epimerization took place in **31** at the C-9 position to the desired ester **34**, which was transformed to the pyruvamide **39** in a four-step sequence. Finally, **39** was subjected to two-step oxidative demethylation to provide (±)-saframycin B (**2**).

Saframycin B (**2**)[1a] is a novel antitumor antibiotic discovered in the culture broths of *Streptomyces lavendulae*[2] along with saframycins A (**1**),[1b] C (**3**),[1a] and D (**4**).[1c] Over the last several years the additional saframycin derivatives, namely, safracins A (**5**) and B (**6**),[3] renieramycins A (**7**) and C (**8**),[4] and saframycins MX 1 (**9**) and Mx 2 (**10**),[5] have been independently isolated from bacterial sources and marine sponges (Chart I). Saframcyins are highly active against gram-positive bacteria and exhibit antitumor activities. Among this group, saframycin A (**1**) has been shown to possess the highest antitumor activity against various tumors including P388 leukemia and Ehrlich ascites tumor.[6] The structure of **2** was elucidated by comparing its spectroscopic data with those of saframycin C

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