1710, 1405, 1250, 1195, 1085, 835, 875; ^{1}H NMR (300 MHz, C_6D_6) δ 9.81 (d, J = 2.0 Hz, 1 H), 3.28 (s, 3 H), 3.17 (d, J = 9.8 Hz, 1 H), 3.1 (d, J = 9.7 Hz, 1 H), 3.14–3.00 (m, 1 H), 2.95–2.87 (m, 1 H), 2.54 (d, J = 16.3 Hz, 1 H), 2.44 (d, J = 16.3 Hz, 1 H), 2.30–1.29 (series of m, 11 H), 0.93 (s, 9 H), 0.73 (s, 3 H), 0.00 (s, 6 H); MS m/z ($M^+ - C_4H_9$) calcd for $C_{18}H_{30}BrO_4Si$ 417.1097, obsd 417.1095.

Finkelstein Reaction and Acetalization of 69. Bromide **69** (11 mg, 0.023 mmol) was dissolved in 1 mL of acetone and treated with sodium iodide (35 mg, 0.23 mmol) at room temperature for 12 h. The mixture was diluted with pentane and filtered. The filtrate was concentrated, and the residual oil was redissolved in trimethyl orthoformate (1 mL). Amberlyst-15 ion exchange resin (20 mg) was introduced, and the mixture was stirred for 4 h. Filtration and concentration gave a cloudy oil, which was purified by silica gel chromatography (elution with 5% ethyl acetate in petroleum ether) to provide 10 mg (77%, overall yield) of **71** as a colorless oil: IR (neat, cm^{-1}) 2950, 2920, 2840, 1730, 1405, 1250, 1090, 830, 770; ^{1}H NMR (300 MHz, C_6D_6) δ 4.58 (d, J = 7.3 Hz, 1 H), 3.38 (s, 3 H), 3.31 (d, J = 9.6 Hz, 1 H), 3.22 (s, 3 H), 3.19 (d, J = 9.7 Hz, 1 H), 3.18 (s, 3 H), 2.94–2.89 (m, 1 H), 2.73–2.64 (m, 1 H), 2.50 (s, 2 H), 2.40 (t, J = 9.2 Hz, 1 H), 2.07 (dd, J = 6.1, 10.5 Hz, 1 H), 1.97–1.21 (series of m, 8 H), 0.97 (s, 9 H), 0.86 (s, 3 H), 0.04 (s, 6 H); MS m/z ($M^+ - C_4H_9$) calcd for $C_{20}H_{35}IO_5Si$ 511.1376, obsd 511.1346.

Acknowledgment. This work was supported by PHS Grant GM 28468. We also thank George Maynard for performing the molecular mechanics calculations and Professor Kosta Steliou for making available the necessary programs. The X-ray analysis was carried out by Dr. Judith Gallucci in our departmental facility. Mass spectra were recorded by Dick Weisenberger and David Chang of the Campus Chemical Instrument Center at The Ohio State University.

Supplementary Material Available: Experimental procedures for the preparation of **15**, **17–20**, **25**, **26**, **28**, **29**, and the dimer of **35b**, as well as details of the X-ray analysis of **56**. Labeling scheme and tables of bond distances, bond angles, positional parameters, anisotropic thermal parameters, calculated positional parameters, and torsion angles for **56** (16 pages). Ordering information is given on any current masthead page.

Formal Synthesis of (–)-Calcimycin (A-23187) via the 3-Methyl-γ-butyrolactone Approach

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A synthesis of (+)-carboxylic acid **2a**, which has been previously converted into the ionophore (–)-calcimycin (A-23187) and analogues thereof, is described. The synthesis involves the use of (*S*)-3-methyl-γ-butyrolactone (**4**) and both enantiomers of allylic alcohol **3a** as the chiral entities.

The antibiotic calcimycin (A-23187, **1a**)[1] is representative of a structurally similar group of divalent ionophores that includes cezomycin (3-demethylaminocalcimycin, **1b**),[2] AC-7230 (3-demethylamino-3-hydroxycalcimycin, **1c**),[3] and X-14885A (3-demethylamino-15-demethyl-3-hydroxycalcimycin, **1d**).[4] The ionophore calcimycin forms a 2:1 monohydrated complex with calcium ion (X-ray)[5,6] that is believed to account for its ability to transport calcium ions across cell membranes[7] and unilaminar vesicles,[8] and through aqueous–organic phases.[9] The biological importance of calcimycin and its unique array of chelating heterocyclic rings and spiroketal nucleus have inspired successful routes to its synthesis.[10] Moreover, the degradation of calcimycin to the carboxylic acid **2a**[11] has expedited the synthesis of benzoxazole derivatives of the ionophore[11,12] as well as serving as an advanced intermediate in the synthesis of calcimycin itself.[10d,f]

We chose to examine the applicability of our 3-methyl-γ-butyrolactone strategy[13] for the synthesis of polypropionates to the carboxylic acid **2a**. The lactone *ent*-**7**[14] had been prepared previously[15] by this method. Accordingly, lactone **7** was available by linear iteration (Scheme I) of (*S*)-3-methyl-γ-butyrolactone (**4**) with

(1) Chaney, M. O.; Demarco, P. V.; Jones, N. D.; Occolowitz, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 1932.
(2) David, L.; Kergomard, A. *J. Antibiot.* **1982**, *32*, 1409.
(3) The stereochemistry of AC-7230 has not been determined. Yaginuma, S.; Awata, M.; Muto, N.; Kinoshita, K.; Mizuno, K. *J. Antibiot.* **1987**, *40*, 239.
(4) (a) Liu, C.-M.; Chin, M.; La T. Prosser, B.; Palleroni, N. J.; Westley, J. W.; Miller, P. A. *J. Antibiot.* **1983**, *36*, 1118. (b) Westley, J. W.; Liu, C.-M.; Blount, J. F.; Sello, L. H.; Troupe, N.; Miller, P. A. *Ibid.* **1983**, *36*, 1275.
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(6) The X-ray structure of the 2:1 magnesium complex of calcimycin has been determined. Alleaume, M.; Barrans, Y. *Can. J. Chem.* **1985**, *63*, 3482.
(7) Pfeiffer, D. R.; Lardy, H. A. *Biochemistry* **1976**, *15*, 935.
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(10) (a) Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789. (b) Martinez, G. R.; Grieco, P. A.; Williams, E.; Kanai, K.; Srinivasan, C. V. *J. Am. Chem. Soc.* **1982**, *104*, 1436. (c) Grieco, P. A.; Williams, E.; Tanaka, H.; Gilman, S. *J. Org. Chem.* **1980**, *45*, 3537. (d) Nakahara, Y.; Fujita, A.; Beppu, K.; Ogawa, T. *Tetrahedron* **1986**, *42*, 6465. (e) Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1987**, *28*, 1063. (f) Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 7553.
(11) Prudhomme, M.; Jeminet, G. *Experientia* **1983**, *39*, 256.
(12) (a) Prudhomme, M.; Dauphin, G.; Guyot, J.; Jeminet, G. *J. Antibiot.* **1984**, *37*, 627. (b) Prudhomme, M.; Dauphin, G.; Jeminet, G. *Ibid.* **1986**, *39*, 922. (c) Prudhomme, M.; Guyot, J.; Jeminet, G. *Ibid.* **1986**, *39*, 934.
(13) Ziegler, F. E.; Kneisley, A.; Thottathil, J. K.; Wester, R. T. *J. Am. Chem. Soc.* **1988**, *110*, 5434.
(14) All structures are the enantiomers shown unless noted otherwise.
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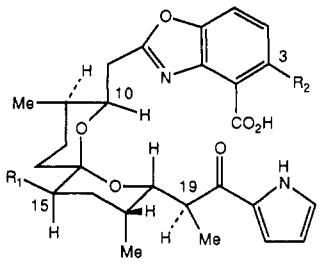
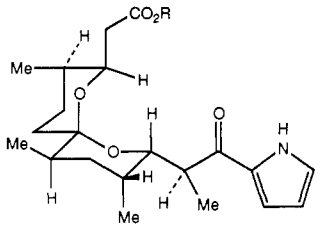
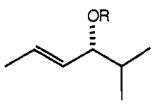


1a, R_1 = Me, R_2 = NHMe
b, R_1 = Me, R_2 = H
c, R_1 = Me, R_2 = OH
d, R_1 = H, R_2 = OH



2a, R = H
b, R = t-Bu
c, R = Me

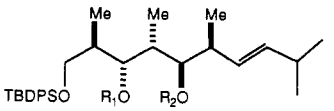


3a, R = H
b, R = $PO(OEt)_2$

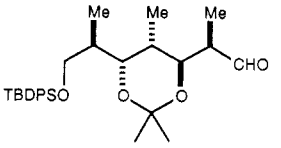
(*S*)-alcohol *ent*-**3a** via the Claisen rearrangement to produce lactone **6** that in turn was converted by palladium-mediated alkylation with phosphate **3b** to a mixture of trans lactone **7** and cis lactone **8**. Although the final operation of Scheme I provided a mixture of the two lactones, they were readily separated. Equilibration of the cis lactone **8** with t-BuOK/t-BuOH gave a 3:1 (**7**:**8**) mixture. Moreover, kinetic protonation of the lithium enolate of lactone **7** provided a 95:5 ratio of the cis to trans lactones, respectively. The ^1H NMR spectra of the two diastereomers were identical with those of their respective enantiomers. The absolute stereochemistries of the centers bearing the three methyl groups and lactone oxygen in **7** and **8** correspond to C_{15} and C_{17}–C_{19} of calcimycin.

Although either lactone **7** or lactone **8** could, in principle, be used for the realization of the goal at hand, the advanced intermediates derived from the cis lactone **8** proved to be unacceptable. Accordingly, trans lactone **7** was subjected to a formal Baeyer–Villiger oxidation (Criegee sequence)[13] that provided the diol **9a** in 35% yield. The initial step of the sequence involves the reaction of methyllithium with lactone **7** (cf. Scheme I). Unfortunately, both desired addition to the carbonyl and unwanted enolization of the lactone occurred to the same extent. The recovered cis lactone was epimerized to the trans isomer and was recycled. The diol **9a** was uneventfully converted to the acetonide **9b** followed by ozonolysis of the olefin to produce the aldehyde **10**. The use of dimethyl sulfide as a reducing agent for the ozonolysis was less effective than $LiAlH_4$ reduction followed by Swern oxidation.[16] By this route the aldehyde **10** was prepared from the diol in 75% yield.

The potential carbon atoms C_{10}–C_{14} of calcimycin were available from the (*R*)-alcohol **3a**. An orthoacetate Claisen rearrangement[17] of the alcohol **3a** followed by $LiAlH_4$ reduction of the resultant ester provided alcohol **11b**, which was converted to the bromide **11c** via the mesylate. Efforts to prepare the Grignard reagent of the bromide were unrewarding as reductive coupling of the bromide proved to be a competing reaction which was not ameliorated by using conditions of dilute, slow addition of the halide to the magnesium. In an effort to conserve the halide, a different approach was employed. The sulfone **11d**, which was prepared from the bromide, was metalated with *n*-butyllithium, and the resultant anion was added to the aldehyde to produce a mixture of four β-hydroxy sulfones. Chromatography failed to separate the hydroxy sulfones from one another and from recovered sulfone **11d**. The chromatographed mixture was directly oxidized under Swern conditions, and the derived keto sulfones were subjected to reductive desulfonation with sodium amalgam[18] to provide the keto olefin **12** in 59% yield.



9a, R_1 = R_2 = H
b, R_1, R_2 = CMe_2



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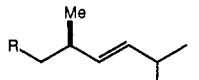
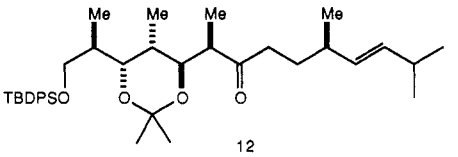
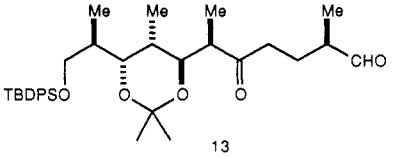


11a, R = CO_2Me
b, R = CH_2OH
c, R = CH_2Br
d, R = CH_2SO_2Ph



12



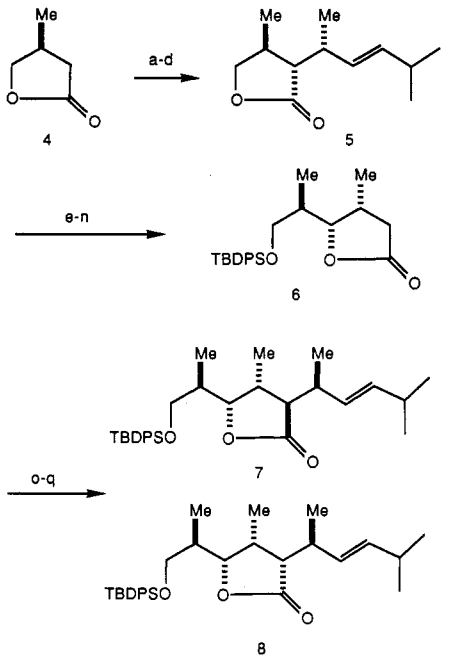
13

Ozonolysis of olefin **12** provided keto aldehyde **13** that set the stage for the introduction of the acetic acid residue present in acid **2a**. This goal was realized via the selective addition of the lithium enolate of *tert*-butyl acetate[19] to the aldehyde group; unfortunately, the syn adduct **14**, whose stereochemistry would be revealed later, was only marginally favored over the anti adduct **15** (56:44). Attempts to improve the stereoselectivity by using zinc enolates, additives (HMPA), or *tert*-butyldimethylsilyl *tert*-butyl keteneacetal in the presence of $TiCl_4$ offered no improvement in stereoselectivity.[20]

Chromatographic and spectroscopic data suggested that the syn β-hydroxy ester **14** is in the open form while the anti isomer **15** exists as the hemiketal. β-Hydroxy ester

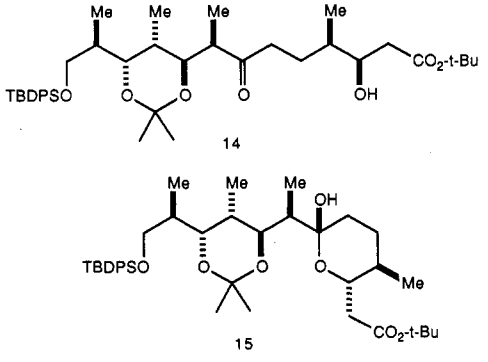
(16) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(17) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-t.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.
(18) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.
(19) Rathke, M. W.; Sullivan, D. F. *J. Am. Chem. Soc.* **1973**, *95*, 3050.
(20) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.

Scheme I[a]

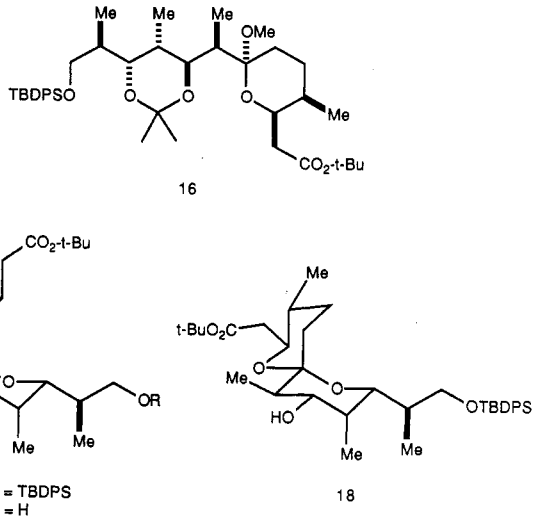


[a] Reagents: (a) $Et_3O^+BF_4^-$; (b) EtONa, EtOH; (c) *ent*-**3a**, toluene, pivalic acid, reflux; (d) t-BuOK, t-BuOH; (e) MeLi; (f) H_2O_2, H^+; (g) Ac_2O; (h) $LiAlH_4$; (i) $Me_2C(OMe)_2$, H^+; (j) O_3; $LiAlH_4$; (k) TsCl, pyr; (l) NaCN, DMSO; (m) HCl, MeOH; (n) *tert*-butyldiphenylsilyl chloride, imidazole, DMF; (o) LDA, $NCCO_2Me$, THF; (p) NaH; **3b**, $(Ph_3P)_4Pd$, Ph_3P, THF: (q) LiCl, DMSO/H_2O.

14 proved to be more polar than **15** [R_f = 0.25 vs 0.53 (20% EtOAc/hexane)]. While the infrared carbonyl region of both compounds showed unresolved absorptions at 1711 and 1718 cm^{-1}, respectively, the former compound had the more intense absorption relative to the C–H region. In addition, the diastereotopic methylene protons adjacent to the ester group appeared as well-resolved signals [δ 2.50 (J = 15.5, 4.0 Hz) and δ 2.30 (J = 15.5, 7.4 Hz)] in hemiketal **15** as they did in all subsequent cyclized structures derived from **14** and **15**; the same signals in **14** were unresolved multiplets.



The spiroketalization of **14** and **15** proved instructive. In the former case, intermediates in the cyclization could be isolated and characterized. Treatment of β-hydroxy ester **14** with *p*-toluenesulfonic acid in methanol at 0 °C for 2 h gave rise to the ketal **16**; prolonged exposure for 6 h at 25 °C provided the dihydroxy spiroketal **17b**. When the reaction mixture was monitored by TLC during the period at ambient temperature, it was evident that **17b** was arising from silyl ether **17a** and that this reaction was occurring while unreacted acetonide **16** was still present. Alternatively, when hemiketal **15** was exposed to the same catalyst system (0 °C, 1 h; 25 °C, 1 h), the spiroketal **18** was formed completely. When this experiment was also conducted at 25 °C for 6 h, desilylation occurred to the extent of 50%.

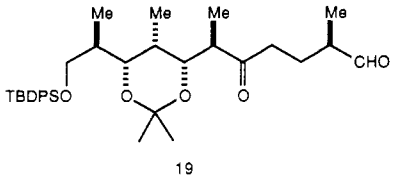


The ^1H NMR spectra of **17b** and **18** readily revealed their lineage. The C_{10} proton of **17b** appeared at δ 4.19 as a doublet of triplets (J = 10.3, 2.8, 2.8 Hz) requiring this proton and the vicinal methine proton to be cis to one another with the anomeric effect operative in both rings. On the other hand, the C_{10} proton of **18** was a triplet of doublets (J = 8.7, 8.7, 3.8 Hz) at δ 3.85, which requires a large coupling constant to the vicinal methine proton, i.e., the substituents are equatorial. An NOE experiment conducted on **18** displayed an enhancement of both the C_{10} methine proton and that diastereotopic proton at C_9 (δ 2.45) that had the 3.8-Hz coupling constant to the C_{10} proton upon irradiation of the C_{11} methyl group. Consequently, spiroketal **18** has only a single anomeric effect.

The secondary, equatorial hydroxyl group of **17** was a critical choice in realizing the spiroketal. Earlier experiments that began with the cis lactone **8** led to dehydration of the axial alcohol. Typical of these experiments was the attempted spiroketalization of keto aldehyde **19** that led to a product assigned structure **20** on the strength of a ^1H NMR spectrum that revealed a single methoxy group, three methyl doublets, and a trisubstituted olefin bearing a methyl group. This elimination may have been facilitated by the Ferrier mechanism[21] operating through a 4-hydroxydihydropyran. Such an elimination was not observed during the formation of spiroketals **17** or **18**. However, this negative evidence does not preclude the intercedence of dihydropyrans during the spirocyclization. Any concern for epimerization at the center of asymmetry adjacent to the ketal carbon was unwarranted as epimerization of this methyl group to the equatorial position was at the heart of the Evans' route to calcimycin.[10a]

The primary hydroxyl group of spiroketal **17b** was reconverted to silyl ether **17a** followed by radical deoxygenation via the phenylthionocarbonate[22] to give rise to the spiroketal **21a** in 58% yield. Tetra-*n*-butylammonium fluoride smoothly liberated the primary alcohol **21b** from the silyl ether **21a**. Oxidation of the primary alcohol to the acid **22a** was accomplished effectively with RuO_2/KIO_4. The pyrrole nucleus was installed as previously described[10d,f] via the 2-pyridylthio ester **22b** and the cuprous salt of pyrrole to provide the *tert*-butyl ester **2b**.

(21) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443.
(22) (a) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 933. (b) Robins, M. J.; Wilson, J. S.; Hansske, F. *Ibid.* **1983**, *105*, 4059.



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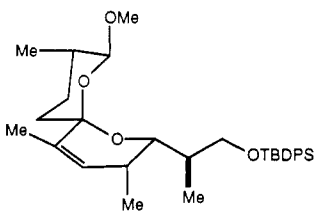

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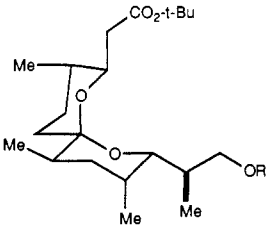
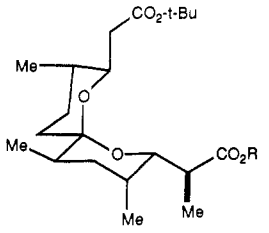


21a, R = TBDPS
b, R = H



22a, R = H
b, R = 2-pyridylthio

Exposure of the ester to trifluoroacetic acid provided carboxylic acid **2a** whose ^{1}H NMR spectrum was similar to, but not identical with, the carboxylic acid prepared from degradation of calcimycin.[11,23] Indeed, the solution ^{1}H NMR spectrum was shown to be concentration-dependent; the possibility of the presence of capricious cations was eliminated by washing the NMR samples with aqueous EDTA. The identity of the *tert*-butyl esters was confirmed by ^{1}H NMR spectroscopy after esterification of the degradation acid with *tert*-butyl alcohol by the method of Mukaiyama[24] or by decomposing the degradation reaction mixture with *tert*-butyl alcohol. Moreover, the derived (CH_2N_2) methyl esters were identical by ^{1}H NMR analysis and the same as the spectrum of a sample of methyl ester **2c** prepared from carboxylic acid **2a** that had been transformed into (−)-calcimycin by Boeckman.[10f]

Experimental Section

All reactions were performed in flame-dried glassware under N_2 unless otherwise noted. Diethyl ether and THF were distilled from sodium benzophenone ketyl under N_2. Diisopropylamine, pyridine, toluene, hexane, CH_2Cl_2, Et_3N, t-BuOH, and dimethyl sulfoxide (DMSO) were distilled from CaH_2. Acetic anhydride and hexamethylphosphoramide (HMPA) were distilled prior to use. All other reagents were used as received. Workup means drying organic extracts over anhydrous $MgSO_4$, filtration, and concentration in vacuo. Flash chromatography employed Baker SiO_2 (~40 μm). Microanalyses were within 0.4%. Title compounds were judged to be >95% pure by ^{1}H NMR spectroscopy. IUPAC numbering is used in compound names; calcimycin numbering is used to designate protons in ^{1}H NMR spectra.

4(*R*)-Methyl-5(*S*)-[1(*R*)-methyl-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]dihydro-2(3*H*)-furanone (6) was prepared as described previously for the enantiomer:[13] mp 83–84 °C (Et_2O/pentane); IR ($CHCl_3$) 1774 cm^{-1}; ^{1}H NMR;[13] $[\alpha]_D$ +33.2° (*c* 1.00, $CHCl_3$). Anal. ($C_{24}H_{32}O_3Si$) C, H.

3(*R*)-[1(*S*),4-Dimethyl-2(*E*)-pentenyl]-4(*R*)-methyl-5-(*S*)-[1(*R*)-methyl-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-dihydro-2(3*H*)-furanone (7) and 3(*S*)-[1(*S*),4-dimethyl-2-(*E*)-pentenyl]-4(*R*)-methyl-5(*S*)-[1(*R*)-methyl-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]dihydro-2(3*H*)-furanone (8) were prepared as previously described for the enantiomers.[15] Trans lactone 7: IR ($CHCl_3$) 1753 cm^{-1}; ^{1}H NMR;[15] $[\alpha]_D$ −16.4° (*c* 1.04, $CHCl_3$). Anal. ($C_{31}H_{44}O_3Si$) C, H. Cis lactone 8: IR ($CHCl_3$) 1767 cm^{-1}; ^{1}H NMR;[15] $[\alpha]_D$ + 3.3° (*c* 1.01, $CHCl_3$). Anal. ($C_{31}H_{44}O_3Si$) C, H.

1-[(*tert*-Butyldiphenylsilyl)oxy]-2(*R*),4(*R*),6(*S*),9-tetramethyldec-7(*E*)-ene-3(*R*),5(*R*)-diol (9a). To a solution of trans lactone 7 (2.48 g, 5.0 mmol) in 83 mL of Et_2O at 0 °C was added MeLi (6.07 mL, 1.4 M MeLi in Et_2O, 2.58 mmol) dropwise over 5 min. The solution was stirred at 0 °C for 3 h and then poured into saturated aqueous $NaHCO_3$, extracted (Et_2O), dried over Na_2CO_3, and concentrated to give a mixture (3.02 g) of unreacted trans lactone 7, cis lactone 8, and desired hemiketals: ^{1}H NMR (250 MHz, partial, $CDCl_3$) δ 1.43 (3 H, s, hemiketal Me). To a 0 °C solution of crude hemiketals (3.02 g) in THF (89 mL) was added 30% aqueous hydrogen peroxide (57 mL) and then acetic acid (1.5 mL) dropwise over 30 min. The solution was allowed to warm to room temperature and then to stir for 15 h. The solution was poured over saturated aqueous $NaHCO_3$, extracted (hexane), and worked up to give 2.61 g of crude hydroperoxy hemiketals: ^{1}H NMR (250 MHz, partial, $CDCl_3$) δ 7.50 (1 H, br s, OOH). Without further purification the hydroperoxy hemiketals were dissolved in 27 mL of CH_2Cl_2, and triethylamine (1.41 g, 13.9 mmol) and 4-(dimethylamino)pyridine (0.06 g, 0.5 mmol) were added. The solution was cooled to 0 °C, and acetic anhydride (1.42 g, 13.9 mmol) was added dropwise over 5 min. The solution was stirred for 1 h at 0 °C and for 2.5 h at room temperature, diluted to 490 mL with CH_2Cl_2, and heated at 40 °C overnight. The solution was cooled to room temperature, diluted with ether, washed (5% aqueous HCl, saturated aqueous $NaHCO_3$, H_2O), and worked up to give 2.85 g of crude acetates. The acetates were dissolved in 29 mL of CH_2Cl_2, and triethylamine (3.72 g, 36.8 mmol) and 4-(dimethylamino)pyridine (0.08 g, 0.66 mmol) were added. The solution was cooled to 0 °C, and acetic anhydride (3.75 g, 36.8 mmol) was added dropwise over 5 min. The solution was stirred for 1 h at 0 °C, 16 h at room temperature and then was diluted with ether, washed (5% aqueous HCl, saturated aqueous $NaHCO_3$, H_2O), and worked up. Flash chromatography (10% EtOAc/hexane) gave 1.08 g of impure diacetate, 0.957 g (1.94 mmol) of cis lactone 8, and 0.429 g (0.87 mmol) of trans lactone 7. Diacetate of **9a**: ^{1}H NMR (250 MHz, partial, $CDCl_3$) δ 1.82 (3 H, s), 1.98 (3 H, s), 2.63 (1 H, m), 3.48 (2 H, m), 4.75 (1 H, t, J = 6.7 Hz), 5.08 (1 H, dd, J = 10.0, 1.5 Hz), 5.22 (1 H, ddd, J = 15.6, 7.7, 0.9 Hz), 5.47 (1 H, dd, J = 15.6, 6.3 Hz). To a −78 °C solution of impure diacetate (1.08 g) in CH_2Cl_2 (45 mL) was added DIBAL (9.85 mL of 1.0 M DIBAL in hexanes, 9.85 mmol). The solution was stirred at −78 °C for 1 h, MeOH (15 mL) was added dropwise, and the solution was allowed to warm to room temperature. The mixture was diluted with ether and shaken with saturated K–Na tartrate until the emulsion cleared (~10 min). The layers were separated, and the aqueous phase was extracted (Et_2O). The combined organic layers were worked up and chromatographed (12% EtOAc/hexane) to give 0.68 g of near pure diol (trace of diastereomer) and 78.8 mg of pure diol (combined yield: 0.76 g, 1.78 mmol; 35% from lactone 7, 92% including recovered lactones): IR ($CHCl_3$) 3451, 2965 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.61 (3 H, d, J = 6.9 Hz), 0.93 (3 H, d, J = 6.7 Hz), 0.95 (3 H, d, J = 6.8 Hz), 1.05 (3 H, d, J = 6.6 Hz), 1.07 (9 H, s), 1.13 (3 H, d, J = 6.6 Hz), 1.85 (2 H, m), 2.22 (1 H, m), 2.40 (1 H, m), 3.26 (1 H, td, J = 8.3, 3.7 Hz), 3.45 (1 H, br d, J = 7.6 Hz), 3.65 (1 H, m), 3.75 (1 H, dd, J = 10.2, 4.1 Hz), 4.05 (1 H, br d, J = 9.4 Hz), 4.31 (1 H, br s), 5.18 (1 H, dd, J = 15.5, 8.5 Hz), 5.41 (1 H, dd, J = 15.5, 6.6 Hz), 7.45 (6 H, m), 7.69 (4 H, m); $[\alpha]_D$ −33.9° (*c* 1.0, $CHCl_3$). Anal. ($C_{30}H_{46}O_3Si$) C, H.

Acetonide of Diol 9a (9b). A solution of diol **9a** (0.76 g, 1.76 mmol) and *p*-TsOH (0.034 g, 0.18 mmol) in 92 mL of 2,2-dimethoxypropane was stirred for 14 h at room temperature. The solution was diluted with Et_2O, washed (saturated aqueous

(23) The degradation procedure (cf., ref 11) involves hydrolysis of calcimycin to the amide (aqueous HCl), treatment with oxalyl chloride, and aqueous workup to give **2a**. Charette, A. B., Ph.D. Thesis, Rochester, 1987. Workup with *tert*-butyl alcohol gives *tert*-butyl ester **2b** in low yield.

(24) Mukaiyama, T.; Usui, M.; Shimada, E.; Saigo, K. *Chem. Lett.* **1975**, 1045.

$NaHCO_3$), and worked up. Chromatography (2% EtOAc/hexane) gave 0.813 g of pure acetonide **9b** (1.56 mmol, 89%): IR ($CHCl_3$) 2965, 2866 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.83 (3 H, d, J = 6.7 Hz), 0.91 (3 H, d, J = 6.6 Hz), 0.99 (6 H, d, J = 6.7 Hz), 1.03 (3 H, d, J = 6.7 Hz), 1.08 (9 H, s), 1.25 (3 H, s), 1.29 (3 H, s), 1.69 (1 H, m), 1.78 (1 H, m), 2.26 (2 H, m), 3.06 (1 H, t, J = 6.5 Hz), 3.71 (3 H, m), 5.31 (1 H, dd, J = 15.5, 7.4 Hz), 5.44 (1 H, dd, J = 15.5, 6.2 Hz), 7.39 (6 H, m), 7.67 (4 H, m); $[\alpha]_D$ −16.0° (c 1.11, $CHCl_3$). Anal. ($C_{33}H_{50}O_3Si$) C, H.

6(*R*)-[1(*R*)-Methyl-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-4(*S*)-[1(*R*)-methyl-2-formylethyl]-2,2,5(*S*)-trimethyl-1,3-dioxane (10). Acetonide **9b** (0.813 g, 1.56 mmol) dissolved in 28 mL of 1:1 $MeOH/CH_2Cl_2$ containing 50 mg of solid $NaHCO_3$ was cooled to −78 °C and treated with O_3 until the blue color persisted. The reaction mixture was purged with nitrogen, filtered through Celite, concentrated, and dissolved in 28 mL of ether. This solution was cooled to 0 °C, and $LiAlH_4$ (0.237 g, 6.24 mmol) was added. The suspension was allowed to warm to room temperature with stirring overnight. The $LiAlH_4$ was decomposed by sequential dropwise addition of 0.24 mL of water, 0.24 mL of 15% NaOH, and 0.72 mL of water. The suspension was stirred for 30 min and then worked up to give crude alcohol (0.763 g). A small portion of the alcohol (52.4 mg) was purified by chromatography (25% EtOAc/hexane) to give 37.8 mg of pure alcohol: IR ($CHCl_3$) 3507, 2860 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (3 H, d, J = 6.7 Hz), 0.96 (3 H, d, J = 6.7 Hz), 1.00 (3 H, d, J = 7.1 Hz), 1.08 (9 H, s), 1.21 (3 H, s), 1.31 (3 H, s), 1.73 (1 H, m), 1.88 (2 H, m), 2.43 (1 H, t, J = 5.5 Hz), 3.50 (1 H, dd, J = 7.2, 2.9 Hz), 3.67 (5 H, m), 7.39 (6 H, m), 7.67 (4 H, m); $[\alpha]_D$ −18.0° (c 2.01, $CHCl_3$). Anal. ($C_{29}H_{44}O_4Si$) C, H. To a solution of oxalyl chloride (9.9 mg, 0.078 mmol) in 0.3 mL of CH_2Cl_2 at −78 °C was added DMSO (6.3 mg, 0.081 mmol) in 0.1 mL of CH_2Cl_2. This mixture was stirred for 3 min at −78 °C, and the crude alcohol (12.6 mg) in 0.1 mL of CH_2Cl_2 was added dropwise. The reaction mixture was stirred for 15 min at −78 °C, and triethylamine (13.1 mg, 0.130 mmol) was added dropwise. The solution was stirred for 15 min at −78 °C and for 20 min at 0 °C and then partitioned between benzene/ether (4:1) and water. The organic layer was washed (brine) and worked up. Chromatography (10% EtOAc/hexane) gave 10.7 mg (0.022 mmol, 84.6%) of pure aldehyde **10**: IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.91 (3 H, d, J = 6.7 Hz), 0.95 (3 H, d, J = 6.8 Hz), 1.08 (9 H, s), 1.18 (3 H, d, J = 7.0 Hz), 1.20 (3 H, s), 1.29 (3 H, s), 1.73 (1 H, m), 1.92 (1 H, m), 2.45 (1 H, m), 3.71 (4 H, m), 7.41 (6 H, m), 7.67 (4 H, m), 9.71 (1 H, d, J = 1.0 Hz).

3(*R*),6-Dimethylhept-4(*E*)-enyl Phenyl Sulfone (11d). A solution of (*R*)-allylic alcohol **3a**[13] (0.828 g, 7.26 mmol), trimethyl orthoacetate (1.10 g, 9.15 mmol), and pivalic acid (74.6 mg, 0.73 mmol) in toluene (56 mL) was heated at reflux for 48 h. The reaction mixture was cooled to room temperature, diluted with ether, washed (5% HCl and water), and worked up to give 1.04 g of crude ester **11a**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (6 H, d, J = 6.7 Hz), 1.03 (3 H, d, J = 6.7 Hz), 2.24 (2 H, m), 2.61 (2 H, m), 3.66 (3 H, s), 5.27 (1 H, dd, J = 15.6, 7.0 Hz), 5.40 (1 H, dd, J = 15.6, 6.4 Hz). To a suspension of $LiAlH_4$ (0.93 g, 24.4 mmol) in ether (27 mL) at 0 °C was added dropwise the crude ester in 12 mL of ether over 30 min. The reaction mixture was allowed to warm to room temperature with stirring overnight. The excess $LiAlH_4$ was decomposed (vide supra) and worked up to give 0.825 g of crude alcohol **11b**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.97 (6 H, d, J = 6.9 Hz), 1.00 (3 H, d, J = 7.0 Hz), 1.55 (2 H, m), 2.24 (2 H, m), 3.66 (2 H, m), 5.23 (1 H, dd, J = 15.4, 7.6 Hz), 5.41 (1 H, dd, J = 15.4, 6.3 Hz). The crude alcohol (0.825 g) dissolved in CH_2Cl_2 (23 mL) containing triethylamine (0.882 g, 8.7 mmol) was cooled to 0 °C, and methanesulfonyl chloride (0.799 g, 7.0 mmol) was added. The reaction mixture was stirred for 30 min at 0 °C, and LiBr (5.04 g, 58.1 mmol) in acetone (46 mL) was added. The resulting suspension was heated at reflux overnight. After the solution was cooled to room temperature, the solvents were removed in vacuo. The residue was dissolved in ether, washed (water), and worked up. Kugelrohr distillation (25 Torr, 90 °C) gave 0.926 g (4.51 mmol, 62.1% from (*R*)-allylic alcohol **3a**) of bromide **11c**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.98 (6 H, d, J = 6.7 Hz), 1.00 (3 H, d, J = 6.7 Hz), 1.79 (2 H, m), 2.17 (1 H, m), 2.27 (1 H, m), 3.36 (2 H, m), 5.13 (1 H, dd, J = 15.5, 8.1 Hz), 5.43 (1 H, dd, J = 15.5, 6.6 Hz). The bromide **30** (0.410 g, 2.00 mmol) and benzenesulfinic acid sodium salt (3.3 g, 20.0 mmol) in 7.0 mL of DMF was stirred overnight at room temperature. The reaction mixture was diluted with ether, washed (water), and worked up. Flash chromatography (25% ether/hexane) gave 0.255 g (0.96 mmol, 48.0%) of sulfone **11d**: IR ($CHCl_3$) 2965, 1309, 1147 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.94 (6 H, d, J = 6.1 Hz), 0.96 (3 H, d, J = 5.9 Hz), 1.68 (2 H, m), 2.15 (2 H, m), 3.06 (2 H, m), 5.05 (1 H, dd, J = 8.0, 15.4 Hz), 5.31 (1 H, dd, J = 6.6, 15.4 Hz), 7.60 (3 H, m), 7.90 (2 H, m); $[\alpha]_D$ −8.49° (c 0.93, $CHCl_3$). Anal. ($C_{15}H_{22}O_2S$) C, H.

6(*R*)-[1(*R*)-Methyl-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-4(*S*)-[2-oxo-1(*R*),5(*R*),8-trimethylnon-6(*E*)-enyl]-2,2,5(*S*)-trimethyl-1,3-dioxane (12). A solution of sulfone **11d** (85.6 mg, 0.32 mmol) in 1.8 mL of THF was cooled to −78 °C, and n-BuLi (241.6 μL, 0.307 mmol, 1.27 M) was added dropwise. The resulting solution was stirred for 45 min at −78 °C, and aldehyde **10** (99.6 mg, 0.207 mmol) in 0.77 mL of THF was added dropwise over 5 min. After the solution was stirred at −78 °C for 50 min and 0 °C for 30 min, the reaction was decomposed by addition of saturated aqueous NH_4Cl. The resulting mixture was diluted with water and extracted with ether. The combined organic layers were worked up. Flash chromatography (12% EtOAc/hexane) gave an inseparable mixture of 152 mg of hydroxy sulfones [IR ($CHCl_3$) 3450, 2866 cm^{-1}; ^1H NMR (250 MHz, partial, $CDCl_3$) δ 4.05 (1 H, m), 5.05 (1 H, m), 5.31 (1 H, m)] and recovered sulfone **11d**. To a solution of oxalyl chloride (77.7 mg, 0.612 mmol) in 2.6 mL of CH_2Cl_2 was added DMSO (49.3 mg, 0.632 mmol) in 0.85 mL of CH_2Cl_2. The mixture was stirred for 3 min at −78 °C, and the hydroxy sulfones (152 mg) in 0.85 mL of CH_2Cl_2 were added dropwise over 3 min. The reaction mixture was stirred for 15 min at −78 °C, and Et_3N (103.0 mg, 1.02 mmol) was added dropwise. The solution was stirred for 15 min at −78 °C and for 20 min at 0 °C and was then partitioned between benzene/ether (4:1) and H_2O. The organic layer was washed (brine) and worked up. Chromatography (10% EtOAc/hexane) gave 112 mg of keto sulfones: IR ($CHCl_3$) 2965, 1718, 1309 cm^{-1}; ^1H NMR (250 MHz, partial, $CDCl_3$) δ 1.11 and 1.09 (9 H, s), 4.54 (1 H, m), 5.0 (1 H, m), 5.38 (1 H, m). The keto sulfones (112 mg) were dissolved in 12.4 mL of MeOH, and disodium hydrogen phosphate (85.6 mg, 0.603 mmol) was added. The resulting solution was cooled to 0 °C, and freshly pulverized 6% Na/Hg (450 mg) was added. After being stirred 2.5 h at 0 °C the reaction mixture was poured over H_2O, extracted (EtOAc), and worked up. Chromatography (5% EtOAc/hexane) gave 74 mg (0.122 mmol) of pure ketone olefin **12** (59% yield from aldehyde **10**): IR ($CHCl_3$) 2859, 1711 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (3 H, d, J = 6.7 Hz), 0.93 (3 H, d, J = 6.8 Hz), 0.97 (6 H, d, J = 6.6 Hz), 0.98 (3 H, d, J = 6.7 Hz), 1.07 (9 H, s), 1.14 (3 H, d, J = 7.0 Hz), 1.20 (3 H, s), 1.27 (3 H, s), 1.49 (1 H, m), 1.67 (2 H, m), 1.86 (1 H, m), 2.02 (1 H, m), 2.23 (1 H, m), 2.47 (2 H, m), 2.64 (1 H, m), 3.66 (4 H, m), 5.15 (1 H, ddd, J = 15.4, 7.9, 0.8 Hz), 5.34 (1 H, dd, J = 15.4, 6.5 Hz), 7.40 (6 H, m), 7.67 (4 H, m); $[\alpha]_D$ −40.4° (c 0.47, $CHCl_3$); HRMS (CI, M + 1) calcd for $C_{38}H_{58}O_4Si(H)$ 607.4185, found 607.4192.

6(*R*)-[1(*R*)-Methyl-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-4(*S*)-[7-(*tert*-butoxycarbonyl)-1(*R*),5(*R*)-dimethyl-6(*R*)-hydroxy-2-oxoheptanyl]-2,2,5(*S*)-trimethyl-1,3-dioxane (14) and Hemiketal of 6(*R*)-[1(*R*)-Methyl-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-4(*S*)-[7-(*tert*-butoxycarbonyl)-1-(*R*),5(*R*)-dimethyl-6(*S*)-hydroxy-2-oxoheptanyl]-2,2,5(*S*)-trimethyl-1,3-dioxane (15). A solution of ketone **12** (37.5 mg, 0.062 mmol) in 4.2 mL of 1:1 $MeOH/CH_2Cl_2$ containing solid $NaHCO_3$ (100 mg) was ozonized at −78 °C until the blue color persisted. The excess ozone was purged with N_2, and 2.6 mL of dimethyl sulfide was added to the suspension at −78 °C. The reaction mixture was stirred for 10 min at −78 °C and for 1.5 h at room temperature. After the volatiles were removed in vacuo, and the residue was dissolved in EtOAc, washed with H_2O, and worked up. The crude product was passed through a short column (15% EtOAc/hexane) to give 27.0 mg (0.048 mmol) of pure keto aldehyde **13** (77%): IR ($CHCl_3$) 2718, 1718 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (3 H, d, J = 6.7 Hz), 0.93 (3 H, d, J = 6.7 Hz), 1.07 (9 H, s), 1.11 (3 H, d, J = 7.4 Hz), 1.15 (3 H, d, J = 7.0 Hz), 1.19 (3 H, s), 1.26 (3 H, s), 1.69 (2 H, m), 1.93 (2 H, m), 2.38 (1 H, m), 2.56 (2 H, m), 2.65 (1 H, m), 3.60 (2 H, m), 3.69 (2 H, m), 7.38 (6 H, m), 7.67 (4 H, m), 9.61 (1 H, d, J = 1.8 Hz). Lithium diisopropylamide was prepared by adding sequentially diiso-

propylamine (64.0 mg, 0.63 mmol) and *n*-BuLi (1.27 M, 498 μL, 0.63 mmol) to 7.3 mL of THF at 0 °C. After the solution was stirred for 20 min it was cooled to −78 °C. *tert*-Butyl acetate (70.0 mg, 0.603 mmol) in 2.8 mL of THF was added dropwise over 5 min. The reaction mixture was stirred for 30 min at −78 °C. A fraction of this solution [211 μL (0.012 mmol)] was added to keto aldehyde **13** (6.5 mg, 0.011 mmol) dissolved in 0.3 mL of THF at −78 °C. After the reaction mixture was stirred for 5 min at −78 °C, it was treated with saturated aqueous NH_4Cl, warmed to room temperature, diluted with water, extracted (ether), and worked up. Flash chromatography (15% EtOAc/hexane) gave 2.3 mg (0.0033 mmol) of hemiketal **15**, 1.4 mg (0.0025 mmol) of keto aldehyde **13**, and 2.9 mg (0.0043 mmol) of keto ester **14** (92% combined yield with recovered keto aldehyde **13**). Keto ester **14**: R_f = 0.25 (20% EtOAc/hexane); IR ($CHCl_3$) 3500, 1711 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (3 H, d, *J* = 6.7 Hz), 0.91 (3 H, d, *J* = 6.3 Hz), 0.93 (3 H, d, *J* = 6.1 Hz), 1.07 (9 H, s), 1.16 (3 H, d, *J* = 7.0 Hz), 1.20 (3 H, s), 1.27 (3 H, s), 1.30 (1 H, m), 1.46 (1 H, m), 1.47 (9 H, s), 1.73 (2 H, m), 1.86 (1 H, m), 2.38 (2 H, m), 2.56 (2 H, m), 2.66 (1 H, m), 3.08 (1 H, m), 3.63 (4 H, m), 3.89 (1 H, m), 7.37 (6 H, m), 7.67 (4 H, m); $[\alpha]_D$ −4.6° (*c* 0.53, $CHCl_3$); HRMS (CI, M + 1 − H_2O) calcd for $C_{40}H_{62}O_7Si$ 665.4239, found 665.4242. Hemiketal **15**: R_f = 0.53 (20% EtOAc/hexane); IR ($CHCl_3$) 3450, 1718 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.83 (3 H, d, *J* = 6.6 Hz), 0.87 (3 H, d, *J* = 6.3 Hz), 0.94 (3 H, d, *J* = 6.7 Hz), 1.04 (3 H, d, *J* = 7.2 Hz), 1.07 (9 H, s), 1.19 (3 H, s), 1.35 (3 H, s), 1.45 (9 H, s), 1.60–1.15 (5 H, m), 1.90–1.62 (3 H, m), 2.30 (1 H, dd, *J* = 15.5, 7.4 Hz), 2.50 (1 H, dd, *J* = 15.5, 4.0 Hz), 3.65 (3 H, m), 4.05 (2 H, m), 4.54 (1 H, d, *J* = 1.6 Hz), 7.38 (6 H, m), 7.67 (4 H, m); $[\alpha]_D$ −13.9° (*c* 0.45, $CHCl_3$); HRMS (CI, M + 1 − H_2O) calcd for $C_{40}H_{60}O_6Si$(H − H_2O) 665.4239, found 665.4208.

4(*S*)-Hydroxy-8(*R*)-[(*tert*-butoxycarbonyl)methyl]-2-(*R*)-[1(*R*)-methyl-2-hydroxyethyl]-3(*R*),5(*R*),9(*R*)-trimethyl-(6*R*)-1,7-dioxaspiro[5.5]undecane (17b): A solution of β-hydroxy ester **14** (12.1 mg, 0.018 mmol) in 1.0 mL of MeOH containing *p*-TsOH (2.7 mg, 0.014 mmol) was stirred for 2 h at 0 °C and then for 6 h at room temperature. The reaction mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc. Workup and chromatography (30% EtOAc/hexane) gave 5.4 mg (0.014 mmol) of pure spiroketal **17b** (78% yield): IR ($CHCl_3$) 3493, 1718 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (3 H, d, *J* = 6.9 Hz, C_{17}-Me), 0.92 (3 H, d, *J* = 6.9 Hz, C_{19}-Me), 0.93 (3 H, d, *J* = 8.5 Hz, C_{11}-Me), 1.08 (3 H, d, *J* = 6.6 Hz, C_{15}-Me), 1.24 (1 H, m, C_{12}-H), 1.45 (9 H, s), 1.52 (2 H, m), 1.63 (1 H, m, C_{11}-H), 1.85 (1 H, m, C_{19}-H), 1.95 (2 H, m), 2.06 (1 H, dt, *J* = 12.6, 3.8 Hz, C_{12}-H), 2.15 (1 H, m, *J* = 15.1, 3.0 Hz, C_9-H), 2.38 (1 H, dd, *J* = 15.1, 10.4 Hz, C_9-H), 3.70 (3 H, m, C_{15}, C_{18}, C_{20}-H), 3.98 (1 H, m, C_{20}-H), 4.19 (1 H, dt, *J* = 10.3, 2.8, 2.8 Hz, C_{10}-H); $[\alpha]_D$ −5.3° (*c* 0.32, $CHCl_3$); HRMS (EI, M) calcd for $C_{21}H_{38}O_6$ 386.2669, found 386.2660.

Cyclic Methoxyketal of 14 (16). To a solution of β-hydroxy ester **14** (6.2 mg, 0.009 mmol) in 0.5 mL of MeOH at 0 °C was added a solution of *p*-TsOH in MeOH (12.5 μL, 0.4 M), and the solution was stirred for 2 h at 0 °C. The reaction mixture was diluted with EtOAc and washed with aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc. Workup and chromatography (10% EtOAc/hexane, then 20% EtOAc/hexane) gave 5.6 mg (0.008 mmol) of pure methoxyketal **16** (88% yield) and 1.2 mg of impure β-hydroxy ester **14**. Methoxyketal **16**: IR ($CHCl_3$) 2929, 1718 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.86 (3 H, d, *J* = 6.6 Hz), 0.90 (3 H, d, *J* = 7.3 Hz), 0.91 (3 H, d, *J* = 7.0 Hz), 0.95 (3 H, d, *J* = 6.7 Hz), 1.07 (9 H, s), 1.19 (3 H, s), 1.31 (3 H, s), 1.40 (2 H, m), 1.45 (9 H, s), 1.8–1.6 (5 H, m), 2.06 (1 H, m), 2.17 (1 H, dd, *J* = 14.4, 3.5 Hz), 2.39 (1 H, dd, *J* = 14.4, 9.6 Hz), 3.16 (3 H, s), 3.59 (2 H, m), 3.71 (2 H, m), 4.20 (1 H, dt, *J* = 9.6, 3.5 Hz), 7.37 (6 H, m), 7.67 (4 H, m); $[\alpha]_D$ −3.8° (*c* 0.26, $CHCl_3$); LRMS for $C_{41}H_{64}O_7Si(-OCH_3)$ 665, found 665.

4(*S*)-Hydroxy-8(*S*)-[(*tert*-butoxycarbonyl)methyl]-2-(*R*)-[1(*R*)-methyl-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-3-(*R*),5(*R*),9(*R*)-trimethyl-(6*S*)-1,7-dioxaspiro[5.5]undecane (18). A solution of hemiketal **15** (7.9 mg, 0.012 mmol) in 0.7 mL of MeOH at 0 °C containing *p*-TsOH (2.1 mg, 0.011 mmol) was stirred for 1 h at 0 °C and for 1 h at room temperature. The solution was diluted with EtOAc and washed with aqueous saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc. Workup and chromatography (20% EtOAc/hexane) gave 4.2 mg (0.007 mmol) of spiroketal **18** (56%): IR ($CHCl_3$) 3400, 2929, 1725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.54 (3 H, d, *J* = 6.1 Hz, C_{11}-Me), 0.89 (3 H, d, *J* = 6.0 Hz, C_{19}-Me), 0.90 (3 H, d, *J* = 6.8 Hz, C_{17}-Me), 0.97 (3 H, d, *J* = 6.8 Hz, C_{15}-Me), 1.08 (9 H, s), 1.28 (2 H, m), 1.40 (2 H, m), 1.45 (9 H, s), 1.67 (2 H, m), 1.93 (2 H, m), 2.12 (1 H, dd, *J* = 13.9, 8.7 Hz, C_9-H), 2.45 (1 H, dd, *J* = 13.9, 3.8 Hz, C_9-H), 3.20 (1 H, dd, *J* = 10.2, 2.1 Hz, C_{18}-H), 3.53 (1 H, m, C_{16}-H), 3.67 (1 H, dd, *J* = 9.4, 6.7 Hz, C_{20}-H), 3.85 (1 H, td, *J* = 8.7, 8.7, 3.8 Hz, C_{10}-H), 4.00 (1 H, dd, *J* = 9.4, 3.1 Hz, C_{20}-H), 7.38 (6 H, m), 7.67 (4 H, m); $[\alpha]_D$ −0.73° (*c* 0.41, $CHCl_3$); HRMS (CI, M + 1) calcd for $C_{37}H_{56}O_6Si$(H) 625.3926, found 625.3880.

4(*S*)-Hydroxy-8(*R*)-[(*tert*-butoxycarbonyl)methyl]-2-(*R*)-[1(*R*)-methyl-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-3-(*R*),5(*R*),9(*R*)-trimethyl-(6*R*)-1,7-dioxaspiro[5.5]undecane (17a). A solution of diol **17b** (7.4 mg, 0.019 mmol), triethylamine (11.5 mg, 0.114 mmol), *tert*-butyldiphenylsilyl chloride (15.8 mg, 0.058 mmol), and 4-(dimethylamino)pyridine (1.2 mg, 0.010 mmol) in 0.73 mL of CH_2Cl_2 was stirred at 25 °C for 18 h. The solution was diluted with ether, washed with cold 0.5% HCl, saturated aqueous $NaHCO_3$, and water, and worked up. Chromatography (15% EtOAc/hexane) gave 11.0 mg (0.018 mmol) of silyl ether **17a** (93% yield): IR ($CHCl_3$) 3613, 1725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.82 (3 H, d, *J* = 7.0 Hz), 0.83 (3 H, d, *J* = 6.8 Hz), 1.01 (6 H, d, *J* = 6.6 Hz), 1.09 (9 H, s), 1.37 (9 H, s), 1.30–1.40 (4 H, m), 1.60 (2 H, m), 1.75 (1 H, m), 1.78 (1 H, m), 1.90 (1 H, m), 1.98 (1 H, dd, *J* = 14.5, 3.8 Hz), 2.22 (1 H, dd, *J* = 14.5, 9.8 Hz), 3.33 (1 H, dd, *J* = 10.5, 1.8 Hz), 3.55 (1 H, t, *J* = 9.8 Hz), 3.69 (2 H, m), 4.23 (1 H, dd, *J* = 9.5, 3.5 Hz), 7.35 (6 H, m), 7.69 (4 H, m); $[\alpha]_D$ +54.4° (*c* 0.55, $CHCl_3$); HRMS (CI, M + 1) calcd for $C_{37}H_{56}O_6Si$(H) 625.3926, found 625.3880.

8(*R*)-[(*tert*-Butoxycarbonyl)methyl]-2(*R*)-[1(*R*)-methyl-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-3(*R*),5(*R*),9-(*R*)-trimethyl-(6*R*)-1,7-dioxaspiro[5.5]undecane (21a). To a solution of alcohol **17a** (20.9 mg, 0.033 mmol) in 1.6 mL of CH_2Cl_2 at 25 °C was added phenyl chlorothionocarbonate (14.4 mg, 0.084 mmol) and pyridine (13.2 mg, 0.167 mmol). The solution was stirred for 5 h at 25 °C. The reaction mixture was diluted with ether, washed with cold 0.5% HCl, saturated aqueous $NaHCO_3$, and water, and worked up. Chromatography (2% EtOAc/hexane, then 20% EtOAc/hexane) gave 17.0 mg of impure thionocarbonate: ^1H NMR (250 MHz, $CDCl_3$) δ 0.83 (3 H, d, *J* = 6.9 Hz), 0.89 (3 H, d, *J* = 6.8 Hz), 1.01 (6 H, d, *J* = 6.6 Hz), 1.10 (9 H, s), 1.18 (1 H, m), 1.27 (2 H, m), 1.39 (9 H, s), 1.64 (1 H, m), 1.74–1.94 (3 H, m), 1.98 (1 H, dd, *J* = 14.4, 3.2 Hz), 2.28 (1 H, dd, *J* = 14.4, 10.0 Hz), 2.45 (1 H, m), 3.42 (1 H, dd, *J* = 10.5, 1.8 Hz), 3.62 (1 H, t, *J* = 9.8 Hz), 3.77 (1 H, m), 4.22 (1 H, dd, *J* = 9.4, 3.5 Hz), 5.34 (1 H, dd, *J* = 11.4, 4.9 Hz), 7.30–7.50 (11 H, m), 7.67 (4 H, m). The impure thionocarbonate derivative (17.0 mg), tri-*n*-butyltin hydride (32.0 mg, 0.110 mmol), and AIBN (1.8 mg, 0.011 mmol) in 3.8 mL of toluene were heated at reflux for 2 h. The cooled solution was titrated with I_2 in CH_2Cl_2 until the red color persisted. Solid sodium bisulfite was added to reduce excess I_2. Saturated aqueous KF solution was added, the resulting suspension was stirred for 2.5 h at 25 °C and filtered through Celite, and the cake was washed with ether. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were worked up. Chromatography (3% ether/hexane) gave 11.6 mg (0.019 mmol, 58% yield) of pure spiroketal **21a**: IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.81 (3 H, d, *J* = 6.9 Hz), 0.83 (3 H, d, *J* = 6.2 Hz), 0.89 (3 H, d, *J* = 6.9 Hz), 0.99 (3 H, d, *J* = 6.7 Hz), 1.08 (2 H, m), 1.09 (9 H, s), 1.24 (2 H, m), 1.38 (9 H, s), 1.60–1.90 (6 H, m), 2.00 (1 H, dd, *J* = 14.0, 4.0 Hz), 2.24 (1 H, dd, *J* = 13.9, 9.4 Hz), 3.29 (1 H, dd, *J* = 10.4, 2.1 Hz), 3.51 (1 H, t, *J* = 9.9 Hz), 3.72 (1 H, m), 4.24 (1 H, dd, *J* = 9.4, 3.6 Hz), 7.37 (6 H, m), 7.67 (4 H, m); $[\alpha]_D$ +40.7° (*c* 0.3, $CHCl_3$); HRMS (CI, M + 1) calcd for $C_{37}H_{56}O_5Si$(H) 609.3977, found 609.3944.

8(*R*)-[(*tert*-Butoxycarbonyl)methyl]-2(*R*)-[1(*R*)-methyl-2-hydroxyethyl]-3(*R*),5(*R*),9(*R*)-trimethyl-(6*R*)-1,7-dioxaspiro[5.5]undecane (21b). To a solution of spiroketal **21a** (11.6 mg, 0.019 mmol) in 1.3 mL of THF at 25 °C was added tetra-*n*-butylammonium fluoride (76.0 μL, 0.076 mmol of a 1.1 M solution). The solution was stirred for 18 h at room temperature. Owing to incomplete reaction (TLC), additional tetra-*n*-butylammonium fluoride (76.0 μL) was added, and stirring was continued for 3.5 h at room temperature. The reaction

mixture was diluted with EtOAc and washed with water, the aqueous layer was back-extracted with EtOAc, and the combined organic layers were worked up. Chromatography (12% EtOAc/hexane) gave 5.8 mg (0.016 mmol, 83% yield) of pure alcohol **21b**: IR ($CHCl_3$) 3479, 1718 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.86 (3 H, d, J = 7.0 Hz), 0.91 (6 H, d, J = 7.1 Hz), 0.93 (3 H, d, J = 6.8 Hz), 1.25 (3 H, m), 1.47 (9 H, s), 1.60–1.80 (5 H, m), 1.92 (1 H, dd, J = 13.4, 4.2 Hz), 2.06 (1 H, dt, J = 13.0, 4.3 Hz), 2.16 (1 H, dd, J = 14.7, 3.2 Hz), 2.40 (1 H, dd, J = 14.7, 10.3 Hz), 3.67 (1 H, dd, J = 10.5, 2.0 Hz), 3.76 (2 H, m), 3.91 (1 H, m), 4.23 (1 H, dt, J = 10.1, 2.9 Hz); $[\alpha]_D$ +63.4° (c 0.29, $CHCl_3$); HRMS (EI) calcd for $C_{21}H_{38}O_5$ 370.2720, found 370.2707.

8(*R*)-[(*tert*-Butoxycarbonyl)methyl]-2(*R*)-[1(*S*)-methyl-2-oxo-2-(pyrid-2-ylthio)ethyl]-3(*R*),5(*R*),9(*R*)-trimethyl-(6*R*)-1,7-dioxaspiro[5.5]undecane (22b). To a suspension of potassium metaperiodate (33.8 mg, 0.147 mmol) and ruthenium dioxide (2.5 mg, 0.019 mmol) in 0.74 mL of acetone and 0.74 mL of water at 25 °C was added dropwise alcohol **21b** (13.6 mg, 0.037 mmol) in 0.56 mL of acetone. The suspension was stirred for 96 h at room temperature with the addition of more potassium metaperiodate (33.8 mg) and ruthenium dioxide (2.5 mg) at 24-h intervals. The reaction mixture was decomposed with saturated aqueous Na_2SO_3, extracted with $CHCl_3$, and worked up to give 13.1 mg of crude acid **22a**: IR ($CHCl_3$) 3627, 1739, 1711 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.90 (3 H, d, J = 7.0 Hz), 0.91 (3 H, d, J = 6.1 Hz), 0.95 (3 H, d, J = 7.0 Hz), 1.20 (3 H, d, J = 7.1 Hz), 1.24–1.44 (3 H, m), 1.47 (3 H, s), 1.58–2.11 (6 H, m), 2.20 (1 H, dd, J = 14.9, 4.0 Hz), 2.40 (1 H, dd, J = 14.9, 9.8 Hz), 2.60 (1 H, m), 4.02 (1 H, dd, J = 9.7, 2.0 Hz), 4.27 (1 H, m). A solution of the crude acid (13.1 mg), 2,2′-dipyridyl disulfide (37.7 mg, 0.171 mmol), and triphenylphosphine (44.9 mg, 0.171 mmol) in 1.9 mL of CH_2Cl_2 was stirred for 3 h at 25 °C. After removal of the volatiles in vacuo the residue was purified by chromatography (10% EtOAc/hexane) to give 12.0 mg (0.025 mmol), 68% from alcohol **21b**) of 2-pyridylthio ester **22b**: IR ($CHCl_3$) 1711, 1577 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.89 (6 H, d, J = 6.3 Hz), 0.97 (3 H, d, J = 7.0 Hz), 1.14 (3 H, d, J = 6.8 Hz), 1.28 (3 H, m), 1.44 (9 H, s), 1.68 (2 H, m), 1.73–1.90 (3 H, m), 2.15 (1 H, m), 2.22 (1 H, dd, J = 13.8, 6.7 Hz), 2.38 (1 H, dd, J = 13.8, 9.0 Hz), 2.85 (1 H, m), 4.01 (1 H, dd, J = 9.5, 2.5 Hz), 4.09 (1 H, m), 7.64 (2 H, m), 7.74 (1 H, m), 8.58 (1 H, m); $[\alpha]_D$ +73.9° (c 0.87, $CHCl_3$); HRMS (EI, M) calcd for $C_{26}H_{39}O_5NS$ 477.2551, found 477.2536.

8(*R*)-[(*tert*-Butoxycarbonyl)methyl]-2(*R*)-[1(*S*)-methyl-2-oxo-2-(1*H*-pyrrol-2-yl)ethyl]-3(*R*),5(*R*),9(*R*)-trimethyl-(6*R*)-1,7-dioxaspiro[5.5]undecane (23b). A 0.5 M solution of pyrrolylmagnesium bromide was prepared in the following manner. To a solution of pyrrole (100.0 mg, 1.49 mmol) in 1.06 mL of ether and 1.5 mL of THF at room temperature was added 0.43 mL of 1 M ethylmagnesium bromide in ether. The resulting solution was stirred for 15 min at 25 °C and used immediately. To a suspension of cuprous iodide (15.6 mg, 0.082 mmol) in 1.1 mL of THF at 0 °C was added 327.0 μL (0.164 mmol, 0.5 M) of pyrrolylmagnesium bromide. The solution was stirred for 30 min at 0 °C as the color changed from dark purple to dark green. To this solution was added pyridylthio ester **22b** (5.2 mg, 0.011 mmol) in 0.15 mL of THF. The reaction mixture was stirred for 1 h at 0 °C, decomposed with saturated aqueous NH_4Cl, extracted with ether, and worked up to give after chromatography (20% EtOAc/hexane) 4.1 mg (0.009 mmol, 86%) of keto pyrrole **2b**: IR ($CHCl_3$) 3444, 1718, 1640 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.78 (3 H, d, J = 7.0 Hz), 0.84 (3 H, d, J = 6.6 Hz), 1.02 (3 H, d, J = 7.1 Hz), 1.08 (3 H, d, J = 6.7 Hz), 1.30 (2 H, m), 1.52 (9 H, s), 1.60–1.90 (7 H, m), 2.20 (1 H, dd, J = 14.3, 7.0 Hz), 2.37 (1 H, dd, J = 14.3, 7.8 Hz), 3.26 (1 H, m), 3.90 (2 H, m), 6.26 (1 H, m), 6.94 (1 H, m), 7.00 (1 H, m), 9.55 (1 H, s); $[\alpha]_D$ +100.5° (c 0.21, $CHCl_3$); HRMS (EI, M) calcd for $C_{25}H_{39}O_5N$ 433.2830, found 433.2837.

8(*R*)-[(Methoxycarbonyl)methyl]-2(*R*)-[1(*S*)-methyl-2-oxo-2-(1*H*-pyrrol-2-yl)ethyl]-3(*R*),5(*R*),9(*R*)-trimethyl-(6*R*)-1,7-dioxaspiro[5.5]undecane (2c). An ether solution (1.0 mL) of synthetic acid **2a** (3.8 mg, 0.01 mmol) was treated with an excess of ethereal diazomethane [*Caution*!]. After 3 min the excess reagent was decomposed by the dropwise addition of HOAc. The resulting solution was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, and worked up. Flash chromatography (20% EtOAc/hexane) gave 2.4 mg (62%) of methyl ester **2c**: IR ($CHCl_3$) 3451, 1732, 1640 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.78 (3 H, d, J = 7.0 Hz), 0.81 (3 H, d, J = 6.5 Hz), 1.02 (3 H, d, J = 6.9 Hz), 1.06 (3 H, d, J = 6.8 Hz), 1.22–1.41 (4 H, m), 1.60–1.84 (5 H, m), 2.29 (1 H, dd, J = 14.7, 5.9 Hz), 2.43 (1 H, dd, J = 14.8, 8.4 Hz), 3.25 (1 H, m), 3.78 (3 H, s), 3.89 (2 H, m), 6.26 (1 H, m), 6.94 (1 H, m), 7.01 (1 H, m), 9.43 (1 H, m); $[\alpha]_D$ +161° (c 0.12, $CHCl_3$);[25] HRMS (EI, M) calcd for $C_{22}H_{33}O_5N$ 391.2360, found 391.2353.[25b]

8(*R*)-(Carboxymethyl)-2(*R*)-[1(*S*)-methyl-2-oxo-2-(1*H*-pyrrol-2-yl)ethyl]-3(*R*),5(*R*),9(*R*)-trimethyl-(6*R*)-1,7-dioxaspiro[5.5]undecane (2a). A solution of synthetic ester **2b** (4.1 mg, 0.009 mmol) dissolved in CH_2Cl_2 (0.4 mL) containing trifluoroacetic acid (7.4 mg, 0.065 mmol) was stirred for 24 h at room temperature. TLC (33% EtOAc/hexane with 1% AcOH) indicated incomplete reaction. Trifluoroacetic acid (4.4 mg, 0.039 mmol) was added, and the reaction mixture was stirred for an additional 24 h. Removal of the volatiles and flash chromatography (33% EtOAc/hexane with 1% AcOH) gave 3.3 mg (0.009 mmol, 92%) of acid pyrrole **2a**: IR ($CHCl_3$) 3451, 3233, 2965, 1739, 1718, 1619 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.83 (3 H, d, J = 6.9 Hz), 0.87 (3 H, d, J = 6.4 Hz), 1.02 (3 H, d, J = 6.8 Hz), 1.06 (3 H, d, J = 7.0 Hz), 1.27–1.42 (4 H, m), 1.49 (1 H, m), 1.65–1.88 (4 H, m), 2.40 (1 H, dd, J = 15.3, 6.2 Hz), 2.54 (1 H, dd, J = 15.3, 7.9 Hz), 3.28 (1 H, m), 3.99 (2 H, m), 6.28 (1 H, m), 7.04 (1 H, m), 7.09 (1 H, m), 10.23 (1 H, m); $[\alpha]_D$ +107° (c 0.18, $CHCl_3$) [lit.[11] $[\alpha]_D$ +131° (c 0.01, $CHCl_3$),[25c] lit.[10f] $[\alpha]_D$ +116° (c 0.15, $CHCl_3$)]; HRMS (EI, M) calcd for $C_{21}H_{31}O_5N$ 377.2203, found 377.2203.

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(25) (a) A sample of methyl ester **2c** prepared from degraded acid showed $[\alpha]_D$ +135° (c 0.17, $CHCl_3$). These determinations were made on sample sizes of about 2.4 mg. An error of 0.1 mg (4%) causes a 14% error in the specific rotation. (b) Methyl ester **2c** from degradation: HRMS (EI, M) calcd for $C_{22}H_{33}O_5N$ 391.2360, found 391.2356. (c) See discussion in 25a.