1 H), 3.78 (s, 3 H), 4.10 (br t, J = 6.6, 1 H), 5.78 (s, 1 H), 6.26 (s, 1 H); MS, m/e (relative intensity) 158 (M^+, 1), 143 (1), 140 (2), 115 (100), 83 (79). **7c**:[13] IR (neat, cm^{-1}) 3410, 1720, 1625, 1490, 955; ^1H NMR δ 3.13 (br s, 1 H), 3.70 (s, 3 H), 5.57 (br d, J = 5.4, 1 H), 5.83 (s, 1 H), 6.33 (s, 1 H), 7.34 (s, 5 H); MS, m/e (relative intensity) 192 (M^+, 100), 191 (73), 160 (72), 132 (41), 105 (25). **7d**: IR (neat, cm^{-1}) 3425, 1720, 1630, 955; ^1H NMR δ 3.17 (br s, 1 H), 3.75 (s, 3 H), 5.60 (br d, J = 6.6, 1 H), 5.95 (s, 1 H), 6.2–6.4 (m, 3 H), 7.36 (s, 1 H). Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.32; H, 5.62. **7e**: IR (neat, cm^{-1}) 3450, 1730, 1635, 970; ^1H NMR δ 0.89 (t, J = 6.0, 3 H), 1.1–1.7 (m, 2 H), 1.9–2.3 (m, 2 H), 2.80 (d, J = 6.0, 1 H), 3.78 (s, 3 H), 4.91 (t, J = 6.0, 1 H), 5.6–5.9 (m, 2 H), 5.84 (s, 1 H), 6.21 (s, 1 H); MS, m/e (relative intensity) 184 (M^+, 1), 166 (1), 141 (51), 109 (100). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.31; H, 9.02.

Reaction of the [α-(Methoxycarbonyl)vinyl]aluminum 2 with 4-Heptanone in the Presence of BF_3·OEt_2. To **2**, generated in a similar way as above from **1** (1.50 mmol), in THF (8 mL) at 0 °C were added 4-heptanone (0.419 mL, 3.00 mmol) and BF_3·OEt_2 (0.369 mL, 3.00 mmol). The mixture was allowed to warm to room temperature, stirred for 15 h, treated with 5 mL of 1 N HCl solution, and extracted with 100 mL of ether. The organic layer was washed three times with 10 mL of 1 N HCl solution and then 10 mL of saturated $NaHCO_3$ solution. The ether solution was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc–hexane = 1:10 v/v) to give **7f**: 206 mg (68%); IR (neat, cm^{-1}) 3510, 1710, 1610, 965; ^1H NMR δ 0.7–1.1 (m, 6 H), 1.1–1.5 (m, 4 H), 1.5–2.0 (m, 4 H), 3.05 (s, 1 H), 3.76 (s, 3 H), 5.76 (s, 1 H), 6.23 (s, 1 H); MS, m/e (relative intensity) 157 (100), 71 (32), 55 (22). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.92; H, 10.35. The compound **7g** was similarly obtained and identified as follows. **7g**: IR (neat, cm^{-1}) 3510, 1710, 1620, 960; ^1H NMR δ 1.3–1.9 (m, 10 H), 3.57 (s, 1 H), 3.78 (s, 3 H), 5.76 (s, 1 H), 6.15 (s, 1 H); MS, m/e (relative intensity) 184 (M^+, 3), 166 (8), 152 (58), 141 (49), 109 (100); HRMS, m/e calcd for $C_{10}H_{16}O_3$ 184.1100, found 184.1086.

Reaction of the Aluminum Allenolate 6a with Butyraldehyde. To a stirred solution of THF (8 mL) and HMPA (0.391 mL, 2.25 mmol) cooled to 0 °C was added a hexane solution of DIBAH (1.65 mmol). After 0.5 h, 1-hexyn-3-one (**4a**) (0.169 mL, 1.50 mmol) was added. The reaction mixture was stirred for 1 h, and the butyraldehyde (0.265 mL, 3.00 mmol) was added. The mixture was allowed to warm to room temperature, stirred for 15 h, treated with 5 mL of 1 N HCl solution, and extracted with 100 mL of ether. The organic layer was washed three times with 10 mL of 1 N HCl solution and then 10 mL of saturated $NaHCO_3$ solution. The ether solution was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by preparative layer chromatography (PLC) on a silica gel plate (20 × 20 × 0.2 cm) to give **8a**: IR (neat, cm^{-1}) 3400, 1670, 1630; ^1H NMR δ 0.94 (t, J = 7.2, 6 H), 1.1–1.9 (m, 6 H), 2.68 (t, J = 7.2, 2 H), 2.89 (br s, 1 H), 4.45 (m, 1 H), 5.95 (s, 1 H), 6.08 (s, 1 H); MS, m/e (relative intensity) 170 (M^+, 1), 152 (2), 127 (100). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.43; H, 10.83. The compound **8b** was similarly obtained and identified as follows. **8b**: IR (neat, cm^{-1}) 3430, 1675, 1630, 1600, 1500, 955; ^1H NMR δ 0.86 (t, J = 7.0, 3 H), 1.58 (sext, J = 7.0, 2 H), 2.64 (t, J = 7.0, 2 H), 3.22 (d, J = 5.4, 1 H), 5.61 (d, J = 5.4, 1 H), 5.93 (s, 1 H), 6.15 (s, 1 H), 7.32 (s, 5 H); MS, m/e (relative intensity) 204 (M^+, 62), 203 (100), 161 (63); HRMS, m/e calcd for $C_{13}H_{16}O_2$ 204.1151, found 204.1142.

Registry No. **1**, 922-67-8; **2**, 107270-46-2; **4a**, 689-00-9; **4b**, 63098-60-2; **4c**, 18998-78-2; **6a**, 112247-17-3; **6b**, 112247-18-4; **6c**, 112247-19-5; **7a**, 18020-64-9; **7b**, 71385-30-3; **7c**, 18020-59-2; **7d**, 87102-10-1; **7e**, 112247-20-8; **7f**, 112247-21-9; **7g**, 112247-22-0; **8a**, 112247-23-1; **8b**, 112247-24-2; *n*-PrCHO, 123-72-8; *i*-PrCHO, 78-84-2; PhCHO, 100-52-7; (*E*)-*n*-PrCH=CHCHO, 6728-26-3; $(n\text{-Pr})_2CO$, 123-19-3; furfural, 98-01-1; cyclohexanone, 108-94-1.

Triply Convergent Synthesis of 1α,25-Dihydroxy-24(*R*)-fluorocholecalciferol

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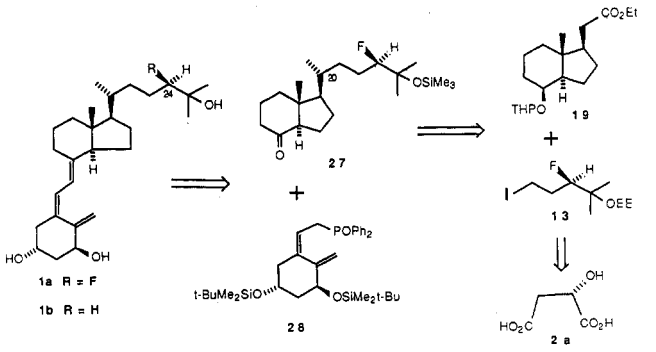
A triply convergent approach to the stereoselective synthesis of 1α,25-dihydroxy-24(*R*)-fluorocholecalciferol (**1a**) is described. The key step in the synthesis is the Wicha alkylation of the C,D-ring synthon **19** with the properly substituted side chain synthon **13**, producing stereoselectively the natural configuration at C-20.

Since the discovery of the physiologically active vitamin D_3 metabolite, 1α,25-dihydroxycholecalciferol [1,25-(OH)$_2$D$_3$][1] (**1b**), we have been interested in the synthesis of an analogue with a longer half-life and increased antirachitogenic activity. As a part of this program, the synthesis of 1α,25-dihydroxy-24(*R*)-fluorocholecalciferol (**1a**) was undertaken. This substance was first synthesized via the conventional cholesterol → 5,7-diene → previtamin → vitamin route.[2] 1α,25-Dihydroxy-24(*R*)-fluorocholecalciferol (**1a**) contains a fluorine atom specifically located at the 24*R* position, one of the principal sites of the calcitriol catabolism. As anticipated, the plasma half-life of this 24(*R*)-monofluoro analogue **1a**, after iv administration in dogs, was 14.4 h, compared to 3.6 h for calcitriol (**1b**). Potent antirachitogenic activity was also demonstrated. An oral dose of this analogue in vitamin D deficient chicks

Scheme I

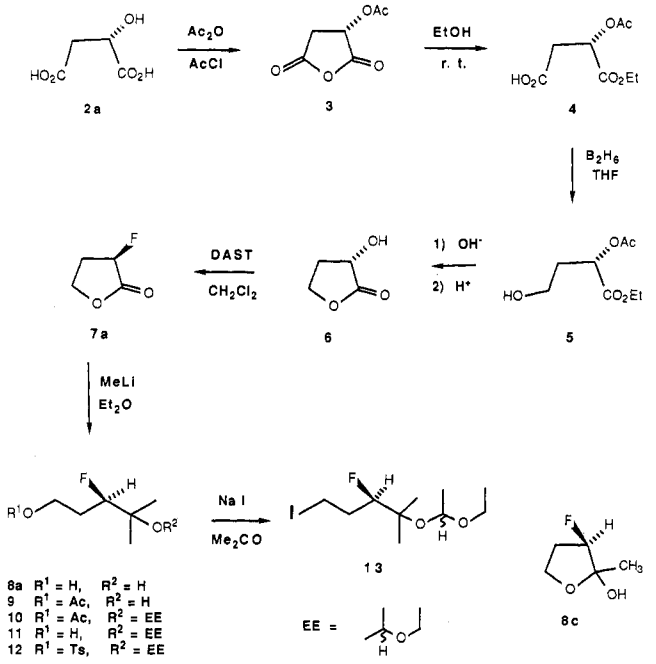


(1) (a) Holick, M. F.; Schnoes, H. K.; DeLuca, H. F.; Suda, J.; Cousins, R. J. *Biochemistry* **1971**, *10*, 2799. (b) Norman, A. W.; Myrtle, J. F.; Midgett, R. J.; Nowicki, H. G.; Williams, V.; Popjak, G. *Science (Washington, D.C.)* **1971**, *173*, 51. (c) Lawson, D. E. M.; Fraser, D. R.; Kodicek, E.; Morris, H. R.; Williams, D. H. *Nature (London)* **1971**, *230*, 228.

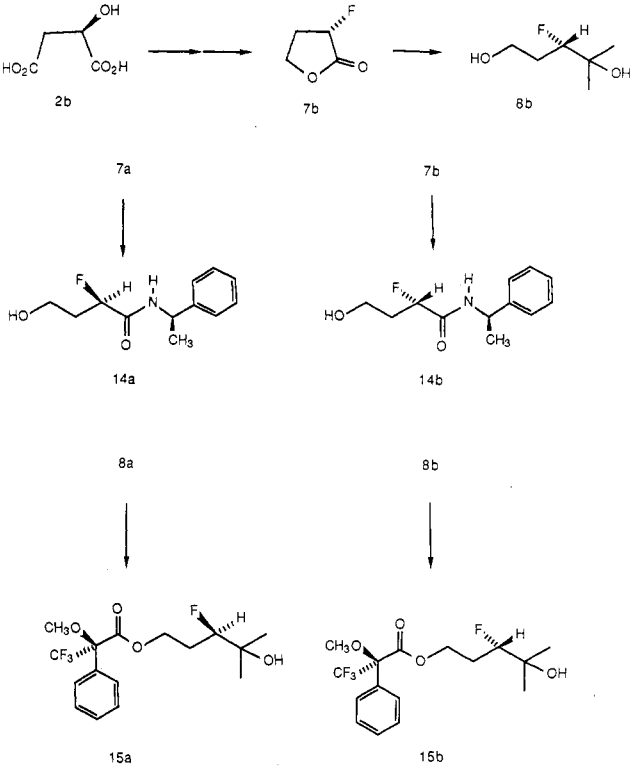
(2) (a) Shiuey, S.-J.; Partridge, J. J.; Chadha, N. K.; Boris, A.; Uskokovič, M. R. *Vitamin D, Chemical, Biochemical and Clinical Update*; Walter de Gruyter: Berlin, 1985; pp 765. (b) Partridge, J. J.; Shiuey, S.-J.; Uskokovič, M. R. U.S. Patent 4 652 405, 1987.

0022-3263/88/1953-1040$01.50/0

Scheme II



Scheme III



increased the mean tibia ash weight to 338 mg compared to 244 mg for an equivalent amount of calcitriol (**1b**).[2] This substance also has a high potential for the prophylactic treatment of milk fever in dairy cattle.[3]

We report herein the novel approach to the synthesis of **1a**, the synthetic strategy of which (Scheme I) is based on a triply convergent plan employing alkylation of ester **19** with the fluorine substituted side chain synthon **13**, followed by formation of the vitamin D triene by a previously described method.[4] The key feature in this plan is application of the Wicha alkylation[5] in order to secure stereoselectively the natural configuration at C-20 as was done in the original partial synthesis.[2] This is the first account of a general procedure used in the synthesis of over a dozen biologically active 1α-hydroxy vitamin D_3 analogues.[6]

For the synthesis of the side-chain synthon **13** (Scheme II), naturally occurring *l*-malic acid (**2a**) was selected as the starting material. Anhydride **3** was obtained in 94% yield by treatment of **2a** with a 1:1 mixture of acetic anhydride and acetyl chloride.[7] Regiospecific opening of **3** with ethanol[8] afforded the crystalline acid ester **4** (58%), which was reduced with diborane in tetrahydrofuran at 0 °C to give hydroxy ester **5** in 99% yield. Hydrolysis followed by acidification produced the hydroxy lactone **6**[9] in 61% yield. As expected, fluorination of compound **6** with (diethylamido)sulfur trifluoride (DAST) gave cleanly the volatile fluoro lactone **7a** in 76% yield with inversion of configuration. Exposure of **7a** to excess methyllithium under carefully controlled conditions[10] furnished the desired fluoro diol **8a** in 62% yield.

In order to determine the optical purity of fluoro lactone **7a** and fluoro diol **8a**, we made the corresponding enantiomers, fluoro lactone **7b** and fluoro diol **8b**, from the unnatural *d*-malic acid (**2b**) by the same procedure (Scheme III). Fluoro lactones **7a** and **7b** were individually treated with *R*-(+)-α-methylbenzylamine and *p*-toluenesulfonic acid catalyst to yield the diastereomeric amides **14a** and **14b**. Analysis by 200-MHz NMR spectroscopy and by HPLC demonstrated >98% enantiomeric excesses (% ee) for the unpurified amides. For the same purpose, fluoro diols **8a** and **8b** were individually esterified with *S*-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[11,12] in pyridine at 0 °C to yield the diastereomeric monoesters **15a** and **15b**, respectively. Analysis by 200-MHz NMR spectroscopy and by HPLC indicated enantiomeric excesses of at least 98% for the unpurified esters. Thus, the fluorinations were essentially stereospecific. However, at this stage, we were not absolutely sure whether the displacement occurred with inversion or retention.[13] The solution to this problem was postponed until a later stage. These results showed, however, that little, if any, epimerization occurred during the methyllithium reaction with α-fluoro lactones **7a** and **7b**.

Fluoro diol **8a** was treated with acetic anhydride and pyridine at 0–25 °C to give monoacetate **9** (91%), which was exposed to excess ethyl vinyl ether and *p*-toluene-

(3) Horst, R. L. National Animal Disease Center, Ames, IA, unpublished results.

(4) (a) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Uskokovič, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2945. (b) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovič, M. R. *J. Org. Chem.* **1986**, *51*, 3098.

(5) (a) Wicha, J.; Bal, K. *J. Chem. Soc., Chem. Commun.* **1975**, 968. (b) Wicha, J.; Bal, K. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1282.

(6) Shiuey, S.-J.; Kulesha, I.; Partridge, J. J.; Uskokovič, M. R., unpublished results.

(7) Paul, K. G.; Johnson, F.; Favara, D. *J. Am. Chem. Soc.* **1976**, *98*, 1285.

(8) Horn, D. H. S.; Pretorius, Y. Y. *J. Chem. Soc.* **1954**, 1460.

(9) Abdallah, M. A.; Shah, J. N. *J. Chem. Soc., Perkin Trans 1* **1975**, 888.

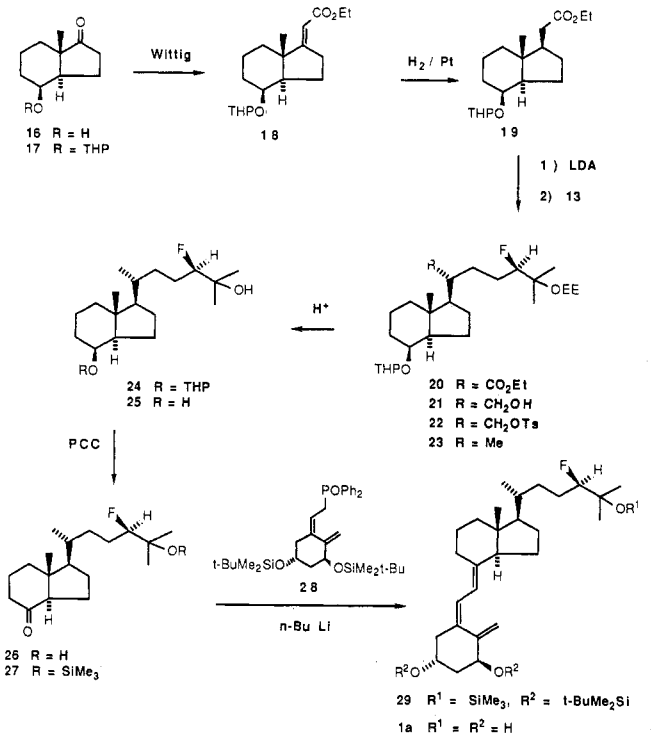
(10) Under less than optimum conditions, the cyclic hemiketal **8c** was also formed: ^{1}H NMR δ 1.45 (s, 1 H, OH), 1.56 (m, 3 H sum, CH_3), 1.95–2.60 (m, 2 H, CH_2), 4.10 (m, 2 H, CH_2O), 4.80 (dm, J = 52 Hz, 1 H sum, CHF); MS, *m/e* (relative intensity) 120 (M^+, 0.5), 105 (7), 103 (5), 60 (26), 43 (100).

(11) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(12) Uskokovič, M. R.; Lewis, R. L.; Partridge, J. J.; Despreaux, C. W.; Preuss, D. L. *J. Am. Chem. Soc.* **1979**, *101*, 6742.

(13) (a) Lowe, G.; Potter, B. V. L. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2029. (b) Shiuey, S.-J.; Kulesha, I.; Partridge, J. J.; Uskokovič, M. R., unpublished results.

Scheme IV



sulfonic acid to give the protected acetate **10** (Scheme II). Reduction with lithium aluminum hydride in ether then afforded alcohol **11** in 84% yield from **9**. Alcohol **11** was treated with *p*-toluenesulfonyl chloride in pyridine at 0 °C to give tosylate **12** in 94% yield. Immediate exposure to sodium iodide in acetone in the presence of *N*-ethyldiisopropylamine[14] at 25 °C then afforded the desired side-chain synthon, iodide **13**, in 88% yield.

The asymmetrically synthesized ketol **16**[15] was used as starting material for the preparation of the C,D-ring portion **19** (Scheme IV). Ketol **16** was treated with dihydropyran and *p*-toluenesulfonic acid to yield keto tetrahydropyran (THP) ether **17** in quantitative yield. Condensation of this substance with triethyl phosphonoacetate in ethanolic sodium ethoxide, a Horner–Wittig reaction, afforded unsaturated ester **18** (70%), which upon catalytic hydrogenation furnished the desired C,D-ring synthon **19** in 88% yield.

Treatment of **19** with lithium diisopropylamide in hexamethylphosphoramide–tetrahydrofuran followed by an addition of the side-chain synthon **13** formed efficiently the desired 20*R*-monoalkylated ester **20** in 87% yield. This alkylation was highly stereoselective with less than 5% of the undesired isomer forming. Ester **20** was sequentially reduced with lithium aluminum hydride to **21**, esterified with *p*-toluenesulfonyl chloride to **22**, and hydrogenolyzed with lithium aluminum hydride to give diacetal **23** in 79% overall yield. Brief treatment of **23** with Bio-Rad AG 50W-X4 cation-exchange resin (H^+ form) in methanol at 0 °C selectively formed the unwanted hydroxy acetal **24**. Thus, the 1-ethoxyethyl ether protecting the tertiary hydroxy group was removed in the presence of a tetrahydropyranyl group that was protecting an axial secondary alcohol. However, treatment of **23** with *p*-toluenesulfonic acid in methanol at 25 °C cleanly afforded the desired diol **25** in 69% yield after recrystallization.

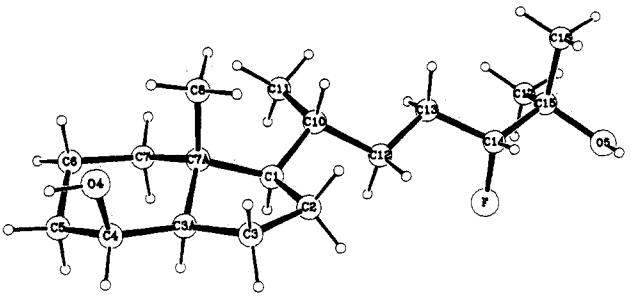


Figure 1. X-ray analysis of the compound **25**.

The stereochemical assignments of C-20 and C-24 made thus far were confirmed by a single-crystal X-ray analysis of diol **25** (Figure 1). This analysis also proved that the fluorination of hydroxy lactone **6** afforded fluoro lactone **7a** with inversion of configuration (Scheme II).

Oxidation of diol **25** with pyridinium chlorochromate in methylene chloride to ketone **26**, followed by alcohol protection using *N*-(trimethylsilyl)imidazole in methylene chloride at 25 °C, gave the protected ketone **27** in 95% overall yield from **25**. The Wittig–Horner coupling reaction with the lithium anion of A-ring synthon **28**[4] proceeded smoothly at −70 °C in tetrahydrofuran to yield the desired triene **29** in 90% yield. A final deprotection step, employing Bio-Rad AG 50W-X4 cation-exchange resin (H^+ form) in methanol, then afforded in 88% yield the desired 1α,25-dihydroxy-24(*R*)-fluorocholecalciferol (**1a**), which was identical in all respects with authentic material.[2]

Experimental Section

Materials and Methods. Melting points were measured on a Büchi-Tottoli apparatus in open capillary tubes and are uncorrected. Infrared spectra were obtained on a Digilab Model FTS-15E spectrometer. Proton NMR spectra were recorded on a Varian XL-400 (400 MHz), Varian XL 200 (200 MHz), or Varian XL 100 (100 MHz) spectrometer in $CDCl_3$ unless otherwise stated. Chemical shifts are reported in parts per million downfield from internal TMS. Mass spectral data were obtained on a Varian MAT CH-5 instrument. Ultraviolet absorption spectra were measured with a Cary Model 14 spectrometer and optical rotations with a Perkin-Elmer 241 polarimeter. Chromatographic purifications were carried out with EM Merck silica gel 60 (particle size 0.063–0.200 mm unless otherwise stated). All chromatographed products were homogeneous by silica gel TLC.

2(*S*)-Acetoxysuccinic Anhydride (3).[7] To a cold (0 °C) mixture of 30 mL (0.32 mol) of acetic anhydride and 30 mL (0.42 mol) of acetyl chloride was added, in several portions, 30.0 g (0.224 mol) of *l*-malic acid (**2a**). The mixture was stirred at 50 °C for 1.5 h. After concentration under reduced pressure, the residual liquid was distilled to afford 33.4 g (94%) of **3** as a colorless liquid: bp 112–118 °C (0.20 mm); $[\alpha]^{20}_D$ −24.3° (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 1883, 1803 (C=O, anhydride), 1758 cm^{-1} (C=O, ester); ^1H NMR δ 2.20 (s, 3 H, CH_3CO), 3.01 (dd, J = 6.5, 19 Hz, 1 H), 3.40 (dd, J = 9.5, 19 Hz, 1 H), 5.53 (dd, J = 6.5 and 9.5 Hz, 1 H, CHO); MS, *m/e* (relative intensity) 86 (22), 43 (100).

Anal. Calcd for $C_6H_6O_5$: C, 45.58; H, 3.83. Found: C, 45.63; H, 3.75.

Ethyl 2(*S*)-Acetoxy-3-carboxypropionate (4).[8] A mixture of 33.3 g (0.211 mol) of **3** and 70 mL of absolute ethanol was stirred at 50 °C for 1 h and then at room temperature for 17 h. The mixture was evaporated to dryness. The residual syrup was recrystallized from ether–hexane to yield 25.0 g (58%) of **4** as colorless crystals: mp 51–53 °C (lit.[8] mp 50–51 °C); $[\alpha]^{21}_D$ −26.1° (*c* 1.05, $CHCl_3$); IR (KBr) 3200, 2700–2500 (OH), 1750, 1735 (C=O) cm^{-1}; ^1H NMR δ 1.28 (t, J = 7 Hz, 3 H, CH_2CH_3), 2.14 (s, 3 H, CH_3CO), 2.95 (d, J = 6 Hz, 2 H, CH_2), 4.26 (q, J = 7 Hz, 2 H, CH_2CH_3), 5.46 (t, J = 6 Hz, 1 H, CHO), 10.57 (br s, 1 H, CO_2H); MS, *m/e* (relative intensity), 159 (3), 131 (10), 43 (100).

Anal. Calcd for $C_8H_{12}O_6$: C, 47.06; H, 5.92. Found: C, 47.25; H, 5.75.

(14) Markezich, R. L.; Willy, W. E.; McCarry, B. E.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, *95*, 4414.

(15) Wovkulich, P. M.; Barcelos, F.; Batcho, A. D.; Sereno, J. F.; Baggiolini, E. G.; Hennessy, B.; Uskoković, M. R. *Tetrahedron* **1984**, *40*, 2283.

Ethyl 2(S)-Acetoxy-4-hydroxybutyrate (5). To a cold (0 °C) solution of 21.8 g (0.106 mol) of **4** in 80 mL of dry THF was added dropwise with stirring 127 mL (0.127 mol) of borane in THF (1.0 M) during a 30-min period. The resulting mixture was stirred at 0 °C for 17 h and then quenched by dropwise addition of water (41 mL). After saturation with NaCl, the mixture was extracted with ether. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated to give 19.9 g (99%) of **5** as an oil: $[\alpha]^{22}_D$ −37.9° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3630 (OH), 1742 (C=O, ester) cm^{-1}; ^1H NMR δ 1.29 (t, *J* = 8 Hz, 3 H, CH_2CH_3), 1.79 (br s, 1 H, OH), 2.06 (m, 2 H, CH_2), 2.15 (s, 3 H, CH_3CO), 3.71 (br s, 2 H, CH_2O), 4.22 (q, *J* = 8 Hz, 2 H, CH_2CH_3), 5.17 (dd, *J* = 6 and 6.5 Hz, 1 H, CHO); MS, *m/e* (relative intensity) 145 (2), 117 (11), 45 (6), 43 (100).

Anal. Calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.21; H, 7.44.

2(S)-Hydroxy-γ-butyrolactone (6).[9] To 15.7 g (0.0825 mol) of **5** was added 57 mL (0.34 mol) of aqueous 6 N NaOH at 0 °C, and the resulting mixture was stirred at room temperature for 17 h. The resulting yellow solution was washed with ether, acidified with aqueous 6 N HCl, and evaporated to dryness. Water in the residue was displaced by toluene azeotrope, and the residue was then extracted with ethyl acetate. The extract was dried ($MgSO_4$) and evaporated to dryness. The residue was purified by column chromatography on silica gel using 50→90% ethyl acetate–hexane to afford 3.96 g (47%) of **6** as a colorless liquid: bp 95 °C (0.1 mm); $[\alpha]^{25}_D$ −65.2° (*c* 1.15, $CHCl_3$); IR ($CHCl_3$) 3565, 3450 (OH), 1778 (C=O) cm^{-1}; ^1H NMR δ 2.1–2.8 (m, 2 H, CH_2), 3.15 (br s, 1 H, OH), 4.1–4.7 (m, 3 H, CH_2O and CHO); MS, *m/e* (relative intensity) 73 (2), 72 (3), 58 (75), 43 (100).

Anal. Calcd for $C_4H_6O_3$: C, 47.06; H, 5.92. Found: C, 46.76; H, 6.14.

2(R)-Fluoro-γ-butyrolactone (7a). To a mixture of 13.4 mL (0.102 mol) of (diethylamido)sulfur trifluoride and 20 mL of dry methylene chloride at −70 °C was added dropwise a solution of 3.50 g (0.0343 mol) of **6** in 30 mL of dry methylene chloride. The mixture was stirred at −70 °C for 1 h, at 0 °C for 0.5 h, and at room temperature for 1 h. The mixture was then poured into a stirring mixture of saturated aqueous $NaHCO_3$ and ice chips. The mixture was extracted with methylene chloride. The organic phase was washed with water, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The oil was purified by column chromatography on silica gel using 30→70% ether–methylene chloride to afford 2.70 g (76%) of **7a** as a volatile oil: $[\alpha]^{22}_D$ +50.3° (*c* 0.95, $CHCl_3$); IR ($CHCl_3$) 1798 (C=O, lactone) cm^{-1}; ^1H NMR δ 2.20–2.84 (m, 2 H, CH_2), 4.26–4.64 (m, 2 H, CH_2O), 5.18 (dt, J_1 = 52 Hz, J_2 = 8 Hz, 1 H, CHF); MS, *m/e* (relative intensity) 104 (M^+, 1), 60 (100), 46 (56); exact mass calcd for $C_4H_5O_2F$ 104.0274, found 104.0284.

2(S)-Fluoro-γ-butyrolactone (7b). In a manner analogous to preparations of **2a** → **3** → **4** → **5** → **6** → **7a**, *d*-malic acid (**2b**) was transformed into **7b** as an oil in comparable yield: $[\alpha]^{23}_D$ −54.8° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1795 (C=O, lactone) cm^{-1}; ^1H NMR δ 2.20–2.84 (m, 2 H, CH_2), 4.26–4.64 (m, 2 H, CH_2O), 5.18 (dt, J_1 = 52 Hz, J_2 = 8 Hz, 1 H, CHF); MS, *m/e* (relative intensity) 104 (M^+, 1), 60 (100), 46 (56).

3(R)-Fluoro-4-methyl-1,4-pentanediol (8a). To a solution of 48 mL of 1.5 M ethereal methyllithium (0.072 mol) at 0 °C was added dropwise a solution of 3.02 g (0.029 mol) of **7a** in 100 mL of dry ether. The mixture was stirred at 0 °C for 0.5 h and at room temperature for 1 h. The reaction was quenched by adding 6 mL of brine at 0 °C. The mixture was poured into brine, and the product was isolated with ether. The combined ether layers were dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was chromatographed on silica gel using 50→90% ethyl acetate–hexane to give 2.46 g (62%) of **8a** as an oil: $[\alpha]^{22}_D$ +39.4° (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) 3605 (OH) cm^{-1}; ^1H NMR δ 1.26 (m, 6 H, CMe_2), 1.64 (br s, 1 H, OH), 1.76–2.22 (m, 3 H, CH_2 and OH), 3.86 (m, 2 H, CH_2O), 4.48 (dm, *J* = 48 Hz, 1 H, CHF); MS, *m/e* (relative intensity) 103 (7), 59 (100), 31 (19); exact mass calcd for $C_6H_{13}O_2F$ + H 137.0978, found 137.0965.

3(S)-Fluoro-4-methyl-1,4-pentanediol (8b). In a manner analogous to the preparation of **8a**, 720 mg (6.92 mmol) of **7b** reacted with methyllithium in ether to give 469 mg (50%) of **8b** as an oil: $[\alpha]^{21}_D$ −35.9° (*c* 0.94, $CHCl_3$); IR ($CHCl_3$) 3605 (OH) cm^{-1}; ^1H NMR δ 1.26 (m, 6 H, CMe_2), 1.64 (br s, 1 H, OH), 1.76–2.26 (m, 3 H, CH_2 and OH), 3.86 (m, 2 H, CH_2O), 4.47 (dm, *J* = 48 Hz, 1 H, CHF); MS, *m/e* (relative intensity) 103 (8), 59 (100), 31 (24).

[R-(R*,R*)]-2-Fluoro-4-hydroxy-N-(1-phenylethyl)butanamide (14a). A mixture of 50 mg (0.48 mmol) of **7a**, 0.50 mL (3.90 mmol) of *R*-(+)-α-methylbenzylamine, 1.0 mL of dry xylene, and 12 mg of *p*-toluenesulfonic acid monohydrate was heated at reflux for 36 h. After cooling, the mixture was diluted with methylene chloride (90 mL), washed with 2 N sulfuric acid and saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated to dryness to give 106 mg of **14a** as a glass:[16] ^1H NMR δ 1.55 (d, *J* = 8 Hz, 3 H, CH_3), 1.96–2.45 (m, 3 H, CH_2 and OH), 3.85 (t, *J* = 7 Hz, 2 H, CH_2O), 5.02 (dt, J_1 = 46 Hz, J_2 = 7 Hz, 1 H, CHF), 5.15 (m, 1 H, $CHCH_3$), 6.63 (br s, 1 H, NH), 7.33 (m, 5 H, Ph); MS, *m/e* (relative intensity) 225 (M^+, 4), 223 (13), 208 (8), 105 (100).

[S-(R*,S*)]-2-Fluoro-4-hydroxy-N-(1-phenylethyl)butanamide (14b). In a manner analogous to the previous experiment, 64 mg (0.61 mmol) of **7b** was converted into 140 mg of **14b** as a glass:[16] ^1H NMR δ 1.54 (d, *J* = 8 Hz, 3 H, CH_3), 1.96–2.60 (m, 3 H, CH_2 and OH), 3.80 (t, *J* = 7 Hz, 2 H, CH_2O), 5.07 (dt, J_1 = 49 Hz, J_2 = 7 Hz, 1 H, CHF), 5.16 (m, 1 H, $CHCH_3$), 5.65 (br s, 1 H, NH), 7.34 (m, 5 H, Ph); MS, *m/e* (relative intensity) 225 (M^+, 15), 223 (8), 210 (5), 208 (4), 105 (100).

[R-(R*,R*)]-α-(Trifluoromethyl)-α-methoxyphenylacetic Acid 3-Fluoro-4-hydroxy-4-methylpentyl Ester (15a). To a cold (0 °C) mixture of 30 mg (0.22 mmol) of **8a** and 1 mL of dry pyridine was added a solution of 137 mg (0.542 mmol) of *S*-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[11,12] in 1 mL of dry pyridine dropwise, and the mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by addition of ice chips. After being stirred for 10 min, the mixture was partitioned between methylene chloride and 2 N sulfuric acid. The organic phase was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to dryness to give an oil. The oil was triturated with warm hexane. The hexane extract (free of Na salt of α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA)) was evaporated to dryness to give 76 mg of **15a** as a crude oil:[17] ^1H NMR δ 1.17 (d, *J* = 2 Hz, 3 H, CH_3), 1.22 (d, *J* = 2 Hz, 3 H, CH_3), 1.70 (br s, 1 H, OH), 1.86–2.15 (m, 2 H, CH_2), 3.57 (s, 3 H, OCH_3), 4.23 (dm, *J* = 48 Hz, 1 H, CHF), 4.52 (m, 2 H, CH_2O), 7.36–7.64 (m, 5 H, Ph).

[S-(R*,S*)]-α-(Trifluoromethyl)-α-methoxyphenylacetic Acid 3-Fluoro-4-hydroxy-4-methylpentyl Ester (15b). In a manner analogous to the previous experiment, 30 mg (0.22 mmol) of **8b** was converted to 82 mg of **15b** as a crude oil:[17] ^1H NMR δ 1.17 (d, *J* = 2 Hz, 3 H, CH_3), 1.21 (d, *J* = 2 Hz, 3 H, CH_3), 1.75 (br s, 1 H, OH), 1.85–2.20 (m, 2 H, CH_2), 3.57 (s, 3 H, OCH_3), 4.08–4.20 (m, 0.5 H, half of CHF), 4.34–4.70 (m, 2.5 H, half of CHF and CH_2O), 7.36–7.64 (m, 5 H, Ph).

3(R)-Fluoro-4-methyl-1,4-pentanediol 1-Acetate (9). To a mixture of 2.35 g (0.0173 mol) of **8a** and 11 mL of dry pyridine at 0 °C was added 11 mL of acetic anhydride, and the mixture was stirred at 0 °C for 20 min and at room temperature for 1.5 h. After cooling at 0 °C, 11 mL of methanol was added and the mixture was stirred for 5 min. After evaporation, the residual oil was diluted with water and extracted with methylene chloride. The organic phase was washed with 2 N aqueous sulfuric acid, saturated aqueous $NaHCO_3$, and brine and dried over $MgSO_4$. The mixture was filtered and evaporated to dryness to yield 2.81 g (91%) of **9** as an oil: $[\alpha]^{22}_D$ +48.8° (*c* 0.52, $CHCl_3$); IR ($CHCl_3$) 3600 (OH), 1740 (C=O, ester) cm^{-1}; ^1H NMR δ 1.23 (d, *J* = 2 Hz, 3 H, CH_3), 1.26 (d, *J* = 2 Hz, 3 H, CH_3), 1.87 (br s, 1 H, OH), 2.00 (m, 2 H, CH_2), 2.08 (s, 3 H, CH_3CO), 4.30 (m, 2 H, CH_2O), 4.42 (dm, 1 H, CHF); MS, *m/e* 179 (M + H, 1), 120 (13), 103 (25), 100 (4), 59 (100).

(R)-4-(1-Ethoxyethoxy)-3-fluoro-4-methyl-1-pentanol Acetate (10). To a mixture of 2.48 g (0.0139 mol) of **9** and 65 mL of ethyl vinyl ether at −45 °C was added 0.32 g of *p*-toluenesulfonic acid monohydrate. The mixture was stirred at 0 °C for 1 h, then quenched by addition of 8 mL of triethylamine,

(16) The yield was near quantitative by silica gel TLC (using 1:1 ether–methylene chloride as a developing solvent).

(17) The yield was near quantitative by silica gel TLC (using ethyl acetate as a developing solvent).

and evaporated to dryness. The residue was dissolved in ether. This solution was successively washed with saturated aqueous $NaHCO_3$ and brine. The ether phase was dried ($MgSO_4$), filtered, and evaporated to dryness to yield 5.1 g[18] of a crude oil containing >98% of **10**: IR ($CHCl_3$) 1740 (C=O, ester), 1090, 1058 (COC) cm^{-1}; ^1H NMR δ 1.10–1.38 (m, 12 H, 4 CH_3), 1.80–2.10 (m, 2 H, CH_2), 2.09 (s, 3 H, CH_3CO), 3.55 (m, 2 H, CH_2O), 4.30 (m, 2 H, CH_2O), 4.42 (dm, J = 42 Hz, 1 H, CHF), 4.96 (m, 1 H, OCHO); MS, m/e 131 (1), 73 (100), 61 (5), 59 (9), 45 (37).

(*R*)-4-(1-Ethoxyethoxy)-3-fluoro-4-methyl-1-pentanol (11). To a mixture of 0.79 g (0.021 mol) of $LiAlH_4$ in 40 mL of dry ether at 0 °C was added dropwise 5.1 g (ca. 0.014 mol) of **10** in 115 mL of dry ether. The mixture was heated at reflux (ca. 35 °C) for 3 h and then was cooled to 0 °C. The mixture was quenched by addition of 1.5 mL of water followed by 1.2 mL of 10% aqueous sodium hydroxide. The mixture was stirred at 25 °C for 0.5 h and filtered. Evaporation of solvent and column chromatography of the residue on silica gel (30→50% ethyl acetate–hexane) afforded 2.84 g (98%) of **11** as an oil: $[\alpha]^{24}_D$ +17.5° (*c* 0.96, $CHCl_3$); IR ($CHCl_3$) 3620 (OH), 1080, 1050 (COC) cm^{-1}; ^1H NMR δ 1.10–1.38 (m, 12 H, 4 CH_3), 1.61 (br s, 1 H, OH), 1.80–2.10 (m, 2 H, CH_2), 3.62 (m, 2 H, CH_2O), 3.84 (br s, 2 H, CH_2O), 4.46 (dm, J = 48 Hz, 1 H, CHF), 4.97 (m, 1 H, OCHO); MS, *m/e* 163 (1), 131 (4), 119 (12), 73 (100).

(*R*)-4-(1-Ethoxyethoxy)-3-fluoro-4-methyl-1-pentanol 4-Methylbenzenesulfonate (12). A mixture of 3.34 g (0.016 mol) of **11**, 12 mL of pyridine, and 4.67 g (0.024 mol) of *p*-toluenesulfonyl chloride was stirred at 0 °C for 18 h. The reaction was quenched with ice chips. The mixture was diluted with water and extracted with methylene chloride. The organic phase was sequentially washed with 1 N sulfuric acid and saturated aqueous $NaHCO_3$. The organic phase was then dried ($MgSO_4$), filtered, and evaporated to dryness to yield 5.45 g (94%) of **12** as an oil: IR ($CHCl_3$) 1600 (aromatic), 1365, 1178 (SO_2) cm^{-1}; ^1H NMR δ 1.08–1.35 (m, 12 H, 4 CH_3), 1.96 (m, 2 H, CH_2), 2.46 (s, 3 H, $CH_3C_6H_4$), 3.47 (m, 2 H, CH_2O), 4.19 (m, 2 H, CH_2OTs), 4.30 (dm, J = 48 Hz, 1 H, CHF), 4.93 (m, 1 H, OCHO), 7.58 (q, 4 H, aromatic CH, A_2B_2, J_{AB} = 8 Hz, $\Delta\nu_{AB}$ = 92 Hz); MS, *m/e* 347 (0.5), 273 (3), 155 (6), 73 (100).

(*R*)-4-(1-Ethoxyethoxy)-3-fluoro-1-iodo-4-methylpentane (13). A mixture of 5.42 g (0.015 mol) of **12**, 70 mL of acetone, 1.25 mL of diisopropylethylamine, and 30.3 g (0.202 mol) of sodium iodide was stirred at 25 °C for 17 h.[14] The residue was partitioned between 5% aqueous sodium sulfite solution and methylene chloride. The organic phase was washed with saturated aqueous $NaHCO_3$, then dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was chromatographed on silica gel using 10→20% ethyl acetate–hexane to give 4.19 g (88%) of **13** as an oil: $[\alpha]^{24}_D$ +42.6° (*c* 0.97, $CHCl_3$); IR ($CHCl_3$) 1385 (CF) 1143, 1115, 1087 (COC) cm^{-1}; UV max (ethanol) 255 nm; ^1H NMR δ 1.10–1.40 (m, 12 H, 4 CH_3), 2.20 (m, 2 H, CH_2), 3.30 (m, 2 H, CH_2I), 3.51 (m, 2 H, CH_2O), 4.31 (dm, J = 48 Hz, 1 H, CHF), 4.95 (m, 1 H, OCHO); MS, *m/e* (relative intensity) 273 (1), 229 (13), 155 (11), 127 (1), 73 (100), 45 (55).

[3a*R*-(3aα,4β,7aβ)]-Octahydro-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-7a-methyl-1*H*-inden-1-one (17). A mixture of 2.00 g (0.0119 mol) of **16**,[15] 3.13 g (0.0373 mol) of distilled dihydropyran, and 57 mL of THF was cooled at 0 °C. *p*-Toluenesulfonic acid monohydrate (70 mg) was added, and the mixture was stirred at 25 °C for 19 h. After being quenched with aqueous $NaHCO_3$, the mixture was extracted with methylene chloride. The extract was washed with brine, dried ($MgSO_4$), and evaporated to dryness to yield 3.35 g (ca. 100%) of **17**: $[\alpha]^{25}_D$ +87.7° (*c* 0.51, $CHCl_3$); IR ($CHCl_3$) 1732 (C=O, ketone), 1113–1075 (COC) cm^{-1}; ^1H NMR δ 1.12 (s, 3 H, CH_3), 3.30–3.68 (m, 1 H, CH of CHO), 3.72–4.26 (m, 2 H, CH of CH_2O and CHO), 4.69 (br d, 1 H, OCHO); MS, *m/e* (relative intensity) 252 (M^+, 2), 151 (14), 133 (8), 85 (100).

[3a*R*-(3aα,4β,7aβ)]-[Octahydro-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-7a-methyl-1*H*-inden-1-ylidene]acetic Acid Ethyl Ester (18). To a mixture of 2.61 g (0.0103 mol) of **17**, 12.3 g (0.0548 mol) of triethyl phosphonoacetate, and 46 mL of dry ethanol was added 3.73 g (0.0548 mol) of sodium ethoxide in 35 mL of dry ethanol. The mixture was stirred at reflux (80 °C) for 22 h, cooled, and concentrated under reduced pressure. The residue was partitioned between water and ether, and the organic phase was washed with brine. The organic phase was then dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was chromatographed on silica gel by using 20% ethyl acetate–hexane to yield 2.32 g (70%) of **18** as a glass: $[\alpha]^{25}_D$ +31.8° (*c* 0.49, $CHCl_3$); IR ($CHCl_3$) 1700 (C=O), 1650 (C=C) cm^{-1}; UV max (ethanol) 220 nm (ϵ 21 490); ^1H NMR δ 1.06, 1.07 (2 s, due to THP, 3 H sum, CH_3), 1.26 (t, J = 7 Hz, 3 H, CH_2CH_3), 2.82 (m, 2 H, allylic CH), 3.50 (br s, 1 H, CH of CH_2O), 3.75–4.06 (m, 2 H, CH of CH_2O and CHO), 4.15 (q, J = 7 Hz, 2 H, CH_2CH_3), 4.62, 4.83 (2 br s, 1 H sum, OCHO), 5.49 (m, 1 H, vinyl CH); MS, *m/e* (relative intensity) 322 (M^+, 0.5), 277 (1), 221 (15), 85 (100).

Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.70; H, 9.42.

[1*R*-(1β,3aα,4β,7aβ)]-Octahydro-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-7a-methyl-1*H*-indene-1-acetic Acid Ethyl Ester (19). A mixture of 2.32 g (0.00719 mol) of **18**, 1.22 g of platinum oxide, and 340 mL of ethanol was stirred in 1 atm of hydrogen for 3 h. The mixture was filtered through a pad of diatomaceous earth, and the solids were washed with methylene chloride. The combined filtrates were evaporated to dryness. The residue was chromatographed on silica gel using 15% ethyl acetate–hexane to yield 2.06 g (88%) of **19** as an oil: $[\alpha]^{25}_D$ −33.5° (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 1725 (C=O, ester), 1137–1075 (COC) cm^{-1}; ^1H NMR δ 0.84, 0.85 (2 s, due to THP, 3 H sum, CH_3), 1.26 (t, J = 8 Hz, 3 H, CH_2CH_3), 3.50 (m, 1 H, CH of CH_2O), 3.80–4.05 (m, 2 H, CH of CH_2O and CHO), 4.13 (q, J = 8 Hz, 2 H, CH_2CH_3), 4.58, 4.73 (2 br s, 1 H sum, OCHO); MS, *m/e* (relative intensity) 324 (M^+, 0.5), 279 (1), 223 (26), 85 (100).

[1*R*-[1β(1*R,3*R**),3aα,4β,7aβ]]-α-[4-(1-Ethoxyethoxy)-3-fluoro-4-methylpentyl]octahydro-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-7a-methyl-1*H*-indene-1-acetic Acid Ethyl Ester (20).** To a solution of 1.12 mL of diisopropylamine in 4.4 mL of THF at −30 °C was added 4.20 mL (0.00672 mol) of 1.6 M solution of *n*-butyllithium in hexane. After the mixture was stirred for 20 min, 1.98 g (0.0061 mol) of **19** in 50 mL of THF was added dropwise. The mixture was stirred for 1 h at −30 °C and cooled to −70 °C. A solution of 3.53 g (0.0111 mol) of **13** in 7 mL of dry HMPA was added dropwise. The mixture was stirred at −70 °C for 1 h and was allowed to warm to 25 °C during 1.5 h. The mixture was then diluted with 1:11 ether–hexane. The solution was washed with water and brine, and the organic phase was dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was purified by column chromatography on silica gel using 10→30% ethyl acetate–hexane to give 3.20 g (87%) of **20** as a glass: $[\alpha]^{25}_D$ +45.9° (*c* 0.30, $CHCl_3$); IR ($CHCl_3$) 1722 (C=O, ester), 1093, 1033 (COC) cm^{-1}; ^1H NMR δ 0.94, 0.95 (2 s, due to THP, 3 H sum, CH_3), 1.14–1.32 (m, 15 H, 5 CH_3), 3.40–3.64 (m, 3 H, CH of CH_2O and CH_2O), 3.80–4.06 (m, 2 H, CH of CH_2O and CHO), 4.15 (q, J = 7 Hz, 2 H, CH_2CH_3), 4.28 (dm, J = 44 Hz, 1 H, CHF), 4.57, 4.72 (2 br s, 1 H sum, OCHO), 5.01 (m, 1 H, OCHO); MS, *m/e* (relative intensity) 468 (0.2), 425 (5), 323 (20), 85 (89), 73 (100).

Anal. Calcd for $C_{29}H_{51}O_6F$: C, 67.67; H, 9.99; F, 3.69. Found: C, 67.55; H, 9.77; F, 3.89.

[1*R*-[1β(1*R,3*R**),3aα,4β,7aβ]]-α-[4-(1-Ethoxyethoxy)-3-fluoro-4-methylpentyl]octahydro-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-7a-methyl-1*H*-indene-1-ethanol (21).** To a mixture of 0.358 g (0.00943 mol) of $LiAlH_4$ and 18 mL of dry ether at 0 °C was added 3.14 g (0.0061 mol) of **20** in 63 mL of dry ether. The mixture was heated at reflux (ca. 35 °C) for 1.3 h and cooled to 0 °C. The mixture was then quenched with the dropwise addition of 0.72 mL of water and 0.58 mL of 10% aqueous sodium hydroxide. The mixture was stirred at 25 °C for 1 h and filtered, and the solids were triturated with ether and filtered. Evaporation of solvent afforded 2.90 g (ca. 100%) of **21** as a glass: $[\alpha]^{25}_D$ +40.8° (*c* 0.38, $CHCl_3$); IR ($CHCl_3$) 3625 (OH), 1085–1003 (COC) cm^{-1}; ^1H NMR δ 0.94, 0.95 (2 s, due to THP, 3 H sum, CH_3), 1.14–1.34 (m, 12 H, 4 CH_3), 3.52 (m, 2 H, CH_2O), 3.60–4.06 (m, 3 H, CH_2O and CHO), 4.25 (dm, J = 48 Hz, 1 H, CHF), 4.58, 4.74 (2 br s, 1 H sum, OCHO), 4.96 (m, 1 H, OCHO); MS, *m/e* 399 (0.5), 383 (0.5), 363 (1), 281 (7), 85 (100).

[1*R*-[1β(1*R,3*R**),3aα,4β,7aβ]]-α-[4-(1-Ethoxyethoxy)-3-fluoro-4-methylpentyl]octahydro-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-7a-methyl-1*H*-indene-1-ethanol 4-Methylbenzenesulfonate (22).** A mixture of 2.84 g (0.00601 mol) of

(18) The crude oil was contaminated with some unknown polymer of ethyl vinyl ether.

21, 15 mL of pyridine, and 2.40 g (0.0123 mol) of *p*-toluenesulfonyl chloride was stirred at 0 °C for 18 h. The mixture was quenched with ice chips, then poured into water, and extracted with methylene chloride. The organic phase was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and evaporated to dryness to yield 3.74 g (99%) of **22** as a glass: IR ($CHCl_3$) 1360, 1175 (SO_2) cm^{-1}; UV max (ethanol) 225 nm (ε 11 990), 251 (1625), 257 (1810), 263 (1440), 273 (525); ^1H NMR δ 0.83, 0.85 (2 s, due to THP, 3 H sum, CH_3), 1.13–1.32 (m, 12 H, 4 CH_3), 2.45 (s, 3 H, $CH_3C_6H_4$), 3.40–3.61 (m, 2 H, CH_2O), 3.80–4.32 (m, 6 H, CH_2OTs, CH_2O, CHO, and CHF), 4.56, 4.71 (2 br s, 1 H sum, OCHO), 4.96 (m, 1 H, OCHO), 7.57 (q, 4 H, aromatic CH, A_2B_2, J_{AB} = 8 Hz, $\Delta\nu_{AB}$ = 92 Hz).

[1*R*-[1β(1*R,3*R**),3aα,4β,7aβ]]-1-[5-(1-Ethoxyethoxy)-4-fluoro-1,5-dimethylhexyl]octahydro-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-7a-methyl-1*H*-indene (23).** To a mixture of 0.790 g (0.0208 mol) of $LiAlH_4$ and 20 mL of dry THF at 0 °C was added 3.70 g (0.0059 mol) of **22** in 70 mL of dry THF. The mixture was heated at reflux (ca. 68 °C) for 50 min and cooled to 0 °C. After dilution with 230 mL of dry ether, the mixture was quenched with the dropwise addition of 1.6 mL of water and 1.3 mL of 10% aqueous sodium hydroxide. The mixture was stirred at 25 °C for 1 h and filtered, and the solids were triturated with ether and filtered. The combined filtrates were evaporated to dryness and chromatographed on silica gel using 15% ethyl acetate–hexane to yield 2.15 g (80%) of **23** as a glass: $[\alpha]^{25}_D$ +53.3° (*c* 0.51, $CHCl_3$); IR ($CHCl_3$) 1112–1002 (COC) cm^{-1}; ^1H NMR δ 0.88–0.98 (m, due to THP, 6 H sum, 2 CH_3), 1.19 (t, *J* = 7 Hz, 3 H, CH_2CH_3), 1.21–1.34 (m, 9 H, CMe_2 and $CHCH_3$), 3.42–3.68 (m, 3 H, CH of CH_2O and CH_2O), 3.82–4.05 (m, 2 H, CH of CH_2O and CHO), 4.22 (dm, *J* = 45 Hz, 1 H, CHF), 4.59, 4.74 (2 br s, 1 H sum, OCHO), 4.99 (m, 1 H, OCHO); MS, *m/e* 411 (1), 367 (1), 85 (48), 73 (12), 45 (100).

Anal. Calcd for $C_{27}H_{49}O_4F$: C, 71.01; H, 10.82; F, 4.16. Found: C, 70.89; H, 10.83; F, 4.30.

[1*R*-[1β(1*R,4*R**),3aα,4β,7aβ]]-β-Fluorooctahydro-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-α,α,ε,7a-tetramethyl-1*H*-indene-1-pentanol (24).** To a solution of 0.200 g (0.411 mmol) of **23** in 30 mL of methanol was added 0.60 g of the H^+ form of cationic exchange resin (AG 50W-X4).[19] The mixture was stirred at 0 °C for 10 min and filtered. The resins were triturated with methanol and filtered. The combined filtrates were evaporated to dryness to give 151 mg (98%) of **24** as a glass: IR ($CHCl_3$) 3595 (OH) cm^{-1}; ^1H NMR δ 0.82–0.98 (m, due to THP, 6 H sum, 2 CH_3), 1.22 (br s, 6 H, CMe_2), 3.40–3.58 (m, 1 H, CH of CH_2O), 3.80–4.14 (m, 2 H, CH of CH_2O and CHO), 4.22 (dm, *J* = 48 Hz, 1 H, CHF), 4.57 (m, 1 H, OCHO), 4.73 (m, 1 H, OCHO); MS, *m/e* (relative intensity) 384 (M^+, 1), 283 (1), 257 (0.5), 189 (2), 85 (100).

[1*R*-[1β(1*R,4*R**),3aα,4β,7aβ]]-β-Fluorooctahydro-4-hydroxy-α,α,ε,7a-tetramethyl-1*H*-indene-1-pentanol (25).** A mixture of 1.75 g (3.83 mmol) of **23**, 100 mL of methanol, and 294 mg of *p*-toluenesulfonic acid monohydrate was stirred at 25 °C for 3 h. The mixture was quenched by addition of excess solid $NaHCO_3$ and evaporated to dryness. The residue was taken up with methylene chloride and filtered, and the solids were triturated with methylene chloride and filtered. The combined filtrates were evaporated to dryness, and the residue was recrystallized from ethyl acetate–hexane to yield 0.802 g (70%) of **25** as colorless crystals: mp 90–92 °C; $[\alpha]^{25}_D$ +65.4° (*c* 0.50, MeOH); IR (KBr) 3380 (OH) cm^{-1}; ^1H NMR (CD_3OD) δ 0.94 (d, *J* = 7 Hz, 3 H, $CHCH_3$), 0.96 (s, 3 H, CH_3), 1.17, 1.18 (2 s, 6 H, CMe_2), 4.03 (br s, 1 H, CHO), 4.10 (dm, *J* = 48 Hz, 1 H, CHF); MS, *m/e* 300 (M^+), 282 (2), 267 (2), 265 (1), 209 (4), 111 (100).

Anal. Calcd for $C_{18}H_{33}O_2F$: C, 71.96; H, 11.07; F, 6.32. Found: C, 71.76; H, 11.07; F, 6.39.

[1*R*-[1β(1*R,4*R**),3aα,7aβ]]-1-(4-Fluoro-5-hydroxy-1,5-dimethylhexyl)octahydro-7a-methyl-4*H*-inden-4-one (26).** To a solution of 0.168 g (0.56 mmol) of **25** in 8 mL of methylene chloride was added a slurry of 0.37 g (1.70 mmol) of pyridinium chlorochromate (98%) in 2 mL of methylene chloride, and the mixture was stirred at 25 °C for 1.3 h. After addition of 15 mL of ether, the mixture was stirred at 25 °C for 5 min and filtered. The solids were triturated with ether and filtered, and the combined filtrates were evaporated to dryness. The residue was purified by column chromatography on 40–63-μm silica gel using 1:1 hexane–ethyl acetate to give 168 mg (100%) of **26** as a glass: $[\alpha]^{25}_D$ +25.5° (*c* 0.51, $CHCl_3$); IR ($CHCl_3$) 3590 (OH), 1705 (C=O, ketone) cm^{-1}; ^1H NMR δ 0.66 (s, 3 H, CH_3), 0.97 (d, *J* = 7 Hz, 3 H, $CHCH_3$), 1.24, 1.26 (2 d, *J* = 2 Hz, 6 H, CMe_2), 2.15–2.32 (m, 2 H, CH_2), 2.45 (m, 1 H, CHCO), 4.19 (dm, *J* = 48 Hz, 1 H, CHF); MS, *m/e* (relative intensity) 298 (M^+, 6), 283 (8), 280 (3), 255 (6), 240 (16), 151 (58), 59 (100).

[1*R*-[1β(1*R,4*R**),3aα,7aβ]]-1-[4-Fluoro-1,5-dimethyl-5-[(trimethylsilyl)oxy]hexyl]octahydro-7a-methyl-4*H*-inden-4-one (27).** To a solution of 0.148 g (0.50 mmol) of **26** in 9 mL of dry methylene chloride was added 0.478 g (3.41 mmol) of 1-(trimethylsilyl)imidazole. The mixture was then stirred at 25 °C for 16 h, quenched by addition of 3.4 mL of water, and stirred at 25 °C for 20 min. The mixture was extracted with ethyl acetate, and the organic phase was washed with brine, dried (Na_2SO_4), and evaporated to dryness. The residue was chromatographed on 40–63-μm silica gel using 2:1 hexane–ethyl acetate to afford 0.171 g (98%) of **27** as a glass: $[\alpha]^{25}_D$ +21.9° ($CHCl_3$); IR ($CHCl_3$) 1707 (C=O, ketone), 842 ($SiMe_3$) cm^{-1}; ^1H NMR δ 0.12 (s, 9 H, $SiMe_3$), 0.64 (s, 3 H, CH_3), 0.96 (d, *J* = 7 Hz, 3 H, $CHCH_3$), 1.20 and 1.24 (2 s, 6 H, CMe_2), 2.15–2.29 (m, 2 H, CH_2), 2.45 (dd, 1 H, CHCO), 4.05 (dm, *J* = 48 Hz, 1 H, CHF); MS, *m/e* 355 (0.5), 312 (5), 297 (1), 131 (100), 73 (34).

(1α,3β,5*Z*,7*E*,24*R*)-24-Fluoro-1,3-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-25-[(trimethylsilyl)oxy]-9,10-secocholesta-5,7,10(19)-triene (29). To a solution of 0.415 g (0.66 mmol) of **28**[4] in 10 mL of dry THF was added dropwise at −70 °C 0.402 mL (0.64 mmol) of a 1.6 M solution of *n*-butyllithium in hexane. After the mixture was stirred for 5 min, a solution of 0.154 g (0.44 mmol) of **27** in 2.5 mL of dry THF was added dropwise. The mixture was stirred at −70 °C for 1.25 h and quenched by addition of a 1:1 mixture of 2 N aqueous potassium hydrogen tartrate and 2 N aqueous potassium bicarbonate. The mixture was extracted with ethyl acetate, and the organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was purifed by column chromatography on 40–63-μm silica gel using 20:1 hexane–ethyl acetate to give 0.240 g (90%) of **29** as a glass: $[\alpha]^{25}_D$ +43.2° (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) 1645, 1635 (C=C), 838 ($SiMe_3$) cm^{-1}; ^1H NMR δ 0.05 (s, 12 H, 2 $SiMe_3$), 0.12 (s, 9 H, $SiMe_3$), 0.54 (s, 3 H, CH_3), 0.88 (s, 18 H, 2 CMe_3), 0.93 (d, *J* = 7 Hz, 3 H, $CHCH_3$), 1.19 and 1.24 (2 s, 6 H, CMe_2), 2.20 (m, 1 H), 2.44 (m, 1 H), 2.82 (m, 1 H), 4.06 (dm, *J* = 48 Hz, 1 H, CHF), 4.18 (br s, 1 H, CHO), 4.37 (br s, 1 H, CHO), 4.88 (s, 1 H, vinyl CH), 5.17 (s, 1 H, vinyl CH), 6.02 (d, *J* = 12 Hz, 1 H, vinyl CH), 6.24 (d, *J* = 12 Hz, 1 H, vinyl CH); MS, *m/e* (relative intensity) 734 (M^+, 13), 719 (2), 677 (1), 602 (46), 587 (4), 471 (3), 383 (3), 368 (2), 73 (100).

1α,25-Dihydroxy-24(*R*)-fluorocholecalciferol (1a). To a solution of 0.274 g (0.372 mmol) of **29** in 13 mL of 1:9 methylene chloride–methanol was added 5.3 g of the H^+ form of cationic exchange resin (AG 50W-X4).[19] The mixture was stirred at 20 °C for 16 h and filtered. The resins were triturated with methanol and filtered, and the combined filtrates were evaporated to dryness. The residue was purified with a Waters Associates liquid chromatograph Model 440 using a Whatman M-9 (9.4 mm × 50 cm) silica gel column and 9:1 ethyl acetate–hexane as an eluent to afford 0.142 g (88%) of 1α,25-dihydroxy-24(*R*)-fluorocholecalciferol (**1a**) as a glass: $[\alpha]^{25}_D$ +67.9° (*c* 0.52, MeOH); IR ($CHCl_3$) 3420 (OH), 1635 (C=C) cm^{-1}; UV max (ethanol) 213 nm (ε 12 500), 265 (16 385); ^1H NMR δ 0.56 (s, 3 H, CH_3), 0.95 (d, *J* = 7 Hz, 3 H, $CHCH_3$), 1.22 and 1.24 (2 s, 6 H, CMe_2), 2.33 (m, 1 H), 2.64 (m, 1 H), 2.84 (m, 1 H), 4.21 (dm, *J* = 48 Hz, 1 H, CHF), 4.26 (br s, 1 H, CHO), 4.46 (br s, 1 H, CHO), 5.01 (s, 1 H, vinyl CH), 5.33 (s, 1 H, vinyl CH), 6.03 (d, *J* = 12 Hz, 1 H, vinyl CH), 6.39 (d, *J* = 12 Hz, 1 H, vinyl CH); MS, *m/e* (relative intensity) 434 (M^+, 13), 416 (11), 398 (3), 375 (2), 287 (7), 152 (36), 134 (100).[20]

X-ray Crystallographic Analysis of 25. Crystals of **25** ($C_{18}H_{33}FO_2$, M_r 300.46], obtained from ether–hexane, are monoclinic, space group *C*2, with *a* = 28.044 (3) Å, *b* = 5.959 (2) Å, *c* = 10.591 (2) Å, β = 96.39 (1)°, and d_{calcd} = 1.135 g cm^{-3} for *Z* = 4. The intensity data were measured on an Enraf-Nonius CAD4

(19) This resin was purchased from Bio-Rad Laboratories, Richmond, CA 94804.

(20) For a recent review of biologically active organofluorine compounds, see: Welch, J. T. *Tetrahedron* **1987**, *43*, 3123.

diffractometer (graphite-monochromated Cu Kα radiation, W-2θ scans). The size of the crystal used for data collection was approximately 0.11 × 0.13 × 0.83 mm; the data were not corrected for absorption. Of the 1406 independent reflections for $\theta < 60°$, 1406 were considered to be observed [$I > 3.0\sigma(I)$]. The structure was solved by a multiple-solution procedure[21] and was refined by full-matrix least squares. In the final refinement, anisotropic thermal parameters were used for the nonhydrogen atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices are $R = 0.054$ and $wR = 0.073$ for the 1406 observed reflections. The final difference map has no peaks greater than 0.3 e Å^{-3}.

(21) Main, P.; Fiske, S.; Hull, S.; Lessinger, L.; Germain, G.; Declercq, J.-P.; Woolfson, M. MULTAN 11/82; University of York, England and University of Louvain, Belgium, 1982.

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Registry No. **1a**, 86677-62-5; **2a**, 97-67-6; **2b**, 636-61-3; **3**, 59025-03-5; **4**, 52485-05-9; **5**, 76224-59-4; **6**, 52079-23-9; **7a**, 86677-74-9; **7b**, 86677-82-9; **8a**, 86677-75-0; **8b**, 86677-83-0; **9**, 86677-76-1; **10**, 107900-37-8; **11**, 107900-38-9; **12**, 107900-39-0; **13**, 107900-40-3; **14a**, 112138-90-6; **14b**, 112138-91-7; **15a**, 112138-92-8; **15b**, 112138-93-9; **16**, 93489-57-7; **17**, 112138-94-0; **18**, 112138-95-1; **19**, 112138-96-2; **20**, 112138-97-3; **21**, 112138-98-4; **22**, 112138-99-5; **23**, 112139-00-1; **24**, 112139-01-2; **25**, 112139-02-3; **26**, 112151-59-4; **27**, 112139-03-4; **28**, 81522-68-1; **29**, 112139-04-5; MeOC(Ph)(CF$_3$)COCl, 20445-33-4; EtOCH=CH$_2$, 109-92-2; (EtO)$_2$POCH$_2$CO$_2$Et, 867-13-0; (*R*)-(+)-methylbenzylamine, 3886-69-9; dihydropyran, 110-87-2.

A Highly Stereocontrolled Route to the Monensin Spiroketal Ring System

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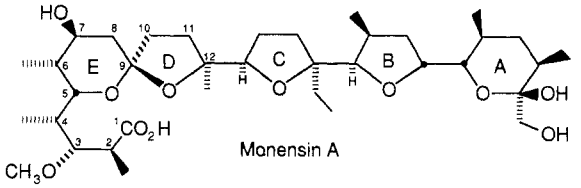
A highly stereoselective approach to the construction of the monensin A spiroketal ring system is illustrated by a total synthesis of enantiomerically pure spiroketal **35**. Key steps include cyclization of the diketo diol deriving from deprotection of dione **33** to the spiroketal ketone **34**, followed by reduction of ketone **34** to afford the target hydroxy spiroketal **35** containing all of the important structural elements of the monensin A DE ring system. The structure of compound **35** is established by single-crystal X-ray analysis. The key intermediate ketone **31** is prepared in enantiomerically pure form by using Evans' asymmetric aldol chemistry.

Introduction

The polyether antibiotics (ionophores) represent especially attractive targets for total synthesis due to their novel and interesting biological activity, physicochemical properties, and structural complexity.[1] Monensin A (hereafter simply referred to as monensin), in particular, has received a large amount of attention from the synthetic community[2] in part due to its historical and commercial importance.



Monensin A

In addition, monensin possesses a moderately complex structure with many of the most interesting features representative of this class of natural products and has been perhaps the most well studied ionophore with respect to physical properties[3] and biosynthesis.[4] Monensin gains additional attractiveness as a target due to its novel Na^+ selectivity: methods developed for construction of monensin may in principle find utility for preparation of more highly Na^+ selective analogues,[3b,d] which could prove useful as biochemical probes, and even as cardiovascular drugs.

Any strategy for the total synthesis of monensin must confront the interesting spiroketal DE ring system. Development of methods for preparation of this structural fragment gain added importance due to the occurrence of similar ring systems in a variety of other natural products, such as phyllanthocin[5] and calyculin.[6] In considering the problem in the context of monensin, the availability of

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(1) *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Westley, J. W., Ed.; Marcel Dekker: New York, 1983; Vol. 1-2.

(2) Total syntheses of monensin A: (a) Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259-260. Fukuyama, T.; Wang, C.-L. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 260-262. Fukuyama, T.; Akasaka, K.; Karenewsky, D. S.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 262-263. (b) Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2117-2118, 2118-2120, and 2120-2121. Syntheses of structural fragments of monensin: (c) Walba, D. M.; Edwards, P. D. *Tetrahedron Lett.* **1980**, *21*, 3531-3534. (d) Walba, D. M.; Wand, M. D. *Tetrahedron Lett.* **1982**, *23*, 4995-4999. (e) Ireland, R. E.; Häbich, D.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3271-3278. Ireland, R. E.; Norbeck D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3279-3285. Ireland, R. E.; Norbeck, D. W.; Mandel, N. S. *J. Am. Chem. Soc.* **1985**, *107*, 3285-3294. (f) Bartlett, P. A.; Holm, K. H.; Morimoto, A. *J. Org. Chem.* **1985**, *50*, 5179-5183. (g) Danishefsky, S.; Harvey, D. F. *J. Am. Chem. Soc.* **1985**, *107*, 6647-6652. Polyene and polyepoxide biomimetic routes to monensin: (h) VanMiddlesworth, F.; Patel, D. V.; Donaubauer, J.; Garnett, P.; Sih, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 2996-2997. Patel, D. V.; VanMiddlesworth, F.; Donaubauer, J.; Gannett, P.; Sih, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 4603-4616. (i) Still, C. W.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105-2106. (j) Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106-2108. (k) Evans, D. S.; DiMare, M. *J. Am. Chem. Soc.* **1986**, *108*, 2476-2478.

(3) See ref 1, Vol. 2. Recent references on crystallography of monensin: (a) Duax, W. L.; Smith, G. D.; Strong, P. D. *J. Am. Chem. Soc.* **1980**, *102*, 6725. (b) Walba, D. M.; Hermsmeier, M.; Haltiwanger, R. C.; Noordik, J. H. *J. Org. Chem.* **1986**, *51*, 245-247. Recent references on thermodynamics and kinetics of metal ion complexation and transport properties of monensin: (c) Cox, B. G.; van Truong, N.; Rzeszotarska, J.; Schneider, H. *J. Chem. Soc., Faraday Trans. 1* **1984**, *80*, 3275-3284. Cox, B. G.; Firman, P.; Schneider, H. *J. Am. Chem. Soc.* **1985**, *107*, 4297-4300. Cox, B. G.; van Truong, N.; Rzeszotarska, J.; Schneider, H. *J. Am. Chem. Soc.* **1984**, *106*, 5965-5969. (d) Walba, D. M.; Hermsmeier, M. *J. Chem. Soc., Chem. Commun.* **1985**, 383-384. (e) Painter, G. R.; Pressman, B. C. *Met. Ions Biol. Syst.* **1985**, *19*, 229-294. (f) Riddell, F. G.; Hayer, M. K. *Biochim. Biophys. Acta* **1985**, *817*, 313-317. (g) Bolte, J.; Caffarel-Mendes, S.; Dauphin, G.; Demuynck, C.; Jeminet, G. *Bull. Soc. Chim. Fr.* **1986**, 370-374. (h) Tsukube, H.; Takagi, K.; Higashiyama, T.; Iwachido, T.; Hayama, N. *J. Chem. Soc., Chem. Commun.* **1986**, 448-449.

0022-3263/88/1953-1046$01.50/0