Efficient Preparation of Intermediates Corresponding to C22–C27 and C28–C34 of FK-506

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Efficient large-scale preparations of aldehyde **2** and sulfone **3** representing the C22–C27 and C28–C34 portions of the immunosuppressant FK-506 (**1**) are described.

In this and two subsequent disclosures we describe a synthetic program which resulted in a formal total synthesis of the powerful immunosuppressant FK-506 (**1**).[2-5] Our first concern was that of gaining access to suitably matched chiral subunits which could be combined to reach our final goal (Figure 1). In this paper we present methods for obtaining units corresponding to the C22–C27 (**2**)[6a] and C28–C34 (**3**)[6b] fragments of FK-506. In the next paper we describe several routes to reach a usable intermediate corresponding to C10-C19. The concluding paper will consider the melding of the various subunits.

We had previously described a route to the C22–C27 intermediate **6**[6a] (Figure 2). This compound was obtained via a seven-step sequence starting with **5**, which is in turn elaborated from the chiral educt D-(−)-quinic acid (**4**).[7] Several considerations prompted the need for a fresh approach to the problem. First, while gram quantities of **6** could be made in this fashion, reproducible scale-up of the steps from **5** to **6** to multigram levels was beset with difficulties. Also, given the way the synthesis unfolded, compound **6** was not optimal. Two steps were expended to convert the C22 aldehyde to a protected alcohol. The eventual retrieval of the aldehyde required two additional steps. Between these manipulations, the C27 ester had to be converted (two steps) to an aldehyde for purposes of coupling.[6] Thus, six steps were required to process the necessary adjustments of oxidation levels of the terminii of **6**.

In this paper we describe a route (Figure 3) to building block **2** from the commercially available tri-*O*-acetyl-D-galactal (**7**).[8] Aside from its implications for FK-506, the work demonstrates some new and highly stereoselective transformations that increase the usefulness of D-galactose for preparing enantiomerically homogeneous synthetic building blocks.

Treatment of **7** with methanol in the presence of stannic chloride (0.3 equiv, 20 °C, 30 min)[9] afforded the somewhat unstable pseudoglycal ether **8**. Bis-deacetylation (sodium methoxide, methanol, 25 °C, 30 min)[9] followed by monosilylation of **9** (t-$BuMe_2SiCl$, Et_3N, CH_2Cl_2) provided **10** (54–72% overall yield from **7**). Epoxidation of **10** with m-chloroperoxybenzoic acid (2 equiv, CH_2Cl_2, reflux) afforded the syn oxirane **11** in 73% yield. The ratio of **11**:**12** was ca. 97:3. Presumably this outcome arises from Henbest-type directivity of the allylic hydroxyl function.[10] Reaction of **11** with Li_2Me_2CuCN[11] (ether, −78 to 0 °C) afforded **13**, the product of trans-diaxial opening.

Reaction of **13** with p-anisaldehyde dimethyl acetal in the presence of camphorsulfonic acid (benzene, reflux) followed by desilylation (n-Bu_4NF, THF) gave a 5:1 mixture of **14**:**15** (56% overall from **11**). The major product is the one in which the p-methoxybenzylidene group is nominally equatorial in the chair-chair form of the system.[12] The mixture was subjected to iodination with the preformed reagent prepared from iodine (1.6 equiv), triphenylphosphine (1.8 equiv), and pyridine (5 equiv) at 45 °C in benzene[13] to afford a 5:1 mixture **16**:**17** (87% combined yield). The pyranose ring was disconnected through a Vasella-type fragmentation[14] (20 equiv of Zn, 95% EtOH, reflux) to provide a mixture of **18**:**2**, where the former predominates.

We investigated the possibility that the relative ther-

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(12) The stereochemistry at the benzylidene acetal center of the major epimer (**14**) was confirmed by ^1H NMR nuclear Overhauser enhancement of the anomeric and C6 hydrogens upon irradiation of the benzylidene acetal proton of iodide **14**. Moreover, molecular mechanics calculations (MM2 force field) of the two diastereomeric alcohols **12** and **13** indicated the former to the more stable by ca. 1.4 kcal/mol: Coleman, R. S.; Linde, R. G. II, unpublished results.

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0022-3263/90/1955-2771$02.50/0

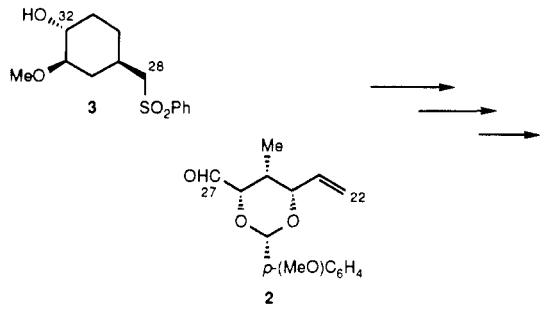


Figure 1.

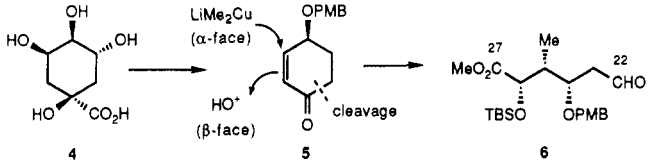


Figure 2.

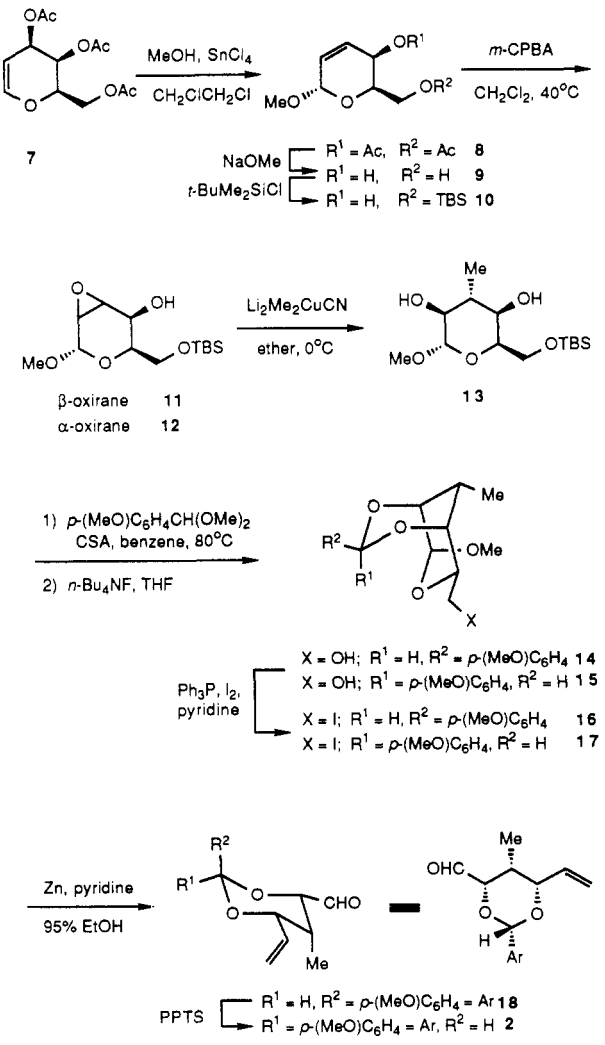
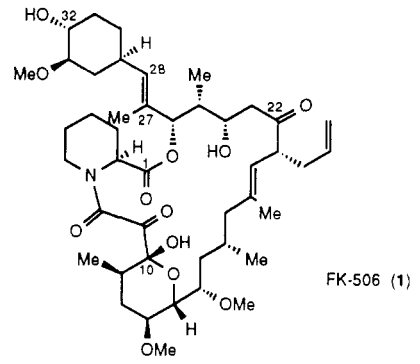
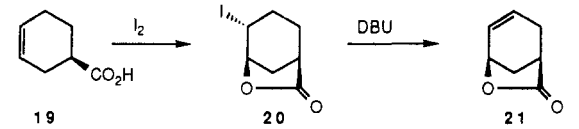


Figure 3.

modynamic stabilities of the two epimeric acetals had changed as a consequence of disconnection of the pyranoid matrix. *It seemed possible that in the post Vasella reaction series the S acetal 2 would be more stable than the R compound 18 since in the former, vinyl, aldehyde, and aryl functions can all be equatorial.*[15] In the event,





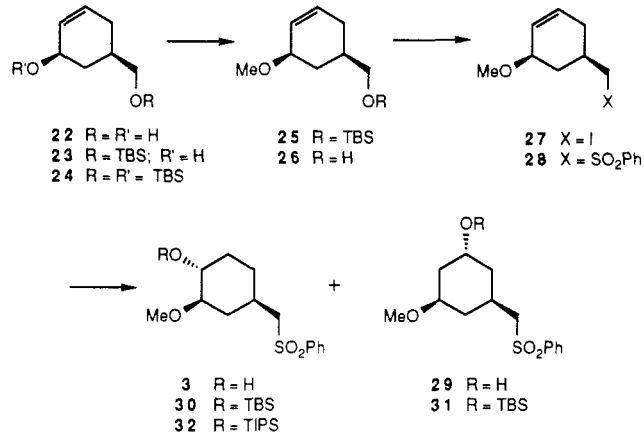


Figure 4.

treatment of the mixture of **18** and **2** with pyridinium *p*-toluenesulfonate (CH_2Cl_2, 25 °C) afforded homogeneous **2** in 93% overall yield from the **16**:**17** mixture. This nine-step sequence of transformations from tri-*O*-acetyl-D-galactal (**7**) to aldehyde **2** proceeded in an overall yield of 24% and proved easy to implement in scale-up.

We now turn to the preparation of the C28–C34[6b] subunit. The requirement we set was that the synthesis be amenable to delivering substantial gram quantities of enantiomerically homogeneous product suitable for coupling with the C22–C27 aldehyde **2**. After some trial and error, we settled upon sulfone **3** as our subgoal. Variations in the precise blocking group at C32 could be introduced late in the scheme and screened as to their adaptability in the total synthesis program. Compounds **30** and **32** were selected as specific possibilities for going forward.

The starting material for our program was the known *R* carboxylic acid **19**.[16a–c] Some of the early steps in

(15) Although installation of the *p*-methoxybenzylidene acetal (**11** → **12**:**13**) also proceeds under thermodynamic control (acid catalysis), the major product **12** possesses the three-atom bridge of the pyran system in a 1,3-diaxial relationship about the chair form of the acetal 1,3-dioxane ring system. Thus, on scission of the pyran ring (**14**:**15** → **16**:**17**), an energitically favorable chair–chair interconversion of the 1,3-dioxane ring occurs so as to relieve this 1,3-diaxial interaction, thereby placing the aryl function of the major product **16** in an unfavorable axial orientation.

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converting this compound to **3** were well known to us as a consequence of our synthesis of actinobolin.[17,18] Iodolactonization followed by elimination of the axial iodide of **20** with DBU afforded the unsaturated lactone **21** in 84% yield (Figure 4). Reduction of **21** with lithium aluminum hydride followed by the selective protection of the primary alcohol of **22** with *tert*-butyldimethylsilyl chloride (imidazole/DMF) provided **23** in 64% yield from **21**. This product was accompanied by the formation of diprotected compound **24** (17%), which could be recycled back to **22** (HF/CH_3CN).

The free alcohol of **23** was converted to its methyl ether derivative, **25**. Cleavage of the silyl protecting group (HF/CH_3CN) was accomplished to afford **26** in 82% from **23**.

The alcohol function of **26** was converted to an iodide through the action of triphenylphosphine–iodine and imidazole. Compound **27**, thus obtained, upon reaction with sodium phenylsulfinate in DMF afforded the sulfone **28** (60% from **26**).

Hydroboration of **28**[19a,b] with borane·DMS was carried out in THF at 0 °C. Oxidation with sodium hydroxide–hydrogen peroxide afforded a 78% yield of a ca. 7.1:1 inseparable mixture of the desired **3** and isomeric **29**. The latter was identified as its TBS derivative **31**. Finally, compound **3** was smoothly converted to its TBS or TIPS derivatives **30** and **32**, respectively, under standard conditions.[20] The isomeric silyl ethers were easily separated by silica gel chromatography to provide homogeneous **30** or **32**.

In this paper we have described efficient routes to key structural subunits **2** and **3**. It will be noted that the termini of **2** can be adjusted such that it can be used in synthetic schemes that require either antipode of the 2-methyl 1,3-diol system. Since this substance is now readily available in substantial gram-scale quantities, compound **2** is likely to be a useful general intermediate in synthesis.

Experimental Section

Methyl 4,6-Di-*O*-acetyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (8).[9] A solution of tri-*O*-acetyl-D-galactal (**7**; 30.0 g, 110 mmol) and methanol (10 mL, 240 mmol, 2 equiv) in 900 mL of dry 1,2-dichloroethane under N_2 at room temperature was treated with a solution of $SnCl_4$ (4.5 mL, 38 mmol, 0.3 equiv) in 120 mL of 1,2-dichloroethane over 5 min. The reaction mixture was stirred for 20 min at room temperature and was treated with 500 mL of saturated $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with 1,2-dichloroethane (200 mL). The combined organics were washed with 100 mL each of saturated $NaHCO_3$, H_2O, and saturated NaCl, dried ($MgSO_4$), and evaporated to provide crude **8**, which was used directly in the next reaction. A sample of crude **8** was purified by SiO_2 chromatography and exhibited spectral properties identical with those reported.[9]

Methyl 2,3-Dideoxy-α-D-*threo*-hex-2-enopyranoside (9).[9] A solution of crude **6** in 500 mL of dry methanol at room temperature was treated with a solution of sodium methoxide in methanol (1.5 mL, 4.37 M, 6.5 mmol), and the reaction mixture was stirred at room temperature for 45 min. Solid NH_4Cl (1.5 g) was added, and the mixture was stirred 15 min and then diluted with 400 mL of ether. The solids were removed by filtration, and the filtrate was concentrated in vacuo to afford crude **9**, which was used directly in the next reaction. A sample of crude **9** was purified by SiO_2 chromatography and was characterized: $[\alpha]^{23}_D$ −69.1° (*c* 0.11, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz) δ 6.16 (dd, 1 H, *J* = 9.9, 5.5 Hz), 5.94 (dd, 1 H, *J* = 9.9, 2.9 Hz), 4.95 (d, 1 H, *J* = 2.9 Hz), 3.8–4.1 (m, 4 H), 3.45 (s, 3 H), 2.30 (dd, *J* = 7.4, 4.7 Hz), 2.10 (d, 1 H, *J* = 8.8 Hz); IR (CH_2Cl_2) ν 3560, 3425, 3040, 2925, 1400, 1190, 1100, 1050, 940 cm^{-1}; EIMS *m/e* (relative intensity) 160 (M^+, 1), 129 (14), 100 (base); CI HRMS *m/e* 160.0736 ($C_7H_{13}O_4$ requires 160.0731).

Anal. Calcd for $C_7H_{13}O_4$: C, 52.49; H, 7.55. Found: C, 52.42; H, 7.56.

Methyl 6-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (10). A solution of crude **9** and Et_3N (23 mL, 165 mmol) in 900 mL of dry CH_2Cl_2 at room temperature was treated with a solution of *tert*-butyldimethylsilyl chloride (20.5 g, 136 mmol) and Et_3N (2.3 mL, 16 mmol) in 120 mL of CH_2Cl_2 in one portion followed by 4-(dimethylamino)pyridine (150 mg, catalytic). The reaction mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of 100 mL of 1 N HCl, the layers were separated, and the organic layer was washed with saturated $NaHCO_3$ (400 mL) and saturated NaCl (200 mL). The aqueous washes were extracted with 200 mL of CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$), concentrated in vacuo, and purified by SiO_2 chromatography (9 × 35 cm, 2:1 hexane/EtOAc) to afford pure **10** (21.6 g, 30.2 g theoretical from **7**, 72% overall yield from **7**) as a colorless oil: $[\alpha]^{23}_D$ −67.34° (*c* 4.44, CH_2Cl_2); ^1H NMR ($CDCl_3$, 490 MHz) δ 6.19 (m, 1 H), 5.94 (dd, 1 H, *J* = 10.0, 3.0 Hz), 4.91 (d, 1 H, *J* = 3.0 Hz), 4.02 (m, 1 H), 3.90 (m, 3 H), 3.44 (s, 3 H), 2.02 (d, 1 H, *J* = 8.2 Hz), 0.92 (s, 9 H), 0.11 (s, 6 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 129.7, 128.2, 95.1, 70.8, 62.7, 61.6, 55.2, 25.8, 18.1, −5.54, −5.5; IR (film) ν 3440, 2960, 2900, 2060, 1475, 1390, 1260, 1195, 1100, 1050, 970, 850, 785 cm^{-1}; EIMS *m/e* (relative intensity) 275 (M^+, 1), 243 (10), 225 (10), 199 (58), 185 (91), 116 (base), 110 (50), 100 (83); CI HRMS *m/e* 275.1679 ($C_{13}H_{27}O_4Si$ requires 275.1685).

Anal. Calcd for $C_{13}H_{27}O_4Si$: C, 56.90; H, 9.55. Found: C, 56.81; H, 9.72.

This three-step procedure routinely provided **10** from **7** in 54–72% overall yield.

Methyl 2,3-Anhydro-6-*O*-(*tert*-butyldimethylsilyl)-α-D-talopyranoside (11). A solution of **10** (10.8 g, 39.3 mmol) in 130 mL of dry CH_2Cl_2 was treated with 85% *m*-chloroperoxybenzoic acid (17.0 g, 78.6 mmol, 2 equiv) and 4,4′-thiobis(2-*tert*-butyl-6-methylphenol)[21] (50 mg), and the reaction mixture was warmed at reflux under N_2 for 38 h. The reaction mixture was cooled to 0 °C and was quenched by the careful addition of saturated Na_2SO_3. The mixture was diluted with 600 mL of CH_2Cl_2, and the layers were separated. The organic layer was washed with saturated $NaHCO_3$ (3 × 150 mL) and saturated NaCl (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by SiO_2 chromatography (5 × 25 cm, 10–15–20% EtOAc–hexane gradient) to provide pure **11** (8.3 g, 11.4 g theoretical, 73%) as a colorless oil: $[\alpha]^{23}_D$ +7.25° (*c* 2.11, CH_2Cl_2); ^1H NMR ($CDCl_3$, 490 MHz) δ 4.88 (s, 1 H), 3.93 (ddd, 1 H, *J* = 8.0, 5.7, 2.3 Hz), 3.78 (dd, 1 H, *J* = 9.9, 5.2 Hz), 3.72 (m, 1 H), 3.67 (dd, 1 H, *J* = 9.9, 6.6 Hz), 3.56 (dd, 1 H, *J* = 5.7, 3.7 Hz), 3.46 (s, 3 H), 3.18 (d, 1 H, *J* = 3.7 Hz), 2.34 (d, 1 H, *J* = 11.1 Hz), 0.90 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 95.1, 69.0, 61.0, 60.7, 54.7, 51.8, 50.9, 25.1, 17.5, −6.1; IR (film) ν 3540, 2960, 2935, 2858, 1470, 1460, 1405, 1390, 1252, 1248, 1090, 1040, 980, 860, 850 cm^{-1}; EIMS *m/e* (relative intensity) 290 (M^+, 1), 259 (base), 233 (8); CI HRMS *m/e* 291.1628 ($C_{13}H_{27}O_5Si$ requires 291.1645).

Anal. Calcd for $C_{13}H_{27}O_5Si$: C, 53.76; H, 9.02. Found: C, 53.90; H, 9.13.

Methyl 6-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-3-methyl-α-D-idopyranoside (13). A slurry of CuCN (3.6 g, 40.3 mmol) in 30 mL of dry ether at −78 °C under argon was treated with an ethereal solution of MeLi (58 mL, 1.4 M, 80.6 mmol), and the mixture was allowed to stir for 10 min at −78 °C and for 10 min at 0 °C. The cuprate was recooled to −78 °C, and a solution of **11** (3.9 g, 13.4 mmol) in 10 mL of dry ether at −78 °C under argon was added via cannula to the cuprate slurry. The reaction mixture was allowed to warm to 0 °C and was stirred a total of 40 min. The reaction mixture was quenched by the careful addition of 100 mL of 1:9 concentrated NH_4OH/saturated NH_4Cl. The mixture was diluted with 250 mL of ether, the layers were sep-

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arated, and the aqueous layer was extracted with 1:1 EtOAc/ether (250 mL) and EtOAc (250 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo, and the residue was carried directly into the next reaction. A small sample of **13** was purified by SiO_2 chromatography and was characterized: $[\alpha]^{23}_D$ +7.29° (*c* 2.1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 490 MHz) δ 4.76 (s, 1 H), 4.57 (d, 1 H, *J* = 1.5 Hz), 4.10 (d, 1 H, *J* = 9.9 Hz), 4.02 (m, 2 H), 3.81 (br s, 1 H), 3.78 (m, 1 H), 3.42 (m, 1 H), 3.37 (s, 3 H), 2.21 (m, 1 H), 1.10 (d, 3 H, *J* = 7.7 Hz), 0.92 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 103.5, 72.5, 70.1, 66.0, 64.9, 54.9, 38.2, 25.7, 18.1, 14.3, -5.6; IR (film) ν 3400, 2960, 2930, 2860, 1740, 1470, 1460, 1260, 1120, 1050, 860, 780 cm^{-1}; EIMS *m/e* (relative intensity) 307 (M^+ + H, 1), 275 (6), 257 (4), 231 (4), 218 (16), 216 (92), 199 (68), 171 (60), 159 (85), 75 (base); CI HRMS *m/e* 307.1956 ($C_{18}H_{30}O_5Si$ requires 307.1941).

Anal. Calcd for $C_{18}H_{30}O_5Si$: C, 54.89; H, 9.87. Found: C, 54.87; H, 9.76.

Methyl 2,4-Di-*O*-(4-methoxybenzylidene)-3-deoxy-3-methyl-α-D-idopyranoside (14). A solution of crude **13** (3.7 g, 12.1 mmol) in 250 mL of dry benzene was treated with *p*-anisaldehyde dimethyl acetal (6.4 mL, ca. 3 equiv) and camphorsulfonic acid (37 mg, 1 wt %), and the reaction mixture was warmed at reflux under N_2 for 1 h, using a Dean–Stark trap to remove the benzene/methanol azeotrope. The reaction mixture was allowed to cool to room temperature and was filtered through a pad of basic Al_2O_3 (ca. 50 g, activity grade I, 80–200 mesh; ether wash). The filtrate was evaporated in vacuo, and the residue was dissolved in 400 mL of dry THF. A solution of *n*-Bu_4NF in THF (12 mL, 1 M, 12 mmol) was added, and the reaction mixture was stirred under N_2 for 6 h at room temperature. The reaction mixture was evaporated to ca. 200 mL and was passed through a pad of SiO_2 (2 × 7 cm, EtOAc wash). The filtrate was evaporated in vacuo, and the residue was purified by SiO_2 chromatography (5 × 20 cm, 2:1 hexane/EtOAc) to afford a 5:1 mixture of **14** and **15** (2.3 g, 4.15 g theoretical from **11**, 56% overall yield from **11**) as a pale orange oil. Pure **14** was characterized: $[\alpha]^{23}_D$ +59.5° (*c* 0.71, CH_2Cl_2); ^1H NMR ($CDCl_3$, 490 MHz) δ 7.41 (d, 2 H, *J* = 8.7 Hz), 6.90 (d, 2 H, *J* = 8.7 Hz), 6.84 (s, 1 H), 5.07 (s, 1 H), 4.19 (m, 1 H), 4.05 (m, 1 H), 3.90 (m, 1 H), 3.86 (m, 1 H), 3.82 (m, 1 H), 3.80 (s, 3 H), 3.45 (s, 3 H), 2.67 (m, 1 H), 2.20 (br s, 1 H), 1.23 (d, 3 H, *J* = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 160.2, 131.9, 128.2, 127.7, 113.7, 101.1, 95.8, 72.3, 71.7, 69.0, 63.7, 55.2, 34.0, 13.7; IR (film) ν 3480, 2993, 2957, 2921, 2835, 1607, 1510, 1455, 1382, 1303, 1237, 1164, 1109, 1042, 963 cm^{-1}; EIMS *m/e* (relative intensity) 310 (M^+, 1), 182 (32), 152 (52), 151 (base), 135 (99), 134 (99), 108 (40), 107 (33); CI HRMS *m/e* 311.1501 ($C_{16}H_{23}O_6$ requires 311.1495). Pure **15** was characterized: $[\alpha]^{23}_D$ +45.0° (*c* 0.20, CH_2Cl_2); ^1H NMR ($CDCl_3$, 490 MHz) δ 7.48 (d, 2 H, *J* = 8.8 Hz), 6.90 (d, 2 H, *J* = 8.8 Hz), 6.21 (s, 1 H), 4.84 (s, 1 H), 4.10 (dd, 1 H, *J* = 3.8 Hz), 4.04 (m, 1 H), 3.9 (m, 2 H), 3.81 (s, 3 H), 3.79 (m, 1 H), 3.46 (s, 3 H), 3.18 (m, 1 H), 2.31 (br d, 1 H, *J* = 2.0 Hz), 1.32 (d, 3 H, *J* = 7.4 Hz); IR (film) ν 3598, 3514, 3049, 3007, 2957, 2922, 2850, 1597, 1506, 1850, 1393, 1302, 1168, 1140, 1111, 1069, 1048, 1020, 823 cm^{-1}; CI HRMS *m/e* 311.1498 ($C_{16}H_{23}O_6$ requires 311.1495).

Methyl 2,4-Di-*O*-(4-methoxybenzylidene)-3,6-dideoxy-6-iodo-3-methyl-α-D-idopyranoside (16). A solution of alcohols **14/15** (2.2 g, 7.1 mmol) in 50 mL of dry benzene was added to the preformed reagent prepared from I_2 (2.9 g, 11.3 mmol), Ph_3P (3.5 g, 13.5 mmol), and pyridine (2.0 mL, 24.8 mmol) in 100 mL of dry benzene at room temperature. The brown-red slurry was warmed at 45 °C under N_2 for 44 h. The reaction mixture was cooled to room temperature and passed through a pad of SiO_2 (2 × 7 cm, 1:1 ether/pentane wash), and the filtrate was evaporated in vacuo. The residue was purified by SiO_2 chromatography (5 × 20 cm, 9:1 hexane/ether to 9:1 hexane/EtOAc gradient) to afford a 5:1 mixture of **16** and **17** (2.6 g, 3.0 g theoretical, 87%) as a colorless oil. Pure **16** was characterized: $[\alpha]^{23}_D$ +96.4° (*c* 1.30, CH_2Cl_2); ^1H NMR ($CDCl_3$, 490 MHz) δ 7.42 (d, 2 H, *J* = 8.6 Hz), 6.91 (d, 2 H, *J* = 8.6 Hz), 6.80 (s, 1 H), 5.07 (br s, 1 H), 4.27 (dd, 1 H, *J* = 7.3, 6.1), 3.96 (br s, 1 H), 3.84 (br s, 1 H), 3.81 (s, 3 H), 3.47 (s, 3 H), 3.45 (m, 1 H), 2.69 (m, 1 H), 1.22 (d, 3 H, *J* = 7.6 Hz); IR (film) ν 2956, 2933, 2910, 1614, 1589, 1518, 1464, 1392, 1305, 1250, 1170, 1114, 1089, 1039, 971, 953, 831, 737 cm^{-1}; EIMS *m/e* (relative intensity) 420 (M^+, 25), 419 (29), 389 (6), 268 (31), 253 (8), 236 (9), 163 (18), 141 (32), 137 (61), 136 (25), 135 (base), 127 (28), 109 (60); CI HRMS *m/e* 421.0483 ($C_{16}H_{21}O_5I$ requires 421.0513).

Anal. Calcd for $C_{16}H_{21}O_5I$: C, 45.73; H, 5.04. Found: C, 45.98; H, 5.12.

Pure **17** was characterized: $[\alpha]^{23}_D$ +58.3° (*c* 0.40, CH_2Cl_2); ^1H NMR ($CDCl_3$, 490 MHz) δ 7.47 (d, 2 H, *J* = 8.7 Hz), 6.90 (d, 2 H, *J* = 8.7 Hz), 6.18 (s, 1 H), 4.78 (br s, 1 H), 4.17 (m, 1 H), 4.06 (apparent t, 1 H, *J* = 6.8 Hz), 3.96 (m, 1 H), 3.81 (s, 3 H), 3.49 (s, 3 H), 3.39 (m, 1 H), 3.15 (m, 1 H), 1.30 (d, 3 H, *J* = 7.3); IR (film) ν 3053, 2986, 1440, 1422, 1265, 1171, 1115, 1040, 770, 697 cm^{-1}; CI HRMS *m/e* 421.0474 ($C_{16}H_{21}O_5I$ requires 421.0513).

(2*R*,4*S*,5*R*,6*R*)-2-(4-Methoxyphenyl)-5-methyl-6-vinyl-1,3-dioxane-4-carboxaldehyde (18). A solution of iodides **16/17** (2.1 g, 5.0 mmol) in 57 mL of 95% EtOH under N_2 was treated with pyridine (5.6 g, 71.4 mmol) and activated, pyridine-washed zinc metal (6.5 g, 100 mmol, 20 g atom equiv), and the reaction mixture was warmed at reflux for 10 min. The warm reaction mixture was filtered through a pad of Celite and neutral Al_2O_3 (ether wash). The filtrate was diluted with 50 mL of heptane and evaporated in vacuo. The residue was diluted with CH_2Cl_2 and was passed through a pad of SiO_2 (4 × 7 cm, 2:1 heane/EtOAc) to afford a 5:1 mixture of **18** and **2**. Compound **18** was characterized: ^1H NMR ($CDCl_3$, 250 MHz) δ 9.68 (s, 1 H), 7.37 (d, 2 H, *J* = 8.7 Hz), 6.94 (d, 2 H, *J* = 8.7 Hz), 6.36 (s, 1 H), 5.79 (ddd, 1 H, *J* = 17.3, 10.8, 4.7 Hz), 5.42 (dm, 1 H, *J* = 17.3 Hz), 5.29 (dm, 1 H, *J* = 10.8 Hz), 4.49 (m, 1 H), 4.37 (d, 1 H, *J* = 2.6 Hz), 3.83 (s, 3 H), 2.03 (m, 1 H), 1.06 (d, 3 H, *J* = 6.7 Hz).

(2*S*,4*S*,5*R*,6*R*)-2-(4-Methoxyphenyl)-5-methyl-6-vinyl-1,3-dioxane-4-carboxaldehyde (2). A solution of the mixture of aldehydes **18** and **2** in 50 mL of CH_2Cl_2 at room temperature was treated with pyridinium *p*-toluenesulfonate (150 mg), and the reaction mixture was stirred under N_2 at room temperature for 18 h. The reaction mixture was passed through a pad of SiO_2 (4 × 7 cm, 2:1 hexane/EtOAc), and the filtrate was evaporated in vacuo to provide a ≤1:20 mixture of **18** and **2** (1.2 g, 93% from iodides **16/17**). Compound **2** was characterized: ^1H NMR ($CDCl_3$, 250 MHz) δ 9.72 (s, 1 H), 7.52 (d, 2 H, *J* = 8.7 Hz), 6.94 (d, 2 H, *J* = 8.7 Hz), 5.84 (ddd, 1 H, *J* = 17.3, 10.8, 4.7 Hz), 5.66 (s, 1 H), 5.37 (dm, 1 H, *J* = 17.3 Hz), 5.27 (dm, 1 H, *J* = 10.8 Hz), 4.51 (m, 1 H), 4.39 (d, 1 H, *J* = 2.6 Hz), 3.83 (s, 3 H), 2.15 (m, 1 H), 1.02 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 63 MHz), δ 202.1, 160.3, 135.4, 130.3, 127.7, 116.2, 113.7, 101.4, 84.4, 80.5, 55.3, 34.1, 7.3; EIMS *m/e* (relative intensity) 262 (M^+, 17), 233 (16), 137 (base), 136 (40), 135 (41), 109 (7); EI HRMS *m/e* 262.1201 ($C_{15}H_{18}O_4$ requires 262.1205).

(1*R*,5*R*)-5-(Hydroxymethyl)-2-cyclohexen-1-ol (22). Lactone **21**[7] (4.02 g, 0.0324 mol) was dissolved in THF (10 mL) and added dropwise to $LiAlH_4$ (32.4 mL, 0.0324 mol, 1 equiv, 1 M/ether) dissolved in THF (70 mL) at 0 °C. A white precipitate formed. After $^1/_2$ h, TLC (20% EtOAc/hexanes) showed no starting material. Water (1.24 mL), 15% aqueous NaOH (1.24 mL), and water (3.67 mL) were added sequentially, and the mixture was allowed to warm to room temperature with stirring over several hours. The salts were removed by filtration, and the solution was dried over $MgSO_4$ and concentrated at room temperature to give **22** as a white solid (3.37 g, 81%): $[\alpha]^{23}_D$ +20.3° (*c* 1.46, MeOH); ^1H NMR ($CDCl_3$, 250 MHz, FK-506 numbering) δ 5.88–5.78 (br d, 1 H, [H_{33}]), 5.75–5.65 (br d, 1 H, [H_{32}]), 4.40–4.27 (br s, 1 H [H_{31}]), 3.59 (d, *J* = 6 Hz, 2 H [H_{28}]), 2.21–2.08 (m, 2 H [H_{34}]), 2.04–1.75 (m, 2 H [H_{30}]), 1.64 (br s, H_2O + OH peaks), 1.38–1.22 (m, 1 H [H_{29}]); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 130.96, 128.25, 67.29, 66.97, 35.27, 35.16, 28.07; IR (CH_2Cl_2) ν 3590, 3440, 3040, 3020, 2910, 1390, 1275, 1090, 1060, 1005 cm^{-1}; CI HRMS *m/e* 129.0926 ($C_7H_{12}O_2$ requires 129.0916); melting point 84 °C uncorrected.

(1*R*,5*R*)-5-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2-cyclohexen-1-ol (23). Diol **22** (2.74 g, 0.0214 mol) was dissolved in dry DMF (25 mL). Imidazole (2.91 g, 0.0428 mol, 2 equiv) was added and dissolved. The solution was cooled to 0 °C, *tert*-butyldimethylsilyl chloride (3.23 g, 0.0214 mol, 1 equiv, in 5 mL of DMF) was added, and the reaction mixture was allowed to warm to room temperature and stir 5 h. TLC (40% EtOAc/hexanes) showed very little starting material. The reaction was quenched by addition to pH 7 buffer and extracted with ether, and the organic layers were dried with brine and $MgSO_4$. Chromatography (SiO_2, elution with 20% EtOAc/hexanes) yielded

4.13 g (80%) of **23** and 1.33 g (17%) diprotected diol **24**. Alcohol **23** was characterized: $[\alpha]^{23}_D$ +2.7° (*c* 1.7, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz, FK-506 numbering) δ 5.75 (ddd, *J* = 9.5, 2.2, and 1.8 Hz, 1 H [H_{33}]), 5.68 (br d, *J* = 9.5 Hz, 1 H [H_{32}]), 4.41–4.28 (m, 1 H [H_{31}]), 3.52 (d, *J* = 5.8 Hz, 2 H [H_{28}]), 2.23–1.85 (m, 5 H, [$H_{30,34,OH}$]), 1.22–1.18 (m, 1 H, [H_{29}]), 0.91 (s, 9 H [H_{Si}]), 0.05 (s, 6 H [H_{Si}]); ^{13}C NMR ($CDCl_3$, 62 MHz) δ 131.22, 128.02, 67.55, 67.31, 35.55, 28.19, 25.84, 18.24, 5.47; IR (CH_2Cl_2) ν 3540, 2930, 2850, 1468, 1260, 1115 cm^{-1}; CI HRMS *m/e* 243.1781 ($C_{13}H_{27}O_2Si$ requires 243.1783).

(1*R*,5*R*)-5-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-1-methoxy-2-cyclohexene (25). Alcohol **23** (1.13 g, 4.67 mmol) was dissolved in THF (2 mL) and added to NaH (0.560 g, 60% dispersion in oil, 0.014 mol, 3 equiv) suspended in THF (8 mL). Methyl iodide (2.90 mL, 0.0467 mol, 10 equiv) was added, and the reaction mixture was stirred at room temperature for 4.5 h. TLC at this time (20% EtOAc/hexanes) showed very little starting material. The reaction was quenched upon addition to water and extracted with ether. The ether layers were dried over $MgSO_4$ and concentrated. Chromatography (SiO_2, elution with 10% EtOAc/hexanes) gave 1.246 g of **25** (>100%), which was carried on to the next step. A sample was rechromatographed (SiO_2, elution with 2% Et_2O/CH_2Cl_2) and characterized: $[\alpha]^{23}_D$ −5.3° (*c* 1.59, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz, FK-506 numbering) δ 5.82–5.70 (m, 2 H, [$H_{32,33}$]), 3.91 (br s, 1 H [H_{31}]), 3.51 (d, *J* = 5.8 Hz, 2 H [H_{28}]), 3.39 (s, 3 H [H_{OMe}]), 2.20–2.00 (m, 2 H), 1.95–1.68 (m, 2 H), 1.25–1.10 (m, 1 H [H_{29}]), 0.92 (s, 9 H [H_{Si}]), 0.05 (s, 6 H [H_{Si}]); IR (CH_2Cl_2) ν 2920, 2845, 1465, 1248, 1110, 1095 cm^{-1}.

(1*R*,5*R*)-5-(Hydroxymethyl)-1-methoxy-2-cyclohexene (26). The bis-ether **25** (1.246 g crude) was dissolved in Et_2O (40 mL), and an acetonitrile/48% aqueous HF solution (95:5) (20 mL) was added. TLC (5% EtOAc/hexanes) after 23 h showed no starting material. The reaction was quenched by addition to pH 7 buffer and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried over $MgSO_4$, filtered, and concentrated to give a two-phase oil. Column chromatography (SiO_2, elution with 5% EtOAc/hexanes) yielded 1.99 g (82% for two steps) of **26** as a colorless oil: $[\alpha]^{23}_D$ +18.1° (*c* 1.62, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz, FK-506 numbering) δ 5.89–5.71 (m, 2 H [$H_{33,32}$]), 3.95–3.85 (m, 1 H [H_{31}]), 3.58 (dt, *J* = 5.8 and 1.2 Hz, 2 H [H_{28}]), 3.39 (s, 3 H [H_{OMe}]), 2.21–1.75 (m, 4 H), 1.72 (t, *J* = 5.8 Hz, 1 H [H_{OH}]), 1.42–1.25 (m, 1 H [H_{29}]); IR (CH_2Cl_2) ν 3600, 3040, 2920, 1275, 1100, 1085 cm^{-1}; EI MS (20 eV) *m/e* 142 (M^+).

(1*R*,5*R*)-5-(Iodomethyl)-1-methoxy-2-cyclohexene (27). Alcohol **26** (2.28 g, 0.0161 mol) was dissolved in dry benzene (50 mL). Triphenylphosphine (4.63 g, 0.0176 mol, 1.1 equiv) was added and allowed to dissolve. Imidazole (2.4 g, 0.0362 mol, 2.25 equiv) was added and allowed to dissolve. Iodine (4.91 g, 0.0193 mol, 1.2 equiv) was dissolved in dry benzene (10 mL) and added in several portions. The solution changed from colorless to white to red as excess I_2 was added. The solution was heated at reflux for 1 h, at which time TLC analysis showed no starting material remained. The reaction was quenched by dilution with Et_2O and washed with pH 7 buffer. The aqueous layer was back-extracted three times with Et_2O. The organic layers were dried with brine and $MgSO_4$. Chromatography (SiO_2, elution with 5% EtOAc/hexanes) yielded 3.04 g (75%) of **27**: ^1H NMR ($CDCl_3$, 250 MHz, FK-506 numbering) δ 5.82–5.68 (m, 2 H [$H_{32,33}$]), 4.00–3.88 (m, 1 H [H_{31}]), 3.42 (s, 3 H [H_{OMe}]), 3.22 (d, *J* = 5.8 Hz, 2 H [H_{28}]), 2.30–2.18 (m, 2 H), 1.92–1.88 (m, 2 H), 1.38–1.20 (m, 1 H [H_{29}]); IR (CH_2Cl_2) ν 3040, 2920, 1275, 1105, 1095 cm^{-1}; EI MS (20 eV) *m/e* 252 (M^+).

(1*R*,5*R*)-5-[(Phenylsulfonyl)methyl]-1-methoxy-2-cyclohexene (28). Iodide **27** (2.42 g, 9.60 mmol) was dissolved in dry DMF (50 mL), and benzenesulfinic acid sodium salt (1.73 g, 0.016 mol, 1.1 equiv) was added. The solution was stirred at room temperature for 4 h and then heated at 30–40 °C for 40 min. TLC (30% EtOAc/hexanes) showed starting material almost completely consumed. The reaction was quenched by addition to pH 7 buffer (180 mL) and extracted with Et_2O. The ether layers were dried with brine and $MgSO_4$. Chromatography (SiO_2, elution with 30% EtOAc/hexanes) yielded 2.05 g (80%) of **28**: pale yellow oil; $[\alpha]^{23}_D$ +14.5° (*c* 1.64, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz, FK-506 numbering) δ 7.95–7.89 (m, 2 H [H_{aryl}]), 7.70–7.48 (m, 3 H [H_{aryl}]), 5.80–5.68 (br s, 2 H [$H_{32,33}$]), 3.91–3.80 (m, 1 H [H_{31}]), 3.34 (s, 3 H [H_{OMe}]), 3.13 (2 dd, *J* = 13.7 and 5.9 Hz, 2 H [H_{28}]), 2.5–2.15 (m, 3 H), 2.02–1.87 (m, 1 H), 1.50–1.28 (m, 1 H [H_{29}]); ^{13}C NMR ($CDCl_3$, 62 MHz) δ 140.13, 133.57, 129.27, 127.52, 74.86, 61.62, 55.76, 34.07, 31.39, 27.69; IR (CH_2Cl_2) ν 3040, 2920, 1445, 1305, 1148, 1085 cm^{-1}; CI HRMS *m/e* 267.1042 ($C_{14}H_{13}O_3S$ requires 267.1056).

(1*R*,2*R*,4*R*)-2-Methoxy-4-[(phenylsulfonyl)methyl]-1-cyclohexanol (3). The ene–sulfone **28** (1.0 g, 3.76 mmol) was dissolved in dry THF (100 mL) and cooled to 0 °C, and borane·DMS (0.830 mL, 8.27 mmol, 10 M, 2.2 equiv) in THF was added dropwise. After 1.5 h, an additional charge of borane·DMS (0.515 mL, 5.15 mmol, 10 M, 1.4 equiv) in THF was added. After 1 h of stirring at 0 °C no starting material was apparent by TLC. The reaction was quenched by addition of H_2O (0.5 mL), followed by 1 N NaOH (50 mL) and 30% H_2O_2 (4.8 mL). The reaction was allowed to warm to room temperature over 2 h. A white emulsion formed. Et_2O was added, and the solution was washed twice with saturated sodium sulfite solution. The ether layer was washed with brine and dried over $MgSO_4$. Chromatography (SiO_2, elution with 2:1 Et_2O/EtOAc) yielded 0.644 g (60%) of an inseparable mixture of alcohols, enriched in **3** (see **30**): ^1H NMR ($CDCl_3$, 490 MHz, FK-506 numbering) δ 7.95–7.91 (m, 2 H [H_{aryl}]), 7.70–7.65 (m, 1 H [H_{aryl}]), 7.61–7.55 (m, 2 H [H_{aryl}]), 3.41–3.35 (m, buried 1 H [H_{32}]), 3.38 (s, 3 H [H_{OMe}]), 3.03 (2 d, *J* = 3.3 Hz, 2 H [H_{28}]), 2.98 (ddd, *J* = 11.4, 8.9, and 4.4 Hz, 1 H [H_{31}]), 2.63 (br s, 1 H [H_{OH}]), 2.37 (ddd, *J* = 12.5, 6.5, and 3.8 Hz, 1 H [H_{30eq}]), 2.18–2.08 (m, 1 H [H_{29}]), 2.04–1.98 (ddd, *J* = 13.0, 8.1, and 3.5 Hz, 1 H [H_{33eq}]), 1.95–1.89 (m, 1 H [H_{34eq}]), 1.41–1.32 (m, 1 H [H_{33ax}]), 1.15 (dq, *J* =12.0 and 3.6 Hz, 1 H [H_{34ax}]), 0.95 (br q, *J* = 12.0 Hz, 1 H [H_{30ax}]); IR (CH_2Cl_2) ν 3560, 3040, 2920, 1445, 1305, 1148, 1085 cm^{-1}; EI MS (20 eV) *m/e* 284 (M^+); CI HRMS *m/e* 285.1156 ($C_{14}H_{20}O_4S$ requires 285.1161).

(1*R*,2*R*,4*R*)-2-Methoxy-4-[(phenylsulfonyl)methyl]-1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]cyclohexane (30). Alcohol **3** (0.644 g, 2.27 mmol) was dissolved in dry CH_2Cl_2 and 2,6-lutidine (1.58 mL, 1.36 mmol, 6 equiv) was added, and the reaction mixture was cooled to 0 °C. *tert*-Butyldimethylsilyl triflate (1.04 ml, 4.5 mmol, 2 equiv) was added dropwise. TLC (40% EtOAc/hexanes) showed starting material had been consumed after 2.5 h. The reaction was quenched by pouring into pH 7 buffer and extracting with CH_2Cl_2, and the organic layer was dried over $MgSO_4$ and concentrated. Chromatography (SiO_2, elution with 20% EtOAc/hexanes) yielded 0.695 g (77%) of **30** and 0.098 g (10%) of another protected alcohol **31**. Colorless oil **30** was characterized: $[\alpha]^{23}_D$ −24.0° (*c* 1.04, $CHCl_3$), $[\alpha]^{23}_D$ −24.96° (*c* 1.49, CH_2Cl_2)]; ^1H NMR ($CDCl_3$, 490 MHz, FK-506 numbering) δ 7.94–7.92 (m, 2 H [H_{aryl}]), 7.67–7.51 (m, 3 H [H_{aryl}]), 3.40–3.35 (m, 1 H [H_{32}]), 3.37 (s, 3 H [H_{OMe}]), 3.04 (d, *J* = 6.2 Hz, 2 H [H_{28}]), 2.92 (ddd, *J* = 10.6, 8.2, and 4.4 Hz, 1 H [H_{31}]), 2.18 (ddd, *J* = 12.7, 6.5, and 3.9 Hz, 1 H [H_{30eq}]), 2.10–2.01 (m, 1 H [H_{29}]), 1.91–1.85 (m, 1 H [H_{33eq}]), 1.85–1.80 (m, 1 H [H_{34eq}]), 1.40–1.31 (m, 1 H [H_{34ax}]), 1.12–1.05 (m, 1 H [H_{33ax}]), 1.05–0.98 (app q, *J* = 11.8 Hz, 1 H [H_{30ax}]); IR (CH_2Cl_2) ν 2920, 2850, 1305, 1148, 1105 cm^{-1}; EI MS (20 eV) *m/e* 399 (M^+ + 1); CI HRMS *m/e* 399.2023 ($C_{20}H_{34}O_4SSi$ requires 399.2026).

Compound **31** was a minor product isolated from the preparation of **30**: ^1H NMR ($CDCl_3$, 250 MHz, FK-506 numbering) δ 7.93–7.92 (m, 2 H), 7.70–7.53 (m, 3 H), 4.20–4.12 (m, 1 H [H_{33}]), 3.51–3.47 (m, 1 H [H_{31}]), 3.31 (s, 3 H [H_{OMe}]), 3.05 (ABX, *J* = 14.2 and 6.4 Hz, Δν = 9.1 Hz, 2 H [H_{28}]), 2.50–2.41 (m, 1 H [H_{29}]), 2.31–2.20 (m, 1 H [H_{30eq}]), 2.10–2.01 (m, 1 H [H_{32eq}]), 1.90–1.82 (m, 1 H [H_{34eq}]), 1.25–1.10 (m, 2 H [$H_{32,34}$]), 1.02–0.89 (app q, 1 H [H_{30ax}]), 0.83 (s, 9 H), 0.03 (s, 3 H), 0.01 (s, 3 H); IR (CH_2Cl_2) ν 2910, 1300, 1140 cm^{-1}.

(1*R*,2*R*,4*R*)-4-[(Phenylsulfonyl)methyl]-2-methoxy-1-[[tris(methylethyl)silyl]oxy]cyclohexane (32). Alcohol **3** (0.120 g, 0.43 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and 2,6-lutidine (0.45 mL, 3.7 mmol) was added, and the reaction mixture was cooled at 0 °C. Triisopropyl triflate (0.32 mL, 1.2 mmol) was added dropwise, and the mixture was stirred for 2 h. The reaction was quenched by the addition of pH 7 buffer and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated. Chromatography (SiO_2, elution with 20% EtOAc/hexanes) gave 0.138 g (75% yield) of **32** as a colorless oil: $[\alpha]^{23}_D$ −12.4° (*c* 0.37, $CHCl_3$)]; ^1H NMR ($CDCl_3$, 250 MHz, FK-506 numbering) δ 7.96–7.85 (m, 2 H [H_{aryl}]), 7.67–7.54 (m, 3 H [H_{aryl}]),

3.58–3.48 (m, 1 H [H_{32}]), 3.35 (s, 3 H [H_{OMe}]), 3.07 (d, J = 6.1 Hz, 2 H, [H_{28}]), 2.95–2.88 (m, 1 H [h_{31}]), 2.20–2.10 (m, 1 H [H_{30eq}]), 2.10–2.01 (m, 1 H [H_{29}]), 1.92–1.87 (m, 2 H [H_{33eq}]), 1.87–1.80 (m, 1 H [H_{34eq}]), 1.40–1.21 (m, 1 H [H_{34ax}]), 1.10–0.85 (m, 5 H), 1.05 (br s, 18 H); IR (CH_2Cl_2) ν 2920, 2860, 1470, 1440, 1300, 1090 cm^{-1}; CI HRMS m/e 441.2494 ($C_{23}H_{40}O_4SSi$ requires 441.2496); ^{13}C NMR ($CDCl_3$, 62 MHz) δ 140.04, 133.56, 129.26, 127.74, 83.32, 73.39, 61.56, 57.34, 34.86, 32.17, 30.42, 29.66, 17.99, 17.80, 12.45.

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Supplementary Material Available: ^1H NMR spectra for **3**, **22**, **23**, **25–28**, and **30–32** and ^{13}C NMR spectra for **22**, **23**, **28**, and **32** (14 pages). Ordering information is given on any current masthead page.

Stereoselective Routes to the C_{10}–C_{19} Fragment of FK-506

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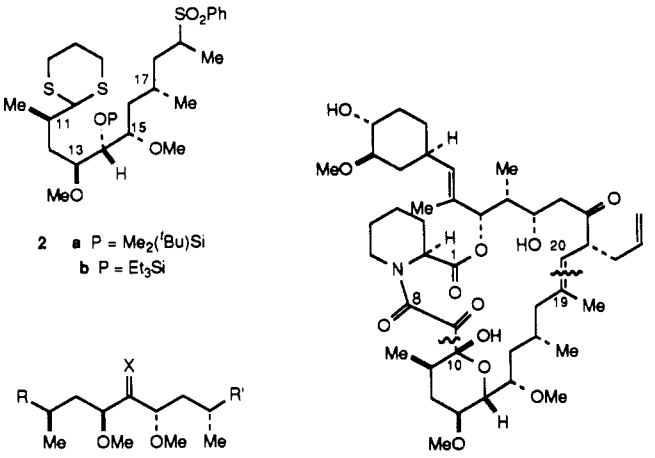
D-Galactose was used as a starting material to reach the titled system. The key elements of one of the syntheses involved directed homogeneous hydrogenation and diastereoselective lactonization reactions (see **26** → **6** and **6** → **7**). In another synthetic route directed catalytic hydrogenation was used to fashion **34** where the end groups were already differentiated.

Background and Synthetic Planning

In this paper we focus on the synthesis of compound **2a**, which was envisioned to be an important building block in a total synthesis of FK-506 (**1**).[1-4] The retrosynthetic dissection indicators on the C_9–C_{10} and C_{19}–C_{20} bonds in **1** indicate, in a general sense, how this system was to be fitted into the overall synthetic scheme. The C_{19}–C_{20} bond would be fashioned from the reaction of a sulfone stabilized C_{19}-carbanion with a C_{20}-aldehyde. The mode of construction of the C_9–C_{10} bond was left open. One obvious format would involve reaction of a dithiane stabilized C_{10}-carbanion with a C_9-electrophile. Alternatively a C_{10}-aldehyde might function as an electrophile in reaction with a C_9-nucleophile (not specified in detail).

Scheme I



Not lost upon us in examining the structure of dithianesulfone **2a** was the syn C_{11}–C_{13} methyl–methoxy relationship which is duplicated in the C_{17}–C_{15} connectivity. If the R and R′ functions in the deliberately unspecified structure **3** are identical, C_{14} is nonstereogenic (C_2 symmetry). Clearly any perturbation that results in nonequivalence of R and R′ in such a structure confers stereogenicity on C_{14} (cf. structures **4** and **5**).

A priori, it seemed unlikely that the energy difference between **4** and its C_{14} epimer (see structure **5**) would be substantial in any acyclic intermediates. Accordingly it seemed unlikely that useful selectivity would arise from a reaction that converted **3** to an acyclic product such as **4** or **5** in which R and R′ were nonidentical.

An approach to improve chances for stereoselectivity in the generation of **4** relative to **5**, via the intermediacy of a C_2 symmetric structure **3**, would be to use lactonization

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