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.

Acknowledgment. This research was supported by National Institutes of Health (PHS Grant AI 16943). An Americal Chemical Society Graduate Fellowship (Division of Organic Chemistry) to M. E. is gratefully acknowledged. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

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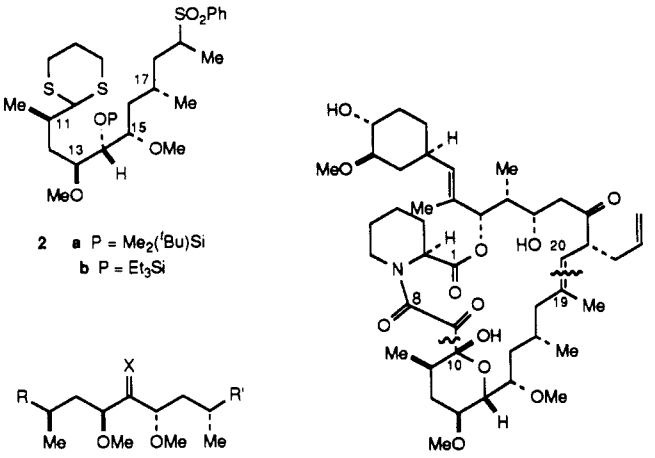
D-Galactose was used as a starting material to reach the titled system. The key elements of one of the syntheses involved directed homogeneous hydrogenation and diastereoselective lactonization reactions (see **26** → **6** and **6** → **7**). In another synthetic route directed catalytic hydrogenation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

(1) For isolation and structure proof see: Kino, T.; Hatanaka, H.; Hashimoto, M.; Nishimaya, M.; Goto, T.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Imanaka, M. *J. Antibiot.* **1987**, *40*, 1249. Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T. Hashimoto, M. *J. Am. Chem. Soc.* **1987**, *109*, 5031.

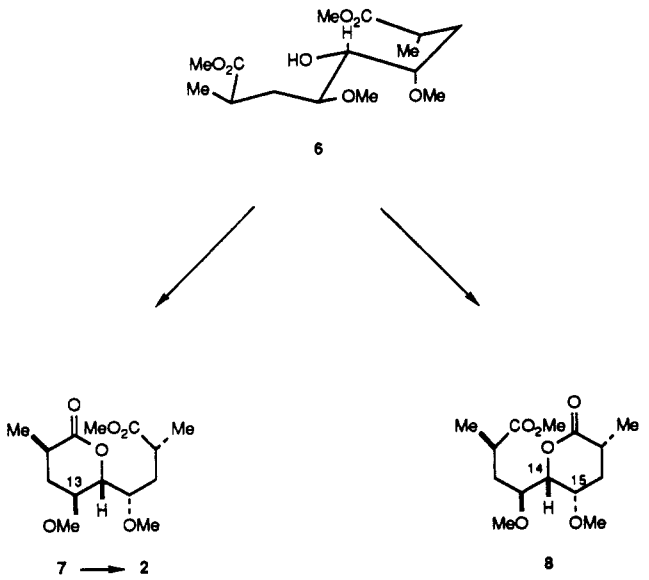
(2) For recent biological data on FK-506, see: (a) Thompson, A. W.; *Immunol. Today* **1988**, *10*, 6. (b) Warty, V.; Diven, W.; Cadoff, E.; Todo, S.; Starzl, T.; Sanghvi, A. *Transplantation* **1988**, *46*, 453.

(3) For synthetic approaches to FK-506, see: (a) Askin, D.; Volante, R. P.; Ryan, K. M.; Reamer, R. A.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 4245 and references to earlier Merck papers. (b) Williams, D. R.; Benbow, J. W. *J. Org. Chem.* **1988**, *53*, 4643. (c) Kocienski, P.; Stocks, M.; Donald, D.; Cooper, M.; Manners, A. *Tetrahedron Lett.* **1988**, *29*, 4481. (d) Ireland, R. E.; Wipf, P. *Tetrahedron Lett.* **1989**, *30*, 919. (e) Smith, A. B. III; Hale, K. J. *Tetrahedron Lett.* **1989**, *30*, 1037. (f) Schreiber, S. L.; Smith, D. B. *J. Org. Chem.* **1989**, *54*, 9. (g) Schreiber, S. L.; Sammakia, T.; Uehling, D. E. *J. Org. Chem.* **1989**, *54*, 15. (h) Ragan, J. A.; Nakatsuka, M.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Org. Chem.* **1989**, *54*, 4267. (i) Egbertson, M.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 12. (j) Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 11. (k) Jones, A. B.; Yamaguchi, M.; Patten, A.; Danishefsky, S. J.; Ragan, J. A.; Smith, D. B.; Schreiber, S. L. *J. Org. Chem.* **1989**, *54*, 17. (l) Wasserman, H. H.; Rotello, V. M.; Williams, D. R.; Benbow, J. W. *J. Org. Chem.* **1989**, *54*, 2785. (m) Corey, E. J.; Huang, H.-C. *Tetrahedron Lett.* **1989**, *30*, 5235. (n) Wang, Z. *Tetrahedron Lett.* **1989**, *30*, 6611. (o) Smith, A. B., III; Hale, K. J.; Laakso, L. M.; Chen, K.; Riéra, A. *Tetrahedron Lett.* **1989**, *30*, 6963.

(4) For the total synthesis of FK-506, see: Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. P.; Shinkai, I. *J. Am. Chem. Soc.* **1989**, *111*, 1157.

0022-3263/90/1955-2776$02.50/0

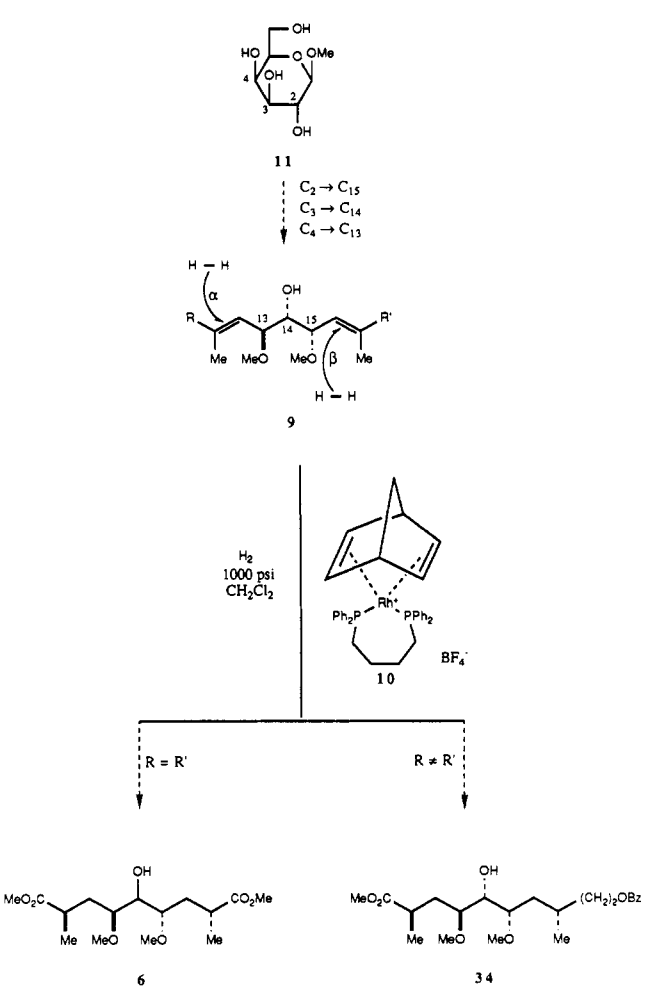
Scheme II



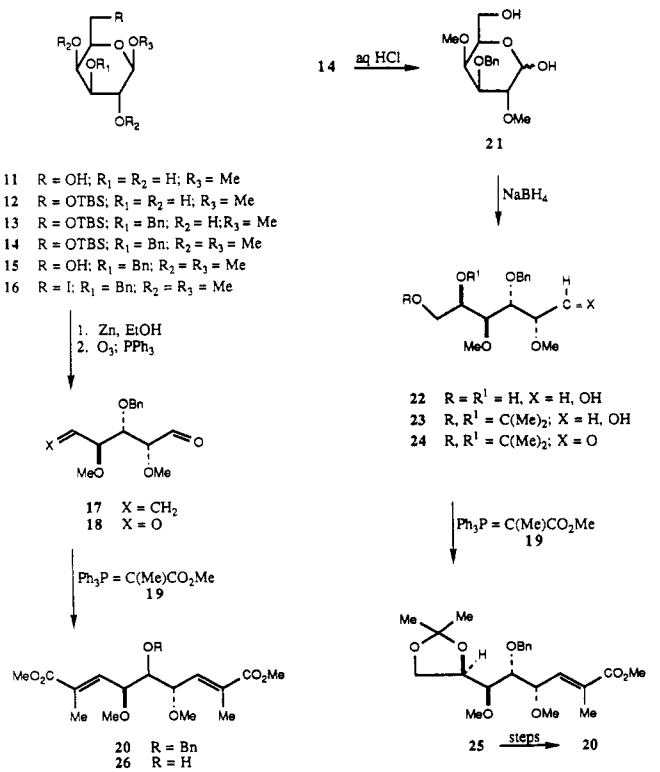
for end group differentiation.[5,6] Consideration of intermediate **6** reveals that lactonization, from the C_{10}- or C_{18}-carbomethoxyl function, would produce compound **7** or **8**, respectively (Scheme II). In lactone **7**, if it adopts a chair conformation, the three ring-bound substituents can each be equatorial. However, lactone **8** must accommodate either a 1,3 diaxial (C_{17}-methyl–C_{15}-methoxy) interaction or, more likely, an axial disposition for the large function at C_{14}. The greater thermodynamic stability expected for **7** relative to **8** would perhaps be mirrored at the kinetic level, in selecting between these lactonization modes.[7] While exploring this interesting possibility, we also investigated an alternative strategy. Toward this end we developed a route where a differentiated intermediate of the type **4** would be produced from the outset (see compound **34**).

It was recognized that the configurations at carbons 2, 3, and 4 of D-galactose (see methyl β-D-galactopyranoside, **11**) could be construed to correspond to those of carbons 15, 14, and 13 (respectively) of target system **2**. *It was further recognized that the required configurations at carbons 11 and 17 might be installed by directed hydrogenation of the generalized system, **9**.* In this analysis we left open the question as to the identity or nonidentity of termini R and R′ as we converged upon **2**. The important feature of the analysis was that with a free homoallylic alcohol as an anchoring element, we could take advantage of the dramatic findings of Evans and co-workers.[8,9] On the basis of these precedents, hydrogenation of **9** with the homogeneous catalyst **10**, under the guidance of the allylic methoxy groups, would be expected to strongly favor the emergence of the required configuration at carbons 11 and 17.

Scheme III



Scheme IV



With these considerations in mind, we specified compounds **26** and **33** as subgoals. The former would hopefully

(5) For formulation and application of the concept of end group differentiation by diastereoselective lactonization see: Hoye, T. R.; Peck, D. R.; Swanson, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 2738.

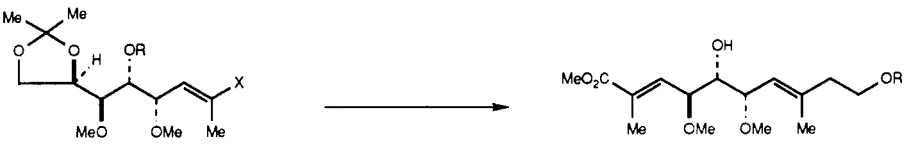
(6) For an exposition of the strategy of two directional chain synthesis, see: Schreiber, S. L. *Chem. Scr.* **1987**, *27*, 563.

(7) Molecular mechanics calculations (MM2 force field) indicate that lactone **7** adopts a twist-chair conformation and is 3.2 kcal/mol more stable that lactone **8**, which prefers a half-chair conformation.

(8) (a) Evans, D. A.; Morrissey, M. M.; Dow, R. C. *Tetrahedron Lett.* **1985**, *26*, 6005. (b) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866.

(9) (a) Brown, J. M.; Naik, R. G. *J. Chem. Soc., Chem. Commun.* **1982**, 348. (b) For a review of the field, see: Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190.

Scheme V



25 → 27 X = CH_2OH; R = Bn
28 X = CH_2Cl; R = Bn
29 X = CH_2CN; R = Bn
30 X = CH_2CH_2OH; R = Bn
31 X = CH_2CH_2OH; R = H

32 R = H
33 R = Bz

lead to structure **6**. Compound **33** would, upon similar reduction, afford **34**, a useful type **4** substrate.

Discussion of Results

The commercially available methyl β-D-galactopyranoside **11** was converted (72%) to its mono *tert*-butyldimethylsilyl (TBS) derivative **12**,[10] and thence, to the C_3-monobenzyl ether **13** (98%) via stannylation and monobenzylation.[11] Methylation of the C_2- and C_4-hydroxyl groups afforded **14** in 95%. Two routes were pursued to reach intermediate **20** (Scheme IV).

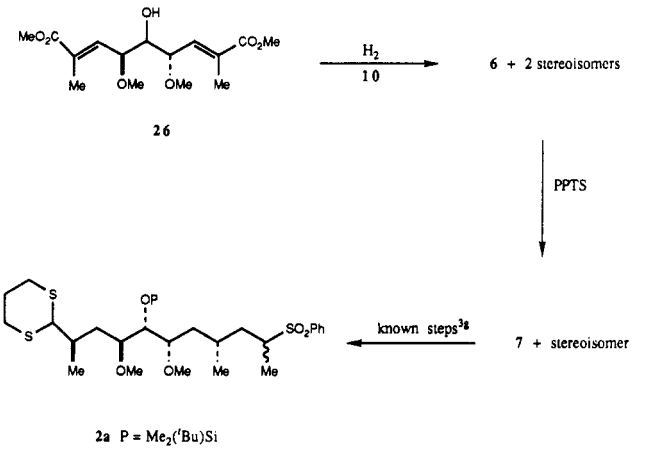
The shorter route started with selective cleavage of the TBS ether (aqueous HOAc, THF) to give alcohol **15** in 95%. Iodination of the primary alcohol (Ph_3P, I_2)[12a-c] afforded compound **16** in 77% yield, which, upon Vasella fragmentation[13] (Zn, EtOH), gave rise to **17** (95% yield). Ozonolysis of **17** followed by reductive workup (Ph_3P) produced the unstable dialdehyde **18** (not isolated), which, upon double Wittig reaction with phosphorane **19**, afforded bis-enoate **20** in 64% yield.

Before this most concise route had been optimized and rendered reproducible, we had worked out a longer but still efficient route to **20** involving sequential rather than concurrent Wittig reactions. Cleavage of both the silyl and methyl glycoside ethers of **14** afforded **21** in 73% yield. The latter was subjected to reductive ring opening with sodium borohydride. Triol **22**, thus obtained in 90% yield, was converted to its isopropylidene derivative **23** in 89% yield. Swern oxidation of **23** followed by Wittig olefination of the resulting aldehyde **24** furnished enoate **25** in 90% yield. Removal of the isopropylidene blocking group (aqueous HOAc) followed by oxidative ($NaIO_4$) cleavage of the diol afforded a crude aldehyde which, on reaction with phosphorane **19**, gave rise to bis-enoate **20** in 79% overall yield.

Deprotection of the benzyl group in **20** was accomplished (88%) with iodotrimethylsilane (traces of HI) in methylene chloride. The resultant compound **26** was an eligible substrate for two-directional reduction and diastereotopic end group differentiation. Before discussing the results of this hydrogenation, we describe a synthesis of diene **33** in which the termini are already distinguished.

A variant of the above route, with compound **25** as a branch point, led to differentiated diene **33** (Scheme V). Treatment of enoate **25** with $LiEt_3BH$ gave a quantitative yield of allylic alcohol **27**. This compound was converted (67% yield) to allylic chloride **28** through the agency of

Scheme VI



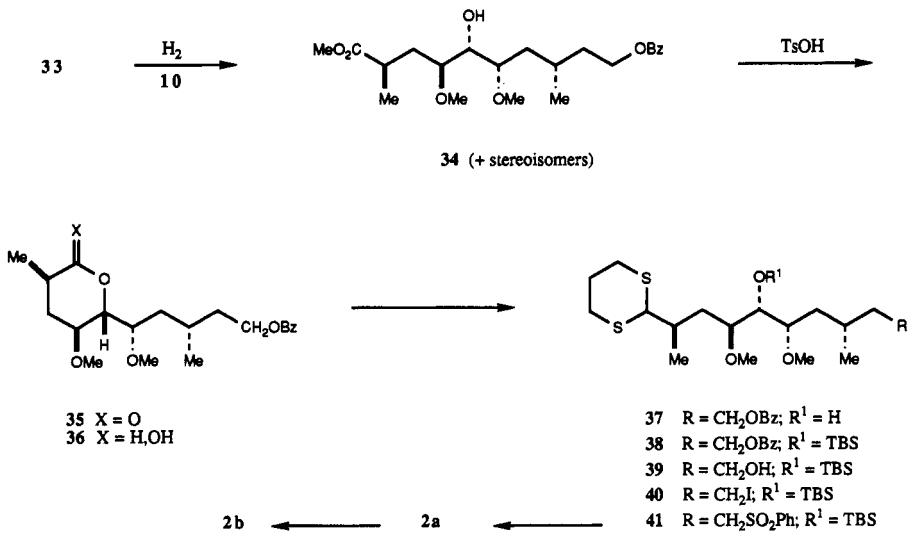
methanesulfonyl chloride-lithium chloride in *s*-collidine. Conversion of **28** to the β,γ-unsaturated nitrile **29** was attended by some difficulty. Reaction of **28** with sodium cyanide in DMF did indeed lead to **29** in 69% yield; however, the reaction also produced the undesired α,β-unsaturated isomer in 22% yield. A two-step reduction sequence [(i) DIBAL-H, CH_2Cl_2; (ii) $NaBH_4$, EtOH] of **29** produced homoallylic alcohol **30** (63%). At this stage it was convenient to cleave the benzyl ether in a reductive fashion (Na, NH_3, −78 °C). Diol **31**, thus obtained in 90% yield from **30**, was deprotected with aqueous acetic acid. The tetraol produced was cleaved with sodium *m*-periodate. Olefination of the resultant unstable β-hydroxy aldehyde followed by selective benzoylation of the primary alcohol in compound **32** afforded **33** (55% overall, four steps). This compound was our other candidate substrate for two-directional hydrogenation, this time in the differentiated mode.

We turn first to the reduction of diene **26** (Scheme VI). Reaction was carried out with hydrogen gas at 1000 psi in methylene chloride at room temperature in the presence of cationic rhodium complex, **10**.[8,9] A three-component mixture of tetrahydro products was produced. GLC analysis indicated the three components to be present in a 19:2.2:1 ratio. The fouth possible permutant was not observed. Preparative-scale chromatographic separation of these components was not feasible at this stage.

The precedents for this type of directed hydrogenation were provided in a thorough series of investigations by Evans and co-workers.[8,9] What emerges from these studies is a trend wherein the major stereochemical determinant is the allylic substituent. In this case, we hoped that the methoxy functions allylic to each double bond would be decisive. The stereochemistry of the anchoring allylic alcohol tends to be of minor importance. On the basis of these Evans[8,9] precedents, the expected major product would be compound **6**. This structural assignment could

(10) Mark, E.; Zbiral, E.; Brandstetter, H. H. *Monastsch. Chem.* **1980**, *111*, 289.
(11) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.
(12) (a) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D.; Williams, D. J. *J. Org. Chem.* **1984**, *49*, 3503. (b) Corey, E. J.; Pyne, S. G.; Su, W. *Tetrahedron Lett.* **1983**, *24*, 4883. (c) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866.
(13) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1984**, *67*, 1328.

Scheme VII



not be proven in the case at hand, particularly in the absence of a homogeneous sample of the major product. Nonetheless, we moved on to the next step, assuming the correctness of the formulation. The total reaction mixture was subjected to lactonization. Heating in the presence of strong acids gave complex reaction mixtures. Attempts to promote lactone formation by base hydrolysis of the esters and acidification also led to a complex collection of products with no apparent selectivity. The best results in our hands involved long-term treatment of the hydroxy diester mixture with pyridinium *p*-toluenesulfonate (PPTS) in methylene chloride. Chromatography on silica gel afforded a major fraction (64% yield) which itself was typically a 4–6:1 mixture of products. NMR analysis indicated that the major lactone had the required C_{11}–C_{13} cis and C_{13}–C_{14} trans relationships in the lactone ring. At this stage, assignment of the configuration at C_{17} rested on the stereochemical logic of the hydrogenation reaction as indicated by the Evans precedents. The correctness of this assignment was strongly suggested later when the same compound was produced as the major lactonization isomer by Schreiber and associates[3g] using a very reasonable but completely separate stereochemical rationale. Eventually the point was proven by the intersection of our total synthesis with a late intermediate in the Merck total synthesis of FK-506.[4,14]

The structure of the minor component of the lactonization mixture has not been determined. We believe that it is in fact lactone **8** arising from lactonization of **6** in the alternative sense. We favor this assignment from the fact that there seems to be more of this compound produced than would be expected from any of the minor tetrahydro isomers (each of which would be likely to lactonize in either of two senses). We believe that the lactones derived from these minor tetrahydro products were those which were successfully separated by the silica gel chromatography.

Conversion of the lactone mixture, with **7** as the major component, to the desired sulfone **2a** was accomplished by Schreiber and associates[3g] in an effort conducted concurrently with the one described here. These steps were readily carried out in our laboratory, with separation of the minor diastereomers being accomplished progressively as the synthesis went along. Of course, the final product **2a** is obtained as a mixture of stereoisomers at C_{19}. The same is true in our synthesis which is described below.

While the lactonization of intermediate **6** was indeed diastereoselective, it was not specific. Hence, another difficult separation was required. Accordingly, we evaluated the practicality of a route which involved directed hydrogenation of intermediate **33** (Scheme VII). As before, we made recourse to high pressures of hydrogen in the presence of catalyst **10**. Again, a major tetrahydro product was produced. While by chromatographic criteria the product (89%) appeared to be a single entity, NMR analysis indicated the presence of ca. 16% of other materials, presumably some of the tetrahydro stereoisomers. Lactonization could now be carried out very smoothly (93%) with *p*-toluenesulfonic acid in methylene chloride. On basis of the Evans precedents, the major tetrahydro product was formulated as **34** and the lactone, accordingly, as **35**. Reduction with L-Selectride (Aldrich) (94%) afforded hemiacetal **36**, which, upon thioacetalization, provided dithiane–alcohol **37** (85%). After conversion to the TBS derivative **38** (97%), cleavage of the benzoate (K_2CO_3, MeOH) afforded primary alcohol **39**. It was during the purification of this compound that complete removal of products arising from the presumed isomeric tetrahydro isomers accompanying **34** could be accomplished.

Iodide **40** obtained from the reaction of **39** with Ph_3P–I_2 was converted to the primary sulfone **41** ($PhSO_2Na$, DMF) in 81% yield. Methylation of this sulfone to produce **2a** was accomplished through deprotonation with *n*-butyllithium followed by alkylation with methyl iodide. There was thus obtained the desired secondary sulfone **2a** in 93% yield (see the Experimental Section). For some purposes it seemed that it would be helpful to install a triethylsilyl protecting group at C_{14}. This was readily accomplished from **2a** by desilylation (HF–CH_3CN) followed by resilylation (Et_3SiOTf, 2,6-lutidine) to afford **2b** in 90% overall yield. In summary, several routes were developed to the desired goal system **2a** or **2b**. Its incorporation in a totally synthetic route to FK-506 is described in the following paper.

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. Low-resolution (EI) and high-resolution (EI, CI, and FAB) mass spectra were determined on a Hewlett-Packard 5985 mass spectrometer and a Kratos MS80RFA spec-

(14) Jones, A. B.; Villalobos, A.; Linde, R. G. II; Danishefsky, S. J. *J. Org. Chem.*, following paper in this issue.

trometer, respectively. High-field ^1H NMR spectra were recorded on a Bruker 490 instrument in $CDCl_3$ with $CHCl_3$ (7.27 ppm) or $Si(CH_3)_4$ (0.0 ppm) as an internal reference. Microanalyses were performed by Galbraith Laboratories, Inc., or Robertson Laboratories, Inc. Flash chromatography was performed on EM Kieselgel 60 (230–400 mesh).

All reactions were carried under a positive pressure of N_2, unless otherwise noted. Tetrahydrofuran (THF) was distilled immediately before use from sodium benzophenone ketyl. Methylene chloride (CH_2Cl_2) was freshly distilled from P_2O_5 before use. Benzene and toluene were distilled from CaH_2, and methanol (MeOH) was distilled from Mg turnings before use. Anhydrous pyridine, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) were purchased from Aldrich Chemical Co. *p*-Toluenesulfonic acid monohydrate was dried before use by dissolving in a minimum amount of EtOH, concentrating from benzene under reduced pressure (twice), and drying under high vacuum. Zn powder was activated as described by Fieser and Fieser (Vol. 1, p 1276) by washing with 1 N HCl, water, MeOH, and ether and drying under high vacuum.

Methyl 6-*O*-[(1,1-Dimethylethyl)dimethylsilyl]-β-D-galactopyranoside (12). *tert*-Butyldimethylsilyl chloride (17.0 g, 0.113 mol) was added to a mixture of methyl β-D-galactopyranoside (20.0 g, 0.103 mol), triethylamine (32 mL, 0.227 mol), and DMAP (1.26 g, 0.0103 mol) in CH_2Cl_2 (200 mL) at room temperature. After 15–20 h, the reaction mixture was filtered and the filtrate was concentrated. Purification by chromatography (50% EtOAc–hex → 100% EtOAc) gave **12** (22.9 g, 72%) as a pale yellow gum: $[\alpha]^{25}_D = -30.5°$ (c = 1.08, $CHCl_3$) [lit.[10] value: $[\alpha]^{25}_D = -10.5°$ (c = 1, $CHCl_3$)]; ^1H NMR δ 4.68 (br s, 1 H, OH), 4.57 (br s, 1 H, OH), 4.16 (d, 1 H, J = 7.6 Hz, OC*H*OMe), 4.00 (apparent br s, 1 H, TBSOCH$_2$CHC*H*), 3.91 (dd, 1 H, J = 10.4 Hz, J = 6.1 Hz, one of TBSOC*H*$_2$), 3.84 (dd, 1 H, J = 10.4 Hz, J = 5.4 Hz, one of TBSOC*H*$_2$), 3.68–3.72 (m, 2 H, OCH(OMe)C*H*OH, and O*H*), 3.57–3.59 (m, 1 H, OCH(OMe)CHC*H*OH), 3.55 (s, 3 H, OCH_3), 3.48 (t, 1 H, J = 5.7 Hz, TBSOCH$_2$C*H*), 0.90 (s, 9 H, $SiC(CH_3)_3$), 0.090 (s, 6 H, $Si(CH_3)_2$); IR (thin film) 3400, 2940, 2920, 2875, 2845, 1465, 1460, 1385, 1250, 1135, 1095, 1070, 840, 775 cm^{-1}; EIMS m/e (relative intensity) 293 (0.1), 278 (0.2), 261 (0.8), 243 (0.7), 219 (70), 201 (47), 171 (22), 159 (39), 143 (30), 117 (100), 105 (35), 75 (60); CIHRMS calcd for $C_{13}H_{28}O_6Si$ 309.1734, found 309.1733.

Methyl 6-*O*-[(1,1-Dimethylethyl)dimethylsilyl]-3-*O*-(phenylmethyl)-β-D-galactopyranoside (13). Bis(tri-*n*-butyltin) oxide (28 mL, 0.056 mol) was added to a solution of triol **12** (22.9 g, 0.074 mol) in toluene (500 mL). The resulting mixture was heated to reflux for 6 h with azeotropic removal of H_2O (Dean–Stark trap). The mixture was allowed to cool to 80 °C, and benzyl bromide (22 mL, 0.19 mol) followed by tetra-*n*-butylammonium bromide (30.0 g, 0.093 mol) was added. After 12 h, more benzyl bromide (5.0 mL, 0.042 mol) and tetra-*n*-butylammonium bromide (6.0 g, 0.019 mol) were added. The mixture was concentrated and purified by chromatography (20 → 50% EtOAc–hexane) to afford **13** (29.1 g, 98%) as a white solid. A small amount was purified further by recrystallization (hexane) for characterization: mp (hexane) 94–95 °C; $[\alpha]^{25}_D = -4.05°$ (c = 3.3, $CHCl_3$); ^1H NMR δ 7.32–7.41 (m, 5 H, ArH), 4.76 (s, 2 H, PhC*H*$_2$O), 4.17 (d, 1 H, J = 7.8 Hz, OC*H*OMe), 4.03–4.04 (m, 1 H, TBSOCH$_2$CHC*H*OH), 3.92 (dd, 1 H, J = 10.3 Hz, J = 6.5 Hz, one of TBSOC*H*$_2$), 3.83 (dd, 1 H, J = 10.3 Hz, J = 5.5 Hz, one of TBSOC*H*$_2$), 3.80 (ddd, 1 H, J = 9.6 Hz, J = 7.8 Hz, J = 2.1 Hz, OCH(OMe)C*H*OH), 3.55 (s, 3 H, OCH_3), 3.41–3.45 (m, 2 H, BnOC*H* and TBSOCH$_2$C*H*), 2.48 (s, 1 H, OH), 2.38 (d, 1 H, J = 2.1 Hz, OH), 0.91 (s, 9 H, $SiC(CH_3)_3$), 0.09 (s, 6 H, $Si(CH_3)_2$); IR (KBr) 3540, 3420, 2950, 2920, 2880, 2840, 1460, 1385, 1250, 1195, 1135, 1090, 1065, 845, 745, 700 cm^{-1}; EIMS m/e (relative intensity) 309 (1.6), 291 (0.7), 91 (100); CIHRMS calcd for $C_{20}H_{34}O_6Si$ 399.2203, found 399.2214.

Anal. Calcd for $C_{20}H_{34}O_6Si$: C, 60.26; H, 8.60. Found: C, 60.13; H, 8.68.

Methyl 6-*O*-[(1,1-Dimethylethyl)dimethylsilyl]-2,4-di-*O*-methyl-3-*O*-(phenylmethyl)-β-D-galactopyranoside (14). Two parallel reactions with diol **13** (14.2 g each) were carried out. A solution of diol **13** (14.2 g, 0.0358 mol) in THF (100 mL) was added slowly to a mixture of pentane-washed NaH (60% mineral oil dispersion, 4.3 g, 0.107 mol) and MeI (22 mL, 0.358 mol) in THF (400 mL) at room temperature. After 1.5 h, both reaction mixtures were poured slowly into cold (0 °C) saturated NH_4Cl. The resulting mixture was extracted with Et_2O (3×), and the combined organic layer was washed with brine (1×), dried ($MgSO_4$), filtered, and concentrated to give crude **14** (28.9 g, 95%) as a pale yellow soft solid. Purification can be carried out by chromatography (20% EtOAc–hexane) or distillation (158–178 °C, 0.05 mmHg). A small amount was purified further by dissolving in acetonitrile, washing with hexanes, concentrating, and redistilling (Kugelrohr) to give a white solid: mp 51–52 °C; $[\alpha]^{25}_D = -34.0°$ (c = 1.19, $CHCl_3$); ^1H NMR δ 7.29–7.42 (m, 5 H, ArH), 4.73 (AB quartet, 2 H, J = 12.0 Hz, PhC*H*$_2$O), 4.14 (d, 1 H, J = 7.1 Hz, OC*H*OMe), 3.80 (dd, 1 H, J = 9.6 Hz, J = 8.2 Hz, one of TBSOC*H*$_2$), 3.71 (dd, 1 H, J = 9.6 Hz, J = 5.5 Hz, one of TBSOC*H*$_2$), 3.62 (s, 3 H, OCH_3), 3.60–3.61 (m, 1 H, TBSOCH$_2$CHC*H*OMe), 3.59 (s, 3 H, OCH_3), 3.51 (s, 3 H, OCH_3), 3.43 (dd, 1 H, J = 9.7 Hz, J = 7.2 Hz, OCH(OMe)C*H*OMe), 3.38 (dd, 1 H, J = 9.6 Hz, J = 2.8 Hz, BnOC*H*), 3.34 (br dd, 1 H, J = 8.2 Hz, J = 5.4 Hz, TBSOCH$_2$C*H*), 0.91 (s, 9 H, $SiC(CH_3)_3$), 0.09 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$); IR (KBr) 2940, 2920, 2870, 2840, 1465, 1380, 1365, 1250, 1105, 1075, 835 cm^{-1}; EIMS m/e (relative intensity) 369 (0.5), 265 (10), 151 (30), 135 (37), 91 (100); CIHRMS calcd for $C_{22}H_{38}O_6Si$ 427.2516, found 427.2520.

Anal. Calcd for $C_{22}H_{38}O_6Si$: C, 61.94; H, 8.98. Found: C, 62.12; H, 9.19.

Methyl 2,4-Di-*O*-methyl-3-*O*-(phenylmethyl)-β-D-galactopyranoside (15). A mixture of fully-protected galactose **14** (2.5 g, 5.87 mmol) in THF (10 mL) and 3:1 HOAc–H_2O was stirred at room temperature for 20 h. Volatiles were removed under reduced pressure, toluene was added, and the mixture was reconcentrated. After azeotroping with toluene two or three times, a pale yellow solid was obtained. Purification by chromatography (50% EtOAc–hexane → 100% EtOAc) afforded **15** (1.75 g, 95%) as a white solid. A small amount was purified further by recrystallization (Et_2O–hexane) for characterization: mp (Et_2O–hexane) 69–70 °C; $[\alpha]^{25}_D = -29.5°$ (c = 1.06, $CHCl_3$); ^1H NMR δ 7.30–7.40 (m, 5 H, ArH), 4.76 (AB quartet, 2 H, J = 12.0 Hz, PhC*H*$_2$O), 4.18 (d, 1 H, J = 7.1 Hz, OC*H*OMe), 3.91 (dd, 1 H, J = 11.3 Hz, J = 7.1 Hz, one of HOC*H*$_2$), 3.73 (dd, 1 H, J = 11.3 Hz, J = 4.9 Hz, one of HOC*H*$_2$), 3.62 (s, 3 H, OCH_3), 3.58 (s, 3 H, OCH_3), 3.54 (s, 3 H, OCH_3), 3.53 (dd, 1 H, J = 2.7 Hz, J = 1.0 Hz, HOCH$_2$CHC*H*OMe), 3.43 (dd, 1 H, J = 9.7 Hz, J = 6.9 Hz, OCH(OMe)C*H*OMe), 3.40 (dd, 1 H, J = 9.7 Hz, J = 3.0 Hz, BnOC*H*), 3.40–3.43 (m, 1 H, HOCH$_2$C*H*), 2.01 (br s, 1 H, OH); IR (KBr) 3320, 3220, 2940, 2865, 2840, 1455, 1370, 1125, 1075, 705 cm^{-1}; EIMS m/e (relative intensity) 211 (0.7), 164 (11), 151 (30), 135 (52), 101 (100), 91 (88); CIHRMS calcd for $C_{16}H_{24}O_6$ 313.1651, found 313.1654.

Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.50, H, 7.58.

Methyl 6-Deoxy-6-iodo-2,4-di-*O*-methyl-3-*O*-(phenylmethyl)-β-D-galactopyranoside (16). Triphenylphosphine (1.18 g, 4.49 mmol) was added to a solution of I_2 (1.06 g, 4.17 mmol) in benzene (20 mL). After stirring for 5–10 min, to the orange-yellow heterogeneous mixture were added pyridine (0.725 mL, 8.97 mmol) and a solution of alcohol **15** (1.0 g, 2.05 mmol) in benzene (50 mL). The resulting mixture was heated to reflux for 1 h. The mixture was allowed to cool to room temperature, diluted with EtOAc, washed with saturated $Na_2S_2O_3$ (2×), saturated $CuSO_4$ (2×), and brine (2×), dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography (10 → 20% EtOAc–hexane) gave **16** (1.04 g, 77%) as a white solid. A small amount was purified further by recrystallization (Et_2O–hexane) for characterization: mp (Et_2O–hexane) 105–106 °C; $[\alpha]^{25}_D = -26.6°$ (c = 0.44, $CHCl_3$); ^1H NMR δ 7.31–7.41 (m, 5 H, ArH), 4.73 (AB quartet, 2 H, J = 11.9 Hz, PhC*H*$_2$O), 4.14–4.16 (m, 1 H, OC*H*OMe), 3.78 (br d, 1 H, J = 1.2 Hz, BnOC*H*), 3.65 (s, 3 H, OCH_3), 3.61 (s, 3 H, OCH_3), 3.54 (s, 3 H, OCH_3), 3.51 (br t, 1 H, J = 7.0 Hz, ICH$_2$C*H*), 3.37–3.41 (overlapping dd, 1 H, J = 4.4 Hz, J = 1.4 Hz, OCH(OMe)C*H*OMe and dd, 1 H, J = 9.9 Hz, J = 7.4 Hz, one of ICH$_2$), 3.38–3.40 (m, 1 H, ICH$_2$CHC*H*OMe), 3.33 (dd, 1 H, J = 9.8 Hz, J = 6.5 Hz, one of ICH$_2$); IR (KBr) 2930, 2840, 1460, 1370, 1205, 1125, 1095, 1080, 1040, 980, 735 cm^{-1}; EIMS m/e (relative intensity) 255 (0.4), 164 (6), 151 (3), 135 (16), 101 (100), 91 (35); CIHRMS calcd for $C_{16}H_{23}IO_5$ 423.0668, found 423.0642.

Anal. Calcd for $C_{16}H_{23}IO_5$: C, 45.51; H, 5.49. Found: C, 45.70; H, 5.42.

5,6-Dideoxy-2,4-di-*O*-methyl-3-*O*-(phenylmethyl)-L-*arabino*-hex-5-enose (17). Activated Zn powder (1.55 g, 23.7 mmol) was added to a solution of iodide **16** (0.50 g, 1.18 mmol) in 95% EtOH (15 mL), and the resulting mixture was heated to reflux for 45 min. The reaction mixture was allowed to cool to room temperature and filtered through a Celite pad. The filtrate was concentrated, and the residue was dissolved in Et_2O. The resulting organic layer was washed with saturated $Na_2S_2O_3$ (1×) and brine (1×), dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography (30% Et_2O–hexane) afforded **17** (0.297 g, 95%) as a clear oil: $[\alpha]^{25}_D$ = +86.0° (c = 1.3, $CHCl_3$); ^1H NMR δ 9.67 (d, 1 H, J = 1.6 Hz, CHO), 7.24–7.32 (m, 5 H, ArH), 5.75–5.82 (m, 1 H, CH_2=C*H*), 5.36–5.39 (overlapping d, 1 H, J = 16.3 Hz, *trans*-C*H*$_2$=CH, and d, 1 H, J = 11.2 Hz, *cis*-C*H*$_2$=CH), 4.54 (AB quartet, 2 H, J = 11.2 Hz, PhC*H*$_2$O), 3.83–3.84 (m, 1 H, OHCC*H*), 3.77–3.78 (overlapping d, 1 H, J = 3.4 Hz, CH_2=CHC*H*, and d, 1 H, J = 1.7 Hz, BnOC*H*), 3.5 (s, 3 H, OCH_3), 3.25 (s, 3 H, OCH_3); IR (thin film) 2935, 2900, 2825, 1730, 1455, 1200, 1100, 940, 745, 705 cm^{-1}; EIMS m/e (relative intensity) 232 (0.2), 201 (0.2), 191 (7), 164 (18), 135 (18), 128 (13), 91 (100); CIHRMS calcd for $C_{15}H_{20}O_4$ 265.1440, found 265.1453.

[*S*-[*R,*R**-(*E*,*E*)]]-4,6-Dimethoxy-2,8-dimethyl-5-(phenylmethoxy)-2,7-nonadienedioic Acid Dimethyl Ester (20).** A stream of O_3 was bubbled through a solution of olefin–aldehyde **17** (110 mg, 0.417 mmol) in CH_2Cl_2 (4 mL) at −78 °C until the blue color persisted. N_2 was bubbled through the system, and a solution of triphenylphosphine (328 mg, 1.25 mmol) in CH_2Cl_2 (2 mL) was added. The cold bath was removed, and the mixture was allowed to stir at room temperature for 17 h. The reaction mixture was cooled to 0 °C and a solution of triphenylphosphorane **19**[15] (580 mg, 1.67 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature gradually. After 72 h, more phosphorane **19** (290 mg, 0.835 mmol) in CH_2Cl_2 (1 mL) was added at 0 °C. The mixture was stirred for another 24 h at room temperature. Concentration and purification by chromatography (10 → 50% Et_2O–hexane) afforded **20** (109 mg, 64%) as a clear oil: $[\alpha]^{25}_D$ = +66.7° (c = 1.31, $CHCl_3$); ^1H NMR δ 725–7.30 (m, 5 H, ArH), 6.71 (dd, 1 H, J = 9.0 Hz, J = 1.4 Hz, C=CH), 6.61 (dd, 1 H, J = 9.4 Hz, J = 1.4 Hz, C=CH), 4.53 (apparent d [close AB quartet], 2 H, $\Delta\nu$ = 1.8 Hz, PhC*H*$_2$O), 4.25–4.30 (overlapping dd, 1 H, J = 9.0 Hz, J = 3.5 Hz, C=CHC*H*OMe, and dd, 1 H, J = 9.4 Hz, J = 6.9 Hz, C=CHC*H*OMe), 3.77 (s, 3 H, CO_2CH_3), 3.76 (s, 3 H, CO_2CH_3), 3.49 (dd, 1 H, J = 6.7 Hz, J = 3.5 Hz, BnOC*H*), 3.31 (s, 3 H, OCH_3), 3.28 (s, 3 H, OCH_3), 1.89 (d, 3 H, J = 1.4 Hz, C=C(CH_3)), 1.87 (d, 3 H, J = 1.4 Hz, C=C(CH_3)); IR (thin film) 2920, 2890, 2820, 1720, 1710, 1650, 1435, 1240, 1190, 1135, 1085, 1025, 750, 700 cm^{-1}; EIMS m/e (relative intensity) 315 (0.1), 263 (2), 231 (2), 203 (1), 143 (100), 117 (0.6), 91 (33); CIHRMS calcd for $C_{22}H_{30}O_7$ 407.2069, found 407.2079.

Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found: C, 65.05; H, 7.46.

2,4-Di-*O*-methyl-3-*O*-(phenylmethyl)-D-galactose (21). A mixture of methyl glycoside **14** (45.0 g, 0.106 mol) in 3 M HCl (1.1 L) and THF (0.7 L) was heated to reflux for 21 h. The mixture was allowed to cool to room temperature and saturated with NaCl. The resulting mixture was extracted with CH_2Cl_2 (5×), and the combined organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography (CH_2Cl_2 → 20% iPrOH–CH_2Cl_2) gave **21** (21.2 g, 68%) as a clear gum. Continuous liquid–liquid extraction of the NaCl-saturated aqueous layer with Et_2O for 48 h afforded, after concentration of the organic layer and chromatography, additional **21** (1.91 g, 73% combined yield): ^1H NMR (both anomers) δ 7.29–7.40 (m, 10 H), 5.44 (t, 1 H, J = 2.9 Hz), 4.71–4.80 (m, 4 H), 4.59 (t, 1 H, J = 6.8 Hz), 4.02–4.05 (m, 1 H), 3.99 (br d, 1 H, J = 6.6 Hz), 3.85–3.93 (m, 2 H), 3.81 (dd, 1 H, J = 9.9 Hz, J = 2.9 Hz), 3.67–3.73 (overlapping dd, 1 H, J = 9.8 Hz, J = 3.5 Hz, and m, 2 H), 3.59 (s, 3 H), 3.64 (br d, 1 H, J = 2.0 Hz), 3.59 (s, 3 H), 3.57 (s, 6 H), 3.49–3.53 (m, 2 H), 3.37–3.46 (m, 3 H), 2.56 (br d, 1 H, J = 6.0 Hz), 2.41 (br d, 1 H, J = 5.5 Hz); IR (thin film) 3380, 2920, 2825, 1495, 1450, 1360, 1190, 1085, 975, 735, 700 cm^{-1}; EIMS m/e (relative intensity) 267 (0.3), 230 (0.4), 217 (0.9), 189 (3), 164 (2), 135 (9), 101 (100), 91 (43); CIHRMS calcd for $C_{15}H_{22}O_6$ 299.1494, found 299.1493.

2,4-Di-*O*-methyl-3-*O*-(phenylmethyl)-D-galactol (22). $NaBH_4$ (5.3 g, 0.141 mol) was added in portions to a solution of hemiacetal **21** (21.0 g, 0.0705 mol) in absolute EtOH (700 mL). The resulting mixture was stirred at room temperature for 5 h. EtOH was removed under reduced pressure, and the concentrate was cooled to 0 °C. Cold (0 °C) saturated NH_4Cl (100 mL) was added slowly, in portions. After stirring for 10–15 min at room temperature, the mixture was extracted with EtOAc (6×). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated to give crude **22** (19.1 g, 90%) as a white solid. A small amount was purified by recrystallization (EtOAc) for characterization: mp (EtOAc) 117–118 °C; $[\alpha]^{25}_D$ = +4.15° (c = 0.97, MeOH); ^1H NMR δ 7.32–7.37 (m, 5 H, ArH), 4.73 (AB quartet, 2 H, J = 11.3 Hz, PhC*H*$_2$O), 3.91–3.92 (m, 1 H, HOCH_2C*H*OH), 3.81–3.83 (m, 2 H, BnOC*H* and one of HOC*H*$_2$CHOMe), 3.74–3.80 (m, 2 H, one of HOC*H*$_2$CHOH and one of HOC*H*$_2$CHOMe), 3.69 (dd, 1 H, J = 11.0 Hz, J = 4.6 Hz, one of HOC*H*$_2$CHOH), 3.51 (s, 3 H, OCH_3), 3.49 (s, 3 H, OCH_3), 3.45–3.52 (m, 2 H, both MeOC*H*), 3.07 (br s, 1 H, OH), 2.18 (br s, 1 H, OH), 1.56 (br s, 1 H, OH); IR (KBr) 3430, 3260, 2920, 2825, 1465, 1450, 1400, 1330, 1225, 1185, 1115, 1090, 1040, 1020, 860, 750, 695 cm^{-1}; EIMS m/e (relative intensity) 269 (0.2), 251 (0.3), 237 (1), 223 (2), 207 (2), 195 (2), 163 (7), 135 (7), 101 (51), 91 (100); CIHRMS calcd for $C_{15}H_{24}O_6$ 301.1651, found 301.1644.

Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 60.04; H, 8.27.

2,4-Di-*O*-methyl-5,6-*O*-(1-methylethylidene)-3-*O*-(phenylmethyl)-D-galactol (23). *p*-Toluenesulfonic acid (1.0 g, 6.3 mmol) followed by 3-Å molecular sieves was added to a suspension of crude triol **22** (19.0 g) in acetone (500 mL). The mixture was stirred at room temperature for 4 h, and solid $NaHCO_3$ (1.0 g) was added. The resulting mixture was stirred for 15 min and filtered through a Celite–$MgSO_4$ pad. The filtrate was concentrated, and the residue was dissolved in EtOAc. The organic layer was washed with H_2O (1×) and brine (2×), dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography (Et_2O) afforded **23** (19.1 g, 89%) as a pale yellow oil: $[\alpha]^{25}_D$ = +16.8° (c = 1.13, $CHCl_3$); ^1H NMR δ 7.30–7.36 (m, 5 H, ArH), 4.67 (apparent d [close AB quartet], 2 H, $\Delta\nu$ = 1.6 Hz, PhC*H*$_2$O), 4.33–4.67 (m, 1 H, C(CH_3)$_2$OC*H*), 4.01 (dd, 1 H, J = 8.1 Hz, J = 6.4 Hz, one of C(CH_3)$_2$OC*H*$_2$), 3.78–3.80 (m, 2 H, HOC*H*$_2$), 3.72 (t, 1 H, J = 8.0 Hz, one of C(CH_3)$_2$OC*H*$_2$), 3.61 (dd, 1 H, J = 6.7 Hz, J = 3.8 Hz, BnOC*H*), 3.56 (s, 3 H, OCH_3), 3.46 (s, 3 H, OCH_3), 3.43–3.47 (m, 2 H, both MeOC*H*), 2.37 (br s, 1 H, OH), 1.45 (s, 3 H, CCH_3), 1.38 (s, 3 H, CCH_3); IR (thin film) 3450, 2980, 2920, 2820, 1490, 1450, 1365, 1250, 1210, 1085, 850, 735, 700 cm^{-1}; EIMS m/e (relative intensity) 325 (0.9), 282 (1), 251 (0.6), 233 (6), 207 (4), 175 (4), 163 (3), 145 (9), 101 (100), 91 (98); CIHRMS calcd for $C_{18}H_{28}O_6$ 341.1964, found 341.1977.

2,4-Di-*O*-methyl-5,6-*O*-(1-methylethylidene)-3-*O*-(phenylmethyl)-D-galactose (24). A solution of DMSO (19.8 mL, 0.279 mol) in CH_2Cl_2 (30 mL) was added slowly to a cold (−78 °C) solution of oxalyl chloride (9.7 mL, 0.112 mol) in CH_2Cl_2 (200 mL). After 15 min, alcohol **23** (19.0 g, 0.056 mol) in CH_2Cl_2 (70 mL) was added. The resulting mixture was stirred for 20 min, followed by addition of Et_3N (78 mL, 0.559 mol). The cooling bath was removed, and after 25 min, the mixture was poured over H_2O. The organic layer was separated and washed with 1 N HCl (2×), H_2O (3×), and brine (1×), dried ($MgSO_4$), filtered, and concentrated to yield crude **24** (18.0 g) as a yellow oil. A small amount was purified by chromatography (30% EtOAc–hexane) for characterization: ^1H NMR δ 9.70 (d, 1 H, J = 1.6 Hz, CHO), 7.28–7.36 (m, 5 H, ArH), 4.55 (apparent d [close AB quartet], 2 H, $\Delta\nu$ = 2.6 Hz, PhC*H*$_2$O), 4.27–4.31 (m, 1 H, C(CH_3)$_2$OC*H*), 3.99 (dd, 1 H, J = 8.2 Hz, J = 6.4 Hz, one of C(CH_3)$_2$OC*H*$_2$), 3.91 (dd, 1 H, J = 7.9 Hz, J = 3.4 Hz, BnOC*H*), 3.82 (dd, 1 H, J = 3.4 Hz, J = 1.7 Hz, OHCC*H*), 3.77 (t, 1 H, J = 8.0 Hz, one of C-(CH_3)$_2$OC*H*$_2$), 3.53 (s, 3 H, OCH_3), 3.48 (s, 3 H, OCH_3), 3.40 (dd, 1 H, J = 7.9 Hz, J = 5.1 Hz, C(CH_3)$_2$OCHC*H*), 1.44 (s, 3 H, CCH_3), 1.38 (s, 3 H, CCH_3); IR (thin film) 2980, 2920, 2820, 1725, 1450, 1380, 1370, 1250, 1210, 1090, 850, 700 cm^{-1}; EIMS m/e (relative intensity) 323 (0.4), 265 (2), 233 (0.6), 207 (3), 177 (1), 164 (7), 145 (3), 129 (9), 101 (100), 91 (58); CIHRMS calcd for $C_{18}H_{26}O_6$ 339.1807, found 339.1805.

(15) House, H. O.; Rasmusson, G. H. *J. Org. Chem.* **1961**, *26*, 4278. Formation of the phosphonium salt was carried out in benzene at 50–55 °C for 2 days.

(2*E*)-2,3-Dideoxy-2-methyl-4,6-di-*O*-methyl-7,8-*O*-(1-methylethylidene)-5-*O*-(phenylmethyl)-D-*galacto*-oct-2-enonic Acid Methyl Ester (25). The above crude aldehyde **24** (18.0 g) was dissolved in CH_2Cl_2 (300 mL) and cooled to 0 °C. A solution of triphenylphosphorane **19**[15] (25.0 g, 72.7 mmol) in CH_2Cl_2 (100 mL) was added dropwise, and the resulting mixture was allowed to warm to room temperature overnight (12 h). The reaction mixture was concentrated and purified by chromatography (50% Et_2O–hexane) to afford **25** (20.5 g, 90% overall, two steps) as a pale yellow oil: $[\alpha]^{25}_D$ = +47.6° (*c* = 0.97, $CHCl_3$); ^1H NMR δ 7.27–7.32 (m, 5 H, ArH), 6.85 (dd, 1 H, *J* = 8.9 Hz, *J* = 1.5 Hz, C=CH), 4.56 (apparent d [close AB quartet], 2 H, Δν = 1.6 Hz, PhCH_2O), 4.27–4.34 (overlapping ddd, 1 H, *J* = 8.1 Hz, *J* = 6.3 Hz, *J* = 4.2 Hz, $C(CH_3)_2OCH$, and dd, 1 H, *J* = 9.0 Hz, *J* = 2.4 Hz, C=CHCHOMe), 4.00 (dd, 1 H, *J* = 8.0 Hz, *J* = 6.3 Hz, one of $C(CH_3)_2OCH_2$), 3.81 (t, 1 H, *J* = 8.1 Hz, one of $C(CH_3)_2OCH_2$), 3.78 (s, 3 H, CO_2CH_3), 3.51 (s, 3 H, OCH_3), 3.50–3.53 (m, 1 H, BnOCH), 3.47 (dd, 1 H, *J* = 8.7 Hz, *J* = 4.1 Hz, $C(CH_3)_2OCHCHOMe$), 1.95 (d, 3 H, *J* = 1.3 Hz, C=C(CH_3)), 1.45 (s, 3 H, CCH_3), 1.37 (s, 3 H, CCH_3); IR (thin film) 2980, 2920, 2820, 1715, 1450, 1435, 1315, 1245, 1140, 1085, 700 cm^{-1}; EIMS *m/e* (relative intensity) 393 (0.1), 287 (0.1), 265 (5), 207 (7), 143 (100), 101 (24), 91 (40); CIHRMS calcd for $C_{22}H_{32}O_7$ 409.2226, found 409.2203.

Anal. Calcd for $C_{22}H_{32}O_7$: C, 64.68; H, 7.90. Found: C, 64.73; H, 7.94.

[*S*-[*R,*R**-(*E*,*E*)]]-4,6-Dimethoxy-2,8-dimethyl-5-(phenylmethoxy)-2,7-nonadienedioic Acid Dimethyl Ester (20).** A mixture of acetonide–ester **25** (2.02 g, 4.95 mmol) in THF (25 mL) and 3:1 HOAc–H_2O (25 mL) was heated to reflux for 5 h. Volatiles were removed under reduced pressure, toluene was added, and the mixture reconcentrated. After azeotroping with toluene two or three times, the crude product (diol) was obtained as a pale yellow oil.

The crude diol obtained above was dissolved in 4:1 THF–H_2O (50 mL), and $NaIO_4$ (1.27 g, 5.94 mmol) was added. The resulting mixture was stirred at room temperature for 5 h. The reaction mixture was filtered, and the filtrate was extrated with EtOAc (2×). The combined organic layer was washed with brine (1×), dried ($MgSO_4$), filtered, and concentrated to give the crude product (aldehyde) as a pale yellow oil.

The above crude aldehyde was dissolved in CH_2Cl_2 (40 mL) and cooled to 0 °C. A solution of triphenylphosphorane **19**[15] (2.1 g, 5.94 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The resulting mixture was allowed to warm to room temperature overnight (12 h). The reaction mixture was concentrated and purified by chromatography (25% EtOAc–hexane) to afford **20** (1.6 g, 79% overall, three steps) as a clear oil, identical by ^1H NMR analysis with the compound obtained from olefin–aldehyde **17**.

[*S*-[*R,*R**-(*E*,*E*)]]-5-Hydroxy-4,6-dimethoxy-2,8-dimethyl-2,7-nonadienedioic Acid Dimethyl Ester (26).** Iodotrimethylsilane (with traces of HI) (0.70 mL, 4.93 mmol) was added dropwise to a solution of diester **20** (1.54 g, 3.79 mmol) in CH_2Cl_2 (35 mL) at room temperature. After 25 min, MeOH (1 mL) was added to the orange-red solution. The mixture was diluted with EtOAc and washed with saturated $Na_2S_2O_3$ (1x), saturated $NaHCO_3$ (1x), and brine (1x), dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography (30 → 50% EtOAc–hexane) yielded **26** (1.06 g, 88%) as a clear oil: $[\alpha]^{25}_D$ = +46.2° (*c* = 1.03, $CHCl_3$); ^1H NMR δ 6.58–6.62 (overlapping dd, 1 H, *J* = 9.3 Hz, *J* = 1.5 Hz, C=CH, and dd, 1 H, *J* = 9.5 Hz, *J* = 1.5 Hz, C=CH), 4.17 (dd, 1 H, *J* = 9.5 Hz, *J* = 5.1 Hz, C=CHCHOMe), 4.10 (dd, 1 H, *J* = 9.3 Hz, *J* = 5.6 Hz, C=CHCHOMe), 3.77 (s, 3 H, CO_2CH_3), 3.75 (s, 3 H, CO_2CH_3), 3.64 (apparent q, 1 H, *J* = 5.3 Hz, HOCH), 3.32 (s, 3 H, OCH_3), 3.30 (s, 3 H, OCH_3), 2.57 (d, 1 H, *J* = 5.4 Hz, OH), 1.92 (d, 3 H, *J* = 1.5 Hz, C=C(CH_3)), 1.91 (d, 3 H, *J* = 1.5 Hz, C=CCH_3); IR (thin film) 3475, 2980, 2920, 2820, 1720, 1710, 1650, 1435, 1385, 1250, 1190, 1130, 1085, 960, 935, 750 cm^{-1}; EIMS *m/e* (relative intensity) 316 (0.7), 253 (1), 221 (1), 210 (2), 193 (1), 173 (1), 144 (100), 143 (17), 129 (17); EIHRMS calcd for $C_{15}H_{24}O_7$ 316.1522, found 316.1520.

Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 57.06, H, 7.90.

(2*E*)-2,3-Dideoxy-2-methyl-4,6-di-*O*-methyl-7,8-*O*-(1-methylethylidene)-5-*O*-(phenylmethyl)-D-*galacto*-oct-2-enitol (27). Lithium triethylborohydride (1 M solution in THF, 110 mL, 0.110 mol) was added dropwise to a cold (−78 °C) solution of ester **25** (19.9 g, 0.0485 mol) in THF (400 mL). The reaction was allowed to warm to −20 °C during 1.5 h. The mixture was poured over cold (0 °C) saturated NH_4Cl (200 mL), allowed to attain room temperature, and stirred for 15 min. The resulting mixture was extracted with EtOAc (3×), and the combined organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography (50% EtOAc–hex → 100% EtOAc) gave **27** (19.0 g, quantitative) as a clear oil: $[\alpha]^{25}_D$ = +65.2° (*c* = 1.32, $CHCl_3$); ^1H NMR δ 7.27–7.35 (m, 5 H, ArH), 5.47 (br dd, 1 H, *J* = 9.2 Hz, *J* = 1.4 Hz, C=CH), 4.61 (narrow AB quartet, 2 H, *J* = 11.3 Hz, PhCH_2O), 4.30–4.34 (m, 1 H, $C(CH_3)_2OCH$), 4.17 (d, 1 H, *J* = 9.2 Hz, C=CHCHOMe), 3.40 (dd, 1 H, *J* = 8.0 Hz, *J* = 6.3 Hz, one of $C(CH_3)_2OCH_2$), 3.94 (s, 2 H, C=CCH_2OH), 3.80 (t, 1 H, *J* = 8.1 Hz, one of $C(CH_3)_2OCH_2$), 3.50 (s, 3 H, OCH_3), 3.46–3.47 (m, 2 H, BnOCH and $C(CH_3)_2OCHCHOMe$), 3.26 (s, 3 H, OCH_3), 1.71 (d, 3 H, *J* = 1.2 Hz, C=CCH_3), 1.44 (s, 3 H, CCH_3), 1.36 (s, 3 H, CCH_3); IR (thin film) 3460, 2980, 2930, 2830, 1455, 1370, 1220, 1085, 890, 860, 740, 700 cm^{-1}; EIMS *m/e* (relative intensity) 265 (2), 233 (2), 207 (11), 175 (2), 141 (5), 115 (71), 101 (28), 98 (100).

Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.29; H, 8.48. Found: C, 66.55; H, 8.54.

(2*E*)-2,3-Dideoxy-1-chloro-2-methyl-4,6-di-*O*-methyl-7,8-*O*-(1-methylethylidene)-5-*O*-(phenylmethyl)-D-*galacto*-oct-2-ene (28). The procedure of Collington and Myers was employed.[16] A solution of LiCl (2.3 g, 53.6 mmol) in DMF (46 mL) was added to a solution of allylic alcohol **27** (18.5 g, 48.7 mmol) in *s*-collidine (7.7 mL, 58.4 mmol). The mixture obtained was cooled to 0 °C, and after a few minutes, a white precipitate formed. Trifluoromethanesulfonyl chloride (6.2 mL, 80.1 mmol) was added dropwise. At 1.5 and 1 h intervals, more reagents (same amounts as above) were added. After last addition, the yellow-orange mixture was kept at 0 °C for an additional hour. The reaction was poured over ice–H_2O (1.5 L), and the aqueous layer was extracted with Et_2O (3×). The combined organic layer was washed with saturated $CuSO_4$ (3×), saturated $NaHCO_3$ (2×), and brine (2×), dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography (10 → 40% EtOAc–hexane) afforded **28** (13.1 g, 67%) as a pale yellow oil and recovered **27** (1.6 g, 8.6%). **28**: $[a]^{25}_D$ = +35.6° (*c* = 2.34, $CHCl_3$); ^1H NMR δ 7.28–7.33 (m, 5 H, ArH), 5.61 (d, 1 H, *J* = 9.0 Hz, C=CH), 4.61 (apparent d [close AB quartet], 2 H, Δν = 1.9 Hz, PhCH_2O), 4.30–4.33 (m, 1 H, $C(CH_3)_2OCH$), 4.16 (dd, 1 H, *J* = 9.0 Hz, *J* = 2.2 Hz, C=CHCHOMe), 4.00 (dd, 1 H, *J* = 7.8 Hz, *J* = 6.7 Hz, one of $C(CH_3)_2OCH_2$), 3.98 (s, 2 H, C=CCH_2Cl), 3.80 (t, 1 H, *J* = 8.0 Hz, one of $C(CH_3)_2OCH_2$), 3.51 (s, 3 H, OCH_3), 3.48 (dd, 1 H, *J* = 8.6 Hz, *J* = 2.4 Hz, BnOCH), 3.46 (dd, 1 H, *J* = 8.6 Hz, *J* = 3.7 Hz, $C(CH_3)_2OCHCHOMe$), 3.28 (s, 3 H, OCH_3), 1.85 (s, 3 H, C=CCH_3), 1.45 (s, 3 H, CCH_3), 1.37 (s, 3 H, CCH_3); IR (thin film) 2980, 2930, 2820, 1455, 1370, 1265, 1215, 1085, 890, 745, 700 cm^{-1}; EIMS *m/e* (relative intensity) 383 (0.2), 319 (0.1), 305 (0.3), 265 (3), 231 (0.4), 229 (1), 207 (18), 171 (1), 169 (4), 135 (29), 133 (100), 98 (35).

Anal. Calcd for $C_{21}H_{31}ClO_5$: C, 63.23; H, 7.83. Found: C, 62.85; H, 7.66.

(2*E*)-2,3-Dideoxy-1-cyano-2-methyl-4,6-di-*O*-methyl-7,8-*O*-(1-methylethylidene)-5-*O*-(phenylmethyl)-D-*galacto*-oct-2-ene (29). NaCN (2.0 g, 40.8 mmol) was added to a solution of allylic chloride **28** (14.0 g, 35.1 mmol) in DMF (320 mL), and the resulting mixture was stirred at room temperature for 3 h. (The reaction was monitored closely by TLC [every 30 min, 50% EtOAc–hexane] in order to avoid excess formation of undesired α,β-unsaturated nitrile.) The mixture was poured over H_2O (3 L) and extracted with Et_2O (4×). The combined organic layer was washed with brine (1×), dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography (20 → 80% Et_2O–hexane) afforded recovered **28** (1.1 g, 7.8%), α,β-unsaturated nitrile (3.1 g, 22%), and β,γ-unsaturated nitrile **29** (9.41 g, 69%) as a clear oil. **29**: $[\alpha]^{25}_D$ = +62.5° (*c* = 1.06, $CHCl_3$); ^1H NMR δ 7.27–7.35 (m, 5 H, ArH), 5.56 (d, 1 H, *J* = 9.0 Hz, C=CH), 4.60 (AB quartet, 2 H, *J* = 11.2 Hz, PhCH_2O), 4.33 (br ddd, 1 H, *J*

(16) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.

= 8.6 Hz, J = 6.4 Hz, J = 3.3 Hz, $C(CH_3)_2OCH$), 4.14 (br d, 1 H, J = 9.0 Hz, C=CHCHOMe), 4.01 (dd, 1 H, J = 7.9 Hz, J = 6.4 Hz, one of $C(CH_3)_2OCH_2$), 3.81 (t, 1 H, J = 8.1 Hz, one of $C(CH_3)_2OCH_2$), 3.5 (s, 3 H, OCH_3), 3.45–3.48 (m, 2 H, BnOCH and $C(CH_3)_2OCHCHOMe$), 3.26 (s, 3 H, OCH_3), 2.98 (s, 2 H, CCH_2CN), 1.81 (s, 3 H, $C=CCH_3$), 1.45 (s, 3 H, CCH_3), 1.37 (s, 3 H, CCH_3); IR (thin film) 2985, 2920, 2820, 2250, 1455, 1370, 1215, 1090, 920, 890, 860, 740, 700 cm^{-1}; EIMS m/e (relative intensity) 307 (0.1), 299 (0.1), 265 (7), 233 (1), 207 (12), 185 (7), 160 (3), 145 (3), 124 (100), 101 (17), 91 (18); CIHRMS calcd for $C_{22}H_{31}NO_5$ 390.2280, found 390.2284.

(3*E*)-2,3,4-Trideoxy-3-methyl-5,7-di-*O*-methyl-8,9-*O*-(1-methylethylidene)-6-*O*-(phenylmethyl)-D-*galacto*-non-3-enitol (30). Diisobutylaluminum hydride (DIBAL-H, 1 M solution in hexanes, 27.8 mL, 27.8 mmol) was added dropwise to a solution of nitrile **29** (9.4 g, 24.2 mmol) in CH_2Cl_2 (300 mL) kept at −78 °C. After 25 min, more DIBAL-H (4.0 mL, 4.0 mmol) was added. The mixture was stirred for an additional 30 min, and absolute EtOH (3.5 mL) was added. The cold mixture was poured over EtOAc/saturated NH_4Cl and stirred for 0.5 h. Saturated potassium sodium tartrate (or saturated Na_2SO_4) was added, and the resulting mixture was stirred for 3 h. The organic layer was separated, and the aquoeus layer was reextracted with EtOAc (5×). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated to yield the crude β,γ-unsaturated aldehyde (9.4 g) as a yellow oil.

The above crude aldehyde (9.4 g) was dissolved in absolute EtOH (300 mL) and cooled to 0 °C. $NaBH_4$ (1.1 g, 29.1 mmol) was added in portions, and the resulting mixture was kept at 0 °C for 2 h. EtOH was removed under reduced pressure, and the concentrated was immersed in an ice bath. Saturated NH_4Cl (250 mL) was added slowly, in portions. The mixture was extracted with CH_2Cl_2 (3×), and the combined organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography (50 → 75% Et_2O–hexane) afforded **30** (6.0 g, 63% overall, two steps) as a pale yellow oil: $[\alpha]^{25}_D$ = +27.2° (c = 2.34, $CHCl_3$); ^1H NMR δ 7.26–7.33 (m, 5 H, ArH), 5.35 (d, 1 H, J = 9.3 Hz, C=CH), 4.63 (AB quartet, 2 H, J = 11.2 Hz, $PhCH_2O$), 4.31 (ddd, 1 H, J = 8.1 Hz, J = 6.3 Hz, J = 4.2 Hz, $C(CH_3)_2OCH$), 4.16 (dd, 1 H, J = 9.3 Hz, J = 2.7 Hz, C=CHCHOMe), 3.98 (dd, 1 H, J = 8.0 Hz, J = 6.3 Hz, one of $C(CH_3)_2OCH_2$), 3.76 (t, 1 H, J = 8.1 Hz, one of $C(CH_3)_2OCH_2$), 3.69–3.71 (m, 2 H, $C=CCH_2$), 3.50 (s, 3 H, OCH_3), 3.40–3.53 (m, 2 H, BnOCH and $C(CH_3)_2OCHCHOMe$), 3.27 (s, 3 H, OCH_3), 2.25–2.34 (m, 2 H, CH_2OH), 1.75 (d, 3 H, J = 1.2 Hz, $C=CCH_3$), 1.52 (br s, 1 H, OH), 1.43 (s, 3 H, CCH_3), 1.35 (s, 3 H, CCH_3); IR (thin film) 3460, 2980, 2930, 2820, 1450, 1380, 1370, 1215, 1085, 890, 740, 700 cm^{-1}; EIMS m/e (relative intensity) 286 (0.4), 271 (5), 233 (2), 207 (12), 196 (4), 177 (1), 129 (100), 91 (24); FABHRMS calcd for $C_{22}H_{34}O_6$ 395.2433, found 395.2452.

(3*E*)-2,3,4-Trideoxy-3-methyl-5,7-di-*O*-methyl-8,9-*O*-(1-methylethylidene)-D-*galacto*-non-3-enitol (31). Na metal (2.0 g, 0.087 g-atom), cut in small pieces, was added to liquid NH_3 (ca. 200 mL) kept at −78 °C. To the resulting deep blue mixture was added a solution of alcohol **30** (5.9 g, 15.0 mmol) in THF (35 mL). The reaction mixture was stirred for 5 min, and solid NH_4Cl was added until the blue color disappeared. The cold bath was removed, and NH_3 was allowed to evaporate slowly. The residue was extracted with EtOAc (3×), and the combined organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography (80% EtOAc–hexane → 100% EtOAc) gave **31** (4.1 g, 90%) as a pale yellow solid. A small sample was purified further by recrystallization (hexane) for characterization: mp (hexane) 52–53 °C; $[\alpha]^{25}_D$ = +51.0° (c = 1.12, $CHCl_3$); ^1H NMR δ 5.29 (br d, 1 H, J = 9.3 Hz, C=CH), 4.27 (apparent td, 1 H, J = 7.9 Hz, J = 6.4 Hz, $C(CH_3)_2OCH$), 4.12 (dd, 1 H, J = 9.3 Hz, J = 3.6 Hz, C=CHCHOMe), 4.06 (dd, 1 H, J = 8.3 Hz, J = 6.4 Hz, one of $C(CH_3)_2OCH_2$), 3.77 (t, 1 H, J = 8.2 Hz, one of $C(CH_3)_2OCH_2$), 3.71–3.74 (m, 2 H, CH_2OH), 3.53 (s, 3 H, OCH_3), 3.46 (dd, 1 H, J = 7.4 Hz, J = 3.6 Hz, HOCH), 3.29–3.31 (m, 1 H, $C(CH_3)_2OCHCHOMe$), 3.29 (s, 3 H, OCH_3), 2.31–2.38 (m, 2 H, $C=CCH_2$), 1.77 (d, 3 H, J = 1.4 Hz, $C=CCH_3$), 1.42 (s, 3 H, CCH_3), 1.37 (s, 3 H, CCH_3); IR (KBr) 3460, 3400, 2980, 2920, 2820, 1440, 1415, 1380, 1370, 1255, 1160, 1110, 1060, 950, 855 cm^{-1}; EIMS m/e (relative intensity) 289 (0.2), 271 (0.3), 257 (2), 197 (5), 175 (17), 155 (2), 141 (6), 129 (100), 117 (35), 97 (28); CIHRMS calcd for $C_{15}H_{28}O_6$ 305.1964, found 305.1942.

Anal. Calcd for $C_{15}H_{28}O_6$: C, 59.19; H, 9.27. Found: C, 59.31; H, 9.19.

[4*S*-(2*E*,4*R,5*S**,6*R**,7*E*)]-5,10-Dihydroxy-4,6-dimethoxy-2,8-dimethyl-2,7-decadienoic Acid Methyl Ester (32).** A mixture of diol **31** (4.0 g, 13.2 mmol) in THF (130 mL) and 3:1 HOAc–H_2O (130 mL) was heated to reflux for 2 h. Volatiles were removed under reduced pressure, toluene was added, and the mixture reconcentrated. After azeotroping with toluene twice, the crude tetraol (3.49 g) was obtained as a pale yellow solid.

The crude tetraol (3.49 g) obtained above was dissolved in 4:1 THF–H_2O (240 mL), and $NaIO_4$ (3.1 g, 14.5 mmol) was added. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure by azeotroping with toluene several times. The crude aldehyde–diol (3.6 g) was obtained as a pale yellow gum. This aldehyde is very unstable and should be used immediately in the next step.

The above crude aldehyde (3.6 g) was dissolved in CH_2Cl_2 (115 mL) and cooled to 0 °C. A solution of triphenylphosphorane **19** (6.4 g, 18.4 mmol) in CH_2Cl_2 (15 mL) was added dropwise. The resulting mixture was allowed to warm to room temperature overnight (12 h). The reaction mixture was concentrated and purified by chromatorgaphy (2% MeOH–EtOAc) to afford **32** which coeluted with triphenylphosphine oxide (total mixture, 7.5 g): ^1H NMR δ 6.68 (dd, 1 H, J = 9.3 Hz, J = 1.4 Hz, $MeO_2C(Me)C=CH$), 5.12 (br d, 1 H, J = 9.7 Hz, $CH_2(Me)C=CH$), 4.12 (dd, 1 H, J = 9.4 Hz, J = 4.6 Hz, $MeO_2C(Me)C=CHCH$), 4.01 (dd, 1 H, J = 9.6 Hz, J = 6.7 Hz, $CH_2(Me)C=CHCH$), 3.77 (s, 3 H, CO_2CH_3), 3.73–3.76 (m, 2 H, CH_2OH), 3.64 (dd, 1 H, J = 6.6 Hz, J = 4.7 Hz, CHOH), 3.29 (s, 3 H, OCH_3), 3.28 (s, 3 H, OCH_3), 2.33–2.36 (m, 2 H, $C=CCH_2$), 1.90 (d, 3 H, J = 1.4 Hz, $C=CCH_3$), 1.75 (d, 3 H, J = 1.3 Hz, $C=CCH_3$); IR ($CHCl_3$) 3450, 2990, 2940, 1710, 1440, 1380, 1255, 1125, 1090, 915, 700 cm^{-1}; EIMS m/e (relative intensity) 270 (1), 252 (1), 238 (1), 220 (0.4), 173 (6), 154 (3), 129 (100), 97 (45); CIHRMS calcd for $C_{15}H_{26}O_6$ 303.1807, found 303.1805.

[4*S*-(2*E*,4*R,5*S**,6*R**,7*E*)]-10-(Benzoyloxy)-5-hydroxy-4,6-dimethoxy-2,8-dimethyl-2,7-decadienoic Acid Methyl Ester (33).** Benzoyl chloride (1.7 mL, 14.5 mmol) was added to a solution of diol **32** (containing triphenylphosphine oxide, 7.5 g) and pyridine (2.3 mL, 29.0 mmol) in THF (120 mL) at room temperature. After 4 h, additional pyridine (0.46 mL, 5.7 mmol) and benzoyl chloride (0.336 mL, 2.9 mmol) were added. The reaction was left a total of 7 h. The mixture was diluted with Et_2O, and the resulting organic layer was washed with 1 N HCl (1×) and brine (1×), dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography (30% EtOAc–hexane) afforded **33** (2.84 g, 55% overall, four steps) as a pale yellow oil: $[\alpha]^{25}_D$ +27.8° (c = 2.86, $CHCl_3$); ^1H NMR δ 8.00 (d, 2 H, J = 7.3 Hz, o-ArH), 7.53 (br t, 1 H, J = 7.7 Hz, p-ArH), 7.41 (t, 2 H, J = 7.7 Hz, m-ArH), 6.66 (d, 1 H, J = 9.5 Hz, $MeO_2C(Me)C=CH$), 5.19 (d, 1 H, J = 9.7 Hz, $CH_2(Me)C=CH$), 4.39–4.47 (m, 2 H, CH_2OBz), 4.04 (dd, 1 H, J = 9.5 Hz, J = 4.4 Hz, $MeO_2C(Me)C=CHCH$), 3.93 (dd, 1 H, J = 9.6 Hz, J = 6.2 Hz, $CH_2(Me)C=CHCH$), 3.73 (s, 3 H, CO_2CH_3), 3.62 (br dd, 1 H, J = 6.1 Hz, J = 4.6 Hz, CHOH), 3.21 (s, 3 H, OCH_3), 3.19 (s, 3 H, OCH_3), 2.48–2.57 (m, 2 H, $C=CCH_2$), 1.84 (s, 3 H, $C=CCH_3$), 1.76 (s, 3 H, $C=CCH_3$); IR (thin film) 3490, 2935, 2900, 2820, 1720, 1710, 1600, 1455, 1390, 1320, 1285, 1100, 970, 760, 720 cm^{-1}; EIMS m/e (relative intensity) 374 (0.2), 356 (0.3), 342 (0.3), 252 (0.4), 233 (1), 193 (2), 173 (3), 144 (58), 111 (100), 97 (18); CIHRMS calcd for $C_{22}H_{30}O_7$ 407.2069, found 407.2070.

2,3,7,8-Tetradeoxy-2,8-dimethyl-4,6-di-*O*-methyl-L-*glycero*-L-*manno*-nonaric Acid Dimethyl Ester (6). Glassware was flame-dried and allowed to cool to room temperature under Ar. A solution of diene **26** (1.05 g, 3.32 mmol) in degassed CH_2Cl_2 (10 mL) was added to a solution of freshly prepared Rh catalyst **10**[17] (0.375 g, 0.53 mmol) in degassed CH_2Cl_2 (70 mL) kept under Ar atmosphere. The contents were frozen by immersing in a liquid N_2 bath. The system was evacuated under high pressure while thawing, refilled with Ar, and allowed to warm to room temperature. The reaction mixture was transferred to a 350-mL

(17) Morrissey, M. M. Ph.D. Dissertation, Harvard University, 1987.

glass-lined high-pressure Parr hydrogenation apparatus via a Teflon tubing under a positive pressure of N_2. The hydrogenation reaction was run at room temperature at 1000 psi for 4 h (longer reaction time resulted in partial lactonization of tetrahydro product). The dark reddish-brown mixture was concentrated, adsorbed over silica gel and purified by chromatography (30 → 50% EtOAc–hexane) to give **6** (0.961 g, 90%) as a clear oil: ^{1}H NMR (major isomer) δ 3.70 (s, 3 H, CO_2CH_3), 3.68 (s, 3 H, CO_2CH_3), 3.52 (br t, 1 H, J = 5.0 Hz, HOC*H*), 3.43 (s, 3 H, OCH_3), 3.33 (s, 3 H, OCH_3), 3.29–3.32 (m, 1 H, MeOC*H*), 3.16 (ddd, 1 H, J = 8.1 Hz, J = 6.0 Hz, J = 3.1 Hz, MeOC*H*), 2.66–2.76 (m, 2 H, both $MeO_2CC\mathit{H}Me$), 2.32 (br s, 1 H, OH), 1.92–2.00 (m, 2 H, MeO_2CCHCH_2), 1.69 (ddd, 1 H, J = 14.5 Hz, J = 8.0 Hz, J = 3.7 Hz, one of MeO_2CCHCH_2), 1.61 (ddd, 1 H, J = 14.2 Hz, J = 7.5 Hz, J = 4.7 Hz, one of MeO_2CCHCH_2), 1.20 (d, 6 h, J = 4.6 Hz, both MeO_2CCHCH_3); IR (thin film) 3460, 2920, 2820, 1730, 1460, 1430, 1370, 1255, 1195, 1170, 1090 cm^{-1}; EIMS m/e (relative intensity) 257 (3), 241 (0.1), 225 (0.4), 201 (1), 175 (4), 145 (100), 143 (8); CIHRMS calcd for $C_{15}H_{28}O_7$ 321.1913, found 321.1906.

Anal. Calcd for $C_{15}H_{28}O_7$: C, 56.23; H, 8.81. Found: C, 56.21; H, 9.06.

2,3,7,8-Tetradeoxy-2,8-dimethyl-4,6-di-*O*-methyl-L-*glycero*-L-*galacto*-nonaric Acid 1-(Methyl ester) 9,5-Lactone (7). Pyridinium *p*-toluenesulfonate (132 mg, 0.526 mmol) was added to a solution of diester–alcohol **6** (84.2 mg, 0.263 mmol) in CH_2Cl_2 (2 mL) at room temperature. After 60–70 h, the reaction mixture was washed with H_2O (1×) and brine (1×), dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography (30% EtOAc–toluene) afforded **7** (48.8 mg, 64%) as a 4–6:1 mixture determined by ^{1}H NMR spectroscopy: ^{1}H NMR (major isomer) δ 4.02 (dd, 1 H, J = 8.1 Hz, J = 2.0 Hz, axial MeOCHC*H*O), 3.69 (s, 3 H, CO_2CH_3), 3.63 (ddd, 1 H, J = 12.2 Hz, J = 8.0 Hz, J = 4.5 Hz, axial MeOC*H*), 3.46 (ddd, 1 H, J = 7.7 Hz, J = 5.2 Hz, J = 2.2 Hz, MeOC*H*), 3.43 (s, 3 H, OCH_3), 3.40 (s, 3 H, OCH_3), 2.65–2.70 (m, 1 H, $MeO_2CC\mathit{H}$), 2.46–2.51 (m, 1 H, axial MeC*H*), 2.31–2.35 (m, 1 H, equatorial CH_2), 1.86–1.90 (m, 2 H, MeO_2CCHCH_2), 1.51 (q, 1 H, J = 12.0 Hz, axial CH_2), 1.30 (d, 3 H, J = 7.0 Hz, equatorial $CHCH_3$), 1.20 (d, 3 H, J = 7.1 Hz, MeO_2CCHCH_3); IR (thin film) 2930, 2820, 1735, 1455, 1370, 1350, 1195, 1170, 1080 cm^{-1}; EIMS m/e (relative intensity) 257 (1), 241 (0.5), 201 (1), 165 (1), 145 (100), 85 (35); CIHRMS calcd for $C_{14}H_{24}O_6$ 289.1651, found 289.1641.

Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.42; H, 8.58.

[2*R*-(2*R,4*S**,5*R**,6*S**,8*S**)]-10-(Benzoyloxy)-5-hydroxy-4,6-dimethoxy-2,8-dimethyldecanoic Acid Methyl Ester (34).** The same procedure described for preparation of compound **6** was followed with diene **33** (3.0 g, 7.39 mmol) and Rh catalyst **10** (0.94 g, 1.33 mmol) in CH_2Cl_2 (125 mL). The hydrogenation reaction was run at room temperature at 1000 psi for 5 h. Purification by chromatography (30 → 50% EtOAc–hexane) afforded **34** (2.71 g, 89%) as a clear oil: ^{1}H NMR (major isomer) δ 8.04 (dd, 2 H, J = 8.3 Hz, J = 1.4 Hz, *o*-ArH), 7.55 (tt, 1 H, J = 7.4 Hz, J = 1.3 Hz, *p*-ArH), 7.44 (apparent t, 2 H, J = 8.0 Hz, *m*-ArH), 4.35–4.46 (m, 2 H, $BzOCH_2$), 3.66 (s, 3 H, CO_2CH_3), 3.46 (dt, 1 H, J = 7.5 Hz, J = 3.1 Hz, HOC*H*), 3.42 (s, 3 H, OCH_3), 3.39–3.42 (m, 1 H, *syn*-HOCHC*H*OMe), 3.32 (s, 3 H, OCH_3), 3.17 (dt, 1 H, J = 7.5 Hz, J = 3.2 Hz, *anti*-HOCHC*H*OMe), 2.69–2.76 (m, 1 H, $MeO_2CC\mathit{H}$), 2.24 (d, 1 H, J = 7.7 Hz, OH), 2.05 (ddd, 2 H, J = 14.1 Hz, J = 10.4 Hz, J = 3.2 Hz, one of MeO_2CCHCH_2), 1.90–1.97 (m, 1 H, one of $BzOCH_2CH_2$), 1.77–1.80 (m, 1 H, $BzOCH_2CH_2C\mathit{H}$), 1.51–1.68 (m, 3 H, one of MeO_2CCHCH_2, one of $BzOCH_2CH_2CHCH_2$, and one of $BzOCH_2CH_2$), 1.48 (br ddd, 1 H, J = 14.0 Hz, J = 7.6 Hz, J = 6.4 Hz, one of $BzOCH_2CH_2CHCH_2$), 1.18 (d, 3 H, J = 7.1 Hz, MeO_2CCHCH_3), 1.02 (d, 3 H, J = 6.6 Hz, $BzOCH_2CH_2CHCH_3$); IR (thin film) 3480, 2925, 2820, 1735, 1720, 1455, 1275, 1105, 715 cm^{-1}; EIMS m/e (relative intensity) 379 (0.1), 291 (0.3), 265 (2), 235 (3), 201 (1), 175 (6), 145 (66), 99 (100), 85 (22); CIHRMS calcd for $C_{22}H_{34}O_7$ 411.2382, found 411.2391.

Anal. Calcd for $C_{22}H_{34}O_7$: C, 64.37; H, 8.35. Found: C, 64.46; H, 8.28.

[3*R*-[3α,5α,6β(1*S,3*S**)]]-6-[5-(Benzoyloxy)-1-methoxy-3-methylpentyl]tetrahydro-5-methoxy-3-methyl-2*H*-pyran-2-one (35).** *p*-Toluenesulfonic acid (0.22 g, 1.29 mmol) and 4-Å molecular sieves were added to a solution of ester **34** (2.65 g, 6.48 mmol) in CH_2Cl_2 (60 mL). After 1.5 h, more 4-Å molecular sieves were added. The reaction was stirred a total of 3 h at room temperature. The mixture was filtered through a Celite pad, and the filtrate was washed with saturated $NaHCO_3$ (2×) and brine (2×), dried ($MgSO_4$), filtered, and concentrated to give crude **35** (2.27 g, 93%) as a pale yellow oil. A small amount was purified by chromatography (5 → 10% EtOAc–CH_2Cl_2) for characterization: ^{1}H NMR (major isomer) δ 8.05 (dd, 2 H, J = 8.4 Hz, J = 1.4 Hz, *o*-ArH), 7.56 (tt, 1 H, J = 7.5 Hz, J = 1.3 Hz, *p*-ArH), 7.44 (apparent t, J = 7.7 Hz, *m*-ArH), 4.39–4.42 (m, 2 H, $BzOCH_2$), 4.08 (dd, 1 H, J = 8.0 Hz, J = 1.8 Hz, axial MeOCHC*H*O), 3.69 (ddd, 1 H, J = 12.5 Hz, J = 8.0 Hz, J = 4.5 Hz, axial MeOC*H*), 3.52 (ddd, 1 H, J = 8.0 Hz, J = 6.5 Hz, J = 1.8 Hz, MeOC*H*), 3.42 (s, 6 H, both OCH_3), 2.46–2.54 (m, 1 H, axial MeC*H*), 2.33 (br ddd, 1 H, J = 12.6 Hz, J = 5.2 Hz, J = 4.6 Hz, equatorial CH_2), 1.90–1.97 (m, 1 H, one of $BzOCH_2CH_2$), 1.75–1.81 (m, 1 H, $BzOCH_2CH_2C\mathit{H}$), 1.59–1.74 (m, 3 H, $BzOCH_2CH_2CHCH_2$ and one of $BzOCH_2CH_2$), 1.52 (apparent q, 1 H, J = 12.6 Hz, axial CH_2), 1.30 (d, 3 H, J = 7.1 Hz, equatorial $CHCH_3$), 1.03 (d, 3 H, J = 6.6 Hz, $BzOCH_2CH_2CHCH_3$); IR (thin film) 2920, 2810, 1730, 1715, 1590, 1445, 1370, 1310, 1265, 1170, 1105, 1020, 710 cm^{-1}; EIMS m/e (relative intensity) 291 (0.1), 235 (3), 187 (0.6), 145 (1), 112 (10), 105 (33), 99 (100); CIHRMS calcd for $C_{21}H_{30}O_6$ 379.2120, found 379.2121.

Anal. Calcd for $C_{21}H_{30}O_6$: C, 66.65; H, 7.99. Found: C, 66.79; H, 7.92.

[2*R*-[2α(γ*S,ε*S**),3β,5β,6β]]-6-Hydroxy-ε,3-dimethoxy-γ,5-dimethyltetrahydro-2*H*-pyran-2-pentanol Benzoate and [2*R*-[2α(γ*S**,ε*S**),3β,5β,6α]]-6-Hydroxy-ε,3-dimethoxy-γ,5-dimethyltetrahydro-2*H*-pyran-2-pentanol Benzoate (36).** The above crude lactone **35** (2.22 g) was dissolved in THF (50 mL) and cooled to −78 °C. Lithium tri-*sec*-butyl borohydride (1 M solution in THF, 6.5 mL, 6.5 mmol) was added dropwise. After 45 min, saturated NH_4Cl (50 mL) was added. The cold bath was removed, and after stirring for 15 min, the mixture was extracted with EtOAc (5×). The combined organic layer washed with brine (1×), dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography (20 → 50% EtOAc–hexane) afforded **36** (2.1 g, 87% overall, two steps) as a clear oil: ^{1}H NMR (major isomer, both anomers) δ 8.01–8.04 (m, 4 H), 7.53–7.57 (m, 2 H), 7.41–7.45 (m, 4 H), 5.02 (br d, 1 H, J = 2.8 Hz), 4.44–4.53 (m, 2 H), 4.29–4.37 (m, 2 H), 4.13 (d, 1 H, J = 8.3 Hz), 3.64 (br d, 1 H, J = 9.0 Hz), 3.54–3.59 (m, 1 H), 3.35–3.44 (m, 3 H), 3.39 (s, 6 H), 3.36 (s, 3 H), 3.35 (s, 3 H), 3.14 (dd, 1 H, J = 9.2 Hz, J = 1.8 Hz), 2.20 (td, 1 H, J = 12.7 Hz, J = 4.4 Hz), 1.97 (td, 1 H, J = 12.0 Hz, J = 4.2 Hz), 1.66–1.86 (m, 7 H), 1.57–1.64 (m, 2 H), 1.41–1.59 (m, 4 H), 0.8–1.2 (m, 1 H), 1.00–1.02 (overlapping d's, 6 H), 0.92–0.95 (overlapping d's, 6 H); IR (thin film) 3430, 2930, 2820, 1715, 1600, 1455, 1315, 1275, 1105, 1030, 715 cm^{-1}; EIMS m/e (relative intensity) 380 (0.1), 348 (0.2), 322 (0.3), 265 (10), 236 (5), 189 (1), 171 (1), 157 (2), 143 (23), 113 (57), 105 (47), 99 (100), 85 (36); CIHRMS calcd for $C_{21}H_{32}O_6$ 381.2277, found 381.2262.

[3*S*-(3*R,5*R**,6*R**,7*R**,9*R**)]-9-(1,3-Dithian-2-yl)-5,7-dimethoxy-3-methyl-1,6-decanediol 1-Benzoate (37).** 1,3-Propanedithiol (0.80 mL, 8.01 mmol) and BF_3·Et_2O (0.79 mL, 6.41 mmol) were added to a cold (−78 °C) solution of lactols **36** (2.03 g, 5.34 mmol). The resulting mixture was allowed to warm to to 0 °C during 1 h and kept at this temperature. After 3 h, more BF_3·Et_2O (0.130 mL, 1.1 mmol) was added. The mixture was stirred for an additional hour and then poured over ice–H_2O. The organic layer was separated, and the aqueous layer was reextracted with CH_2Cl_2 (2×). The combined organic layer was washed with brine (1×), dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography (30% EtOAc–hexane) afforded **37** (2.15 g, 85%) as a clear oil: ^{1}H NMR (major isomer) δ 8.04 (apparent d, 2 H, J = 7.5 Hz, *o*-ArH), 7.55 (t, 1 H, J = 7.4 Hz, *p*-ArH), 7.33 (t, 2 H, J = 7.5 Hz, *m*-ArH), 4.35–4.45 (m, 2 H, $BzOCH_2$), 4.22 (d, 1 H, J = 3.5 Hz, SCHS), 3.48–3.50 (m, 1 H, HOC*H*), 3.45 (s, 3 H, OCH_3), 3.40–3.45 (m, 1 H, *syn*-HOCHC*H*OMe), 3.38 (s, 3 H, OCH_3), 3.26–3.30 (m, 1 H, *anti*-HOCHC*H*OMe), 2.82–2.94 (m, 4 H, $SCH_2CH_2CH_2S$), 2.15–2.20 (m, 1 H, SCHC*H*Me), 2.07–2.12 (m, 1 H, one of SCH_2CH_2), 1.92–1.99 (m, 2 H, one of $SCHCHCH_2$ and one of $BzOCH_2CH_2$), 1.78–1.86 (m, 2 H, one of SCH_2CH_2 and $BzOCH_2CH_2C\mathit{H}$), 1.47–1.65 (m, 4 H, one of $SCHCHCH_2$, $BzOCH_2CH_2CHCH_2$, and one of $BzOCH_2CH_2$), 1.45 (d, 3 H, J = 6.9 Hz, $SCHCHCH_3$), 1.03 (d, 3 H, J = 6.6 Hz,

$BzOCH_2CH_2CHCH_3$); IR (thin film) 3470, 2920, 2820, 1710, 1600, 1450, 1275, 1110, 720 cm^{-1}; EIMS *m/e* (relative intensity) 470 (1), 438 (1), 420 (0.3), 363 (1), 299 (1), 261 (1), 205 (48), 173 (4), 146 (100), 119 (51), 99 (50); CIHRMS calcd for $C_{24}H_{38}O_5S_5$ 471.2239, found 471.2216.

Anal. Calcd for $C_{24}H_{38}O_5S_2$: C, 61.24; H, 8.14; S, 13.62. Found: C, 61.22; H, 8.20; S, 13.44.

[γS-(γR*,εR*,ζS*,ηR*,μS*)]-ζ-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-ε,η-dimethoxy-γ,μ-dimethyl-1,3-dithiane-2-nonanol Benzoate (38). *tert*-Butyldimethylsilyl trifluoromethanesulfonate (2.05 mL, 8.94 mmol) was added to a solution of dithiane–alcohol **37** (2.10 g, 4.47 mmol) and 2,6-lutidine (2.08 mL, 17.9 mmol) in CH_2Cl_2 (40 mL). The reaction mixture was stirred at room temperature for 1.5 h. The mixture was washed wit 1 N HCl (1×), saturated $NaHCO_3$ (1×), and brine (2×), dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography yielded 38 (2.53 g, 97%) as a clear oil: ^1H NMR (major isomer) δ 8.04 (dd, 2 H, *J* = 8.3 Hz, *J* = 1.3 Hz, *o*-ArH), 7.56 (br tt, 1 H, *J* = 7.4 Hz, *J* = 1.3 Hz, *p*-ArH), 7.44 (apparent t, 2 H, *J* = 8.0 Hz, *m*-ArH), 4.35–4.45 (m, 2 H, $BzOCH_2$), 4.18 (d, 1 H, *J* = 3.4 Hz, SCHS), 3.90 (dd, 1 H, *J* = 6.2 Hz, *J* = 1.4 Hz, TBSOC*H*), 3.44 (s, 3 H, OCH_3), 3.33 (s, 3 H, OCH_3), 3.28 (br d, 1 H, *J* = 10.2 Hz, *anti*-TBSOCHC*H*OMe), 3.17 (ddd, 1 H, *J* = 9.3 Hz, *J* = 6.1 Hz, *J* = 2.7 Hz, *syn*-TBSOCHC*H*OMe), 2.81–2.95 (m, 4 H, SCH_2CHCH_2S), 2.11–2.18 (m, 1 H, SCHC*H*Me), 2.00–2.11 (m, 2 H, one of SCH_2CH_2 and one of $BzOCH_2CH_2$), 1.88–1.95 (m, 1 H, $BzOCH_2CH_2CH$), 1.79–1.88 (m, 1 H, one of SCH_2CH_2), 1.75 (ddd, 1 H, *J* = 15.1 Hz, *J* = 8.8 Hz, *J* = 2.2 Hz, one of $SCHCHCH_2$), 1.46–1.59 (m, 3 H, one of $SCHCHCH_2$, one of $BzOCH_2CH_2CHCH_2$, and one of $BzOCH_2CH_2$), 1.40 (ddd, 1 H, *J* = 14.3 Hz, *J* = 9.7 Hz, *J* = 4.7 Hz, one of $BzOCH_2CH_2CHCH_2$), 1.12 (d, 3 H, *J* = 7.0 Hz, $SCHCHCH_3$), 1.04 (d, 3 H, *J* = 6.7 Hz, $BzOCH_2CH_2CHCH_3$), 0.91 (s, 9 H, $SiC(CH_3)_3$), 0.093 (s, 3 H, $SiCH_3$), 0.088 (s, 3 H, $SiCH_3$); IR (thin film) 2940, 2930, 2890, 2850, 1720, 1605, 1465, 1455, 1380, 1280, 1110, 960, 840, 780, 720 cm^{-1}; EIMS *m/e* (relative intensity) 527 (23), 495 (1), 421 (2), 389 (1), 349 (2), 261 (5), 205 (100), 146 (23), 99 (66); CIHRMS calcd for $C_{30}H_{52}O_5SiS_2$ 585.3104, found 585.3108.

Anal. Calcd for $C_{30}H_{52}O_5SiS_2$: C, 61.60; H, 8.96; S, 10.96. Found: C, 61.85; H, 9.10; S, 11.17.

[γS-(γR*,εR*,ζS*,ηR*,μS*)]-ζ-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-ε,η-dimethoxy-γ,μ-dimethyl-1,3-dithiane-2-nonanol (39). Anhydrous K_2CO_3 (1.76 g, 12.8 mmol) was added to a solution of benzoate **38** (1.49 g, 2.55 mmol) in MeOH (25 mL), and the resulting mixture was stirred at room temperature for 4 h. The reaction mixxture was filtered through a Celite pad, and the filtrate was acidified to pH 1–2 with 1 N HCl. After concentrating the filtrate, CH_2Cl_2 and brine were added to the residue. The aqueous layer was separated and reextracted with CH_2Cl_2 (2×). The combined organic layer was washed with brine (1×), dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography afforded pure **39** (932 mg, 76%) as a clear oil. It is at this stage that the minor isomers from the high-pressure hydrogenation reaction can be separated: $[\alpha]^{25}_D$ = −33.9° (*c* = 1.36, $CHCl_3$); ^1H NMR δ 4.19 (d, 1 H, *J* = 3.4 Hz, SCHS), 3.89 (dd, 1 H, *J* = 6.2 Hz, *J* = 1.5 Hz, TBSOC*H*), 3.65–3.70 (m, 1 H, one of $HOCH_2$), 3.72–3.77 (m, 1 H, one of $HOCH_2$), 3.44 (s, 3 H, OCH_3), 3.33 (s, 3 H, OCH_3), 3.27 (br td, 1 H, *J* = 10.0 Hz, *J* = 1.9 Hz, *anti*-TBSOCHC*H*OMe), 3.16 (ddd, 1 H, *J* = 9.3 Hz, *J* = 6.2 Hz, *J* = 2.9 Hz, *syn*-TBSOCHC*H*OMe), 2.83–2.97 (m, 4 H, $SCH_2CH_2CH_2S$), 2.08–2.17 (m, 2 H, one of SCH_2CH_2 and SCHC*H*Me), 1.78–1.88 (m, 2 H, one of SCH_2CH_2 and $HOCH_2CH_2CH$Me), 1.71–1.76 (m, 2 H, one of $SCHCHCH_2$ and one of $HOCH_2CH_2$), 1.59 (br s, 1 H, OH), 1.50–1.56 (m, 2 H, one of $SCHCHCH_2$ and one of $HOCH_2CH_2CHCH_2$), 1.34–1.42 (m, 2 H, one of $HOCH_2CH_2CHCH_2$ and one of $HOCH_2CH_2$), 1.12 (d, 3 H, *J* = 7.0 Hz, $SCHCHCH_3$), 0.98 (d, 3 H, *J* = 6.7 Hz, $HOCH_2CH_iCHCH_3$), 0.91 (s, 9 H, $SiC(CH_3)_3$), 0.092 (s, 3 H, $SiCH_3$), 0.087 (s, 3 H, $SiCH_3$); IR (thin film) 3420, 2940, 2920, 2880, 1455, 1375, 1245, 1085, 830, 775 cm^{-1}; EIMS *m/e* (relative intensity) 423 (18), 391 (12), 359 (2), 317 (1), 285 (5), 261 (10), 205 (100), 173 (7), 146 (23), 99 (70); CIHRMS calcd for $C_{23}H_{48}O_4SiS_2$ 481.2842, found 481.2855.

Anal. Calcd for $C_{23}H_{48}O_4SiS_2$: C, 57.45; H, 10.06; S, 13.34. Found: C, 57.65; H, 10.32; S, 13.10.

[1R-[1R*(1S*,3R*),2S*,4R*]]-(1,1-Dimethylethyl)[[1-[3-(1,3-dithian-2-yl)-1-methoxybutyl]-2-methoxy-4-methyl-6-iodohexyl]oxy]dimethylsilane (40). The same procedure described for the preparation of **16** was followed with alcohol **39** (932 mg, 1.94 mmol), triphenylphosphine (815 mg, 3.11 mmol), I_2 (764 mg, 3.01 mmol), and pyridine (0.50 mL, 6.21 mmol) in benzene (30 mL). Purification by chromatography (hexane → 20% EtOAc–hexane) gave **40** (1.03 g, 89.5%) as a clear oil: $[\alpha]^{25}_D$ = −33.9° (*c* = 1.69, $CHCl_3$); ^1H NMR δ 4.19 (d, 1 H, *J* = 3.4 Hz, SCHS), 3.90 (br d, 1 H, *J* = 6.0 Hz, TBSOC*H*), 3.46 (s, 3 H, OCH_3), 3.34 (s, 3 H, OCH_3), 3.30–3.34 (m, 1 H, one of ICH_2), 3.27 (br d, 1 H, *J* = 10.4 Hz, *anti*-TBSOCHC*H*OMe), 3.19 (q, 1 H, *J* = 8.0 Hz, one of ICH_2), 3.11 (ddd, 1 H, *J* = 9.2 Hz, *J* = 6.2 Hz, *J* = 2.7 Hz, *syn*-TBSOCHC*H*OMe), 2.84–2.97 (m, 4 H, $SCH_2CH_2CH_2S$), 2.09–2.17 (m, 2 H, one of SCH_2CH_2 and SCHC*H*Me), 2.01–2.08 (m, 1 H, one of ICH_2CH_2), 1.78–1.89 (m, 2 H, one of SCH_2CH_2 and ICH_2CH_2CHMe), 1.72 (ddd, 1 H, *J* = 15.0 Hz, *J* = 8.7 Hz, *J* = 2.0 Hz, one of $SCHCHCH_2$), 1.58–1.65 (m, 1 H, one of ICH_2CH_2), 1.50–1.56 (m, 2 H, one of $SCHCHCH_2$ and one of $ICH_2CH_2CHCH_2$), 1.34 (ddd, *J* = 14.3 Hz, *J* = 9.6 Hz, *J* = 4.8 Hz, one of $ICH_2CH_2CHCH_2$), 1.13 (d, 3 H, *J* = 7.0 Hz, $SCHCHCH_3$), 0.95 (d, 3 H, *J* = 6.7 Hz, $ICH_2CH_2CHCH_3$), 0.92 (s, 9 H, $SiC(CH_3)_3$), 0.097 (s, 3 H, $SiCH_3$), 0.094 (s, 3 H, $SiCH_3$); IR (thin film) 2940, 2920, 2880, 1460, 1380, 1250, 1090, 840, 780 cm^{-1}; EIMS *m/e* (relative intensity) 533 (61), 501 (3), 427 (4), 385 (5), 349 (2), 261 (5), 241 (30), 205 (100), 159 (17), 146 (22), 119 (26), 99 (21); CIHRMS calcd for $C_{23}H_{47}IO_3SiS_2$ 591.1860, found 591.1868.

Anal. Calcd for $C_{23}H_{47}IO_3SiS_2$: C, 46.76; H, 8.02. Found: C, 47.10; H, 8.10.

[1R-[1R*(1S*,3R*),2S*,4R*]]-(1,1-Dimethylethyl)[[1-[3-(1,3-dithian-2-yl)-1-methoxybutyl]-2-methoxy-4-methyl-6-(phenylsulfonyl)hexyl]oxy]dimethylsilane (41). Benzenesulfinic acid, sodium salt (357 mg, 2.18 mmol) was added to a solution of iodide **40** (988 mg, 1.67 mmol) in DMF (16 mL) at room temperature. After stirring for 20 h, the reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (4×). The combined organic layer was washed with brine (1×), dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography (20 → 40% EtOAc–hexane) yielded recovered **40** (29 mg, 3%) and **41** (821 mg, 81%). **41**: $[\alpha]^{25}_D$ = −33.2° (*c* = 1.94, $CHCl_3$); ^1H NMR δ 7.92 (apparent d, 2 H, *J* = 7.3 Hz, *o*-ArH), 7.65 (br t, 1 H, *J* = 7.4 Hz, *p*-ArH), 7.57 (t, 2 H, *J* = 7.4 Hz, *m*-ArH), 4.16 (d, 1 H, *J* = 3.4 Hz, SCHS), 3.86 (br d, 1 H, *J* = 5.9 Hz, TBSOC*H*), 3.31 (s, 6 H, both OCH_3), 3.24 (br d, 1 H, *J* = 10.2 Hz, *anti*-TBSOCHC*H*OMe), 3.08–3.18 (m, 2 H, $PHSO_2CH_2$), 3.03 (ddd, 1 H, *J* = 9.4 Hz, *J* = 6.0 Hz, *J* = 2.6 Hz, *syn*-TBSOCHC*H*OMe), 2.79–2.95 (m, 4 H, $SCH_2CH_2CH_2S$), 2.07–2.16 (m, 2 H, one of SCH_2CH_2 and $SCHCHCH_3$), 1.80–1.89 (m, 2 H, one of SCH_2CH_2 and one of $PhSO_2CH_2CH_2CH_2$), 1.72–1.80 (m, 1 H, $PhSO_2CH_2CH_2CH$Me), 1.65 (br ddd, 1 H, *J* = 15.1 Hz, *J* = 8.8 Hz, *J* = 2.2 Hz, one of $SCHCHCH_2$), 1.43–1.55 (m, 3 H, one of $SCHCHCH_2$, one of $PhSO_2CH_2CH_2CHCH_2$, and one of $PhSO_2CH_2CH_2$), 1.33 (ddd, 1 H, *J* = 14.6 Hz, *J* = 9.9 Hz, *J* = 4.9 Hz, one of $PhSO_2CH_2CH_2CHCH_2$), 1.11 (d, 3 H, *J* = 7.0 Hz, $SCHCHCH_3$), 0.91 (d, 3 H, *J* = 6.8 Hz, $PhSO_2CH_2CH_2CHCH_3$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.07 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$); IR (thin film) 2940, 2890, 2820, 1465, 1450, 1310, 1255, 1150, 1095, 840, 780, 700 cm^{-1}; EIMS *m/e* (relative intensity) 547 (10), 441 (1), 409 (1), 349 (2), 255 (10), 205 (100), 146 (26), 119 (16); CIHRMS calcd for $C_{29}H_{52}O_5SiS_3$ 605.2825, found 605.2811.

Anal. Calcd for $C_{29}H_{52}O_5SiS_3$: C, 57.57; H, 8.66; S, 15.90. Found: C, 57.49; H, 8.89; S, 15.89.

Formation of Sulfone Epimers (2a). *n*-BuLi (1.39 M solution in hexanes, 0.68 mL, 0.95 mmol) was added dropwise to a solution of primary sulfone **41** (520 mg, 0.86 mmol) in THF (8.5 mL) kept at −78 °C. After 10–15 min, to the yellow solution was added MeI (0.11 mL, 1.72 mmol) all at once. The resulting mixture wsa stirred at −78 °C for 45 min. Saturated $NaHCO_3$ was added, and the mixture allowed to attain room temperature and extracted with EtOAc (3×). The combined organic layer was washed with saturated $Na_2S_2O_3$ (1×) and brine (1×), dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography (20 → 30% EtOAc–hexane) gave **2a** (495 mg, 93%) containing ca. 10–15% of gem-dimethylated sulfone as determined by ^1H NMR (on smaller scales, formation of dimethylated sulfone is not observed).

Diastereomeric **2a** was separated by preparative thick-layer chromatography (20% EtOAc–hexane, developed 2–3 times) for characterization purposes.

Higher R_f diastereomer (R_f 0.29, 20% EtOAc–hexane): $[\alpha]^{25}_D$ = −20.5° (*c* = 1.07, $CHCl_3$); ^1H NMR δ 7.89 (apparent dd, 2 H, *J* = 8.5 Hz, *J* = 1.4 Hz, *o*-ArH), 7.64 (tt, 1 H, *J* = 7.4 Hz, *J* = 1.3 Hz, *p*-ArH), 7.56 (apparent t, 2 H, *J* = 7.6 Hz, *m*-ArH), 4.18 (d, 1 H, *J* = 3.4 Hz, SCHS), 3.92 (dd, 1 H, *J* = 5.7 Hz, *J* = 1.3 Hz, TBSOC*H*), 3.33 (s, 3 H, OCH_3), 3.32 (s, 3 H, OCH_3), 3.27–3.31 (overlapping apparent d, 1 H, *J* = 10.1 Hz, *anti*-TBSOCHC*H*OMe, and m, 1 H, $PhSO_2CH$Me), 3.08 (ddd, 1 H, *J* = 9.3 Hz, *J* = 5.7 Hz, *J* = 2.4 Hz, *syn*-TBSOCHC*H*OMe), 2.76–2.96 (m, 4 H, $SCH_2CH_2CH_2S$), 2.06–2.17 (m, 2 H, one of SCH_2CH_2 and SCHC*H*Me), 2.02 (ddd, 1 H, *J* = 13.1 Hz, *J* = 8.4 Hz, *J* = 4.3 Hz, one of $PhSO_2CHCH_2$), 1.78–1.86 (m, 2 H, one of SCH_2CH_2 and $PhSO_2CHCH_2CH$Me), 1.68 (ddd, 1 H, *J* = 15.1 Hz, *J* = 8.8 Hz, *J* = 2.2 Hz, one of SCHCHC*H2*), 1.46–1.55 (m, 2 H, one of $SCHCHCH_2$ and one of $PhSO_2CHCH_2CHCH_2$), 1.22–1.30 (m, 2 H, one of $PhSO_2CHCH_2CHCH_2$ and one of $PhSO_2CHCH_2$), 1.24 (d, 3 H, *J* = 6.9 Hz, $PhSO_2CHCH_3$), 1.11 (d, 3 H, *J* = 7.0 Hz, $SCHCHCH_3$), 0.98 (d, 3 H, *J* = 6.7 Hz, $PhSO_2CHCH_2CHCH_3$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.08 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$); IR (thin film) 2950, 2930, 2890, 1460, 1445, 1305, 1150, 1090, 840, 735 cm^{-1}.

Lower R_f diastereomer (R_f 0.23, 20% EtOAc–hexane): $[\alpha]^{25}_D$ = −39.0° (*c* = 1.27, $CHCl_3$); ^1H NMR δ 7.89 (apparent dd, 2 H, *J* = 8.2 Hz, *J* = 1.3 Hz, *o*-ArH), 7.66 (tt, 1 H, *J* = 7.5 Hz, *J* = 1.3 Hz, *p*-ArH), 7.57 (apparent t, 2 H, *J* = 7.6 Hz, *m*-ArH), 4.17 (d, 1 H, *J* = 3.5 Hz, SCHS), 3.86 (dd, 1 H, *J* = 6.1 Hz, *J* = 1.3 Hz, TBSOC*H*), 3.37 (s, 3 H, OCH_3), 3.32 (s, 3 H, OCH_3), 3.25 (br d, 1 H, *J* = 10.3 Hz, *anti*-TBSOCHC*H*OMe), 3.07–3.15 (overlapping ddd, 1 H, *J* = 9.4 Hz, *J* = 6.3 Hz, *J* = 3.3 Hz, *syn*-TBSOCHC*H*OMe, and m, 1 H, $PhSO_2CH$Me), 2.78–2.96 (m, 4 H, $SCH_2CH_2CH_2S$), 2.08–2.16 (m, 2 H, one of SCH_2CH_2 and SCHC*H*Me), 1.80–1.89 (m, 1 H, one of SCH_2CH_2), 1.72–1.79 (m, 1 H, $PhSO_2CHCH_2CH$Me), 1.69 (ddd, 1 H, *J* = 15.1 Hz, *J* = 8.8 Hz, *J* = 2.2 Hz, one of $SCHCHCH_2$), 1.59–1.62 (m, 2 H, $PhSO_2CHCH_2$), 1.51 (ddd, 1 H, *J* = 15.1 Hz, *J* = 10.5 Hz, *J* = 4.6 Hz, one of $SCHCHCH_2$), 1.38–1.48 (m, 2 H, $PhSO_2CHCH_2CHCH_2$), 1.28 (d, 3 H, *J* = 6.8 Hz, $PhSO_2CHCH_3$), 1.13 (d, 3 H, *J* = 7.0 Hz, $SCHCHCH_3$), 0.91 (s, 9 H, $SiC(CH_3)_3$), 0.86 (d, 3 H, *J* = 6.6 Hz, $PhSO_2CHCH_2CHCH_3$), 0.08 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$); IR (thin film) 2940, 2920, 2880, 1455, 1440, 1300, 1245, 1140, 1085, 835, 755 cm^{-1}.

Diastereomeric mixture: EIMS *m/e* (relative intensity) 618 (1), 561 (50), 529 (3), 455 (4), 423 (2), 381 (2), 349 (7), 269 (33), 205 (100); CIHRMS calcd for $C_{30}H_{54}O_5SiS_3$ 619.2982, found 619.2970.

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Supplementary Material Available: Characterizations of intermediates in the sequences going from **25** → **20** and from **29** → **32** (3 pages). Ordering information is given on any current masthead page.

A Formal Synthesis of FK-506. Exploration of Some Alternatives to Macrolactamization

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The coupling of the previously described subunits **2**, **3**, and **4** is described. The C_{28}–C_{27} *E*-double bond is fashioned from a sulfurane induced dehydration of alcohol **11**. The C_{19}–C_{20} *E*-double bond was constructed via a modified Julia process culminating in a reductive elimination of a vicinal trifluoracetoxy sulfone (see **22** → **23** → **24** and **25**). The synthesis of intermediates anticipating potential macrolactonization are also described.

Introduction

The extraordinary immunosuppressive properties of FK-506 (**1**), as well as its novel structure, have engendered a great deal of interest in its clinical potential, mechanism of action, and chemistry.[1-3] Not surprisingly, considerable attention has also been directed to its synthesis. Though many approaches to the total synthesis problem have been recorded,[4] only one comprehensive solution has been achieved. Earlier this year a group of scientists at the Merck, Sharpe and Dohme Research Laboratories reported the total synthesis of FK-506.[5] In the terminal stage of this landmark effort, systems of the type **7** (including the specific compound **7c**) were converted to FK-506 by insertion of a two carbon (glycolate) fragment, followed by macrolactamization. Such compounds were also identified as strategic goals in our synthetic effort.

In earlier papers in this issue,[6] we described straightfoward routes to properly matched, enantiomerically pure, subunits **2**, **3**, and **4**. Herein we describe in detail the

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(4) For a comprehensive listing of synthetic efforts as of this writing refer to footnote 3 within ref 6b.

(5) For the total synthesis of FK-506, see: Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. D.; Shinkai, I. *J. Am. Chem. Soc.* **1989**, *111*, 1157.

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