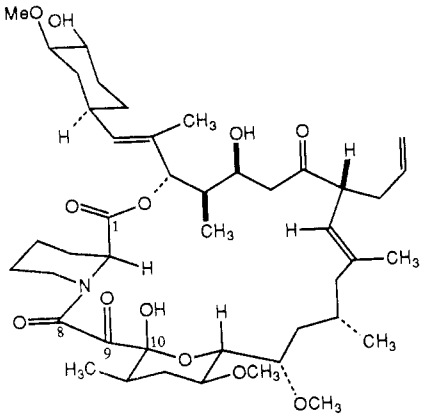


Figure 1. Structure of FK-506.

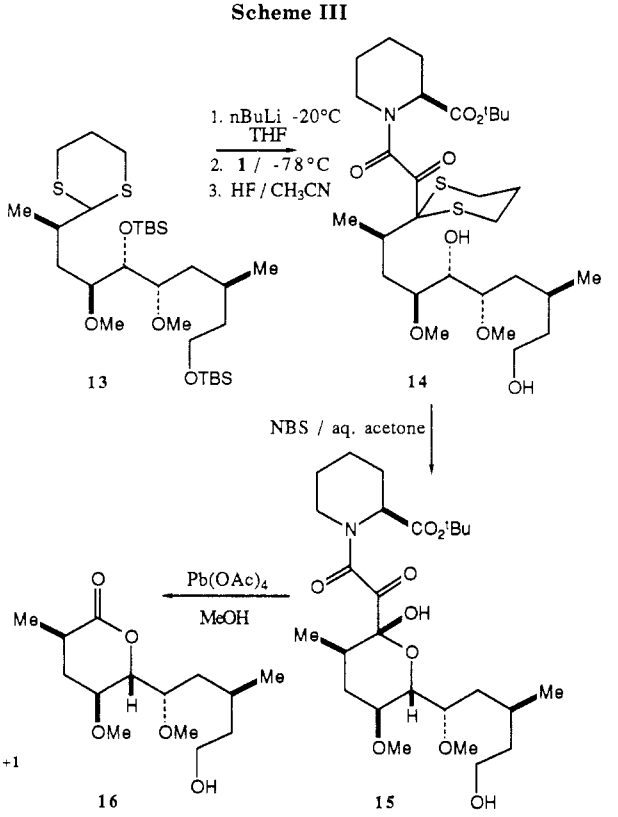
to ester **1**. The more polar **9a** gave rise to lactone **10**, and the less polar **9b**[6] afforded **11**, i.e., ent **10**. The absolute configuration of **10** was established by ozonolytic conversion of the lactone to the Prelog–Djerassi lactone–ester **12** ($[\alpha]_D$ = +35° (*c* = 0.1, CH_2Cl_2); lit. $[\alpha]_D$ = +39° (*c* = 0.2, CH_2Cl_2) of known absolute configuration.[7]

Further exploration of the possibilities of this approach was accomplished by using dithiane **13** (Scheme III) obtained by total synthesis. Treatment of **13** with nBuLi at −20 °C and addition of **1** at −78 °C followed by treatment of the crude reaction product with HF/CH_3CN led to the isolation of **14** in 48% yield (based on recovering starting material). Cleavage of the dithiane as described above gave the lactol **15** (45%). Evidence for the presence of a six-membered lactol was provided by cleavage with lead tetraacetate in methanol to give ester **1** and lactone **16**.

In summary, a straightforward synthesis of the tricarbonyl system of FK-506 has been accomplished in two model systems. Efforts to improve the efficiency of the sequence and to apply it to the total synthesis of FK-506 are in progress.

Acknowledgment. This research was supported by PHS Grant AI 16943. An American 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. Many stimulating conversations with Professor Stuart Schreiber are recalled.

Scheme III



Supplementary Material Available: Experimental data for compounds **1**, **4–8**, **9a,b**, **10**, and **14–16**, spectra (250 MHz, $CDCl_3$) for compounds **5**, **9a,b**, **10**, **13**, **14**, and **16**, and spectra (490 MHz, $CDCl_3$) for compounds **1** and **15** (15 pages). Ordering information is given on any current masthead page.

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(6) Compounds **9a,b** were separated by HPLC, 2% Et_2O/CH_2Cl_2 on a Porasil column. The enantiomeric lactones **10** and **11** were identified by spectral comparisons with the racemic mixture.[5]

(7) Martin, S. F.; Guinn, D. E. *J. Org. Chem.* **1987**, *52*, 5588.

Stereoselective Syntheses of FK-506 Subunits by the Rhodium(I)-Catalyzed Hydrogenation of Dienes. The Synthesis and Coupling of a C_{10}–C_{19} Fragment

Summary: A key fragment (C_{10}–C_{19}) of FK-506 bearing a dithiane at one terminus and a methyl-branched sulfone at the other has been prepared and shown to be viable in a model Julia coupling.

Sir: In this paper we describe our approach to the construction of the C_{10}–C_{19} fragment of FK-506 and some model studies that address the feasibility of a Julia type coupling for construction of the C_{19}–C_{20} double bond.[2] Our experiments were organized around two recognitions. First, the configurations at carbons 13, 14, and 15 (FK-506 numbering) of a prototype goal structure (cf. **7**) correspond to those at C_4, C_3, and C_2, respectively, of D-galactose (Figure 1). Further examination of **7** reveals that the 1,3-syn relationship between the methyl group at C_{11} and the C_{13} methoxyl function is duplicated for the same functions attached to carbons 17 and 15, respectively. Moreover, both relationships could be established by concurrent hydrogenation of a diolefin under guidance by a homoallylic C_{14} hydroxyl group with the rhodium-centered [Rh(NBD)DIPHOS-4]BF_4 catalyst (**1**) pioneered for such applications by Evans[3] and Brown.[4] The diolefin that is to undergo bis reduction might be symmetric (cf. **2**, R = R′) or nonsymmetric (cf. **3**, R ≠ R′). Both versions

(1) National Institutes of Health Postdoctoral Fellow, 1987–1989.
(2) For the structure of FK-506 and related work, see accompanying paper by Egbertson and Danishefsky.

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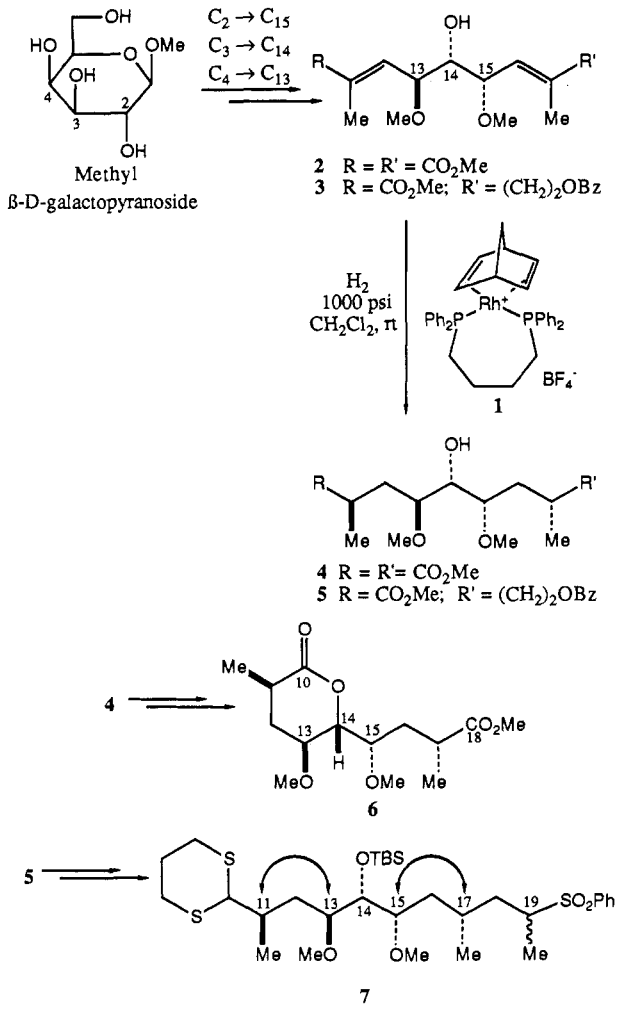

Figure 1.

were investigated and shown to provide high margins of stereoselectivity. Products **4** and **5** were converted to target structures **6** and **7**, respectively.[5]

The synthesis of lactone–ester **6** was approached by two different routes (Figure 2). Selective mono-*tert*-butyldimethylsilylation of methyl-ß-D-galactopyranoside[6] was followed by formation of the 3,4-stannylene derivative and monobenzylation[7] thereof. After methylation, there was thus obtained the differentially blocked galactose derivative **8** (path A). Cleavage of the silyl group (aqueous HOAc) followed by iodination (I_2, Ph_3P)[8] of the resulting alcohol **9** led to **10**. The olefinic aldehyde **11** was accessible through a Vasella reaction[9] on **10**. Ozonolysis of **11** (CH_2Cl_2, −78 °C; PPh_3, room temperature) followed by Wittig reaction of the resulting product with phosphorane **12** afforded diester **13** (64% overall from **11**). The latter, upon debenzylation through the action of Me_3SiI (trace of HI), gave the desired homoallylic alcohol **2**. While this route to **6** has the virtue of conciseness, at the present writing a slightly longer variation has proven to be more reproducible and amenable to large-scale work (path B). Acidic hydrolysis (aqueous HCl, THF) converted **8** to diol **14**. Reduction with $NaBH_4$ followed by acetonide protection of the C_5–C_6 diol and Swern oxidation of the alcohol gave aldehyde **15**. Condensation of **15** with **12** as before, acidic removal of the acetonide, and oxidative cleavage of the diol afforded aldehyde **17**. A second Wittig condensation with **12** afforded **13** in 74% yield from **16**.

Indeed, reduction of **2** with hydrogen in methylene chloride (1000 psi) using the Evans catalyst did afford **4** as the principal product. The ratio of **4** to the two other apparent tetrahydro compounds was 20:2.25:1. The fourth hypothetical permutant was not detected. The lactonization of **4** [pyridinium *p*-toluenesulfonate (PPTS), CH_2Cl_2, room temperature] afforded primarily the all-equatorial product **6**. However, for reasons not well understood, the selectivity of this diastereotopic end group

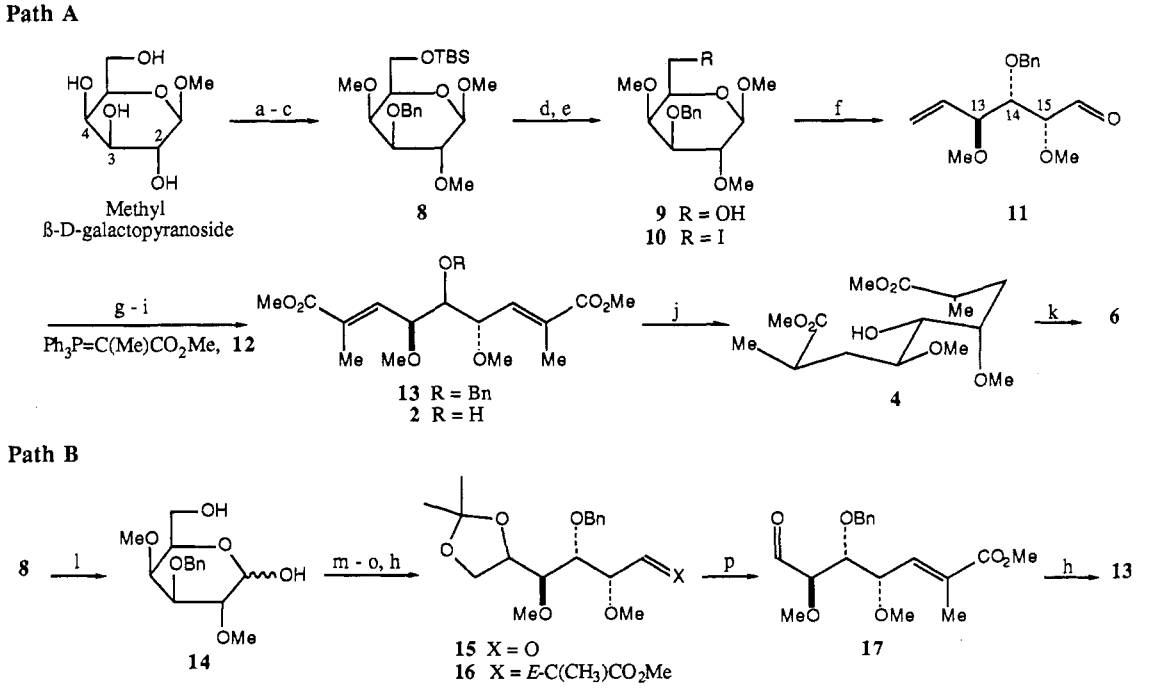

Figure 2. (a) TBSCl, Et_3N, cat. DMAP, CH_2Cl_2, room temperature, 72%; (b) (n-Bu_3Sn)$_2O$, toluene, reflux; BnBr, TBAI, 80 °C, 98%; (c) MeI, NaH, THF, room temperature, 93%; (d) 1:1 HOAc–H_2O, THF, room temperature, 95%; (e) PPh_3–I_2 (precomplexed), pyr, PhH, reflux, 77%; (f) Zn, 95% EtOH, reflux, 95%; (g) O_3, CH_2Cl_2, −78 °C; PPh_3 workup; (h) **12**, CH_2Cl_2, 0 °C → room temperature, 64% (overall steps g, h); (i) TMSI (traces of HI), CH_2Cl_2, room temperature, 80%; (j) H_2, [Rh(NBD)DIPHOS-4]BF_4, 1000 psi, CH_2Cl_2, room temperature, 89%; (k) PPTS, CH_2Cl_2, room temperature, 63% plus 20% recovered starting material; (l) 3 M HCl, THF, reflux, 73%; (m) $NaBH_4$, EtOH, room temperature, 90%; (n) acetone, TsOH, 3-Å molecular sieves, room temperature, 89%; (o) (i) $(ClCO)_2$, DMSO, TEA, CH_2Cl_2, −78 °C; (ii) step h, 90% overall; (p) (i) 3:1 HOAc–H_2O, THF, reflux; (ii) $NaIO_4$, 1:1 THF–H_2O, (iii) step h, 74% overall.

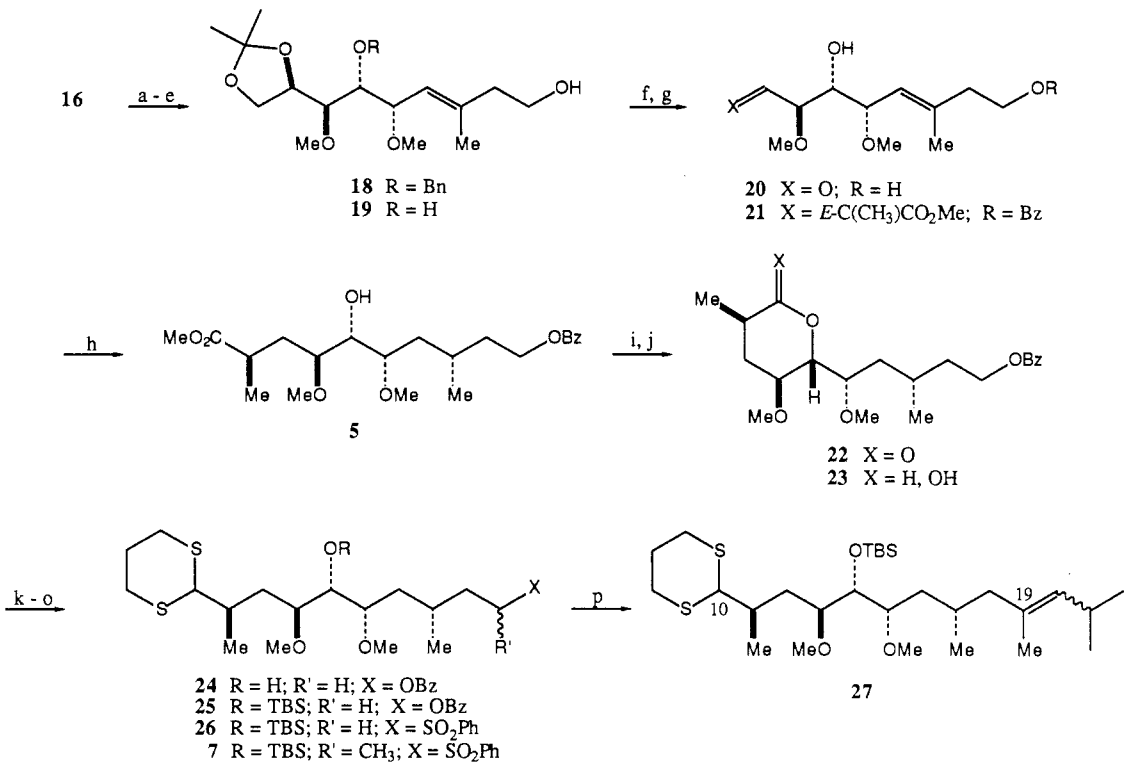

Figure 3. (a) $LiEt_3BH$, THF, −78 °C → −20 °C, quantitative; (b) MsCl, LiCl, *s*-collidine, DMF, 0 °C, 67% plus 10% recovered starting material; (c) NaCN, DMF, room temperature, 69% plus 8% recovered starting material; (d) (i) $(i\text{-Bu})_2AlH$, CH_2Cl_2, −78 °C; (ii) $NaBH_4$, EtOH, room temperature, 69% overall; (e) Na, NH_3(liq), −78 °C, 90%; (f) (i) 3:1 HOAc–H_2O, THF, reflux; (ii) $NaIO_4$, 1:1 THF–H_2O, room temperature, (g) (i) **12**, CH_2Cl_2, 0 °C → room temperature, (ii) BzCl, pyr, THF, room temperature, 55% overall steps f, g; (h) H_2, [Rh(NBD)DIPHOS-4]BF_4, 1000 psi, CH_2Cl_2, room temperature, 94%; (i) TsOH, 4-Å molecular sieves, CH_2Cl_2, room temperature, 93%; (j) Li(*s*-Bu)$_3$BH, THF, −78 °C, 94%; (k) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C → 0 °C, 85%; (l) TBSOTf, 2,6-lutidine, CH_2Cl_2, room temperature, 97%; (m) K_2CO_3, MeOH, room temperature, 84%; (n) (i) MsCl, TEA, CH_2Cl_2, 0 °C, 84%; (ii) NaI, acetone, reflux, 97%; (o) (i) $PhSO_2^-Na^+$, DMF, room temperature, 86%; (ii) *n*-BuLi, THF, −78 °C, CH_3I, 88%; (p) (i) *n*-BuLi, THF, −78 °C, $(CH_3)_2CHCHO$, 83%; (ii) Ac_2O, pyr, reflux; (iii) 5% Na–Hg, KH_2PO_4, 4:1 THF–MeOH, −20 °C, 33% overall from ii.

differentiation was disappointing (ca. 4–6:1).[10]

For the synthesis of dithiane–sulfone **7**, we have explored an alternate route wherein the differentiated termini inherent in compound **16** are exploited (Figure 3). While this is longer than sequences available through **6**, it has proven to be quite amenable to the throughput of gram quantities of material. Acetonide–ester **16** was homologated by a conventional sequence [(i) $LiEt_3BH$; (ii) MsCl, LiCl; (iii) NaCN; (iv) $(i\text{-Bu})_2AlH$; and (v) $NaBH_4$] to afford alcohol **18**. Debenzylation with Na in liquid ammonia afforded diol **19**. This compound was transformable to the β-hydroxy aldehyde **20** by treatment with AcOH followed by $NaIO_4$. Remarkably, the latter underwent smooth Wittig condensation with **12** and monobenzoylation to give a 55% yield of **21** (overall from **19**). The latter, upon homogeneous catalytic reduction as before, gave **5** (94%), which lactonized smoothly to afford **22** (93%). Reduction of **22** with Li(*s*-Bu$_3$)BH gave lactols **23**. Thioacetalization (1,3-propanedithiol, $BF_3{\cdot}Et_2O$) and protection of the resulting alcohol **24** as its TBS ether afforded dithiane **25** (82% overall).[11] The latter was converted to the primary sulfone **26** by the sequence (i) K_2CO_3, MeOH; (ii) MsCl, Et_3N; (iii) NaI; and (iv) $PhSO_2Na$ in good overall yield. Methyl branching could be introduced at C_{19} by treatment of **26** with *n*-butyllithium followed by methyl iodide to give target **7** in 88% yield. The possibilities for using this secondary sulfone in a Julia type coupling were explored. In a model reaction, lithiation of **7** (*n*-BuLi, −78 °C, THF) followed by addition of isobutyraldehyde gave a mixture of hydroxysulfones which, upon acetylation (Ac_2O, pyridine, reflux) and reductive elimination (Na–Hg, 4:1 THF–MeOH, KH_2PO_4), gave rise to olefin mixture **27**. The *E*/*Z* ratio by this protocol ranged from 2:1 to 2.5:1. This type of Julia olefination sequence can be applied to a more elaborated aldehyde which is more pertinent with respect to the total synthesis of FK-506. The results of this work will be described in due course.

Acknowledgment. This research was supported by PHS Grant AI 16943. A PHS Fellowship (Grant GM 11747) to A.V. 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

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(11) For use of the debenzoylated version of **25**, see ref 2.

7916210. Many stimulating conversations with Professor Stuart Schreiber are recalled.

Supplementary Material Available: ^{1}H NMR spectra for **4**, **5**, **26**, and **27** (4 pages). Ordering information is given on any current masthead page.

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Studies Relating to the Synthesis of the Immunosuppressive Agent FK-506: Application of the Two-Directional Chain Synthesis Strategy to the Pyranose Moiety

Summary: The asymmetric synthesis of the C_{10}–C_{19} fragment of FK-506 is reported. The two-directional chain synthesis strategy resulted in a considerable degree of double processing along the nascent chain.

Sir: As part of a program aimed at a modular synthesis of the potent immunosuppressive agent FK-506,[1] we required an efficient synthesis of the phosphine oxide **3** (Figure 1). Our plan entails the utilization of this compound as a synthon for the C_{10}–C_{19} chain of the natural product. The synthesis allows the incorporation of intermediates into other targets whose structures have been formulated to elucidate the structural requirements for binding to cellular mediators and suppression of immune systems.[2]

The two-directional chain synthesis strategy offers certain advantages over conventional chain synthesis strategies provided the problem of terminus differentiation of the two-directionally homologated chain can be surmounted.[3] The synthesis of the target chain **3** illustrates the efficiency of the double processing that is characteristic of the strategy and a solution to the problem of terminus differentiation that entails the use of a diastereotopic group-selective reaction.

The two stereocenters of commercially available arabitol (**1**) correspond to those at C_{13} and C_{15} of FK-506 (Scheme I). Treatment of the tetraol with the acid chloride reagent developed by Moffatt[4] provided the crude dichloro diacetate **4**, which was converted to the bisepoxide benzyl ether **5** in 45% overall yield by saponification with sodium methoxide and alkylation with benzyl bromide. The bisepoxide was simultaneously homologated in two directions by reaction with 1-lithio-2-ethoxyacetylene in the presence of boron trifluoride etherate[5] to give the hydrolytically labile bisalkyne diol **6**, which was directly transformed into the bislactone **7** by treatment with methanolic HCl. The dilactone **7** was isolated as a crystalline solid (mp 65–68 °C, $[\alpha]^{22}_D$ = +2.6°, c = 1.0, $CHCl_3$) after silica gel chromatography in 62% overall yield from the bisepoxide. Formation of the bisenolate with 2.2 equiv of LDA and alkylation with excess iodomethane provided a mixture of products, from which the desired dimethyl bislactone **8** (mp 76–77 °C, $[\alpha]^{22}_D$ = +23.6°, c = 1.1, $CHCl_3$) was isolated in 54% yield after careful chromatography.[6] A sequence consisting of saponification of the lactone, removal of water

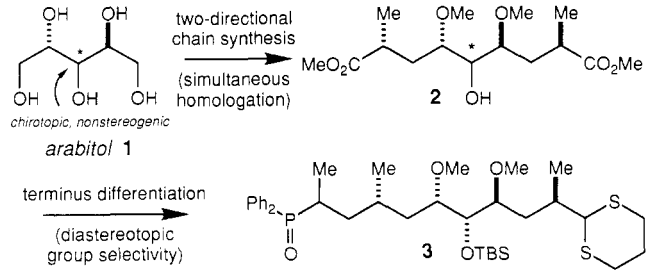

Figure 1. Two-directional chain synthesis: class C chain.

to leave the solid bis(sodium carboxylate), and exhaustive alkylation with methyl iodide in DMF in the presence of sodium hydride produced the desired dimethyl ester dimethyl ether **9** [$(\alpha]^{22}_D$ = −37.5°, c = 1.6, $CHCl_3$) in 51% yield following chromatography. Analysis by ^{1}H NMR revealed that the compound so obtained consisted of >90% of a single diastereomer, indicating that negligible epimizeration had occurred during the methylation process.

Following removal of the benzyl protecting group by hydrogenolysis in the presence of Pearlman's catalyst, differentiation of the termini of the resulting hydroxy bis(methyl ester) **2** ($[\alpha]^{22}_D$ = −24.2°, c = 1.8, $CHCl_3$) was required. A similar problem had been encountered by Hoye in the course of a different synthetic objective.[7] A solution to the present problem follows closely the method employed in that earlier work. A group-selective lactonization of **2** with pyridinium *p*-toluenesulfonate[8] in methylene chloride gave rise to a 6:1 mixture of lactones with **10** as the dominant isomer in 65% yield, together with 25% recovered starting material. Attempts to drive the reaction to completion by prolonged treatment under these conditions or use of stronger acids led to unsatisfactory diastereomer ratios. Selective reduction of the lactone in the presence of the methyl ester was achieved with L-Selectride (Aldrich) to provide a 1:1 mixture of lactol anomers **11** in 99% yield. Installation of the dithiane protecting group under standard conditions resulted in concomitant lactonization to generate the highly crystalline lactone dithiane **12** in 90% yield (mp 126–127 °C, $[\alpha]^{22}_D$ = −21.7°, c = 0.5, $CHCl_3$). Reduction of **12** to the corresponding diol ($[\alpha]^{22}_D$ = +2.7°, c = 1.7, $CHCl_3$), selective conversion of the primary alcohol to the corresponding iodide, and protection of the secondary alcohol delivered **13**, which was readily extended to the target phosphine oxide. Addition of an excess of the lithio salt of diphenylethylphosphine oxide (formed by treatment of diphenylethylphosphine oxide with *n*-butyllithium at 0 °C in THF)[9] to the iodide

(1) See: (a) Accompanying papers in this issue. (b) Askin, D.; Volante, R. P.; Reamer, R. A.; Ryan, K. M.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 277. (c) Mills, S.; Desmond, R.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 281.

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