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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Received October 18, 1988

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

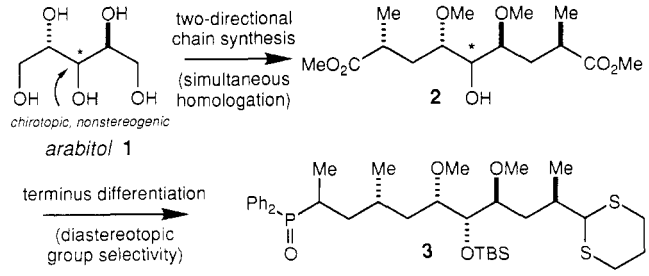

Figure 1. Two-directional chain synthesis: class C chain.

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.

(2) For a discussion of natural products binding and scaffolding domains, see: Schreiber, S. L.; Anthony, N. J.; Dorsey, B. D.; Hawley, R. C. *Tetrahedron Lett.* In press.

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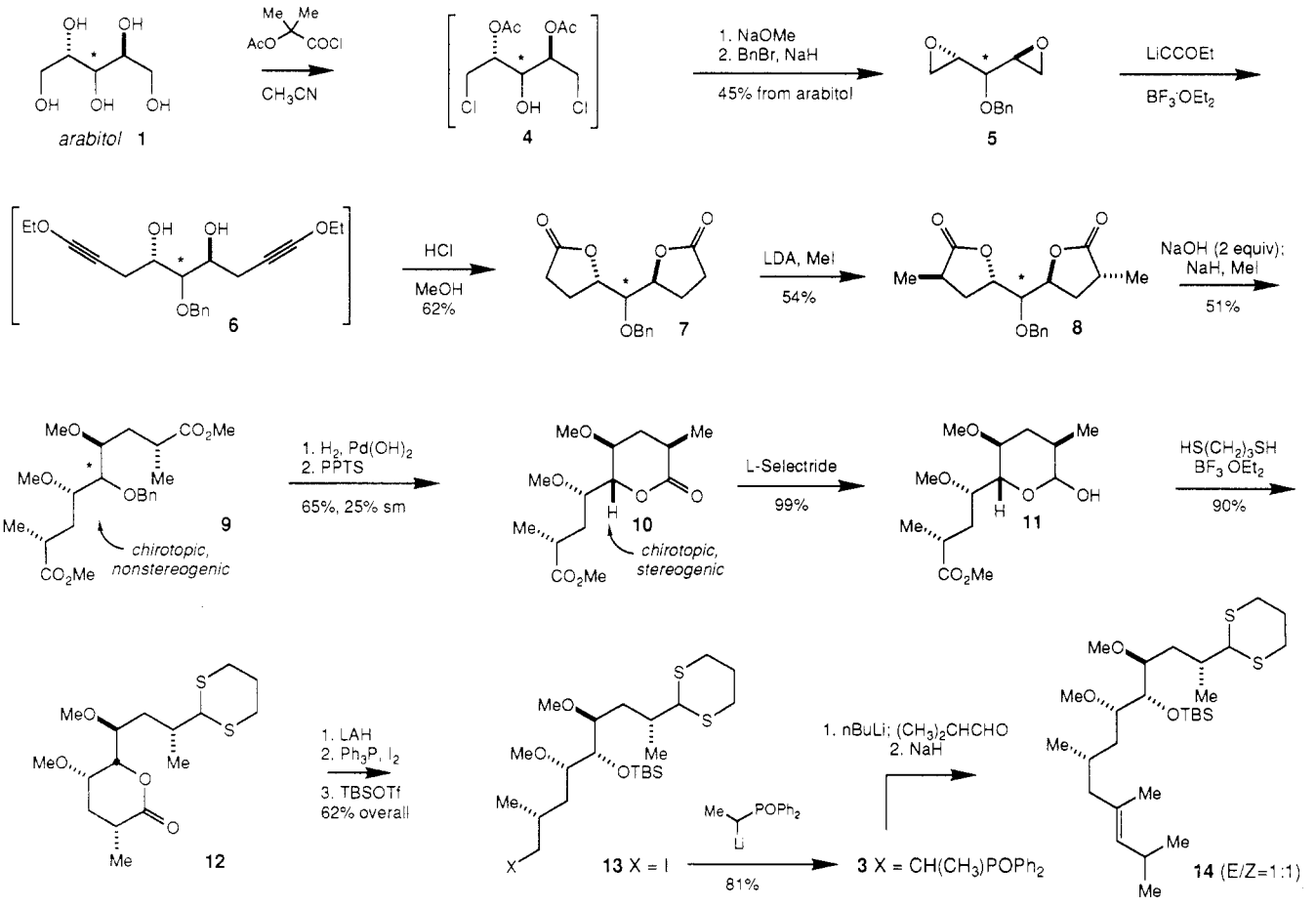
0022-3263/89/1954-0015$01.50/0

Scheme I



in THF at 0 °C and warming the mixture to room temperature led to the isolation of **3** in 81% overall yield from iodide **13**. In addition, related two-carbon nucleophiles have been found to undergo efficient substitution reactions with **13** to provide analogues of **3** (i.e., X = $CH(CH_3)$-SO_2Ph, $CH(CH_3)PO(NEt_2)_2$).

A model coupling reaction was performed with **3** and isobutyraldehyde according to a protocol developed by Warren.[10] Chemoselective lithiation at the carbon α to the phosphinoyl group was achieved by treatment of **3** with *n*-butyllithium at −78 °C in THF. Condensation with isobutyraldehyde provided a mixture of diastereomeric β-hydroxy phosphine oxides that were converted to a 1:1 *E*/*Z* mixture of alkenes **14** upon subsequent reaction with NaH. Current research efforts are focused on the coupling of **3** with aldehyde partners that correspond to the C_{20}–C_{34} fragment of FK-506[1a] with defined β-hydroxy phosphinoyl stereochemistry and subsequent stereospecific olefination.[10]

(10) Buss, A. D.; Warren, S. *Tetrahedron Lett.* **1983**, *24*, 111.

Acknowledgment. Financial support of this project by the NIGMS, the NSF, Pfizer, and Hoffmann-La Roche Inc. is gratefully acknowledged. We thank Professor Samuel Danishefsky and Dr. Annabella Villalobos for stimulating discussions and exchange of information.

Supplementary Material Available: ^1H NMR spectra for **5** and **7**–**14** (13 pages). Ordering information is given on any current masthead page.

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Received October 18, 1988