Synthetic Route to the "Tricarbonyl" Region of FK-506

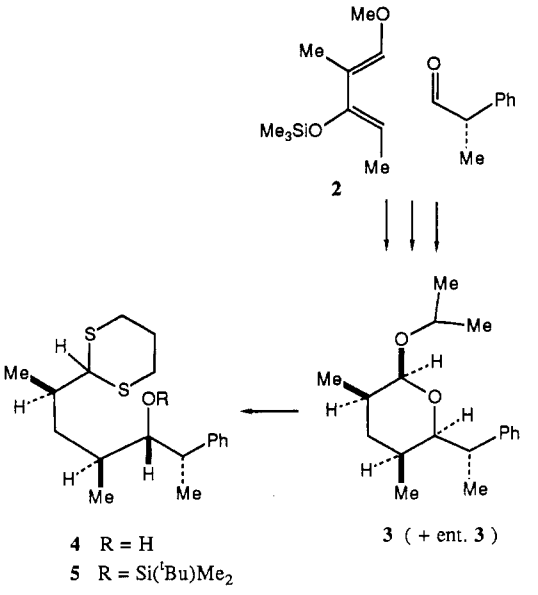
Summary: Coupling of a complex lithiodithiane to (*S*)-*tert*-butyl *N*-methoxalylpipecolate leads in three steps to the title substructure.

Sir: The discovery by Fujisawa scientists of the metabolite FK-506 with immunosuppressive potency greater than that of cyclosporin A presents the organic chemist with significant challenges and opportunities.[1,2] Examination of compounds available via synthesis and degradation might provide insight into the minimal structural requirements for immunosuppression. Not the least intriguing feature of FK-506 is the connection of the (*S*)-pipecolyl residue to C_{11} through a "tricarbonyl spacer" masked at C_{10} as a hemiketal (Figure 1). In this paper we provide an approach to the synthesis of such systems. A construction of the C_1–C_{16} sector of FK-506 is described.

Bond formations between C_9 and C_{10} were investigated. We favored a strategy wherein the (*S*)-pipecolyl residue with its amide bond to C_8 would already be in place during this coupling process. Compound **1** emerged as a potential electrophile.[3] A suitable model partner with nucleophilic potential was the dithiane **5**[4] (Scheme I). This compound was generated from racemic isopropyl glycoside **3**, which was prepared via a sequence starting with 2-phenylpropanal and diene **2**, as previously described.[5] Compound **4**, obtained by treatment of **3** with 1,3-propanedithiol (CH_2Cl_2, $BF_3{\cdot}OEt_2$, −78 °C → room temperature), was converted to its *tert*-butyldimethylsilyl ether **5** (90% overall). Treatment of **5** with BuLi/TMEDA at −20 °C for 2 h followed by addition of **1** at −78 °C gave a 60% yield of a ca. 1:1 mixture of **6a,b** (Scheme II). Cleavage of the dithiane to produce **7a,b** or a hydrated version thereof was unsuccessful. A more productive sequence started with cleavage of the OTBS group. Treatment of **6a,b** with HF/acetonitrile followed by exposure of **8a,b** to the action of *N*-bromosuccinimide in aqueous acetone gave **9a,b** (80%). The components were separated by preparative HPLC.

The NMR spectra of **9a** and **9b** are complicated by the fact that these compounds, like FK-506, exist as a mixture of amide bond rotamers. Strong presumptive evidence was brought to bear showing that **9a** and **9b** exist as six-membered hemilactols (as is the case in FK-506). Treatment of each compound with $Pb(OAc)_4$ in methanol gave rise

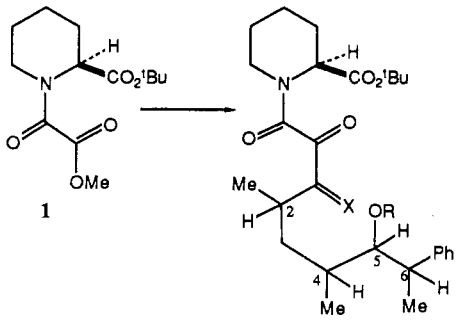
Scheme I



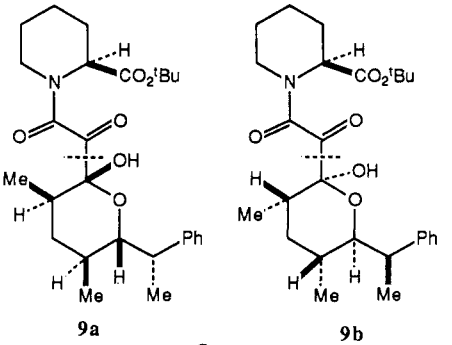
4 R = H
5 R = Si(ᵗBu)Me$_2$

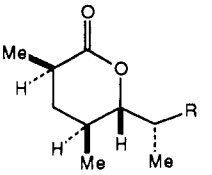
3 (+ ent. 3)

Scheme II



6 X = S(CH$_2$)$_3$S; R = TBS
7 X = O; R=TBS
8 X = S(CH$_2$)$_3$S; R = H
a series H_2, H_4 = α; H_5, H_6 = β
b series H_2, H_6 = β; H_5, H_6 = α





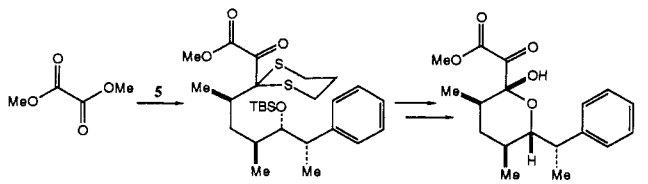
10 R = Ph
11 = ent **10**
12 R = CO_2Me

(1) Kino, F.; Hatanaka, H.; Hashimoto, M.; Nishiyama, 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) Askin, D.; Volante, R. P.; Reamer, R. A.; Ryan, K. M.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 277. Mills, S.; Desmond, R.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 281. For a recent synthesis of a related tricarbonyl system, see: Williams, D. R.; Benbow, J. W. *J. Org. Chem.* **1988**, *53*, 4643.

(3) L-(*S*)-Pipecolic acid was obtained by resolution of the tartrate salt reported by V. W. Rodwell (*Methods Enzymol.* **1971**, *17*, Part B, 174–188) ($[\alpha]_D$ of salt = −19.3°, c = 10.6, H_2O). Peresterification of the tartrate salt, under pressure with H_2SO_4 and isobutylene in dioxane, followed by extractive separation led to the isolation of pipecolic acid *tert*-butyl ester. Acylation was accomplished (75%) by using methoxalyl chloride, CH_2Cl_2, DMAP, and pyridine at 0 °C.

(4) For an analogous acylation, cf.: Corey, E. J.; Pan, B.; Hua, D.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 6818. A sequence analogous to 1 → 6 → 8 → 9 has been accomplished in 30% overall yield using dimethyl oxalate as the electrophile in place of 1.



(5) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246.

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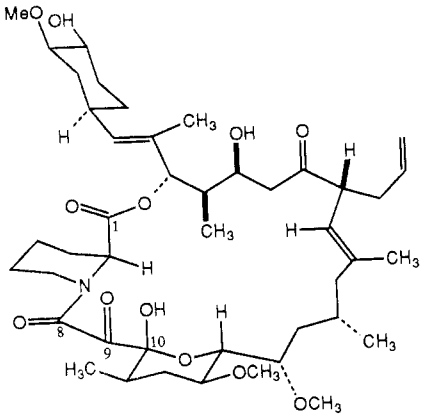

Figure 1. Structure of FK-506.

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.

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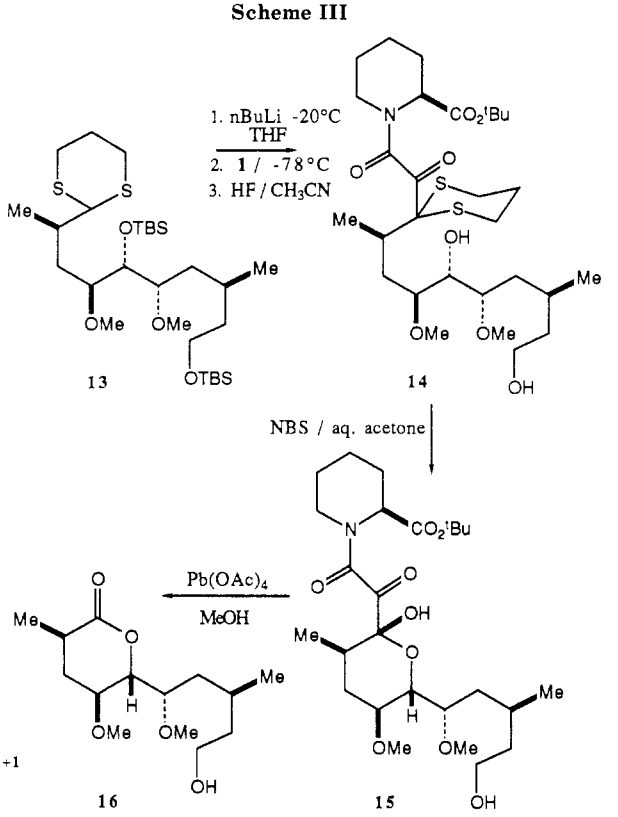
Scheme III



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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