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A DIASTEREOSPECIFIC, NON-RACEMIC SYNTHESIS OF THE C.10-C.18 SEGMENT OF FK-506

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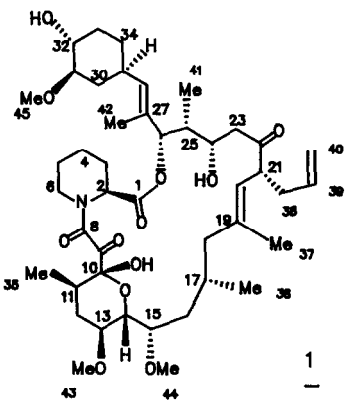
Summary: An efficient stereocontrolled route to construct the C.10-C.18 moiety of FK-506 is reported.

The novel 23-membered tricyclo-macrolide FK-506, (1)[1], very recently isolated and characterized by Tanaka, Kuroda, and co-workers, has been shown to possess exceptional immunosuppressive activity. The potential usefulness of such an agent in bone marrow and organ transplantations coupled with its unique structural features has prompted us to initiate an effort directed towards the total synthesis of FK-506. We wish to report here a highly diastereoselective synthesis of a protected C.10-C.18 subunit 2, in its correct absolute configuration.



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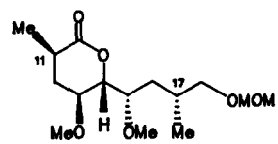

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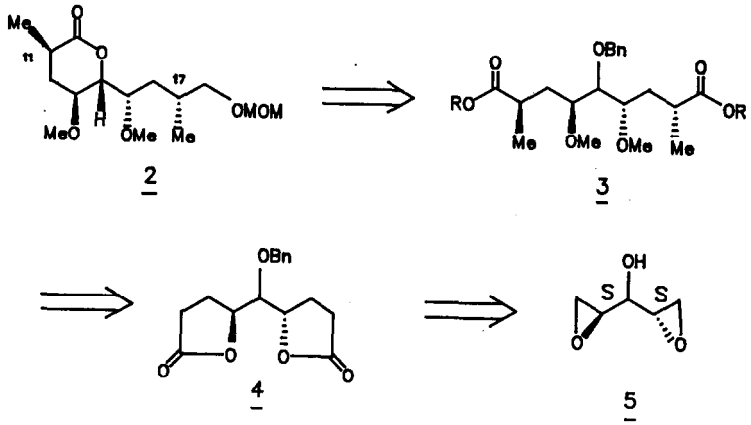
Our initial strategy for the synthesis of 2 was based on the retrosynthetic analysis outlined below (scheme I). We envisioned formation of 2 via diastereoselective lactonization of diester 3[2]. The C.11 and C.17 (FK-506 numbering) methyl substituents of 3 would be introduced by the simultaneous, diastereospecific methylation of the non-racemic bis-lactone 4.[3] Bis-lactone 4 would be available from the (hypothetical) bis-epoxide 5 via benzylation, simultaneous acetate enolate alkylation, and lactonization. The chiral, non-racemic (S,S)-bis-epoxide 5, in principle, could be

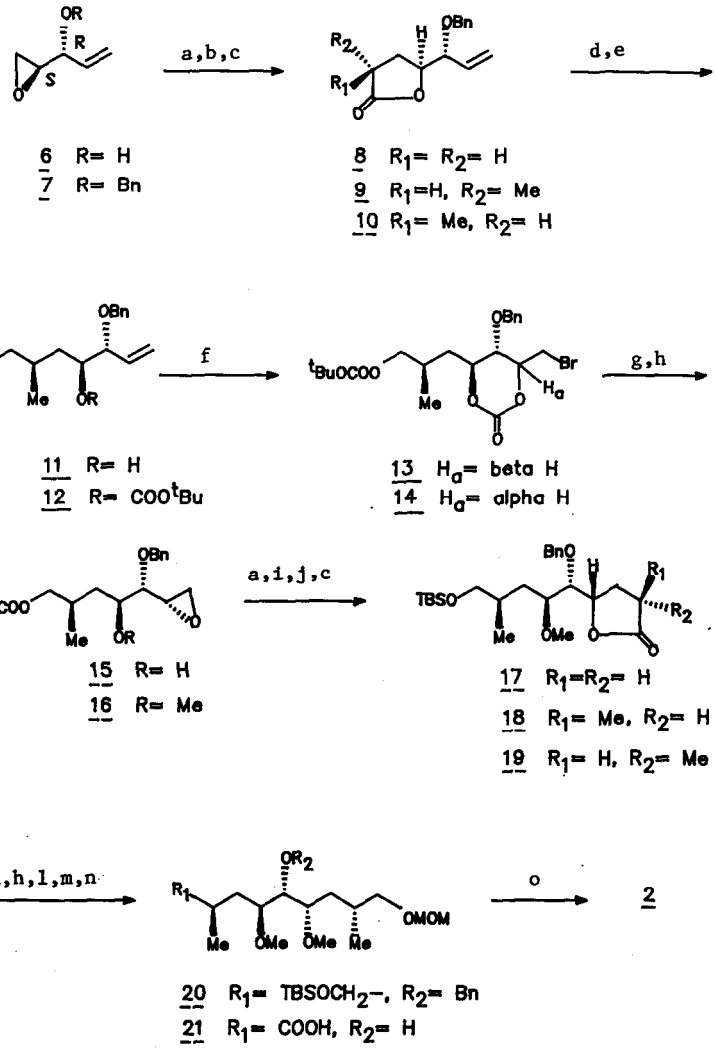
Scheme I



obtained from 1,4-pentadien-3-ol[4] by double Sharpless epoxidation reactions.[5] However, to simplify the problem of product structure determination, we chose to first investigate an approach wherein the stereocenters are created sequentially. An iterative approach of this type also provides direct access to a selectively protected species, eg. 20, without the need for additional terminus differentiation methodology as would be required for diester 3. The successful execution of this plan is outlined in Scheme II.

The monoepoxy alcohol 6[6,7] is available in high diastereomeric (99%, ^{13}C NMR) and enantiomeric[6c] (≥97%) purity. The benzyl ether 7, (76% yield, bp. 88-90°C, 0.5 torr) was prepared from 6 by standard methodology. Treatment of 7 with lithioacetonitrile[8] (1.1 eq) followed by lactonization gave the butyrolactone 8[9] in 76% isolated yield. Methylation of 8[10] resulted in a mixture of lactones 9[9] and 10[9] (91% yield) with the lactone 9 as the predominant species (9:10=87:13, as determined by capillary gc analysis). Lactones 9 and 10 were separated by silica gel chromatography and their structures were independently confirmed by NOE difference spectroscopy.[11] Lactone 9 was reduced with lithium aluminum hydride and the resultant diol 11[9] was converted to the bis-t-butylcarbonate 12. Treatment of 12 with bromine in the presence of potassium carbonate at -80°C produced the bromocarbonates[9,12] 13 and 14 (74% overall yield from lactone 9; 13:14=11:1 as determined by ^{1}H NMR). The stereochemistry of the desired bromocarbonate 13 was determined by NOE difference spectroscopy.[11] Subjection of the mixture of bromocarbonates to sodium methoxide/methanol effected selective saponification of the cyclic carbonate function to afford the epoxy-alcohol 15[9,13]. Standard methylation of the secondary hydroxyl function of 15 gave the methyl ether 16[9] (65% overall yield from 13). Conversion of 16 to the butyrolactone 17 was accomplished,

Scheme II



(a) $LiCH_2CN$, THF, -78°C to 25°C; (b) 12N HCl, MeOH, reflux, 3h. (c) LDA (1.0 eq), THF, -78°C to -50°C, 1h; MeI, -78°C, 1h. (d) LAH (4.0 eq), THF, +25°C, 2h. (e) 2-(t-butoxy-carbonyloxyimino)-2-phenylacetonitrile (2.05 eq), NaH, THF, 60°C, 48h. (f) Br_2 (1.5 eq), K_2CO_3 (1.5 eq), CH_2Cl_2, -80°C, 4h. (g) NaOMe (2.5 eq), MeOH, +25°C, 7h. (h) MeI (18 eq), NaH, THF, +25°C. (i) 2N HCl, dioxane, reflux, 4 h. (j) TBSCl (1.5 eq), imidazole (1.5 eq), DMF, +25°C, 3h. (k) MOMBr (1.5 eq), $EtN(iPr)_2$ (1.5 eq), CH_2Cl_2, 0°C, 6h. (l) $nBu_4N^+F^-$ (4 eq), THF, +25°C, 3h. (m) PDC (15 eq), DMF, +25°C, 24 h. (n) H_2, $Pd(OH)_2$, EtOH, +25°C, 3h. (o) Ac_2O, dichloroethane, reflux.

as before, by epoxide opening with lithioacetonitrile and lactonization, followed by protection of the primary hydroxyl group as its t-butyldimethylsilyl ether (51% yield from 16). Trans-selective methylation of 17 afforded lactones 18[9,11] and 19[9,11] in 93% yield (18:19=94:6, as determined by capillary gc). Reduction of the mixture with lithium aluminum hydride gave the corresponding diols which were separable by silica gel chromatography. Selective protection of the primary hydroxyl function as its methoxymethyl ether followed by methylation of the exposed secondary hydroxyl gave the open chain fragment 20[9] in 72% overall yield from 18. Desilylation of 20 (tetrabutylammonium fluoride) followed by oxidation (pyridinium dichromate in dimethyl formamide[14]) and hydrogenolysis of the benzyl ether function gave a mixture of hydroxy-acid 21 and lactone 2[9]. Lactonization was completed by heating in 1,2-dichloroethane with acetic anhydride at reflux temperature to afford 2[9] in 76% overall yield from 20. The coupling of 2 with the C.20-C.34 segment[15] and strategy directed towards elaboration to FK-506 will be reported in due course.

References and Notes

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2) For an example of a diastereoselective lactonization of this type, see: Hoye, T.R.; Peck, D.R.; Swanson, T.A. J. Am. Chem. Soc. 1984, 106, 2738.
3) For an example of a simultaneous bis-methylation of a spiro-dilactone, see: Hoye, T.R.; Peck, D.R.; Trumper, P.K. J. Am. Chem. Soc. 1981, 103, 5618.
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5) Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. J. Am. Chem. Soc. 1987, 109, 5765.
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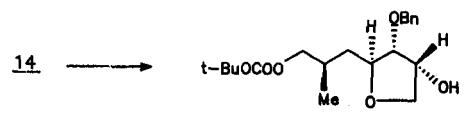
8) Creger, P.L., J. Org. Chem. 1972, 37, 1907.
9) Satisfactory ^{1}H NMR, ^{13}C NMR, IR and mass spectral analysis were obtained for this compound.
10) a) Takano, S.; Chiba, K.; Yonaga, M.; Ogasawara, K. J. Chem. Soc., Chem. Commun. 1980, 616. b) Tomioka, K.; Cho, Y.S.; Sato, F.; Koga, K. Chem. Lett. 1981, 1621.
11) Details of the NOE experiments will be disclosed elsewhere.
12) Babine, R.E. Tetrahedron Lett. 1986, 27, 5791.
13) The minor bromocarbonate 14 was selectively destroyed during the bromocarbonate saponification by conversion to tetrahydrofuran 22. This process is apparently much slower for the major isomer 13.



22

14) Corey, E.J.; Schmidt, G. Tetrahedron Lett. 1979, 20, 399.

15) Mills, S.; et al., See accompanying communication.

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