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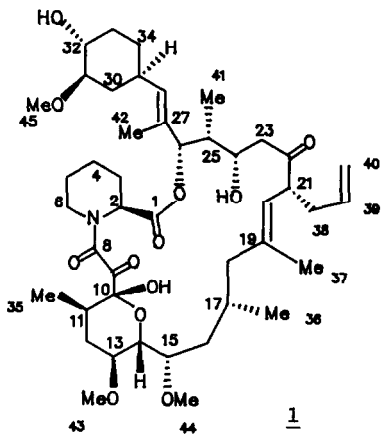
DIASTEREOSPECIFIC, NON-RACEMIC SYNTHESIS OF THE C.20-C.34 SEGMENT OF THE NOVEL IMMUNOSUPPRESSANT FK-506

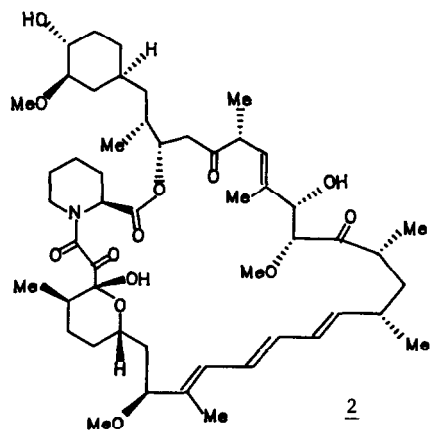
S. Mills*, R. Desmond, R.A. Reamer, R.P. Volante and I. Shinkai
Merck Sharp and Dohme Research Laboratories
Division of Merck & Co., Inc.
P.O. Box 2000
Rahway, New Jersey 07065

Summary: An efficient stereocontrolled route to construct the C.20-C.34 moiety of FK-506 is described.

The isolation and structure elucidation of the novel 23-membered tricyclo-macrolide FK-506 (1) was recently reported by Tanaka, Kuroda, and co-workers[1]. The interesting structural features of this molecule in conjunction with its highly potent and selective immunosuppressive activity have resulted in intensive efforts directed towards its total synthesis[2]. We were particularly intrigued by the C.20-C.34 carbon fragment of 1 and its similarity to the analogous moiety of the macrolide antifungal antibiotic, Rapamycin (2)[3]. A key structural feature, which is common to both molecules, is seen to be the C.28-C.34 cyclohexane carboxaldehyde derived fragment 3a (FK-506 numbering). This molecule has been previously synthesized in its racemic form[1]; however, a convenient source of the desired (29R,31R,32R)-aldehyde 3a has been lacking. In this communication we would like to report an efficient, chiral, non-racemic synthesis of 3a and its stereocontrolled homologation to the C.20-C.34 chain of 1.



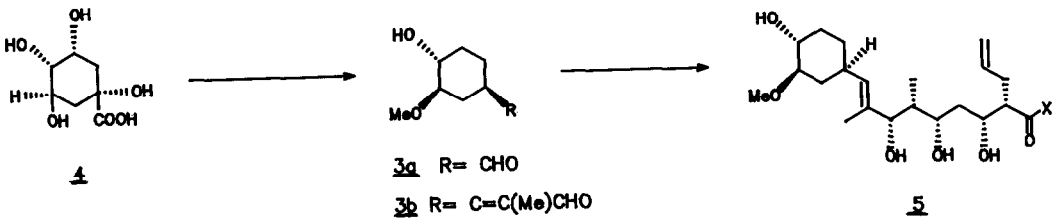
1



2

We envisioned aldehyde 3a to be attainable from naturally occurring (1R,3R,4R,5R)-quinic acid (4) by the stereospecific and regioselective reductive cleavage of the hydroxyl groups at C1 and C5 (Scheme I). Selective methylation of the C3 hydroxyl group followed by reduction of the carboxyl function would then yield the desired non-racemic cyclohexane carboxaldehyde 3a. Homologation of aldehyde 3a to the α,β-unsaturated aldehyde 3b followed by a series of diastereocontrolled aldol additions would be expected to yield the desired C.20-C.34 chain 5.

Scheme I



4

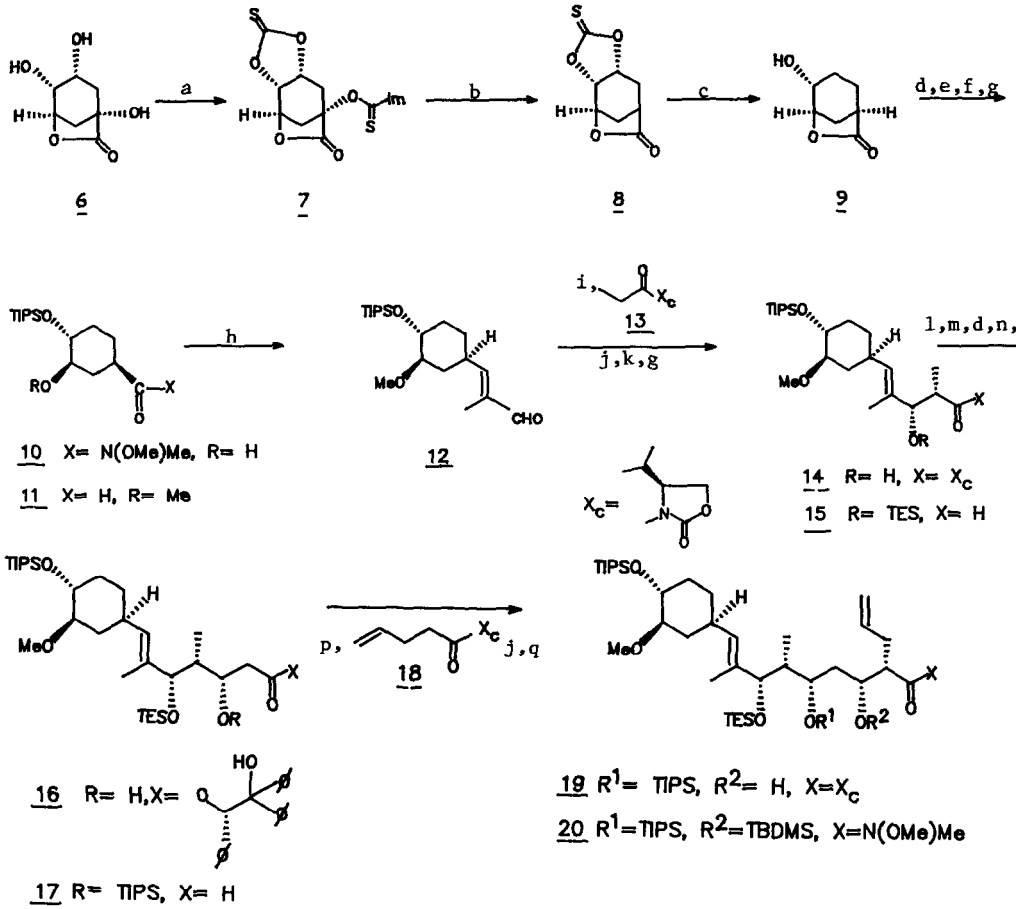
3a R= CHO

3b R= C=C(Me)CHO

5

The known lactone 6 (readily available from quinic acid)[4], was converted to the bis-thiocarbonyl lactone 7[5] in 74% isolated yield (see scheme II). Treatment of lactone 7 with tributyltin hydride produced the thiocarbonate 8 in 80% yield (^{1}H NMR). Although 8 was isolable, direct treatment of the crude reaction mixture with additional tributyltin hydride in the presence of azobisisobutyronitrile gave the non-racemic lactone 9[5] more efficiently (40% isolated yield from 7). Protection of the hydroxyl function as the triisopropylsilyl (TIPS) ether and subjection of the crude reaction mixture to methylchloroaluminum N-methoxy-N-methylamide[6] gave the N-methoxy-N-methylamide 10[5] in 85% overall yield from 9. Methylation of the 4-hydroxyl function and reduction with diisobutylaluminum hydride gave aldehyde 11[5] in 85% yield. Aldehyde 11 was then condensed with 2-lithio-2-triethylsilylpropanal t-butylimine[7] to give α,β-unsaturated aldehyde 12[5] in 78% isolated yield after aqueous-acidic imine hydrolysis and chromatographic purification (E:Z≥100:1). Treatment of aldehyde 12 with the boron enolate of imide 13[8] afforded alcohol 14[5] (≥99:1). Application of standard synthetic transformations allowed the conversion of alcohol 14 to the fully protected aldehyde 15[5] (88% yield from 12). Addition of the lithium enolate of S(-)-2-acetoxy-1,1,2-triphenyl-ethanol to 15 gave the alcohol 16[5] in 60% yield (C.24 S:R=4.5:1). After transesterification of 16 with methanol, protection of the free hydroxyl as its

Scheme II



a) Thiocarbonyldiimidazole (3.0 equiv), CH_2ClCH_2Cl, reflux. b) Bu_3SnH (1.5 equiv), xylenes, 140°C, 45 min. c) Bu_3SnH (2.0 equiv), AIBN (0.01 equiv), xylenes 140°C, 1 hr. d) Triisopropylsilyl triflate (1.3 equiv), 2,6-lutidine (2.2 equiv) CH_2Cl_2, 0°C. e) Me(MeO)NAlCl(Me), (2.0 equiv), toluene. f) Methyl triflate, 2,6-di-t-butyl-4-methyl pyridine, CH_2Cl_2, 22-24°C, 24 h. g) $(iBu)_2AlH$ (1.5 equiv), THF, -75°C, 1 hr. h) 2-lithio-2-triethylsilylpropanal t-butylimine (2.0 equiv), THF, -78°C to -10°C. i) 13, n-Bu_2BOTf, Diisopropylethylamine, -78°C to 0°C, CH_2Cl_2, 2 h. j) Me(MeO)NAlCl(Me), (2.0 equiv), -20°C to 22°C, 12 h, CH_2Cl_2. k) Triethylsilyl triflate (1.5 equiv), 2,6-lutidine, (2.5 equiv), CH_2Cl_2, 0°C. l) S(-)-2-acetoxy-1,1,2-triphenylethanol (1.5 equiv) LDA (1.5 equiv), THF, -78°C. m) NaOMe, methanol, 0°C. n) $(i\text{-}Bu)_2AlH$ (2.5 equiv), THF, 0°C. o) Pyr-SO_3, Et_3N (4.0 equiv), DMSO-CH_2Cl_2, 22°C to 24°C. p) 18, n-Bu_2BOTf, Diisopropylethylamine, CH_2Cl_2, -78°C to 0°, 3 hr. q) t-Butyl- dimethylsilyl triflate (2.0 equiv), 2,6-lutidine (3.0 equiv), CH_2Cl_2, 0°C.

TIPS-ether, reduction of the carboxymethyl group with diisobutylaluminum hydride, and oxidation with sulfur trioxide-pyridine (66% yield from 16) the resulting aldehyde 17[5] was treated with imide 18 to give the hydroxy-imide 19[5] in 95% yield. Weinreb aminolysis[6] and protection of the free hydroxyl as its TBDMS-ether then gave the highly functionalized and fully protected C.20-C.34 FK-506 fragment 20[5].

Thus we have demonstrated efficient methodology for both the synthesis of the (1R,3R,4R)-3-methoxy-4-hydroxy-1-cyclohexane carboxaldehyde and its subsequent diastereospecific transformation to a fully protected C.20-C.34 carbon fragment of FK-506. Homologation and coupling with the C.10-C.18 segment[2] will be reported in due course.

References and Notes

1. Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; and Hashimoto, M.; Aoki, H.; Imanaka, H.; J. Am. Chem. Soc., 1987, 109, 5031.
2. Askin, D., et al. See accompanying communication.
3. Findlay, J.A.; Radics, L.; Can. J. Chem. 1980, 58, 579.
4. Philippe, M.; Supulchre, A.M.; Gero, S.D,; Loibner, H.; Streidher, W.; Stutz, P. J. Antibiotics 1982, 35, 1507.
5. Satisfactory ^{1}H NMR, ^{13}C NMR, IR and mass spectra were obtained for this compound.
6. Levin J.I.; Turos, E.; Weinreb, S.M. Syn Communications 1982, 12 989; Nahm, S.; Weinreb, S.M. Tetrahedron Lett. 22, 1981, 3815; Basha, A.; Lipton, M.; Weinreb, S.M. Tetrahedron Lett. 1977, 4171.
7. Schlessinger, R.H.; Poss, M.A.; Richardson, S.; Lin, P. Tetrahedron Lett. 1985, 26, 2391; Corey, E.J.; Enders, D.; Bock, M.G. Tetrahedron Lett. 1976, 7.
8. Evans, D.A. Bartroli, J.; Shih, T.L. J. Am. Chem. Soc. 1981, 103, 2127; Evans, D.A. Aldrichima Acta, 1982, 15, 23.
9. Braun, M.; Devant, R. Tetrahedron Lett. 1984, 25, 5031.

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