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Studies Directed Towards the Synthesis of Rapamycin : Stereoselective Synthesis of C-1 to C-15 segment.

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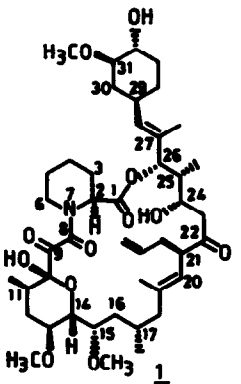
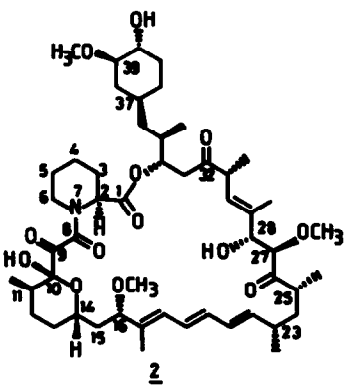
Abstract : Stereoselective synthesis of a suitably functionalized C-1 to C-15 segment of rapamycin is described.

The impressive immunosuppressant activity of the two macrolide lactones, FK-506 (**1**)[1] and rapamycin (**2**)[2] has inspired several synthetic organic chemists to work on developing new avenues towards their synthesis. Despite their structural similarity and the fact that they bind to the same immunophillin (FKBP), they have different modes of action in suppressing T-cell activation at different stages. FK-506 has been exhaustively studied from the synthetic point of view[3], including two reports on its total synthesis[4]. In contrast, the chemistry of rapamycin has been explored less[5], except for the recent report of its total synthesis by Nicolaou's group[6].



1



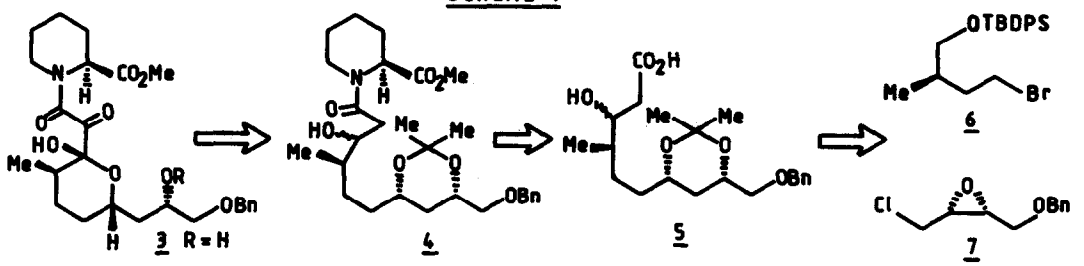
2

We earlier reported[7] the synthesis of C-1 to C-20 and C-20 to C-34 segments of FK-506. Both FK-506 and rapamycin have in common the tricarbonyl subunit which has been demonstrated to be the "key structural unit" responsible for their immunosuppressant activity[8]. We now report a stereoselective synthesis of this key segment (**3**) of rapamycin[9].

Scheme 1 depicts the retrosynthesis of C-1 to C-15 segment (**3**). The methyl ester of L-pipecolic acid was coupled with the acid **5**, followed by Dess-Martin oxidation of the resultant amide to give **3**. Our synthetic approach towards the construction of **5** is based on the coupling of (R)-4-bromo-2-methyl-butanolsilyl ether (**6**) with the epoxychloride (**7**), making use of the base-induced double elimination protocol to give the propargylic alcohol which could be transformed to **5**.

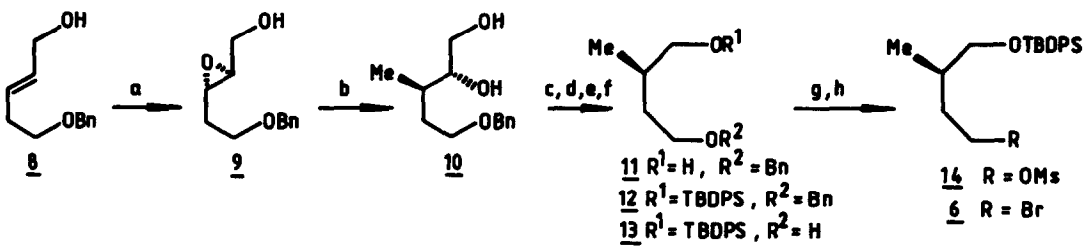
IICT Communication No. 3257

SCHEME-1



Scheme 2 outlines the synthesis of **6** starting with the epoxyalcohol (**9**), obtained by Sharpless epoxidation[10] of **8** with (+) DET as the chiral auxiliary in 95% ee. The regioselective opening of **9** with Me_3Al in pentane : DCM (90:10) proceeded smoothly to provide the diol **10**[11], $[\alpha]_D$ +3.9 (c 1.0, $CHCl_3$) in 90% yield. Periodate cleavage of **10**, followed by $NaBH_4$ reduction afforded the alcohol **11**. Silylation followed by hydrogenolysis[12] gave the alcohol **13**, $[\alpha]_D$+4.7° (c 3.3, $CHCl_3$) in 80% yield. Mesylation of **13** followed by treatment with LiBr in THF furnished the bromide[13] (**6**) in 60% yield.

SCHEME-2

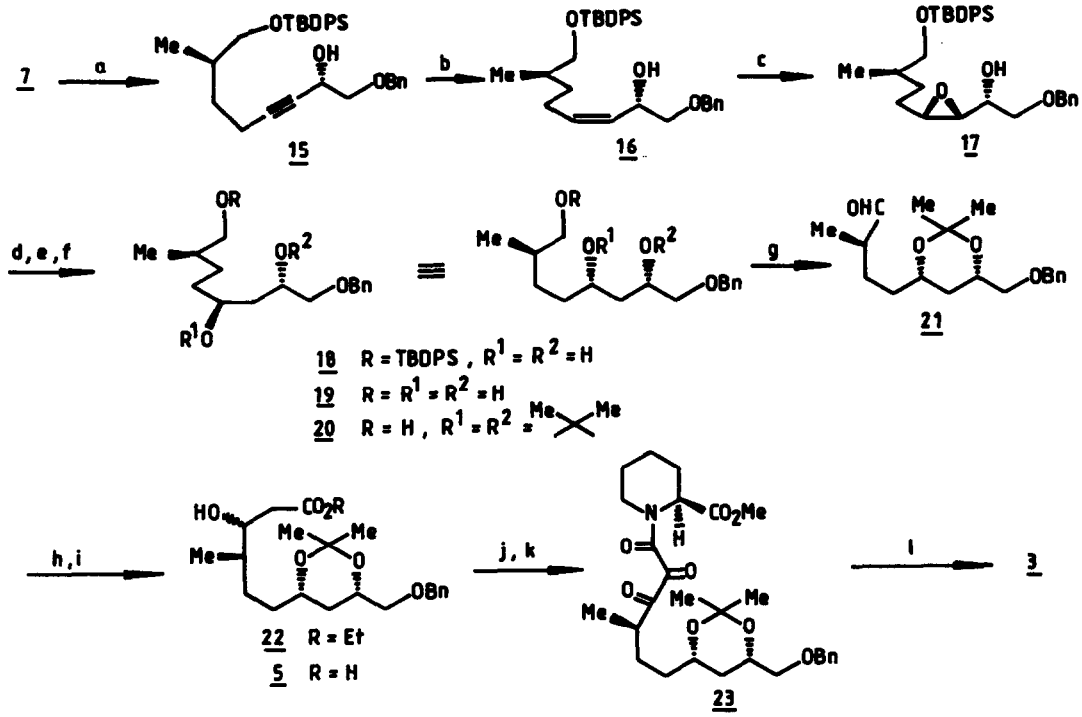


a) +DET, TBHP, TIP, 3A molecular sieves; b) Me_3Al, pentane:DCM (90:10), 23°C; c) $NaIO_4$, THF:H_2O (1:1), 0°C; d) $NaBH_4$, MeOH, 0°C; e) TBDPSCl, imidazole, DMF, 0°C; f) H_2, 10% Pd-C, MeOH, r.t.; g) MsCl, TEA, DCM, 0°C; h) LiBr, $NaHCO_3$, THF, r.t.

Scheme 3 summarizes the coupling of **6** with the epoxychloride (**7**) by base via the chiral propargylic alcohol generated in situ[14] to give **15**, $[\alpha]_D$ +3.0° (c 2.5, $CHCl_3$) in 60% yield. Selective hydrogenation of the acetylene derivative over Lindlar's catalyst gave the cis olefin[15] **16** in 95% yield. Sharpless epoxidation[10] using (-)DIPT furnished the epoxyalcohol **17** $[\alpha]_D$ +16.0 (c 0.5, $CHCl_3$) (85% ee) in 60% yield based on the recovery of starting material[16]. Regioselective reductive opening with Red-Al at ambient temperature in THF yielded the diol **18** $[\alpha]_D$ +15.0° (c 0.5, $CHCl_3$) as the major product[17] in 75% yield. Desilylation with Bu_4NF followed by protection of the 1,3-diol resulted the acetonide **20**. Swern oxidation of **20** gave the aldehyde **21** in 80% yield which was then subjected to Reformatsky reaction with Zn/ethyl bromoacetate to afford the ester (**22**) in 70% yield. As expected, the Reformatsky reaction did not show any selectivity and proceeded to give a 1:1 mixture of diastereomers as was evident from its ^1H NMR spectrum. However, since the hydroxyl group was to be oxidized at a later stage, we did not make efforts to separate these diastereomers. Mild hydrolysis of **22** with LiOH in dime-

thoxyethane provided the desired acid **5** in 70% yield.

SCHEME- 3



a) $LiNH_2/NH_3$, -33°C, 2h, 6, -33°C, 16 h; b) Lindlar's catalyst, quinoline, MeOH; c) (-) DIPT, TIP, TBHP, 3A molecular sieves, DCM; d) Red-Al, THF, r.t.; e) Bu_4NF, THF, r.t.; f) Acetone, PTSA; g) $(COCl)_2$, DMSO, TEA, DCM, -78°C; h) Zn, $BrCH_2CO_2Et$, benzene, reflux; i) LiOH, DME; j) Pentafluorophenol, DMAP, DCC, L-pipecolic acid methyl ester, DCM; k) Dess-Martin periodinanne, pyridine, DCM; l) 0.001N HCl in methanol.

The active ester generated in situ from the acid **5** using pentafluorophenol and dicyclohexylcarbodiimide was coupled with the L-pipecolic acid methyl ester[7] to yield the amide **4** in 75% yield. Dess-Martin oxidation[18] of the amide **4** afforded the triketo segment **23** in 60% yield which on acetonide hydrolysis furnished the hemiketal **3** as a mixture of rotamers in 70% yield the spectral data of which was comparable with reported data[19].

In summary, the asymmetric synthesis of the key tricarbonyl segment **3** of rapamycin has been accomplished from readily available precursors. Work on these lines culminating in the synthesis of rapamycin (**2**) is being pursued.

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9. The spectroscopic properties of all new compounds were fully consistent with the assigned structures. Yields refer to homogenous isolated compounds.

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12. Desilylation or silyl migration was not noticed under these conditions.

13. Alternatively the bromide was synthesised from the commercially available synthon methyl S(+)3-hydroxy-2-methyl propionate in 6 steps.

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15. Cis olefin confirmed from characteristic PMR pattern of olefinic protons ($CDCl_3$): δ5.55 (dt, J 11.0, 7.4 Hz), 5.38 (dd, J 9.3 Hz).

16. Recovered starting material was recycled the overall yield being 35%. Ti(O-i-Pr)$_4$ and (-) DIPT were used in stoichiometric ratios. Characteristic PMR pattern of cis epoxide protons ($CDCl_3$): δ 2.97 (dt, J 10 Hz, 4 Hz), 2.94 (dd, J 7.2 Hz). For epoxidations with other reagents see Murphy P.J.; Procter, G.; Tetrahedron Lett. **1990**, 31, 1059.

17. The periodate cleavage removed the 1,2-diol formed as a minor product.

18. For oxidation of amide alcohols to tricarbonyls see a) Batchelor, M.J.; Gillespie, R.J.; Golec, M.C.J.; Hedgehock, C.J.R. Tet. Lett. **1993**, 34, 167; for references see b) Dess, D.B.; Martin, J.C. J. Am. Chem. Soc. **1991**, 113, 7277.

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