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Studies Towards the Total Synthesis of Rapamycin: Preparation of the Cyclohexyl C_{33}-C_{42} Fragment and Further Coupling to Afford the C_{22}-C_{42} Carbon Unit.

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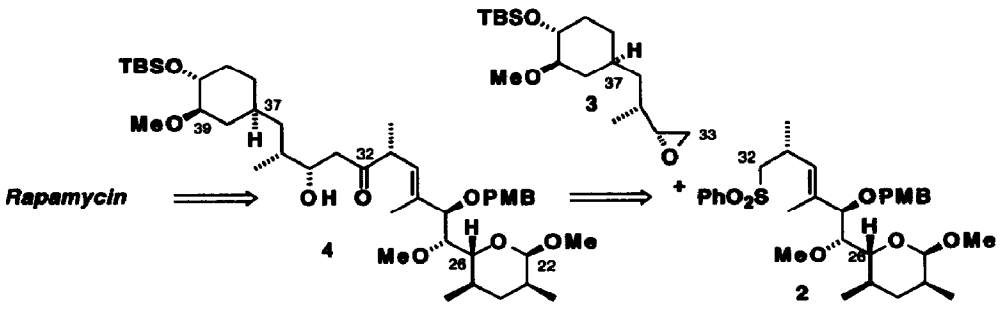
Abstract: A short and stereoselective synthesis of the C_{33}-C_{42} fragment **3** of rapamycin and its coupling with the previously prepared C_{22}-C_{32} fragment **2** is described. The synthesis of **3** involves the preparation of enantiomerically enriched methylene cyclohexane derivative **7**, followed by side-chain elaboration. The coupling is made by reaction of the lithio anion of the dithioacetal monosulfone **11** on the epoxide **3**.

In the previous paper,[1] we reported our general synthetic plan towards the potent immunosuppressive agent rapamycin.[2] We also described the synthesis of the C_{22}-C_{32} portion **2** of this molecule. Here we discuss the preparation of the C_{33}-C_{42} cyclohexyl epoxide fragment **3** and its subsequent coupling with **2** to afford a fully functionnalized C_{22}-C_{42} carbon framework **4** necessary for later transformation to the natural product (Scheme 1).

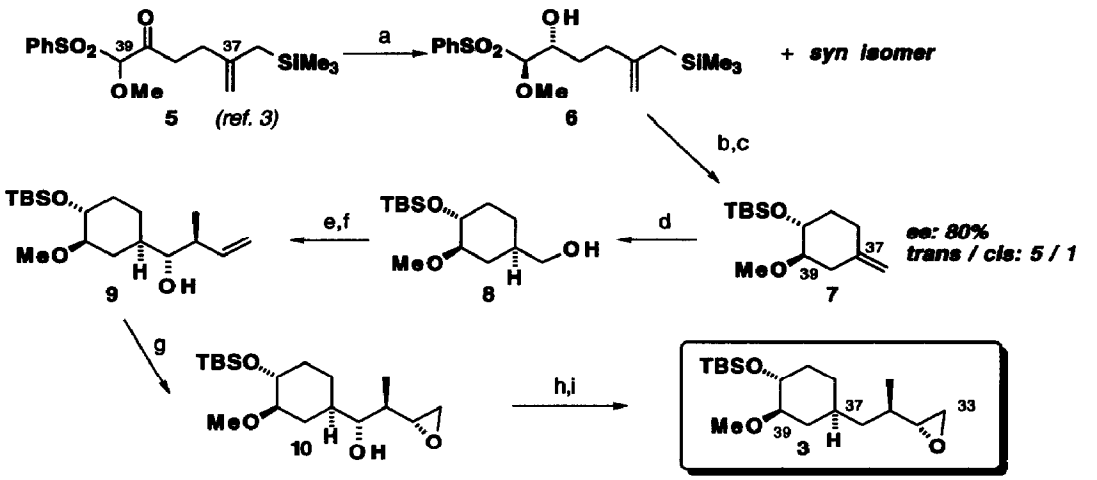
Scheme 1



For the synthesis of **3**, we have developed a method for the stereoselective synthesis of methylene cyclohexane derivatives as key intermediates, involving intramolecular reaction of an allylsilane with an oxonium cation generated from an α-alkoxysulfone.[3] Thus, the previously prepared β-ketosulfone **5** was

subjected to asymmetric reduction using borane.DMS and 10% of the CBS oxaborolizidine catalyst[4] to give the β-hydroxysulfone **6** along with the *syn* isomer in the ratio of 1:2 in quantitative yield.[5] The enantiomeric excess of the *anti* isomer was determined to be of 80%.[6] The unwanted *syn* isomer could be readily oxidized (PDC, DCM) to **5** for recycling. The *anti* isomer **6**, after silylation with *tert*-butyldimethylsilyl trifluoromethane sulfonate (TBS triflate) was treated with a solution of tin tetrachloride in dichloromethane at -78°C to give **7** in 60% overall yield, as a 5:1 ratio of *trans/ cis* isomers. Hydroboration of **7** to the alcohol **8** proceeded well and the minor stereoisomer from cyclization was removed at this stage.[7] Following oxidation of **8** using Swern conditions[8] to give the intermediate aldehyde, addition (-)-(*E*) crotyl diisocampheylborane afforded, after oxidative work-up, **9** as the major product in 64% yield, readily separable from any contaminating isomers. The hydroxyl group in the side chain is ideally placed to direct the final epoxidation reaction using standard conditions[9] (TBHP, $VO(acac)_2$) to give **10** as a 4:1 mixture of diastereoisomers readily separable by chromatography. The major isomer was further deoxygenated *via* its thionocarbonate derivative by reduction with tributyltin hydride[10] to give the desired epoxide **3**[11] in 70% yield for two steps (Scheme 2).

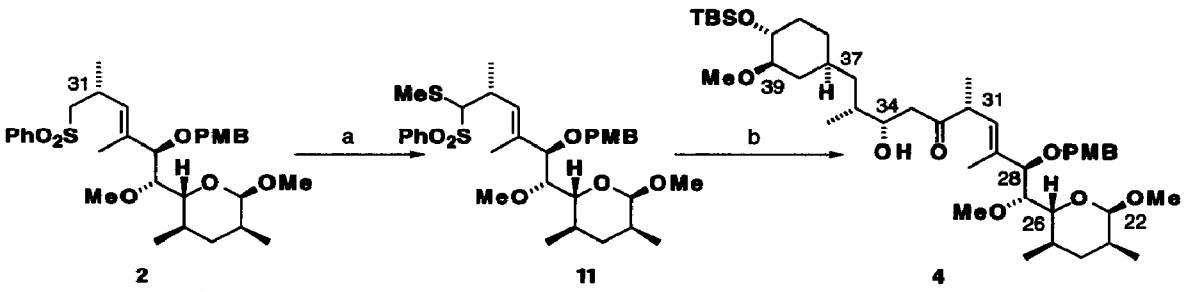
Scheme 2



a: BH_3/ DMS, 10% CBS, THF, 100%; *syn / anti*: 2:1; *ee anti*: 80%;b: TBSOTf, Pyridine, DMAP, CH_2Cl_2, 0°C; c: $SnCl_4$, CH_2Cl_2, -78°C, 60% overall; d: 9-BBN, THF, 0° to 25°C, H_2O_2, NaOH, 80%, separation of isomers; e: $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 90%; f: (-)-(*E*)-$(iPc)_2$-CH_2-CH=CH-CH_3, THF/ Et_2O, -78°C, H_2O_2, OH^-, separation of diastereoisomers; 70%; g: ^tBuOOH, $VO(acac)_2$, CH_2Cl_2, 90%; h: ^nBuLi, THF, -20°C, ClC(=S)OPh, 85%; i: $^nBu_3SnH$, AIBN, Benzene, reflux, 80%.

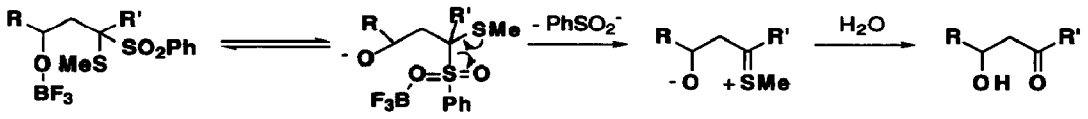
For the coupling of the components, we have chosen to use the methodology of Tokate[12] and co-workers whereby α-sulfenyl sulfones are used as acyl anion equivalents. Accordingly, sulfone **2** was deprotonated (^tBuLi, THF, -78°C) and treated with dimethyl disulfide to give **11** as a 1:1 mixture of diastereoisomers (81% yield) which was not purified but directly used in the next reaction. Thus, deprotonation of **11** (^tBuLi, THF, -78°C), addition of a solution of the epoxide **3** (1.1 eq.) followed by addition of boron trifluoride etherate (BF_3 etherate, 2 eq.) gave after 2 h (-78° to 0°C) the coupled product **4** in an unoptimised 46% yield (Scheme 3).

Scheme 3



It is interesting to notice that upon work-up **4** is obtained with the ketone function already deprotected[13]. According to the work of Tokate, the hydrolysis of dithioketal monosulfones requires stronger conditions and long reaction times ($CuCl_2$, SiO_2 or anodic hydrolysis). In our case, we attribute the easy hydrolysis to the presence of BF_3 etherate which can hydrolyse *in situ* the dithioketal to thioketone derivative (Scheme 4). This explains the need for two equivalents of BF_3 etherate in the coupling reaction.

Scheme 4



In conclusion, in a short sequence of reactions, the epoxide **3** has been prepared and coupled to a derivative of **2** to afford the C_{22}-C_{42} carbon framework of rapamycin. Further functional group manipulation and completion of the synthesis are currently under investigation and will be reported in due course.

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References and footnotes

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4. Corey, E.J., Bashki, R.K. and Shibata, S., *J. Am. Chem. Soc.*, **1987**, *109*, 5551; this catalyst was derived from (+) L-proline and prepared according to the procedure of Merck & Co: Mathre, D.J., Jones, T.K., Xavier, L.C., Blacklock, T.J., Reamer, R.A., Mohan, J.J., Tirner Jones, E.T., Hoogsteen, K., Baum, M.W. and Grabowski, E.J.J., *J. Org. Chem*, **1991**, *56*, 751.
5. Satisfactory spectral and analytical data were obtained for all the proposed structures. Complete experimental data for intermediates **5**, **6** and **7** (as racemic mixtures) can be found in ref. 3.
6. The enantiomeric excess of *anti* **6** was diffucult to determinate by derivatization due to the low reactivity of the hydroxyl function. It was found easier to determinate the *ee* on a later intermediate.
7. The *ee* of **8** was determinated to be ca. 80% by ^{19}F NMR analysis of the Mosher's ester derivative. Desilylation of **8** (HF, CH_3CN) furnished (*1R 2R 4R*) 4-hydroxymethyl 2-methoxy 1-cyclohexanol, $[\alpha]_D$ -45 (*c*= 0.6, $CHCl_3$), which is a degradation product of FK-506 and the optical rotation of which is reported to be -57 (*c*= 0.5, $CHCl_3$): Tanaka, H., Kuroda, A., Murasawa, H., Hatanaka, H., Kino, T., Goto, T., Hashimoto, M. and Taga, T., *J. Am. Chem. Soc.*, **1987**, *109*, 5031.
8. Mancuso, A.J. and Swern, D., *Synthesis*, **1981**, 165.
9. Mihelich, E.D., Daniels, K. and Eickoff, D.J., *J. Am. Chem. Soc.*, **1981**, *103*, 7690.
10. Robins, M.J. and Wilson, J.S., *J. Am. Chem. Soc.*, **1981**, *103*, 932.
11. Data for epoxide **3**: $[\alpha]_D$= -20.95 (*c*= 0.99, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, rapamycin numbering): δ (ppm): 3.39 (3H, s, OMe), 3.38 (1H, partially obscured m, C_{39}-H), 2.89 (1H, dt, J= 9 and 2 Hz, C_{40}-H), 2.67 (2H, m, C_{33}-H x 2), 2.45 (1H, ddd, J= 6, 5 and 3, C_{34}-H), 2.02 (1H, dt, J= 9 and 2, C_{38}-H ax.), 1.82 (1H, m, C_{35}-H), 1.67 (1H, m, one of C_{41}-H), 1.48 (1H, m, one of C_{42}-H), 1.45-1.35 (3H, m, one of C_{36}-H, C_{37}-H and one of C_{41}-H), 1.22 (1H, m, one of C_{36}-H), 0.91 (1H, partially obscured m, one of C_{42}-H), 0.90 (3H, d, J= 7 Hz, C_{35}-Me), 0.88 (9H, s, ^{t}BuSi), 0.83 (1H, partially obscured m, C_{38}-H eq.), 0.07 and 0.05 (6H, 2s, Me_2Si); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 84.5 (C_{39}), 75.7 (C_{40}), 58.0 (C_{34}), 57.2 (OMe), 45.5 (C_{33}), 41.7 (C_{36}), 36.6 (C_{38}), 33.9 (C_{41}), 33.5 (C_{37}), 33.2 (C_{35}), 31.3 (C_{42}), 25.9 ((CH_3)$_3$-C-Si), 18.2 (Me_3-C-Si), 16.1 (C_{35}-CH_3), -4.5 and -4.7 (Me_2-Si); Mass (EI): m/z: 329 ($MH^{+\cdot}$), 328 ($M^{+\cdot}$), 313 (M-Me), 271, 239, 165, 147, 135, 121, 105, 89 (100%), 73; HRMS calculated for $C_{18}H_{36}O_3Si$; Calc: 328.2433: Found: 328.2405.
12. Murata, Y., Inomata, K., Kinoshita, H. and Tokate, H., *Bull. Chem. Soc. Jpn.*, **1983**, *56*, 2534.
13. Data for compound **4**: ^1H NMR (400 MHz, $CDCl_3$, rapamycin numbering): δ (ppm): 71.7 and 6.84 (2H, 2d, J= 8.3 Hz, Ar-H), 5.76 (1H, d, J= 9, C_{30}-H), 4.53 (1H, d, J= 3, C_{22}-H), 4.35 (1H, m, C_{34}-H), 4.20 and 4.11 (2H, 2d, J= 10, CH_2-Ar), 3.97 (1H, d, J= 8, C_{28}-H), 3.79 (3H, s, OMe), 3.71 (1H, m, probably OH), 3.68 (1H, d, J= 7, C_{26}-H), 3.40 (3H, s, OMe), 3.39 (1H, partially obscured m, C_{39}-H), 3.28 (3H, s, OMe), 3.25 (3H, s, OMe), 3.30 (1H, masked d, C_{27}-H), 2.91 (1H, dt, C_{40}-H), 2.32-2.22 (3H, m, C_{31}-H and C_{33}-H x 2), 2.05 (1H, m, one of C_{38}-H), 1.88 (2H, m, C_{23}-H and C_{25}-H), 1.76 (2H,m, C_{35}-H and one of C_{41}-H), 1.55 (3H, d, J= 0.8, C_{29}-Me), 1.60-1.36 (5H, m, one of C_{24}-H, C_{36}-H x 2, C_{37}-H and one of C_{42}-H, 1.28-1.12 (2H, m, one of C_{24}-H and one of C_{41}-H), 0.95 (3H, d, J= 7, C_{35}-Me, 0.91 (1H, masked m, one of C_{42}-H, 0.88 (18H, broad s, ^{t}BuSi, C_{23}-Me, C_{25}-Me and C_{31}-Me), 0.83 (1H, masked m, one of C_{38}-H, 0.07 and 0.06 (6H, 2s, Me_2Si); the presence of the ketone function is further confirmed by a signal at 216.3 ppm on the ^{13}C spectrum (50 MHz, $CDCl_3$); Mass (FAB): m/z: 763 ($MH^{+\cdot}$), 744 (M- H_2O), 655, 637, 623, 605, 591, 587, 467, 437; HRMS calculated for $C_{43}H_{75}O_9Si$ ($MH^{+\cdot}$): Calcd: 763.5180; found: 763.5187.

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