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Studies Towards the Total Synthesis of Rapamycin: Preparation of the C_{10}-C_{17} Carbon Unit.

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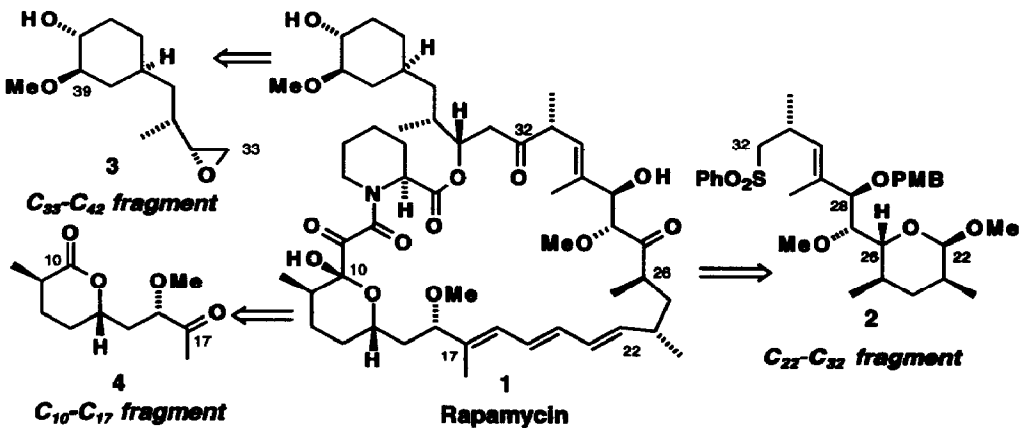
Abstract: The preparation of the C_{10}-C_{17} carbon unit of the immunosuppressive agent rapamycin is reported *via* two routes leading to the substituted lactone **4**.

In the preceeding papers we have delineated our synthetic strategy towards the immunosuppressive agent rapamycin **1**.[1] We also reported on the preparation of key coupling components **2** and **3** for this synthesis and here we describe the construction of the lactone component **4** which constitutes the C_{10}-C_{17} carbon portion of rapamycin (Scheme 1).

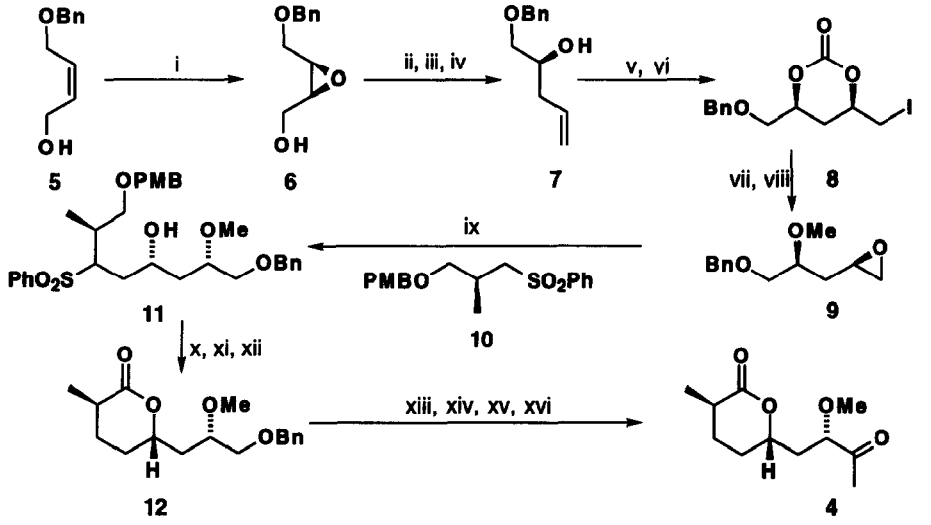
Scheme 1



We have devised two routes to the synthesis of **4** which employ a common allylic alcohol **5** as starting material (Scheme 2).[2] In the first of these syntheses **5** was subjected to an asymmetric Sharpless epoxidation to give **6** in 75% yield with an enantiomeric excess of 92%.[3,4] Epoxide **6** was then readily transformed to the alkene **7** by pyridine-sulfur trioxide activated dimethylsulfoxide oxidation,[5] Wittig methylenation and selective opening of the epoxide[6] in 41% overall yield. Compound **7** was converted to the cyclic carbonate **8** using reaction conditions described by Smith.[7] The stereoselectivity obtained was generally very good (diastereoselectivity typically of 11:1), however the yields tended to vary between 30 and 57%. Nevertheless,

with good supplies of **8** in hand this was converted to the terminal epoxide **9** by reaction with potassium carbonate in methanol followed by Purdie methylation[8] with methyl iodide and silver oxide in 95% yield. Epoxide **9** was then coupled with the lithio anion generated from the sulfone **10**[9] to give **11** in excellent yield employing $BF_3{\cdot}Et_2O$ to promote epoxide ring opening.[10] This product was converted to the lactone **12**[11] in a sequence of reactions involving desulfonation by lithium naphthalenide reduction, deprotection of the *para*methoxybenzyl group and finally selective oxidation with tetra-*n*-propylammonium perruthenate (TPAP[12]) to afford **12** in 83% yield.[13] Further elaboration of the side chain of **12** involved hydrogenolysis of the benzyl group, oxidation with the Dess-Martin periodinane reagent,[14] methyl Grignard addition and a second oxidation which afforded the key lactone coupling partner **4** in 70% yield over the four steps (Scheme 2).[15] This synthetic lactone **4** was identical to a sample previously obtained from the degradation of rapamycin.[16]

Scheme 2

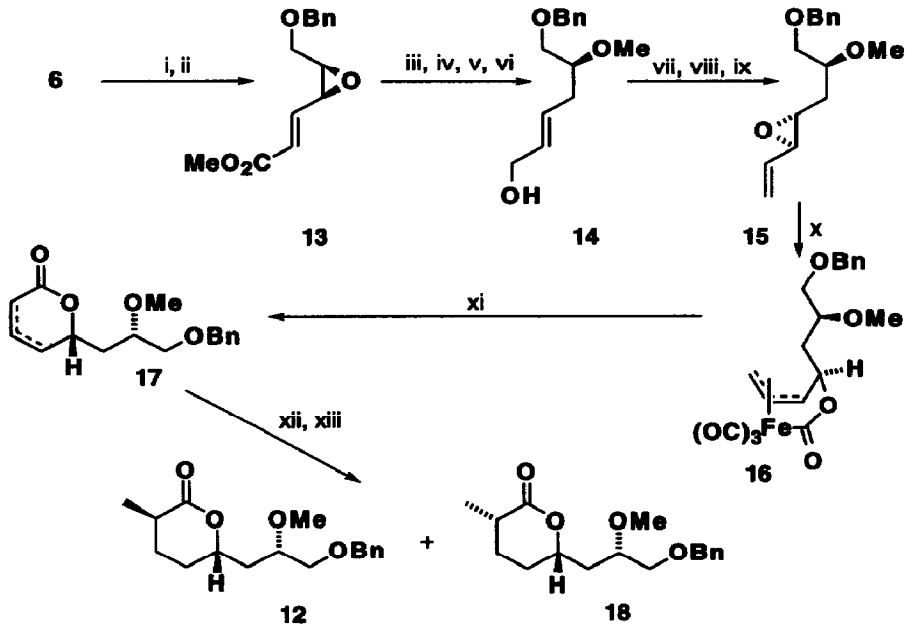


i) $Ti(O^iPr)_4$, (+)-diethyl tartrate, ^{t}BuOOH, CH_2Cl_2, -25°C, 75%; ii) py.SO_3, Et_3N, DMSO, CH_2Cl_2, 0°C to rt; iii) $MePPh_3Br$, KHMDS, THF, 0°C to rt; iv) DIBAL-H, toluene, -78°C, 41% overall; v) ^{n}BuLi, Et_2O, rt, followed by BOC-ON, THF, rt, 90%; vi) IBr, toluene, CH_2Cl_2, -85°C, 30-57%; vii) K_2CO_3, MeOH, rt, 90%; viii) MeI, Ag_2O, DMF, rt, 95%; ix) **10**, ^{n}BuLi, THF, -78°C, followed by **9**, $BF_3.Et_2O$, THF, -78°C to rt, quant.; x) 1M Lithium naphthalenide, THF, -90°C, 72-93%; xi) DDQ, CH_2Cl_2, H_2O, rt, quant.; xii) TPAP, NMO, CH_2Cl_2, 4Å powdered molecular sieves, 83%; xiii) $Pd(OH)_2$/ C, H_2, 1 atm., EtOAc, rt, quant.; xiv) Dess-Martin periodinane, ^{t}BuOH, py, CH_2Cl_2; xv) MeMgBr, Et_2O, THF, -78°C; xvi) Dess Martin periodinane, ^{t}BuOH, py, CH_2Cl_2, 70% overall.

In a conceptually different approach[17] to the same lactone **12** we have explored the use of π-allyltricarbonyliron lactone complexes as precursors as these have proved useful to us in several other natural product syntheses.[18] The previously synthesised epoxide **6** was therefore oxidised and treated with methyl diethyl phosphonoacetate to give **13** with excellent *E* selectivity (Scheme 3). Following DIBAL reduction and conversion to the allylic alcohol **14** this was subjected to a catalytic Sharpless epoxidation. Oxidation using TPAP and a Wittig reaction afforded the alkenyl epoxide **15**,[19] in 90% diastereomeric excess as the precursor for the iron carbonyl chemistry. Reaction of **15** with $Fe_2(CO)_9$ in THF[20] gave the *endo* complex

16[21] as the predominant product in 72% yield. Exhaustive carbonylation[22] with CO at 280 atm in benzene at 70°C gave **17** in 85% yield as a mixture of α,β– and β,γ–unsaturated lactones in a ratio of 7:3 respectively. Hydrogenation employing Adam's catalyst and methylation afforded the required lactone **12** which was identical to the sample prepared previously, together with the epimeric lactone **18**.[23] At present this methylation, using lithium diisopropylamide as base and quenching with methyl iodide, gives **18** and **12** in a 60:40 ratio.[24] However it is possible to recycle **18** *via* deprotonation/reprotonation to provide further supplies of **12**.

Scheme 3



i) $Py.SO_3$, Et_3N, DMSO, CH_2Cl_2, 0°C to rt, 80%; ii) LiCl, $(EtO)_2P(O)CH_2CO_2CH_3$, DBU, CH_3CN, rt, 68%; iii) DIBAL-H, CH_2Cl_2, -78°C; iv) PivCl, py, CH_2Cl_2, 0°C, 69% overall; v) NaH, MeI, 0°C, 94%; vi) DIBAL-H, CH_2Cl_2, -78°C, 88% vii) 10% $Ti(O^iPr)_4$,14% (-)-diethyl tartrate, ^tBuOOH, 4Å powdered molecular sieves CH_2Cl_2, -23°C, 80%; viii)TPAP, NMO, CH_2Cl_2, CH_3CN, 4Å powdered molecular sieves, 60%; ix) $MePPh_3Br$, KHMDS, THF, 0°C to rt, 83%; x) $Fe_2(CO)_9$, degassed THF, 72%; xi) CO, 280 atm., benzene, 70°C, 2 days, 85%; xii) PtO_2, H_2, 1 atm., EtOAc, rt, 82% xiii) LDA, THF, -78°C, MeI, 80%.

In summary, we have devised two routes to the lactone **4** which we intend using as the C_{10}-C_{17} carbon unit during our synthesis of rapamycin.

Couplings of the fragments which have been proposed here and in the preceeding papers will be reported at a later date.

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References and footnotes

1. i) Anderson, J.C., Ley, S.V., Marsden, S.P. ii) Kouklovsky, C., Ley, S.V., Marsden, S.P., preceeding papers in this issue.
2. *cis*-4-Benzyloxy-2-buten-1-ol, **5** was purchased from Aldrich Chemical Company, Inc. and used without purification.
3. Satisfactory spectral and analytical data were obtained for all proposed structures.
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8. Purdie, T., Irvine, J.C., *J. Chem. Soc. Perkin Trans. II*, **1903**, *83*, 1021.
9. Sulfone **10** was prepared by known transformations from the commercially available methyl-(*R*)-3-hydroxy-2-methylpropionate.
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11. Data for **12**: $[\alpha]_D$= + 16.76 (*c*= 0.72, $CHCl_3$); IR ($CHCl_3$): ν_{max} (cm^{-1}): 2932, 2873, 1728, 1495, 1454, 1376, 1361, 1241, 1177, 1092, 1035, 749, 699; ^1H NMR (250 MHz, $CDCl_3$, rapamycin numbering): δ (ppm): 7.31 (5H, m, Ar-H), 4.53 (2H, 2d, J= 12 Hz, CH_2-Ar), 4.32 (1H, m, C_{14}-H), 3.55 (3H, m, C_{16}-H and C_{16}-H x 2), 3.37 (3H, s, OMe), 2.39 (1H, m, C_{11}-H), 1.90 (4H, m, C_{12}-H x 2 and C_{13}-H x 2), 1.57 (2H, m, C_{15}-H x 2), 1.19 (3H, d, J= 7 Hz, C_{11}-Me). ^{13}C NMR (50 MHz, $CDCl_3$):δ (ppm): 174.2 (C=O), 138.2, 128.4, 127.8 and 127.7 (Ar), 78.9 (C_{16}), 76.4 (CH_2-Ar), 73.3 (C_{17}), 70.5 (C_{14}), 57.2 (OMe), 37.7 (C_{15}), 36.1 (C_{11}), 29.3 (C_{13}), 28.5 (C_{12}), 17.4 (C_{11}-Me); mass (EI): m/z: 292 ($M^{+\cdot}$), 246, 204, 171, 160, 149, 113, 91, 85; HRMS, calculated for $C_{17}H_{24}O_4$: calcd: 292.1674; found: 292.1670.
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15. Data for **4**: ^1H NMR, δ ppm (400 MHz, $CDCl_3$) : 1.28 (3H, d, J 7Hz), 1.59 (2H, m), 1.92 (2H, m), 2.05 (2H, m), 2.21 (3H, s), 2.42 (1H, m), 3.38 (3H, s), 3.76 (1H, t, J 6Hz), 4.44 (1H, m).
16. Ley, S.V., Cappi, M.W., unpublished results.
17. We thank Dr. Roberto D' Alessio for initial studies in this area.
18. i) Horton, A.M., and Ley, S.V., *J. Organomet. Chem.*, **1985**, 285, C17-C20. ii) Ley, S.V., *Phil. Trans. R. Soc. Lond. A.*, **1988**, *326*, 633. ii) Diéz-Martin, D., Kotecha, N.R., Ley, S.V., Mantegani, S., Menéndez, J.C., Organ, H.M., White, A.D., *Tetrahedron*, **1992**, *48*, 7899.
19. The diastereomeric excess of **15** was determined by GC analysis.
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21. Data for complex **16**: ^1H NMR (400 MHz, C_6D_6): δ (ppm) : 7.33 (5H, s), 4.30 (2H, s), 4.19 (1H, dd, J 5, 12Hz), 3.86 (1H, dd, J 5, 8Hz), 3.62 (1H, dt, J 8, 13.2Hz), 3.34 (2H, d, J 1.5Hz), 3.28-3.41 (1H, m), 3.15 (3H, s), 2.77 (1H, dd, J 1.5, 8.4Hz), 2.72 (1H, dd, J 1.5, 13.2Hz), 1.74 (2H, dd, J 5, 7Hz); ^{13}C NMR (50 MHz, C_6D_6); δ (ppm) : 208.8, 207.1, 203.8, 200.1, 139.0, 128.3, 127.8, 90.8, 82.3, 78.1, 73.8, 73.4, 71.4, 58.5, 57.0, 38.8.
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23. Data for **18**: ^1H NMR (250 MHz, $CDCl_3$): δ (ppm): 7.33 (5H, m, Ar-H), 4.55 (2H, 2d, J= 12 Hz, CH_2-Ar), 4.33 (1H, m, C_{14}-H), 3.55 (3H, m, C_{16}-H and C_{16}-H x 2), 3.39 (3H, s, OMe), 2.49 (1H, m, C_{11}-H), 1.91 (4H, m, C_{12}-H x 2 and C_{13}-H x 2), 1.55 (2H, m, C_{15}-H x 2), 1.19 (3H, d, J= 7 Hz, C_{11}-Me). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm): 174.2, 138.1, 128.4, 127.8 and 127.7, 76.3, 74.9, 73.3, 70.5, 57.2, 36.8, 33.0, 26.8, 25.5, 16.0.
24. Lactones **12** and **18** are readily separable by HPLC.

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