Pergamon

Tetrahedron Letters, Vol. 35, No. 13, pp. 2087-2090, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0227-O

Studies Towards the Total Synthesis of Rapamycin: A Convergent and Stereoselective Synthesis of the C_{22}-C_{32} Carbon Framework.

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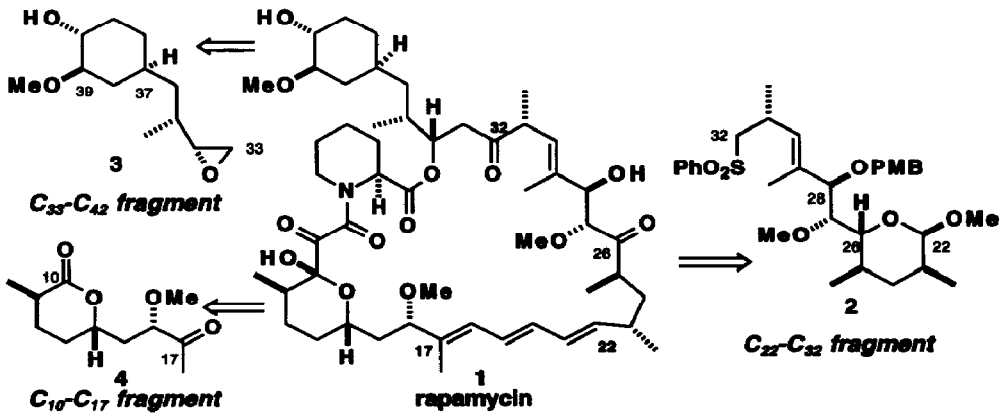
Abstract: A convergent synthesis of the C_{22}-C_{32} portion of rapamycin has been achieved by way of a Nozaki-Kishi coupling of vinyl iodide **14** with aldehyde **13**. This aldehyde is available by the stereoselective addition of organometallic reagents to aldehyde **5**, synthesised by either of two selenium mediated electrophilic cyclisations. Optically active starting materials for this synthesis are prepared by an enzymatic acylation of *meso*-diol **6**.

Rapamycin **1**, a 29-membered macrolide isolated in 1975 from *Streptomyces hygroscopicus*,[1] which in common with the structurally related natural product FK-506 displays potent immunosuppressive properties, has been the subject of intensive investigation. The complex structure of the molecule, together with the presence of many sensitive functional groups, has stimulated considerable synthetic interest, culminating in recent total syntheses.[2] In view of these recent developments, we wish to disclose our progress in the area.

Shown below are three major fragments from which we seek to construct rapamycin (Scheme 1); this paper details the synthesis of the C_{22}-C_{32} unit **2**, while the following papers report the synthesis of the C_{33}-C_{42} portion, together with its coupling with **2**, and the preparation of the lactone fragment **4**.[3]

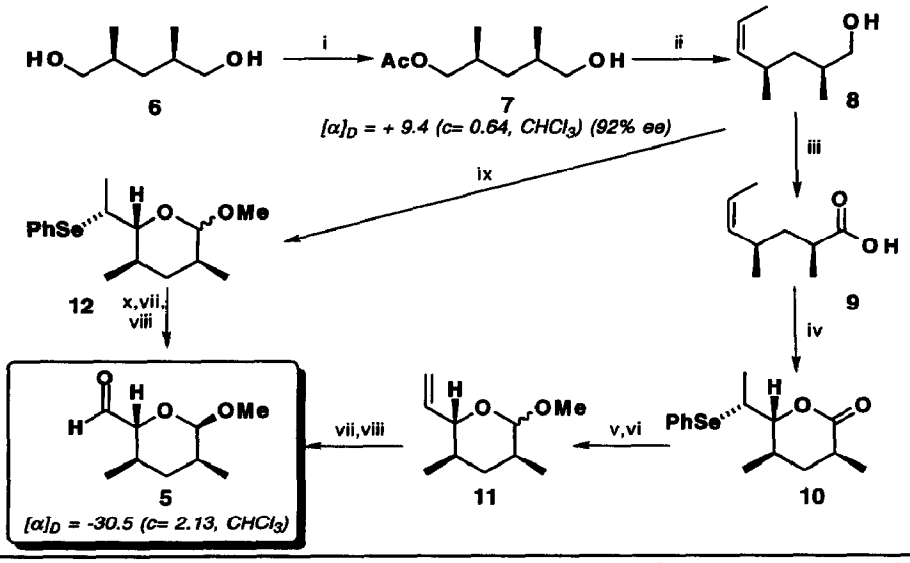
Scheme 1



One of the key strategic steps in our synthesis would be the coupling on an acyl anion equivalent at C_{32} with the epoxide **3**. For the synthesis of **2**, we wished to protect the potentially sensitive C_{22} centre at the aldehyde oxidation level, as a cyclic acetal with a reduced form of the C_{26} ketone. This strategy would also inhibit any unfavourable β-elimination processes from a C_{26} ketone. The cyclic acetal will not only be used as a protecting group but will also dictate, by stepwise transfer of chirality, the nature of the stereocentres at C_{27} and C_{28}.

Our first synthetic goal was therefore aldehyde **5**, which has the acetal in place together with a suitable functional group for the introduction of the C_{27} stereocentre. The starting material for this synthesis was the *meso*-diol **6**, the diacetate of which is known to undergo porcine pancreatic lipase catalysed monohydrolysis.[4] However, we found this procedure unsuitable for a large scale synthesis, and found a better procedure to be the use of crude porcine pancreatic lipase suspended on celite[5] to effect the enantioselective acyl transfer of diol **6** with methyl acetate. This provided monoacetate **7** in 55% yield (92% *ee*)[6] together with 33% of the diacetylated material.[7] Elaboration to ω-hydroxy alkene **8** and stepwise oxidation of the terminal hydroxyl group gave the olefinic acid **9**, which was subjected to known cyclisation conditions[8] using *N*-phenylselenophthalimide (N-PSP) and tin (IV) chloride to furnish lactone **10** in good yield (82%) (Scheme 2).

Scheme 2



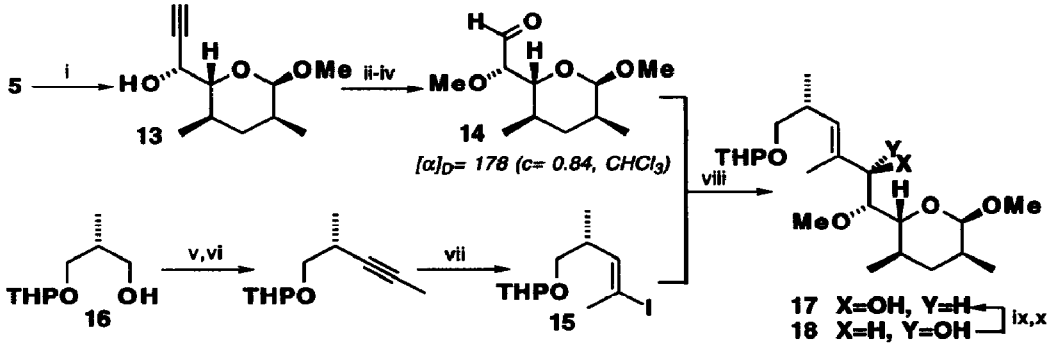
i) PPL on celite, MeOAc, 55%; ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 to 25°C, followed by $EtPPh_3Br$, ^nBuLi, THF, 0°C, followed by 3N NaOH, THF, Bu_4NOH (cat.), 60°C, 86% overall; iii) $(COCl)_2$, DMSO, Et_3N,CH_2Cl_2, -78 to 25°C, followed by NaO_2Cl, KH_2PO_4, 2-methyl-2-butene, $^tBuOH/H_2O$, 81%; iv) N-PSP, 10% $SnCl_4$, CH_2Cl_2, 82%; v) H_2O_2, THF, 0°C, 75%; vi) 1eq. DIBAL-H, toluene, -78°C, followed by MeOH, Amberlyst 15, 59% overall; vii) separation of anomers; viii) O_3, CH_2Cl_2, -78°C, then PPh_3, -78 to 25°C, 83%; ix) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 to 25°C, followed by N-PSP, MeOH, CH_2Cl_2, 66% overall; x) H_2O_2, THF, DHP, 98%

Oxidative elimination of the phenylselenenyl moiety gave a single diasteromer of the corresponding alkene, which was converted *via* the mixture of anomeric acetals **11** to the desired aldehyde **5**. A more direct

and higher yielding route to these materials was achieved by interrupting the oxidation of **8** at the aldehyde stage. Treatment of this aldehyde with N-PSP in the presence of excess methanol resulted in the electrophilic trapping of intermediate hemiacetals[9] and the isolation of a pleasing **66%** yield of acetals **12**, which were readily converted to the desired aldehyde **5**. The acetals were again formed as single diastereomers at the C_{26} centre; the stereoselectivity in both cyclisations may be rationalised by considering a chair-like transition state for cyclisation, in which both of the methyl groups and the side chain are equatorial.

Aldehyde **5** then underwent a stereoselective reaction with ethynylmagnesium bromide, to give **13** as a 10:1 mixture of diastereomers at the C_{27} centre.[10] Interestingly, the corresponding reaction with the acetal bearing the equatorial methoxy- group displayed only mild stereoselection (7:4). Conversion of **13** to a C_{28} aldehyde **14** was readily accomplished in 3 steps. The synthesis of a C_{29}-C_{32} coupling partner **15** could be achieved in 3 steps from the alcohol **16**, itself prepared from the commercially available (*S*)-3-hydroxy-2-methyl propionate. Coupling of the two fragments using the method of Nozaki and Kishi[11] furnished a 3:1 mixture of diasteromeric allylic alcohols **17** and **18** (Scheme 3).[12]

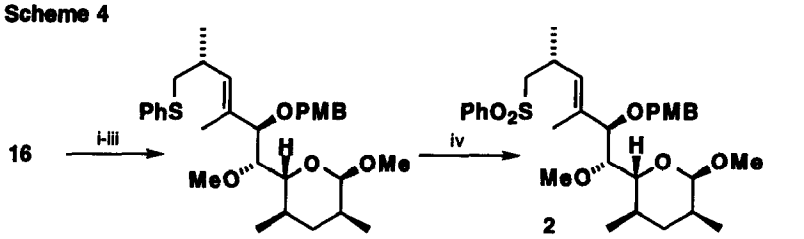
Scheme 3



i)Ethynylmagnesium bromide, toluene/THF, -78°C, 90%; ii) Zn, MeOH/H_2O, 88%; iii) NaH, MeI, THF, 99%; iv) O_3,CH_2Cl_2, -78°C, then PPh_3, -78 to 25°C; v) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 to 25°C followed by CBr_4, PPh_3,CH_2Cl_2, 0°C, 77% overall; vi) 2eq. ^nBuLi, THF, -78°C then MeI, 99%; vii) 1.5eq. Cp_2ZrHCl, THF, rt, then I_2, 85%; viii) 3eq. **14**, 1eq. **13**, 6eq. $CrCl_2$ (doped with 0.5% $NiCl_2$), DMSO, 49% **17**, 18% **18**; ix) TPAP, NMO, CH_2Cl_2, 98%; x) $Zn(BH_4)_2$, Et_2O, 0°C, 81%

Confirmation of the 1,2-*anti* stereochemistry expected for the major diastereomer from such couplings was obtained by an oxidation / chelation controlled reduction sequence employing TPAP[13] followed by zinc borohydride, which returned **17** as shown. This sequence also proved useful for recycling the minor diastereomer **18**. Finally, we needed to convert **17** to the C_{32} sulfone **2**, which will serve as the precursor of an acyl anion equivalent for addition to epoxide **3**. Protection of the free hydroxyl group as a *p*-methoxybenzyl (PMB) ether was followed by removal of the THP ether and substitution of the free hydroxyl for a thiophenyl group. Oxidation to the sulfone was achieved using Oxone® to furnish our target fragment **2** (Scheme 4).

Scheme 4



i) NaH, PMB-Cl, NaI, THF, 0 to 25°C, 75%; ii) MeOH, Amberlyst 15, 84%; iii) Bu_3P, *N*-phenylthiosuccinimide, benzene, 85%; iv) Oxone®, pH4 buffer, THF/MeOH, 93%

In summary, we have achieved a convergent, stereoselective synthesis of material representing the C_{22}-C_{32} carbon framework of rapamycin. Notable points of our synthesis include the use of a novel enzymatic acylation, the flexible synthesis of pyranose rings by either of two diastereoselective, selenium-mediated cyclisations, and the use of an internal protection of the C_{22} and C_{26} positions to provide a chiral template to influence the formation of stereocentres at C_{27} and C_{28}. Coupling of the fragments **2** and **3** is reported in the following paper.

Acknowledgements:We thank the SERC for a Quota Award and Zeneca Agrochemicals for a postgraduate scholarship (to SPM), the Royal Society 1812 fund for a postdoctoral fellowship (to JCA) and BP for a Research Professorship Endowment (to SVL).

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12. Data for **17**: $[\alpha]_D^{24}$ = -47.8 (*c*=1.45, $CHCl_3$); IR (film) ν_{max} (cm^{-1}): 3854, 2925, 1492, 1460, 1381, 1190, 1093, 970; ^1H NMR (400 MHz with COSY, $CDCl_3$, rapamycin numbering): δ (ppm): 7.90 (2H, m, Ar-SO_2), 7.56 (3H, m, Ar-SO_2), 7.19 and 6.85 (2H, 2d, J= 8.6 Hz, Ar-OMe), 5.44 (1H, d, J= 9.25, C_{30}-H), 4.51 (1H, d, J= 3.1, C_{22}-H), 4.31 and 4.12 (2H, 2d, J=10.7, CH_2-Ar), 3.97 (1H, d, J= 9.15, C_{28}-H), 3.79 (3H, s, OMe), 3.66 (1H, d, J= 10, C_{26}-H), 3.32 (3H, s, OMe), 3.28 (1H, d, J= 9, C_{27}-H), 3.26 (3H, s, OMe), 3.12 (1H, m, C_{31}-H), 3.04 (2H, m, C_{32}-H), 1.86 (2H, m, C_{23}-H and C_{25}-H), 1.61 (3H, d, J= 0.8, C_{29}-Me), 1.48 (1H, dt, J= 12.8 and 3.9, C_{24}-H ax.), 1.29 (1H, d, J= 12.5, C_{24}-H eq.), 1.20 (3H, d, J= 6.6, C_{31}-Me), 0.89 and 0.84 (6H, 2d, J= 6.6, C_{23}-Me and C_{25}-Me) ; HRMS, calculated for $C_{21}H_{37}O_5$ $(M\text{-}OH)^+$: 383.2797; found: 383.2827.
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(*Received in UK* 2 *December* 1993; *revised* 18 *January* 1994; *accepted* 28 *January* 1994)