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AN APPLICATION OF THE SUÁREZ REACTION TO THE REGIOSPECIFIC AND STEREOSPECIFIC SYNTHESIS OF THE C_{28}-C_{42} SEGMENT OF RAPAMYCIN

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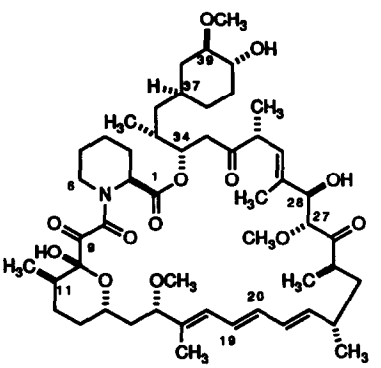
Abstract: Specific lactonization of a TBS ether followed by iodinative scisson of a γ-lactol are the key elements of a strategy for maintaining continuous chemical distinction between the latent C_{34} and C_{32} hydroxyl groups of starting material **3** en route to **14**, the C_{28}-C_{42} fragment of rapamycin.

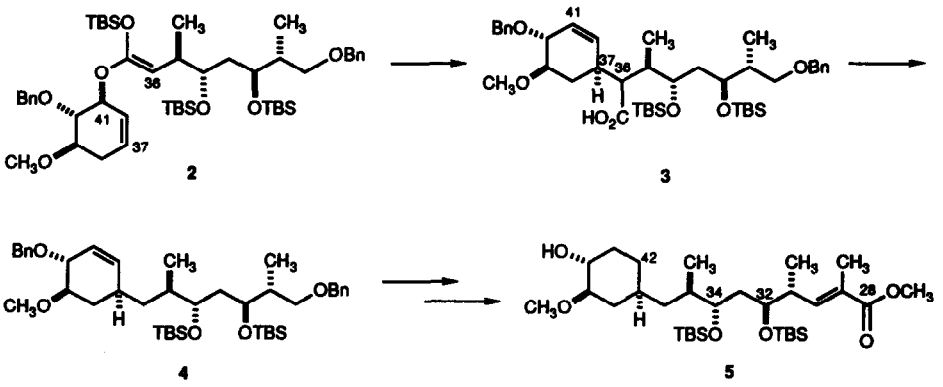
Several laboratories[1] including our own[2] have been investigating the synthesis of rapamycin (**1**). Recently, the first total synthesis of rapamycin was achieved by Nicolaou and coworkers.[3] A major element in our approach to rapamycin involved an Ireland ester enolate Claisen rearrangement in the construction of the C_{28}-C_{42} fragment.[2a] The critical step was the rearrangement of silyl ketene acetal **2** to produce **3**. The attraction of the strategy was that it allowed for the initial joining of the two major chiral subunits via an ester linkage (i.e. the precursor of **2**). The suprafacial nature of the chirality transfer of the Claisen step provided stereodefinition in fashioning the C_{36}-C_{37} carbon-carbon bond. The now extraneous carboxyl function projecting from carbon 36 was removed through a free radical mediated decarboxylation.[4] The resultant product **4** was then converted to **5** in a straightforward manner.



1

While this protocol served to merge the chiral subunits, it left unattended the important problem of distinguishing the oxygen functions at carbons 32 and 34. In this *Letter* we describe an interesting solution to this problem which takes advantage of the otherwise extraneous C_{36} carboxyl of **3** to achieve the first stage of the differentiation. The distinction among the oxygens, is maintained through an application of the Suárez oxidative cleavage of lactols (see initial transformation of **7** → **8**).[5] This method allows us to reach compound **14** without recourse to selective operations on equivalent hydroxyl groups at C_{32} and C_{34}.

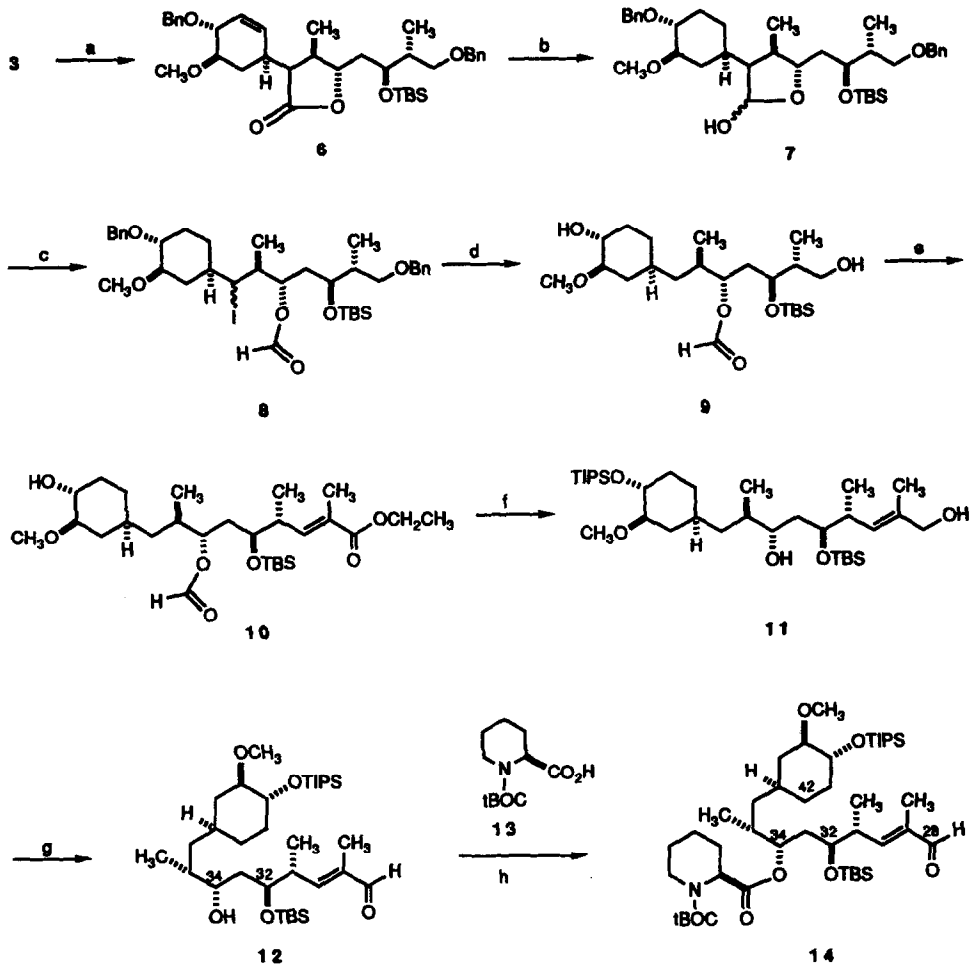
Scheme 1



Treatment of the bis OTBS acid, **3**, with oxalyl chloride in the presence of DMAP provided lactone **6**[6] in ca 70% yield. Diimide reduction of the double bond[7] was followed by reduction of the lactone with diisobutlylaluminum hydride to afford lactol **7**. Suárez oxidation of this compound produced a mixture of iodoformates **8** (~ 85% yield from **6**).[8] The formate ester was remarkably durable (*vide infra*). De-iodination of **8** was accomplished in 90% yield through the action of triphenyltin hydride. Hydrogenation of the resulting compound over Pearlman's catalyst resulted in cleavage of both benzyl ethers providing **9** in 90% yield. Regiospecific oxidation of the primary alcohol at C_{30} with 4-hydroxy-TEMPO benzoate[9] was followed by Wittig type elongation of the resultant C_{30} aldehyde to afford **10** (73% for two steps from **9**).

It was now an appropriate stage to protect the C_{40} hydroxyl group as its TIPS ether. The formate ester at C_{34} was then cleaved reductively through the action of DIBAL, a process which also resulted in reduction of the C_{28} ethyl ester to give diol **11**. Selective oxidation of the primary allylic alcohol function in **11** led to enal **12** (90% yield) bearing the unique hydroxyl at C_{34}. Acylation of this alcohol[10] with *t*-BOC-L-pipecolic acid **13** afforded an 85% yield of **14**.

Scheme 2



(a) oxalyl chloride, DMAP, CH_2Cl_2, 70%. (b) i) $TsNHNH_2$, DME, 90°C; NaOAc, H_2O; ii) DIBAL, $PhCH_3$, -78°C. (c) I_2, $PhI(OAc)_2$, c-(C_6H_{12}), hv, 85% from 6. (d) i) Ph_3SnH, AIBN, $PhCH_3$, reflux, 90%; ii) H_2, $Pd(OH)_2$, EtOAc, 90%. (e) i) 4-hydroxy-TEMPO benzoate, $Ca(OCl)_2$, CH_2Cl_2/5% aq $NaHCO_3$; ii) $Ph_3PC(CH_3)CO_2CH_2CH_3$, $PhCH_3$, 80°C, 73%. (f) i) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 88%; ii) DIBAL, $PhCH_3$, -78°C, 78%. (g) MnO_2, CH_2Cl_2, 90%. (h) 13, DCC, DMAP, CH_2Cl_2, -20°C, 85%.

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† Formerly published as Cheryl D. Myers.

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