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A Novel Ring Contraction Of Rapamycin

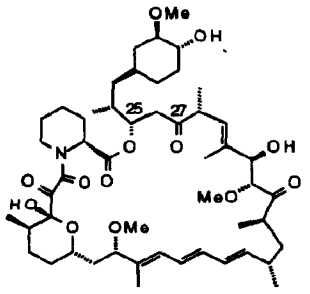
Frances C. Nelson,* Shawn J. Stachel, and James F. Mattes

Chemical Sciences
Wyeth-Ayerst Research, CN 8000, Princeton, New Jersey 08543-8000

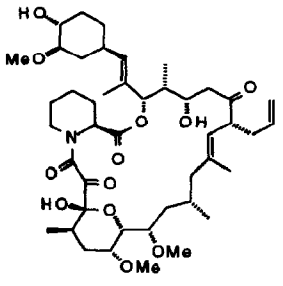
Abstract: The first synthesis of a novel ring contracted analogue of rapamycin is reported. The synthesis employs a stereoselective and regioselective reduction of the C_{27} ketone followed by a 1,3-acyl migration.

Rapamycin (**1**) and FK506 (**2**) (Figure 1) are well known as potent immunosuppressive agents.[1] A great deal of effort has been devoted to determining the biological mode of action of these structurally similar macrolides. While both of these compounds block T-cell activation, they do so by different mechanisms. FK506 was found to exert its effects early during the cell cycle by inhibition of the protein phosphatase calcineurin via the formation of an initial complex with FKBP (FK506 binding protein).[2] Rapamycin, which binds to FKBP, does not inhibit calcineurin; rather, it interferes with events at a later stage of the cell cycle.[3] Its downstream target, which remains elusive, is the subject of many recent investigations.[4]

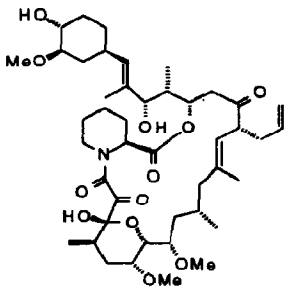
Figure 1



1 Rapamycin



2 FK506



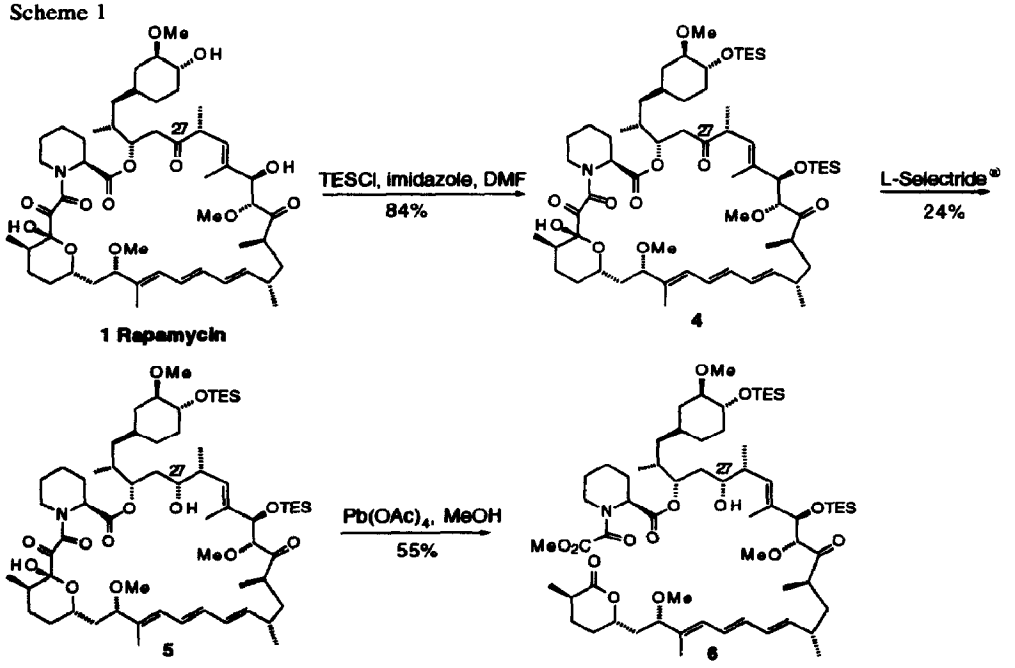
3 *iso*-FK506

Our interest in rapamycin was focused on the chemical level: the synthesis of novel analogues of rapamycin with a different ring structure.[5] In a related piece of work, researchers at Sandoz recently reported on the isolation of a ring contracted version of FK506 (Figure 1, ***iso*-FK506, 3**). [6] To synthesize a ring contracted analogue of rapamycin, we had to recognize the chemical liabilities present in the molecule. The aldol site, the tricarbonyl moiety, and the macrolactone linkage are known regions of instability.[7] Our goal

therefore was to carry out our desired tranformations within the C25-C27 region without interfering with the rest of this complex substrate. With these considerations in mind, we set out to prepare a ring contracted version of rapamycin.

Our path towards this novel analogue pivoted on a 1,3-acyl migration in the C25-C27 region of rapamycin. This transformation requires the selective reduction of the C27 ketone of rapamycin. Prior to the reduction, however, protection of alcohols at C31 and C42 is required in order to preclude their interference in subsequent transformations. Treatment of rapamycin with triethylsilylchloride and imidazole in DMF lead to an 84% yield of the bis-triethylsilyl protected derivative **4** (Scheme 1).[8] The C27 ketone was stereoselectively reduced (the other diastereomer was not detected) with L-Selectride®[9] to provide the requisite rearrangement precursor **5**. Although the yield was low,[10] no reduction of the other ketones present in the molecule was observed. Recovered starting material (38%) as well as decomposition accounted for the remainder of the material in this reaction. The stereochemistry at C27 was determined by conversion of the C27 alcohol in **6** [derived from **5** via ring cleavage with $Pb(OAc)_4$][11] to the (*R*) and (*S*) O-methyl mandelate esters.[12] Detailed analysis of the NMR spectrum of both substrates revealed that the configuration about C27 was R.[13] The assignment is in agreement with the results obtained by Danishefsky, who reported on the reduction of C27 in a ring-opened analogue.[10]

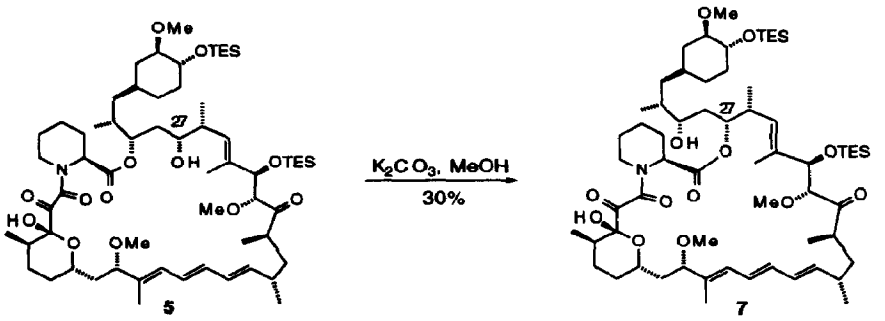
Scheme 1



Initial rearrangement studies on the reduced, protected material proved fruitless. Subjection of **5** to imidazole or DMAP in DMF at or above room temperature[6] led only to recovered starting material. Precedent for the use of K_2CO_3 for effecting similar transformations on erythromycin[14] prompted us to explore the use of

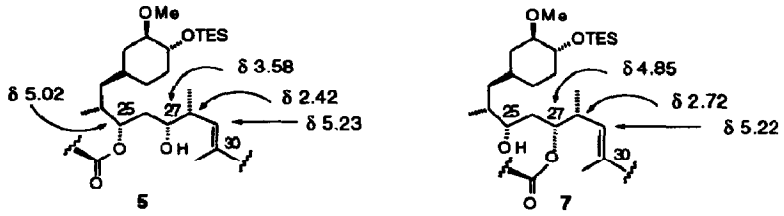
this base. Treatment of **5** with 0.8 equivalents of K_2CO_3 in MeOH at 0 °C produced a 30% isolated yield (as well as 27% of recovered starting material) of the desired product (Scheme 2). The translactonized material **7** appears to be thermodynamically favored over the starting alcohol. Reexposure of **7** to the reaction conditions led to a trace of the original alcohol **5** (3-5%), recovered **7** (53%) and decomposition products. Extended reaction times resulted in only further decomposition.

Scheme 2



Confirmation that **7** was the translactonized product was derived by a combination of ^{1}HNMR and 2-D COSY experiments (Figure 2). The assignment of protons contained in the C_{25}-C_{29} region was critical. In the complex proton spectrum of compound **5**, the chemical shifts of the protons at C_{25} (δ 5.02) and C_{29} (δ 5.23) are especially distinct and useful. C_{29} displays a correlation to one proton at δ 2.42 (C_{28}) that in turn shows a correlation to the methine proton at C_{27} (δ 3.58). In the translactonized product **7**, the proton signal at δ 5.22 exhibits a correlation to a proton at δ 2.72 which in turn has a correlation to a downfield proton at δ 4.85 (the methine at C_{27}), consistent with a secondary alcohol that has now been esterified. This chemical shift (C_{27}, δ 4.85) compares favorably with the analogous methine proton in compound **5**, C_{25}, which appears at δ 5.02.

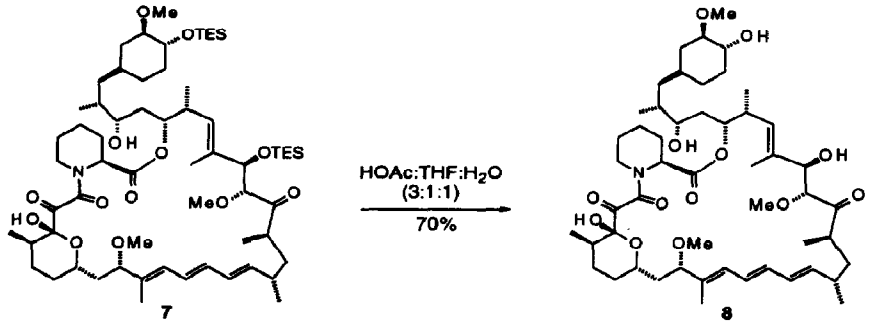
Figure 2



The final step to preparing the rearranged product was the removal of the protecting groups. Both TES moieties could be removed with HOAc:THF:H_2O (3:1:1) to provide compound **8** in 70% yield (Scheme 3).

In summary, we report the first synthesis of a novel ring contracted analogue of rapamycin via a stereo- and regioselective reduction of the C_{27} ketone followed by a 1,3-acyl migration. This ring contracted analogue **8** should be valuable for mechanistic as well as biological evaluations.

Scheme 3



7 8

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