Tetrahedron Letters, Vol.31, No.34, pp 4845-4848, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

DEGRADATIVE STUDIES ON THE TRICARBONYL CONTAINING MACROLIDE RAPAMYCIN

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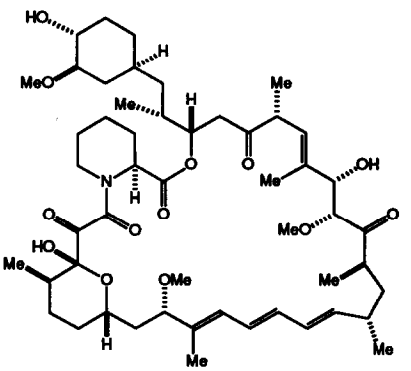
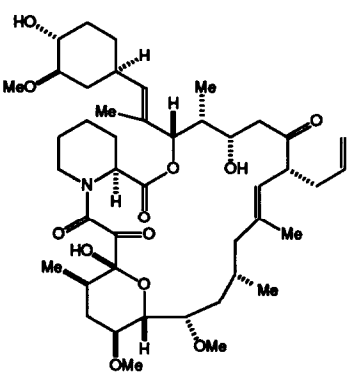
Abstract The degradation of rapamycin, a tricarbonyl containing macrolide similar in structure to the potent immunosuppressant FK-506, is described. Three principal fragments are obtained in this process that should have utility in the semi-synthesis of FK-506 and rapamycin congeners.

Rapamycin **1** characterized by Findlay and co-workers in 1978[1] is a 31-membered macrolide isolated from *S. hygroscopicus* and found to exhibit antifungal as well as modest immunomodulating behavior.[2] The striking structural similarity of rapamycin to the recently reported immunosuppressant FK-506[3] **2** makes the former an attractive alternate source of material for semi-synthetic efforts in this area.[3a,4] Herein we describe our studies on the degradative chemistry of rapamycin for the excision of fragments similar to FK-506.



rapamycin **1**

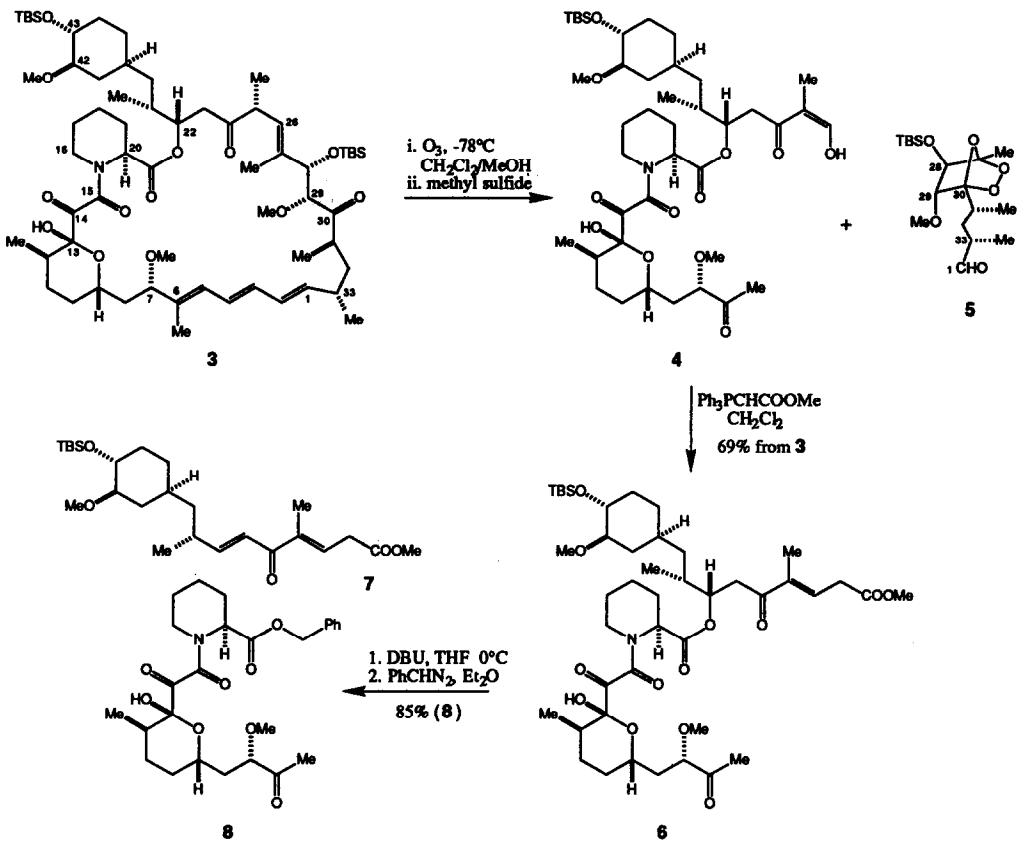


FK-506 **2**

Selective protection of the C-43 and C-28 hydroxyl groups of rapamycin was accomplished by treatment with *t*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and 2,6-lutidine to form the bis(TBS ether) **3** (Scheme 1). Exhaustive ozonolysis of **3** followed by reduction with methyl sulfide provided enol **4** and the bicyclic peroxide **5**[5,6] as the two major products in high yield. The stability of the tricarbonyl segment toward oxidative cleavage in this reaction was gratifying in view of reported difficulties encountered with this transformation[3a]. Fragment **4** contains the desired FK-506-like functionality and was the subject of further degradative work. Following isolation by silica gel chromatography, the unstable enol **4** was treated with methyl triphenylphosphoranylacetate to form the homologated ester for storage. Interestingly, an olefin isomerization occurs in this reaction to produce only enone **6**. Disconnection of the substituted cyclohexane moiety from the tricarbonyl containing portion was accomplished by elimination of the C-22 acyl group using diazabicycloundecene (DBU) in THF. Treatment of the crude, acidified product with phenyldiazomethane[7] allowed for the convenient

chromatographic purification of fragments **7** and **8**. No evidence of epimerization at C-7 or C-38 was detected in this transformation.

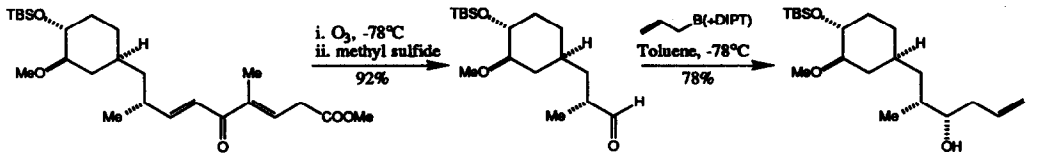
Scheme 1



To regenerate the C-22 hydroxyl group, dienone **7** was subjected to ozonolysis and methyl sulfide reduction to yield aldehyde **9** (Scheme 2). Treatment of **9** with the (+) DIPT-modified allylboronate reagent[8] gave homoallylic alcohol **10** (ds = 8:1) predicted to contain the natural *S* configuration at C-22.

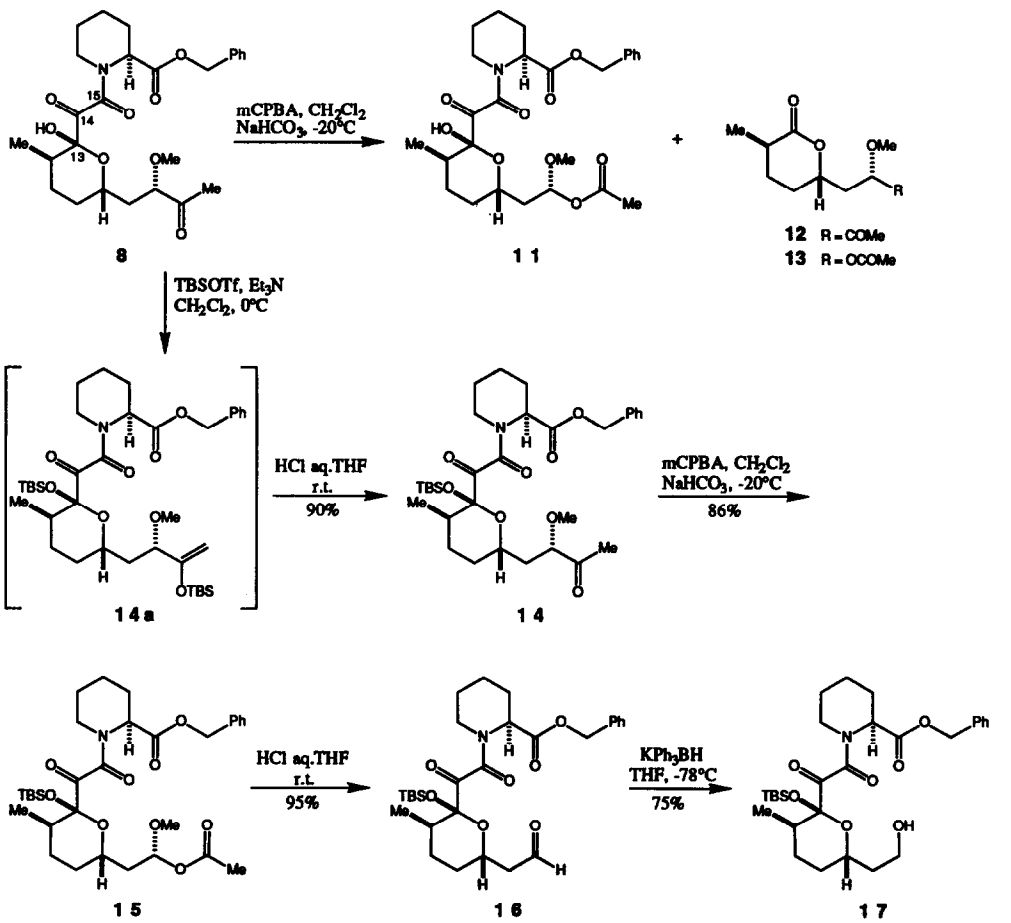
The further degradation of fragment **8** was investigated to provide a primary functionalized site at C-7 for subsequent manipulation. Cleavage of the C-6, C-7 bond by a Baeyer-Villiger reaction, followed by hydrolysis of the mixed acetal product would be a means of achieving this goal. In the event, however, treatment of **8** with *m*CPBA resulted in a low yield of desired C-7 acetal **11**, with competing C-13, C-14 bond cleavage leading to the lactone products **12** and **13** (Scheme 3). To suppress undesired reaction in the tricarbonyl region, the C-13 hydroxyl group was protected as the TBS ether **14**. A two-step procedure involving bis-silylation followed by

Scheme 2



hydrolysis of the silyl enol ether product **14a** was required to effect this transformation. Baeyer-Villiger oxidation of **14** proceeded in excellent yield to form **15** with no detectable C-13, C-14 bond cleavage. The reason for this attenuation of reactivity is unclear, however, one possibility is that the reactive species in transformation

Scheme 3



8⟶**12** is the "opened" tricarbonyl. Hydrolysis of acetal **15** to the C-7 aldehyde **16** provided the desired primary functionalized site. Finally, a selective reduction of aldehyde **16** to the corresponding alcohol in the presence of the C-14 carbonyl group was conducted using potassium triphenylborohydride.[9] Unlike the Baeyer-Villiger oxidation, the chemoselectivity of this reaction is independent of C-13 hydroxyl group protection and can be performed equally well on the free hemiketal (not shown). With an efficient preparation of fragments **10** and **17** in hand, their use in the construction of FK-506 and rapamycin congeners is being investigated.

Acknowledgement The authors express their appreciation to Dr. Robert Borris for supplying the rapamycin used in this study, and Drs. K.M. Rupprecht, and D.M. Armistead for their helpful discussions.

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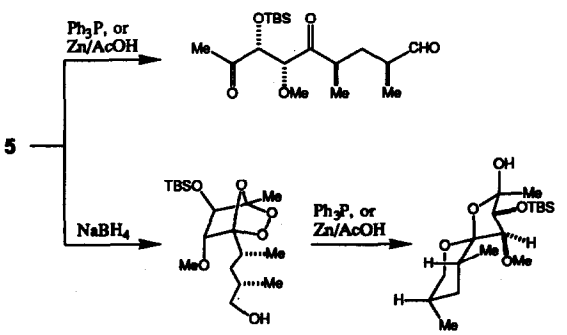
5. The trapped ozonide **5** was formed as virtually a single diastereomer of unknown configuration at the newly generated stereocenters C-27, C-30. Only one of the two possible isomers is depicted. In the course of characterization, peroxide **5** was found to exhibit some interesting properties shown below:



6. Satisfactory ^1H NMR and mass spectral data were obtained on all reaction products.
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(Received in USA 7 June 1990)