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Construction of an FK-506 Analog From Rapamycin-Derived Materials

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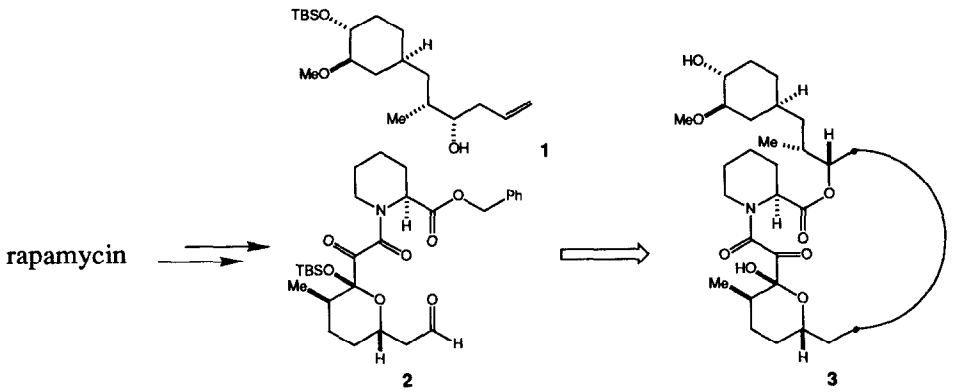
Key Words: FK-506; rapamycin; immunosuppressant; semi-synthesis; macrolactonization

Abstract: *Fragments derived from the degradation of rapamycin have been reassembled to form a tricarbonyl containing macrocycle similar in structure to FK-506.*

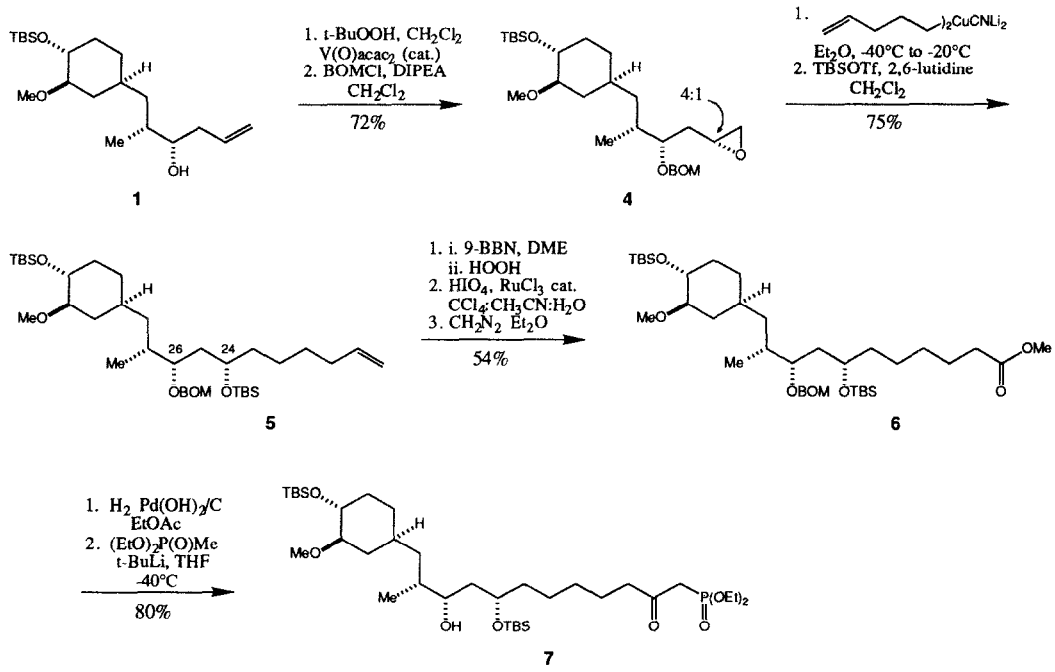
The potent immunosuppressant activity of FK-506[1] has driven an intense chemical synthesis effort toward this target of otherwise noteworthy structural complexity.[2] The rationale is that by total synthesis an unlimited number of non-naturally occuring analogs of potential therapeutic interest would be available.[3] A variation of this approach would be to utilize naturally-derived fragments in the reconstruction of non-natural analogs. The advantage of the latter approach is evident in instances where one wishes to maintain a structurally complex region(s) of the lead compound while varying the remaining portion.[4] In the present case, we have utilized an ability to cleanly excise fragments **1** and **2** from the related macrolide rapamycin[5] for use in the synthesis of FK-506 analogs of general formula **3**.[6] Herein we describe the synthesis of an analog obtained in this manner.



FK-506 analog **3** can be viewed as a three-component system consisting of units derived from **1**, **2**, and a linking group or "backbone". An ideal synthesis of **3** would follow the sequence: (**1**+ backbone) + **2** ⟶ **3**, to minimize the number of transformations conducted on tricarbonyl containing material. An interesting series of analogs could be produced by varying the backbone unit, once general procedures for the connection of **2** and conversion to **3** are developed.

Attachment of a simple alkyl chain backbone to **1** is depicted in Scheme 1. Vanadium-catalyzed epoxidation followed by protection of the alcohol as the benzyloxymethyl (BOM) ether provided a 4:1 mixture of epoxides **4**, the major isomer being assigned as *syn* based upon literature precedent.[7,8] The mixture was subjected to ring opening by the action of a higher order cyanocuprate prepared from 4-pentenyllithium to give the now separable diastereomeric adducts in good yield. Silylation of the resultant major alcohol provided **5** in a suitably protected form. Extension of **1** through an epoxide intermediate of this type allows for the introduction of a hydroxyl group of *S* configuration at C-24 (FK-506 numbering), the site of a similar hydroxyl group in the natural product. Conversion of **5** into a ß-keto phosphonate for eventual coupling to **2** was accomplished in the following manner. Oxidation of the primary carbon to form methyl ester **6** was conducted in a three-step sequence consisting of hydroboration followed by treatment with ruthenium tetraoxide[9] then diazomethane. Earlier studies had revealed that removal of the BOM protecting group was most easily achieved at this stage, and was effected by hydrogenation using Pearlman's catalyst. Addition of the lithium anion of diethyl methylphosphonate[10] to the crude hydroxy-ester provided the Horner-Emmons reagent **7**.

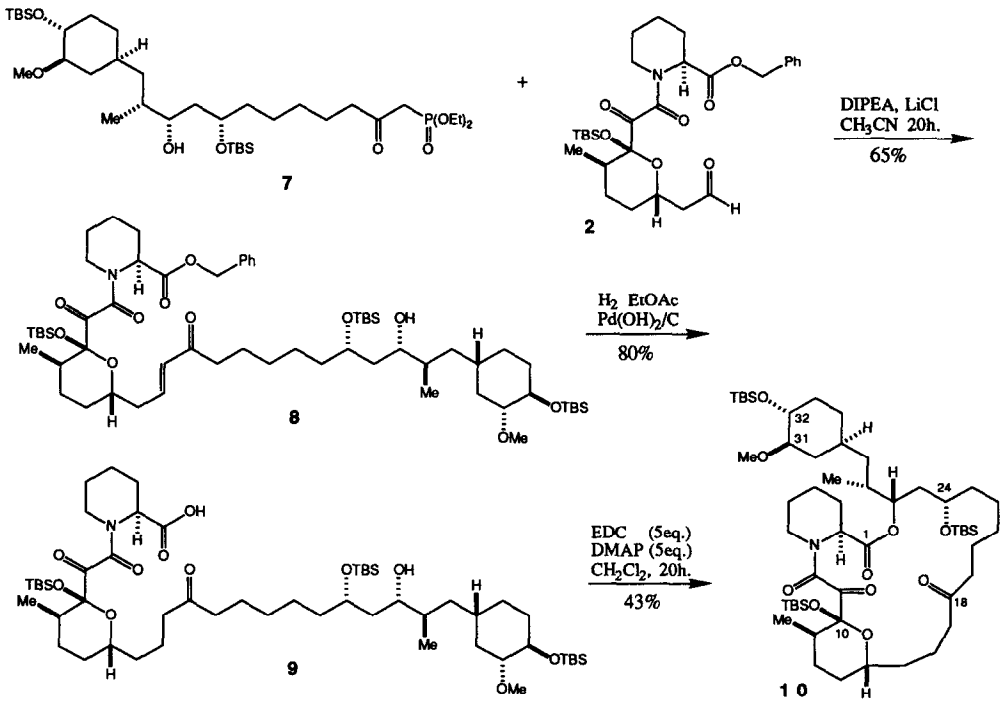
Scheme 1



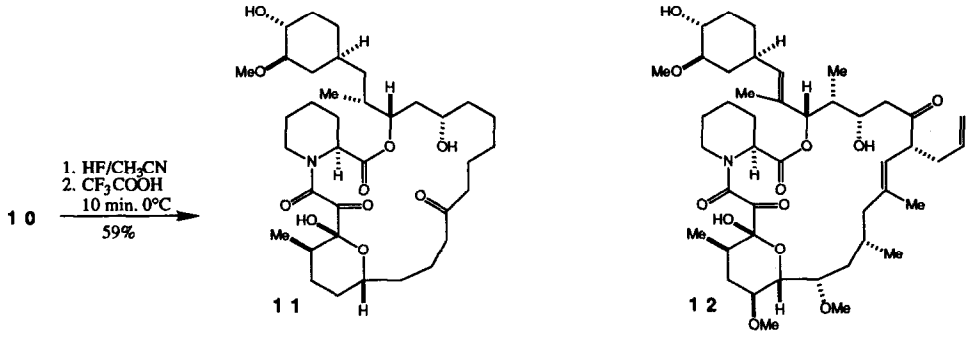
Condensation of **7** with aldehyde **2** was accomplished using the Masamune-Roush procedure[11] to provide the seco-ester **8** as a single, *trans* olefin isomer by 300 MHz ^{1}H NMR analysis (Scheme 2). This transformation effectively rejoins two *natural* segments linked by a nine-carbon *synthetic* spacer. To expose the C-1 carboxylic acid, a non-hydrolytic method of de-esterification was required due to the acid and base sensitive functionality present. In anticipation of this circumstance, a benzyl ester protecting group was chosen during the degradative

work[5] which was now readily removed by hydrogenolysis using Pearlman's catalyst. These conditions also reduced the enone function to provide the saturated acid **9**. A survey of several esterification techniques revealed the singularly successful method of EDC (1-ethyl-3-(3-dimethylamino)propylcarbodiimide) with DMAP

Scheme 2



catalysis [12] for macrolactonization to form **10** in 43% yield. Use of the Mukaiyama[13] or BOP[14] reagents under typical conditions resulted in degradation of the seco-acid with no macrolide product observed. There was no evidence of epimerization at C-2 in **10** or any of the subsequent products (^{1}H NMR) in spite of problems encountered with this transformation in related systems.[2a,b] Treatment of **10** with 2% aq. HF-acetonitrile



FK-506 analog

FK-506

promoted rapid removal of the TBS ethers at C-32 and C-24 while the C-10 TBS ether remained unaffected even after prolonged exposure. Concurrent model studies on acyclic systems had shown this tertiary TBS ether to be surprisingly recalcitrant toward removal by standard methods. A protodesilylation using neat trifluoroacetic acid, however, was found to deliver the fully deprotected FK-506 analog **11** in 59% yield. Analog **11** maintains the same 23-membered ring size as FK-506 (**12**) but is considerably simpler in structure, lacking most of the functionality found in the C-13 to C-22 region. It is interesting that **11**, like rapamycin, exists predominantly as the *trans* amide rotamer in chloroform solution (5:1 *trans:cis*), while FK-506 prefers the *cis* rotamer (1:2).[15]

Using the sequence developed for the synthesis of **11** from rapamycin-derived **1** and **2**, additional analogs should be available wherein the size and degree of functionalization along the macrolide can be varied by choice of an appropriate backbone unit. The preparation of novel FK-506 analogs by this strategy and their activity as immunosuppressants will be the subject of a future report.

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References and Notes

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15. ^{1}H NMR chemical shifts for the C-2 H with Major and minor amide rotamers noted (ppm in $CDCl_3$):

11:	5.43m	5.11M
FK-506:	5.32M	5.19m
rapamycin:	5.48m	5.26M

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