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RAPAMYCIN SYNTHETIC STUDIES. 1. CONSTRUCTION OF THE C(27)-C(42) SUBUNIT

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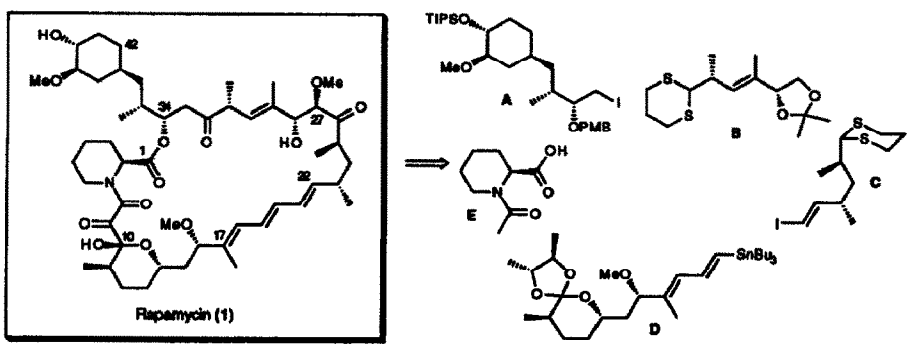
Summary: A convergent synthetic approach to the C(27)-C(42) fragment of the immunosuppressive macrocycle rapamycin is described.

In 1975, researchers at Ayerst Laboratories (Canada) reported the discovery of rapamycin (AY-22,989), a new antibiotic produced by *Streptomyces hydroscopicus* (NRRL 5491) in Easter Island soil samples.[1] Subsequent studies revealed that rapamycin not only inhibits various *Candida* species, but also suppresses the immune response in rats.[2] Both rapamycin and the related immunomodulator FK506 bind to the macrophilin FKBP-12 with comparable affinity[3] and inhibit T-cell activation at subnanomolar concentrations.[4] Moreover, the two distinct protein-ligand complexes interfere with signaling events at different stages of the immune response.[5] Whereas the FK506-FKBP-12 complex blocks signal transduction from the T-cell receptor to the nucleus, the rapamycin-immunophilin complex inhibits a calcium-independent pathway mediated through the IL-2 receptor. Several findings have implicated the inhibition of the p70 S6 kinase or the cyclin dependent kinase as downstream events which prevent T-cell entry into the S phase and thus are responsible for rapamycin's immunosuppressant activity.[6]

The structure and relative stereochemistry of rapamycin (1, Scheme I) were determined by single-crystal X-ray analysis;[7] the absolute configuration was then assigned via isolation of L-pipecolinic acid as a degradation product.[8] Rapamycin embodied a completely new type of macrocycle, a 31-membered ring containing both lactam and lactone linkages. In addition to the pipecolinic acid moiety, notable substructures include a 1,2,4-trisubstituted cyclohexane, an E,E,E-triene moiety, two stereochemically complex aldol units [C(25)-C(28), C(31)-C(35)], and an α,β-diketoamide partially masked via C(10) hemiketal formation. The architectural intricacy of 1, in conjunction with its potential utility as a therapeutic agent in organ transplantation[9] and as a probe for the "black box" of intracellular signal transduction,[10] have established rapamycin as a singularly important target for total synthesis.[11] To date, three successful approaches have been reported.[12] Extensive degradation studies have been performed as well.[13]

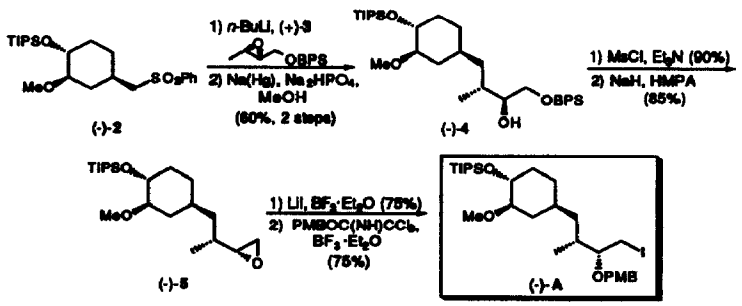
Scheme I



We have recently initiated a rapamycin synthetic venture. Here and in the accompanying Letter, we wish to describe our strategy and initial results. Our synthetic analysis of 1 generated fragments A through E, of similar size and complexity (Scheme I). This highly convergent approach is designed to provide unusual flexibility during the final assembly of the macrocycle. The present communication focuses on the construction of subtargets A and B, their coupling, and further requisite functionalization. The second paper describes the preparation and union of fragments C and D.[14]

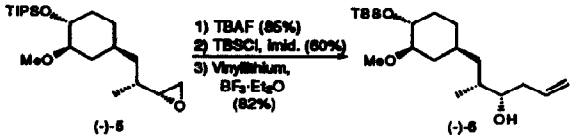
The preparation of subunit A began with sulfone (-)-2 (Scheme II), a compound employed in our recent formal synthesis of FK506.[15] The lithium derivative of 2 added regioselectively to epoxide (+)-3,[16] the latter readily available via Sharpless asymmetric epoxidation of *(E)*-crotyl alcohol.[17] Reductive desulfonylation then gave the desired alcohol (-)-4[16] in 60% overall yield. Mesylation of 4 and removal of the *tert*-butyldiphenylsilyl (BPS) group with NaH in HMPA[18] provided epoxide (-)-5[11f] in good yield. The corresponding iodohydrin was generated via Lewis acid catalyzed opening of the epoxide with LiI; protection of the secondary alcohol as its PMB ether under acidic conditions[19] furnished (-)-A.[16]

Scheme II



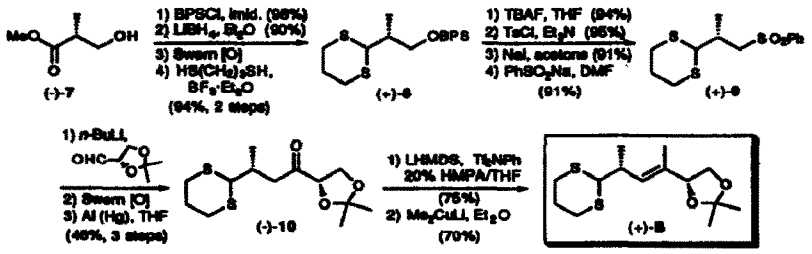
The stereochemistry of (-)-A was confirmed by a synthesis of the known homoallylic alcohol (-)-6, prepared previously at Merck Research Laboratories from a compound obtained by degradation of natural rapamycin.[13a,c] Following replacement of the triisopropylsilyl group in (-)-5 by *tert*-butyldimethylsilyl (Scheme III), the epoxide was opened regioselectively with vinyllithium and boron trifluoride etherate. Synthetic (-)-6 proved to be identical in all respects with an authentic sample generously provided by Dr. Mark T. Goulet of Merck.

Scheme III



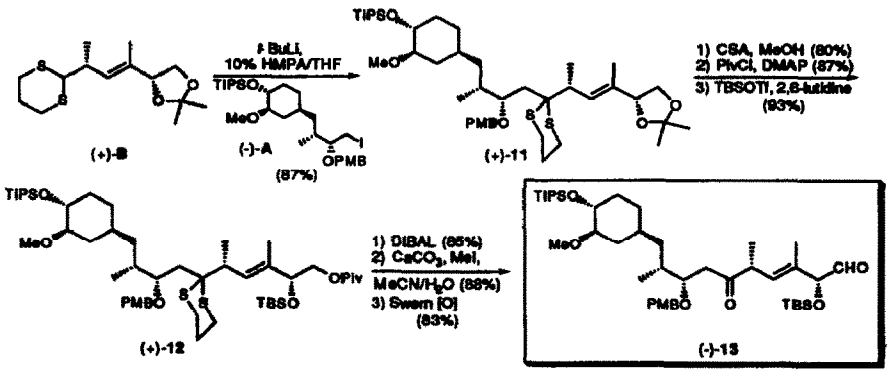
The construction of fragment (+)-B is outlined in Scheme IV. Dithiane (+)-8[16] was prepared in four steps from commercially available *(R)*-(-)-methyl 3-hydroxy-2-methylpropionate [(-)-7].[20] Conversion of 8 to sulfone (+)-9[16] likewise followed standard procedures. The lithium salt of 9 was then added to the isopropylidene derivative of *(S)*-glyceraldehyde, prepared in three steps from L-arabinose.[21] Swern oxidation and desulfonylation afforded a single ketone (-)-10[16] in 46% yield from 9. The Z enolate, selectively generated by treatment of 10 with lithium hexamethyldisilazide in 20% HMPA/THF at -78 °C, was effectively trapped with *N*-phenyltrifluoromethanesulfonimide. Coupling of the resultant vinyl triflate with lithium dimethylcuprate provided (+)-B[16] in good yield.[22] Neither the E triflate nor the trisubstituted regioisomer was detected.

Scheme IV



Union of the fragments entailed metalation of dithiane (+)-**B** with *t*-BuLi and alkylation with iodohydrin (-)-**A** (10% HMPA/THF, -78 °C), affording (+)-**11**[16] in 87% yield (Scheme V). Following acetonide hydrolysis, sequential protection of the primary and secondary alcohols as a pivaloate ester and TBS ether, respectively, gave (+)-**12**[16] (65%, three steps). DIBAL reduction of the pivaloate and dithiane removal (MeI, $CaCO_3$, 4:1:1 acetonitrile/THF/water) then proceeded smoothly. Swern oxidation of the resultant primary alcohol furnished aldehyde (-)-**13**[16] in 62% yield from **12**.

Scheme V



In summary, subtarget (-)-**A** was synthesized from the known intermediate (-)-**2** (6 steps, 26% overall yield), and fragment (+)-**B** was prepared from commercially available hydroxy ester (-)-**7** (13 steps, 15% overall yield). The coupling of **A** and **B** and requisite further manipulations provided the 19-carbon C(27)-C(42) subunit of rapamycin, suitably functionalized for further elaboration.

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15. Smith, A. B., III; Chen, K.; Robinson, D. J.; Laakso, L. M.; Hale, K. J. *Tetrahedron Lett.* in press. The formal total synthesis of FK506 was first disclosed at the Cope Scholar Symposium at the Fourth Chemical Congress of North America, New York, NY, August 25-30, 1991.
16. All synthetic compounds were purified by flash chromatography on silica gel. The structure assigned to each new compound is in accord with its infrared, 500-MHz ^{1}H NMR and either 62.5- or 125-MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high resolution mass spectrometry. In addition, **8**, **9**, **10**, **B**, and **14** gave satisfactory C and H combustion analyses.
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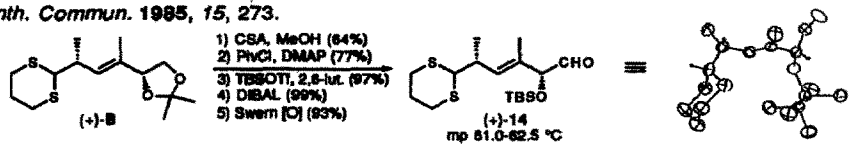
22. The relative stereochemistry of (+)-**B** was confirmed via single-crystal X-ray analysis of (+)-**14**.



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