

Total Synthesis of Rapamycin and Demethoxyrapamycin

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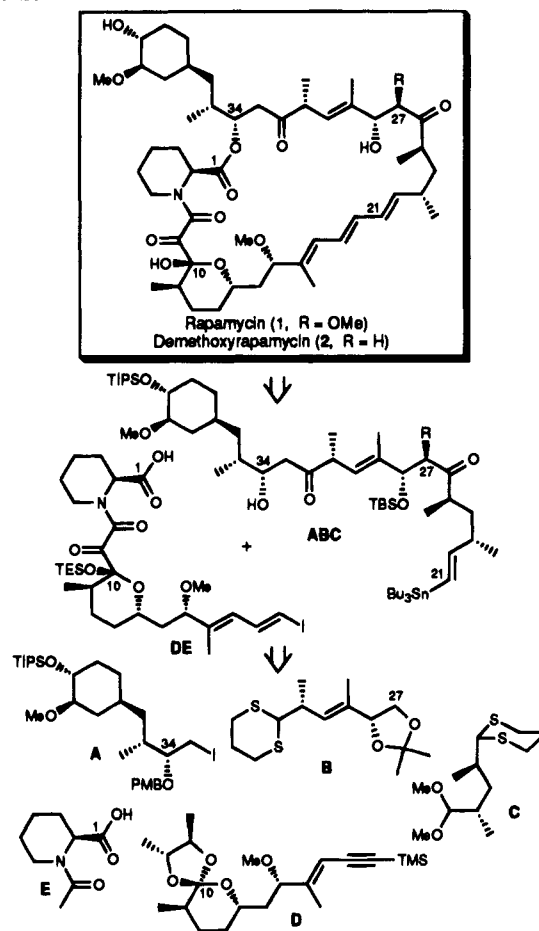
Rapamycin (**1**) and demethoxyrapamycin (**2**) have gained prominence as members of a growing family of macrocyclic natural products with marked immunosuppressive properties.¹ These targets have stimulated intensive synthetic activity, including three total syntheses of **1**.² Rapamycin and its structurally-related cousin FK506 both bind to the cytosolic immunophilin FKBP, a strict requirement for the observed physiological response.³ Although the specific role of **1** in signal transduction and immunosuppression remains unclear, it has been established that rapamycin interferes with a Ca²⁺-independent signaling pathway emanating from the IL-2 receptor.⁴

From the retrosynthetic perspective (Scheme 1), we envisioned the elaboration of rapamycin and the 27-demethoxy congener via couplings of fully functionalized ABC fragments with a common DE element, all derived in turn from the building blocks A–E.⁵ Final assembly of the macrocycle could then be effected by intermolecular acylation at C(34) and intramolecular Pd(0)-catalyzed Stille coupling, or via initial formation of the triene seco acid followed by macrolactonization. Herein we report the application of the former strategy to the total syntheses of rapamycin (**1**) and demethoxyrapamycin (**2**). This first successful route to **2** confirmed the proposed structure, which until now was assigned solely on the basis of spectral comparisons with **1**.^{1b} Our highly convergent approach is also intended to permit the straightforward preparation of designed analogs.

The ABC fragment of demethoxyrapamycin derived from the previously described AB acetonide (+)-**3** (Scheme 2).⁵ Following ketal hydrolysis, standard manipulations provided a highly acid-labile terminal epoxide which was used without purification in coupling to dithiane (–)-**C**.⁵ Silylation of the resultant C(28) alcohol afforded (+)-**4**.⁶

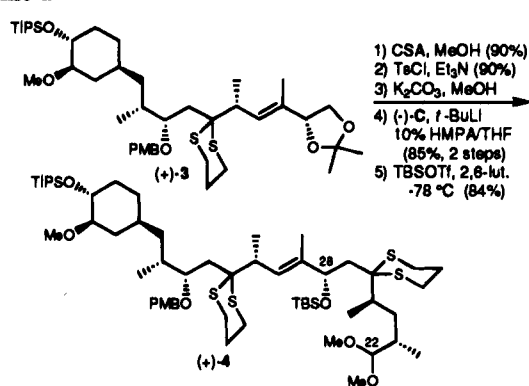
To introduce the requisite C(27) oxygen in the analogous rapamycin ABC subunit (**7**, Scheme 3), we employed aldehyde (+)-**6**⁶ as an electrophilic AB component. The aldehyde was assembled via lithiation of dithiane (+)-**5**,⁵ alkylation with primary iodide (–)-**A**,⁵ and acetal hydrolysis. Metalation of dithiane (–)-**C** and addition to **6** then furnished the epimeric

Scheme 1



C(27) alcohols, with the unwanted diastereomer in slight excess (1.2:1). Methylation gave fragment **7**, admixed with the corresponding 27-epi material.⁷

Scheme 2



Our point of departure for the preparation of the common DE fragment was orthoester (+)-**D**,⁵ hydrolysis, silylation, ester reduction, and Swern oxidation provided aldehyde (–)-**8**⁶ (Scheme 4). Following condensation of the latter with the dianion of L-N-acetylpipecolic acid (**E**),⁸ diazomethane esterification of the crude aldol mixture and Dess–Martin oxidation (5 equiv) gave the desired tricarbonyl species, via the procedure developed by Golec et al.⁹ Desilylation at C(14) gave a single hemiketal (+)-**9**,⁶ as evidenced by the ¹³C NMR spectrum.¹⁰ The hemiketal was effectively trapped with TESOTf; free-radical

(7) The configuration at C(27) was determined by X-ray crystallographic analysis of an intermediate not described in this Communication. Separation of the C(27) epimers was most readily effected via flash chromatography of the Corey–Fuchs vinyl dibromides (see Scheme 5).

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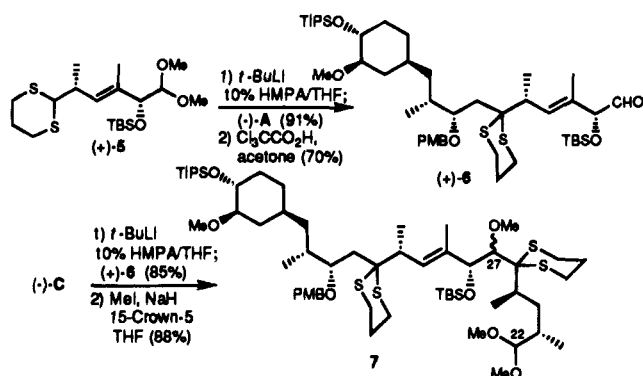
(3) (a) Bierer, B. E.; Mattila, P. S.; Standaert, R. F.; Herzenberg, L. A.; Burakoff, G.; Crabtree, G.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 9231. (b) Somers, P. K.; Wandless, T. J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 8045.

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(5) For the syntheses of A, B, C, and D in >97% ee, see: (a) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leahy, J. W.; Leazer, J. L., Jr.; Maleczka, R. E., Jr. *Tetrahedron Lett.* **1994**, *35*, 4907. (b) Smith, A. B., III; Maleczka, R. E., Jr.; Leazer, J. L., Jr.; Leahy, J. W.; McCauley, J. A.; Condon, S. M. *Tetrahedron Lett.* **1994**, *35*, 4911.

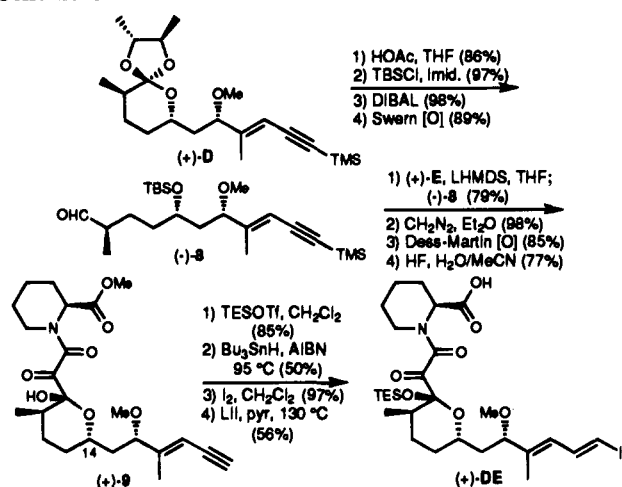
(6) All synthetic compounds were purified by flash chromatography on silica gel. The structure assigned to each new compound is in accord with its infrared, 500-MHz ¹H NMR, and 62.8- or 125-MHz ¹³C NMR spectra, as well as appropriate parent ion identification by high resolution mass spectrometry. In addition, compounds **4–6**, **7β**, **9–11** gave satisfactory combustion analysis.

Scheme 3



hydrostannylation and tin-halogen exchange completed installation of the required *E,E*-dienyl iodide moiety. Finally, demethylation of the ester yielded the subtarget (+)-DE.⁶

Scheme 4



Elaboration of fragments $7\beta^6$ and 4 to rapamycin and demethoxyrapamycin proceeded as outlined in Scheme 5. In each case, unmasking of the C(22) aldehyde and Corey-Fuchs homologation¹¹ provided the requisite terminal acetylene [(+)-10⁶ and (+)-11⁶, respectively]. Following removal of the PMB and dithiane protective groups, palladium(0)-mediated hydrostannylation¹² installed *E*-vinylic tin moieties, completing the preparation of ABC intermediates (-)-12⁶ and (-)-13.⁶ Linkage with the common fragment (+)-DE was then effected via a carbodiimide-induced [1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride] acylation to afford seco precursors (-)-14⁶ and (-)-15.⁶ Because of the well-documented propensity of rapamycin to undergo base-induced β -elimination at the C(32)-C(34) aldol linkage,¹³ we were gratified to observe that the acylation proceeded without complication in the presence of the C(32) carbonyl group. Intramolecular Stille coupling with [(2-furyl)₃P]₂PdCl₂¹⁴ in DMF/THF cleanly generated the macrolide rings.¹⁵ Finally, desilylation afforded rapamycin (1) and demethoxyrapamycin (2), identical with the natural products in all respects (¹H and ¹³C NMR, IR, HRMS, optical rotation, and TLC in three solvent systems).¹⁶

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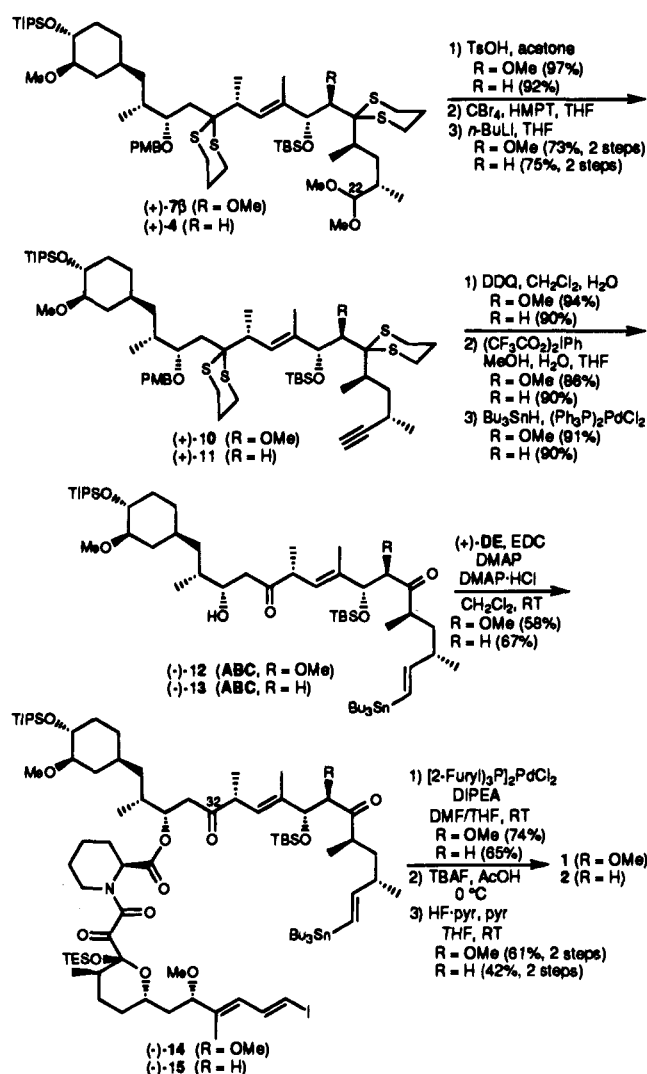
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Scheme 5



In summary, we have successfully devised and executed a highly convergent strategy for the total synthesis of rapamycin (1) and have achieved the first total synthesis of demethoxyrapamycin (2), confirming the assigned structure. The macrocyclic framework was assembled in only two steps by union of fully functionalized ABC and DE intermediates. For rapamycin, the longest linear sequence from the first point of convergence is 14 steps. We believe that the ready accessibility of the five subtargets and their adaptability toward structural modification provide significant potential for rational analog design.

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Supplementary Material Available: Spectroscopic and analytical data for all compounds pictured as well as selected experimental procedures (15 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(15) To our knowledge, the first example of a palladium-catalyzed intramolecular Stille coupling for macrolide construction was reported by Stille and Tanaka: Stille, J. K.; Tanaka, M. *J. Am. Chem. Soc.* **1987**, *109*, 3785. Also see: Kalivretanos, A.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1991**, *56*, 2883. Nicolaou's synthesis of rapamycin^{2a} elegantly extended this methodology with a Stille-type "stitching-cyclization" to install the C(19)-C(20) vinyl unit and simultaneously close the macrocycle in 28% yield.

(16) We thank Professor Koji Nakanishi and Wyeth-Ayerst (Princeton) for natural demethoxyrapamycin and rapamycin, respectively.