Total Synthesis of Rapamycin

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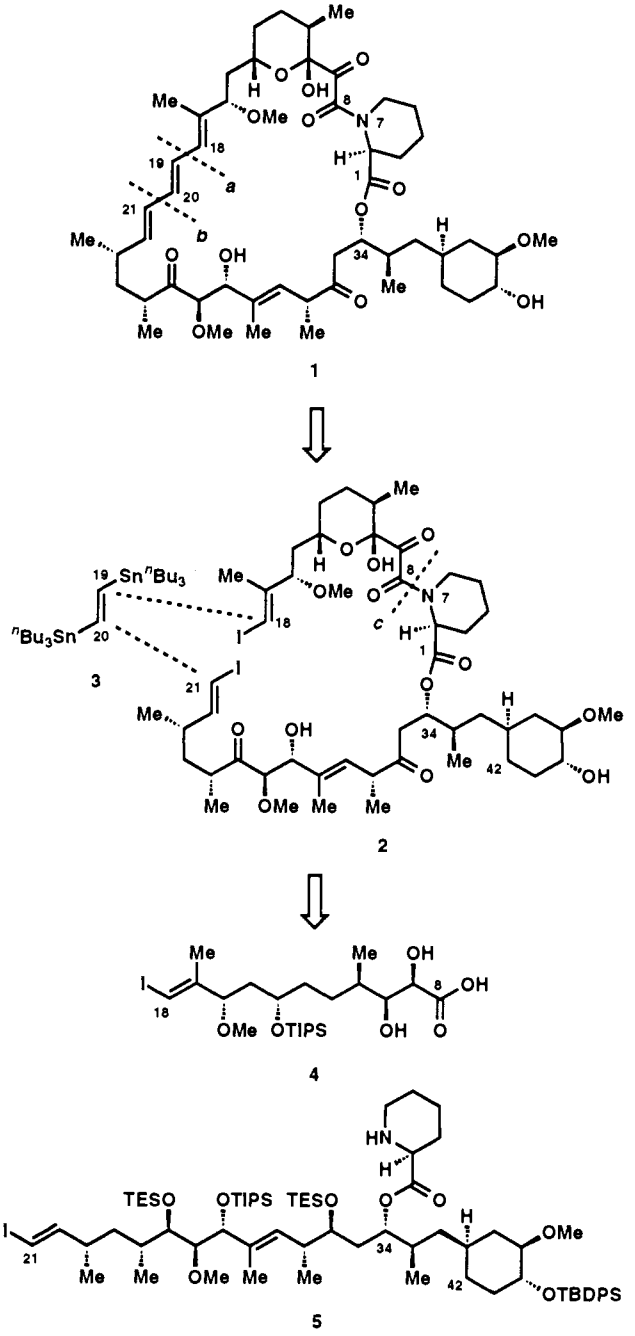
Rapamycin (**1**)[1,2] is a novel, naturally occurring substance, with potent antibiotic, cytotoxic, and immunosuppressive activity. Isolated from *Streptomyces hygroscopicus* found in an Easter Island soil sample, this synthetically challenging molecule is currently under intense investigation as a rival to the immunosuppressive agents FK506 and cyclosporin.[3] Herein we report the first total synthesis of rapamycin (**1**) in its naturally occurring enantiomeric form.[4]

Rapamycin (**1**) with its 31-membered ring, plethora of asymmetric and geometrical centers, and sensitive functionality presents to the synthetic chemist a formidable challenge. A rather daring approach to this target is outlined in Scheme I. According to this strategy, rapamycin (**1**) was to be constructed by a single operation from a fully functionalized acyclic precursor (**2**), via a "stitching–cyclization" process that would bring in the two missing carbons as the central olefinic unit (C_{19}–C_{20}) of the triene moiety. The bridging unit, enedistannane **3**,[5] was expected to bring together the two terminal vinyl iodides of precursor **2** in a Stille-type[6,7] coupling–cyclization reaction to furnish the natural product in a single step. Such a strategy would ensure a direct approach to **1** and avoid instability problems, deprotection steps, and late stage oxidation state adjustments. Precursor **2** was expected to be derived from advanced key intermediates **4** and **5** (Scheme I).

Coupling of advanced intermediates **4**[8] and **5**[9] in the presence of 1-hydroxybenzotriazole and diisopropylcarbodiimide proceeded smoothly to afford the amide **6** in 95% yield (Scheme II). Swern oxidation of dihydroxy amide **6** afforded the pale yellow diketo amide **7** in high yield. This compound was then subjected to selective desilylation with HF·pyr leading to the corresponding diol intermediate. A second Swern oxidation furnishes the hexacarbonyl compound **8**. Finally, removal of the remaining silyl groups under the influence of aqueous HF in acetonitrile led to the desired precursor, divinyl diiodide **2**, in 70% overall yield from compound **6**.

The crucial "stitching" of the long chain precursor **2** with the missing two-carbon olefinic segment (C_{19}–C_{20}) was accomplished by utilizing vinylenedistannane **3**[5] in the presence of $Pd(CH_3CN)_2Cl_2$ and Hunig's base in DMF/THF according to the Stille method[6] (Scheme II). Rapamycin (**1**) was obtained from this reaction in 28% yield together with unreacted starting material (ca. 30%) and an iodo–stannane intermediate[10] (ca. 30% yield).

Scheme I. Retrosynthetic Analysis of Rapamycin (**1**)[a]



[a] TIPS = triisopropylsilyl; TES = triethylsilyl; TBDPS = *tert*-butyldiphenylsilyl.

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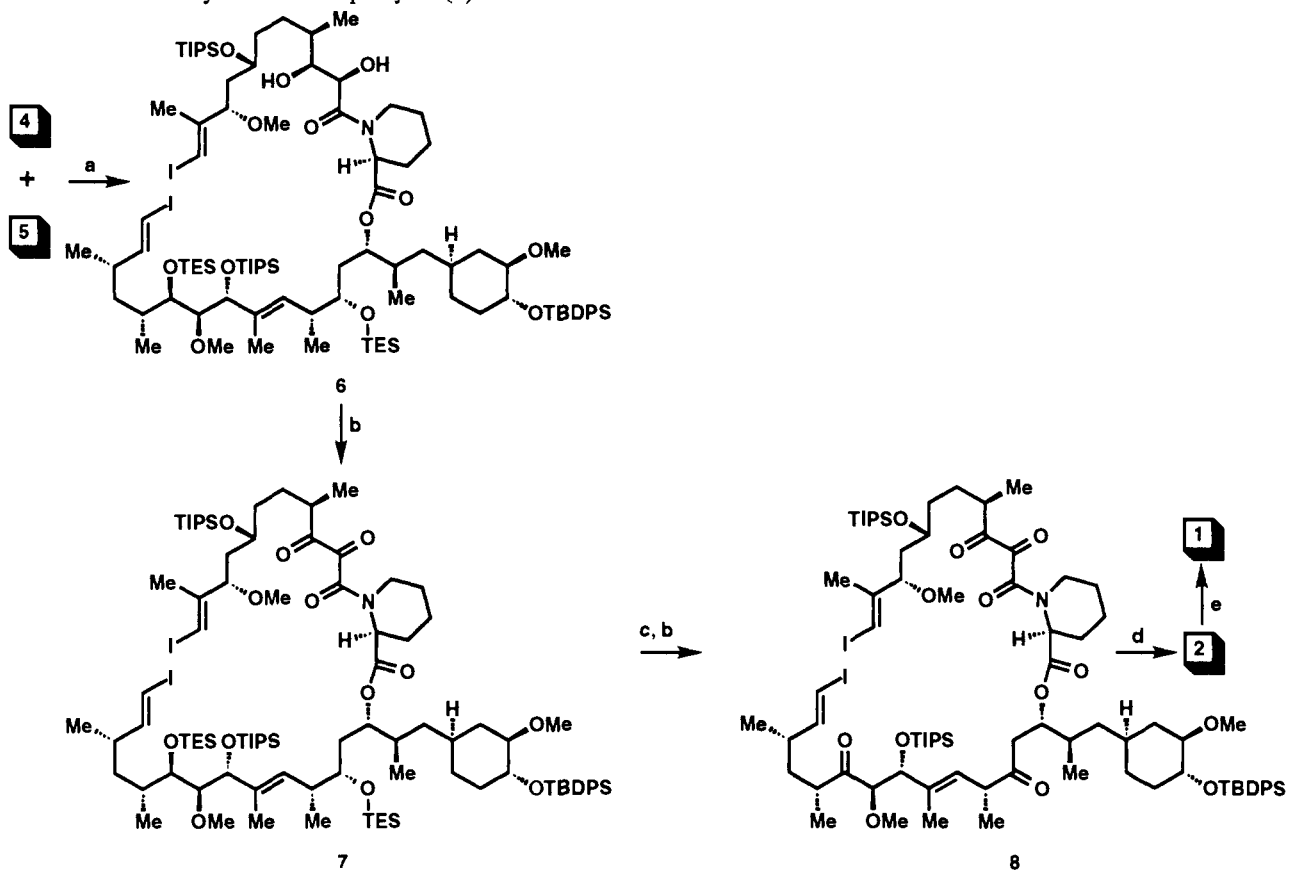
Scheme II. Total Synthesis of Rapamycin (**1**)[a]



[a] Reagents and conditions: (a) **4** (2 equiv), 1-hydroxybenzotriazole (2 equiv), diisopropylcarbodiimide (2 equiv), CH_2Cl_2, 0 °C, 0.5 h, and then **5** (1 equiv), 0–25 °C, 2 h, 95%; (b) $(COCl)_2$ (10 equiv), DMSO (32 equiv), CH_2Cl_2, −78 °C, 15 min, then **6** (1 equiv), −78 °C, 0.5 h followed by Et_3N (50 equiv), −78 to −10 °C, 1 h; (c) excess HF/pyridine, THF, 25 °C, 2 h; (d) aqueous HF in CH_3CN (10%), 25 °C, 60 h, overall 70% yield in four steps from **6**; (e) **3** (1.2 equiv), diisopropylethylamine (1.5 equiv), $Pd(CH_3CN)_2Cl_2$ (20 mol %), DMF/THF (1:1) (0.003 M), 25 °C, 24 h, 28% [plus recovered starting material (ca. 30%) and intermediate iodostannane precursor (ca. 30%)].

This intermediate was converted to rapamycin (**1**) (ca. 60%) under similar conditions, as expected. Synthetic rapamycin (**1**) exhibited physical and spectroscopic data (TLC, HPLC, $[\alpha]^{25}_D$, ^1H and ^{13}C NMR, mass, IR, and UV spectra) identical with those of an authentic sample.[11]

The described total synthesis of rapamycin (**1**) is distinctly direct, represents a new approach to complex polyene macrocyclic structures, and provides an entry into a wide variety of designed immunophilin ligands for biological studies.[12]

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Supplementary Material Available: A listing of selected physical data for compounds **2**, **4**, **5**, and **6** (5 pages). Ordering information is given on any current masthead page.

(10) This iodo–stannane intermediate was not fully characterized, but it was presumed to be the one formed by initial coupling at the less substituted C_{21}–C_{22} vinyl iodide.

(11) We thank Dr. J. Meier (Sandoz Pharma., Basel, Switzerland) and Dr. N. Jensen (Wyeth-Ayerst, Princeton, NJ) for generous samples of rapamycin.

(12) New compounds exhibited satisfactory spectral and exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.