Synthetic Investigations of Rapamycin. 1. Synthesis of a C_{10}–C_{21} Fragment

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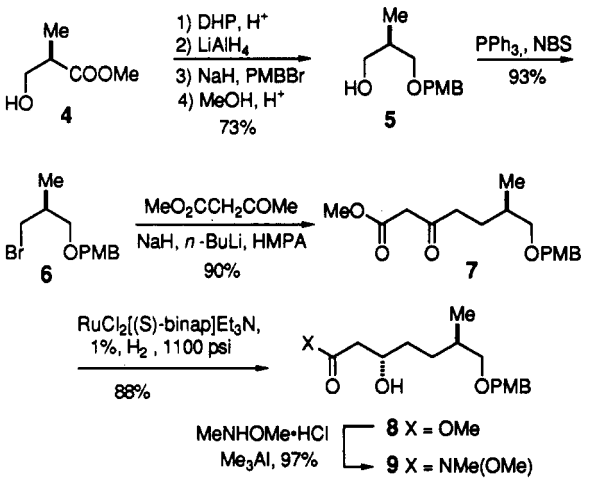
Summary: Phosphine oxide **2**, representing the C_{10}–C_{21} portion of rapamycin, was stereoselectively synthesized and was demonstrated to undergo a Horner–Wittig reaction to form triene **25** as an 8:1 mixture of trans–cis isomers.

Studies of natural products can provide insights into the cellular processes they modulate.[1,2] Few natural products exhibit as much potential in this regard as rapamycin[3] (**1**, Figure 1). When complexed to its intracellular receptor, FKBP,[4,5] rapamycin blocks a previously unrecognized step in signal transduction pathways originating from growth factor receptors.[6,7] The result is that rapamycin-sensitive cells undergo cell cycle arrest; they permanently reside in the G_1 phase of the cell cycle, unable to initiate DNA synthesis (the S phase). This is in contrast to other antiproliferative agents that exhibit general toxicity (an example is taxol[8]). In addition, rapamycin's unique actions are restricted to a limited number of cell types.[9] As there is much to be learned of the steps involved in cell cycle progression, the search for the target of the FKBP–rapamycin complex has been intensive. Our own studies have focused on this problem as well as several other aspects of rapamycin structure and function.[6,10–13] In this and the accompanying paper, we now report our studies that have resulted in the preparation of two fragments (**2**, **3**, Figure 1) that appear to be well-suited for eventual total syntheses of rapamycin and related molecules.[14]

The synthesis of the C_{10}–C_{21} fragment began with (*R*)-methyl 3-hydroxy-2-methylpropionate (Scheme I), which was converted to alcohol **5** by a four-step process: protection as the THP ether (DHP, TsOH·H_2O, Et_2O, 16 h), $LiAlH_4$ reduction, *p*-methoxybenzyl ether formation (NaH, PMB–Br, THF, 14 h), and deprotection (TsOH·H_2O, MeOH, 14 h).[15] Ester **7** was prepared by alkylation (THF, 0 °C) of methyl acetoacetate[16] with bromide **6**, which was derived from **5** (PPh_3, NBS, CH_2Cl_2, 0 °C → rt). Catalytic reduction following the conditions of Noyori[17] provided β-hydroxy ester **8**, which was then converted to its Weinreb amide.[18] Thus, decagram quantities of amide **9** were produced in 54% overall yield from an inexpensive starting material.

Scheme I



Vinyl bromide **10**[19] (Scheme II) was metalated (THF, −90 °C) with two equiv of *t*-BuLi, and the resulting vinyllithium was combined with the lithium alkoxide of Weinreb amide **9** (THF, −78 °C, 30 min); an 85% yield of adduct **11** was obtained, with 10% recovery of amide **9**.[20] Removal of the PMB-protecting group (DDQ, CH_2Cl_2, pH 7 buffer) followed by boron chelation-controlled, 1,3-syn-selective reduction using the conditions of Prasad[21] gave triol **13** as a single isomer in 88% yield for the two steps.

The unfunctionalized **13** required differentiation of the 1,3-diol and oxidation of the primary alcohol; selective oxidation[22] (0.85 equiv of $RuCl_2(PPh_3)_3$, benzene, air, 1.5 h) accomplished both. The resulting mixture of lactols was chromatographed to remove a minor overoxidation product (allylic) and most of the reagent byproduct. Direct double

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(9) For example, we have observed an antiproliferative effect of rapamycin in hematopoietic cells [Jurkat (T lymphocyte), RBL-2H3 (mast cell), IM-9 (B lymphocyte) K562 (erythrocyte)], but not in neurons (PC12) or fibroblasts (NIH 3T3); unpublished results of Sheng Luan and S.L.S.
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(20) On larger than gram scale, significant (15%) butyl adduct was a byproduct. Therefore, it may be better to sacrifice an extra equivalent of **10** rather than to preform the alkoxide of **9** using *n*-BuLi.
(21) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repič, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155–158.
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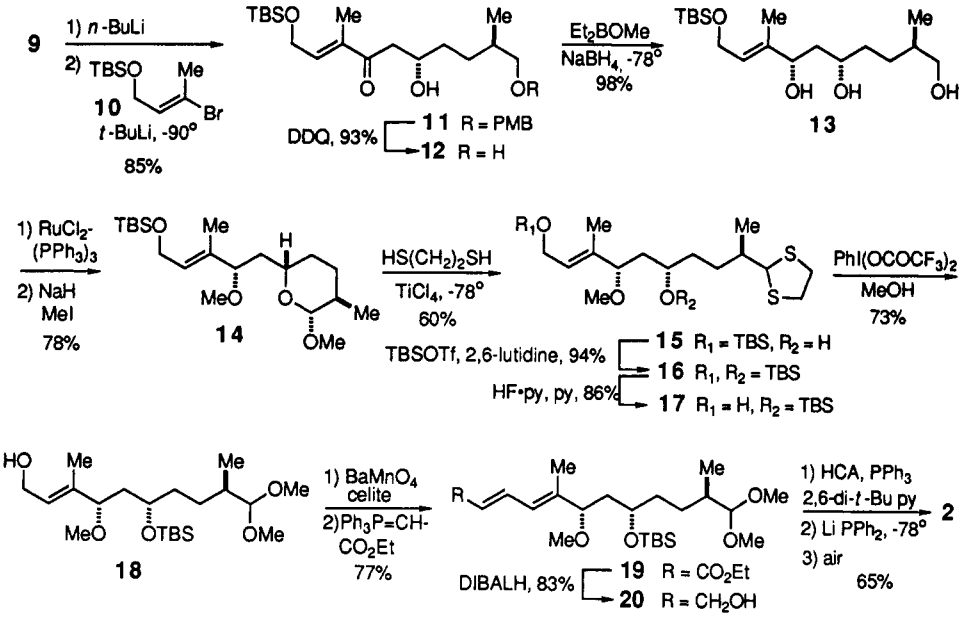
Scheme II



Scheme III

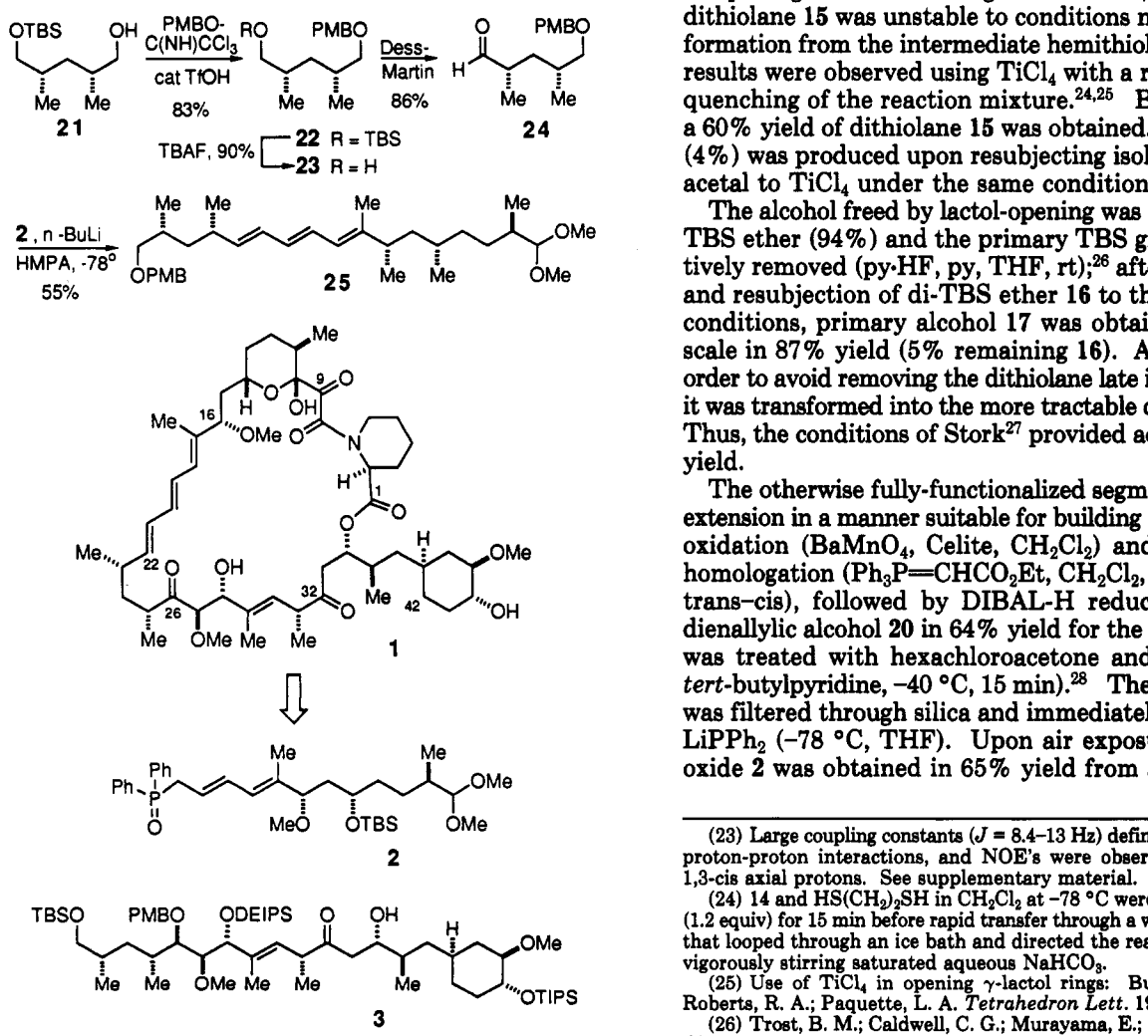


Figure 1. Structure of rapamycin 1 and synthetic precursors 2 and 3.

methylation (NaH, MeI, THF, 0 °C → rt, 2.5 h) gave the β-anomer of methyl lactol 14 in 78% yield from triol 13. NMR analysis of 14 confirmed the indicated relative stereochemistry of substituents around the ring.[23]

Opening of the lactol ring was difficult, as the product dithiolane 15 was unstable to conditions necessary for its formation from the intermediate hemithiolactol. Optimal results were observed using $TiCl_4$ with a rapid warming–quenching of the reaction mixture.[24,25] By this method, a 60% yield of dithiolane 15 was obtained. Additional 15 (4%) was produced upon resubjecting isolated hemithioacetal to $TiCl_4$ under the same conditions.

The alcohol freed by lactol-opening was protected as its TBS ether (94%) and the primary TBS group was selectively removed (py·HF, py, THF, rt);[26] after one isolation and resubjection of di-TBS ether 16 to the deprotection conditions, primary alcohol 17 was obtained on a gram scale in 87% yield (5% remaining 16). At this point, in order to avoid removing the dithiolane late in the synthesis, it was transformed into the more tractable dimethyl acetal. Thus, the conditions of Stork[27] provided acetal 18 in 73% yield.

The otherwise fully-functionalized segment 18 required extension in a manner suitable for building a triene: Allylic oxidation ($BaMnO_4$, Celite, CH_2Cl_2) and direct Wittig homologation ($Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 3 days; 15:1 trans–cis), followed by DIBAL-H reduction, provided dienallylic alcohol 20 in 64% yield for the three steps. 20 was treated with hexachloroacetone and PPh_3 (2,6-di-*tert*-butylpyridine, −40 °C, 15 min).[28] The crude chloride was filtered through silica and immediately titrated with $LiPPh_2$ (−78 °C, THF). Upon air exposure, phosphine oxide 2 was obtained in 65% yield from alcohol 20.[29]

(23) Large coupling constants (J = 8.4–13 Hz) defined all trans-diaxial, proton-proton interactions, and NOE's were observed between most 1,3-cis axial protons. See supplementary material.

(24) 14 and $HS(CH_2)_2SH$ in CH_2Cl_2 at −78 °C were stirred with $TiCl_4$ (1.2 equiv) for 15 min before rapid transfer through a wide Teflon cannula that looped through an ice bath and directed the reaction mixture into vigorously stirring saturated aqueous $NaHCO_3$.

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Finally, phosphine oxide **2** was tested in a triene-forming reaction. For this purpose, alcohol **21**[30] was converted to aldehyde **24**, which served as a truncated model of **3**. α-Lithiated phosphine oxide **2** reacted with **24** (THF, −78 °C) to give an 8:1 trans–cis ratio of triene **25** (55%). Also isolated were the noneliminated adducts (35%), identified by their ability to convert to triene **25** upon resubjection to *n*-BuLi and HMPA. Model compound **25** is stable to mild acid and to storage over months, so the triene appears to confer no special instability to the molecule.[14a] In short, the successful use of phosphine oxide **2** in a model reaction and the ease with which it is made demonstrate its promise as a coupling partner for the C_{22}–C_{42} segment of rapamycin whose synthesis is described in the following paper.

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Supplementary Material Available: Full experimental details (for all numbered reaction products except **21–24**), spectral and analytical data for **2** and **6–25**, and ^1H and ^{13}C spectra for **2**, **6–9**, **11–20**, and **25** (35 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(30) Romo, D.; Johnson, D. D.; Plamondon, L.; Miwa, T.; Schreiber, S. L. *J. Org. Chem.*, following communication in this issue.

Synthetic Investigations of Rapamycin. 2. Synthesis of a C_{22}–C_{42} Fragment

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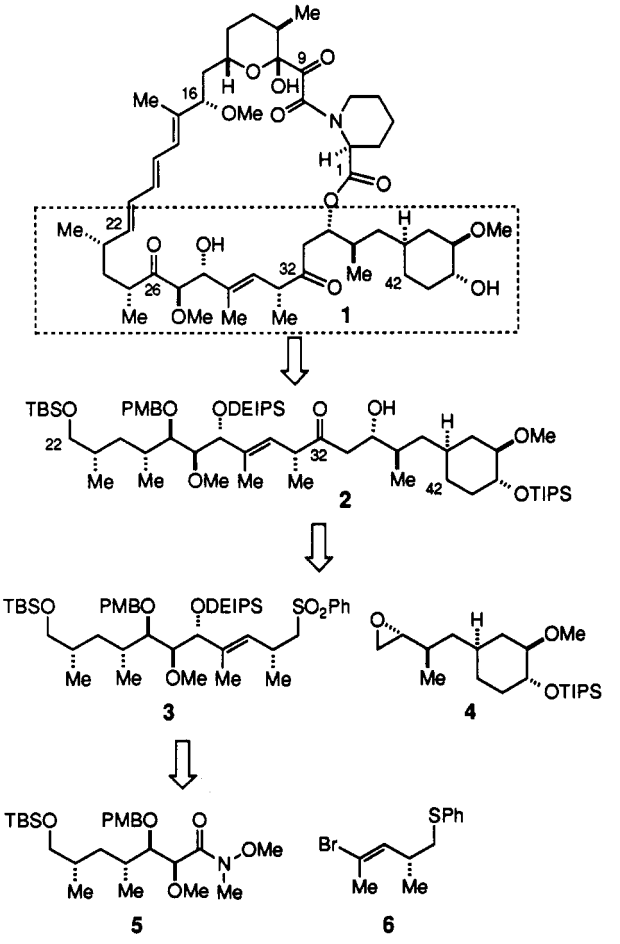
Summary: A concise, modular synthesis of a protected C_{22}–C_{42} segment of rapamycin is reported including as key coupling steps a vinyllithium addition to a Weinreb amide (**5** + **6** → **24**) and a nucleophilic epoxide opening with an α-lithio sulfone mediated by BF_3·OEt_2 (**4** + **27** → **28**).

In the preceding paper,[1] a synthesis of a fully protected C_{10}–C_{21} fragment of the antiproliferative agent rapamycin **1** was described. Herein, we detail a synthesis of a protected C_{22}–C_{42} fragment suitable for coupling to the previously described C_{10}–C_{21} fragment en route to a planned total synthesis of rapamycin and related molecules. The convergent synthesis of the C_{22}–C_{42} segment of rapamycin (**2**) relied on the preparation and subsequent coupling of the Weinreb amide **5**, the vinyl bromide **6**, and the epoxide **4** (Scheme I). Retrosynthetically, we envisioned obtaining the β-hydroxy ketone **2** by oxidative desulfonylation of a γ-hydroxy sulfone resulting from nucleophilic opening of the epoxide **4** by the lithiated sulfone derived from phenyl sulfone **3**. Alkylative coupling of the vinyllithium species generated from bromide **6** and the Weinreb amide **5** was expected to deliver a precursor to phenyl sulfone **3**.

Preparation of Coupling Partners 4–6. The synthesis of the Weinreb amide **5** began by DIBALH half-reduction (CH_2Cl_2, −90 °C, 2.5 h)[2] of the known ester **7** (Scheme II).[3] Direct Wittig olefination (CH_2Cl_2, rt, 18 h) of the crude aldehyde afforded the α,β-unsaturated ester **8** in 80% yield for the two steps. Reduction to the alcohol **9** (DIBALH, CH_2Cl_2, −78 → 0 °C), protection as its *tert*-butyldimethylsilyl ether (TBSCl, CH_2Cl_2, cat. DMAP, rt, 10 h), and debenzylation under dissolving metal conditions (Na^0, NH_3, −78 °C, 15 min) provided the homoallylic alcohol **10** in 93% overall yield. Hydroxyl-directed hydrogenation (CH_2Cl_2, rt, 5 h) employing 4 wt % of the rhodium catalyst described by Evans and co-workers[4] gave the desired 1,3-

Scheme I



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