Total Synthesis of (−)-Rapamycin Using an Evans–Tishchenko Fragment Coupling

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Both rapamycin (**1**) and FK506 form high-affinity complexes with their intracellular receptor FKBP12.[1] The complexes potently interfere with distinct signaling components of the cell cycle. Whereas FKBP–FK506 blocks the entry of resting immune cells into the cell cycle, FKBP–rapamycin blocks the progression of many cell types through an early phase of the cycle, thereby causing cell cycle arrest.[2] Although FKBP–rapamycin's molecular actions have not yet fully been defined, they have provided new insights into growth factor receptor-mediated signaling pathways involved in proliferative disorders such as cancer.[3] For example, FKBP–rapamycin blocks a step necessary for the association of a regulatory cyclin with cyclin-dependent kinases and for the appearance of a cyclin-dependent kinase activity.[4]

The high-resolution X-ray structure of FKBP–rapamycin[5] suggests structural modifications of the ligand that may increase its affinity for the receptor; one of these would have an (*S*)-carbinol in place of the ketone at C_{32} of rapamycin.[6] We reasoned that the C_{32}-(*S*)-carbinol (**2**) could be synthesized by application of the Evans–Tishchenko reaction[7] to the fragment coupling of substructure **3** and Boc-pipecolinal (**4**) (Figure 1). We now report a total synthesis of rapamycin that follows from these considerations.[8]

Our reported synthesis of the rapamycin fragment **6**[8e] suffered from an inefficient oxidative desulfonylation of **5**. An improved procedure takes advantage of the greater reactivity of the α-lithio carbanion of sulfone **5** toward a carbenoid electrophile (Scheme I). Olefination of sulfone **5** according to the method of Julia[9] (73% yield after one recycle of recovered sulfone), regioselective osmylation, and periodate cleavage[10] provided ketone **6** in 69% overall yield for the three steps. A 1:4 mixture of β-hydroxy ketone **6** and (*S*)-Boc-pipecolinal (**4**) was treated at 0 °C with 30 mol % of $(PhCHO)_2SmI$–SmI_3, formed by the addition of 1.1 equiv of SmI_2 to benzaldehyde (0 °C, THF).[7] These conditions provided the coupled product **7** in 95% yield as a >20:1 mixture of anti and syn 1,3-diol monoesters.[11] This fragment coupling is believed to proceed through a transition state ensemble resembling that depicted in Figure 1. That the stereochemical integrity of (*S*)-Boc-pipecolinal was maintained during the Evans–Tischenko reaction was confirmed by reductive deacylation of a compound related to intermediate **7**. Conversion of the resulting Boc-pipecolinol to its Mosher ester and comparison to Mosher esters derived from racemic Boc-pipecolinol indicated that no racemization occurred during the fragment coupling.

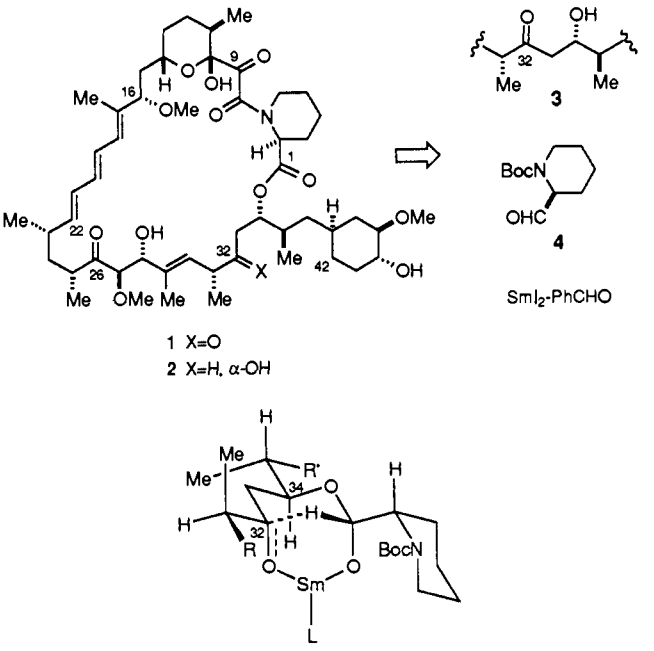

Figure 1. Structures of rapamycin (**1**), C_{32}-(*S*)-dihydrorapamycin (**2**), and synthetic intermediates **3** and **4**; proposed transition-state structure of the Evans–Tishchenko fragment coupling.

Oxidative deprotection of the *p*-methoxybenzyl ether in the presence of solid sodium bicarbonate was followed by the protection of the resulting diol as the bis allyl carbonate with allyl chloroformate and a 10:1 mixture of 2,6-lutidine and pyridine (87% yield, two steps). Selective deprotection of the primary TBS group with buffered *p*-toluenesulfonic acid gave the alcohol **8** in 71% yield after one recycling of recovered starting material (86% yield based on recovered materials).[12] Swern oxidation[13] provided aldehyde **9** (96% yield), which upon condensation with the lithium salt of the previously reported phosphine oxide **10**[8d] provided dimethyl acetal **11** (12:1 trans–cis) in 71% yield[14] based on aldehyde **9**.[15]

Hydrolysis of triene acetal **11** with pyridinium *p*-toluenesulfonic acid[16] (56% yield, 76% yield based on recovered acetal) was

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(2) (a) Schreiber, S. L. *Cell* **1992**, *70*, 365–368. (b) Rosen, M. K.; Schreiber, S. L. *Angew. Chem., Int. Ed. Eng.* **1992**, *31*, 384–400.

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(9) De Lima, C.; Julia, M.; Verpeaux, J.-N. *Synlett* **1992**, 133–134.

(10) Daumas, M.; Vo-Quang, Y.; Vo-Quang, L.; Le Goffic, F. *Synthesis* **1989**, 64–65.

(11) At this time, the assumption of predominantly *anti*-1,3-diol stereochemistry is based on precedent and the proposed transition state model for the Evans–Tishchenko reaction (ref 7).

(12) Recovered materials refers to starting material (8%) and the C_{22},C_{28}-diol (10%, rapamycin numbering). The latter could be reprotected as the bis-DEIPS C_{22},C_{28}-diol and recycled.

(13) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.

(14) In addition to triene **11**, β-hydroxy phosphine oxide adducts were isolated (27%) that could be converted to triene **11** in 89% yield by treatment with lithium hexamethyldisilazide (THF, −78 → 0 °C).

(15) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskoković, M. R. *J. Org. Chem.* **1986**, *51*, 3098–3108.

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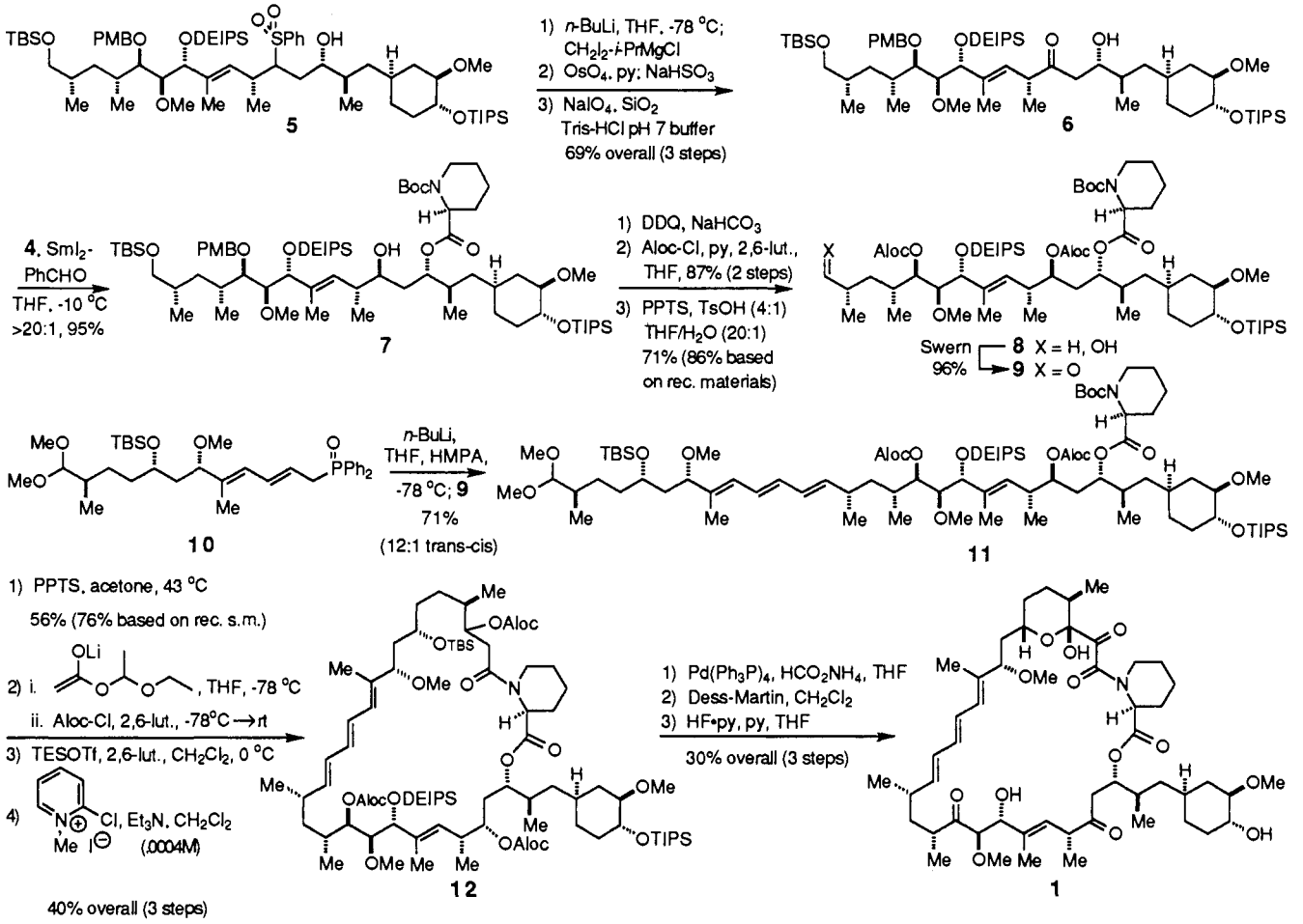
Scheme I[a]



[a] TBS = *tert*-butyldimethylsilyl; PMB = *p*-methoxybenzyl; DEIPS = diethylisopropylsilyl; TIPS = triisopropylsilyl; Boc = *tert*-butoxycarbonyl; Aloc = (allyloxy)carbonyl; TES = triethylsilyl; 2,6-lut. = 2,6-lutidine.

followed by an aldol reaction with the lithium enolate (LDA, THF, –78 °C) of ethoxyethyl acetate[17] and a quench with allyl chloroformate (–78 °C → room temperature). Treatment of the crude aldol adducts with triethylsilyl triflate and exposure of the resulting silyl ethers to silica gel provided an amino acid that was directly subjected to Mukaiyama macrocyclization conditions.[18] The fully protected macrocycle **12** was obtained as a mixture of two diastereomers (~1:1) in 40% overall yield (three steps).

Following removal of the three allyl carbonates,[19] treatment with the Dess–Martin periodinane reagent resulted in the rapid oxidation of the three alcohols and a subsequent oxidation of the C_9 methylene.[20] Final deprotection of the resultant tetraketone with HF·pyridine buffered with excess pyridine gave totally synthetic rapamycin (**1**), which is identical to natural rapamycin as judged by a comparison of their physical properties and spectral data (TLC, HPLC, $[\alpha]_D$, FAB-HRMS, ^{1}H-NMR, ^{13}C-NMR, IR, and UV).

The synthesis of rapamycin described herein relies upon a stereoselective fragment coupling to yield a monoester of an *anti*-1,3-diol. We intend to use this fragment coupling and other features of the synthesis to explore both existing and potential interactions between FKBP12 and rapamycin.

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Supplementary Material Available: A listing of physical and spectral data for intermediates **4**, **7**, **8**, **11**, and **12** and analytical and spectral data for synthetic and authentic rapamycin (21 pages). Ordering information is given on any current masthead page.

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(19) Hayakawa, Y.; Kato, H.; Mamaoru, U.; Kajino, H.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 2400–2402.
(20) Batchelor, M. J.; Gillespie, R. J.; Golec, J. M. C.; Hedgecock, C. J. R. *Tetrahedron Lett.* **1993**, *34*, 167–170. This oxidation was most readily monitored by FAB-MS analysis of aliquots removed during the course of the reaction. Oxidation to the triketone is complete within 30 min while oxidation to the tetraketone requires an additional 3–4 h.