Total Synthesis of Rapamycin via a Novel Titanium-Mediated Aldol Macrocyclization Reaction

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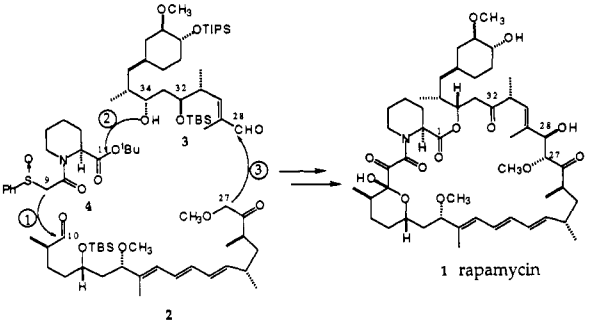
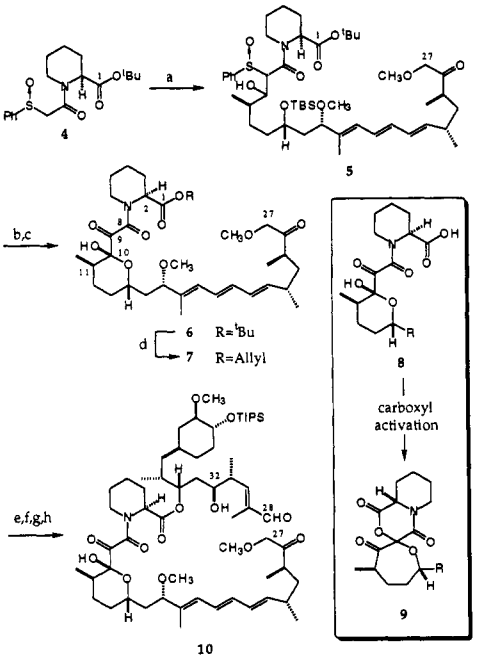
The advent of the two "tricarbonyl" macrolactam–macrolactone immunosuppressive agents rapamycin (**1**)[1,2] and FK-506[3] has provided exciting multidisciplinary scientific challenges.[4] Indeed, by drawing upon the powerful resources of chemistry (both synthetic and structural)[5,6] in conjunction with those of molecular and cell biology, Schreiber and associates are in the process of defining the mechanisms of action of these drugs in striking detail.[7] Total[8,9] as well as formal[10] syntheses of FK-506 have been achieved. The total synthesis of rapamycin was first reported by Nicolaou *et al.*[11] and has also been accomplished by Schreiber and associates.[12]

Our laboratory has been engaged in degradative[13–15] as well as synthetic[16,17] studies centered around FK-506 and rapamycin. The long-term aim of both efforts is to pinpoint the substructural features which are critical for binding to natural receptors and for immunosuppressive function.[18] In the case of rapamycin, we recently described investigations which led to the syntheses of compounds **2**[19] and **3**[20] (Scheme I). Another building block, **4**, was readily obtained from L-pipecolic acid.[21] Herein, we disclose the total synthesis of rapamycin *featuring as a key step the highly novel macroaldolization of seco intermediate* ***11*** *via its titanium enolate to establish the 31-membered ring.*

Scheme I



Scheme II[a]



[a] (a) LDA, THF, −78 °C; **2**, 57%. (b) Dess–Martin periodinane, CH_2Cl_2, pyridine, 25 °C. (c) HF·pyridine, THF, 25 °C, 32% from **5**. (d) (i) HCO_2H, CH_2Cl_2, 25 °C; (ii) allyl bromide, K_2CO_3, catalytic n-$Bu_4N^+I^-$, DMF, 25 °C, 66%. (e) TMS–imidazole, catalytic DMAP, DMF, 25 °C, 94%. (f) 20 mol % $Pd(PPh_3)_4$, catalytic PPh_3, CH_2Cl_2, 25 °C, 70%. (g) **3**, DCC, catalytic DMAP, CH_2Cl_2, −20 °C, 85%. (h) n-$Bu_4N^+F^-$, HOAc, THF, 50 °C, 50%.

We combined the synthetic building blocks **2**, **3**, and **4** in the sequence shown in Scheme I (see arrows) and by the methods specified in Scheme II. We defined as an interim goal compound **6**, which contains the sensitive tricarbonyl and triene sectors of **1** as well as the enolate source for a projected macroaldolization (*vide infra*). For this purpose, **4** was converted to its lithio derivative, which condensed with **2**, thereby producing **5** in 57% yield. Upon oxidation with Dess–Martin periodinane[22] followed by desilylation, the desired **6** was obtained in 32% overall yield. We emphasize the simplicity of this new method of tricarbonyl synthesis[23] and its compatibility with the rather fragile functionality of this system.[24]

At this stage, we were in a position to exploit another piece of chemistry developed in our laboratory, i.e., that of generating a competent acylating agent from the pipecolinyl section of a

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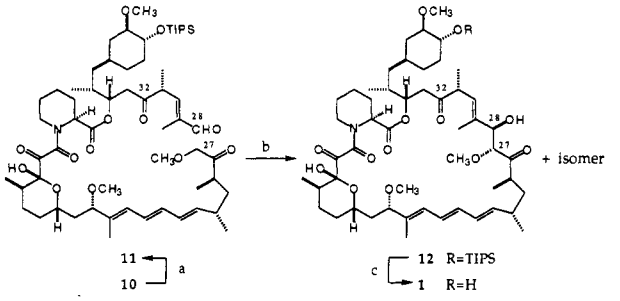
Scheme III[a]



[a] (a) Dess–Martin periodinane, CH_2Cl_2, pyridine, 25 °C, 89%. (b) $TiCl_3$(OiPr), CH_2Cl_2, -78 °C; Et_3N, 11%. (c) HF·pyridine, THF, 25 °C, 85%.

secorapamycin which, though truncated, does contain the hemiketal and triene linkages.[25] The difficulty that had to be overcome was the tendency of systems bearing the free hemiketal hydroxyl to undergo lactonization (see transformation **8** → **9**)[26] upon attempted esterification with various external alcohol constructs.

Accordingly, the *tert*-butyl ester function of **6** was cleaved, and the resulting acid was converted to its allyl ester **7**. After protection of the tertiary hemiketal hydroxyl group as its trimethylsilyl ether,[25] the allyl ester was cleaved through the agency of $Pd(PPh_3)_4$[27] to afford an acid. This acid was esterified with the C-34 hydroxyl (rapamycin numbering) of compound **3**[20] using DCC–DMAP[8] in 85% yield. Selective twofold desilylation of the C-10 and C-32 silyloxy groups afforded **10**. Finally, oxidation of the C-32 hydroxyl of **10** with Dess–Martin periodinane led to the C-40-silylated secorapamycin **11**, the substrate for the projected intramolecular macroaldolization (Scheme III).[28]

With compound **11** in hand, an extensive investigation of macroaldol cyclization methods was initiated. The first sets of conditions surveyed were those which were expected to generate metalloenolates of the type well known to participate in aldol condensations. These efforts were unsuccessful. For instance, attempts to generate either lithium[29] or cerium[30] enolates of **11** by standard protocols did not lead to detectable cyclization products. Similarly, recourse to reagents such as $(cyclohexyl)_2BCl$,[31a] $Sn(OTf)_2$,[31b] Bu_3SnCl,[31c] $SnCl_4$,[31d] $ZnCl_2$,[31e] and $ZrCp_2Cl_2$[31f] each in the presence of prescribed amines also led to no detectable cyclization products.

The first success that was realized resulted from recourse to a presumed titanium enolate generated under conditions (**11** + $TiCl_4$, CH_2Cl_2, -78°C; Et_3N) described by Evans.[32] There were thus isolated a 7% yield of C-40 TIPS rapamycin **12**, a 14% yield of an apparent stereoisomer of **12**,[33] and a 35–45% yield of recovered **11**. The use of isopropoxytitanium trichloride as the promoter[34] afforded a 33% yield (42% based on recovered **11**) of a 1:2.3 ratio of **12** to the same stereoisomer that was observed in the reaction mediated by $TiCl_4$. The identity of synthetic **12** was established by comparison of its NMR, infrared, and FAB mass spectra as well as its chromatographic mobility to those of **12** prepared from silylation of native rapamycin. The structure of **12** was further proven by desilylation (HF·pyridine) to afford rapamycin itself.[35]

Many features of the fascinating formation of the C-27–C-28 bond of rapamycin by intramolecular aldolization are being explored (including the use of biomimetic schemes for cyclization). This work will be described in due course. Also awaiting full clarification are issues relating to the thermodynamic stabilities and kinetic connectivities among these and possibly other C-27–C-28 stereoisomers. Finally, we note that the capacity to interpolate compound **3** between the pipecolinic acid (C-1) and carbon-27 in the manner described might well be exploited to create new analogs of rapamycin for biological investigation.

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Supplementary Material Available: Analytical data for compounds **7**, persilylated **10**, **11**, and **12**, and synthetic **1** (6 pages). Ordering information is given on any current masthead page.

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