RAPAMYCIN SYNTHETIC STUDIES. 2. ELABORATION OF THE C(10)-C(26) PERIMETER


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Summary: The C(10)-C(26) subunit of the potent immunomodulator rapamycin has been constructed via a highly convergent approach, exploiting palladium-mediated σ-bond formation to generate the sensitive triene moiety.

We have undertaken the total synthesis of rapamycin (1), a naturally occurring immunosuppressant of considerable promise both in organ transplantation and in studies of intracellular signal transduction. The unique—albeit as yet unresolved—mechanism of action of 1 is complementary to those of cyclosporin A and FK506. From the synthetic perspective, the intriguing, architecturally complex polyketide framework presents a formidable challenge. Our analysis of the structure generated the key building blocks A-E (Scheme I) via a series of disconnections which allow for considerable flexibility, both in the construction of 1 and ultimately in the preparation of analogs. The accompanying Letter outlines the elaboration and union of subtargets A and B. Herein we describe the synthesis of the C(10)-C(26) segment of rapamycin.

Scheme I

From the outset, we envisioned that the potentially sensitive E,E,E-triene unit could be introduced in regio- and stereocontrolled fashion via palladium-mediated σ-bond construction. Successful C(20)-C(21) coupling of C with D would generate 2 (Scheme II), an advanced intermediate which effectively encompasses the C(10)-C(26) segment of 1. Thus, we initially designed enantioselective syntheses of the coupling partners D and C, envisioning that these intermediates would derive from aldehyde 3, previously employed in our latrunculin synthetic program, and the well-known meso diester 4, respectively.

We planned to elaborate the stannyl diene unit of D via free-radical hydrostannylation of the corresponding vinyl acetylene (cf., Scheme IV). Recognizing that this approach would also effect Z-to-E isomerization of the Δ17,18 trisubstituted olefin, we were able to consider both 5 and 6 (Scheme III) as building blocks for the diene moiety.
In the event, both the E and Z enynes could be selectively prepared by hydrostannylation of the known silyl diyne with the appropriate stanny cuprate.  

**Scheme II**

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\begin{align*}
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\]

**Scheme III**

Following transmetalation of 5 and 6 (n-BuLi, THF, -78 °C), the vinyl lithium species were added to aldehyde (+)-3 (Scheme IV). The E isomer 5 led to the diastereomeric alcohols 9 \((1:1:1)\) in 73% yield. In contrast, the lithium derivative of 6 induced significantly higher stereoselectivity, affording 9 \(6:1\) mixture of epimers (65%). Following chromatographic separations, the major secondary alcohols were methylated with concomitant cleavage of the trimethylsilyl protecting groups to afford enynes \((+)-10^6\) and \((+)-11^6\) in good yield. The stage was set for formation of the E,E...
di-enyltinannane and, as anticipated, treatment of both the E and Z enynes 10 and 11 with n-Bu$_3$SnH and AIBN (toluene at reflux) gave key intermediate (+)-D (50-55% yield), indicating that die to trans isomerization had indeed occurred.

The synthesis of the C(21)-C(26) fragment C began with the desymmetrization of the meso diester 4 (Scheme V). Enzymatic hydrolysis with α-chymotrypsin provided the half acid in 80% yield and 94% ee and reduction of the carboxyl group with borane methyl sulfide cleanly afforded the primary alcohol (-)-12. Following protection as the tert-butyldiphenylsilyl (BPS) ether, the ester moiety was converted to the corresponding aldehyde via DIBAL reduction and Swern oxidation (65% yield, three steps). Exposure to 1,3-propanedithiol and boron trifluoride etherate then furnished aldehyde (+)-13 in 90% yield. Without purification, the aldehyde was subjected to Takai-Nozaki olefination, affording the desired vinyl iodide (+)-C in 90% yield.

**Scheme V**

We were now prepared to investigate the critical coupling of dienyl tin (+)-D with vinyl iodide (+)-C. Unfortunately, a variety of coupling protocols inefficiently furnished the desired triene 2 as a mixture of E and Z isomers, accompanied by significant quantities of the homocoupled tetratriene (+)-15 (e.g., Scheme VI).

**Scheme VI**

Attributing the formation of the undesired products, at least in part, to slow insertion of palladium into the carbon-iodine bond of C, we decided to transpose the reactive functionalities of C and D (Scheme VII). To this end, vinyl iodide (+)-C was metallated at 78 °C with t-BuLi in diethyl ether; treatment of the resultant vinyl lithium species with freshly distilled n-Bu$_3$SnI provided vinyl stannane (+)-16 in 78% yield. Dienyl stannane (+)-D furnished the corresponding iodide (+)-17 quantitatively upon reaction with I$_2$. Coupling of 10 with 17 then gave (+)-2 as the major triene (64%), accompanied by the product of vinyl stannane homocoupling (18%) and traces of unidentified isomers of 2.12
In summary, we have developed a convergent, stereocontrolled approach to the C(10)-O(20) triene segment of rapamycin. Studies directed toward further refinement of the coupling process and the total syntheses of rapamycin and congeners thereof will be reported in due course.

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REFERENCES AND NOTES

1. Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leahy, J. W.; Leazer, J. L., Jr.; Maleczka, R. E., Jr., preceding Letter in this issue. This paper contains extensive references to previous studies of rapamycin: isolation, biological activity, and synthetic approaches.


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 62.5- or 125-MHz 13C NMR spectra, as well as appropriate parent ion identification by high resolution mass spectrometry. In addition, 10-14, and 1D gave satisfactory C and H combustion analyses.


9. The relative and absolute stereochemistry of the β epimer of 10 was determined by single-crystal X-ray analysis.

10. The methylation of (+)-9 furnished furan (+)-1 as the major product when Mel was introduced after KOH; see: Bonnet, P. H.; Bohlmann, F. Chem. Ber. 1971, 104, 1616.


12. Proton decoupling experiments enabled us to unambiguously assign the 1H NMR signals for the triene array of (−)-2. The observed proton-proton coupling constants are in close agreement with those reported for natural rapamycin. For 2: 1H NMR (500 MHz, CDCl3) δ 6.38 [dd, J = 14.5, 11.0 Hz, H(19)], 6.20 [d, J = 11.0 Hz, H(18)]. 6.18 [dd, J = 14.5, 10.5 Hz, H(20)], 6.10 [dd, J = 14.5, 10.5 Hz, H(21)], 5.47 [dd, J = 14.8, 8.8 Hz, H(22)].


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