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

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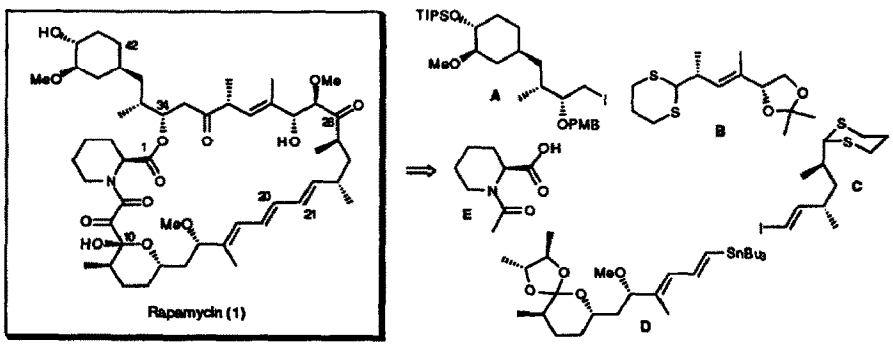
Summary: The C(10)-C(26) subunit of the potent immunomodulator rapamycin has been constructed via a highly convergent approach, exploiting palladium-mediated σ-bond formation to generate the sensitive triene moiety.

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.[1] Herein we describe the synthesis of the C(10)-C(26) segment of rapamycin.

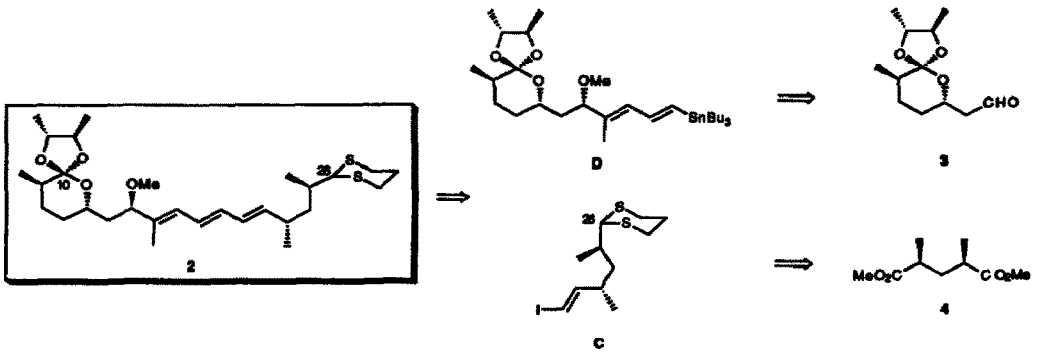
Scheme I



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.[2] 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,[3] and the well-known meso diester **4**,[4] respectively.

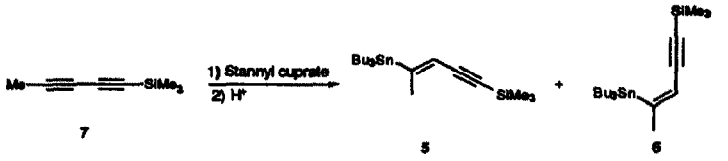
We planned to elaborate the stannyl diene unit of **D** via free-radical hydrostannylation of the corresponding vinyl acetylene (cf., Scheme IV). Recognizing that this approach would also effect Z-to-E isomerization of the $\Delta^{17,18}$-trisubstituted olefin,[5] we were able to consider both **5** and **6** (Scheme III) as building blocks for the diene moiety.

Scheme II



In the event, both the E and Z enynes[6] could be selectively prepared by hydrostannylation of the known silyl diyne 7[7] with the appropriate stannyl cuprate.[8]

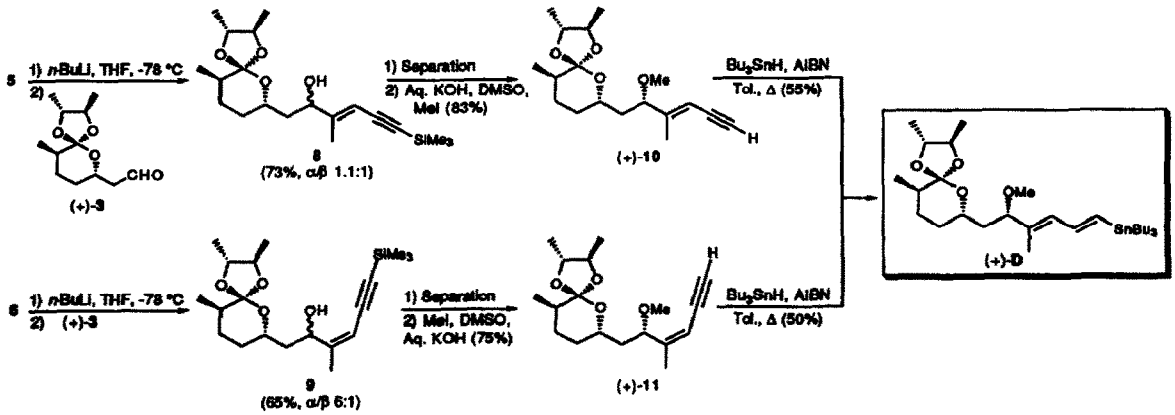
Scheme III



Reaction Conditions	E/Z Ratio (5 : 6)
1) $Bu_3Sn(Bu)Cu(CN)Li_2$, THF, -78 °C; 2) NH_4Cl/MeOH (65%, 2 steps)	27 : 1
1) $Bu_3Sn(Me)Cu(CN)Li_2$, THF, -78 to -30 °C; 2) NH_4Cl/MeOH (71%, 2 steps)	1 : >50

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 **8**[6] (1.1:1 ratio) in 73% yield. In contrast, the lithium derivative of **6** induced significantly higher stereoselectivity, affording **9**[6] as a 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.[9,10] The stage was set for formation of the E,E

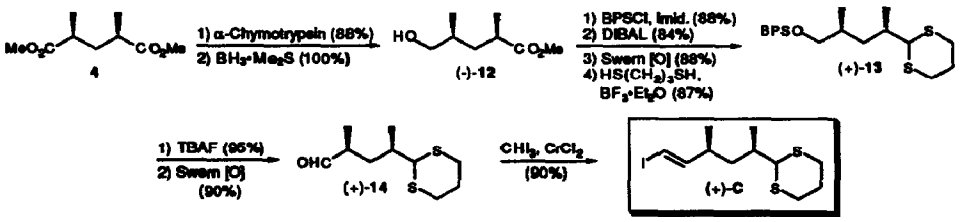
Scheme IV



dienylstannane and, as anticipated, treatment of both the E and Z enynes **10** and **11** with *n*-Bu_3SnH and AIBN (toluene at reflux) gave key intermediate (+)-**D** (50-55% yield), indicating that cis-to-trans isomerization had indeed occurred.

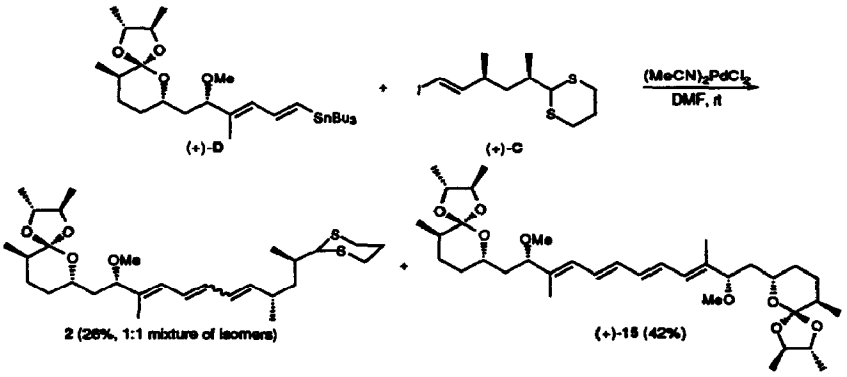
The synthesis of the C(21)-C(26) fragment **C** began with the desymmetrization of the meso diester **4** (Scheme V). Enzymatic hydrolysis with α-chymotrypsin provided the half acid in 88% yield and 94% ee[4] and reduction of the carboxyl group with borane methyl sulfide cleanly afforded the primary alcohol (-)-**12**.[6] Following protection as the *t*-butyl(diphenyl)silyl (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 dithiane (+)-**13**[6] (87%). Desilylation of **13** and Swern oxidation gave aldehyde (+)-**14**[6] in 90% yield. Without purification, the aldehyde was subjected to Takai-Nozaki olefination,[11] affording the desired vinyl iodide (+)-**C**[6] in 90% yield.

Scheme V



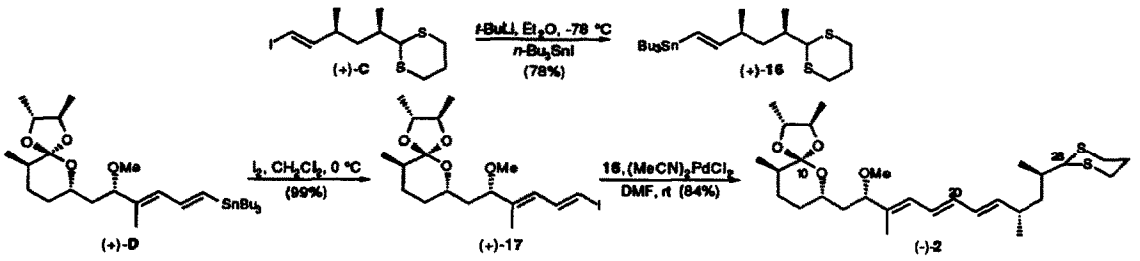
We were now prepared to investigate the critical coupling of dienyl tin (+)-**D** with vinyl iodide (+)-**C**. Unfortunately, a variety of coupling protocols[2] inefficiently furnished the desired triene **2** as a mixture of E and Z isomers, accompanied by significant quantities of the homocoupled tetraene (+)-**15**[6] (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 metalated at -78 °C with *t*-BuLi in diethyl ether; treatment of the resultant vinyl lithium species with freshly distilled *n*-Bu_3SnI provided vinyl stannane (+)-**16**[6] in 78% yield. Dienyl stannane (+)-**D** furnished the corresponding iodide (+)-**17**[6] quantitatively upon reaction with I_2. Coupling of **16** with **17** then gave (-)-**2** as the major triene (84%), accompanied by the product of vinyl stannane homocoupling (18%) and traces of unidentified isomers of **2**.[12]

Scheme VII



In summary, we have developed a convergent, stereocontrolled approach to the C(10)-C(26) 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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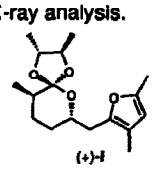
9. The relative and absolute stereochemistry of the β epimer of **10** was determined by single-crystal X-ray analysis.
10. The methylation of (+)-**9** furnished furan (+)-**I** as the major product when MeI was introduced after KOH; see: Bonnet, P. H.; Bohlmenn, F. *Chem. Ber.* **1971**, *104*, 1616.



(+)-I

11. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
12. Proton decoupling experiments enabled us to unambiguously assign the ^{1}H NMR signals for the triene array of (-)-**2**. The observed proton-proton coupling constants are in close agreement with those reported for natural rapamycin.[13] For **2**: ^{1}H NMR (500 MHz, C_6D_6) 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 = 14.8, 10.5 Hz, H(21)], 5.47 [dd, J = 14.8, 8.6 Hz, H(22)].
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