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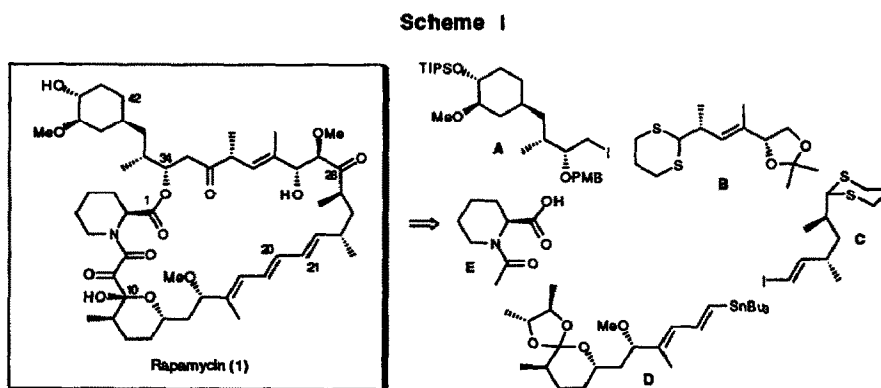
## RAPAMYCIN SYNTHETIC STUDIES. 2. ELABORATION OF THE C(10)-C(26) PERIMETER

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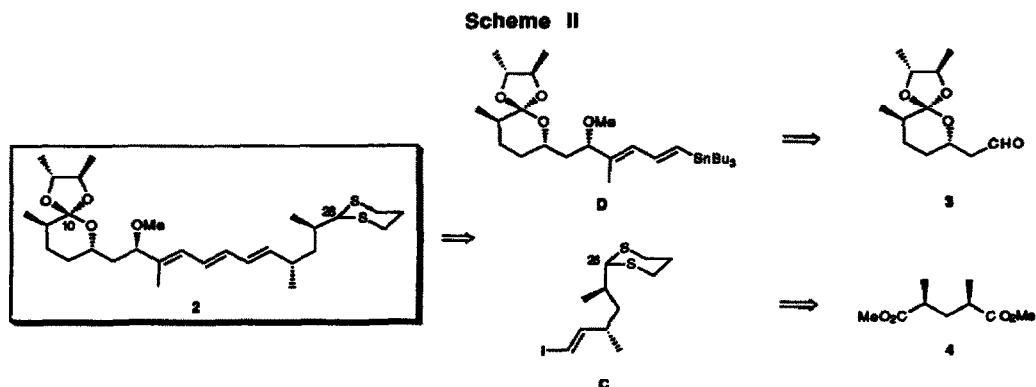
**Summary:** The C(10)-C(26) subunit of the potent immunomodulator rapamycin has been constructed via a highly convergent approach, exploiting palladium-mediated  $\sigma$ -bond formation to generate the sensitive triene moiety.

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.<sup>1</sup> Herein we describe the synthesis of the C(10)-C(26) segment of rapamycin.



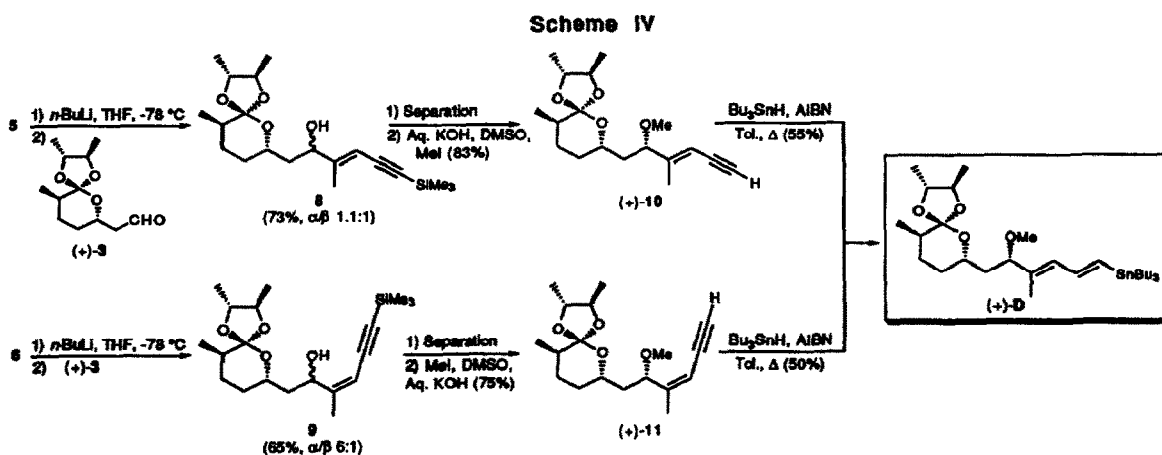
From the outset, we envisioned that the potentially sensitive E,E,E-triene unit could be introduced in regio- and stereocontrolled fashion via palladium-mediated  $\sigma$ -bond construction.<sup>2</sup> Successful C(20)-C(21) coupling of C with D would generate 2 (Scheme II), an advanced intermediate 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,<sup>3</sup> and the well-known meso diester 4,<sup>4</sup> 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,<sup>5</sup> 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<sup>6</sup> could be selectively prepared by hydrostannylation of the known silyl diyne **7**<sup>7</sup> with the appropriate stannyl cuprate.<sup>8</sup>

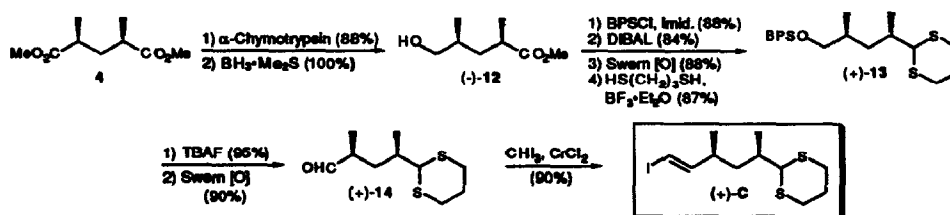
Following transmetalation of **5** and **6** (*n*-BuLi, THF,  $-78^\circ\text{C}$ ), the vinyl lithium species were added to aldehyde (+)-**3** (Scheme IV). The E isomer **5** led to the diastereomeric alcohols **8**<sup>6</sup> (1.1:1 ratio) in 73% yield. In contrast, the lithium derivative of **6** induced significantly higher stereoselectivity, affording **9**<sup>6</sup> 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**<sup>6</sup> and (+)-**11**<sup>6</sup> in good yield.<sup>9,10</sup> The stage was set for formation of the E,E



dienylstannane and, as anticipated, treatment of both the E and Z enynes **10** and **11** with *n*-Bu<sub>3</sub>SnH and AIBN (toluene at reflux) gave key intermediate (+)-**D** (50–55% yield), indicating that cis-to-trans isomerization had indeed occurred.

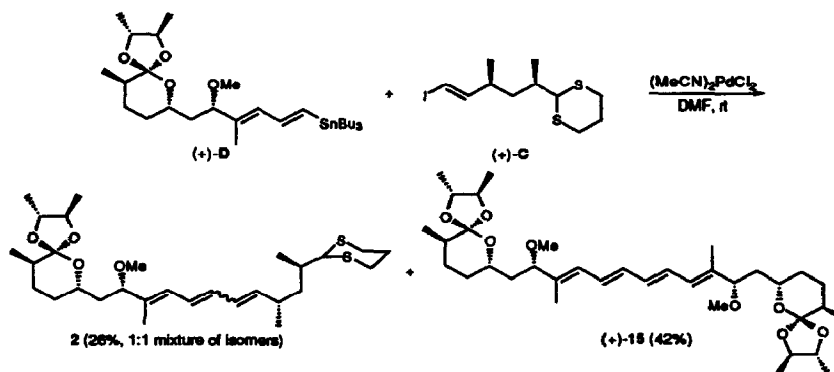
The synthesis of the C(21)–C(26) fragment **C** began with the desymmetrization of the meso diester **4** (Scheme V). Enzymatic hydrolysis with α-chymotrypsin provided the half acid in 88% yield and 94% ee<sup>4</sup> and reduction of the carboxyl group with borane methyl sulfide cleanly afforded the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

Scheme V



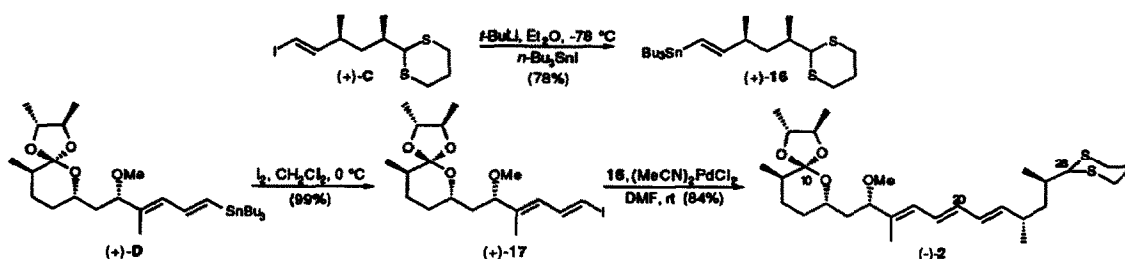
We were now prepared to investigate the critical coupling of dienyl tin (+)-**D** with vinyl iodide (+)-**C**. Unfortunately, a variety of coupling protocols<sup>2</sup> inefficiently furnished the desired triene **2** as a mixture of E and Z isomers, accompanied by significant quantities of the homocoupled tetraene (+)-**15**<sup>6</sup> (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<sub>3</sub>SnI provided vinyl stannane (+)-**16**<sup>6</sup> in 78% yield. Dienyl stannane (+)-**D** furnished the corresponding iodide (+)-**17**<sup>6</sup> quantitatively upon reaction with I<sub>2</sub>. 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**.<sup>12</sup>

## Scheme VII

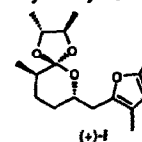


In summary, we have developed a convergent, stereocontrolled approach to the C(10)-C(26) triene segment of rapamycin. Studies directed toward further refinement of the coupling process and the total syntheses of rapamycin and congeners thereof will be reported in due course.

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- The relative and absolute stereochemistry of the  $\beta$  epimer of **10** was determined by single-crystal X-ray analysis.
- The methylation of (+)-**9** furnished furan (+)-**1** as the major product when MeI was introduced after KOH; see: Bonnet, P. H.; Bohlmann, F. *Chem. Ber.* **1971**, *104*, 1616.
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- Proton decoupling experiments enabled us to unambiguously assign the  $^1\text{H}$  NMR signals for the triene array of (-)-**2**. The observed proton-proton coupling constants are in close agreement with those reported for natural rapamycin.<sup>13</sup> For **2**:  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  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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