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SPONGISTATIN SYNTHETIC STUDIES. 3. CONSTRUCTION OF THE C(1-17) SPIROKETAL

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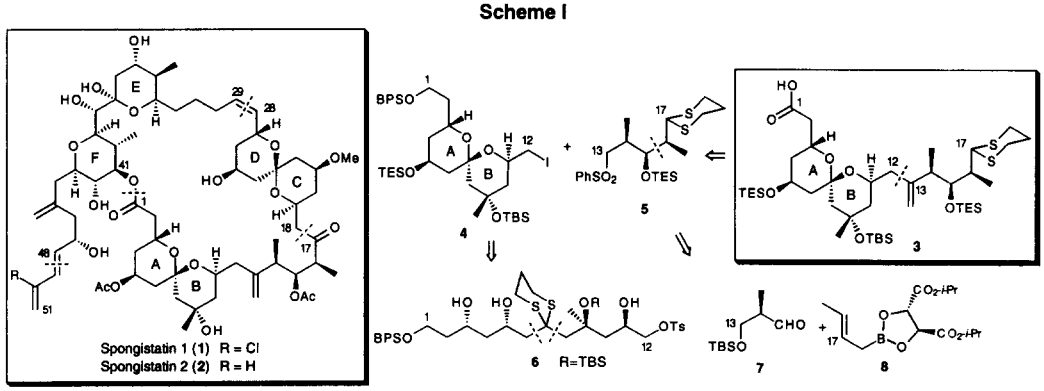
Summary: A convergent synthesis of the C(1-17) AB-ring subunit of the spongistatins, exceedingly scarce and highly antimitotic polyether macrolides, has been achieved via a one-flask dithiane bisalkylation, stereocontrolled spiroketalization, and Julia sulfone coupling/methylenation. © 1997 Elsevier Science Ltd.

In the first two Letters in this series,[1] we described considerable progress toward the total synthesis of the spongistatins (e.g., **1** and **2**, Scheme 1), a family of rare and architecturally novel sponge metabolites with unprecedented antitumor activity.[2] Herein we report the assembly of the C(1-17) AB-ring spiroketal subunit **3**.

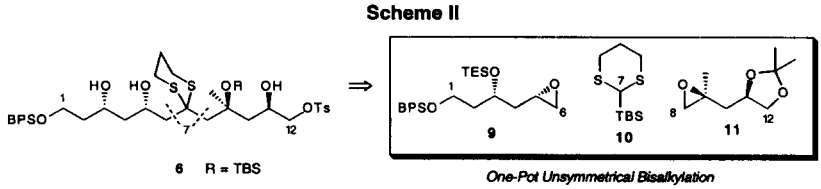
Scheme I



Initial retrosynthetic disconnection of **3** generated the iodo spiroketal **4** and sulfone **5** (Scheme I). The AB-ring spiro moiety of the spongistatins is stabilized by two anomeric interactions;[3] MM2 calculations[4] confirmed that the requisite spiro configuration in **4** is thermodynamically favored. Accordingly, the acyclic dithiane **6** was envisioned as a suitable precursor. The sulfone fragment **5** was expected to derive from aldehyde **7**[5] via coupling with (*E*)-crotylborane **8**[6] according to the procedure of Roush.[6]

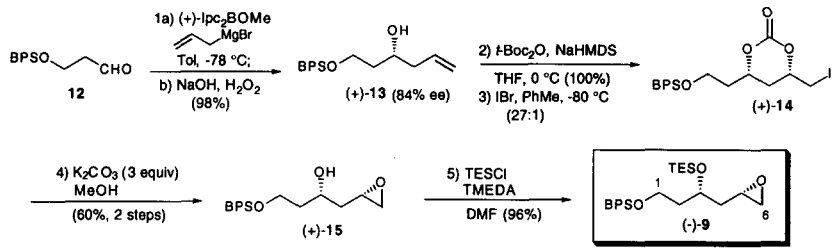
Analysis of dithiane **6** (Scheme II) revealed another opportunity to exploit the one-pot unsymmetrical bisalkylation of 2-TBS-1,3-dithiane (**10**), developed in these laboratories[7] and advantageously employed in our synthesis of the spongistatin AB-ring spiroketal.[1] This tactic concisely affords polyol chains with rigorous stereochemical control and differentiation of the hydroxyl groups. Application to the ketalization substrate **6** required the C(1-6) and C(8-12) epoxides **9** and **11** as coupling partners.[8]

Scheme II



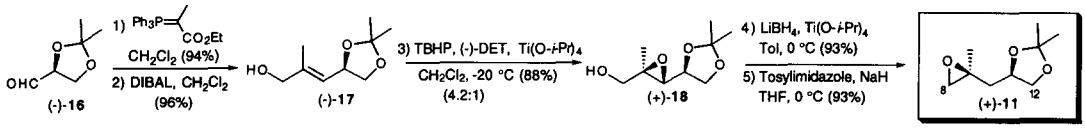
Construction of **9** began with known aldehyde **12**[9] (Scheme III), available in two steps from 1,3-propanediol. Addition of allyl(diisopinocampheyl)borane[10] provided allylic alcohol (+)-**13**[11] in 98% yield and 84% ee (Mosher analysis).[12] Following acylation with *t*-Boc anhydride, our modification[13] of the Bartlett carbonate cyclization[14] (IBr, toluene, -80 °C) generated iodo carbonate (+)-**14**[11] with 27:1 diastereoselectivity. Treatment of the crude mixture with K_2CO_3 in methanol furnished epoxy alcohol (+)-**15**[11] (60% yield, two steps). Removal of the minor diastereomer by flash chromatography and silylation (TESCl, TMEDA, DMF, 96%) gave the C(1-6) building block (-)-**9**.[11]

Scheme III



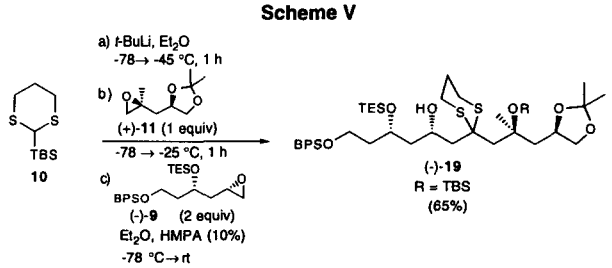
Epoxide (+)-**11** was efficiently prepared from the isopropylidene derivative of L-glyceraldehyde [(-)-**16**;[15] Scheme IV]. The two-step method of Fukumoto[16] (i.e., Wittig olefination followed by DIBAL reduction) furnished allylic alcohol (-)-**17**[11] in excellent yield. Despite a mismatched reagent-substrate pair,[17] Sharpless asymmetric epoxidation[18] provided (+)-**18**[11] as an acceptable 4.2:1 mixture of diastereomers (88% yield) on a 50-g scale. After separation via flash chromatography, chelation-controlled reduction[19] of (+)-**18**[11] [$LiBH_4$, $Ti(O\text{-}i\text{-}Pr)_4$, CH_2Cl_2, -20 °C; 88%] and a modified Kishi cyclization[20] of the resultant diol (tosylimidazole, NaH; 93%) completed the synthesis of the C(8-12) epoxide (+)-**11**.[11]

Scheme IV

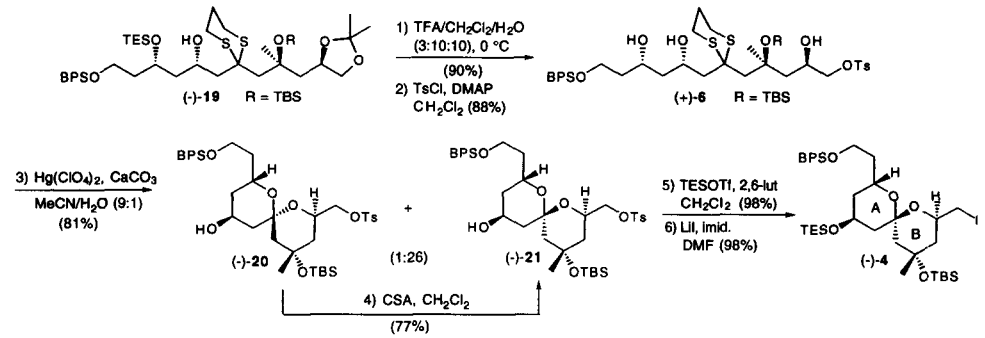


The unsymmetrical bisalkylation of dithiane **10** with epoxides (-)-**9** and (+)-**11** was carried out via the protocol we described earlier,[7] providing the desired coupling product (-)-**19**[11] in 65% yield (Scheme V). With the requisite polyol in hand, we turned next to the generation of the AB-ring spiroketal (Scheme VI). Exposure of dithiane (-)-**19** to TFA/CH_2Cl_2/H_2O (3:10:10) at 0 °C removed both the TES and isopropylidene groups (90% yield). Selective tosylation of the primary alcohol (TsCl, DMAP, CH_2Cl_2; 88%) then provided triol (+)-**6**.[11] Treatment of the dithiane with mercuric perchlorate in aqueous acetonitrile (1:9, calcium carbonate buffer) afforded a separable 26:1 mixture of spiroketals (-)-**21**[11] and (-)-**20**[11] in 81% yield.[21] The minor isomer (-)-**20** readily isomerized to (-)-**21** (CSA, CH_2Cl_2; 77%); the relative stereochemistry of the spiro center was confirmed by ^1H NOE studies. Protection of the secondary alcohol as a TES ether and introduction of the primary iodide (LiI, imid., DMF; 96%, two steps) generated the C(1-12) fragment (-)-**4**.[11]

Scheme V

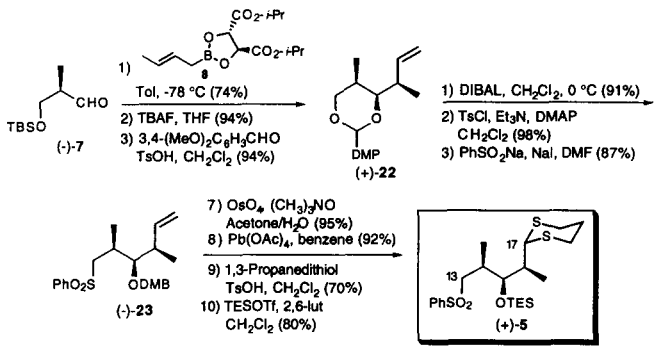


Scheme VI



Sulfone **5** derived from the known aldehyde (-)-**7**[5] (Scheme VII). Roush asymmetric crotylboration[6] with **8** (74% yield, 18:1 selectivity) followed by desilylation (TBAF, THF; 94%) and acetal formation (3,4-dimethoxybenzaldehyde, TsOH, CH_2Cl_2; 94%) furnished (+)-**22**.[11] Reductive cleavage of the acetal (DIBAL, CH_2Cl_2, 0 °C; 91% yield), tosylation of the resultant primary alcohol (TsCl, Et_3N, DMAP; 98%), and coupling with $PhSO_2Na$ (87%) then provided sulfone (-)-**23**.[11] The dithiane moiety was introduced in 61% overall yield via oxidative cleavage of the terminal olefin and thioacetalization. The latter procedure also removed the 3,4-dimethoxybenzyl ether; reprotection (TESOTf, 2,6-lut, CH_2Cl_2; 80%) afforded the C(13-17) segment (+)-**5**.[11]

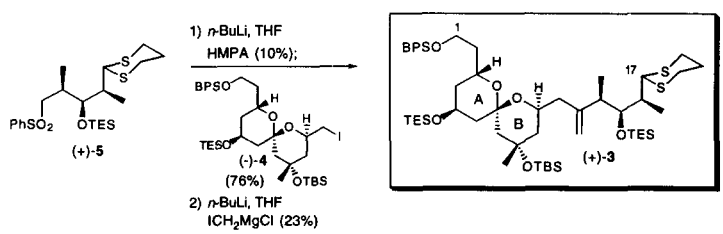
Scheme VII



Alkylation of the lithio derivative of sulfone (+)-**5** with iodide (-)-**4** proceeded smoothly (76% yield, Scheme VIII). Julia methylenation (*n*-BuLi, THF, ICH_2MgCl; 23%),[22] used earlier to introduce the C(45) exomethylene moiety,[1] then generated (+)-**3**,[11] the C(1-17) AB-ring spiroketal advanced intermediate.

In summary, we have completed the first synthesis of the C(1-17) subunit of the spongistatins, exploiting a one-pot dithiane unsymmetrical bisalkylation, a stereocontrolled spiroketalization, and a Julia sulfone coupling/methylenation protocol, the latter to unite (-)-**4** and (+)-**5**. With the ready availability of the C(18-28) and C(29-48) advanced intermediates, described in the first two Letters in this series, completion of the spongistatin synthetic venture is under active investigation.

Scheme VIII



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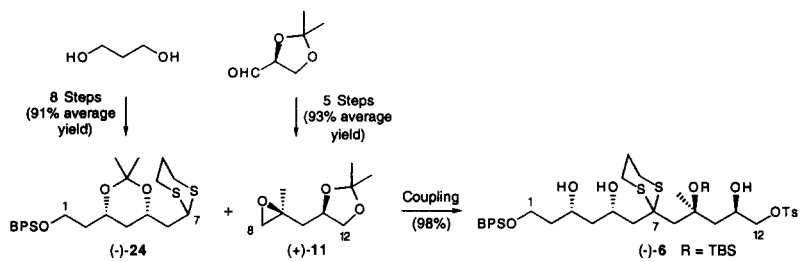

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