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SPONGISTATIN SYNTHETIC STUDIES. 2. ASSEMBLY OF THE C(18-28) SPIROKETAL

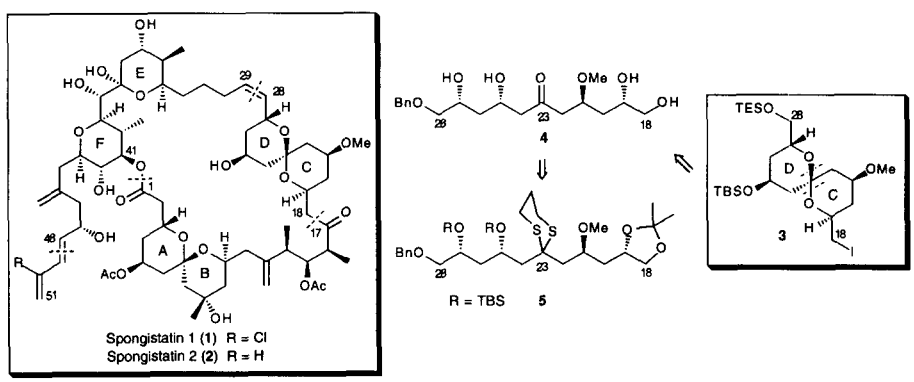
Amos B. Smith, III,* Linghang Zhuang, Christopher S. Brook, Qiyan Lin, William H. Moser, Robert E. Lee Trout, and Armen M. Boldi

Department of Chemistry, Laboratory for Research on the Structure of Matter, and Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, PA 19104, U.S.A.

Summary: The C(18-28) CD-ring spiroketal subunit of the spongistatins, marine polyether macrolides with unprecedented antitumor activity, has been generated via a highly convergent and completely stereocontrolled sequence. Key operations include a one-flask dithiane bisalkylation and a metal-assisted spiroketal equilibration. © 1997 Elsevier Science Ltd.

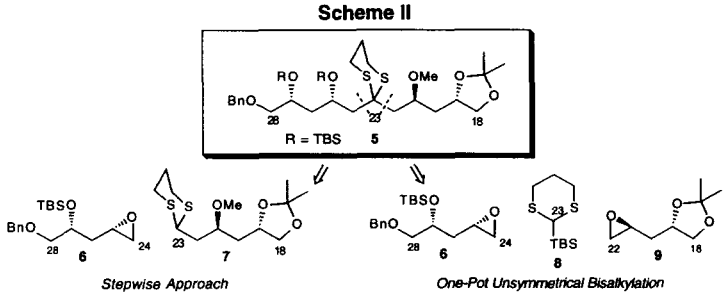
The spongistatins (e.g., **1** and **2**, Scheme I), structurally unique sponge metabolites available only in miniscule amounts, are extraordinarily potent inhibitors of cancer cell growth.[1] In the first Letter in this series,[2] we described our overall synthetic strategy as well as the construction of a C(29-48) advanced intermediate. We now report a convergent, stereocontrolled approach to the synthesis of the C(18-28) CD-ring spiroketal building block **3**. Key operations include a one-flask dithiane bisalkylation and a metal-assisted spiroketal equilibration.

Scheme I



Retrosynthetic cleavage of the spiroketal moiety in **3** led to the acyclic tetrahydroxy ketone precursor **4** (Scheme I). Based on MM2 calculations,[3] we and others[4a] anticipated that spirocyclization of **4** would produce a mixture of isomers at the spiroketal center. However, we were hopeful that a method for perturbing the equilibrium ratio toward the desired R configuration could be developed. The spiroketalization substrate **4**, in turn, was envisioned to derive from the fully protected dithiane **5**. As outlined in Scheme II, we evaluated two approaches to the assembly of **5**. Stepwise construction would entail the union of epoxide **6** with the lithio derivative of dithiane **7**, which would be prepared via thioacetalization of the corresponding aldehyde. Alternatively, the one-pot unsymmetrical bis-alkylation of silyl dithianes, developed in our laboratory,[5] held the promise of a more concise and efficient route which would, in addition,

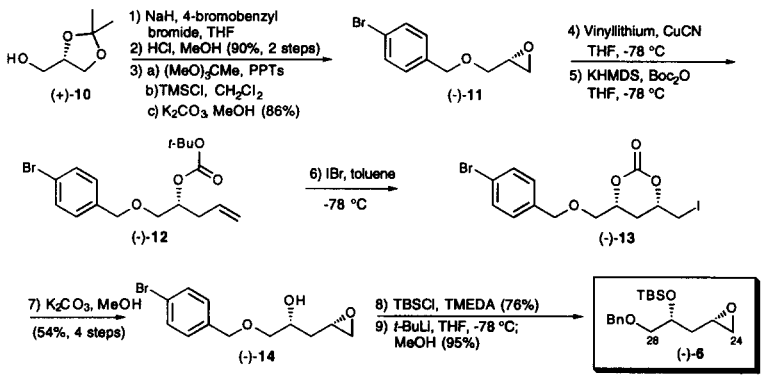
Scheme II



directly install the C(25) TBS ether required for further elaboration.[4]

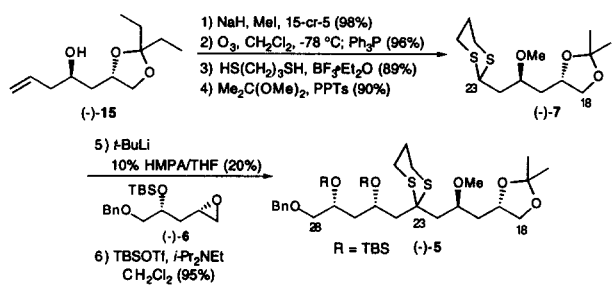
Synthesis of the CD-ring subunit **3** began with the generation of the C(24-28) epoxide (-)-**6**[6] from commercially available (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol [(+)-**10**; Scheme III]. O-Alkylation of (+)-**10** with 4-bromobenzyl bromide followed by methanolysis of the isopropylidene group (HCl, MeOH; 90% yield, two steps) and Sharpless ring closure[7] (86% yield) afforded epoxide (-)-**11**.[6] Addition of the higher-order cuprate[8] prepared from vinyllithium to (-)-**11** and acylation of the resultant alcohol with *t*-Boc anhydride then furnished *t*-butyl carbonate (-)-**12**.[6] Our modification[9] of the Bartlett reaction[10] (IBr, toluene, -78 °C) produced exclusively the desired syn iodo carbonate (-)-**13**.[6] Interestingly, the *p*-bromo group was required to decrease the nucleophilicity of the benzylic oxygen, which otherwise competed with the carbonate in capture of the iodonium intermediate. Treatment of (-)-**13** with K_2CO_3 in methanol provided epoxide (-)-**14**[6] [54% overall yield from (-)-**11**]. Hydroxyl protection as the TBS ether (76%) and removal of the *p*-bromo group via metal-halogen exchange (95%) completed construction of epoxide (-)-**6**.[6]

Scheme III



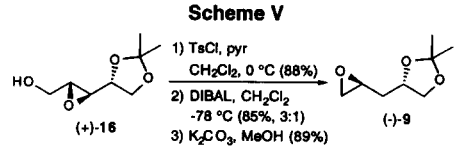
The C(18-23) dithiane (-)-**7**, required for the stepwise approach, was synthesized from homoallylic alcohol (-)-**15**, prepared previously in connection with our acutiphycin synthesis[11] in four steps (30% overall yield) from (*S*)-(-)-malic acid. O-Methylation (NaH, MeI, 15-cr-5; 98%) followed by ozonolysis and acetalization with 1,3-propanedithiol introduced the dithiane moiety with concomitant loss of the 3-pentanone ketal. Reprotection [$Me_2C(OMe)_2$, PPTs; 90%] furnished the building block (-)-**7**.[6] Metalation with *t*-BuLi in 10% HMPA/THF and alkylation with epoxide (-)-**6** provided the desired alcohol, albeit in only modest yield (20%); silylation (TBSOTf, *i*-Pr_2NEt; 95%) then afforded (-)-**5**.[6]

Scheme IV



For the alternative one-pot protocol, epoxide (-)-**9** was prepared from known epoxy alcohol (+)-**16**[12] (Scheme V), the latter available in three steps from D-glyceraldehyde acetonide. Tosylation of (+)-**16** (88%) followed by reductive cleavage[13] of the epoxide (DIBAL, CH_2Cl_2, -78 °C; 85%) led to a mixture of 2- and 3-hydroxy tosylates (3:1). Separation via flash chromatography and ring closure (K_2CO_3, MeOH; 89%) provided (-)-**9**.[6]

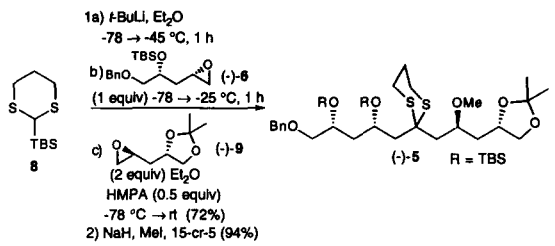
Scheme V



With the requisite epoxides (-)-**6** and (-)-**9** in hand, we implemented the one-pot bisalkylation tactic[5] (Scheme VI). Silyl dithiane **8** was metalated with *t*-BuLi in Et_2O and alkylated with (-)-**6**; Brook rearrangement triggered by HMPA (0.5

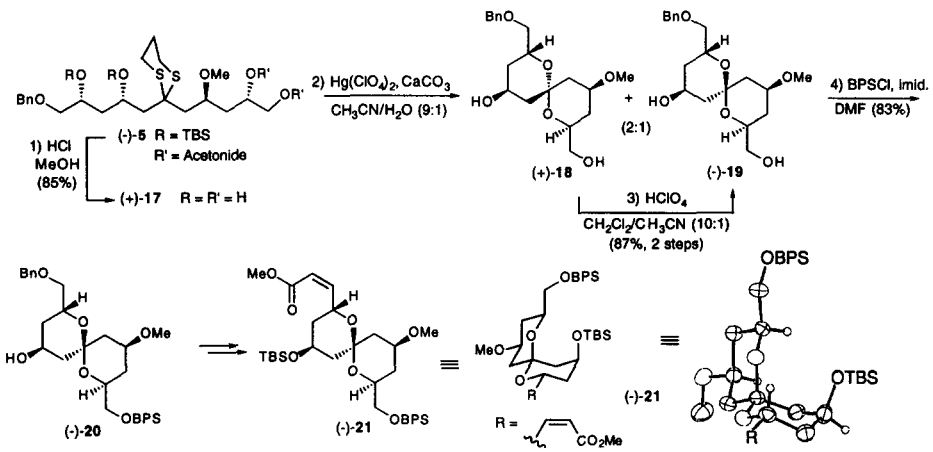
equiv) and union with (-)-**9** afforded the coupled product in 72% yield. O-Methylation (NaH, MeI, 15-cr-5; 94%) then completed the synthesis of (-)-**5**.[6] As expected, the bisalkylation protocol not only eliminated two steps, but also proved more efficient than the stepwise sequence.[5]

Scheme VI



The conversion of acyclic dithiane (-)-**5** to the desired spiroketal is outlined in Scheme VII. Removal of the isopropylidene and TBS protecting groups (HCl, MeOH; 85%) furnished the tetrahydroxy precursor (+)-**17**.[6] Treatment with mercuric perchlorate and calcium carbonate in aqueous acetonitrile removed the dithiane moiety and induced spiroketalization, affording as anticipated a mixture (2:1) of the undesired epimer (+)-**18**[6] and the spongistatin intermediate (-)-**19**.[4] To our delight, exposure of the crude mixture to perchloric acid *in CH_2Cl_2/CH_3CN (10:1)* effected complete conversion to (-)-**19** (87% yield, two steps). Further experiments have revealed that residual Ca(II) ions play a critical role in the isomerization; we are currently investigating possible complexation of Ca(II) with (-)-**19**.[14] Silylation of the primary hydroxyl in (-)-**19** (BPSCl, imidazole, DMF; 83%) next provided (-)-**20**. The ^{1}H NOE data[15] for (-)-**20** were consistent with those reported by Kitagawa[16] and Fusetani,[17] providing the first evidence that the natural spiroketal configuration had been secured. Subsequently the relative stereochemistry of the derived α,β-unsaturated ester (-)-**21**[6] was verified by single-crystal X-ray analysis.

Scheme VII

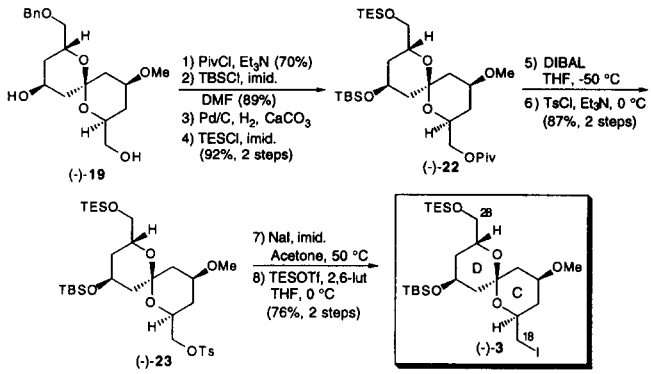


Final elaboration of the CD-ring spiroketal **3** began with selective pivalylation of the primary alcohol in (-)-**19** (70% yield), followed by silylation of the C(25) secondary hydroxyl (89%; Scheme VIII). Replacement of the benzyl moiety with a TES group (92% yield, two steps) then provided (-)-**22**.[6] Tosylate (-)-**23**[6] was obtained in 87% yield via reductive cleavage of the pivalate (DIBAL, THF, -50 °C) and treatment with tosyl chloride. Installation of the C(18) iodide (NaI, imidazole, acetone, 50 °C) also led to removal of the TES ether, which was reintroduced (TESOTf, 2,6-lut, THF, 0 °C) to furnish the C(18-28) spiroketal building block (-)-**3**[6] (76% yield, two steps).

In summary, we have completed a convergent and completely stereocontrolled synthesis of the spongistatin CD-ring spiroketal subunit, exploiting a one-pot dithiane bisalkylation and a metal-assisted spiroketal equilibration. The following Letter describes the construction of an AB-ring spiroketal intermediate.

Acknowledgments. We thank the National Institutes of Health (National Cancer Institute, grant CA-70329), SmithKline Beecham, Dupont Merck Pharmaceutical Co., and Zeneca Inc. for financial support. A. M. B., C. S. B., and W. H. M. gratefully acknowledge the award of National Institutes of Health Postdoctoral Fellowships.

Scheme VIII



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