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SPONGISTATIN SYNTHETIC STUDIES. 1. CONSTRUCTION OF A C(29-48) SUBTARGET

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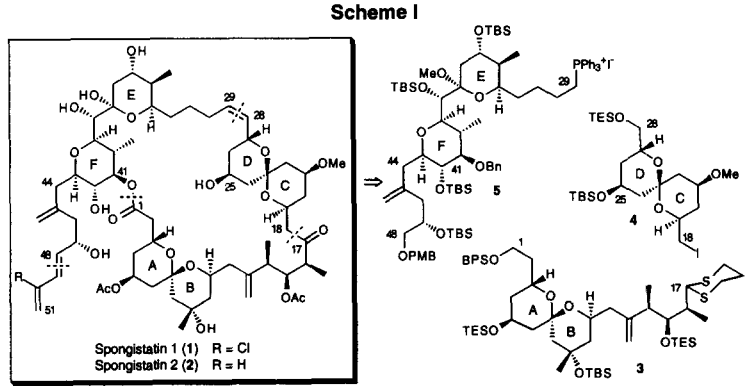
Summary: In this Letter, the first in a series of three, we outline our overall strategy and describe the assembly of a C(29-48) EF-ring advanced intermediate for the total synthesis of the spongistatins, rare and structurally unique polyether macrolides with unprecedented antitumor activity. © 1997 Elsevier Science Ltd.

The spongipyrans, a new family of sponge metabolites available only in minute quantities, appear to be the most potent inhibitors of cancer cell growth discovered to date.[1a] Pettit et al. described the first examples, spongistatins 1-3, in 1982[1a] and subsequently isolated congeners 4-9.[1b] Spongistatin 1 (**1**, Scheme I), the most abundant compound, proved to be extraordinarily active against several chemoresistant tumor types, including human melanoma and lung, colon, and brain cancers, with GI_{50}s of 2.5-3.5 x 10^{-11} M.[1c] Further investigations revealed that **1** inhibits mitosis by binding to tubulin and blocking microtubule assembly. Other sponges produce cinachyrolide A and the altohyrtins A-C, isolated by the Fusetani[2] and Kitagawa[3] groups; these substances likewise display remarkable cytotoxicity against cancer cell lines.

Scheme I



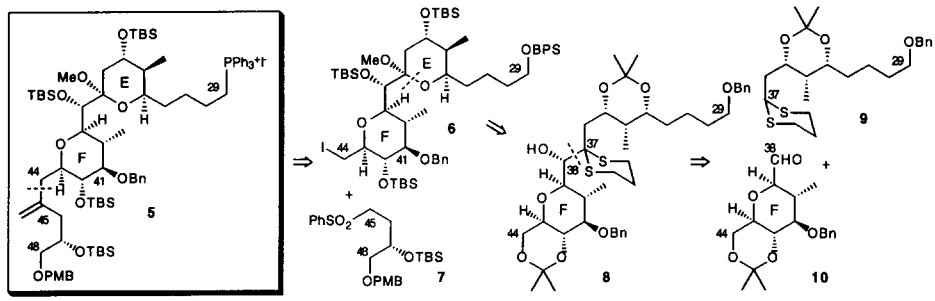
The spongipyran structures have not, as yet, been verified by X-ray analysis, degradation, or synthesis. Current consensus[4] holds that spongistatin 1 and altohyrtin A are identical, as are spongistatin 2 and altohyrtin C as well as spongistatin 4 and cinachyrolide A. In addition, the Kitagawa assignments of relative and absolute stereochemistry (e.g., **1**), based upon modified Mosher analysis and the circular-dichroism exciton chirality method, are believed to be correct.[4] The formidable architecture of the spongipyrans embodies two spiroketal moities and two other highly substituted tetrahydropyran rings in a 32-membered macrolide framework, with 24 stereocenters and triene side-chains. Interestingly, the CD-ring spiroketal adopts a C(23) configuration stabilized by only one anomeric interaction[5] and an intramolecular hydrogen bond.

The known marine sources contain miniscule amounts of the spongipyrans. Thus, 400 kg of an Indian Ocean sponge has furnished 13.8 mg of **1**; Pettit and co-workers are currently reisolating the spongistatins from 13 tons (!) of sponge to permit NCI preclinical evaluation.[4] The extreme scarcity, unprecedented cytotoxicity, and structural complexity of these metabolites provide exceptionally strong impetus for total synthesis, which we undertook late in 1994. In this Letter we outline our overall strategy and describe the construction of a C(29-48) advanced intermediate. The two succeeding communications detail the generation of the C(1-17) and C(18-28) spiroketals.[6]

Consistent with our longstanding philosophy of developing unified synthetic strategies, our approach is designed to permit the efficient assembly of several natural spongipyrans, including **1** and its 50-dechloro congener, spongistatin 2 (**2**), as well as a variety of analogs. Retrosynthetic cleavage of the side-chain diene and initial disconnection of the macrolide

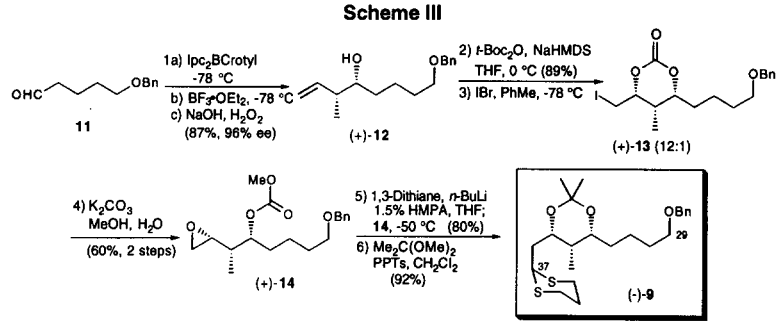
yielded three fragments of similar complexity, the AB-, CD-, and EF-ring subunits **3-5** (Scheme I). This approach should provide considerable end-game flexibility, as fragment coupling could proceed in either clockwise or counterclockwise fashion. The C(29-48) EF subtarget **5** was envisioned to derive from the C(45-48) sulfone **7** and iodide **6**, the latter accessible from **8** after coupling of the C(29-37) dithiane **9** with the C(38-44) pyran aldehyde **10** (Scheme II).

Scheme II



Dithiane (-)-**9** is readily available in six steps and 34% overall yield from the known[7] aldehyde **11** (Scheme III). Brown asymmetric crotylboration[8] with the reagent prepared from (-)-Ipc$_2$BOMe cleanly furnished homoallylic alcohol (+)-**12**[9] in 87% yield and 96% enantiomeric excess (Mosher analysis).[10] Following acylation with *t*-BOC anhydride (89% yield), our IBr modification[11] of the Bartlett cyclization[12] generated iodo carbonate (+)-**13**[9] with diastereoselectivity >12:1; methanolysis (K_2CO_3/methanol) then afforded epoxide (+)-**14**[9] in 60% yield for the two steps. Dithiane addition with concomitant removal of the methyl carbonate (80%) and protection of the resultant diol as the acetonide (92%) furnished the desired C(29-37) dithiane (-)-**9**.[9]

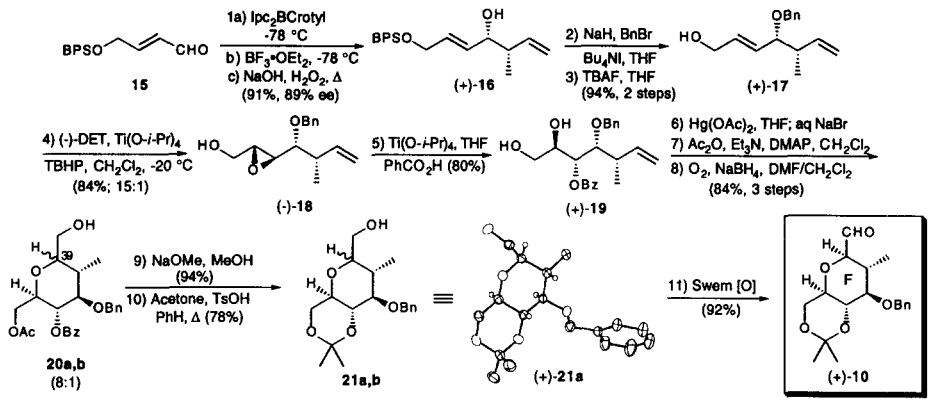
Scheme III



The synthesis of pyran (+)-**10** (11 steps, 29% overall yield; Scheme IV) began with the antipodal asymmetric crotylboration reagent,[8] which transformed the known[13] silyloxy aldehyde **15** to alcohol (+)-**16**[9] in 91% yield and 89% ee (Mosher analysis).[10] Following benzylation and removal of the BPS unit, Sharpless asymmetric epoxidation[14] of the resultant allylic alcohol (+)-**17**[9] generated epoxide (-)-**18**[9] with >15:1 diastereoselectivity; regiocontrolled ring opening with benzoic acid and titanium isopropoxide[15] then led to diol (+)-**19**[9] as the only isolable product. Mercuric acetate cyclization with an aqueous sodium bromide quench, acetylation, and oxidation[16] with O_2 furnished an 8:1 mixture of the axial and equatorial C(39) alcohols **20a,b**[9] (84% yield, three steps).[17] Saponification of both esters (94%) and acetonide formation (78%) gave **21a,b**.[9] Swern oxidation equilibrated the axial aldehyde to the equatorial isomer, providing the C(38-44) building block (+)-**10**.[9] The relative stereochemistry of (+)-**21a** was confirmed by X-ray analysis.

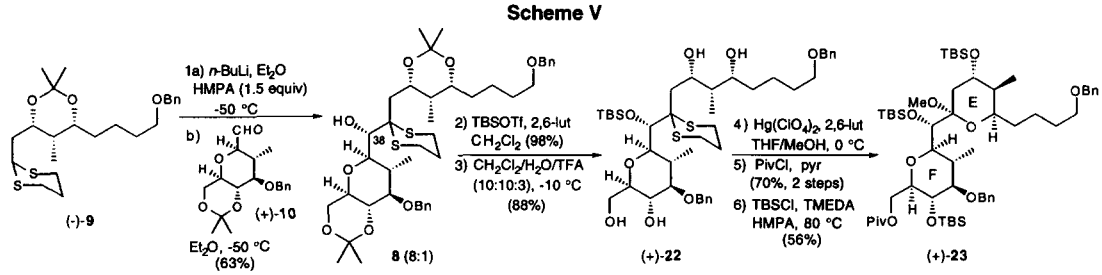
After considerable experimentation, efficient union of the fragments was achieved via metalation of dithiane (-)-**9** (*n*-BuLi, 1.5 equiv HMPA) and addition to aldehyde (+)-**10** in ether at -50 °C; the desired alcohol **8**[9] was obtained as an 8:1 epimer mixture (63% yield) after flash chromatography (Scheme V). The configuration at C(38) was elucidated by removal of the dithiane and formation of both diastereomeric Mosher esters. Kakisawa-Kashman analysis[10b] confirmed the predominance of the anti-Felkin-Anh addition product, consistent with either chelation control or a sterically driven process in which the C(40) methyl group disfavors Felkin approach.[18]

Scheme IV



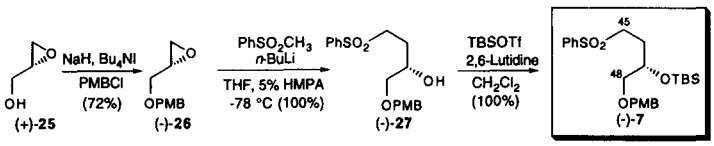
Confident that we had generated the requisite alcohol, we turned to elaboration of ring E (Scheme V). Silylation of **8** and deketalization afforded tetraol (+)-**22**.[9] Stepwise removal of the dithiane moiety and acid-catalyzed installation of the methyl ketal proved futile, affording primarily elimination products. Closure of ring E with in situ ketal formation was eventually achieved via exposure to $Hg(ClO_4)_2$ and 2,6-lutidine [THF/MeOH (2:1), 0 °C]. Acylation of the primary hydroxyl (70% yield, two steps) and exhaustive silylation under forcing conditions (TBSCl, TMEDA, HMPA, 80 °C, 2 days) then gave the EF fragment (+)-**23**[9] (56% yield) accompanied by the epimeric ketal **24** (10%; not shown).[9] The relative stereochemistry of ring E in (+)-**23** was confirmed by a series of NOE experiments and further supported by NOE analysis of **24**.

Scheme V



Successful model studies, to be described elsewhere, set the stage for completion of the advanced EF-ring intermediate **5** and eventual installation of the C(48-51) side-chain diene moiety. In our unified approach to the spongistatins, the labile conjugated diene will be introduced at the end of the synthesis by elaboration of a C(48) PMB ether. Incorporation of the latter group required the C(45-48) building block sulfone **7**, obtained in three steps from commercially available (*R*)-(+)-glycidol [(+)-**25**; Scheme VI]. Protection as the *p*-methoxybenzyl (PMB) ether (-)-**26** (NaH, Bu_4NI, PMBCl; 72% yield) and quantitative epoxide opening with the lithio derivative of methyl phenyl sulfone furnished (-)-**27**;[9] the absolute configuration was confirmed by Mosher analysis.[10] Silylation (TBSOTf, 2,6-lut, CH_2Cl_2; 100%) then gave (-)-**7**.[9]

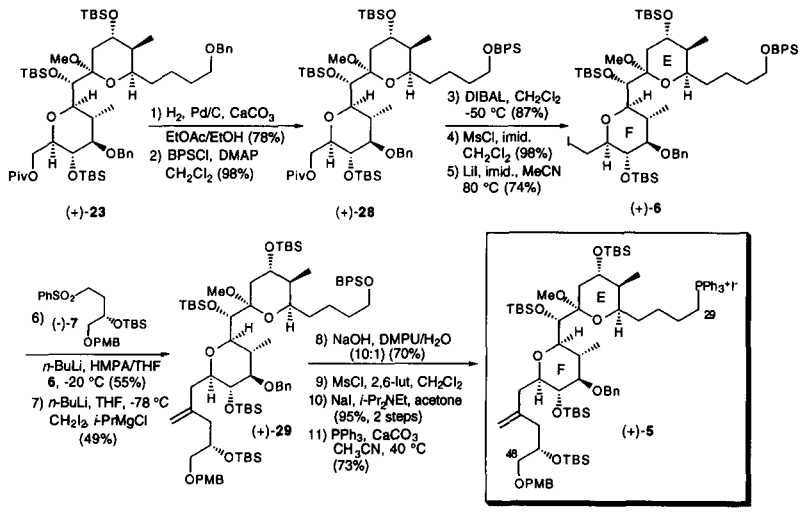
Scheme VI



At this juncture the C(29-44) iodide **6** was generated from **23** in preparation for the sulfone alkylation (five steps, 48% overall yield; Scheme VII). The hindered environment of the secondary benzyl ether enabled us to selectively unmask the C(29) primary hydroxyl; silylation of the resultant alcohol then gave (+)-**28**.[9] Reductive cleavage of the pivalate, mesylation, and displacement with lithium iodide furnished (+)-**6**.[9]

Coupling of iodide (+)-**6** with sulfone (-)-**7** produced an inconsequential mixture of C(45) epimers in 55% yield; Julia methylenation[19] in turn provided (+)-**29**[9] (49%). Finally, removal of the BPS protecting group [NaOH, DMPU/H_2O (10:1); 70% yield], conversion of the primary alcohol to the iodide (MsCl, 2,6-lutidine, CH_2Cl_2, then NaI, *i*-Pr_2NEt, acetone; 95%), and Wittig salt formation (PPh_3, $CaCO_3$, CH_3CN; 73%) furnished the C(29-48) subtarget (+)-**5**.[9]

Scheme VII



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