

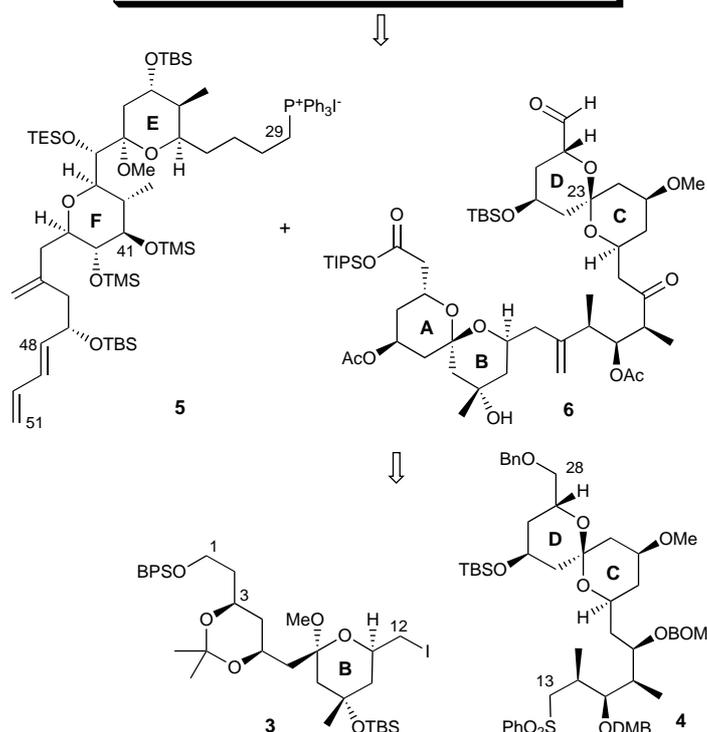
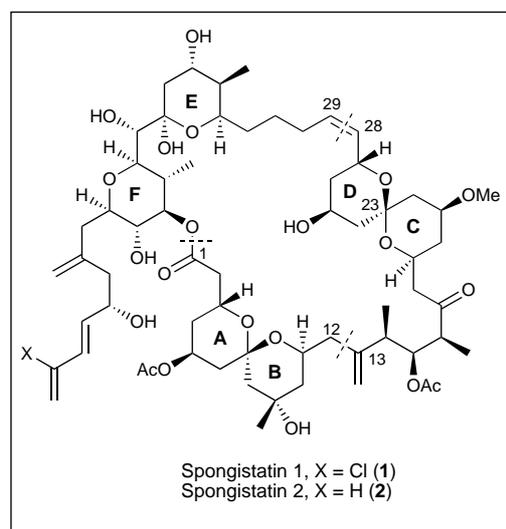
## The Spongistatins: Architecturally Complex Natural Products—Part One: A Formal Synthesis of (+)-Spongistatin 1 by Construction of an Advanced ABCD Fragment\*\*

Amos B. Smith III,\* Victoria A. Doughty, Qiyang Lin, Linghang Zhuang, Mark D. McBriar, Armen M. Boldi, William H. Moser, Noriaki Murase, Kiyoshi Nakayama, and Masao Sobukawa

The spongipyran family of architecturally unique bis-spiroketal macrolides that display extraordinary (subnanomolar) antitumor activities against a wide variety of human cancer cell lines, including melanoma, lung, colon, and brain.<sup>[1]</sup> Three research groups (those of Pettit,<sup>[1a, 2]</sup> Fusetani,<sup>[3]</sup> and Kitagawa<sup>[4]</sup>) independently isolated members of the spongipyran family in minute amounts, naming them in turn the spongistatins, cinachryolide, and the altohyrtins.<sup>[5]</sup> Whereas the carbon skeleton was common to all three families, the structures differed in the assignment of the relative stereochemical relationships. Kitagawa and co-workers assigned the correct relative and absolute stereochemistries based on extensive Mosher analysis and circular dichroism studies.<sup>[4c]</sup> These assignments were subsequently confirmed by the total syntheses of (+)-altohyrtin C [spongistatin 2 (**2**)] by Evans et al.<sup>[6]</sup> and (+)-altohyrtin A [spongistatin 1 (**1**)] by Kishi and co-workers.<sup>[7]</sup> The elegant syntheses at Harvard University demonstrated unequivocally that the altohyrtins and spongistatins were indeed identical.

The spongistatins have attracted wide interest<sup>[8]</sup> as a result of their architectural complexity, which includes two [6,6] spiroketal moieties,<sup>[9]</sup> two highly substituted tetrahydropyran rings encased in a 42 membered macrolide framework, 24 stereogenic centers, and a delicate triene side chain. Particularly intriguing is the CD spiroketal possessing only a single anomeric interaction in conjunction with an intramolecular hydrogen bond that stabilizes the axial–equatorial configuration.

To assemble the complex spongipyran skeleton, we envisioned Wittig union of **5** with **6** (Scheme 1), followed by regioselective macrolactonization at C(41), first demonstrated



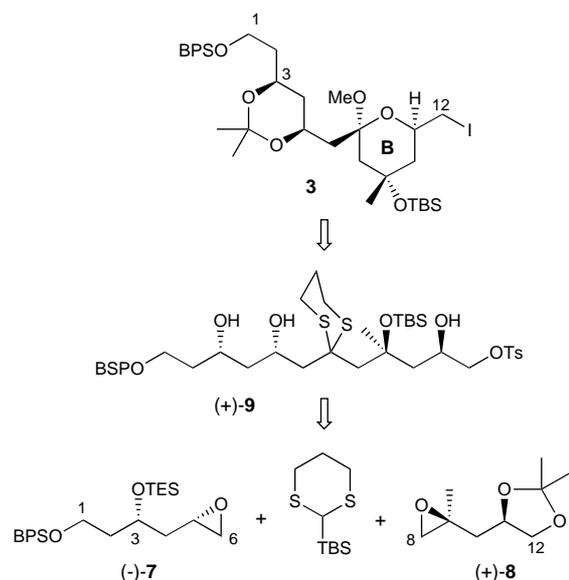
Scheme 1. Retrosynthetic analysis of spongistatin 2 (see ref. [20] for abbreviations).

[\*] Prof. A. B. Smith III, Dr. V. A. Doughty, Dr. Q. Lin, Dr. L. Zhuang, Dr. M. D. McBriar, A. M. Boldi, Dr. W. H. Moser, Dr. N. Murase, Dr. K. Nakayama, Dr. M. Sobukawa  
Department of Chemistry  
Laboratory for Research on the Structure of Matter  
and Monell Chemical Senses Center, University of Pennsylvania  
Philadelphia, PA 19104 (USA)  
Fax: (+1) 215-898-5129  
E-mail: smithab@sas.upenn.edu

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by Evans et al.<sup>[6]</sup> Advanced intermediate **6** would in turn arise from a sulfone-mediated coupling of subunits **3** and **4** followed by Julia methylenation,<sup>[10]</sup> elaboration of the AB spiroketal, and oxidation at C(1) and C(28). Herein we report the synthesis of an advanced C(1–28) subunit for the spongistatins. Central to this venture was the development of epimerization conditions to control the C(23) configuration of the CD spiroketal. In conjunction with this effort we achieved a formal synthesis of spongistatin 1 (**1**). In the following communication we describe the synthesis of **5**, fragment assembly, and final elaboration to (+)-spongistatin 2 (**2**).

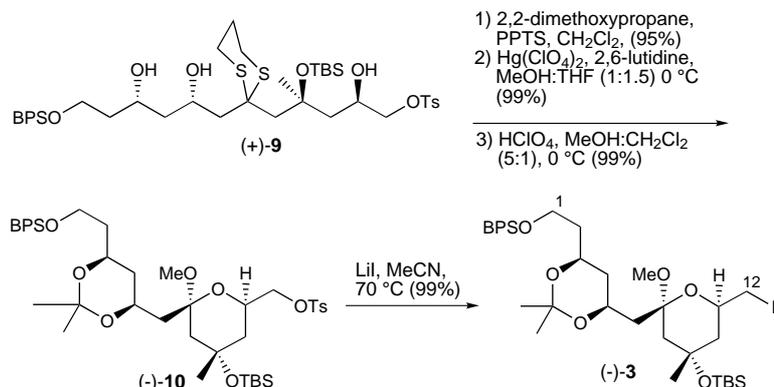
Continuing with the synthetic analysis, disconnection of methylketal **3** (Scheme 2) revealed the opportunity to exploit a one-pot unsymmetrical bisalkylation of 2-TBS-1,3-dithiane



Scheme 2. Retrosynthetic analysis of the AB subunit revealing a one-pot unsymmetrical bis-alkylation disconnection (see ref. [20] for abbreviations).

with Brook rearrangement recently reported by our laboratory.<sup>[11]</sup> The development of this route and the synthesis of fragments (–)-7, (+)-8, and (+)-9 were disclosed earlier.<sup>[8b]</sup>

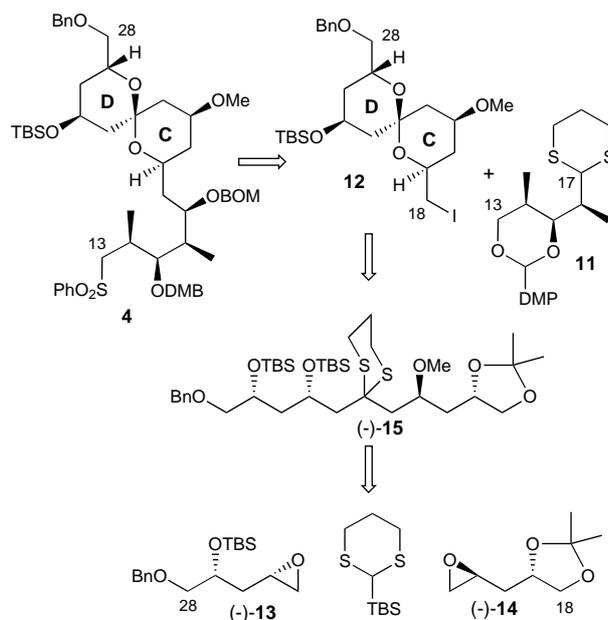
Completion of subunit (–)-3<sup>[12]</sup> required four steps beginning with (+)-9<sup>[8b]</sup> (Scheme 3). Protection of the 1,3-diol as the



Scheme 3. Synthesis of the AB subunit (–)-3 (see ref. [20] for abbreviations).

acetone, mercury perchlorate mediated removal of the dithiane<sup>[13]</sup> in the presence of methanol to furnish a mixture of methyl ketals, and acid-catalyzed equilibration led to the thermodynamically more stable ketal (–)-10 (d.r. > 10:1). Treatment with lithium iodide completed the construction of the AB fragment (–)-3; the overall yield was 92% (four steps).

The CD fragment (4) was envisioned to arise through the coupling of dithiane 11 with iodide 12 (Scheme 4). Disconnection of 12 at the spiroketal provided another opportunity to employ the one-pot bis-alkylation tactic.<sup>[11]</sup> Indeed, the coupling of (–)-13 and (–)-14 with the lithium anion of 2-TBS-1,3-dithiane followed by methylation furnished (–)-15 in 68% yield (two steps).<sup>[8m]</sup>



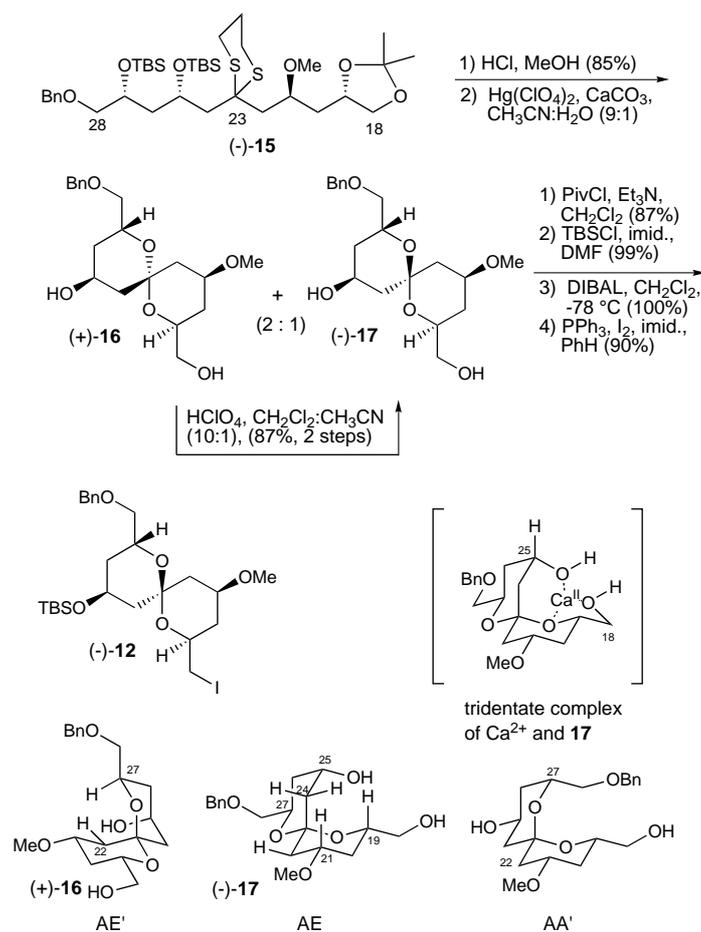
Scheme 4. Retrosynthesis of the CD spiroketal 4 revealing a one-pot unsymmetrical bis-alkylation disconnection (see ref. [20] for abbreviations).

Assembly of the CD spiroketal required removal of both the TBS and acetone groups (HCl/MeOH) in (–)-15 (Scheme 5), followed by treatment with mercury perchlorate buffered with calcium carbonate; the result was a mixture of spiroketals (+)-16 and (–)-17 (2:1). After separation, NOE experiments revealed that both spiroketals possessed an “axial–equatorial (AE)” configuration;<sup>[14]</sup> the “axial–axial (AA)” congener was not observed. Importantly, treatment of the mixture with perchloric acid prior to purification furnished only the desired spiroketal (–)-17 (87%, two steps). Subsequent experiments<sup>[15]</sup> demonstrated that the calcium ion, a remnant of dithiane removal, stabilizes spiroketal (–)-17, presumably through coordination with the hydroxyl groups at C(18) and C(25) as well as the C-ring pyran oxygen atom. This observation would prove critical late in the synthesis (see below). Conversion of (–)-17 into iodide (–)-12 was then achieved in four steps: pivaloylation of the primary

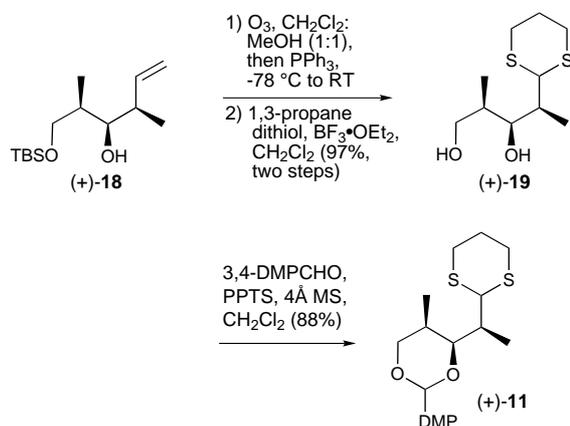
hydroxyl group, protection of the secondary hydroxyl group (TBSCl), reductive removal of the pivaloate (DIBAL), and conversion of the primary hydroxyl group into the iodide completed the synthesis of (–)-12.

Construction of dithiane (+)-11 (Scheme 6) required three steps, beginning with (+)-18;<sup>[8b]</sup> ozonolysis, introduction of the dithiane with concomitant loss of the TBS group, and protection of the diol (+)-19 as the DMP acetal furnished (+)-11 in 85% yield (three steps).

The coupling of (+)-11 and (–)-12 proceeded with high efficiency (95%) to furnish (+)-20 (Scheme 7). Removal of the dithiane followed by reduction of the resultant ketone (NaBH<sub>4</sub>) then led to a mixture of alcohols (3.5:1; 97% yield), favoring the C(17) β-epimer 21. After protection of the



Scheme 5. Synthesis of the CD spiroketal iodide (–)12 (see ref. [20] for abbreviations).

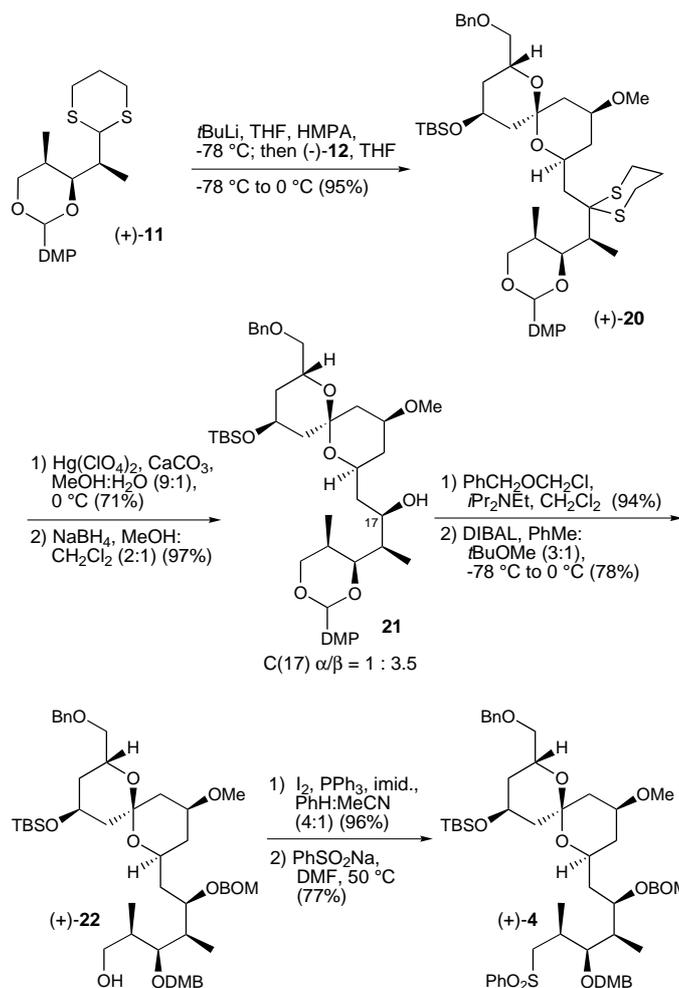


Scheme 6. Synthesis of dithiane (+)-11 (see ref. [20] for abbreviations).

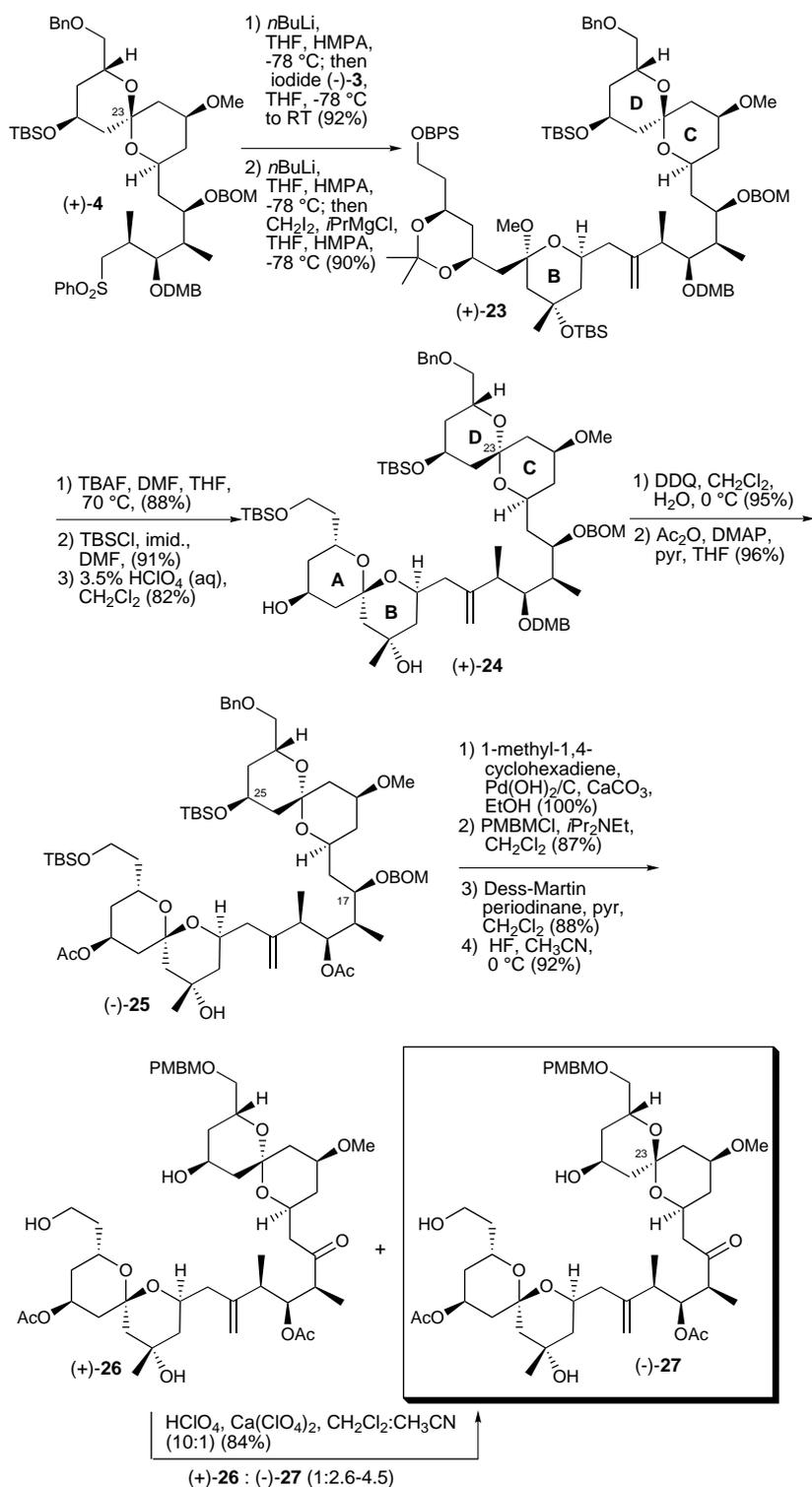
secondary hydroxyl group (BOMCl), the mixture was separated, and although both epimers were potentially useful, only the major  $\beta$ -epimer was carried forward. Regioselective reduction (DIBAL) of the acetal led to (+)-22. The weakly coordinating co-solvent, *tert*-butylmethyl ether, proved essential to minimize reduction of the spiroketal. Conversion of (+)-22 into the iodide and subsequent introduction of the phenyl sulfone completed the assembly of the CD fragment (+)-4.

The coupling of (+)-4 with iodide (–)3 also proceeded in excellent yield to furnish an inconsequential mixture of sulfone epimers (Scheme 8). In contrast to a system explored earlier, which possessed a fully elaborated AB spiroketal,<sup>[16]</sup> Julia methylenation<sup>[10]</sup> in this case proceeded smoothly to furnish (+)-23 (90%). Removal of the silicon protecting groups with TBAF, followed in turn by reprotection of both the primary and secondary hydroxyl groups as TBS ethers and hydrolysis of the acetonide with concomitant spiroketalization then furnished spiroketal (+)-24. Although not surprising in the retrospect that epimerization of the CD spiroketal had occurred under the acidic conditions, this fact went undetected until the spectroscopic properties of the fully elaborated 23-*epi*-spongistatin was compared with those of an authentic sample of (+)-spongistatin 2 (1). Undaunted, we reasoned that it should be possible to correct the CD spiroketal stereochemistry by epimerization (for example, with HClO<sub>4</sub>/Ca<sup>2+</sup>) at a late stage in the synthesis.

To confirm rigorously the stereochemistry of (+)-24, we prepared (–)27, an advanced intermediate employed in the total synthesis of (+)-spongistatin 1 (1) by Kishi and co-workers.<sup>[7]</sup> Toward this end, oxidative removal of the DMB ether (DDQ), followed by bis-acylation of the triol gave diacetate (–)25. Removal of the C(25) TBS group (HF/CH<sub>3</sub>CN) set



Scheme 7. Synthesis of sulfone (+)-4 (see ref. [20] for abbreviations).



Scheme 8. C(23) Epimerization attempts: Completion of a formal synthesis of (+)-spongistatin 1 (**1**) (see ref. [20] for abbreviations).

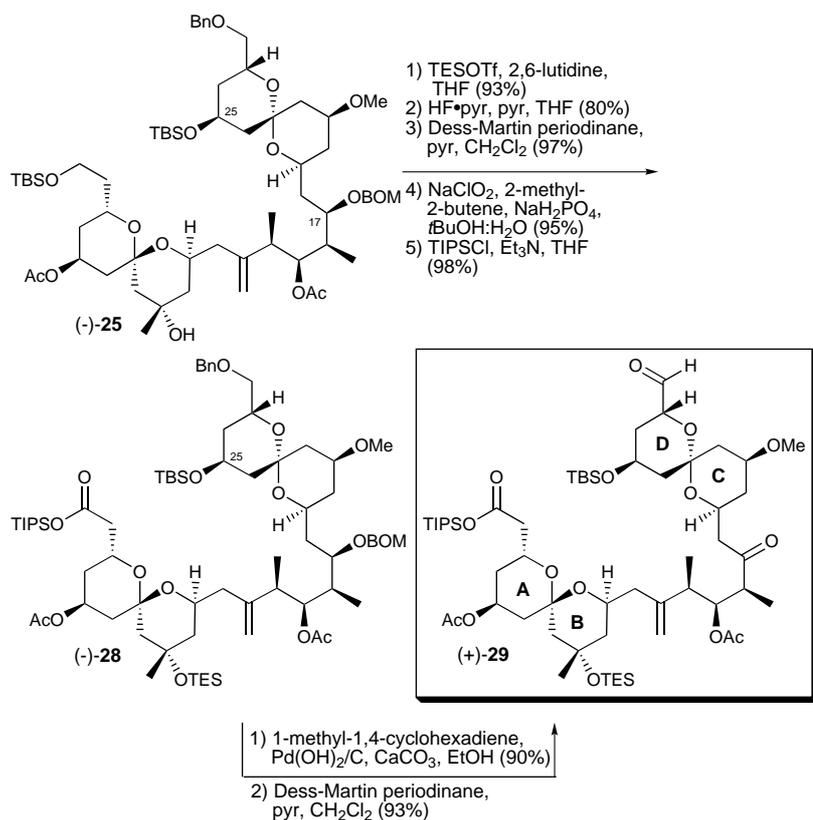
the stage for spiroketal correction. Unfortunately, all attempts to effect epimerization at C(23) employing our previously optimized conditions failed. We reasoned that the bulky C(17) BOM group precluded epimerization. Accordingly, the BOM and benzyl groups were removed (transfer hydrogenolysis). Selective protection of the primary hydroxyl group with PMBMCl, oxidation of the secondary hydroxyl group, and

treatment with HF/CH<sub>3</sub>CN then afforded the desired spiroketal (-)-**27** along with the epimer (+)-**26** (ca. 1:1.3) in 92% yield. Importantly, epimerization of (+)-**26** (HClO<sub>4</sub>/Ca<sup>2+</sup>) proceeded consistently with high mass recovery (ca. 80–84%), although the ratio of spiroketals was variable (2.6–4.5:1). In this fashion (-)-**27** could be obtained in approximately 75% yield. Treatment of (+)-**26** with only HClO<sub>4</sub> established the critical requirement for a calcium ion; both (+)-**26** and (-)-**27** (6.1:1, 81%) were obtained. The synthesis of (-)-**27**, which was identical to that prepared by Kishi and co-workers, constitutes both a formal total synthesis of (+)-spongistatin 1 (**1**) and confirms our stereochemical assignments.<sup>[7, 17]</sup>

Continuing with the synthesis of the advanced ABCD fragment (+)-**29** (Scheme 9) for spongistatin 2 (**2**; see accompanying communication), protection of the tertiary hydroxyl group as a TES ether<sup>[18]</sup> was followed by selective removal of the primary TBS group in the presence of both the secondary TBS and tertiary TES ethers. A two-step oxidation (Dess–Martin periodinane<sup>[19]</sup> and buffered NaClO<sub>2</sub>), followed by silylation of the resulting carboxylic acid led to (-)-**28** (67%, five steps). Removal of the benzyl and benzyloxymethyl groups in the presence of the exo-methylene group (transfer hydrogenolysis) then proceeded smoothly. Finally, Dess–Martin oxidation furnished aldehyde (+)-**29**. In the following communication we describe the synthesis of the C(29–51) subunit (**5**), its coupling with (+)-**29**, and final elaboration to afford (+)-spongistatin 2 (**2**).

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Scheme 9. Synthesis of (+)-**29** (see ref. [20] for abbreviations).

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- [15] Treatment of a purified mixture of (+)-**16** and (–)-**17** (2:1) with HClO<sub>4</sub> afforded a 1:1 mixture of spiroketals. Addition of Ca(ClO<sub>4</sub>)<sub>2</sub> to the reaction provided a 9:1 mixture favoring the desired spiroketal (–)-**17**.
- [16] See ref. [8b]. With the fully formed spiroketal in place, only modest yields for the installation of the exo-methylene group could be obtained.
- [17] We thank Prof. Y. Kishi for providing the <sup>1</sup>H NMR spectra of advanced intermediates **26** and **27**.
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- [20] Abbreviations used: PG = protecting group; Ac = acetyl; TES = triethylsilyl; TBS = *tert*-butyldimethylsilyl; TMS = trimethylsilyl; BPS = *tert*-butylbiphenylsilyl; TIPS = triisopropylsilyl; DMB = 3,4-dimethoxybenzyl; Bn = benzyl; BOM = benzyloxymethyl; Ts = tosyl = toluene-4-sulfonyl; DMP = dimethoxyphenyl; Piv = pivaloyl = 2,2-dimethylpropanoyl; PPTS = pyridinium *p*-toluenesulfonate; DIBAL = diisobutylaluminum hydride; imid. = imidazole; MS = molecular sieves; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMAP = 4-dimethylaminopyridine; pyr = pyridine; HMPA = hexamethylphosphoramide; DMF = dimethylformamide; PMBM = *para*-methoxybenzyloxymethyl; TBAF = tetrabutylammonium fluoride; THF = tetrahydrofuran.