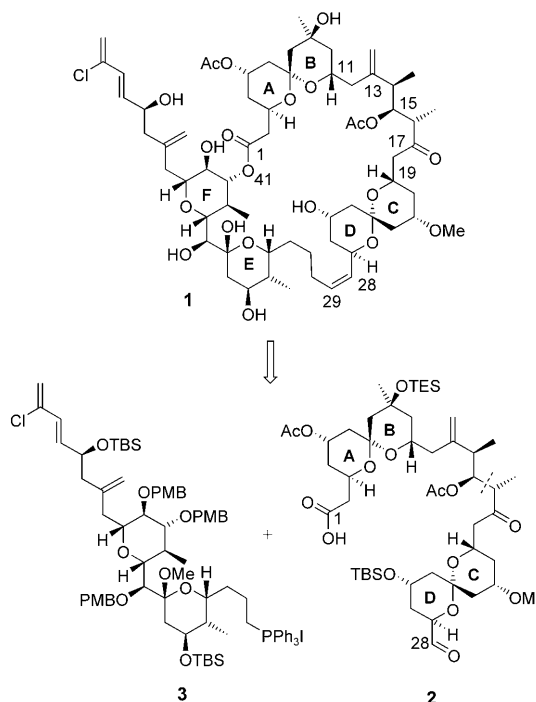


lines. These unique natural products were isolated independently by Pettit, Kitagawa and Fusetani in 1993,^[1] although the absolute structure remained unknown until confirmation by synthesis in 1997.^[2] The spongistatin family includes 9 macrolides, all of which possess remarkable growth inhibition properties against the US National Cancer Institute's panel of sixty human cancer cell lines. Spongistatin 1 (**1**) was extremely potent against a subset of highly chemoresistant tumor types, with typical GI₅₀ values of 2.5–3.5 × 10^{−1} M. Cell lines derived from human melanoma were also found to be especially sensitive to Spongistatin 1,^[1f,h] the most active of this family of macrolides (Scheme 1).



Scheme 1. Structure and retrosynthetic analysis of Spongistatin 1 (**1**). TES = triethylsilyl, TBS = *tert*-butyldimethylsilyl, PMB = *p*-methoxybenzyl.

Spongistatin 1 (**1**) comprises a 42-membered macrolide ring, 24 asymmetric centers, a chlorodiene side chain, two spiroketals (of which only one contains full anomeric stabilization) and two pyranyl units. The complex molecular architecture and exciting biological profile of these natural products have attracted significant interest resulting in total syntheses by six groups.^[2–3] Our initial synthetic analysis for **1** was consistent with established endgame strategies and corresponded to a C1–C41(OH) macrolactonization and C28–C29 Wittig olefination, resulting in two advanced fragments (ABCD fragment **2** and EF fragment **3**) and hence enabling a convergent approach to the target (Scheme 1).^[2–3] Furthermore, we recognized the utility of the *anti*-selective aldol coupling demonstrated by the groups of Evans,^[2a] Paterson,^[3d] Heathcock^[3f] and more recently Smith^[3a] and Crimmins,^[3e] to join the AB and CD units together to form the basis of fragment **2** in their total syntheses. Accordingly, we envisaged that appropriately protected AB aldehyde **4** and

Natural Product Synthesis

DOI: 10.1002/ange.200502008

Total Synthesis of Spongistatin 1: A Synthetic Strategy Exploiting Its Latent Pseudo-Symmetry**

Matthew Ball, Matthew J. Gaunt, David F. Hook,
Alan S. Jessiman, Shigeru Kawahara, Paolo Orsini,
Alessandra Scolaro, Adam C. Talbot, Huw R. Tanner,
Shigeo Yamanoi, and Steven V. Ley*

The spongistatins comprise an important family of architecturally complex marine macrolides that display extraordinary antitumor activities against a variety of human cancer cell

[*] Dr. M. Ball, Dr. M. J. Gaunt, Dr. D. F. Hook, A. S. Jessiman, S. Kawahara, P. Orsini, A. Scolaro, A. C. Talbot, H. R. Tanner, Dr. S. Yamanoi, Prof. Dr. S. V. Ley
Department of Chemistry, University of Cambridge
Lensfield Road, Cambridge, CB2 1EW (UK)
Fax: (+44) 1223-333-6442
E-mail: svl1000@cam.ac.uk

[**] The authors thank Novartis for the Novartis Research Fellowship (S.V.L.) and a fully funded studentship (H.T.), the British Ramsey Trust and Magdalene College, Cambridge for a research fellowship (M.J.G.), Pfizer Global Research and Development, Sandwich (UK) (A.S.J.), Pharmacia, Italy (P.O. and A.S.), Ajinomoto Inc., Japan (S.K.), the Uehara Memorial Foundation for a postdoctoral fellowship (S.Y.), the EPSRC for studentships (A.C.T. and D.F.H.) and a postdoctoral fellowship (M.B.). We also acknowledge the contribution of Dr. Richard Turner (University of Cambridge) whose expertise in preparative HPLC proved invaluable.

CD ketone **5** would be suitable coupling partners for this transformation (Scheme 2).

We have previously reported independent syntheses of both the AB (**4**) and CD (**5**) fragments,^[4] employing acetylide–aldehyde C–C-bond formation–oxidation followed by addition of 1,3-propanedithiol to the resulting ynone as the key coupling approach for polyketide synthesis. Despite the high efficiency in these syntheses (average yield per step: 89 % (**4**); 92 % (**5**)), we felt that the overall sequence length, (64 discrete steps to assemble the ABCD precursors) precludes the synthesis of significant quantities of the spongistatins. As a result, we have developed an innovative second-generation route towards the ABCD bis(spiroketal) moiety **2**, which is reported here along with completion of the synthesis of the natural product.^[5]

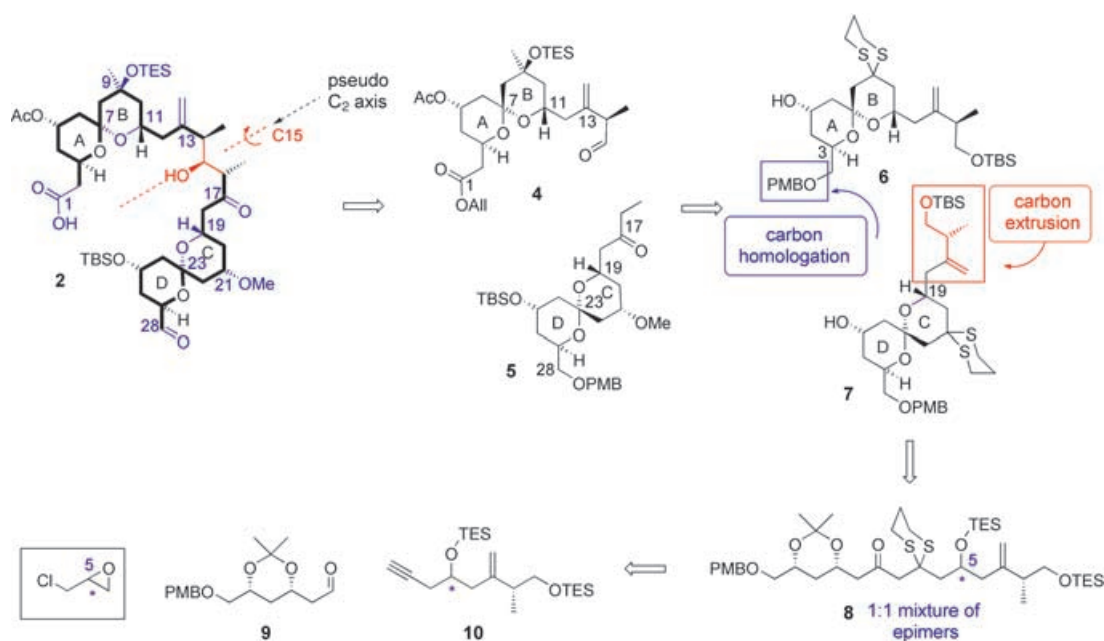
Close examination of the ABCD fragment **2** of Spongistatin 1 reveals a high level of latent C_2 -symmetry about the C15 atom namely, the carbon framework from C1 to C14 is very similar to that of C16 to C28 (Scheme 2).^[6] The A and D rings of the spiroketals are essentially identical and differ principally due to their anomeric arrangements and the C11 and C19 stereocenters, which are oppositely configured. We have already shown that the functionality at both C9 and C21 can be introduced through a carbonyl group interconversion.^[4] Therefore, C1–C12 and C18–C28 differ by only one carbon atom and one stereocenter. Furthermore, the sp^2 -carbon atoms at C13 and C17 are pseudo-symmetric about C15, as are the methyl groups at C14 and C16. These observations suggest that it may be possible to access the C1–C15 and C15–C28 fragments from an epimeric mixture of acyclic precursor **8**, dramatically decreasing the number of steps required to assemble the ABCD fragment (Scheme 2).

From an acyclic precursor **8**, one C5 epimer will furnish the AB spiroketal core **6**, whilst the opposite C5 epimer would yield the CD framework **7**. Post-spiroketalization modifica-

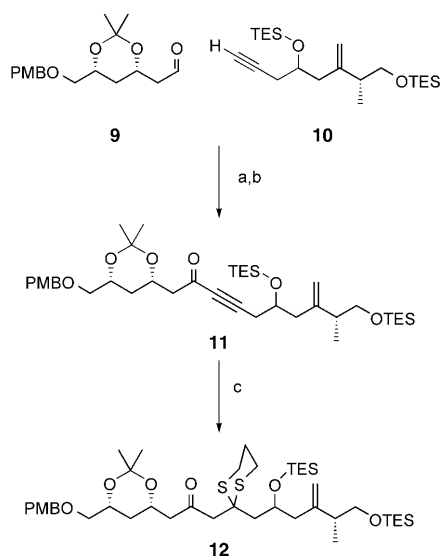
tion should enable interception of our original routes to AB (**4**) and CD (**5**) subunits. Towards this goal, the AB spiroketal unit **6** requires one-carbon homologation in the C3 sidechain to generate the allyl ester **4**. In contrast, the CD unit **7** requires conversion of the exocyclic alkene into a ketone followed by effective formyl extrusion (via decarboxylation) from the C19 terminus to afford the ethyl ketone **5**. The utility of this pseudo-symmetric strategy hinges upon the ability to efficiently facilitate sidechain interconversion and is of central importance to the success of our second-generation synthetic strategy (Scheme 2).

The synthesis begins with the preparation of the acyclic precursor **8**. We have previously prepared key aldehyde **9** from (*S*)-glycidol in the first-generation synthesis of the CD ketone.^[4a] Formation of alkyne **10** as an epimeric mixture at C5 was achieved by adaptation of previously developed chemistry towards the AB spiroketal, in this case employing racemic epichlorohydrin as the central electrophilic component.^[4b] Addition of the anion of alkyne **10** (formed through treatment with *i*PrMgCl) to aldehyde **9** generated a propargylic alcohol as a 1:1 mixture of diastereomers in 85 % yield. Oxidation with Dess–Martin periodinane lead to ynone **11**, which afforded acyclic spiroketal precursor **12** in excellent yield by double conjugate addition of 1,3-propanedithiol (83 % over 3 steps, Scheme 3).

Treatment of ketone **12** with dilute perchloric acid generated three different spiroketals corresponding to the AB double anomeric stabilized unit **13** (AB_{AA}) and the two CD anomeric isomers, bis-anomeric **14** (CD_{AA}) and mono-anomeric **15** (CD_{AE}), in a ratio of $AB_{AA}/CD_{AA}/CD_{AE}$ 1.00:0.74:0.26 (Scheme 4). The three spiroketals were separated by preparative HPLC^[7] to afford the key cores of the AB and CD fragments in a total of only 26 discrete steps (17 longed linear sequence). The bis-anomeric **14** (CD_{AA}) spiroketal was equilibrated under calcium perchlorate epi-



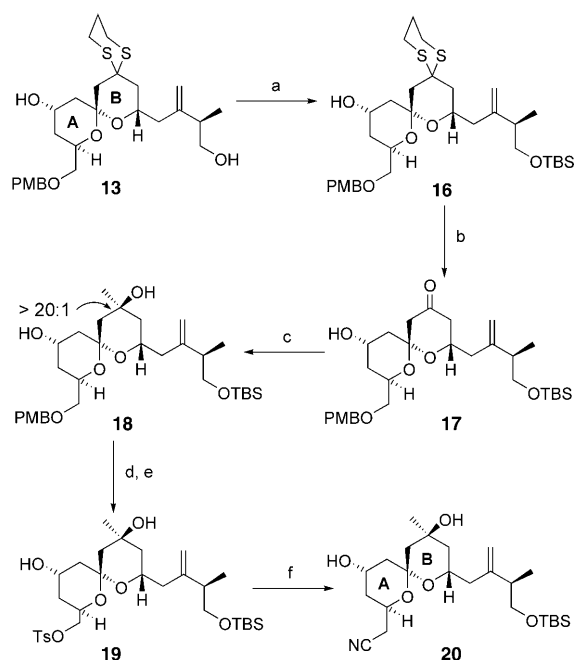
Scheme 2. Pseudo-symmetric retrosynthetic analysis of the ABCD bis(spiroketal) fragment **2**.



Scheme 3. Reagents and conditions: a) *i*PrMgCl, **10**, THF, 2 h, RT; then **9**, THF, -20°C , 1 h; b) Dess–Martin periodinane, CH_2Cl_2 , RT, 1 h, 85% over two steps; c) $\text{HS}(\text{CH}_2)_3\text{SH}$, NaOMe, $\text{MeOH}-\text{CH}_2\text{Cl}_2$, $-10^{\circ}\text{C} \rightarrow \text{RT}$, 16 h, 97%.

merization conditions^[3a,4] and cleanly converted into the desired mono-anomeric spiroketal **15** (CD_{AE}) (87% yield after a 3-step recycle sequence). The equilibration process required 16 h to afford a 3:1 mixture in favor of the desired isomer. Interestingly, the presence of the primary hydroxy group in the C19 sidechain increased the proportion of **15** (CD_{AE}) after equilibration. This observation is in agreement with the results of Evans et al.^[2a] and Smith et al.^[3a] and in accord with our findings in our earlier CD fragment synthesis, which lacked oxygen substitution in the C19 sidechain^[4a] (first generation $\text{CD}_{\text{AA}}/\text{CD}_{\text{AE}} = 1.0:2.2$, second generation $\text{CD}_{\text{AA}}/\text{CD}_{\text{AE}} = 1.0:3.0$). With an efficient method for the formation of both AB and CD spiroketal core structures now available, we investigated subsequent side-chain manipulation to afford the aldol-coupling fragments **4** and **5**.

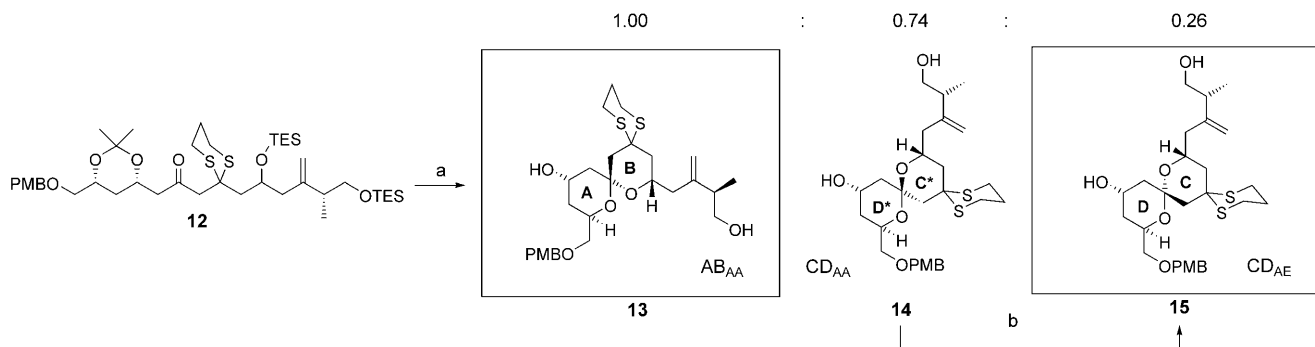
Elaboration of spiroketal **13** began by the selective protection of the primary hydroxy group as its silyl ether followed by iodine-facilitated cleavage of the dithiane unit^[8] to afford the corresponding ketone **17** in excellent yield over two steps (Scheme 5). Methyl group addition mediated by the



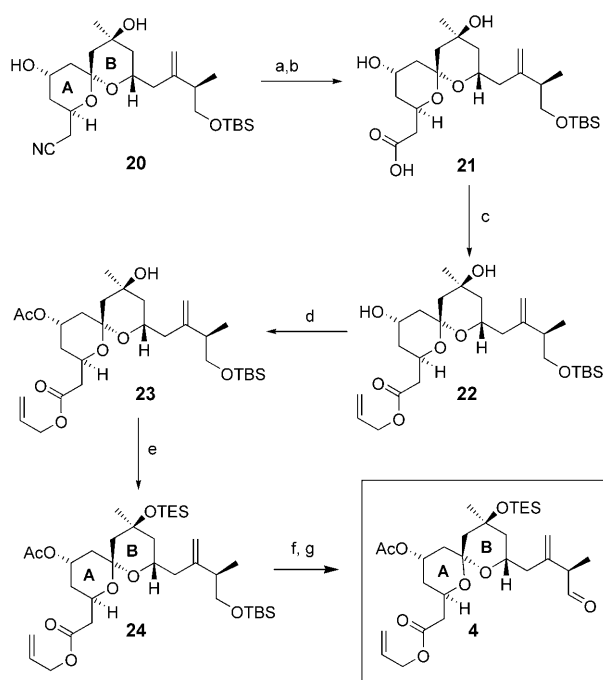
Scheme 5. Reagents and conditions: a) TBSCl, imidazole, CH_2Cl_2 , RT, 17 h, 94%; b) I_2 , aq. NaHCO_3 , MeCN, 0°C , 1 h, 99%; c) MeLi, CeCl_3 , THF, -78°C , 1 h, 94%; d) DDQ, pH 7 buffer, CH_2Cl_2 , 2 h, RT, 98%; e) *p*-TsCl, CH_2Cl_2 , pyridine, RT, 19 h, 97%; f) NaCN, DMF, 70°C , 6 h, 80%. DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; *p*-TsCl = *p*-toluenesulfonyl chloride; DMF = *N,N*-dimethylformamide.

organocerium reagent derived from MeLi and CeCl_3 formed the tertiary alcohol **18** as a single diastereomer (d.r. > 20:1). Oxidative cleavage of the *p*-methoxybenzyl ether with DDQ and subsequent mono-tosylation of the resulting primary alcohol activated the C3 sidechain for carbon homologation. Tosylate displacement with NaCN^[9] afforded **20** in good yield.

Cyanide **20** was converted into the corresponding acid **21** via reduction to the aldehyde followed by Pinnick oxidation (Scheme 6).^[10] Alkylation of the carboxy group by allyl bromide–cesium carbonate furnished the full AB spiroketal skeleton **22**. Selective acetylation of the secondary alcohol followed by TES protection of the tertiary hydroxy group formed **24** in good yield over two steps. HF–pyridine complex removed the *tert*-butylsilyl group and subsequent oxidation of the primary hydroxy group using Dess–Martin periodinane^[11]



Scheme 4. Reagents and conditions: a) 10% aq. HClO_4 , $\text{MeCN}-\text{CH}_2\text{Cl}_2$, RT, 30 min, 86%; b) 3.5% aq. HClO_4 , 5 equiv $\text{Ca}(\text{ClO}_4)_2 \cdot 4\text{H}_2\text{O}$, $\text{MeCN}-\text{CH}_2\text{Cl}_2$, RT, 18 h, 87% after three recycles.

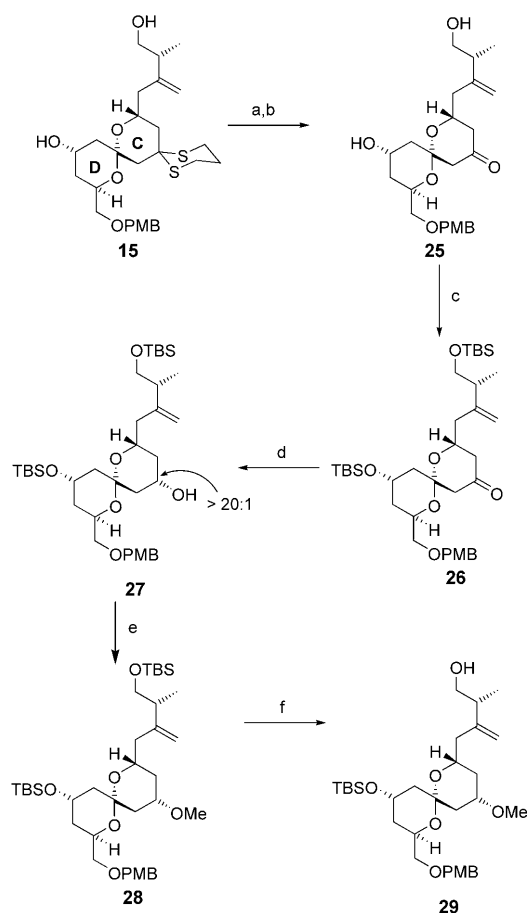


Scheme 6. Reagents and conditions: a) DIBAL-H (1 M in CH_2Cl_2), CH_2Cl_2 $-78^\circ\text{C} \rightarrow \text{RT}$, 6 h; b) NaClO_2 , $t\text{BuOH}$, 2-methyl-2-butene, pH 7 buffer, RT, 2 h; c) allyl bromide, Cs_2CO_3 , THF, RT, 17 h, 51% over three steps; d) Ac_2O , pyridine, DMAP, CH_2Cl_2 , RT, 65 h, 86%; e) TESOTf, 2,6-lutidine, $-78 \rightarrow 0^\circ\text{C}$, 1 h, 99%; f) HF-pyridine, pyridine-THF, RT, 7 h; g) Dess–Martin periodinane, py, CH_2Cl_2 , RT, 3 h, 66% over two steps. DIBAL-H = diisobutylaluminum hydride; DMAP = 4-(*N,N*-dimethylamino)pyridine; Tf = trifluoromethanesulfonyl.

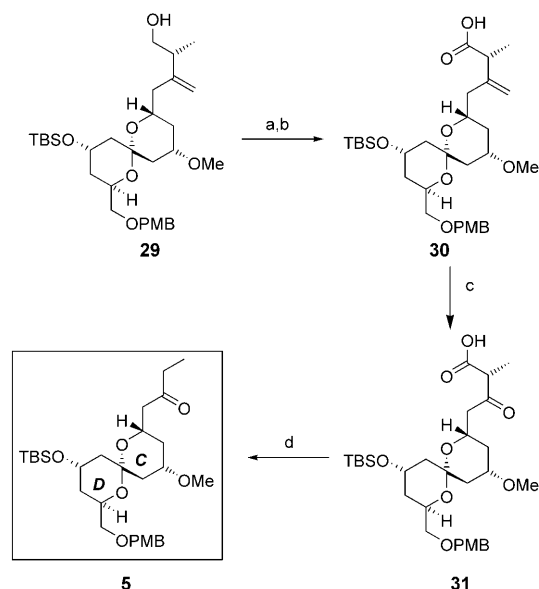
afforded key aldehyde **4** that was used immediately in the aldol coupling.

After efficient generation of the anomeric **15** (CD_{AE}) spiroketal unit we began its manipulation towards the CD ethyl ketone **5** (Scheme 7). Initially, two-step dithiane cleavage via the dimethylketal afforded ketone **25** in good yield; this procedure circumvents product decomposition that occurred under a variety of other cleavage conditions.^[4a,12] Treatment of diol **25** with TBSCl and imidazole in DMF formed the bis(silyl ether) in excellent yield over the opening sequence (82% over 3 steps). Reduction under modified Luche conditions^[13] afforded the desired equatorial C15 alcohol as essentially one diastereomer **27** (d.r. > 20:1), arising from the expected axial hydride delivery. Methylation proceeded with excellent yield, followed by selective primary silyl ether cleavage, forming the basis for investigation into the required carbon extrusion chemistry. Results from model studies on formyl group expulsion indicated that decarboxylation of a β -ketoacid would be the most reliable tactic.

To this end, oxidation of alcohol **29** with Dess–Martin periodinane^[11] followed by Pinnick oxidation^[10] afforded the acid **30**, and brief treatment with ozone in dichloromethane cleanly delivered the β -ketoacid **31** without affecting the primary *p*-methoxybenzyl ether (Scheme 8). The crude material could be smoothly decarboxylated with gentle heating in a toluene/pyridine (2:1) mixture, efficiently delivering the CD



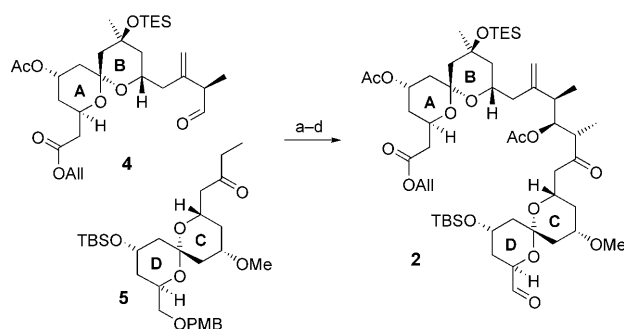
Scheme 7. Reagents and conditions: a) 2 equiv $\text{PhI}(\text{Tfa})_2$, MeOH, 0°C , 40 min; b) aq. NaHCO_3 , AcOH -THF- H_2O , 30°C , 6 h; c) TBSCl, imidazole, DMF, RT, 14 h, 82% over three steps; d) NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, THF, MeOH, -78°C , 1 h, 87%; e) NaH, MeI, THF, $0^\circ\text{C} \rightarrow \text{RT}$, 22 h, 96%; f) HF-Pyridine, pyridine-THF, RT, 7 h, 75%. Tfa = trifluoroacetyl.



Scheme 8. Reagents and conditions: a) Dess–Martin periodinane, CH_2Cl_2 , RT, 1 h; b) NaClO_2 , $t\text{BuOH}$, 2-methyl-2-butene, pH 7 buffer, RT, 2 h; c) O_3 , CH_2Cl_2 , -78°C , 3 min; then Me_2S , concentrate; d) toluene/pyridine (2:1), 40°C , 3 h, 57% over four steps.

ethyl ketone spiroketal unit **5** ready for use in the aldol coupling.

With gram-quantities of the key fragments available, we investigated the aldol union of the CD ketone **5** and AB aldehyde **4** (Scheme 9). Initially, we used the aldol conditions

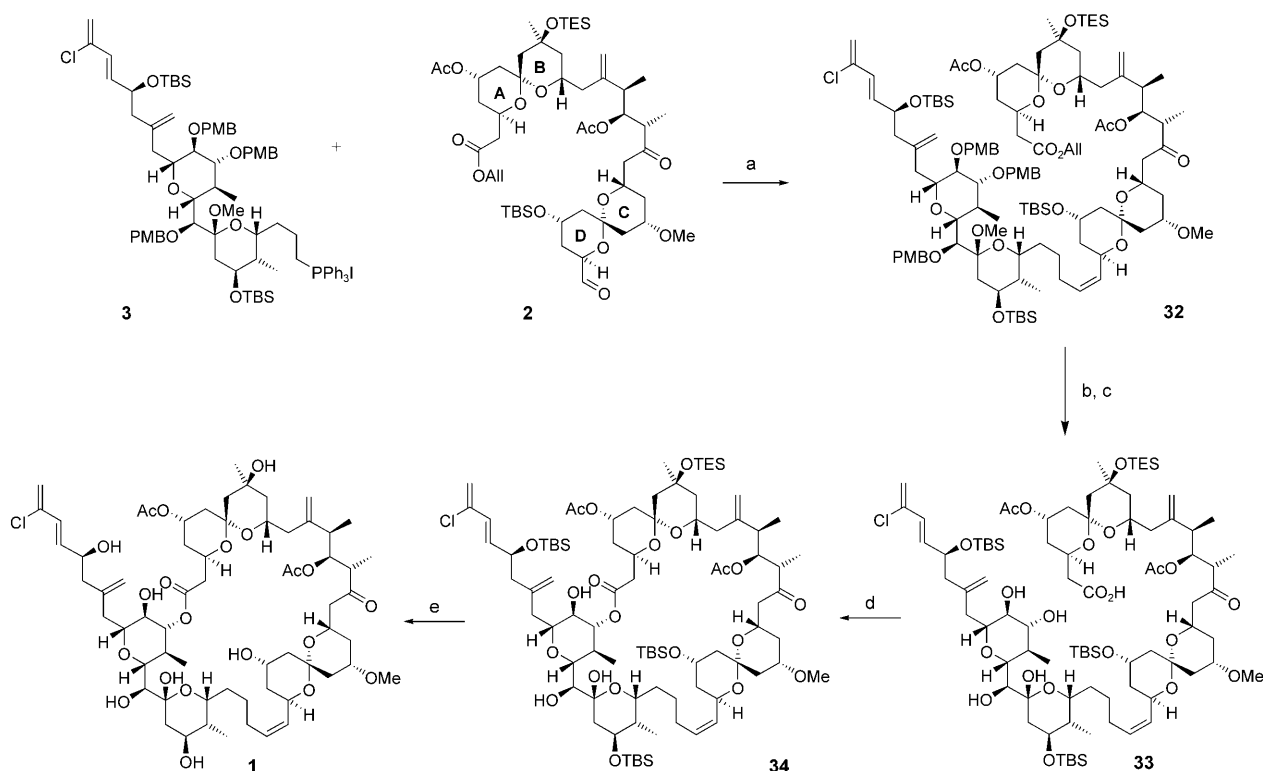


Scheme 9. Reagents and conditions: a) BCl_2Cl , Et_3N , Et_2O , $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$, 10 min; $0^\circ\text{C} \rightarrow -78^\circ\text{C}$; **4**, 1 h; $-78^\circ\text{C} \rightarrow -30^\circ\text{C}$, 16 h, 78%, d.r. = 5:1; b) Ac_2O , pyridine, $0^\circ\text{C} \rightarrow \text{RT}$, 5 h; c) DDQ, CH_2Cl_2 -pH 7 buffer, 0°C , 5 h; d) Dess–Martin periodinane, CH_2Cl_2 , RT, 3 h, 66% over three steps. Cy = cyclohexyl.

described by Evans' group employing pentane as the solvent. Treatment of ketone **5** with dicyclohexylboron chloride formed the *E*-boron enolate and following reaction with aldehyde **4** formed the *anti*-aldol product as an 8:1 mixture of diastereomers (45% yield of desired diastereoisomer). Given

the subtle structural differences between our substrates and the Evans fragments^[2a] we initiated a solvent screen which showed that upon switching to diethyl ether^[3d] the reaction efficiency was greatly increased (78% yield) to afford a 5:1 mixture of diastereoisomers (65% of desired *anti*-adduct). Subsequent acetylation, PMB ether cleavage and oxidation proceeded in high yield to furnish ABCD aldehyde **2**, ready for Wittig coupling with the EF phosphonium salt **3**.

We have previously reported model studies^[14] and recently the completion of the EF phosphonium Wittig salt **3**,^[15] which we subsequently employed in hemisphere unification. The difficulties associated with late-stage Wittig coupling between ABCD aldehyde **2** and EF phosphonium salt **3** have been widely reported^[2,3] and are in accord with our experience (Scheme 10). After experimentation with a variety of literature conditions, we used a modification of the procedure reported by Heathcock and co-workers^[3f] (MeLi-LiBr), employing CaH_2 to remove residual water that may reduce yields due to hydrate formation. Furthermore, the addition of HMPA facilitated ylide formation and subsequent treatment with aldehyde **2** afforded the *cis* alkene **32** with comparable^[3f] efficiency and selectivity (yield 50%). Oxidative removal of all *p*-methoxybenzyl protecting groups in a biphasic solvent system (CH_2Cl_2 -THF-pH 7 buffer) was accompanied by complete hydrolysis of the C37 methoxyketal. Cleavage of the allyl ester protecting group with Pd^0 efficiently furnished the key secoacid intermediate **33**. Macrolactonization of **33** under modified Yamaguchi conditions^[2a] yielded silyl-protected Spongistatin 1 **34**. Global



Scheme 10. Reagents and conditions: a) **3** treated with MeLi-LiBr , THF, -78°C ; then **2** (after drying over CaH_2), $-78^\circ\text{C} \rightarrow \text{RT}$, 50%; b) DDQ, THF- CH_2Cl_2 -pH 7 buffer, RT, 65%; c) $[\text{Pd}(\text{PPh}_3)_4]$, morpholine, RT; d) 2,4,6-trichlorobenzoylchloride, $i\text{Pr}_2\text{NEt}$, DMAP, toluene, 90°C , 56% over two steps; e) 48% HF, CH_3CN , -21°C , 57%.

silyl group removal by treatment with 48% HF yielded Spongistatin 1 (**1**), which was identical in all respects to an authentic sample.^[16]

We have completed a synthesis of Spongistatin 1 (**1**) using established synthetic procedures and methods developed within our research group, including the introduction and subsequent manipulation of β -keto dithiane precursors. Furthermore, the pseudo-symmetric strategy used in forming the ABCD bis(spiroketal) unit **2** represents a new approach towards the family of Spongistatin natural products. The AB spiroketal unit **4** was prepared in 36 steps (overall yield 10% over a 27 step longest linear sequence, average yield 90% per step) and the CD fragment **5** in 37 steps (overall yield 6% over a 28 step longest linear sequence, average yield per step 89%). By applying the pseudo-symmetric approach we are able to access much larger quantities of the key ABCD fragment **2** than from our original route, hence providing the basis for a pragmatic and expedient assembly of the ABCD fragment. By application of the pseudo-symmetric strategy the route is decreased from 65 to only 46 discrete steps from commercially available starting materials. Ongoing work in our laboratories is focusing on further improving the efficiency and scale of the synthetic sequences towards the goal of producing significant quantities of Spongistatin 1.

Received: June 10, 2005

Published online: August 1, 2005

Keywords: dithianes · natural products · pseudo-symmetry · spongistatin 1 · total synthesis

- [1] a) G. R. Pettit, *J. Nat. Prod.* **1996**, 59, 812; b) G. R. Pettit, Z. A. Cichacz, F. Goa, C. L. Herald, M. R. Boyd, J. M. Schmidt, J. N. A. Hooper, *J. Org. Chem.* **1993**, 58, 1302; c) G. R. Pettit, A. Z. Cichacz, F. Goa, C. L. Herald, M. R. Boyd, *J. Chem. Soc. Chem. Commun.* **1993**, 1166; d) G. R. Pettit, C. L. Herald, Z. A. Cichacz, F. Goa, M. R. Boyd, N. D. Christie, J. M. Schmidt, *Nat. Prod. Lett.* **1993**, 5, 329; e) G. R. Pettit, Z. A. Cichacz, C. L. Herald, F. Goa, M. R. Boyd, E. Hamel, R. Bai, *J. Chem. Soc. Chem. Commun.* **1994**, 1605; f) R. Bai, Z. A. Cichacz, C. L. Herald, G. R. Pettit, E. Hamel, *Mol. Pharmacol.* **1993**, 44, 757; g) R. K. Pettit, S. McAllister, G. R. Pettit, *Antimicrob. Agents* **1998**, 9, 147; h) R. Bai, G. F. Taylor, Z. A. Cichacz, C. L. Herald, J. A. Keplar, G. R. Pettit, E. Hamel, *Biochemistry* **1995**, 34, 9714; i) M. Kobayashi, S. Aoki, H. Sakai, K. Kawazoe, N. Kihara, T. Sasaki, I. Kitagawa, *Tetrahedron Lett.* **1993**, 34, 2795; j) M. Kobayashi, S. Aoki, I. Kitagawa, *Tetrahedron Lett.* **1994**, 35, 1243; k) M. Kobayashi, S. Aoki, H. Sakai, N. Kihara, T. Sasaki, I. Kitagawa, *Chem. Pharm. Bull.* **1993**, 41, 989; l) M. Kobayashi, S. Aoki, I. K. Gato, I. Kitagawa, *Chem. Pharm. Bull.* **1996**, 44, 2142; m) N. Fusetani, K. Shinoda, S. Matsunaga, *J. Am. Chem. Soc.* **1993**, 115, 3977.
- [2] a) D. A. Evans, P. J. Coleman, L. C. Dias, *Angew. Chem.* **1997**, 109, 2951; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2737; D. A. Evans, B. W. Trotter, B. Côté, P. J. Coleman, *Angew. Chem.* **1997**, 109, 2954; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2741; D. A. Evans, B. W. Trotter, B. Côté, P. J. Coleman, L. C. Dias, A. N. Tyler, *Angew. Chem.* **1997**, 109, 2957; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2744; D. A. Evans, B. W. Trotter, P. J. Coleman, B. Côté, L. C. Dias, H. A. Rajapaske, A. N. Tyler, *Tetrahedron* **1999**, 55, 8671; b) J. Guo, K. J. Duffy, K. L. Stevens, P. I. Dalko, R. M. Roth, M. M. Hayward, Y. Kishi, *Angew. Chem.* **1998**, 110, 198; *Angew. Chem. Int. Ed.* **1998**, 37, 187; M. M. Hayward, R. M. Roth, K. J. Duffy, P. I. Dalko, K. L. Stevens, J. Guo, Y. Kishi, *Angew. Chem.* **1998**, 110, 202; *Angew. Chem. Int. Ed.* **1998**, 37, 190.
- [3] a) A. B. Smith III, V. A. Doughty, Q. Lin, L. Zhuang, M. D. McBriar, A. M. Boldi, W. H. Moser, N. Murase, K. Nakayama, M. Sobukawa, *Angew. Chem.* **2001**, 113, 197; *Angew. Chem. Int. Ed.* **2001**, 40, 191; b) A. B. Smith III, Q. Lin, V. A. Doughty, L. Zhuang, M. D. McBriar, J. K. Kerns, C. S. Brook, N. Murase, K. Nakayama, M. Sobukawa, *Angew. Chem.* **2001**, 113, 202; *Angew. Chem. Int. Ed.* **2001**, 40, 196; c) A. B. Smith III, V. A. Doughty, C. Sfougataki, C. S. Bennett, J. Koyanagi, M. Takeuchi, *Org. Lett.* **2002**, 4, 783; d) I. Paterson, M. J. Coster, D. Y.-K. Chen, R. M. Oballa, D. J. Wallace, R. D. Norcross, *Org. Biomol. Chem.* **2005**, 3, 2399; I. Paterson, M. J. Coster, D. Y.-K. Chen, K. R. Gibson, D. J. Wallace, *Org. Biomol. Chem.* **2005**, 3, 2410; I. Paterson, M. J. Coster, D. Y.-K. Chen, J. L. Aceña, J. Bach, L. E. Keown, T. Trieselmann, *Org. Biomol. Chem.* **2005**, 3, 2420; I. Paterson, D. Y.-K. Chen, M. J. Coster, J. L. Aceña, J. Bach, D. J. Wallace, *Org. Biomol. Chem.* **2005**, 3, 2431; I. Paterson, D. Y.-K. Chen, M. J. Coster, J. L. Acena, J. Bach, K. R. Gibson, L. E. Keown, R. M. Oballa, T. Trieselmann, D. J. Wallace, A. P. Hodgson, R. D. Norcross, *Angew. Chem.* **2001**, 113, 4179; *Angew. Chem. Int. Ed.* **2001**, 40, 4055; e) M. T. Crimmins, J. D. Katz, D. G. Washburn, S. P. Allwein, L. F. McAtee, *J. Am. Chem. Soc.* **2002**, 124, 5661; f) M. M. Claffey, C. J. Hayes, C. H. Heathcock, *J. Org. Chem.* **1999**, 64, 8267; J. L. Hubbs, C. H. Heathcock, *J. Am. Chem. Soc.* **2003**, 125, 12836; C. H. Heathcock, M. McLaughlin, J. Medina, J. L. Hubbs, G. A. Wallace, R. Scott, M. M. Claffey, C. J. Hayes, G. R. Ott, *J. Am. Chem. Soc.* **2003**, 125, 12844.
- [4] a) M. J. Gaunt, D. F. Hook, H. R. Tanner, S. V. Ley, *Org. Lett.* **2003**, 5, 4815; b) M. J. Gaunt, A. S. Jessiman, P. Orsini, H. R. Tanner, D. F. Hook, S. V. Ley, *Org. Lett.* **2003**, 5, 4819.
- [5] First reported at the *Chemistry A European Journal Symposium*, Strasbourg, France, April 15, 2005.
- [6] This structural feature has also been noted by Roush et al. who applied a double inversion tactic as the basis of forming the AB and CD spiroketal cores from a common intermediate. E. B. Holson, W. R. Roush, *Org. Lett.* **2002**, 4, 3719–3722; E. B. Holson, W. R. Roush, *Org. Lett.* **2002**, 4, 3723–3725.
- [7] The spiroketals can also be separated by two successive column-chromatography operations. However in terms of overall efficiency, preparative HPLC proved to be the method of choice. Employing this separation method, multi-gram quantities of crude spiroketal reaction mixture could be purified and separated in one day.
- [8] M.-K. Chen, G. E. Hardtmann, K. Prasad, O. Repic, M. J. Shapiro, *Tetrahedron Lett.* **1987**, 28, 155.
- [9] R. Baker, M. J. O'Mahony, C. J. Swain, *J. Chem. Soc. Perkin Trans. 1* **1987**, 1623.
- [10] B. S. Bal, W. E. Childers, H. W. Pinnick, *Tetrahedron* **1981**, 37, 2091.
- [11] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, 48, 4383.
- [12] Conditions based on modification of procedure reported in G. Stork, K. Zhao, *Tetrahedron Lett.* **1989**, 30, 287.
- [13] A. L. Gemal, J.-L. Luche, *J. Am. Chem. Soc.* **1981**, 103, 5454.
- [14] E. Fernandez-Megia, N. Gurlaouen, S. V. Ley, G. J. Rowlands, *Synlett* **1998**, 991.
- [15] S. Kawahara, M. J. Gaunt, A. Scolaro, S. Yamanoi, S. V. Ley, *Synlett* **2005**, DOI: 10.1055/s-2005-871960.
- [16] The authentic sample of Spongistatin 1 (**1**) was kindly provided by Professor Pettit.