Synthesis of AB and CD Spiroketal of Spongistatin 1

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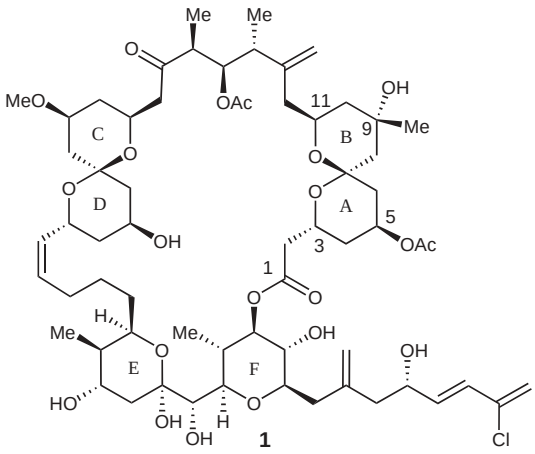
The manuscript is dedicated to Professor Edward Piers of University of British Columbia for his retirement.

Abstract: The AB (C_1-C_{13}) and CD (C_{17}-C_{29}) spiroketal of spongistatin 1 were prepared diastereoselectively from *syn*- and *anti*-3,5-dihydroxy-6-heptenoate derived from 2-deoxy-D-ribose.

Key words: spiro compounds, natural products, stereoselective synthesis, glycosides, alkylations

Spongistatins are a class of highly cytotoxic macrolides isolated from marine sponges.[1–3] These compounds have been shown to exhibit potent antitumor activities against a number of human multi-drug resistant cell lines.[4] The limited supply from natural sources has stimulated significant efforts in the synthesis of these compounds.[5–11] Recently, we published the synthesis of all four diastereomers of *syn*- and *anti*-3,5-dihydroxy-6-heptenoates as potential synthetic precursors to polyol natural products.[12] We now report the synthesis of the AB and CD spiroketals of spongistatin 1 (Figure 1) starting from two of these chiral diol precursors.

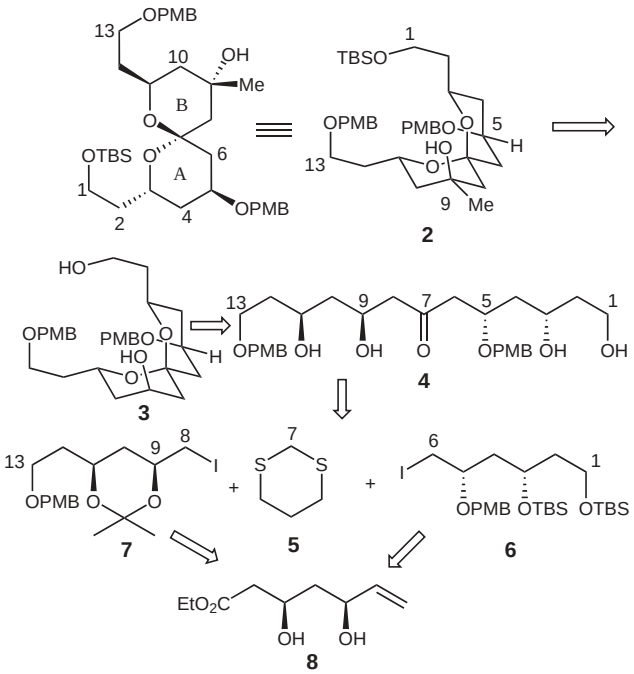


Spongistatin 1, Altohyrtin A

Figure 1

The key to our approach to the synthesis of the AB spiroketal **2** is the stereoselective preparation of the acyclic polyol precursor **4** from a single chiral *syn*-1,3-diol synthon derived from 2-deoxy-D-ribose. We envisaged that the pseudo-C_2-symmetric polyol **4** could be constructed from the sequential dithiane coupling of iodides **6** and **7**, which are basically the same compound bearing different protecting groups. The alcohols of the resulting coupling product **4** are thus differentiated to facilitate further elaboration (Scheme 1). Iodides **6** and **7** can be prepared from (3*R*),(5*S*)-dihydroxy-6-heptenoate (**8**), whose absolute stereochemistry was derived from its starting material, 2-deoxy-D-ribose[12] (Scheme 1).

Based on previous work by other groups, acid-catalyzed cyclization of **4** would give the expected thermodynamically more stable AB spiroketal **3**.[8a,11a] The C_9 alcohol can be readily oxidized to the corresponding ketone which can then be alkylated to give the tertiary alcohol **2** stereoselectively.[5d,11a,p]



Scheme 1 Retrosynthetic analysis of AB spiroketal.

Similar strategy can be employed to synthesize the CD spiroketal **9** (Scheme 2). Since the stereo-configuration of C_{25} and C_{27} of the CD spiroketal is the same as that of the diol of iodide **7**, dithiane coupling of **7** with the epoxide **12** would then give the spiroketal precursor **11**. Epoxide **12** can be prepared from the (3*S*),(5*S*)-dihydroxy-6-heptenoate (**13**).[12] Earlier work by other groups suggested that

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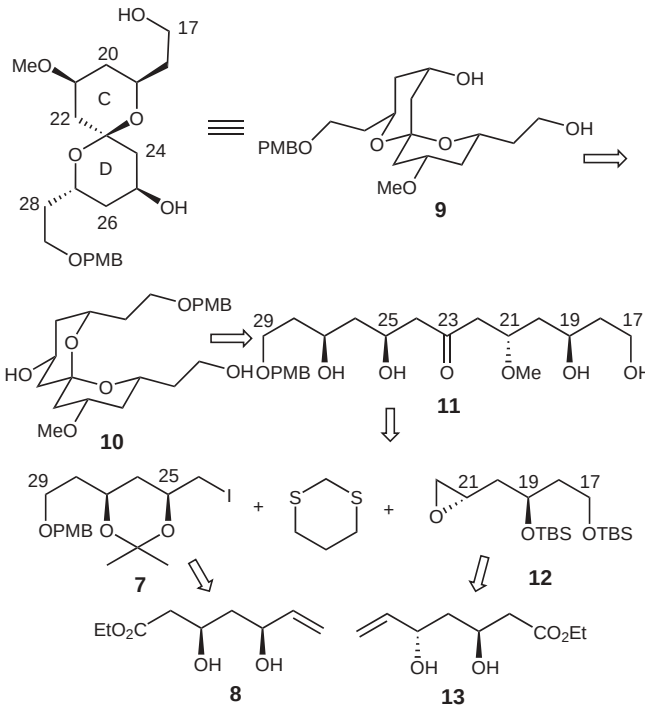
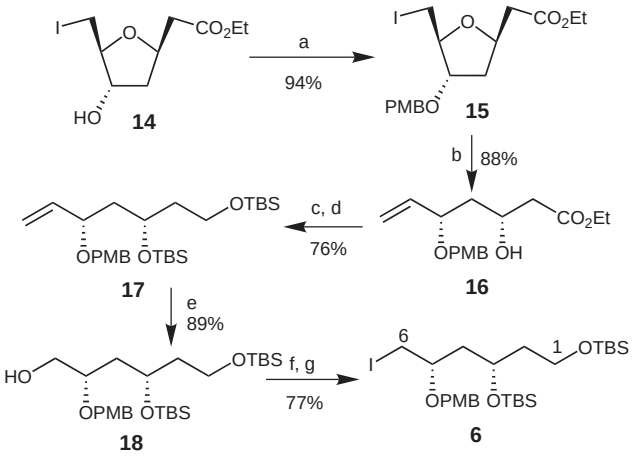
acid-catalyzed cyclization of **11** is expected to give the thermodynamically favored undesirable axial axial CD spiroketal **10** which can be equilibrated under Lewis acid catalysis to the desired axial equatorial isomer **9**.[5d,7a] Essentially, both the AB and CD spiroketals can be prepared from the *syn*- and *anti*-diols **8** and **13**.



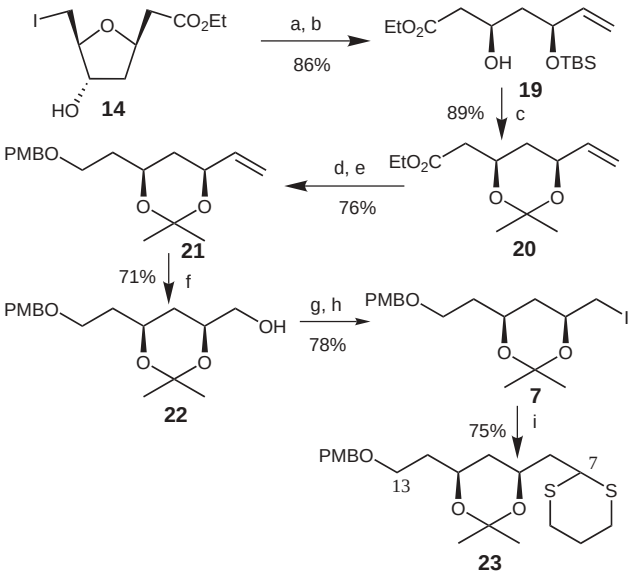
Scheme 2 Retrosynthetic analysis of CD spiroketal.

The synthesis of the C_1-C_6 iodo intermediate **6** began with the iodofuran **14** (Scheme 3) which was prepared from 2-deoxy-D-ribose in 3 steps.[12] The secondary alcohol was protected as the *p*-methoxybenzyl (PMB) ether **15** (94%). Reductive ring-opening of **15** with zinc dust in refluxing dry ethanol gave **16**, the mono-protected derivative of **8**, in 88% yield. The ester was reduced by DIBALH (84%) and the resulting diol was protected as the bis-*t*-butyldimethylsilyl (TBS) ether **17** (90%). Ozonolysis of the terminal olefin, followed by reductive workup with $NaBH_4$ gave the primary alcohol **18** in 89% yield. The primary alcohol was transformed to the iodide **6** via the corresponding tosylate (77%, 2 steps).[13]

The synthesis of the C_7-C_{13} intermediate **7** also starts from **14** (Scheme 4). Protection of the alcohol as a TBS ether followed by ring opening with zinc/ethanol gave the mono-protected diol **19** in 86% yield over two steps. Treatment of **19** with dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid cleaved the TBS ether in situ and formed the acetonide **20** in 89% yield. A better yield of the ring opening reaction was obtained when the alcohol **14** was protected as TBS ether. The ester was reduced by $LiAlH_4$ in THF and the resulting alcohol was protected as the PMB ether **21** (76%). Ozonolysis of the terminal olefin, followed by reductive workup with $NaBH_4$ gave the primary alcohol **22** in 71% yield. The primary alcohol was transformed to the corresponding iodide **7** via the tosylate (78%, 2 steps).[14] Displacement of the iodide with 1,3-dithiane anion in the presence of 2 equivalents of HMPA gave the key intermediate **23** in 75% yield.



Scheme 3 Synthesis of iodide **6**. *Reagents and conditions*: a) PMBOC=NHCCl$_3$, CSA, CH_2Cl_2, r.t., 20 h; b) Zn, EtOH, 70 °C, 1 h; c) DIBALH, toluene, –78 °C to r.t., 1.5 h; d) TBDMSCl, DMAP, Et_3N, CH_2Cl_2, r.t., 72 h; e) O_3, CH_2Cl_2, MeOH, –78 °C; then $NaBH_4$, r.t., 1.5 h; f) TsCl, DMAP, Et_3N, CH_2Cl_2, 1.5 h; g) NaI, $NaHCO_3$, butanone, Δ, 3 h.

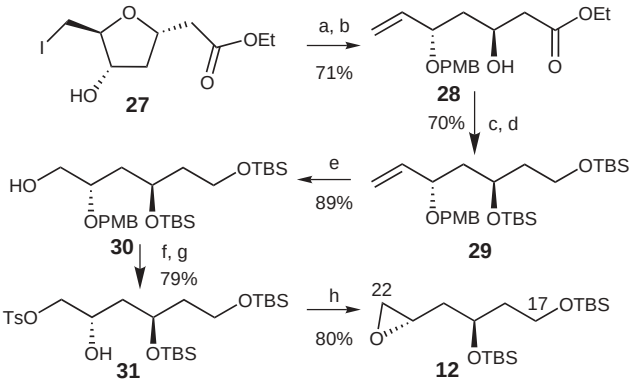


Scheme 4 Synthesis of dithiane **23**. *Reagents and conditions*: a) TBDMSCl, DMAP, Et_3N, CH_2Cl_2, r.t., 20 h; b) Zn, EtOH, 70 °C, 1 h; c) dimethoxypropane, TsOH, DMF, r.t., 7 d; d) $LiAlH_4$, THF, 0 °C, 10 min; e) PMBOC=NHCCl$_3$, CSA, CH_2Cl_2, r.t., 20 h; f) O_3, CH_2Cl_2, –78 °C; then $NaBH_4$, EtOH, H_2O, r.t., 1.5 h; g) TsCl, DMAP, Et_3N, CH_2Cl_2, r.t., 1.5 h; h) NaI, $NaHCO_3$, 2-butanone, Δ, 8 h; i) 1,3-dithiane, *n*-BuLi, HMPA, THF, –20 °C, 1 h then **7**, –20 °C, 1 h.

Coupling of **6** and **23** was achieved by treating **23** with 1.2 equivalents of *t*-butyllithium in THF at –78 °C in the presence of 2 equivalents of HMPA followed by the addition of **6** (Scheme 5). The coupled product **24** was obtained in 88% yield. Sequential coupling of dithiane with iodide **6**

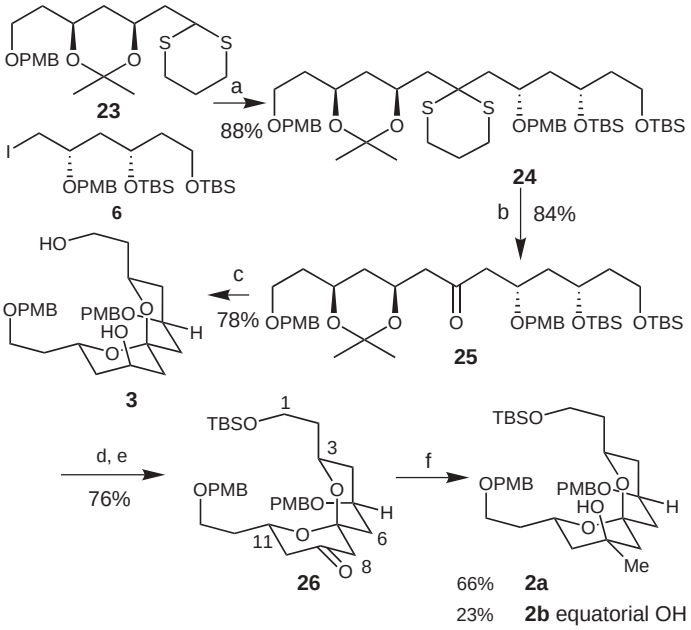
first and then with iodide **7** was also attempted. The overall yield was only 50%. Furthermore, dithiane **7** can also be used in the synthesis of the CD spiroketal, making this sequence more attractive. Reaction of thioacetal **24** with $Hg(ClO_4)_2$ in MeCN–H_2O gave an 84% yield of the ketone **25**.[15] Treatment of **25** with HF in aqueous MeCN deprotected both the TBS ethers and the acetonide with concomitant cyclization to give the spiroketal **3** as the only product in 78% yield. Protection of the primary alcohol followed by oxidation of the secondary alcohol to the ketone with Dess–Martin periodinane (DMP) gave the ketone **26** (76%, 2 steps). ^{1}H NMR, 2D-COSY and NOESY spectra of **26** is consistent with the stereochemistry of the AB spiroketal of spongistatin 1.[16] Alkylation of the ketone **26** with MeMgI in diethyl ether gave only 66% yield of the desired axial alcohol **2a**. In contrast to similar reactions reported in literature,[8a,9a] the epimer **2b** was also isolated in 23% yield. The axial configuration of the tertiary alcohol of **2a** was confirmed by NOE experiments.[17] Other alkylation method will be investigated in the future to improve the selectivity. The two primary alcohols of **2a** are differentiated and deprotection of the primary vs. the secondary PMB ether should be possible.

For the CD spiroketal, synthesis of the C_{17}-C_{22} fragment **12** followed the same synthetic sequence as that of **6** due to the similarity between the two compounds. Thus, protection of the secondary alcohol of **27** (the C_1 α-isomer of **14**)[12] with a PMB ether followed by zinc/ethanol ring-opening gave the mono-protected *anti*-diol **28** (71% in 2 steps, Scheme 6). The ester was reduced by DIBALH and the resulting diol was protected as the *bis*-TBS ether **29** (70%, 2 steps). Ozonolysis of the terminal olefin, followed by reductive workup with $NaBH_4$ gave the primary alcohol **30** in 89% overall yield. Tosylation of the primary alcohol followed by deprotection of the PMB ether with DDQ in aqueous CH_2Cl_2 gave the secondary alcohol **31** (79%, 2 steps). Treatment of **31** with NaOEt in EtOH gave the epoxide **12** in 80% yield.[18]

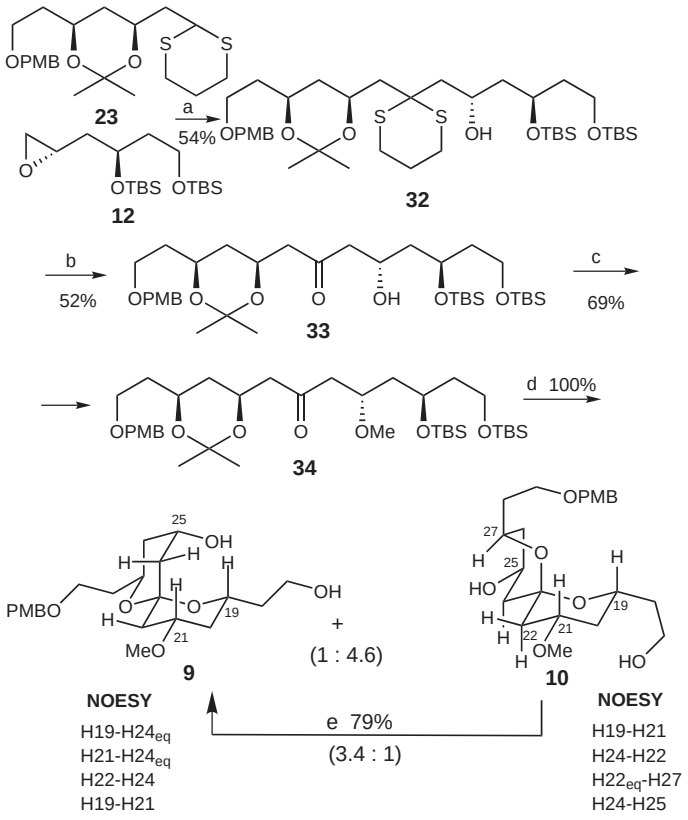


Scheme 6 Synthesis of epoxide **12**. *Reagents and conditions*: a) $PMBOC{=}NHCCl_3$, CSA, CH_2Cl_2, r.t., 20 h; b) Zn, EtOH, 70 °C, 1.5 h; c) DIBALH, toluene, –78 °C to 0 °C, 30 min; d) TBDMSCl, DMAP, Et_3N, CH_2Cl_2, Δ, 3.5 h; e) O_3, CH_2Cl_2, MeOH, –78 °C; then $NaBH_4$, r.t. 1 h; f) TsCl, DMAP, Et_3N, CH_2Cl_2, 20 h; g) DDQ, CH_2Cl_2–H_2O (9:1), 0 °C, 3 h; h) NaOEt, EtOH, r.t., 15 min.

As mentioned earlier, the C_7-C_{13} fragment **23** also represent the C_{23}-C_{29} fragment of the CD spiroketal. Coupling of the dithiane anion of **23** with the epoxide **12**, under the same reaction conditions described above for the formation of **6**, gave the key intermediate **32** in 54% yield. Significant amount of starting materials **23** and **6** (28% and 40%, respectively) were recovered in the reaction. Attempts to push the reaction to completion by raising the reaction temperature were not successful. Dethioacetalization of **32** with $Hg(ClO_4)_2$ gave a 52% yield of the hydroxyketone **33**. A mixture of the primary and secondary



Scheme 5 Synthesis of AB spiroketal **2**. *Reagents and conditions*: a) **23**, *t*-BuLi, 2 equiv HMPA, THF, –78 °C, 30 min, then **6**, –78 °C, 0.5 h; b) $Hg(ClO_4)_2$, THF–H_2O (5:1), 10 min; c) HF, MeCN–H_2O (2:1), r.t., 6 h; d) TBDMSCl, DMAP, Et_3N, CH_2Cl_2, r.t., 20 h; e) DMP, CH_2Cl_2, r.t., 4 h; f) MeMgI, Et_2O, –78 °C to –10 °C, 5 h.



Scheme 7 Synthesis of CD spiroketal **9**. *Reagents and conditions*: a) **23**, *t*-BuLi, 2 equiv HMPA, THF, –78 °C, 30 min, then **12**, –20 °C, 4 h; b) $Hg(ClO_4)_2$, $CaCO_3$, THF–H_2O (5:1), 10 min; c) $Me_3O^+BF_4^-$, 2,6-di-*t*-butyl-4-methylpyridine, CH_2Cl_2, r.t., 6 h; d) HF, MeCN–H_2O (2:1), r.t., 3 h; e) $ZnBr_2$, CH_2Cl_2, r.t., 1 h.

TBS deprotected alcohols was also isolated (38%). The poor yield of this reaction in contrast to that of **24** → **25** may be attributed to the presence of the adjacent hydroxyketone. The secondary alcohol was then methylated with $Me_3O^+BF_4^-$ to give a 69% yield of **34** (Scheme 7).[19]

Treatment of **34** with HF in aqueous MeCN gave quantitatively a mixture of the spiroketals **9** and **10** in the ratio of 1:4 favoring the undesirable axial axial isomer **10**. The mixture was treated with 1.2 equivalents of anhydrous $ZnBr_2$ in CH_2Cl_2 for 1 hour[5d,10a] to give 61% of the desired isomer **9** and 18% of **10** after chromatography. The configurations of the spiroketals **9** and **10** were confirmed via ^1H NMR, 2D-COSY and NOESY experiments.[20] Spiroketal **9** exhibits diagnostic strong NOEs between H19-H21, H19-$H24_{eq}$, H21-$H24_{eq}$ and $H22_{eq}$-$H24_{ax}$. For spiroketal **10**,[21] strong NOE was observed between H19-H21, confirming the chair conformation of the C_{19}-C_{22} segment. The second ring (C_{23}-C_{27}) adopts a more boat like conformation as defined by NOEs observed between H22-H24, H24-H25, and the most telling NOE between $H22_{eq}$ and H27.[11p]

In summary, we have achieved a highly stereoselective and convergent synthesis of both the AB and CD spiroketals of spongistatin 1 starting from derivatives of the *syn*- and *anti*-3,5-dihydroxy-6-heptenoates of predefined stereo configuration that were derived from 2-deoxy-D-ribose.

References

(1) (a) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. *J. Org. Chem.* **1993**, *58*, 1302. (b) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R. *J. Chem. Soc., Chem. Commun.* **1993**, 1166. (c) Pettit, G. R.; Herald, C. L.; Cichacz, Z. A.; Gao, F.; Boyd, M. R.; Christie, N. D.; Schmidt, J. M. *Nat. Prod. Lett.* **1993**, *3*, 239. (d) Pettit, G. R.; Herald, C. L.; Cichacz, Z. A.; Gao, F.; Schmidt, J. M.; Boyd, M. R.; Christie, N. D.; Boettner, F. E. *J. Chem. Soc., Chem. Commun.* **1993**, 1805. (e) Pettit, G. R.; Cichacz, Z. A.; Herald, C. L.; Gao, F.; Boyd, M. R.; Schmidt, J. M.; Hamel, E.; Bai, R. *J. Chem. Soc., Chem. Commun.* **1994**, 1605.

(2) (a) Kobayashi, M.; Aoki, S.; Sakai, H.; Kawazon, K.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Tetrahedron Lett.* **1993**, *34*, 1993. (b) Kobayashi, M.; Aoki, S.; Sakai, H.; Kawazon, K.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1993**, *41*, 989. (c) Kobayashi, M.; Aoki, S.; Kitagawa, I. *Tetrahedron Lett.* **1994**, *35*, 1243.

(3) Fusetanai, N.; Shinoda, K.; Matsunaga, S. *J. Am. Chem. Soc.* **1993**, *115*, 3977.

(4) Pettit, G. R. *J. Nat. Prod.* **1996**, *59*, 812.

(5) (a) Evans, D. A.; Coleman, P. J.; Dias, L. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2738. (b) Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2741. (c) Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J.; Dias, L. C.; Tyler, A. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2744. (d) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671.

(6) (a) Guo, J.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi, Y. *Angew. Chem. Int. Ed.* **1998**, *37*, 187. (b) Hayward, M. M.; Roth, R. M.; Duffy, K. J.; Dalko, P. I.; Stevens, K. L.; Guo, J.; Kishi, Y. *Angew. Chem. Int. Ed.* **1998**, *37*, 192.

(7) (a) Smith, A. B. I. I. I.; Zhuang, L.; Brook, C. S.; Lin, Q.; Moser, W. H.; Trout, R. E. L.; Boldi, A. M. *Tetrahedron Lett.* **1997**, *38*, 8671. (b) Smith, A. B. III.; Doughty, V. A.; Lin, Q.; Zhuang, L.; McBriar, M. D.; Boldi, A. M.; Moser, W. H.; Murase, N.; Nakayama, K.; Sobukawa, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 191. (c) Smith, A. B. III.; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Kerns, J. K.; Brook, C. S.; Murase, N.; Nakayama, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 196. (d) Smith, A. B. III.; Doughty, V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett.* **2002**, *4*, 783. (e) Smith, A. B. III.; Zhu, W.; Shirakami, S.; Sfouggatakis, C.; Doughty, V. A.; Bennett, C. S.; Sakamoto, Y. *Org. Lett.* **2003**, *5*, 761.

(8) (a) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581. (b) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585. (c) Paterson, I.; Keown, L. E. *Tetrahedron Lett.* **1997**, *38*, 5727. (d) Paterson, I.; Oballa, R. M. *Tetrahedron Lett.* **1997**, *38*, 8241. (e) Paterson, I.; Wallace, D. J.; Gibson, K. R. *Tetrahedron Lett.* **1997**, *38*, 8911. (f) Paterson, I.; Chen, D. Y.-K.; Coster, M. J.; Aceña, J. L.; Bach, J.; Gibson, K. R.; Keown, L. E.; Oballa, R. M.; Trieselmann, T.; Wallace, D. J.; Hodgson, A. P.; Norcross, R. D. *Angew. Chem. Int. Ed.* **2001**, *40*, 4055.

(9) (a) Crimmins, M. T.; Washburn, D. G. *Tetrahedron Lett.* **1998**, *39*, 7487. (b) Crimmins, M. T.; Katz, J. D.; McAtee, L. C.; Tabet, E. A.; Kirincich, S. J. *Org. Lett.* **2001**, *3*, 949. (c) Crimmins, M. T.; Katz, J. D. *Org. Lett.* **2000**, *2*, 957. (d) Crimmins, M. T.; Katz, J. D.; Washburn, D. G.; Allwein, S. P.; McAtee, L. F. *J. Am. Chem. Soc.* **2002**, *124*, 5661.

(10) (a) Hubbs, J. L.; Heathcock, C. H. *J. Am. Chem. Soc.* **2003**, *125*, 12836. (b) Heathcock, C. H.; McLaughlin, M.; Medina, J.; Hubbs, J. L.; Wallace, G. A.; Scott, R.; Claffey, M. M.; Hayes, C. J.; Ott, G. R. *J. Am. Chem. Soc.* **2003**, *125*, 12844. (c) Wallace, G. A.; Scott, R. W.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 4145. (d) Claffey, M. M.; Hayes, C. J.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8267.

(11) For a comprehensive list of leading references to synthetic approaches from other laboratories, see the references cited in ref.[10a] and the following: (a) Zuev, D.; Paquette, L. A. *Org. Lett.* **2000**, *2*, 679. (b) Terauchi, T.; Nakata, M. *Tetrahedron Lett.* **1998**, *39*, 3795. (c) Lemaire-Audoire, S.; Vogel, P. *Tetrahedron Lett.* **1998**, *39*, 1345. (d) Lemaire-Audoire, S.; Vogel, P. *J. Org. Chem.* **2000**, *65*, 3346. (e) Zemribo, R.; Mead, K. T. *Tetrahedron Lett.* **1998**, *39*, 3895. (f) Fernandez-Megia, E.; Gourlaouen, N.; Ley, S. V.; Rowlands, G. J. *Synlett* **1998**, 991. (g) Gaunt, M. J.; Hook, D. F.; Tanner, H. R.; Ley, S. V. *Org. Lett.* **2003**, *5*, 4815. (h) Gaunt, M. J.; Jessiman, A. S.; Orsini, P.; Tanner, H. R.; Hook, D. F.; Ley, S. V. *Org. Lett.* **2003**, *5*, 4819. (i) Micalizio, G. C.; Pinchuk, A. N.; Roush, W. R. *J. Org. Chem.* **2000**, *65*, 8730. (j) Anderson, J. C.; McDermott, B. P. *Tetrahedron Lett.* **1999**, *40*, 7135. (k) Samadi, M.; Munoz-Letelier, C.; Poigny, S.; Guyot, M. *Tetrahedron Lett.* **2000**, *41*, 3349. (l) Terauchi, T.; Terauchi, T.; Sato, I.; Tsukada, T.; Kanoh, N.; Nakata, M. *Tetrahedron Lett.* **2000**, *41*, 2649. (m) Kary, P. D.; Roberts, S. M. *Tetrahedron: Asymmetry* **1999**, *10*, 217. (n) Kim, H.; Hoffmann, M. R. *Eur. J. Org. Chem.* **2000**, 2195. (o) Barrett, A. G. M.; Braddock, D. C.; de Koning, P. D.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 375. (p) Holson, E. B.; Roush, W. R. *Org. Lett.* **2002**, *4*, 3719. (q) Holson, E. B.; Roush, W. R. *Org. Lett.* **2002**, *4*, 3723.

(12) Lau, C. K.; Zakrewski, P. *Synlett* **2003**, *2*, 215.

(13) Physical data of **6**: $[\alpha]_D^{25}$ –16.5 (*c* 1.79, $CHCl_3$). ^{1}H NMR (500 MHz, acetone-d_6): δ = 7.31 (d, 2 H, *J* = 8.7 Hz), 6.90 (d, 2 H, *J* = 8.7 Hz), 4.58 (d, 1 H, *J* = 11.1 Hz), 4.42 (d, 1 H, *J* = 11.2 Hz), 4.07–4.01 (m, 1 H), 3.78 (s, 3 H), 3.74–3.66 (m, 2 H), 3.56–3.52 (m, 1 H), 3.41–3.39 (m, 2 H), 1.87–1.81 (m, 1 H), 1.77–1.69 (m, 2 H), 1.65–1.58 (m, 1 H), 0.88 (s, 18 H), 0.08 (s, 6 H), 0.05 (s, 6 H). ^{13}C NMR (100 MHz, acetone-d_6): δ = 170.5, 141.6, 140.4, 124.7, 85.1, 81.3, 77.5, 70.6, 65.7, 53.8, 51.2, 36.5, 28.9, 28.8, 22.3, 6.1, 5.9, 5.1. HRMS: *m/z* calcd for $C_{26}H_{48}O_4Si_2I$: for [M – H] 607.2136. Found: 607.2138.

(14) Physical data of **7**: $[\alpha]_D^{25}$ –0.9 (*c* 4.47, $CHCl_3$). ^{1}H NMR (500 MHz, acetone-d_6): δ = 7.28 (d, 2 H, *J* = 8.6 Hz), 6.92 (d, 2 H, *J* = 8.6 Hz), 4.42 (q, 2 H, *J* = 9.6 Hz), 4.12–4.06 (m, 1 H), 3.94–3.87 (m, 1 H), 3.80 (s, 3 H), 3.58–3.48 (m, 2 H), 3.26 (dd, 1 H, *J* = 4.8, 10.1 Hz), 3.17 (dd, 1 H, *J* = 6.4, 10.2 Hz), 1.82–1.74 (m, 1 H), 1.71 (q, 2 H, *J* = 6.2 Hz), 1.43 (s, 3 H), 1.32 (s, 3 H), 1.10 (q, 1 H, *J* = 11.8 Hz). ^{13}C NMR (100 MHz, acetone-d_6): δ = 164.3, 136.1, 134.2, 118.7, 103.9, 77.2, 74.1, 70.9, 70.7, 59.8, 41.9, 41.5, 34.6, 24.5, 15.2.

(15) Physical data of **25**: $[\alpha]_D^{25}$ –7.3 (*c* 3.75, CH_2Cl_2). ^{1}H NMR (500 MHz, acetone-d_6): δ = 7.27 (m, 4 H), 6.91 (m, 4 H), 4.46 (d, 2 H, *J* = 11.0 Hz), 4.42 (d, 2 H, *J* = 10.6 Hz), 4.39–4.34 (m, 1 H), 4.08–4.02 (m, 3 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 3.78–3.70 (m, 2 H), 3.55–3.47 (m, 2 H), 2.69–2.61 (m, 2 H), 2.48 (dd, 1 H, *J* = 5.0, 15.6 Hz), 1.83–1.76 (m, 2 H), 1.68–1.58 (m, 6 H), 1.42 (s, 3 H), 1.27 (s, 3 H), 1.09 (m, 1 H), 0.94 (s, 9 H), 0.91 (s, 9 H), 0.10 (m, 6 H), 0.08 (s, 6 H). ^{13}C NMR (100 MHz, acetone-d_6): δ = 206.91, 159.61, 131.46, 131.43, 129.52, 129.40, 113.92, 113.86, 98.57, 72.80, 72.46, 70.95, 66.89, 66.28, 66.13, 65.99, 59.86, 55.00, 50.38, 48.83, 43.18, 40.52, 37.23, 37.00, 25.86, 19.60, 18.31, 18.10, –4.55, –4.77, –5.56, –5.58. HRMS: *m/z* calcd for $C_{44}H_{74}O_9Si_2K$: for [M + K^+] 841.4508. Found: 841.4505.

(16) Physical data of **26**: $[\alpha]_D^{25}$ –67.4 (*c* 6.5, CH_2Cl_2). ^{1}H NMR (500 MHz, acetone-d_6): δ = 7.36 (d, 2 H, *J* = 8.5 Hz), 7.17 (d, 2 H, *J* = 8.5 Hz), 6.92 (d, 2 H, *J* = 8.6 Hz), 6.88 (d, 2 H, *J* = 8.6 Hz), 4.61 (d, 1 H, *J* = 11.1 Hz), 4.43 (d, 1 H, *J* = 11.1 Hz), 4.27 (d, 1 H, *J* = 11.4 Hz), 4.16 (d, 1 H, *J* = 11.4 Hz), 4.13–4.08 (m, 1 H, H3), 4.07–4.03 (m, 1 H, H11), 3.90 (br s, 1 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.72–3.68 (m, 1 H), 3.66–3.60 (m, 2 H), 3.54–3.50 (m, 1 H), 2.54 (d, 1 H, *J* = 14.1 Hz, $H8_{ax}$), 2.34 (d, 1 H, *J* = 8.5 Hz, $H6_{ax}$), 2.29–2.23 (m, 3 H), 1.89 (d, 1 H, *J* = 13.9 Hz, $H4_{ax}$), 1.84–1.80 (m, 2 H), 1.62–1.55 (m, 3 H), 1.52–1.46 (m, 1 H, $H4_{eq}$), 0.89 (s, 9 H), 0.03 (s, 6 H). ^{13}C NMR (150 MHz, acetone-d_6): δ = 204.78, 159.89, 159.35, 132.36, 129.66, 129.24, 128.96, 113.64, 113.63, 99.82, 72.51, 70.88, 69.66, 66.61, 66.15, 62.44, 59.88, 54.89, 54.86, 52.24, 46.94, 38.97, 36.17, 36.13, 35.74, 25.84, 18.20, –5.67. The stereochemistry of AB spiroketal was determined by 2D-COSY and NOESY experiments. NOEs were observed between $H6_{ax}$ and $H8_{ax}$, $H6_{eq}$ and $H8_{eq}$ as well as $H3_{ax}$ and $H11_{ax}$ which were consistent with the proposed spiroketal junction reported in the literature. HRMS: *m/z* calcd for $C_{35}H_{52}O_8SiK$: for [M + K^+] 667.3069. Found: 667.3066.

(17) Physical data of **2a**: $[\alpha]_D^{25}$ –50.0 (*c* 1.2, CH_2Cl_2). ^{1}H NMR (500 MHz, acetone-d_6): δ = 7.33 (d, 2 H, *J* = 8.5 Hz), 7.17 (d, 2 H, *J* = 8.4 Hz), 6.89 (dd, 4 H, *J* = 8.6, 11.4 Hz), 4.56 (d, 1 H, *J* = 11.1 Hz), 4.38 (d, 1 H, *J* = 11.1 Hz), 4.28 (d, 1 H, *J* = 11.4 Hz), 4.23–4.15 (m, 3 H), 4.01 (t, 1 H, J = 10.5 Hz), 3.85 (s, 1 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.76–3.73 (m, 1 H), 3.71–3.61 (m, 2 H), 3.53–3.47 (m, 1 H), 2.11 (s, 1 H, H6),

1.89 (d, 1 H, *J* = 12.6 Hz, H4), 1.75–1.65 (m, 5 H), 1.56–1.49 (m, 4 H), 1.29 (t, 1 H, *J* = 12.3 Hz, H10), 1.10 (s, 3 H, CH_3), 0.90 (s, 9 H), 0.06 (s, 6 H). ^{13}C NMR (150 MHz, acetone-d_6): δ = 160.48, 160.44, 132.35, 132.31, 129.14, 129.04, 113.95, 113.91, 98.56, 72.30, 70.90, 69.63, 69.16, 66.85, 62.94, 62.81, 60.41, 54.85, 54.83, 46.45, 44.53, 39.18, 37.00, 36.04, 29.95, 25.79, 18.15, –5.18. The stereochemistry of the axial C9-OH was determined by 2D-COSY and NOESY experiments. NOE was observed between $H11_{ax}$ and C9-OH, CH_3 and $H8_{eq}$ as well as CH_3 and $H10_{eq}$. HRMS: *m/z* calcd for $C_{36}H_{56}O_8SiK$: for [M + K^+] 683.3382. Found: 683.3382. Physical data of **2b**: $[\alpha]_D^{25}$ –46.0 (*c* 0.43, CH_2Cl_2). ^{1}H NMR (500 MHz, acetone-d_6): δ = 7.33 (d, 2 H, *J* = 8.6 Hz), 7.18 (d, 2 H, *J* = 8.6 Hz), 6.89–6.87 (m, 4 H), 4.56 (d, 1 H, *J* = 11.1 Hz), 4.36 (d, 1 H, *J* = 11.1 Hz), 4.29 (d, 1 H, *J* = 11.5 Hz), 4.18 (d, 1 H, *J* = 11.5 Hz), 4.11–4.05 (m, 1 H, H3), 3.85–3.81 (m, 2 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.73–3.67 (m, 2 H), 3.64–3.58 (m, 1 H), 3.51–3.47 (m, 2 H), 2.10–2.08 (m, 1 H, H6), 1.86–1.82 (m, 1 H, H4), 1.74–1.59 (m, 6 H), 1.53–1.45 (m, 3 H), 1.41 (s, 3 H, CH_3), 1.38–1.31 (m, 1 H, H10), 0.90 (s, 9 H), 0.05 (s, 6 H). ^{13}C NMR (150 MHz, acetone-d_6): δ = 159.60, 159.54, 131.60, 131.48, 129.71, 129.65, 114.06, 113.99, 97.71, 72.23, 71.10, 69.63, 67.16, 64.80, 61.92, 60.63, 54.83, 54.82, 49.75, 46.32, 39.71, 37.69, 36.54, 36.12, 29.14, 26.10, 18.16, –5.18. NOEs were observed between $H11_{ax}$ and CH_3, $H8_{eq}$ and CH_3 as well as $H3_{ax}$ and $H11_{ax}$ which were consistent with the spiroketal structure with the equatorial C9-OH. HRMS: *m/z* calcd for $C_{36}H_{56}O_8SiNa$: for [M + Na^+] 667.3642. Found: 667.3638.

(18) Physical data of **12**: $[\alpha]_D^{25}$ –2.53 (*c* 4.5, CH_2Cl_2). ^{1}H NMR (500 MHz, acetone-d_6): δ = 4.17–4.11 (m, 1 H), 3.75 (t, 2 H, *J* = 6.3 Hz), 2.98–2.96 (m, 1 H), 2.72 (t, 1 H, *J* = 4.6 Hz), 2.44 (dd, 1 H, *J* = 2.5, 5.2 Hz), 1.77–1.71 (m, 2 H), 1.71–1.61 (m, 2 H), 0.95 (s, 9 H), 0.92 (s, 9 H), 0.14 (m, 6 H), 0.09 (s, 6 H). ^{13}C NMR (100 MHz, acetone-d_6): δ = 67.81, 59.66, 49.26, 46.92, 41.19, 41.03, 25.83, 25.80, 18.28, 18.11, –4.80, –4.88, –5.62. HRMS: *m/z* calcd for $C_{18}H_{41}O_3Si_2$: for [M + H^+] 361.2594. Found: 361.2593.

(19) Physical data of **34**: $[\alpha]_D^{25}$ –19.3 (*c* 0.15, CH_2Cl_2). ^{1}H NMR (500 MHz, acetone-d_6): δ = 7.28 (d, 2 H, *J* = 8.5 Hz), 6.92 (d, 2 H, *J* = 8.5 Hz), 4.43–4.36 (m, 3 H), 4.10–4.05 (m, 2 H), 3.89–3.83 (m, 1 H), 3.80 (s, 3 H), 3.77–3.71 (m, 2 H), 3.56–3.48 (m, 2 H), 3.28 (s, 3 H), 2.82–2.78 (m, 1 H), 2.63 (dd, 1 H, *J* = 7.5, 15.9 Hz), 2.56–2.46 (m, 2 H), 1.72–1.66 (m, 5 H), 1.62–1.58 (m, 1 H), 1.55–1.49 (m, 1 H), 1.44 (s, 3 H), 1.28 (s, 3 H), 1.13–1.05 (m, 1 H), 0.96 (s, 9 H), 0.92 (s, 9 H), 0.13 (s, 6 H), 0.08 (s, 6 H). ^{13}C NMR (100 MHz, acetone-d_6): δ = 206.62, 159.62, 131.43, 129.39, 113.92, 98.57, 74.04, 72.45, 67.11, 66.29, 66.01, 65.98, 59.67, 55.82, 54.99, 50.23, 48.15, 43.15, 41.48, 37.22, 37.00, 25.90, 25.81, 19.59, 18.27, 18.15, –4.48, –4.71, –5.64. HRMS: *m/z* calcd for $C_{37}H_{68}O_8Si_2K$: for [M + K^+] 735.4090. Found: 735.4087.

(20) Physical data of **9**: $[\alpha]_D^{25}$ –26.8 (*c* 0.67, CH_2Cl_2). ^{1}H NMR (500 MHz, acetone-d_6): δ = 7.31 (d, 2 H, *J* = 8.5 Hz), 6.91 (d, 2 H, *J* = 8.5 Hz), 4.59–4.53 (m, 1 H), 4.45 (q, 2 H, *J* = 10.1 Hz), 4.18 (d, 1 H, *J* = 5.3 Hz), 4.11 (s, 1 H), 3.94 (t, 1 H, *J* = 6.3 Hz, OH), 3.85–3.81 (m, 2 H), 3.80 (s, 3 H), 3.59–3.51 (m, 4 H), 3.30 (s, 3 H), 2.37 (d, 1 H, *J* = 14.6 Hz, $H24_{eq}$), 2.04–2.00 (m, 2 H), 1.74–1.59 (m, 5 H), 1.53–1.45 (m, 2 H), 1.21 (t, 1 H, *J* = 11.9 Hz, $H22_{ax}$), 1.08 (q, 1 H, *J* = 11.7 Hz, $H20_{ax}$). ^{13}C NMR (150 MHz, acetone-d_6): δ = 159.20, 131.01, 129.04, 114.01, 99.09, 74.00, 72.51, 67.69, 66.36, 64.04, 62.21, 58.39, 54.91, 54.58, 43.74, 38.92, 38.60, 38.38, 36.52, 34.11. The stereochemistry of CD spiroketal was determined by 2D-COSY and NOESY experiments. NOEs were observed between $H19_{ax}$ and $H24_{eq}$, H21 and $H24_{eq}$, $H22_{eq}$ and $H24_{ax}$ as well as H21 and H-19. HRMS: *m/z* calcd for $C_{22}H_{34}O_7K$: for [M + K^+] 449.1942. Found: 449.1940.

(21) Physical data of **10**: $[\alpha]_D^{25}$ +0.3 (*c* 1.7, CH_2Cl_2). ^{1}H NMR (500 MHz, acetone-d_6): δ = 7.30 (d, 2 H, *J* = 8.3 Hz), 6.92 (d, 2 H, *J* = 8.4 Hz), 4.48–4.41 (m, 2 H), 4.20–4.18 (m, 1 H, H25), 4.17–4.11 (m, 1 H, H27), 4.08–4.05 (m, 1 H, H19), 3.80 (s, 3 H), 3.80–3.79 (m, 1 H, OH), 3.69–3.62 (m, 3 H), 3.58–3.50 (m, 2 H), 3.37 (t, 1 H, *J* = 5.1 Hz, OH), 3.24 (s, 3 H), 2.69 (d, 1 H, *J* = 10.2 Hz, $H22_{eq}$), 2.08–2.03 (m, 1 H, H20), 1.84–1.78 (m, 3 H), 1.73–1.58 (m, 5 H), 1.07–0.99 (m, 2 H). ^{13}C NMR (150 MHz, acetone-d_6): δ = 159.23, 130.98, 129.05, 113.52, 98.95, 72.98, 72.10, 66.68, 66.64, 66.51, 62.38, 58.68, 54.60, 54.40, 43.65, 39.96, 39.26, 38.19, 37.62, 35.99. The stereochemistry of CD spiroketal was determined by 2D-COSY and NOESY experiments. NOEs were observed between H19 and H21, H24 and H25, H22 and H24 as well as $H22_{eq}$ and $H27_{ax}$ which was consistent with the spiroketal junction with a chair conformation for the C19-C22 fragment and a boat like conformation for the C24-C27 segment. HRMS: *m/z* calcd for $C_{22}H_{34}O_7K$: for [M + K^+] 449.1942. Found: 449.1940.