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Enantio- and stereocontrolled formation of the bisspiroacetal core of spirolide B

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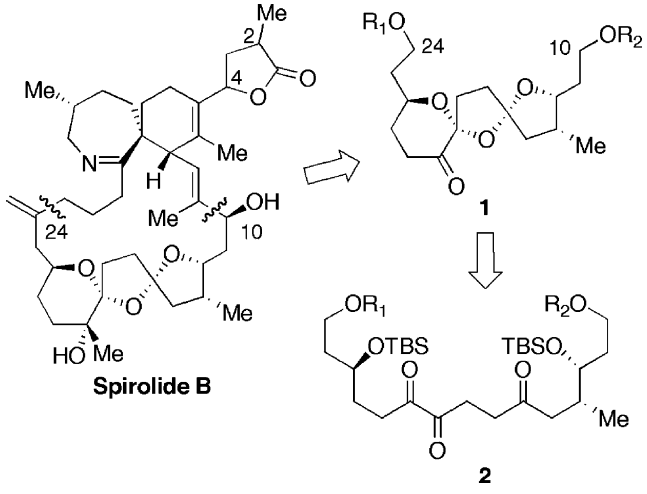
Abstract—The bisspiroacetal core of spirolide B, a marine natural toxin, was synthesized from triketone **10** via one-step bisspiroacetalization, methylation, and silylation accompanied by isomerization of the C-15 spirocenter. The equilibrium of two isomers under acidic conditions was also examined.

Recently, a new class of marine toxins containing an azaspirocyclic moiety such as spirolides,[1] pinnatoxins,[2] gymnodimines,[3] and pteriatoxins,[4] has been isolated from shellfish and dinoflagellate. The toxicological properties of these compounds would be attributed to the spirocyclic imine moiety,[5] which would be biogenetically constructed by an intramolecular Diels–Alder reaction via exo-addition.[2,3] In the course of our synthetic studies of the azaspirocyclic compounds, we have successfully constructed the azaspirocyclic moiety based on asymmetric Diels–Alder reaction of a *N*-carbamate α-methylene-lactam.[6] Spirolides were isolated from the digestive glands of mussels *Mytilus edulis* and scallops *Placopecten magellanicus*, and its origin was known to be the dinoflagellate *Alexandrium ostenfeldii*.[7,8] The structure was featured by the macrocyclic framework containing the azaspirocyclic moiety and the bisspiroacetal. The biological properties are characterized by the rapid onset of symptoms in the mouse bioassay, and the potential effects of spirolides are evaluated with respect to an acetylcholine receptor.[9] Although the relative stereochemistry of spirolides has been investigated on the basis of NMR and molecular modeling method, the stereochemistries at C-2 and C-4 have remained uncertain except for their *syn*-relationship.[7a] Since spirolides bear a very close structural resemblance to pinnatoxin, the absolute structure is predicted to be similar to that of pinnatoxin.[10] The unique structural feature and biological activity prompted us to synthesize spirolide B. Herein we disclosed the enantio- and stereocontrolled synthesis of the C-10/C-24 segment, bisspiroacetal core of spirolide B.

Our synthetic strategy of spirolide B involves one-step formation of bisspiroacetal **1** from acyclic triketone **2** (Scheme 1). We assumed that methylation of **1** would proceed with high diastereoselectivity due to the axial attack of nucleophile to the cyclic ketone.[11] The bisspiroacetal moiety appears in some polyether ionophores



Scheme 1. Spirolide B and its retrosynthetic analysis.

Keywords: Spirolide; Bisspiroacetal.
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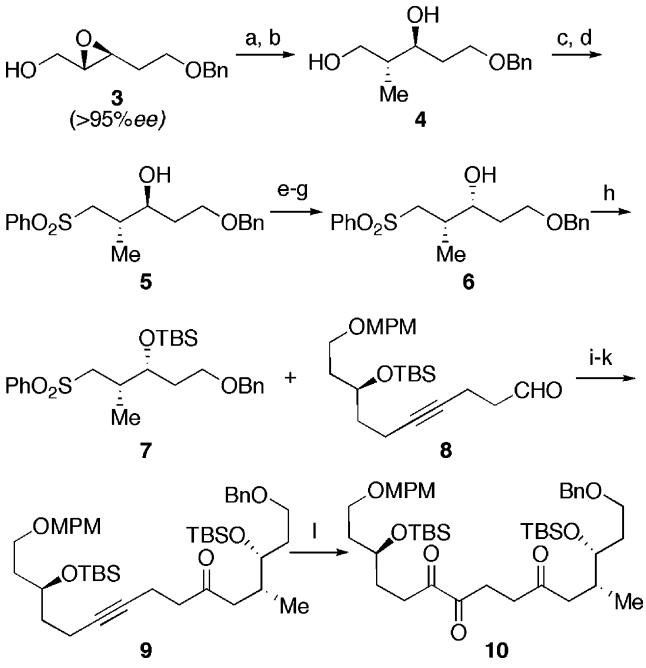
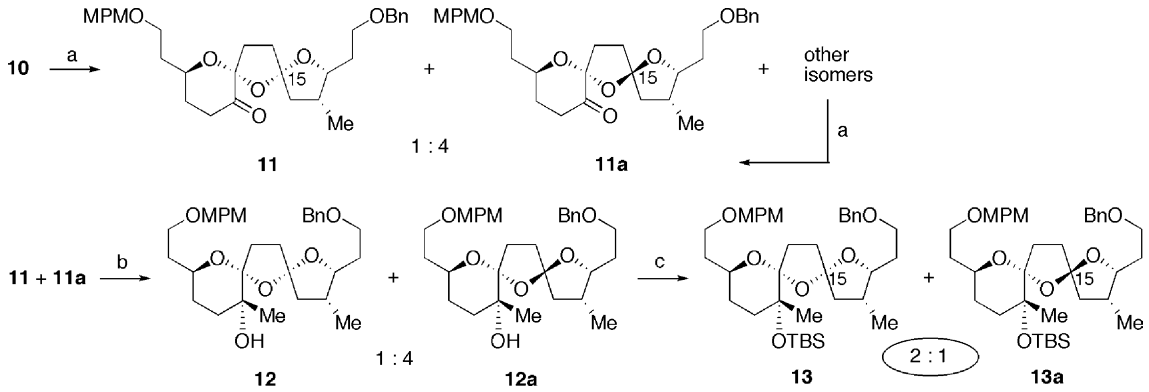
and marine natural products.[12] However, the stereoselective formation of 1,7,9-trioxadispiro[5.1.4.2]tetradecane moiety occurring in spirolides has not been established yet. Since bisspiroacetalization of **2** might produce eight possible isomers including four 6,5,5-tricyclic acetals and four 5,6,5-ones, it is very much challenging to construct the desired tricyclic bisspiroacetal core stereoselectively.[13]

Cleavage of epoxide **3**[14] with $Me_2CuCNLi_2$[15] afforded a mixture of desired 1,3-diol **4** and the corresponding 1,2-diol, which was easily removed by treatment with $NaIO_4$ (Scheme 2). Selective iodination of the primary alcohol in **4**, followed by sulfonylation, gave **5** in good yield. The secondary alcohol in **5** was inverted by a three-step sequence involving mesylation, displacement with acetoxy anion, and removal of the acetyl group to afford **6** in good yield. For this purpose, Mitsunobu inversion turned out to be unsuccessful. Silylation of **6** afforded sulfone **7** quantitatively. Another subunit **8** was prepared from 3-butyn-1-ol according to the procedure we have established earlier.[16] Coupling of both subunits **7** and **8**, followed by oxidation and desulfurization, furnished compound **9** in 86% overall yield (Scheme 2). Ruthenium tetraoxide oxidation of the alkyne in **9** led to triketone **10** in 74% yield.[17]



Scheme 2. Reagents and conditions: (a) $Me_2CuCNLi_2$, THF–Et_2O (2:1), −20 °C, 19 h (**4**:1,2-diol = 6.7:1); (b) $NaIO_4$, MeOH–pH 5.5 buffer (2:1), 23 °C, 30 min (68% for two steps); (c) I_2, PPh_3, imidazole, THF, 0 °C, 1.5 h (77%); (d) $NaSO_4Ph{\cdot}2H_2O$, DMF, 23 °C, 10 h (85%); (e) MsCl, Et_3N, DMAP, CH_2Cl_2, 23 °C, 2.5 h; (f) Bu_4NOAc, PhMe, reflux, 18 h; (g) K_2CO_3 MeOH, 23 °C, 10 h (90% for three steps); (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1.5 h (100%); (i) BuLi, THF, −78 °C, 30 min then **7**; (j) DMPI, $NaHCO_3$, CH_2Cl_2, 23 °C, 40 min; (k) SmI_2, MeOH, THF, 0 °C, 40 min (86% for three steps); (l) $RuO_2{\cdot}H_2O$, $NaIO_4$, CCl_4–MeCN–H_2O (1:1:1:5), 23 °C, 10 h (74%).

With the required triketone **10** in our hands, we then investigated its one-step bisspiroacetalization (Scheme 3). When **10** was exposed to HF–pyridine in MeCN at 23 °C for 8.5 h, the acetalization proceeded smoothly to generate a 1:4 mixture of the desired compound **11** and its C-15 epimer **11a** in 81% yield, along with a small amount of other spiro-isomers. These unidentified spiro-isomers were also converted to **11** and **11a** under the above-mentioned acetalization conditions. As a result, a 1:4 mixture of **11** and **11a** was obtained in 85% total yield. It is interesting to note that, in this particular reaction, the corresponding 5,6,5-membered bisspiroacetals were not produced at all. Although **11** and **11a** were separable by HPLC, this mixture was directly subjected to the subsequent methylation to afford a 1:4 mixture of **12** and **12a**.[18] It should be noted that the methylation proceeded exclusively by virtue of the axial attack to **11** as well as **11a**. Silylation of the carbinol in **12** and **12a** with TBSOTf and 2,6-lutidine resulted in the isomerization of the C-15 spirocenter to give a 2:1 mixture of **13** and **13a**.[19] Eventually desired acetal **13** was obtained as a major isomer in spite of the possibility of production of eight bisspiroacetals. It is rationalized that the protection of the methyl carbinol in **12a** would deprive the stabilization of the intramolecular hydrogen bonding between the *tert*-hydroxyl group and the acetal oxygen. X-ray crystallographic analysis of di-*p*-bromobenzoate **14** derived from **13** confirmed its stereochemistry as shown in Figure 1. The stereochemistry of **13a**



Scheme 3. Reagents and conditions: (a) HF·py, MeCN, 23 °C, 8.5 h, 85% (one recycle); (b) MeLi, THF, −78 °C, 30 min, 99%; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C → 20 °C, 1 h, **13**: 53%, **13a**: 29%.

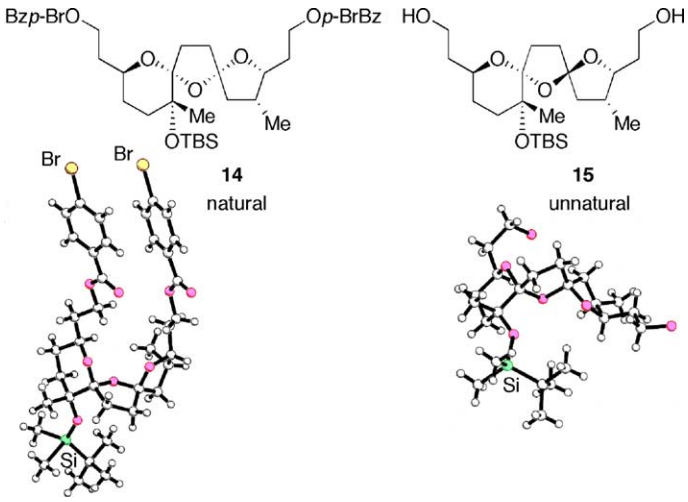
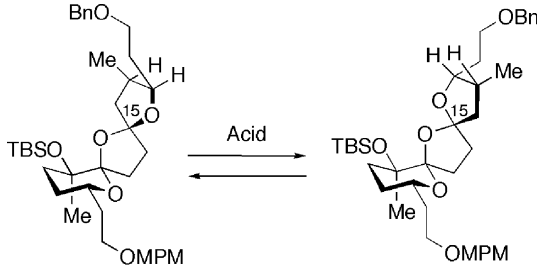


Figure 1. X-ray crystallography of acetal compounds.

was deduced by X-ray crystallographic analysis of diol **15**.[20]

We next examined acid-catalyzed isomerization of acetals (Table 1). When **13a** was exposed to a catalytic amount of CSA, a 1:2 mixture of **13** and **13a** was obtained (run 1). Treatment of **13** with CSA also afforded the same 1:2 mixture (run 7), suggesting that these reactions were thermodynamically controlled. The equilibrium ratio of **13** and **13a** could be evaluated to be ca. 1:2 in the presence of either Brønsted acid or Lewis acid capable of coordinating to the acetal oxygens (runs 2–6). Molecular mechanics calculation was performed on the possible spiroacetal isomers, using AMBER force field. The calculations show that unnatural isomers at C-15 **11a**, **12a**, and **13a** were preferred energetically to other isomers including natural isomers (**11**, **12**, **13**). For instance, the potential energy of **12** was 3.2 kcal/mol higher than **12a**, and silyl ether **13** has 1.8 kcal/mol higher energy than **13a**. Notably, the differential potential energy between **13** and **13a** is lower than that between **12** and **12a**. In the event, the hydrogen bonding of the C-15 hydroxyl group with the spiroacetal oxygen play an important role for stabilization of **12a**. On the other hand, treatment of **13a** either with TBSOTf and 2,6-lutidine (run 8) or with TfOH and 2,6-lutidine (run 9) caused no isomerization. These results suggest that the isomerization of the C-15 acetal would proceed before silylation of the tertiary alcohol. One explanation for the results is that silylation of **12** would take place faster than that of **12a**, so that **13** would be preferentially produced through equilibrated isomerization of **12**.

Table 1. Isomerization of spiroacetals



13 **13a**

Run	Substrate	Condition	**13**:**13a**
1	**13a**	CSA (0.1 equiv), MeCN, 23 °C, 15 h	36:64
2	**13a**	$ZnBr_2$ (0.2 equiv), CH_2Cl_2, 23 °C, 4 d	33:67
3	**13a**	Et_2AlCl (1.0 equiv), CH_2Cl_2, −60 °C, 19 h	25:75
4	**13a**	$SnCl_2$ (0.1 equiv), CH_2Cl_2, 23 °C, 5.5 h	33:67
5	**13a**	$CuCl_2$ (excess), CH_2Cl_2, 23 °C, 5.5 h	33:67
6	**13a**	HF·py (excess), MeCN, 23 °C, 2.5 h	40:60
7	**13**	CSA (0.1 equiv), MeCN, 23 °C, 1.5 h	36:64
8	**13a**	TBSOTf, 2,6-lutidine, CH_2Cl_2, 23 °C, 3 d	~0:100
9	**13a**	TfOH, 2,6-lutidine, CH_2Cl_2, 23 °C, 1 d	~0:100

All reactions proceeded quantitatively.

In conclusion, we have established the formation of bisspiroacetal core of spirolide B involving one-step bisspiroacetalization, and further studies toward the synthesis of spirolide B are in progress in our laboratory.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 245421 and 245422. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

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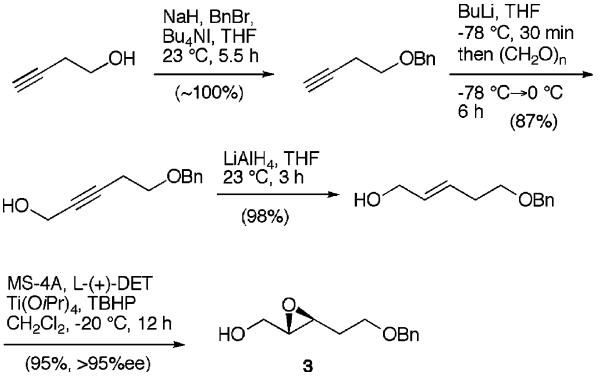
14. The chiral epoxide **3** was readily prepared from 3-butyn-1-ol for four steps.



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18. The stereochemistries of **11**, **11a**, **12**, **12a** were determined by ^{1}H NMR analysis as well as the chemical conversion. At first, we converted **12** and **12a** to the corresponding TES ethers, using TESCl and imidazole in DMF. The TES ethers were reconvertible to parent **12** and **12a** by treatment with Bu_4NF, respectively. The ^{1}H NMR spectra of the TES ethers of **12** was quite similar to that of TBS ethers **13**, and the TES ether of **12a** was corresponding to **13a**. These results suggested that the stereochemistry at C-15 of **11**, **12**, and the TES ether of **12** should be corresponding to **13**, and **11a**, **12a**, and the TES ether of **12a** should have the same configuration to **13a**.
19. For compound **13**: a colorless oil; $[\alpha]_D^{27}$ +19.8 (*c* 0.64, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.32–7.19 (5H, m), 7.21 (2H, d, J = 8.5 Hz), 6.85 (2H, d, J = 8.5 Hz), 4.55 (1H, d, J = 11.5 Hz), 4.42 (1H, d, J = 11.5 Hz), 4.36 (2H, s), 4.09–4.05 (1H, m), 4.01–3.95 (1H, m), 3.75 (3H, s), 3.62–3.52 (3H, m), 3.48–3.44 (1H, m), 2.28 (1H, quint, J = 6.7 Hz), 2.21–2.06 (4H, m), 1.99 (1H, dd, J = 6.0, 13.0 Hz), 1.98–1.94 (1H, m), 1.88–1.77 (1H, m), 1.75–1.67 (4H, m), 1.65–1.53 (4H, m), 1.41 (1H, ddd, J = 4.0, 11.3, 14.7 Hz), 1.28 (3H, s), 1.06 (3H, d, J = 7.0 Hz), 0.88 (9H, s), 0.09 (6H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 160.75, 139.95, 131.85, 130.51, 128.79, 128.70, 128.58, 117.66, 114.72, 111.49, 80.77, 74.48, 73.96, 73.61, 69.44, 68.92, 68.50, 55.68, 46.34, 37.57, 36.93, 36.88, 26.45, 24.83, 18.99, 14.74, −1.52, −1.71; IR (neat) ν_{max} (cm^{-1}) 2943, 2859, 1612, 1510, 1458, 1369, 1248, 1173, 1099, 1943, 931, 829; EI-MS-LR *m*/*z* (Int. %) 654 (M^+, 4.1), 597 (M^+-tBu, 10), 121 (100); EI-MS-HR, found 654.3945, calcd for $C_{38}H_{58}O_7Si$ (M^+) 654.3952. For compound **13a**: a colorless oil; $[\alpha]_D^{27}$ +48.4 (*c* 0.63, MeOH); ^{1}H NMR (125 MHz, C_6D_6) δ 7.38–7.09 (5H, m), 7.25 (2H, d, J = 8.5 Hz), 6.81 (2H, d, J = 8.5 Hz), 4.45 (1H, d, J = 12.0 Hz), 4.36 (1H, d, J = 11.5 Hz), 4.33 (1H, d, J = 11.5 Hz), 4.30 (1H, dd, J = 7.5, 14.0 Hz), 4.10 (1H, ddd, J = 4.0, 7.6, 15.6 Hz), 3.68–3.55 (3H, m), 3.49–3.45 (1H, m), 3.31 (3H, s), 2.49–2.39 (2H, m), 2.28 (1H, dd, J = 7.0, 12.5 Hz), 2.26–2.19 (2H, m), 1.88 (1H, dd, J = 8.0, 12.0 Hz), 1.77–1.65 (5H, m), 1.54–1.48 (2H, m), 1.49 (1H, dd, J = 9.5, 13.0 Hz), 1.38–1.20 (2H, m), 1.32 (3H, s), 1.12 (9H, s), 0.74 (3H, d, J = 7.0 Hz), 0.26 (3H, s), 0.19 (3H, s); ^{13}C NMR (125 MHz, C_6D_6) δ 159.67, 139.56, 131.35, 129.26, 128.46, 127.50, 114.89, 114.02, 110.09, 78.22, 73.18, 73.03, 72.85, 68.61, 67.02, 66.19, 54.74, 46.08, 36.50, 35.20, 34.88, 34.64, 32.30, 31.77, 31.00, 30.81, 30.16, 26.33, 25.11, 23.08, 18.58, 14.54, 14.32, −1.66, −1.83; IR (neat) ν_{max} (cm^{-1}) 2943, 2856, 1610, 1516, 1458, 1362, 1248, 1155, 1101, 1038, 966, 827; EI-MS-LR *m*/*z* (Int. %) 654 (M^+), 597 (M^+-tBu, 6.7), 121 (100); EI-MS-HR, found 654.3930, calcd for $C_{38}H_{58}O_7Si$ $(M)^+$ 654.3952.
20. Crystal data for **14**: $C_{37}H_{50}Br_2O_8Si$, M 810.69, monoclinic, $P2_1$, a = 8.052 (1), b = 11.788 (2), c = 20.548 (3) Å, β = 97.625 (1)°, U = 1933.0 (5) Å^3, Dc (Z = 2) = 1.393 g cm^{-3}, μ = 21.82 cm^{-1}, T = 153 K. The final R value is 0.043 for 4672 independent reflections with $I > 3\sigma I$ and 414 parameters. For **15**: $C_{23}H_{44}O_6Si$, M 444.68, orthorhombic, $P2_12_12_1$, a = 7.354 (2), b = 18.909 (5), c = 37.967 (10) Å, U = 5279.6 (2) Å^3, Dc (Z = 8, two independent molecules) = 1.119 g cm^{-3}, μ = 1.21 cm^{-1}, T = 293 K. The final R value is 0.073 for 2967 independent reflections with $I > 1.5\sigma I$ and 542 parameters.