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Synthesis of the BCD ring system of azaspiracid: construction of the trispiro ring structure by the thioether approach

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Abstract—The synthesis of the BCD ring system of azaspiracid **1** has been attained. Construction of the stereochemistry of the C_{13} position was successfully controlled by connection between the B ring and the C ring with a sulfur atom.
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Azaspiracid **1** and its congeners **2**–**5**, a family of marine polyethers isolated from the blue mussel *Mytilus edulis* in Killary Harbor, Ireland, are known as novel shellfish poisons (Fig. 1).[1] Azaspiracids share a unique structure consisting of an azaspiro ring, a 2,9-dioxabicyclo[3.3.1]nonane ring, and trispiro ring units. However, the relative stereochemistry of the molecules and details of their biological mode of action are still obscure. Accordingly, azaspiracids are attractive synthetic targets for organic chemists. Although several groups are working toward their total synthesis, no accomplishment has been reported.[2,3] The challenging framework of azaspiracids as well as their biological activity therefore prompted us to initiate a synthetic study to determine the complete structure and to understand the structure–activity relationship.

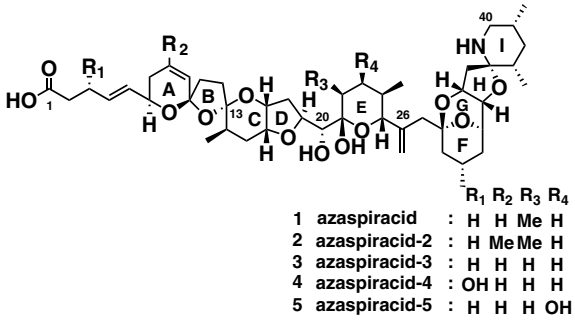

Figure 1. Azaspiracids.

Although synthesis of the FGHI ring part of **1** was reported by several groups,[2i,j,l] only the Nicolaou group has constructed the ABCD ring system using an intramolecular hydrogen bonding.[2k] It was described in several papers that construction of the correct structure of the ABCD ring system was unsuccessful under usual acetalization conditions.[2b,g,k] Therefore, we planned a new access to the stereochemistry of the spirocenter at the C_{13} position in the BC ring, the stereochemical control of which might be impeded by an anomeric effect and steric hindrance. In the strategy, the spirocenter would be controlled by connecting the B ring to the C ring with a sulfur atom. After cyclization, a mild removal of the sulfur atom would afford the desired trispiro-ring system of azaspiracid **1**. We describe herein the construction of the BCD ring system, having the desired stereochemistry of the spirocenter at C_{13} position (**6**), as a model of the natural molecule.

In our synthetic strategy (Scheme 1), spiroacetal **6** would be reductively produced from acetal **7** with simultaneous introduction of a methyl group at the C_{14} position. Compound **7** would be obtained by stepwise manipulation of tetrahydrothiofuran **8**, which would be produced from alcohol **11** through **9** and **10**. Compound **11** would be constructed by cyclization of **12**, easily prepared from L-malic acid.

The synthesis commenced with selective protection of **13**[4] (Scheme 2). Thus, hydroxyl groups of **13** were

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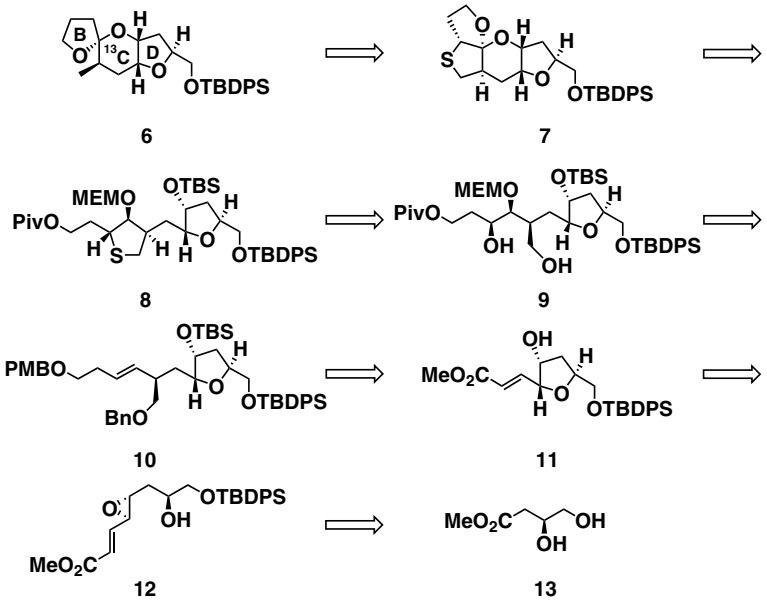
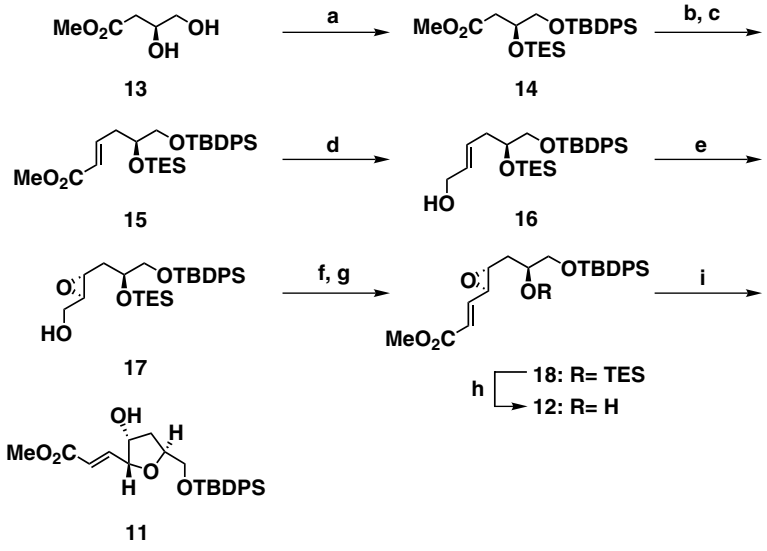


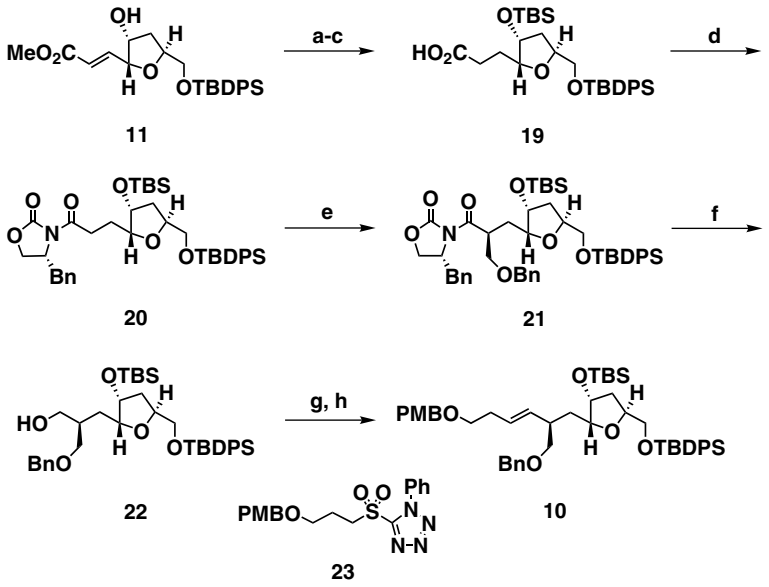
Scheme 1. Our strategy for construction of the BCD ring system.



Scheme 2. Reagents and conditions: (a) TBDPSCl, Imid., DMF, then TESCl, 95%; (b) DIBAL, toluene, −78 °C; (c) $Ph_3P{=}CHCO_2Me$, benzene, 80% in two steps; (d) DIBAL, CH_2Cl_2, −78 °C, 87%; (e) $Ti(O^iPr)_4$, D-(−)-DET, TBHP, CH_2Cl_2, 81%; (f) SO_3·Pyr, DMSO, Et_3N, CH_2Cl_2; (g) $Ph_3P{=}CHCO_2Me$, benzene, 79% in two steps; (h) CSA, MeOH, 0 °C, 82%; (i) $Pd_2(dba)_3{\cdot}CHCl_3$, Ph_3P, CH_2Cl_2, rt, 90%.

protected stepwise to afford silylether **14** in 95% yield. Reduction of **14** with DIBAL, followed by the Wittig reaction, gave α,β-unsaturated ester **15** in good yield, which on DIBAL reduction gave allyl alcohol **16**. Asymmetric epoxidation of **16** by the Sharpless protocol generated epoxy alcohol **17** in 90% yield. Oxidation of **17** with SO_3·Pyr–DMSO, followed by Wittig reaction yielded ester **18**. The TES group of **18** was selectively deprotected under acidic conditions (CSA/MeOH) to afford alcohol **12** in 81% yield. To construct highly substituted tetrahydrofuran **11** from **12**, Hirama's method was used at this stage.[5] Thus, treatment of **12** with $Pd_2(dba)_3$ and Ph_3P in CH_2Cl_2 at room temperature provided tetrahydrofuran **11** as a single isomer in excellent yield.

Protection of **11** as a TBS ether was followed by hydrogenation and saponification to give carboxylic acid **19** (Scheme 3). Condensation of **19** with (*R*)-4-benzyl-2-oxazolidinone[6] produced oxazolidinone **20**, which on introduction of a benzyloxymethyl group gave benzyl ether **21**, as a single diastereomer. Reductive removal of the oxazolidinone with $LiBH_4$ afforded alcohol **22**. After TPAP oxidation of **22**, the result-



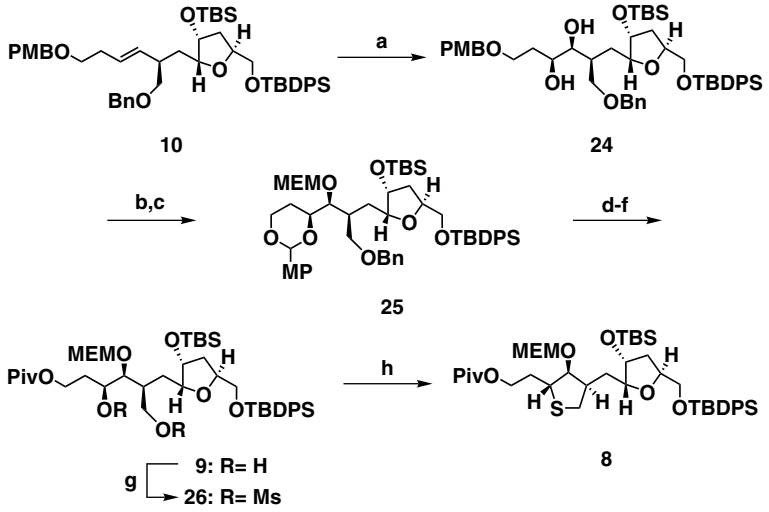
Scheme 3. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 86%; (b) H_2, Pd–C, EtOH; (c) LiOH, MeOH–THF–H_2O, 98% in two steps; (d) PivCl, Et_3N, THF, 0 °C, then (*R*)-4-benzyl-2-oxazolidinone, LiCl, 0 °C to rt, 88%; (e) LHMDS, THF, −78 °C, then BOMCl, LiI, −78 to −30 °C, 78%; (f) $LiBH_4$, THF–EtOH–H_2O, 91%; (g) TPAP, NMO, MS4Å, CH_2Cl_2; (h) **23**, LHMDS, THF, −78 °C, 90% in two steps.

ing aldehyde was subjected to the Julia olefination[7] with sulfone **23**,[8] to afford olefin **10** in 90% yield (two steps).

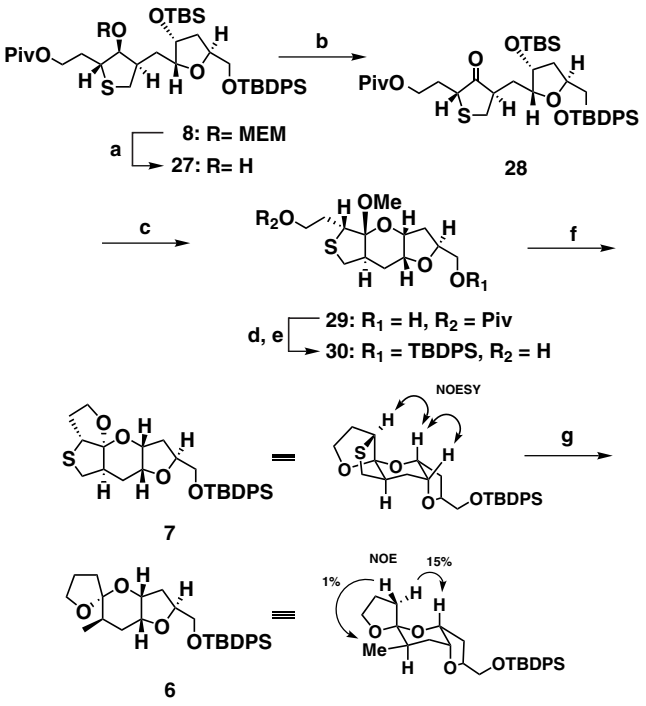
Introduction of a sulfur atom to control the spirocenter at the C_{13} position is shown in Scheme 4. Thus, dihydroxylation of **10** under the Sharpless conditions[9] gave diol **24**. DDQ oxidation of **24**, followed by protection with an MEM group, gave **25**. After removal of the anisilidene group of **25** under acidic conditions, the resulting alcohol was protected as a pivalate ester, followed by hydrogenolysis to afford diol **9**. Dimesylation of **9** gave **26** in 95% yield. Finally, treatment of **26** with Na_2S at 100 °C afforded tetrahydrothiofuran **8** in 70% yield.

In the next stage, removal of an MEM ether from **8** gave alcohol **27**,[10] which was oxidized with SO_3·Pyr–DMSO to give ketone **28** in 89% yield (Scheme 5). Reaction of **28** with CSA in MeOH afforded methylacetal **29** (86%), as a single isomer, which was reprotected with a TBDPS group. Reductive removal of the ester gave alcohol **30** (79% in two steps). Treatment of **30** with $Yb(OTf)_3$[11] in CH_3CN gave acetal **7** in 98% yield. Desulfurization of **7** with Raney Ni W-4 in EtOH afforded the desired spiroacetal **6**[12] in 95% yield. The acetal structure of **6** was determined by the NOE experiments.

In conclusion, we have accomplished the synthesis of the BCD ring system of azaspiracid **1**, based on the structural control of the spirocenter at the C_{13} position by



Scheme 4. Reagents and conditions: (a) AD-mix-α, $MeSO_2NH_2$, ^{t}BuOH–H_2O, 68%; (b) DDQ, MS4Å, CH_2Cl_2, 61%; (c) MEMCl, $^i Pr_2NEt$, CH_2Cl_2, 88%; (d) 80% AcOH aq, rt, 92%; (e) PivCl, Pyr, 0 °C to rt, 88%; (f) H_2, $Pd(OH)_2$–C, EtOAc, 77%; (g) MsCl, Et_3N, CH_2Cl_2, 95%; (h) Na_2S, DMF, 100 °C, 70%.



Scheme 5. Reagents and conditions: (a) $ZnBr_2$, CH_2Cl_2, 83%; (b) SO_3·Pyr, DMSO, $^iPr_2NEt$, CH_2Cl_2, 89%; (c) CSA, MeOH, 86%; (d) TBDPSCl, Et_3N, DMAP, CH_2Cl_2; (e) DIBAL, CH_2Cl_2, −78 °C, 79% in two steps; (f) $Yb(OTf)_3$, CH_3CN, rt, 98%; (g) Raney Ni W-4, EtOH, reflux, 95%.

connection between the B ring and the C ring with a sulfur atom. Further synthetic studies toward azaspiracid **1** are in progress.

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12. **7**: colorless oil; $[\alpha]_D^{23}$ −16.0 (*c* 0.37, $CHCl_3$); IR (film) *v* 2929, 1427, 1113, 1074, 1020 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.85–7.79 (complex, 4H), 7.24–7.21 (complex, 6H), 4.56 (m, 1H), 4.02 (ddd, 1H, $J = 8.3, 7.8, 5.4$ Hz), 3.76 (dd, 1H, $J = 10.8, 3.9$ Hz), 3.75 (br s, 1H), 3.70 (br d, 1H, $J = 2.4$ Hz), 3.67 (m, 1H), 3.55 (dd, 1H, $J = 10.8, 4.4$ Hz), 2.54 (ddd, 1H, 13, 6.8, 4 Hz), 2.09–2.03 (complex, 2H), 1.91 (ddd, 1H, $J = 12.7, 9.3, 4.4$ Hz), 1.75 (m, 1H), 1.61 (ddd, 1H, $J = 12.7, 7.9, 3.4$ Hz), 1.45 (m, 1H), 1.31 (m, 1H), 1.17 (s, 1H), 1.13 (m, 1H), 0.31 (d, 1H, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 136.1, 134.2, 129.9, 128.5, 110.5, 79.2, 76.3, 76.1, 67.8, 66.8, 36.5, 34.5, 31.0, 27.2, 25.4, 24.5, 19.7, 15.9; HREIMS calcd for $C_{28}H_{38}O_4Si$ (M^+): 466.2536, found: *m*/*z* 466.2530.