Natural Product Synthesis

Total Synthesis of the Proposed Azaspiracid-1 Structure, Part 1: Construction of the Enantiomerically Pure C1–C20, C21–C27, and C28–C40 Fragments**

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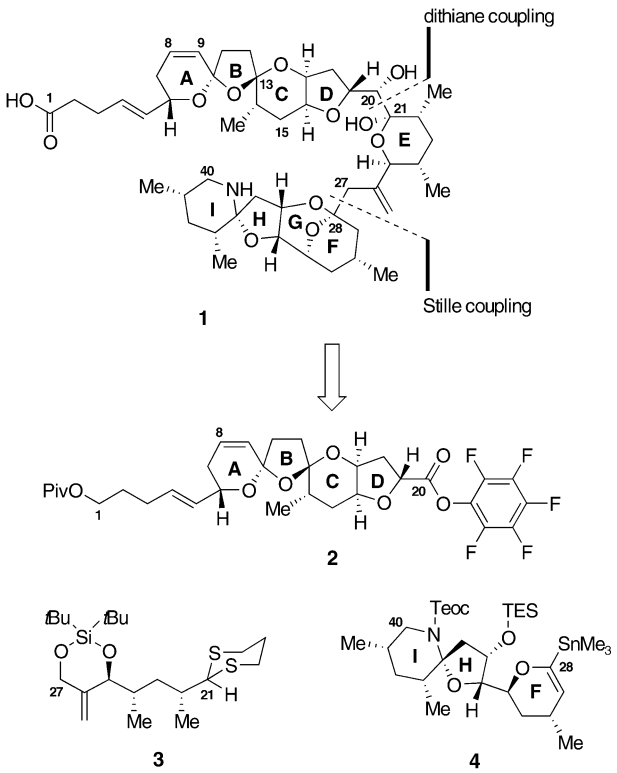
An incident of human poisoning in the Netherlands in 1995 with diarrhetic shell poisoning (DSP)-like symptoms was traced to the consumption of mussels (*Mytilus edulis*), which had been collected in Killary Harbour, Ireland.[1] Following an intense investigation, Yasumoto and co-workers reported the isolation of azaspiracid-1, the major biotoxin credited with these severe symptoms.[2] Both the structure of the substance and its pathologic effects were sufficiently different from those associated with the previously known DSP, so that a new toxic syndrome was declared and named azaspiracid poisoning (AZP). In addition to its immediate and apparent harmful effects, azaspiracid-1 has been shown to also cause lung, liver, spleen, and lymphocyte damage, as well as lung-tumor formation in mice.[3] It was on the basis of sophisticated analytical techniques that the Yasumoto group proposed the structure of azaspiracid-1 as **1**. This unprecedented structure is characterized by a trioxadispiroketal system fused to a tetrahydrofuran moiety (ABCD ring system), an azaspiro ring fused to a 2,9-dioxabicyclo[3.3.1]nonane system (FGHI ring system), a six-membered hemiketal bridge (E ring system), and a γ,δ-unsaturated terminal carboxylic acid moiety (Scheme 1). In total, there are nine rings and 20 stereogenic centers within this synthetically challenging and novel molecular architecture. Despite the heroic spectroscopic attempts to elucidate fully the structure of azaspiracid-1,[2] its daunting molecular framework yielded neither its relative stereochemistry between domains ABCDE (C1–C27) and FGHI (C28–C40) nor its absolute stereochemistry. In view of the health and environmental hazards posed by this molecule, and to clarify its molecular structure, we initiated a program directed towards its total synthesis.[4] Herein and in the following Communication[5] we report the total synthesis of the proposed structure **1** for azaspiracid-1 and its FGHI diastereoisomer, which led to the conclusion that this structure is, in fact, in error.



Scheme 1. Retrosynthetic analysis of the proposed structure **1** of azaspiracid-1, leading to key fragments **2** (C1–C20), **3** (C21–C27), and **4** (C28–C40). Relative stereochemistry between ABCDE (C1–C27) and FGHI (C28–C40) domains and absolute stereochemistry of **1** unknown. TES = triethylsilyl, Teoc = 2-(trimethylsilyl)ethoxycarbonyl.

As shown in Scheme 1, our proposed synthetic strategy was based on a twofold disconnection of the polycyclic array of azaspiracid-1 at the C20–C21 and C27–C28 junctures to provide the key synthetic precursors **2** (C1–C20 fragment), **3** (C21–C27 fragment), and **4** (C28–C40 fragment). The positions of the strategic bond scissions were carefully chosen to ensure optimum convergence and to allow the necessary flexibility to address the relative stereochemical issue between the ABCDE and FGHI domains of the molecule. The C20–C21 bond was envisaged to arise through the application of lithiated dithiane coupling technology,[6] whereas the C27–C28 bridging linkage was reserved for a palladium-mediated C(sp^2)–C(sp^3) Stille coupling.[7] We previously reported the preparation of the ABCD[8] and FGHI[9] ring systems with the desired skeletal and stereochemical arrangements, featuring the use of an auxiliary stereocontrolling group at C9 to induce the desired 13*R* stereochemistry

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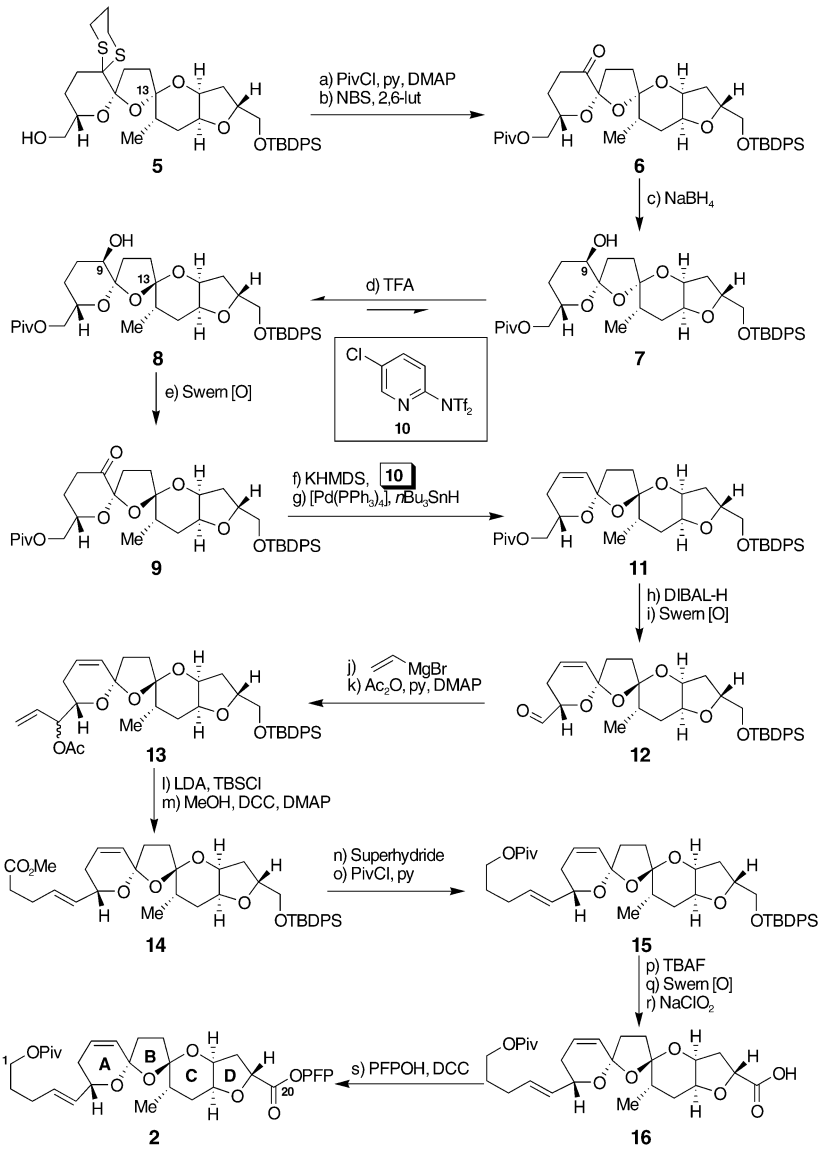
and the employment of a $Hg(OAc)_2$-mediated ring closure to forge the G ring of the FGHI ring system. Herein we describe the adaptation and refinement of our original sequence, and its application to the construction of appropriately functionalized fragments **2**, **3**, and **4** needed for the key carbon–carbon bond-forming reactions outlined in this retrosynthetic blueprint. To determine the relative and absolute stereochemical assignment of the nominal azaspiracid-1 (**1**) unambiguously, all three fragments **2**, **3**, and **4** were prepared in both enantiomeric forms. For conciseness, the following discussion will be limited to only one series of enantiomers (arbitrarily chosen). The synthesis of **1** and its FGHI diastereoisomer is sufficient to reveal both the relative and absolute stereochemistry of the nominal azaspiracid-1 (**1**), even though one more attempt may be needed to synthesize it.

The construction of key intermediate **2** (C1–C20 fragment) began with the protection of the previously reported alcohol **5**[8] as a pivaloate ester (with the wrong 13*S* configuration, see Scheme 2), followed by oxidative removal (NBS, 2,6-lutidine; for abbreviations of reagents and protecting groups, see legends in schemes) of the dithiane group to provide ketone **6** (75% yield over two steps). $NaBH_4$-mediated reduction of **6** afforded alcohol **7** as the major isomer (> 9:1 ratio), which was isolated in 87% yield, setting the stage for the proposed C9-OH-induced equilibration to establish the desired 13*R* spirocyclic configuration. As anticipated, upon exposure of alcohol **7** to TFA in CH_2Cl_2 at ambient temperature, an equilibrium mixture consisting of the desired tetracycle **8** and starting alcohol **7** was reached (ca. 2:1 ratio), from which **8** was isolated in pure form by flash column chromatography (66% yield). Recycling of **7** increased the supply of **8**. The auxiliary hydroxy group at C9 was then removed by a three-step sequence involving Swern oxidation, enol triflate formation[10] (KHMDS, reagent **10**, 92% yield), and $[Pd(PPh_3)_4]/nBu_3SnH$-mediated reductive elimination[11] (which generated the desired C8–C9 unsaturation, 95% yield) to afford **11**.



Scheme 2. Construction of **2**: a) PivCl (3.0 equiv), pyridine (10.0 equiv), DMAP (catalytic), CH_2Cl_2, 0→25 °C, 12 h; b) NBS (8.0 equiv), 2,6-lutidine (16 equiv), $MeCN/H_2O$ (4:1), 25 °C, 1 h, 75% over two steps; c) $NaBH_4$ (1.1 equiv), MeOH, −78→−60 °C, 3 h, 87%; d) TFA (2.0 equiv), CH_2Cl_2, 0→25 °C, 2 h, 66%; e) $(COCl)_2$ (2.0 equiv), DMSO (4.0 equiv), CH_2Cl_2, −60 °C, 2 h; then Et_3N (8.0 equiv), −60→−30 °C, 1 h, 94%; f) **10** (2.5 equiv), KHMDS (0.5 M in toluene, 2.5 equiv), THF, −78 °C, 1 h, 92%; g) LiCl (3.0 equiv), $[Pd(PPh_3)_4]$ (0.2 equiv), nBu_3SnH (3.0 equiv), THF, 25 °C, 45 min, 95%; h) DIBAL-H (1.0 M in toluene, 2.5 equiv), toluene, −78 °C, 20 min, 92%; i) $(COCl)_2$ (5.0 equiv), DMSO (11 equiv), CH_2Cl_2, −78 °C, 1 h, −60 °C, 1 h; then Et_3N (22 equiv), −78→−30 °C, 1 h, 92%; j) vinylmagnesium bromide (1.0 M in THF, 1.6 equiv), Et_2O, 0 °C, 30 min, 78%; k) Ac_2O (5.0 equiv), pyridine (10.0 equiv), DMAP (catalytic), CH_2Cl_2, 0 °C, 1 h, 94%; l) LDA (1.5 equiv), TBSCl (1.5 equiv), HMPA (1.5 equiv), THF, −78→25 °C, 72 h, 82%; m) MeOH (10.0 equiv), DCC (1.2 equiv), DMAP (0.1 equiv), CH_2Cl_2, 0→25 °C, 2 h, 86%; n) Superhydride (1.0 M in THF, 5.0 equiv), THF, −78→0 °C, 30 min, 96%; o) PivCl (3.0 equiv), pyridine (10.0 equiv), DMAP (1.0 equiv), CH_2Cl_2, 0→25 °C, 12 h, 95%; p) TBAF (1.0 M in THF, 2.0 equiv), THF, 0→25 °C, 3 h, 93%; p) $(COCl)_2$ (5.0 equiv), DMSO (11 equiv), CH_2Cl_2, −78 °C, 1 h, −60 °C, 1 h; then Et_3N (22 equiv), −78→−30 °C, 1 h, 89%; r) $NaClO_2$ (4.0 equiv), NaH_2PO_4 (4.0 equiv), 2-methyl-but-2-ene (5.0 equiv), *t*BuOH/H_2O (5:1), 25 °C, 2 h, 95%; s) PFPOH, (1.2 equiv), DCC (1.5 equiv), CH_2Cl_2, 25 °C, 2 h, 82%. TBDPS = *tert*-butyldiphenylsilyl, Piv = pivaloyl = trimethylacetyl, py = pyridine, DMAP = *N*,*N*-dimethyl-4-aminopyridine, NBS = *N*-bromosuccinimide, 2,6-lut = 2,6-lutidine, TFA = trifluoroacetic acid, KHMDS = potassium bis(trimethylsilyl)amide, DIBAL-H = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide, LDA = lithium diisopropylamide, TBS = *tert*-butyldimethylsilyl, HMPA = hexamethylphosphoramide, DCC = 1,3-dicyclohexylcarbodiimide, Superhydride = lithium triethylborohydride, TBAF = tetra-*n*-butylammonium fluoride, PFPOH = pentafluorophenol.

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With tetracycle **11** in hand, we then turned our attention to the installation of the unsaturated C1–C5 carboxylic acid side chain. To this end, an Ireland modification[12] of the Claisen rearrangement was used to ensure the introduction of the desired *trans* double bond and the required four-carbon chain. Thus, the pivaloate group was cleaved from **11** by exposure to DIBAL-H (92% yield), and the resulting alcohol was treated under Swern conditions to afford aldehyde **12** in 92% yield. The latter compound, **12**, was immediately treated with vinylmagnesium bromide, and the resulting allylic alcohol (78% yield) was converted into its acetate **13** (mixture of diastereoisomers, 92% yield). Acetate **13** was exposed to LDA at −78 °C in the presence of TBSCl and HMPA, and the mixture was then warmed to room temperature to provide the corresponding γ,δ-unsaturated acid, which was subsequently esterified (MeOH, DCC, DMAP), furnishing the targeted methyl ester **14** in 71% overall yield for the two steps.

With the C1–C5 side chain in place, attention was then focused on the further elaboration of the C20 terminus in preparation for the anticipated C20–C21 bond-forming reaction. The first task was the reduction of methyl ester **14** (Superhydride, 96% yield) and protection of the resulting primary alcohol as a pivaloate ester (95% yield), a precautionary maneuver undertaken to enable the pending dithiane coupling step. The obtained intermediate **15** was then transformed into carboxylic acid **16** (Table 1) by desilylation (TBAF, 93% yield), followed by a two-step oxidation involving Swern conditions (89% yield) and $NaClO_2$ (95% yield). Finally, coupling of carboxylic acid **16** with pentafluorophenol in the presence of DCC led to pentafluoroester **2** in 82% yield, a coupling partner which proved, as we shall see, superior to its aldehyde progenitor.

The construction of the dithiane C21–C27 fragment **3** commenced from the previously synthesized lactone **17**[13] (Scheme 3). Reduction of **17** with DIBAL-H afforded the corresponding lactol in equilibrium with its open-chain hydroxy–aldehyde, which was trapped with 1,3-propanedithiol in the presence of $BF_3{\cdot}OEt_2$ to furnish hydroxy dithiane **18** in 99% overall yield. Swern oxidation then led to aldehyde **19** (94% yield), which was coupled with vinyl iodide **21** (obtained from propargyl alcohol in two steps as shown in Scheme 3) under the Nozaki–Hiyama–Kishi conditions[14] ($CrCl_2$, $NiCl_2$), leading to an epimeric mixture of allylic alcohols **22** in 95% yield. The desired stereochemistry at C25 was then set by an oxidation (IBX, 90% yield)–reduction (Red-Al, 80% yield) protocol, yielding the expected alcohol **23** (stereochemistry confirmed by NMR spectroscopic analysis), which was then desilylated by the action of TBAF to give diol **24** (99% yield). Protection of the 1,3-diol system within **24** as its silylene acetal (tBu$_2$Si(OTf)$_2$, 2,6-lut, 75% yield) then completed the synthesis of fragment **3** (Table 1).

The remaining coupling partner, C28–C40 fragment **4**, was constructed as outlined in Scheme 4. Thus, following our previous studies,[9] azide **25** was reduced (10% Pd/C, H_2) and the resulting primary amine was protected as its 2-(trimethylsilyl)ethoxy carbamate (Teoc) with reagent **26**[15] in the presence of Et_3N to afford derivative **27** (80% overall yield), setting the stage for the required spiroaminal formation. This crucial cyclization was found to proceed in good and

Table 1: Selected data for **3**, **16**, **30**, **33**, and **39**.

3: R_f = 0.25 (silica gel, Et_2O/hexanes 5:95); $[\alpha]_D$ = +76.1 ($CHCl_3$, c = 1.4); IR (film): $\tilde{\nu}_{max}$ = 2930, 2856, 1632, 1470, 1383, 1085, 1006, 826, 775, 650 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.10 (s, 1H), 4.91 (s, 1H), 4.53 (d, J = 11.4 Hz, 1H), 4.17 (d, J = 15.0 Hz, 2H), 4.16 (d, J = 10.6 Hz, 1H), 2.97–2.91 (m, 1H), 2.86–2.80 (m, 3H), 2.18 (ddd, J = 12.2, 8.4, 4.0 Hz, 1H), 2.12–2.05 (m, 2H), 1.86–1.77 (m, 2H), 1.13 (d, J = 7.0 Hz, 3H), 1.04 (s, 9H), 0.98 (s, 9H), 0.84 ppm (d, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 146.0, 114.0, 81.5, 67.4, 54.5, 37.0, 36.5, 36.3, 31.4, 30.6, 27.3, 26.9, 36.4, 21.4, 20.9, 18.2, 16.3 ppm; MS (ESI): calcd for $C_{21}H_{40}NO_2S_2SiCl^-$ [M+Cl$^-$]: 451, found: 451

16: R_f = 0.24 (silica gel, CH_2Cl_2/MeOH 9:1); $[\alpha]_D$ = −31.5 ($CHCl_3$, c = 2.0); IR (film): $\tilde{\nu}_{max}$ = 3436, 2960, 1727, 1456, 1396, 1320, 1285, 1231, 1160, 1090, 1026, 976, 878, 802, 732, 671 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.99 (ddd, J = 9.9, 5.7, 2.2 Hz, 1H), 5.69 (d, J = 5.7 Hz, 1H), 5.69–5.65 (m, 1H), 5.50 (dd, J = 15.4, 6.1 Hz, 1H), 4.85 (dd, J = 8.5, 7.9 Hz, 1H), 4.41 (ddd, J = 11.8, 5.1, 4.4 Hz, 1H), 4.21 (m, 1H), 4.03 (dd, J = 6.6, 6.4 Hz, 2H), 4.01 (m, 1H), 2.54 (dd, J = 13.6, 7.4 Hz, 1H), 2.24–1.95 (m, 11H), 1.72–1.68 (m, 2H), 1.50–1.46 (m, 1H), 1.19 (s, 9H), 0.91 ppm (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 178.6, 176.0, 131.2, 130.8, 128.8, 128.7, 111.4, 104.3, 77.6, 76.0, 75.4, 68.9, 63.6, 38.5, 35.6, 33.2, 30.7, 30.0, 28.7, 28.0, 27.2, 27.2, 23.5, 15.5 ppm; HRMS (MALDI): calcd for $C_{26}H_{38}O_8Na^+$ [M+Na$^+$]: 501.2459, found: 501.2467

30: R_f = 0.45 (silica gel, EtOAc/hexanes 1:4); $[\alpha]_D$ = −26.5 ($CHCl_3$, c = 0.85); IR (film): $\tilde{\nu}_{max}$ = 2955, 2914, 1745, 1697, 1460, 1392, 1350, 1253, 1170, 1067, 841, 741 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.57 (m, 2H), 4.20 (dd, J = 7.0, 4,4 Hz, 1H), 4.18–4.08 (m, 2H), 3.69 (ddd, J = 13.2, 4.0, 1.5 Hz, 1H), 3.03 (dd, J = 13.0, 11.9 Hz, 1H), 2.79 (dd, J = 14.3, 7.3 Hz, 1H), 2.55 (m, 2H), 2.28–2.15 (m, 2H), 2.05 (ddd, J = 16.5, 10.3, 6.2 Hz, 1H), 1.89 (m, 1H), 1.68 (dt, J = 13.9, 4.6 Hz, 1H), 1.58–1.42 (m, 2H), 1.29 (q, J = 12.5 Hz, 1H), 1.09 (d, J = 6.6 Hz, 3H), 1.02–0.95 (m, 2H), 0.94 (t, J = 7.9 Hz, 9H), 0.80 (d, J = 6.6 Hz, 3H), 0.79 (d, J = 7.7 Hz, 3H), 0.59 (q, J = 7.9 Hz, 6H), 0.04 ppm (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.3, 156.2, 96.6, 82.8, 76.3, 71.8, 63.1, 49.2, 43.6, 37.9, 37.8, 37.5, 31.1, 30.9, 24.0, 21.0, 18.6, 17.7, 16.7, 6.8, 4.6, −1.5 ppm; HRMS (MALDI): calcd for $C_{28}H_{53}NO_6Si_2Na^+$ [M+Na$^+$]: 578.3303, found: 578.3303

33: R_f = 0.40 (silica gel, EtOAc/hexanes 1:6); $[\alpha]_D$ = +12.1 ($CHCl_3$, c = 7.0); IR (film): $\tilde{\nu}_{max}$ = 2955, 1695, 1459, 1394, 1351, 1254, 1218, 1171, 1132, 1065, 840, 757 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.76–5.69 (m, 1H), 5.24 (d, J = 17.1 Hz, 1H), 5.13 (d, J = 17.1 Hz, 1H), 4.74 (m, 1H), 4.24 (d, J = 5.3 Hz, 1H), 4.10–4.06 (m, 3H), 3.86 (d, J = 6.1 Hz, 1H), 3.74–3.71 (m, 2H), 3.18 (t, J = 12.9 Hz, 1H), 2.98 (dd, J = 13.8, 9.0 Hz, 1H), 2.49 (dd, J = 14.0, 5.7 Hz, 1H), 2.26 (dd, J = 14.5, 6.1 Hz, 1H), 2.03–1.97 (m, 1H), 1.87 (dt, J = 14.0, 5.7 Hz, 1H), 1.57–1.50 (m, 2H), 1.34–1.23 (m, 3H), 0.96 (d, J = 5.7 Hz, 3H), 0.97–0.93 (m, 2H), 0.79 (d, J = 6.1 Hz, 3H), 0.79 (d, J = 6.1 Hz, 3H), 0.03 ppm (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 157.1, 132.0, 120.5, 98.1, 97.9, 79.6, 75.0, 72.9, 63.8, 50.0, 49.8, 47.4, 41.0, 39.7, 37.5, 32.2, 31.8, 29.2, 25.7, 19.6, 18.8, 17.3, −0.5 ppm; HRMS (MALDI): calcd for $C_{25}H_{42}INO_5SiNa^+$ [M+Na$^+$]: 614.1769, found: 614.1785

39: R_f = 0.30 (silica gel, EtOAc/hexanes 1:1); $[\alpha]_D$ = −9.8 ($CHCl_3$, c = 0.2); IR (film): $\tilde{\nu}_{max}$ = 3436, 2930, 1725, 1725, 1460, 1402, 1350, 1155, 1025, 979, 879, 585 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.98 (ddd, J = 9.8, 5.6, 2.1 Hz, 1H), 5.70 (ddd, J = 9.8, 2.3, 1.0 Hz, 1H), 5.42 (s, 1H), 5.22 (s, 1H), 4.66 (dt, J = 10.1, 6.1 Hz, 1H), 4.31 (d, J = 6.1 Hz, 1H), 4.24–4.20 (m, 1H), 4.15 (m, 1H), 4.14–4.09 (m, 3H), 4.08–4.05 (m, 2H), 3.89 (m, 1H), 2.23–2.20 (m, 2H), 2.16–2.13 (m, 1H), 2.11–2.07 (m, 2H), 2.04–1.94 (m, 6H), 1.87–1.77 (m, 2H), 1.46–1.37 (m, 2H), 1.19 (s, 9H), 1.02 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 0.86 ppm (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 178.9, 146.4, 129.6, 128.1, 118.1, 112.0, 104.5, 100.4, 98.6, 81.5, 78.2, 75.9, 75.6, 73.7, 67.0, 66.9, 63.4, 38.7, 36.7, 36.1, 34.3, 33.7, 31.1, 27.6, 27.0, 24.6, 24.2, 23.8, 18.0, 16.5, 16.3 ppm; HRMS (MALDI): calcd for $C_{33}H_{47}ClO_{10}Na^+$ [M+Na$^+$]: 661.2750, found: 661.2749

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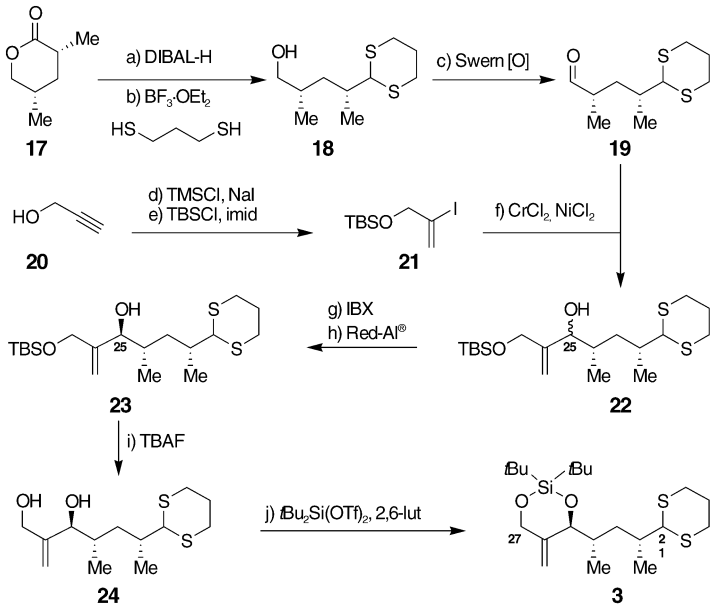
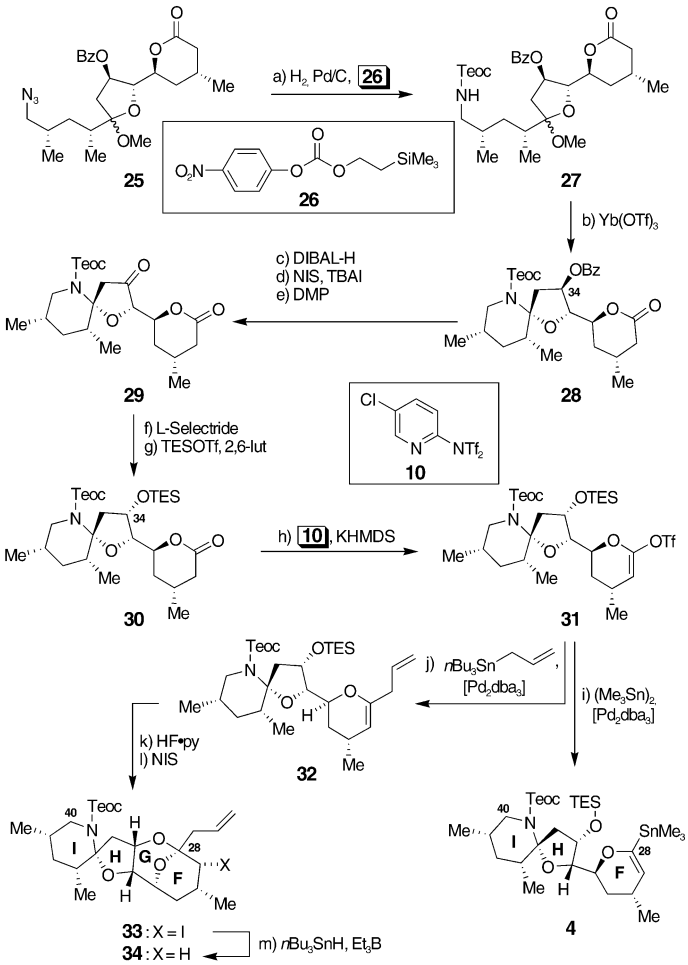


Scheme 3. Construction of **3**: a) DIBAL-H (1.0 M in CH_2Cl_2, 1.1 equiv), CH_2Cl_2, −78 °C, 1.5 h; b) 1,3-propanedithiol (1.1 equiv), $BF_3{\cdot}OEt_2$ (1.5 equiv), CH_2Cl_2, 0 °C, 1 h, 99% over two steps; c) $(COCl)_2$ (1.2 equiv), DMSO (2.4 equiv), CH_2Cl_2, −78 °C, 30 min; then Et_3N (5.0 equiv), −78 → −20 °C, 94%; d) TMSCl (1.2 equiv), NaI (1.2 equiv), H_2O (0.6 equiv), CH_3CN, 0 → 25 °C, 1.5 h, 51%; e) TBSCl (1.2 equiv), imidazole (2.5 equiv), DMF, 25 °C, 36 h, 96%; f) $NiCl_2$ (0.02 equiv), $CrCl_2$ (4.0 equiv), DMF, 0 °C; then **19** (1.0 equiv), **21** (2.5 equiv), 0 → 25 °C, 15 h, 95%; g) IBX (2.0 equiv), DMSO/THF (4:1), 25 °C, 2 h, 90%; h) Red-Al (2.5 equiv), toluene, −78 °C, 1 h, 80%; i) TBAF (2.2 equiv), THF, 25 °C, 1 h, 99%; j) tBu$_2$Si(OTf)$_2$ (1.6 equiv), 2,6-lutidine (4.0 equiv), CH_2Cl_2, −30 °C, 30 min, 75%. TMS = trimethylsilyl, imid = imidazole, DMF = *N*,*N*-dimethylformamide, IBX = *o*-iodoxybenzoic acid, Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride, Tf = trifluoromethanesulfonyl.

reproducible yields in the presence of $Yb(OTf)_3$,[16] in contrast to the previously employed $BF_3{\cdot}OEt_2$[17] procedure, which proved to be unreliable. An oxidation–reduction sequence was then carried out to invert the stereochemistry at C34. Thus, exposure of benzoate lactone **28** to DIBAL-H resulted in the formation of the corresponding hydroxylactol, which was oxidized stepwise back to the hydroxylactone (NIS, TBAI,[18] 88% overall yield) and then to ketolactone **29** (DMP, 95% yield). Treatment of ketolactone **29** with L-Selectride at −78 °C furnished, exclusively, the α-hydroxy compound (85% yield), which was silylated (TESOTf, 2,6-lutidine, 86% yield) to afford the desired intermediate **30** (Table 1). In preparation for the projected Stille coupling, lactone **30** was efficiently converted into vinyl stannane **4** through the intermediacy of enol triflate **31** (KMHDS, **10**,[10] 91% yield; $(Me_3Sn)_2$, $[Pd_2dba_3]$,[19] 98% yield). Although triflate **31** itself can potentially serve as a coupling partner with an allyl stannane, model studies suggested the reverse partnership as the most efficient variant for the azaspiracid-1 framework—and thus the choice of **4** as the FHI coupling partner. At this juncture, we needed further improvements of our approach to the final steps for the casting of the FGHI ring system. Specifically, our previously developed protocol for the formation of ring G employing $Hg(OAc)_2$[20] proved problematic in the presence of the entire, highly oxygenated azaspiracid-1 skeleton, and therefore an alternative tactic was sought to achieve this objective. It was in the search of such a protocol that the model substrate **32** was synthesized from **31** by reaction with allyltri-*n*-butyltin in the presence of $[Pd_2dba_3]$, TFP,[21] and LiCl (95% yield). Upon considerable experimentation, it was found that selective removal of the TES group from **32** under the mild conditions provided by HF·py buffered with additional pyridine led to the generation of the desired hydroxy enol ether precursor, which upon



Scheme 4. Construction of **4** and model FGHI ring system **34**: a) Pd/C (10% w/w, 0.1 equiv), EtOAc, H_2, 25 °C, 5 h; then filtration through celite; then Et_3N (5.0 equiv), **26** (4.0 equiv), 25 °C, 12 h, 80%; b) $Yb(OTf)_3$ (0.1 equiv), CH_3CN, 25 °C, 3 min, 71%; c) DIBAL-H (1.0 M in THF, 4.0 equiv), toluene, −78 °C, 25 min; d) NIS (10.0 equiv), TBAI (2.0 equiv), CH_2Cl_2, 25 °C, 40 min, 88% over two steps; e) DMP (1.5 equiv), pyridine (12.5 equiv), CH_2Cl_2, 0 → 25 °C, 30 min, 95%; f) L-Selectride (1.0 M in THF, 1.8 equiv), THF, −78 °C, 20 min, 85%; g) TESOTf (1.1 equiv), 2,6-lutidine (1.5 equiv), −78 °C, 10 min, 86%; h) **10** (5.0 equiv), KHMDS (5.0 equiv), THF, −78 °C, 40 min, 91%; i) $(Me_3Sn)_2$ (10.0 equiv), TFP (0.5 equiv), LiCl (3.0 equiv), $[Pd_2dba_3]$ (0.1 equiv), THF, 25 °C, 1 h, 98%; j) allyltri-*n*-butyltin (10.0 equiv), TFP (0.5 equiv), LiCl (3.0 equiv), $[Pd_2dba_3]$ (0.1 equiv), THF, 25 °C, 1 h, 95%; k) HF·py (5.0 equiv), THF/pyridine (1:1), 0 → 25 °C, 2 h; l) NIS (10.0 equiv), $NaHCO_3$ (30.0 equiv), THF, 0 °C, 12 h, 75% over two steps; m) Et_3B (1.0 M in hexanes, catalytic), nBu$_3$SnH/toluene (1:2), 0 °C, 5 min, 94%. Bz = benzoyl, NIS = *N*-iodosuccinimide, TBAI = tetra-*n*-butylammonium iodide, DMP = Dess–Martin periodinane, L-Selectride = lithium tri-*sec*-butylborohydride, TFP = tri-2-furylphosphane, dba = dibenzylideneacetone.

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treatment with *N*-iodosuccinimide[22] in the presence of $NaHCO_3$ furnished the FGHI iodide **33** (Table 1) in a pleasing yield of 75% overall for the two steps. The formation of **33** as a single, crystalline product gave us the opportunity to confirm its stereochemistry by X-ray crystallographic analysis (see ORTEP drawing of *ent*-**33**, Figure 1)[23] and to test the next step, that of removing the facilitating, but now extraneous, iodine residue, without compromising the rest of the molecule. Indeed, this crucial operation (**33**→**34**) was successfully executed by the reductive rupture of the carbon–iodine bond by the mild action of nBu$_3$SnH and Et$_3$B[24] (94% yield).

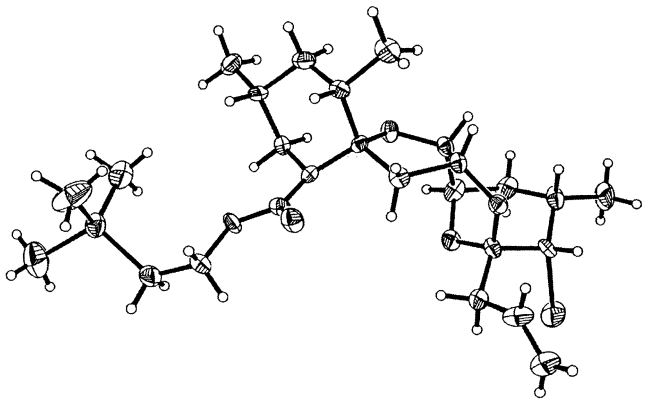
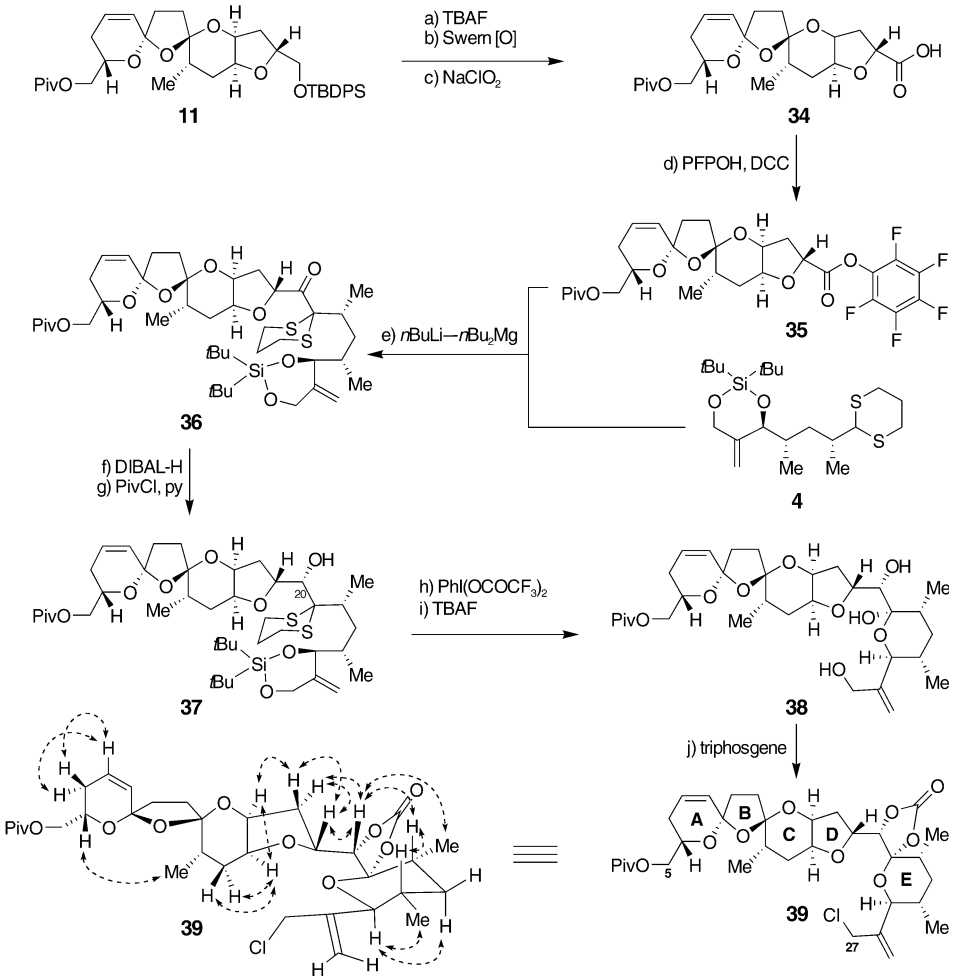


Figure 1. ORTEP drawing of compound *ent*-**33**.

Having chartered an appropriate route to access the FGHI domain of azaspiracid-1, we then turned our attention to scouting the ground for a possible means to construct the demanding C20–C21 bond and completing the requisite ABCDE domain. Thus, we targeted advanced model system **39** (Scheme 5), which contains all the rings and stereocenters embedded in the C5–C27 region of structure **1**. It was after the recognition of the reluctance of the aldehyde functionality at C20 of various ABCD-domain substrates to participate as an electrophilic partner in coupling reactions with organometal-



Scheme 5. Model dithiane coupling and structural confirmation of all stereocenters in ABCDE ring system (**39**, C5–C27 domain): a) TBAF (1.0 M in THF, 5.0 equiv), THF, 25 °C, 2 h, 88%; b) $(COCl)_2$ (5.0 equiv), DMSO (11 equiv), CH_2Cl_2, −78 °C, 30 min; then Et_3N (22 equiv), −78→0 °C, 94%; c) $NaClO_2$ (6.0 equiv), NaH_2PO_4 (6.0 equiv), 2-methyl-but-2-ene (excess), tBuOH/H_2O (4:1), 25 °C, 1.5 h; d) PFPOH (1.5 equiv), DCC (2.0 equiv), 25 °C, 2.5 h, 56% over two steps; e) **4** (9.0 equiv), nBuLi–nBu$_2$Mg (1.1 M in hexanes, 6.0 equiv), THF, 0→25 °C, 1.5 h; then **35**, −90 °C, 15 min, 63%; f) DIBAL-H (1.0 M in CH_2Cl_2, 10.0 equiv), CH_2Cl_2, −90 °C, 1.5 h, 55%; g) PivCl (3.0 equiv), pyridine (10.0 equiv), 0→25 °C, 12 h, 75%; h) $PhI(OCOCF_3)_2$ (2.2 equiv), MeCN/pH7 buffer (4:1), 0 °C, 78%; i) TBAF (1.0 M in THF, 5.0 equiv), THF, 25 °C, 16 h, 85%; j) triphosgene (2.0 equiv), pyridine (15 equiv), CH_2Cl_2, −78→25 °C, 1 h, 54%.

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lic species (such as the lithiated derivative of dithiane **4**) that we focused on the corresponding pentafluorophenyl ester as a potential alternative for this pivotal coupling. Thus, silyl derivative **11** (obtained as described in Scheme 2) was desilylated by treatment with TBAF (88% yield), and the resulting alcohol was oxidized stepwise, first under Swern conditions (94% yield) and then with $NaClO_2$, to afford carboxylic acid, **34**, as shown in Scheme 5. Subsequent coupling of the latter compound **34** with pentafluorophenol was accomplished in the presence of DCC in 56% overall yield from the corresponding aldehyde. The rather labile pentafluorophenyl ester **35** was carefully purified by flash column chromatography and immediately employed in the coupling reaction with the lithiated form of dithiane **4** (nBuLi–nBu$_2$Mg)[25] at −90 °C to afford ketone **36** in 63% yield. The required stereoselective reduction of the C20 carbonyl group was then accomplished through the use of DIBAL-H. However, the pivaloate group at C1 was cleaved concomitantly, leading to the corresponding diol in 55% yield. This diol was reprotected selectively (PivCl, py, 75% yield) at the primary position, leading to advanced intermediate **37**. In a carefully orchestrated sequence, the dithiane moiety was cleaved from **37** through the action of PhI(O-COCF$_3$)$_2$[26] to liberate the corresponding ketone (78% yield), from which the silicon tether was removed by exposure to TBAF, furnishing the azaspiracid-1-like lactol **38** through spontaneous ring closure as a single isomer (85% yield). With the aim of imparting more structural rigidity to the ABCDE truncate of azaspiracid-1 for detailed NMR studies, the hydroxy groups at C20 and C21 were conformationally constrained within a cyclic carbonate upon exposure to triphosgene and pyridine to provide cyclic carbonate **39** (54% yield) in which the terminal position was now occupied by a chlorine residue. Despite this unexpected occurrence, however, chloride **39** proved quite useful in providing us with the required structural information (Table 1). Thus, extensive NOE studies of compound **39** (see Scheme 5) revealed the key spatial correlations for the assigned stereochemistry, particularly around the C20 stereocenter.

The described chemistry provided ample quantities of building blocks **2**, **3**, and **4**, and powerful synthetic technologies pertaining to their coupling as a prelude to further forays along the designed path to the proposed structure **1** for azaspiracid-1. In the following Communication,[5] we report the final drive to two diastereoisomers of this structure and their comparison with the natural substance.

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Keywords: asymmetric synthesis · azaspiracid-1 · natural products · neurotoxins · structural revision · total synthesis

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[23] CCDC-210122 (*ent*-**33**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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