Natural Product Synthesis

Total Synthesis of the Proposed Azaspiracid-1 Structure, Part 2: Coupling of the C1–C20, C21–C27, and C28–C40 Fragments and Completion of the Synthesis**

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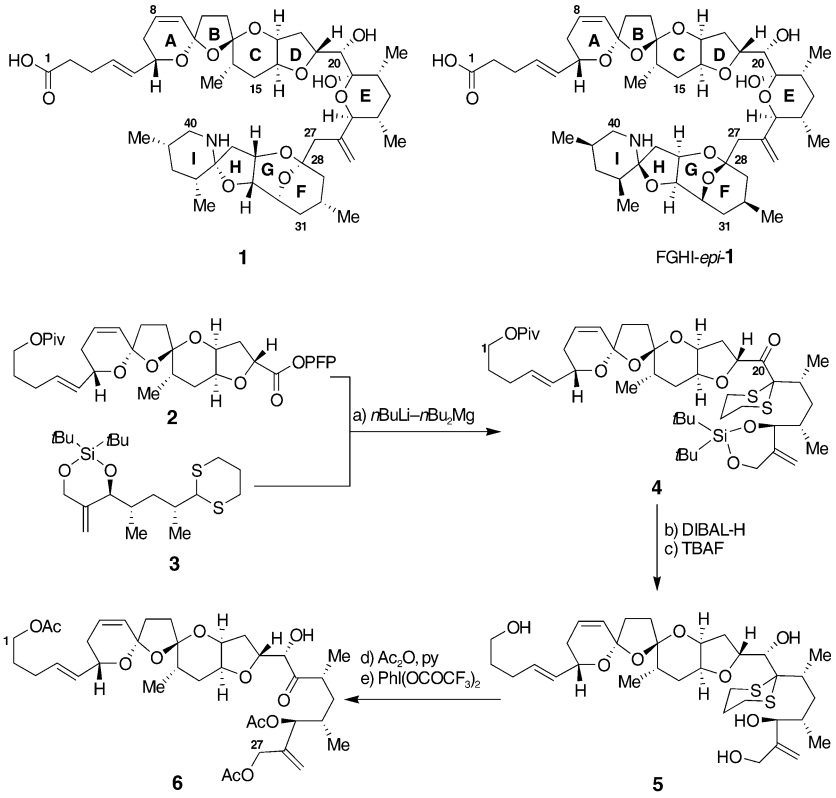
In the preceding paper[1] we described enantioselective constructions of the required C1–C20, C21–C27, and C28-C40 fragments for a projected total synthesis of the proposed structure of azaspiracid-1 (**1** or FGHI-*epi*-**1**),[2] and model studies for their potential fusion into the targeted entities. Herein we report the successful union of these fragments and the completion of the total synthesis of both structures **1** and its epimer FGHI-*epi*-**1**, neither of which exhibited the spectral data reported for natural azaspiracid-1.

As delineated in the preceding paper,[1] the proposed total synthesis called for two crucial couplings to forge the C20–C21 (dithiane coupling)[3] and C27–C28 (Stille coupling)[4] bonds. With the precise arrangement between the two major domains of azaspiracid-1 clouded by the uncertainty of their relative configuration,[2] the order of assembly involving dithiane coupling (C20–C21 bond) first and then Stille coupling (C27–C28 bond) was chosen as the most prudent approach to the expedient construction of both diastereoisomers **1** and FGHI-*epi*-**1**.

The first union, that between segments **2** (C1–C20) and **3** (C21–C27), was accomplished as shown in Scheme 1. Thus, we applied the conditions developed on model systems as described in the preceding paper,[1] and dithiane **3** was treated with the *n*BuLi–*n*Bu$_2$Mg[5] reagent mixture to prepare its activated organometallic species, which reacted with the freshly prepared and purified



Scheme 1. Structures of **1** and FGHI-*epi*-**1**, the coupling of key intermediates **2** and **3** and synthesis of advanced intermediate **6**: a) **3** (9.0 equiv), *n*BuLi–*n*Bu$_2$Mg (1.1 M in hexanes, 6.0 equiv), THF, 0→25 °C, 1.5 h; then **2**, −90 °C 15 min, 63%; b) DIBAL-H (1.0 M in CH_2Cl_2, 10.0 equiv), CH_2Cl_2, −90 °C, 1.5 h, 55%; c) TBAF (1.0 M in THF, 5.0 equiv), THF, 25 °C, 16 h, 78%; d) Ac_2O (50 equiv), pyridine/CH_2Cl_2 (1:1), 0→25 °C, 16 h, 84%; e) PhI(OCOCF$_3$)$_2$ (2.2 equiv), MeCN/pH7 buffer (4:1), 0 °C, 78%. PFP = pentafluorophenyl, Piv = trimethylacetyl, DIBAL-H = diisobutylaluminum hydride, TBAF = tetra-*n*-butylammonium fluoride, py = pyridine.

pentafluorophenyl ester **2** to furnish ketone **4** (Table 1) in a pleasing 63% yield (based on **2**). The reduction of the C20 carbonyl group within **4** proceeded stereoselectively under the influence of DIBAL-H (−90 °C, 55% yield), as expected from the previous model studies,[1] to afford a single dihydroxy product formed by concomitant cleavage of the pivaloate ester at C1. Although the coupling constant between 19-H and 20-H was in accord with the desired stereochemistry of C20,[6] the final proof for this assignment came later through X-ray crystallographic analysis (see below). Proceeding with the synthesis, the next desired step was the removal of the silyl protecting group from this diol, an objective that was smoothly accomplished by exposure to TBAF, unraveling tetraol **5** in 78% yield. In preparation for the pending Stille coupling, and in a rather daring maneuver, tetraol **5** was exposed to excess Ac_2O and pyridine, affording the corresponding triacetate (84% yield) with the hydroxy group at C20 remaining free, presumably as a result of the

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Table 1: Selected physical properties for compounds **4**, **6**, **10**, **11**, **16**, **17**, **1**, and FGHI-*epi*-**1**.

4: $R_f = 0.52$ (silica gel, EtOAc/hexanes 2:1); $[\alpha]_D = -53.2$ ($CHCl_3$, $c = 3.0$); IR (film): $\tilde{\nu}_{max} = 2933, 2860, 1728, 1707, 1531, 1515, 1467, 1383, 1320, 1284, 1234, 1157, 1084, 980, 914, 871, 826, 802, 732, 652\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 5.97$ (ddd, $J = 10.1, 5.7, 1.7$ Hz, 1H), 5.69–5.64 (m, 2H), 5.50 (dd, $J = 15.3, 6.2$ Hz, 1H), 5.36 (dd, $J = 9.0, 6.6$ Hz, 1H), 5.10 (s, 1H), 4.95 (s, 1H), 4.55 (d, $J = 11.4$ Hz, 1H), 4.40 (ddd, $J = 10.5, 5.0, 4.9$ Hz, 1H), 4.25 (d, $J = 6.5$ Hz, 1H), 4.23 (br s, 1H), 4.17 (d, $J = 11.8$ Hz, 1H), 4.16 (br s, 1H), 4.03 (t, $J = 6.6$ Hz, 2H), 2.91 (t, $J = 13.6$ Hz, 1H), 2.85 (t, $J = 12.7$ Hz, 1H), 2.59 (tt, $J = 14.5, 4.0$ Hz, 2H), 2.29 (dd, $J = 12.7, 6.6$ Hz, 2H), 2.25–2.18 (m, 3H), 2.12–1.96 (m, 10H), 1.92–1.86 (m, 1H), 1.76–1.68 (m, 1H), 1.69 ppm (t, $J = 7.0$ Hz, 2H), 1.45 (dt, $J = 13.8, 3.1$ Hz, 1H), 1.37–1.32 (m, 1H), 1.18 (s, 9H), 1.12 (d, $J = 6.5$ Hz, 3H), 1.04 (s, 9H), 0.98 (s, 9H), 0.88 (d, $J = 6.6$ Hz, 3H), 0.87 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 204.6, 178.7, 145.8, 131.2, 130.8, 129.0, 128.5, 114.4, 111.6, 104.2, 80.7, 77.6, 76.3, 76.0, 69.4, 68.8, 67.7, 63.6, 40.5, 38.7, 38.4, 36.3, 35.7, 35.1, 33.3, 30.9, 30.7, 30.0, 28.6, 28.0, 27.3, 27.3, 27.2, 27.0, 24.6, 23.3, 21.5, 21.0, 17.2, 16.7, 15.5$ ppm; HRMS (MALDI): calcd for $C_{47}H_{76}O_9S_2SiNa^+$ [M+Na^+]: 899.4597, found: 899.4601

6: $R_f = 0.15$ (silica gel, EtOAc/hexanes 1:1); $[\alpha]_D = +1.7$ ($CHCl_3$, $c = 0.9$); IR (film): $\tilde{\nu}_{max} = 3448, 2954, 2925, 1738, 1455, 1437, 1370, 1236, 1090, 1067, 1019, 981, 867, 803\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 5.99$ (ddd, $J = 11.7, 6.6, 3.1$ Hz, 1H), 5.72–5.64 (m, 2H), 5.51 (dd, $J = 18.4, 7.5$ Hz, 1H), 5.30 (s, 1H), 5.17 (s, 1H), 5.11 (d, $J = 8.0$ Hz, 1H), 4.84 (t, $J = 11.0$ Hz, 1H), 4.63 (d, $J = 16.3$ Hz, 1H), 4.56 (d, $J = 16.3$ Hz, 1H), 4.42–4.39 (m, 1H), 4.23 (dd, $J = 6.4, 2.2$ Hz, 1H), 4.19 (br s, 1H), 4.04 (t, $J = 7.9$ Hz, 2H), 3.83 (br s, 1H), 3.68 (d, $J = 6.2$ Hz, 1H), 2.94–2.91 (m, 1H), 2.46–2.39 (m, 1H), 2.11 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 2.15–1.90 (m, 14H), 1.73–1.67 (m, 1H), 1.40–1.33 (m, 1H), 1.11 (d, $J = 8.3$ Hz, 3H), 1.01–0.92 (m, 1H), 0.86 (d, $J = 7.9$ Hz, 3H), 0.85 ppm (d, $J = 8.4$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 212.4, 171.1, 170.5, 170.4, 141.1, 131.1, 130.8, 129.1, 128.6, 115.0, 111.3, 104.2, 78.6$ (2 x), 78.5, 76.1, 75.6, 68.8, 64.1, 63.8, 38.4, 35.8, 35.7, 33.9, 33.9, 32.3, 31.1, 30.0, 28.6, 28.0, 23.4, 21.0, 21.0, 20.9, 19.5, 16.3, 15.5 ppm; HRMS (MALDI): calcd for $C_{37}H_{54}O_{12}Na^+$ [M+Na^+]: 713.3507, found: 713.3491

10: $R_f = 0.60$ (silica gel, EtOAc/hexanes 1:1); $[\alpha]_D = +7.6$ ($CHCl_3$, $c = 2.4$); IR (film): $\tilde{\nu}_{max} = 2957, 1734, 1703, 1455, 1431, 1358, 1243, 1176, 1127, 1067, 982, 860, 727, 593\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 5.99$ (ddd, $J = 9.8, 5.6, 1.9$ Hz, 1H), 5.71 (d, $J = 10.1$ Hz, 1H), 5.66 (m, 1H), 5.54 (s, 1H), 5.50 (dd, $J = 15.6, 6.4$ Hz, 1H), 5.33 (s, 1H), 5.06 (m, 2H), 4.95–4.92 (m, 1H), 4.59(dd, $J = 18.0, 9.2$ Hz, 1H), 4.40 (m, 1H), 4.29 (s, 1H), 4.22 (d, $J = 8.3$ Hz, 1H), 4.19 (br s, 1H), 4.16–4.12 (m, 3H), 4.04 (t, $J = 6.6$ Hz, 2H), 3.99 (d, $J = 8.8$ Hz, 1H), 3.86 (m, 1H), 3.69–3.67 (m, 1H), 3.15–3.08 (m, 4H), 2.48–2.45 (m, 2H), 2.10 (s, 3H), 2.10–2.06 (m, 5H), 2.04 (s, 3H), 1.99–1.95 (m, 5H), 1.92–1.89 (m, 2H), 1.84–1.81 (m, 2H), 1.71–1.69 (m, 2H), 1.41–1.29 (m, 4H), 1.07 (d, $J = 7.0$ Hz, 3H), 0.99–0.96 (m, 3H), 0.93 (d, $J = 6.6$ Hz, 3H), 0.88 (d, $J = 7.0$ Hz, 3H), 0.85 (d, $J = 7.0$ Hz, 3H), 0.79 (d, $J = 6.6$ Hz, 3H), 0.69 (d, $J = 6.6$ Hz, 3H), 0.02 ppm (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 212.1, 172.3, 171.7, 157.2, 140.8, 132.1, 131.8, 130.1, 129.3, 118.0, 112.2, 105.2, 98.7, 97.9, 80.6, 80.4, 80.0, 77.6, 77.4, 76.9, 76.7, 73.9, 69.9, 64.8, 64.2, 50.7, 50.4, 47.3, 42.0, 38.1, 36.7, 35.7, 34.1, 33.1, 32.2, 32.0, 31.4, 31.0, 29.7, 29.2, 29.1, 29.0, 27.4, 24.6, 24.4, 22.0, 22.0, 20.3, 19.5, 18.3, 17.4, 16.6, −0.3$ ppm; HRMS (MALDI): calcd for $C_{57}H_{88}INO_{15}SiNa^+$ [M+Na^+]: 1204.4860, found: 1204.4833

Table 1 (Continued)

11: $R_f = 0.50$ (silica gel, EtOAc/hexanes 1:1); $[\alpha]_D = -2.8$ ($CHCl_3$, $c = 1.2$); IR (film): $\tilde{\nu}_{max} = 2956, 1737, 1713, 1596, 1449, 1390, 1355, 1243, 1173, 1067, 978, 855, 837, 756\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 5.98$ (ddd, $J = 9.8, 6.2, 1.8$ Hz, 1H), 5.70 (d, $J = 9.6$ Hz, 1H), 5.66 (m, 1H), 5.50 (dd, $J = 15.4, 6.1$ Hz, 1H), 5.46 (s, 1H), 5.29 (s, 1H), 5.07 (s, 2H), 4.84–4.82 (m, 1H), 4.75 (dd, $J = 12.5, 6.4$ Hz, 1H), 4.66 (br s, 1H), 4.40 (m, 1H), 4.23 (d, $J = 5.7$ Hz, 1H), 4.19–4.17 (m, 3H), 4.04–4,02 (m, 4H), 3.92–3.91 (m, 2H), 3.76 (dd, $J = 13.4, 4.2$ Hz, 1H), 3.64 (dd, $J = 14.7, 5.0$ Hz, 1H), 3.19 (t, $J = 12.5$ Hz, 1H), 3.01–2.99 (m, 1H), 2.88 (d, $J = 14.5$ Hz, 1H), 2.69 (dd, $J = 22.4, 7.5$ Hz, 1H), 2.45–2.38 (m, 2H), 2.15–2.08 (m, 6H), 2.08 (s, 3H), 2.03 (s, 3H), 1.99–1.92 (m, 6H), 1.90–1.85 (m, 2H), 1.71–1.68 (m, 3H), 1.34–1.24 (m, 8H), 1.06 (d, $J = 7.5$ Hz, 3H), 1.06–0.96 (m, 3H), 0.97 (d, $J = 6.1$ Hz, 3H), 0.82 (d, $J = 7.5$ Hz, 3H), 0.81 (d, $J = 7.0$ Hz, 3H), 0.78 (d, $J = 6.6$ Hz, 3H), 0.02 ppm (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 212.5, 172.1, 171.5, 157.4, 140.4, 132.2, 131.8, 130.1, 129.6, 116.3, 112.4, 105.1, 98.5, 98.2, 81.0, 79.9, 79.6, 78.1, 77.2, 76.4, 74.8, 74.3, 69.8, 64.8, 64.0, 52.6, 50.1, 44.8, 41.4, 39.5, 39.2, 37.7, 36.8, 36.7, 35.1, 32.9, 32.6, 32.2, 32.1, 31.9, 31.0, 30.7, 29.7, 29.0, 28.9, 25.4, 24.4, 22.0, 22.0, 20.6, 19.6, 18.5, 18.0, 17.4, 16.6, −0.5$ ppm; HRMS (MALDI): calcd for $C_{57}H_{88}INO_{15}SiNa^+$ [M+Na^+]: 1204.4860, found: 1204.4832

16: $R_f = 0.35$ (silica gel, chloroform/methanol/H_2O 20:3:1); $[\alpha]_D = +22.4$ ($CHCl_3$, $c = 0.38$); IR (film): $\tilde{\nu}_{max} = 3333, 2957, 1731, 1574, 1456, 1425, 1373, 1242, 1138, 1043, 1020, 983, 803, 755\ cm^{-1}$; ^1H NMR (600 MHz, CD_3OD): $\delta = 6.00$ (ddd, $J = 9.6, 5.5, 1.8$ Hz, 1H), 5.77–5.73 (m, 1H), 5.66 (dt, $J = 9.9, 1.9$ Hz 1H), 5.50 (dd, $J = 15.3, 6.1$ Hz, 1H), 5.39 (br s, 1H), 5.10 (s, 1H), 5.05 (s, 1H), 4.80–4.79 (m, 2H), 4.33(dd, $J = 13.8, 6.8$ Hz, 1H), 4.28 (br s, 1H), 4.24 (d, $J = 4.4$ Hz, 1H), 4.14 (d, $J = 2.2$ Hz, 1H), 3.87 (br s, 1H), 3.70 (d, $J = 3.5$ Hz, 1H), 3.19–3.16 (m, 1H), 2.66 (t, $J = 11.4$ Hz, 1H), 2.56 (dd, $J = 11.2, 4.2$ Hz, 1H), 2.40–2.28 (m, 5H), 2.24–2.18 (m, 3H), 2.09 (s, 3H), 2.10–1.98 (m, 7H), 1.98–1.87 (m, 4H), 1.81–1.71 (m, 3H), 1.70–1.62 (m, 2H), 1.55–1.45 (m, 3H), 1.05 (d, $J = 7.0$ Hz, 3H), 0.97–0.90 (m, 3H), 0.92 (d, $J = 5.7$ Hz, 3H), 0.91 (d, $J = 5.7$ Hz, 3H), 0.88 (d, $J = 6.6$ Hz, 3H), 0.86 (d, $J = 6.6$ Hz, 3H), 0.85 ppm (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD): $\delta = 216.7, 182.8, 173.1, 144.1, 133.9, 131.9, 130.7, 130.7, 116.6, 113.8, 106.6, 98.6, 96.9, 82.1, 80.9, 80.2, 79.2, 79.1, 78.5, 76.5, 73.5, 71.3, 50.4, 48.3, 44.2, 43.5, 40.9, 40.4, 39.6, 38.9, 37.8, 37.6, 36.5, 35.8, 35.5, 33.9, 33.2, 32.6, 32.1, 31.4, 27.2, 25.2, 24.8, 22.0, 20.7, 20.4, 18.4, 17.1, 17.0$ ppm; HRMS (MALDI): calcd for $C_{49}H_{73}NO_{13}H^+$ [M+H^+]: 884.5154, found: 884.5119

17: $R_f = 0.30$ (silica gel, chloroform/methanol/H_2O 20:3:1); $[\alpha]_D = -9.5$ ($CHCl_3$, $c = 0.60$); IR (film): $\tilde{\nu}_{max} = 3422, 2956, 1734, 1649, 1562, 1449, 1403, 1373, 1320, 1240, 1132, 1043, 980, 755\ cm^{-1}$; ^1H NMR (600 MHz, CD_3OD): $\delta = 6.00$ (ddd, $J = 9.9, 3.7, 3.7$ Hz, 1H), 5.76–5.73 (m, 1H), 5.66 (dt, $J = 10.1, 2.0$ Hz, 1H), 5.50 (dd, $J = 15.8, 6.1$ Hz, 1H), 5.33 (d, $J = 4.8$ Hz, 1H), 5.12 (s, 1H), 5.04 (s, 1H), 4.79–4.75 (m, 2H), 4.33(dd, $J = 13.8, 7.7$ Hz, 1H), 4.27–4.19 (m, 2H), 3.87 (m, 1H), 3.72 (d, $J = 3.1$ Hz, 1H), 3.18–3.13 (m, 1H), 2.69–2.62 (m, 2H), 2.39–2.26 (m, 5H), 2.24–2.18 (m, 3H), 2.08 (s, 3H), 2.10–1.98 (m, 7H), 1.98–1.84 (m, 4H), 1.81–1.66 (m, 4H), 1.70–1.62 (m, 1H), 1.55–1.35 (m, 4H), 1.07 (d, $J = 7.0$ Hz, 3H), 1.05–0.90 (m, 3H), 0.91 (d, $J = 6.1$ Hz, 3H), 0.90 (d, $J = 6.6$ Hz, 3H), 0.87 (d, $J = 7.0$ Hz, 3H), 0.87 (d, $J = 6.6$ Hz, 3H), 0.84 ppm (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD): $\delta = 215.7, 182.3, 172.7, 143.9, 133.5, 131.5, 130.4, 130.2, 116.5, 113.4, 106.1, 98.3, 96.4, 81.7, 80.4, 79.9, 78.8, 78.3, 78.0, 76.1, 73.1, 70.8, 47.6, 45.5, 43.7, 42.0, 40.5, 40.0, 39.2, 38.4, 37.3, 37.3, 35.9, 35.3, 35.2, 33.1, 32.8, 32.2, 32.1, 31.8, 31.0, 26.8, 24.8, 24.2, 21.4, 20.4, 20.0, 17.8, 16.6$ ppm ; HRMS (MALDI): calcd for $C_{49}H_{73}NO_{13}H^+$ [M+H^+]: 884.5154, found: 884.5119

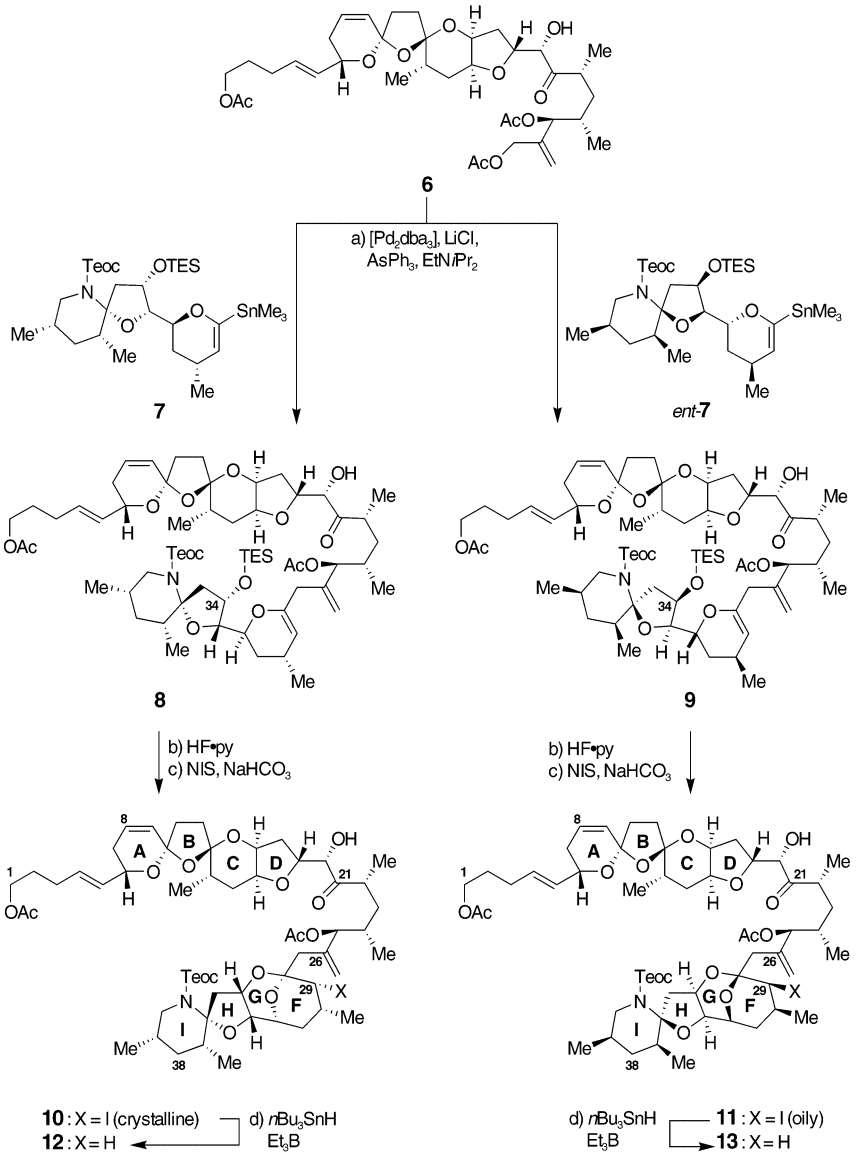
severe steric hindrance associated with this site. At this stage it was decided to remove the dithiane moiety by treatment with $PhI(OCOCF_3)_2$,[7] which furnished the triacetoxy hydroxy ketone **6** (Table 1) in 78% yield. The latter was adopted as an ideal substrate for the projected Stille coupling by virtue of its delicate and carefully installed functionalities, easy accessibility from **5**, and prospects for final elaboration after the merger. Thus, it was anticipated that the primary allylic acetate at C27 within **6** would be the most suitable site for the palladium-catalyzed coupling, in contrast to the secondary

allylic acetate (C25) whose steric hindrance should be prohibiting. Furthermore, based on model studies, the hydroxy ketone functionality at C20–C21 was expected to remain indifferent to the expected palladium reaction conditions.

Despite the careful fine-tuning of the two Stille coupling partners **6** and **7** and its enantiomer *ent*-**7** (Scheme 2), their union proved far from routine, requiring instead further attention. The challenge was mainly to find ways to prevent competitive or subsequent reaction of the secondary allylic acetate embedded within the starting component and the product, and to ensure the survival of the rather sensitive vinyl stannane functionalities within **7** and *ent*-**7**. Indeed, it was after considerable experimentation that conditions were finally found to achieve this final coupling. Thus, to modulate the effective bulkiness and electronic character of the reactive palladium species, $AsPh_3$[8] was employed together with $[Pd_2dba_3]$ (1:1 ratio), with the former ligand providing sufficient, but not prohibitive, steric hindrance to stop the secondary coupling. A slow addition of the stannane component minimized its destruction prior to its engagement in the desired process. Under these optimized conditions, compounds **8** and **9** were obtained from **6** and **7** and *ent*-**7** in 52 and 66% yields, respectively, as shown in Scheme 2.

Having assembled the complete carbon framework of the proposed azaspiracid-1 structure in advanced intermediates **8** and **9**, only the casting of two rings and the adjustment of a few functional groups remained before arrival at the targeted molecules. First to be installed from the missing cyclic motifs was ring G. Thus, the TES group was selectively removed from the hydroxy group at C34 of **8** and **9** by the action of HF·py in the presence of excess pyridine, and the resulting compound was subjected to iodoetherification with *N*-iodosuccinimide[9] and $NaHCO_3$ to afford the diastereomeric iodides **10** and **11** (Table 1) in 67 and 63% yields, respectively. Much to our delight, iodide **10** crystallized beautifully and yielded to X-ray crystallographic analysis (see ORTEP drawing, Figure 1),[10] which confirmed its molecular architecture, including all the ring and stereochemical elements of the proposed azaspiracid-1 structure, with the exception of ring E and the C21 stereocenter, whose formation was still pending. The spectral data for the oily iodide **11**, particularly when compared to those of **10**, were supportive of its structure. Initial attempts to remove the iodide residue from **10** and **11** proved problematic as the standard nBu$_3$SnH-based methods, including the mild nBu$_3$SnH–Et$_3$B protocol,[11] were plagued with complications of another product (ca. 1:1 ratio with the expected product) suspected to be formed through participation of the neighboring double bond in the radical cascade involved in the reduction. Pleasingly, it was determined that increasing the amount of nBu$_3$SnH from 5.0 equiv to a large excess solved this problem by rapidly quenching the initially formed radical at C29 before it had a chance to attack the C=C bond at C26, leading to excellent yields of 92 and 94% of **12** and **13**, respectively.

The remaining operations before arriving at **1** and FGHI-*epi*-**1** were care-



Scheme 2. Coupling of advanced intermediates **6** with **7** and *ent*-**7**, and elaboration to **12** and **13**: a) $[Pd_2dba_3]$ (0.3 equiv), $AsPh_3$ (0.3 equiv), LiCl (6.0 equiv), $EtNiPr_2$ (12 equiv); then **7** or *ent*-**7** (0.03 M in THF, syringe pump addition), NMP, 45 °C, 4 h, 52% (**8**), 66% (**9**); b) HF·py (excess), THF/pyridine (1:1), 0→25 °C, 2.5 h; c) NIS (10.0 equiv), $NaHCO_3$ (30 equiv), THF, 0 °C, 16 h, 67% (**10**), 63% (**11**) over two steps; d) Et_3B (1.0 M in hexanes, catalytic), nBu$_3$SnH/toluene (1:2), 0 °C, 5 min, 92% (**12**), 94% (**13**). TES = triethylsilyl, Teoc = 2-(trimethylsilyl)ethoxycarbonyl, dba = dibenzylideneacetone, NMP = *N*-methylpyrrolidone, NIS = *N*-iodosuccinimide.

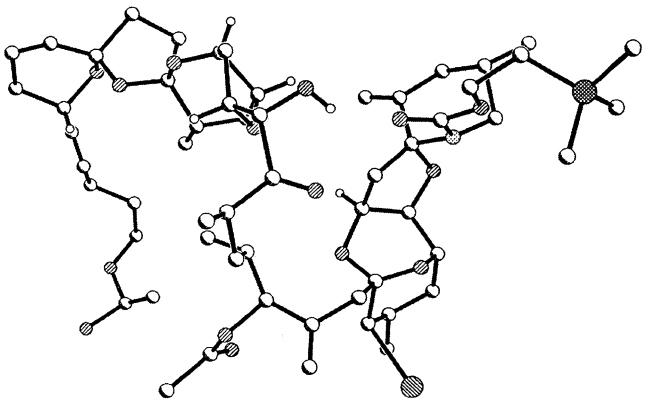


Figure 1. ORTEP drawing for compound **10**.

fully designed and navigated based on extensive experimentation and model studies (Scheme 3). Thus, in preparation for oxidation adjustment of C1, the hydroxy group at C20 was temporarily masked with a TES group, and the hydroxy group at C1 was selectively unveiled. A two-step oxidation protocol then led to carboxylic acids **14** (48% overall yield from **12**) and **15** (56% overall yield from **13**). All that now remained was the removal of the three protecting groups guarding the hydroxy groups at C20 and C25 and the secondary amine. The two fluoride-labile moieties were detached through the use of TBAF in a simple operation, leading to **16** and **17** (Table 1) in 87 and 92% yields, respectively. Finally, the acetate group of **16** and **17**, which held these molecules from folding into their resting places, was removed by the action of LiOH in MeOH, an event that led to the generation of **1** and its FGHI epimer, FGHI-*epi*-**1** (Table 1). Unlike azaspiracid-1, which was reported as a single compound, synthetic **1** and FGHI-*epi*-**1** were found to exist as mixtures of inseparable isomers. More disturbing was the realization that neither of these compounds matched, by TLC and HPLC, the naturally derived sample of azaspiracid-1, whose ^{1}H NMR data were also different from those of the synthetic samples.[12] In light of these studies, we concluded that the proposed structure **1** for azaspiracid-1 (or its epimer FGHI-*epi*-**1**) is in error, unless the error lies somewhere in the sequence after the octacyclic iodide **10** whose X-ray analysis unambiguously proved the structure of our intermediates up to that point. Pending this unlikely scenario, it seems prudent to continue the search for the true structure of azaspiracid-1, a goal which we are currently pursuing by synthetic and analytical techniques in collaboration with the Satake group in Japan.

The final outcome notwithstanding, the described chemistry herein and in the preceding Communication[1] opens new avenues to complex molecular architectures never visited before, and holds promise in the construction of further structures within this new class of potent biotoxins, including that of azaspiracid-1. Among the most powerful synthetic technologies developed in this campaign, the two C–C bond-forming reactions used to assemble the final framework and the ring closures employed to construct the delicate spiroketal moieties of the target stereoselectively stand out as both highly enabling and uniquely novel.[13]

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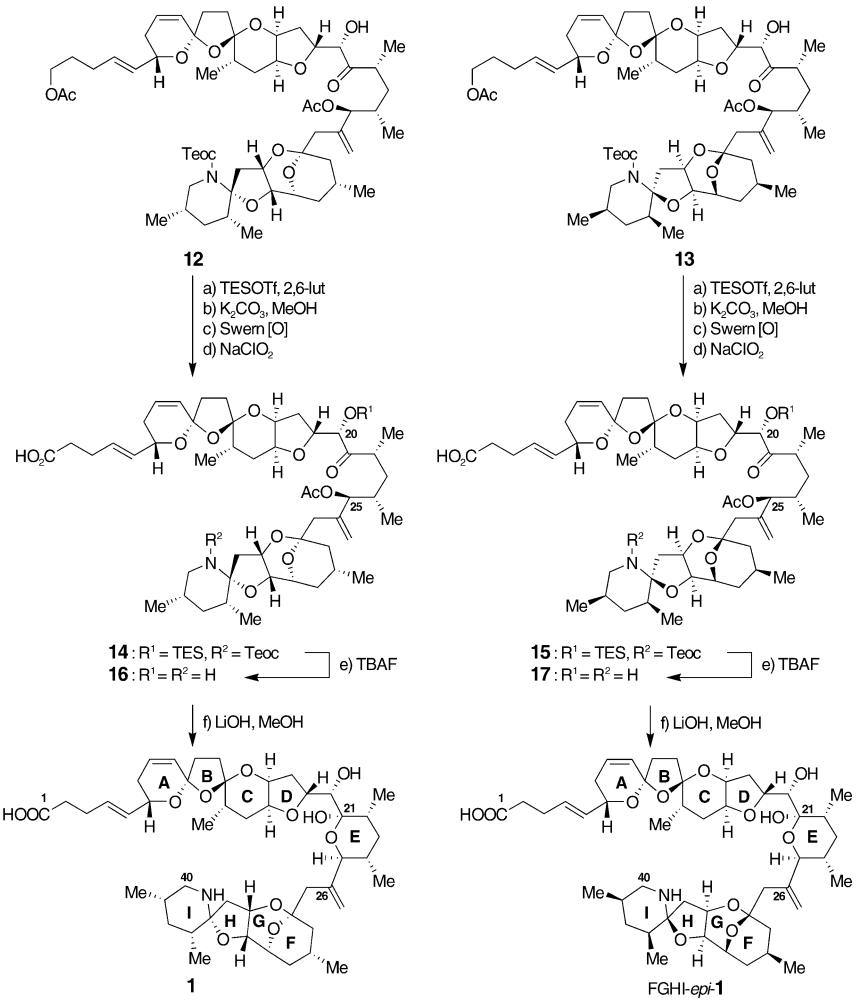
Keywords: asymmetric synthesis · azaspiracid-1 · natural products · neurotoxins · structural revision · total synthesis



Scheme 3. Final stages and completion of the synthesis of the proposed azaspiracid-1 structures (**1** and FGHI-*epi*-**1**): a) TESOTf (10.0 equiv), 2,6-lutidine (20 equiv), CH_2Cl_2, −78→0 °C, 10 min; b) K_2CO_3 (catalytic), MeOH, 25 °C, 2 h; c) $(COCl)_2$ (10.0 equiv), DMSO (20 equiv), CH_2Cl_2, −78 °C, 1 h; then Et_3N (50 equiv), −78→−20 °C, 30 min; d) $NaClO_2$ (10.0 equiv), NaH_2PO_4 (10.0 equiv), 2-methyl-but-2-ene (excess), *t*BuOH/H_2O (4:1), 25 °C, 30 min, 48% (**14**) and 56% (**15**) over four steps; e) TBAF (5.0 equiv), THF, 25 °C, 2 h, 87% (**16**), 92% (**17**); f) LiOH (excess), MeOH/H_2O (5:1), 25 °C, 16 h, 45% (**1**) and 37% (FGHI-*epi*-**1**). Tf = tifluoromethanesulfonyl, DMSO = dimethyl sulfoxide.

[1] See preceding Communication in this issue: K. C. Nicolaou, Y. Li, N. Uesaka, T. V. Koftis, S. Vyskocil, T. Ling, M. Govindasamy, W. Qian, F. Bernal, D. Y.-K. Chen, *Angew. Chem.* **2003**, *115*, 3771–3776; *Angew. Chem. Int. Ed.* **2003**, *42*, 3643–3648.

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[6] The ^{1}H NMR (600 MHz, $CDCl_3$) signal observed for 20-H ($\delta =$ 3.62 ppm, $J = 9.6$ Hz) after reduction of compound **4** with DIBAL-H was essentially identical in terms of both chemical shift and coupling constant to that observed after the reduction of compound **36** with DIBAL-H described in the preceding Communication.[1]

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[10] CCDC-210123 (**10**) 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 CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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[12] We thank Dr. Masayuki Satake for an authentic sample of azaspiracid-1 and for providing us with NMR spectra. Comparison of authentic azaspiracid-1 against **1** and FGHI-*epi*-**1** by TLC (chloroform/methanol/H_2O 20:3:1) showed that the authentic sample is more polar than either of the synthetic materials. In addition, the ^{1}H NMR (600 MHz, 0.5 % CD_3COOD in CD_3OD) spectra of compounds **1** and FGHI-*epi*-**1** were noticeably different from that of the natural azaspiracid-1,[2] particularly in the olefinic region; natural azaspiracid-1: $\delta = 5.74$ (4-H), 5.46 (5-H), 5.76 (8-H), 5.65 (9-H), 5.36 (44_a-H), 5.18 ppm (44_b-H); synthetic **1**: $\delta = 5.79$ (4-H), 5.57 (5-H), 6.02 (8-H), 5.76 (9-H), 5.35 (44_a-H), 5.31 ppm (44_b-H); synthetic FGHI-*epi*-**1**: $\delta = 5.79$ (4-H), 5.57 (5-H), 6.02 (8-H), 5.76 (9-H), 5.38 (44_a-H), 5.33 ppm (H-44_b). The values for the synthetic materials correspond to those of the major product in each case. It was also observed that the chemical shifts for the "upper" domain olefinic protons (4-H, 5-H, 8-H, and 9-H) remain relatively constant, whereas those of the "lower" region of the molecule (44_a-H and 44_b-H) change considerably upon addition of CD_3COOD.

[13] Note added in proof: Based on available information, we propose that the true azaspiracid-1 structure differs from that of FGHI-*epi*-**1** by the position of the double bond in ring A (7,8 instead of 8,9). Ongoing studies aim to confirm this conjecture.

