Natural Products Synthesis

Structural Revision and Total Synthesis of Azaspiracid-1, Part 2: Definition of the ABCD Domain and Total Synthesis**

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The preceding communication in this issue[1] detailed studies that led to the absolute structural definition of the EFGHI segment (C21–C40 domain) of azaspiracid-1 (see one of the four originally proposed structures, **1-i**, Figure 1), but left the final structural assignment for the ABCD framework (C1–C20 domain) as an open question, despite considerable effort to resolve this issue. Herein we present the remainder of the azaspiracid-1 saga that led to the complete definition of the ABCD ring framework. The total synthesis of azaspiracid-1 (**1-c**) has finally revealed the long-sought structure of this marine neurotoxin, rendering it readily available for biological investigations.

In recapping the studies on the ABCD domain of azaspiracid-1 described in the preceding paper,[1] we note that the degradatively derived fragment did not match either structure **2** ($\Delta^{8,9}$, Figure 1), which was designed on the basis of the originally proposed structure of azaspiracid-1 (**1-i**), or compound **3** ($\Delta^{7,8}$, Figure 1), whose adoption as possible candidate for the correct architecture was based on the structure of lissoketal. These findings still left us with a multiple choice as to which stereoisomer of structure **3** (which by now became our favorite representation of the coveted subtarget molecule) to pursue next. However, based on our knowledge at the time, we could decrease the reasonable isomer possibilities to a small number that included compound **4** (Figure 2). This isomer appeared to benefit from a double anomeric effect (based on manual molecular modeling) and to fulfil the crucial requirement for the NOE effect between 6-H and the methyl group at C14 (see Figure 2) observed for the natural product[2] and its ABCD-domain degradation product.[1] It was precisely because of this latter observation that compound **4** became our next priority target. Its attempted synthesis (Scheme 1) was met with unexpected, but nevertheless, path-pointing observations. Thus, substrate **9** was prepared from building blocks[3] **6**, **7**, and **8** according to our previously reported route,[3] with the appropriate modification of building block **7** to accommodate the new stereochemical requirement at C14 in subtarget **4**. The intermediate **9** was then subjected to deprotection–cyclization cascade conditions.[3] Interestingly, however, the major product formed in this double spiroketalization process (**9**→**10**) was that with the opposite stereochemistry at C13 from the one proposed in the C14-*epi* target intermediate **4**. This rather distressing signal became even more ominous four steps further along the sequence when an attempt was made to correct the stereochemistry at C13. Thus, when intermediate **11** (obtained from **10** by 1) pivaloate formation; 2) dithiane cleavage; and 3) reduction with sodium borohydride) was exposed to TFA, an equilibrium was reached in which the isomer **12** with the isomerized C13 center predominated (≈55:45). Although NOE studies revealed a strong effect between 6-H and the methyl group at C14 in **12**, the chemical shift of the latter signal differed significantly from the corresponding signal in the natural product, suggesting the axial orientation for this methyl substituent (C14). Indeed, the observed thermodynamic stability of azaspiracid-1 under acidic conditions[2] did not bode well for isomer **4** as the correct representation of the ABCD domain of the natural product. Its construction, therefore, was abandoned at this stage in favor of another synthesis, this time directed toward the next suspected structure, namely **5** (Figure 2). The latter structure, in which the C6 stereocenter is inverted, also enjoys the thermodynamic stability (manual molecular modeling) derived from two anomeric effects, provided that the two spirocenters are inverted into the opposite configurations as shown in Figure 2 (structure **5**).

Compound **5** was synthesized stereoselectively as shown in Scheme 2. Thus, starting with the ketophosphonate **6** derived from L-malic acid (natural), and following our

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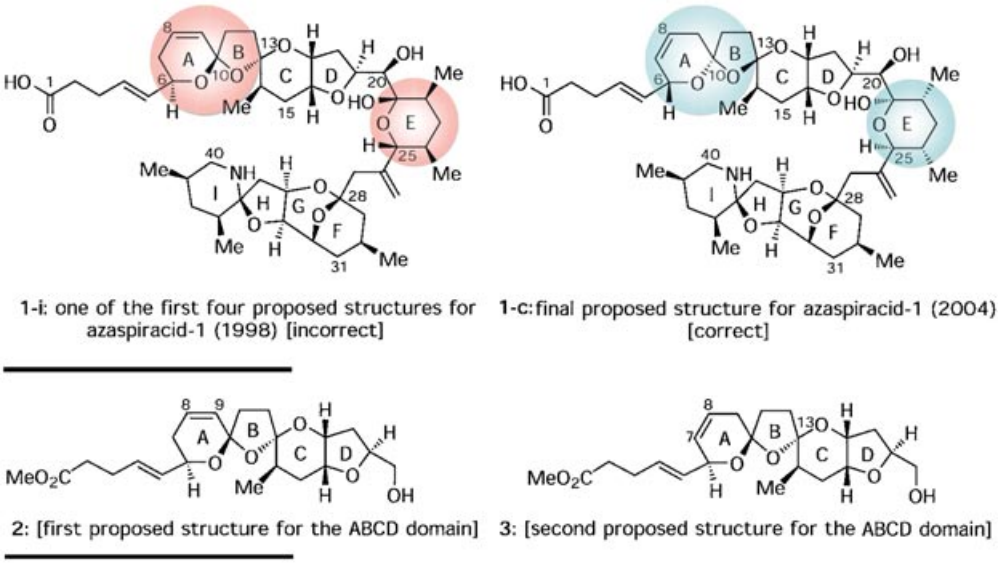


Figure 1. Originally (**1-i**) and newly (**1-c**) proposed structures of azaspiracid-1, and unsuccessful attempts to match synthetic materials (**2** and **3**) with naturally derived ABCD fragment.

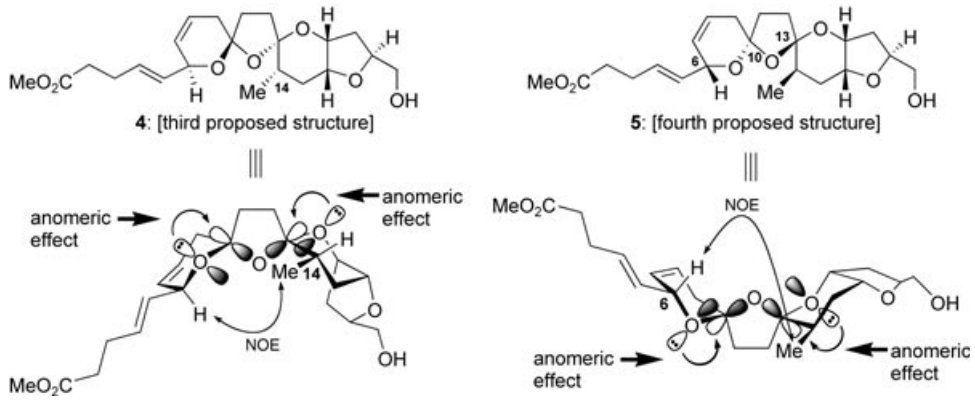
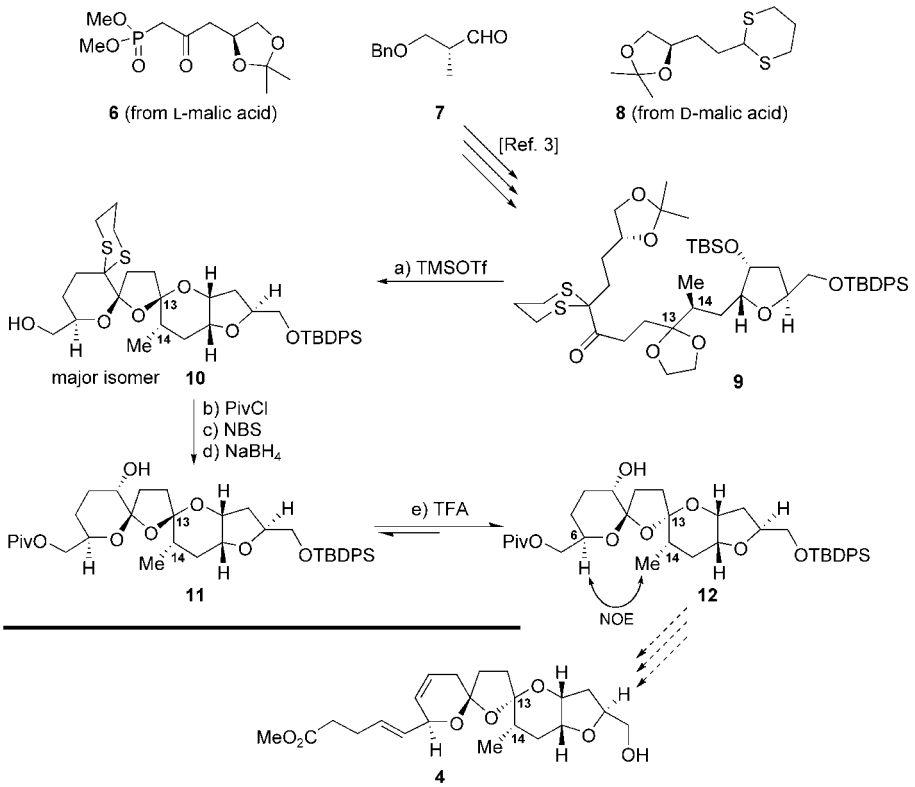


Figure 2. Third and fourth proposed structures (**4** and **5**) of the ABCD domain of azaspiracid-1 with expected anomeric effects and NOE interactions.

previously described route,[3] intermediate **13** was prepared in 12 steps in good overall yield. To accommodate the requirements of the new subtarget **5**, a substantially modified sequence from **13** to **5** had to be developed. To facilitate the pending cyclization to the ABCD tetracycle (see below), the TBS group of **13** was exchanged with a TES group, followed by cleavage of the double bond to give aldehyde **14** in excellent overall yield. Coupling of **14** with dithiane **15** (also derived from L-malic acid)[3] under the influence of *n*BuLi afforded the corresponding secondary alcohol as a mixture of diastereoisomers (≈1:1, 98% yield) whose oxidation with DMP transformed it into the required cyclization precursor **16** in 90% yield. The anticipated deprotection–double spirocyclization of **16** proceeded smoothly under the influence of TMSOTf in CH_2Cl_2 at −90 °C to furnish the desired polycycle **17** in 89% yield as a single stereoisomer. The observed NOE interaction between 6-H and C14-Me confirmed the anticipated structure **17** and provided support for our proposition of its thermodynamic stability. To decrease the number of steps required for the side-chain attachment, an olefin metathesis protocol was applied instead of the previously reported procedure.[1] Thus, Swern oxidation of alcohol **17** followed by Wittig olefination of the resulting aldehyde furnished the desired terminal olefin **19** in 81% overall yield. Cross-metathesis of **19** with olefin **21** was effected by the action of Grubbs catalyst **20**,[4] yielding the corresponding *E* olefin as the major product, from which the minor *Z* olefin was easily separated chromatographically (95% yield total after three cycles, ≈60% conversion in each cycle, $E/Z \approx 10{:}1$). The dithiane moiety was then removed from the resulting olefin by exposure to PhI-$(OCOCF_3)_2$, leading to ketone **22** in 90% yield. The introduction of the required α,β-unsaturation within **22** was successfully carried out by the Mukaiyama method (LDA–*t*BuN=SPhCl)[5] to afford **23** in 81% yield. Regio- and stereoselective reduction of the enone functionality of **23** with $NaBH_4$–$CeCl_3$, followed by exposure to $ClCO_2Me$ in the presence of pyridine, led to allylic carbonate **24** through the intermediacy of the corresponding alcohol in 70% overall yield. Compound **24** served well as a precursor to olefin **25**



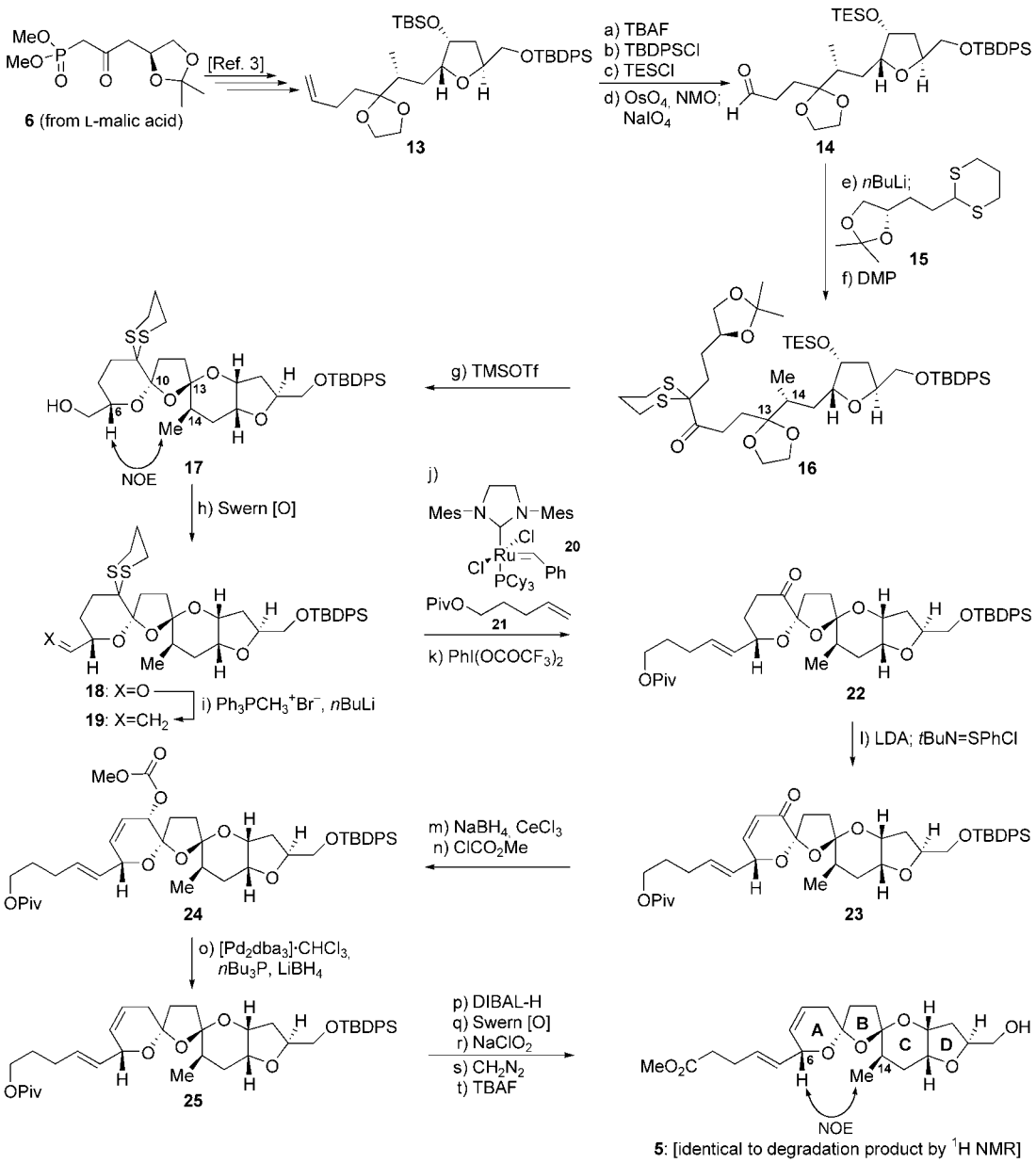
Scheme 1. On the way to proposed intermediate **4** (C14-*epi*): a) TMSOTf (4.0 equiv), CH_2Cl_2, −90 °C, 30 min, 89 %; b) PivCl (3.0 equiv), pyridine (10.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 0→25 °C, 12 h; 95 %; c) NBS (8.0 equiv), 2,6-lutidine (16 equiv), MeCN/H_2O (4:1), 25 °C, 1 h, 80 %; d) $NaBH_4$ (1.1 equiv), MeOH, −78→−60 °C, 3 h, 92 %; e) TFA (2.0 equiv), CH_2Cl_2, 0 °C, 1.5 h, 98 % (**12**/**11** ≈ 55:45). TMS = trimethylsilyl, Piv = trimethylacetyl, 4-DMAP = 4-(dimethylamino)pyridine, NBS = *N*-bromosuccinimide, TFA = trifluoroacetic acid.

under a palladium-catalyzed reductive protocol ([Pd_2dba_3]·$CHCl_3$, nBu_3P, $LiBH_4$, DME),[6] furnishing the desired $\Delta^{7,8}$ olefinic compound **25** as the predominant product (82 % yield, $\Delta^{7,8}/\Delta^{8,9} \approx 7{:}1$; the undesired $\Delta^{8,9}$ isomer was chromatographically removed at this stage). The key intermediate **5** was then generated from **25** in 71 % overall yield by a five-step sequence: 1) DIBAL-induced cleavage of the pivaloate group; 2) Swern oxidation of the resulting alcohol to the aldehyde; 3) further oxidation to the corresponding carboxylic acid; 4) methylation with diazomethane; and 5) desilylation with TBAF (Scheme 2). Synthetic **5** matched the degradatively derived material by ^{1}H NMR spectroscopy.[7] This was indeed a pleasing moment in the azaspiracid-1 campaign, although the minute supplies of the degradation product did not permit optical rotation comparisons, and, therefore, the absolute stereochemistry of **5** still remained elusive. This gap in our intelligence gathering dictated the synthesis of the other enantiomer of **25** as well (*ent*-**25**, see Scheme 3), a task that was easily accomplished starting from the enantiomer of **6** (prepared from D-malic acid, see Scheme 2) and proceeding in the manner described above for **25**.

Having secured adequate supplies of both enantiomers of **25** and being assured that one of them corresponded to the ABCD domain of our target natural product, we set out to reach the final target. The first enantiomer to reach the end was that derived from non-natural D-malic acid (i.e. *ent*-**25**), only to find that it did not correspond to azaspiracid-1. The final drive toward azaspiracid-1 from enantiomer **25** (derived from L-malic acid) was then undertaken in earnest, following the convergent strategy previously employed in these laboratories for the synthesis of the originally proposed structure (**1-i**).

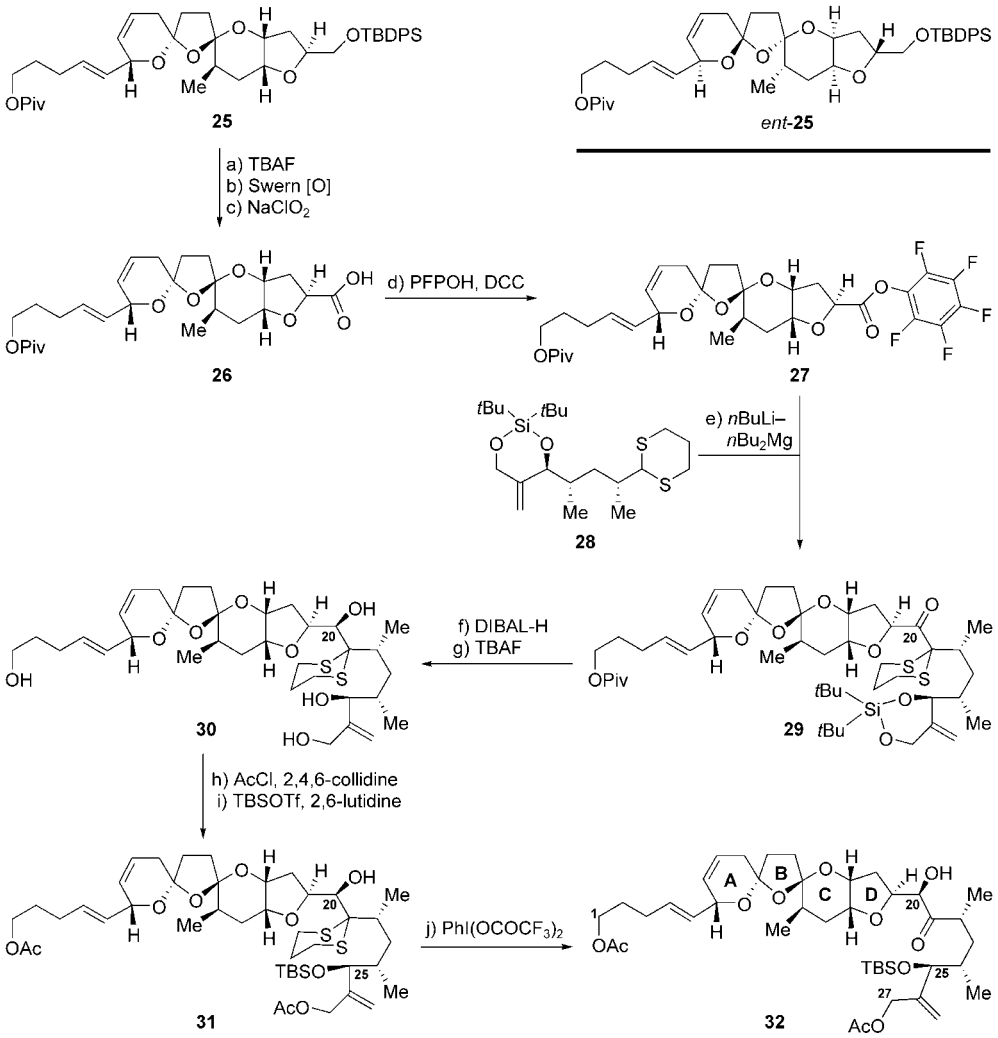
Owing to the problems that arose in the final deprotection step of our previous route[8] to azaspiracid-1, we opted to adopt a TBS protecting group for the hydroxy group of C25, as opposed to the originally employed acetate group. The new sequence toward advanced intermediate **32** (see Scheme 3), which was required for the planned palladium-catalyzed coupling reaction with the FHI segment, began with intermediate **25** and proceeded along the path delineated in Scheme 3. Thus, the TBDPS protecting group was removed from **25** by exposure to TBAF to reveal the primary alcohol (98 % yield), which was oxidized in a two-step procedure to carboxylic acid **26** in 90 % overall yield. Compound **26** was converted into its pentafluorophenyl ester **27** by DCC-facilitated coupling with pentafluorophenol in 84 % yield. The activated form of dithiane **28** (nBuLi–$n$$Bu_2Mg$) was then treated with **27** at −90 °C to generate the coupled product **29** in 50 % yield. A two-step sequence involving excess DIBAL-H followed by TBAF was then used to convert **29** into **30** in 44 % overall yield. The indicated stereochemistry at C20 was assigned to tetraol **30** by analogy to our previous results[8,9] in the synthesis of the originally proposed azaspiracid-1 structure. The activation–protection required for **30** prior to coupling with the FHI segment was introduced by selective acetylation of its primary hydroxy groups (90 % yield) and silylation of the C25-OH group (86 % yield) to afford intermediate **31**. Final unmasking of the keto group of **31** by treatment with $PhI(OCOCF_3)_2$ furnished the advanced C1–C27 fragment **32** (68 % yield) ready for further elaboration.

The second crucial coupling in the synthesis, that between the ABCD (C1–C27) and FHI (C28–C40) fragments **32** and **33**, was brought about by the action of [Pd_2dba_3] catalyst in the presence of LiCl, $AsPh_3$, and Et$Ni$$Pr_2$ and led to intermediate **34** (55 % yield), which contains all the carbon atoms required for azaspiracid-1, but lacks rings G and E (Scheme 4). Ring G was cast first through the intervention of TBAF to remove the TES group selectively followed by ring closure as induced by NIS and reductive removal of the residual iodine atom ($n$$Bu_3$SnH–$Et_3B$) to afford octacyclic compound **36** through intermediate iodide **35** in 43 % overall yield. The construction of ring E was left until last, and not before all the necessary functionality for the final target was in place. Thus, a TES group was called upon to temporarily



Scheme 2. Synthesis of key intermediate **5** and confirmation of the structure of the ABCD domain. Reagents and conditions: a) TBAF (1.0 M in THF, 3.0 equiv), THF, 25 °C, 48 h, 99%; b) TBDPSCl (1.2 equiv), Et_3N (3.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 0 °C, 12 h, 90%; c) TESCl (1.5 equiv), imidazole (3.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 0 °C, 30 min, 95%; d) OsO_4 (0.03 equiv), NMO (2.0 equiv), *t*BuOH/THF/H_2O (10:2:1), 25 °C, 12 h; then $NaIO_4$ (5.0 equiv), pH 7 buffer, 25 °C, 5 h, 95%; e) *n*BuLi (1.6 M in hexanes, 3.5 equiv), **15** (3.5 equiv), THF, −30 °C, 30 min, 98%; f) DMP (1.2 equiv), py (10.0 equiv), CH_2Cl_2, 0 °C, 1 h, 90%; g) TMSOTf (4.0 equiv), CH_2Cl_2, −90 °C, 30 min, 89%; h) $(COCl)_2$ (5.0 equiv), DMSO (11 equiv), CH_2Cl_2, −78→−60 °C, 1.5 h; then Et_3N (22 equiv), −25 °C; i) $Ph_3PCH_3^+Br^-$ (5.0 equiv), *n*BuLi (4.0 equiv), THF, −78→0 °C, 1 h; then −78 °C; then **18**, −78→0 °C, 30 min, 81% from **17**; j) **21** (3.0 equiv), **20** (0.1 equiv), CH_2Cl_2, 40 °C, 12 h, 60%, $E/Z \approx 10:1$; k) $PhI(OCOCF_3)_2$ (3.0 equiv, slow addition), MeCN/pH 7 buffer (4:1), 0 °C, 30 min, 90%; l) LDA (1.5 equiv), *t*BuN=SPhCl (1.5 equiv), THF, −78 °C, 10 min, 81%; m) $NaBH_4$ (3.1 equiv), $CeCl_3 \cdot 7H_2O$ (1.0 equiv), MeOH, −65 °C, 40 min, 80%; n) $ClCO_2Me$ (25 equiv), 4-DMAP (1.0 equiv) CH_2Cl_2:py (2:1), −10 °C, 3 h, 87%; o) $[Pd_2dba_3]\cdot CHCl_3$ (0.125 equiv), nBu_3P (0.48 equiv), $LiBH_4$ (10.0 equiv), DME, 0 °C, 1 h, 82%, $\Delta^{7,8}/\Delta^{8,9} = 7:1$; p) DIBAL-H (1.0 M in CH_2Cl_2, 2.0 equiv), CH_2Cl_2, −78 °C, 15 min; q) $(COCl)_2$ (5.0 equiv), DMSO (11 equiv), CH_2Cl_2, −78→−60 °C, 1.5 h; then Et_3N (22 equiv), −25 °C; r) $NaClO_2$ (10.0 equiv), NaH_2PO_4 (10.0 equiv), 2-methyl-2-butene (excess), *t*BuOH/H_2O (4:1), 25 °C, 1 h; s) CH_2N_2 (excess), Et_2O, 25 °C; t) TBAF (1.0 M in THF, 2.0 equiv), THF, 25 °C, 1 h, 71% from **25**. TBAF = tetra-*n*-butylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, TES = triethylsilyl, NMO = *N*-methylmorpholine *N*-oxide, DMP = Dess–Martin periodinane, Tf = trifluoromethanesulfonyl, DMSO = dimethyl sulfoxide, LDA = lithium diisopropylamide, dba = dibenzylideneacetone, DME = 1,2-dimethoxyethane, DIBAL-H = diisobutylaluminum hydride.

protect the C20-OH group of compound **36** (91% yield); removal of the acetate group from C1 with K_2CO_3 in MeOH furnished the corresponding primary alcohol (81% yield), which was sequentially oxidized, first to the aldehyde and then to the carboxylic acid, to afford the penultimate precursor, compound **37** (70% over two steps). Finally, all



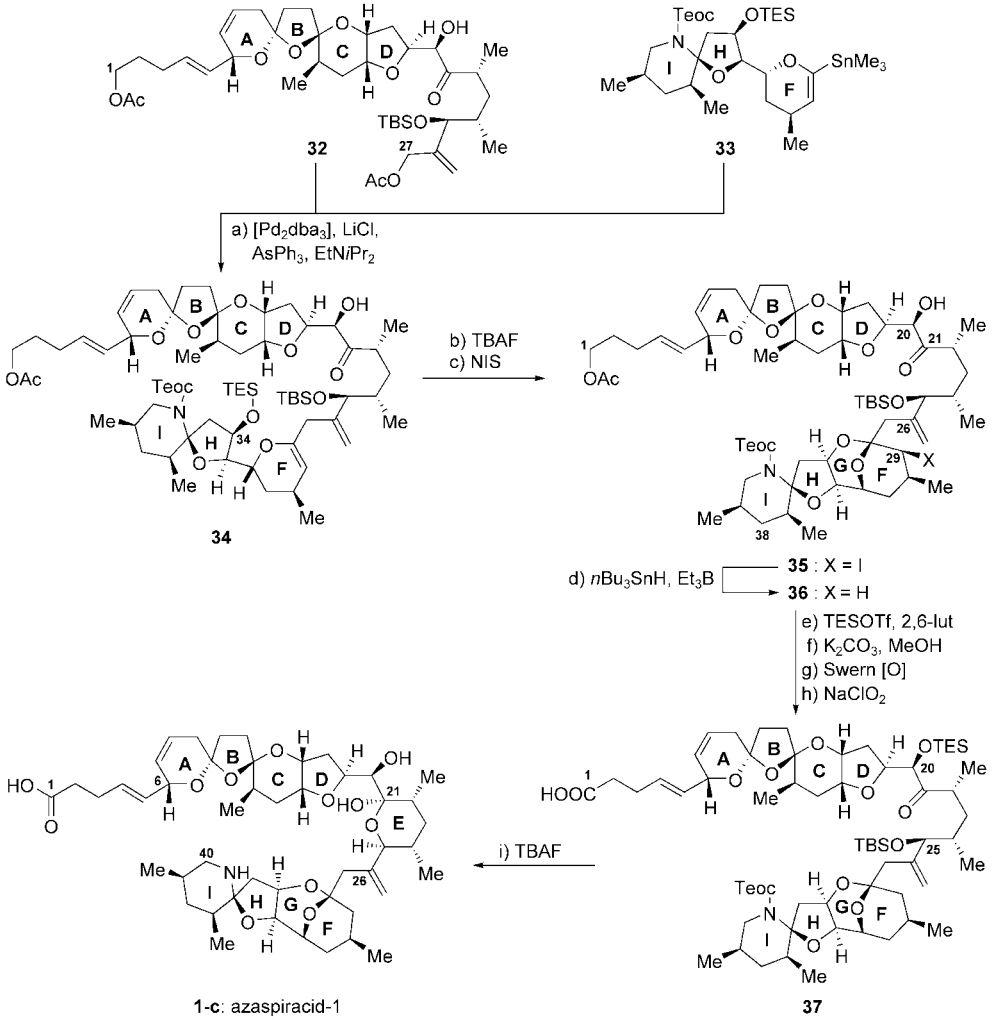
Scheme 3. Construction of key intermediate **32**. Reagents and conditions: a) TBAF (1.0 M in THF, 2.0 equiv), THF, 25 °C , 2 h, 98%; b) $(COCl)_2$ (5.0 equiv), DMSO (11 equiv), CH_2Cl_2, −78 °C, 30 min; then Et_3N (22 equiv), −78→0 °C; c) $NaClO_2$ (6.0 equiv), NaH_2PO_4 (6.0 equiv), 2-methyl-2-butene (excess), *t*BuOH/H_2O (4:1), 25 °C, 1 h, 90% over two steps; d) PFPOH (1.5 equiv), DCC (2.0 equiv), CH_2Cl_2, 25 °C, 2.0 h, 84%; e) **28** (7.0 equiv), *n*BuLi–nBu_2Mg (1.1 M in hexanes, 4.7 equiv), THF, 0→25 °C, 1.5 h; then −90 °C; then **27**, 30 min, 50%; f) DIBAL-H (1.0 M in CH_2Cl_2, 10.0 equiv), CH_2Cl_2, −90 °C, 1 h; g) TBAF (1.0 M in THF, 2.0 equiv), THF, 25 °C, 8 h, 44% over two steps; h) AcCl (20 equiv), 2,4,6-collidine (40 equiv), CH_2Cl_2, −78 °C, 6 h, 90%; i) TBSOTf (10.0 equiv), 2,6-lutidine (20 equiv), CH_2Cl_2, −78→0 °C, 30 min, 86%; j) $PhI(OCOCF_3)_2$ (2.0 equiv), MeCN/pH 7 buffer (4:1), 0 °C, 10 min, 68%. PFP = pentafluorophenyl, DCC = dicyclohexylcarbodiimide, TBS = *tert*-butyldimethylsilyl.

three remaining protecting groups on **37** (TES, TBS, and Teoc) were removed concurrently by exposure to excess TBAF in THF at ambient temperature to reveal the desired structure **1-c**, which was spontaneously formed upon collapse of the liberated C25-OH group onto the carbonyl functionality at C21 (Scheme 4). This time, the TLC profile of the synthetic material matched that of natural azaspiracid-1 obtained from the Yasumoto–Satake group.[7] More convincingly, and delightfully, all data (^{1}H NMR, ^{13}C NMR, MS, TLC, optical rotation) for the synthetic and natural samples of azaspiracid-1 were identical.[7]

Thus, the long-sought structural elucidation of azaspiracid-1, the notorious marine neurotoxin originally isolated from mussels (*Mytilus edulis*) collected in European waters, ended with its total synthesis, an accomplishment that also renders this valuable, but scarce, substance available for much-needed biological investigations. Among such investigations, those directed towards the development of assays for its detection and measurement in seafood and seawater and the elucidation of its mechanism of action must rank high on the list.

Experimental Section

5: $R_f = 0.24$ (silica gel, EtOAc/hexanes 2:1); $[\alpha]_D^{25} = -2.7$ ($CHCl_3$, $c = 0.45$); IR (film): $\tilde{\nu}_{max} = 3413, 2929, 2871, 1739, 1433\ cm^{-1}$; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.77$–5.69 (m, 2H), 5.63 (dt, $J = 10.5$, 1.0 Hz, 1H), 5.49 (dd, $J = 15.5$, 7.5 Hz, 1H), 4.80 (br s, 1H), 4.35 (ddt, $J = 6.0$, 5.5, 3.0 Hz, 1H), 4.22 (m, 1H), 3.90 (m, 1H), 3.73 (dd, $J = 7.0$, 3.0 Hz, 1H), 3.67 (s, 3H), 3.49 (dd, $J = 7.0$, 5.5 Hz, 1H), 2.51 (dm, $J = 17.5$ Hz, 1H), 2.44–2.37 (m, 3H), 2.30 (dt, $J = 12.0$, 7.5 Hz, 1H), 2.15 (dt, $J = 12.0$, 7.0 Hz, 1H), 2.13–2.04 (m, 2H), 2.02 (dt, $J = 13.0$, 7.5 Hz, 1H), 1.92 (dd, $J = 13.0$, 6.5 Hz, 1H), 1.71–1.89 (m, 4H), 1.67 (dd, $J = 12.5$, 7.0 Hz, 1H), 0.93 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.1, 131.1, 130.4, 128.1, 122.6, 110.0, 105.7, 79.0, 76.7,$



Scheme 4. Total synthesis of azaspiracid-1 (**1-c**). Reagents and conditions: a) **32**, $[Pd_2dba_3]$ (0.3 equiv), $AsPh_3$ (0.3 equiv), LiCl (6.0 equiv), $EtNiPr_2$ (12 equiv); then **33** (3.0 equiv, 0.03 M in THF, syringe pump addition), NMP, 40 °C, 1 h, 55%; b) TBAF (1.0 M in THF, 1.2 equiv), THF, 0 °C, 20 min, 80%; c) NIS (2.0 equiv), $NaHCO_3$ (10.0 equiv), THF, 0 °C, 12 h, 62%; d) Et_3B (1.0 M in hexanes, 0.2 equiv), nBu_3SnH/toluene (1:2), 0 °C, 5 min, 86%; e) TESOTf (10.0 equiv), 2,6-lutidine (20 equiv), CH_2Cl_2, −78→0 °C, 10 min, 91%; f) K_2CO_3 (2.0 equiv), MeOH, 25 °C, 1 h, 81%; g) $(COCl)_2$ (10.0 equiv), DMSO (20 equiv), CH_2Cl_2, −78 °C, 1 h; then Et_3N (50 equiv), −78→−20 °C, 30 min; h) $NaClO_2$ (10.0 equiv), NaH_2PO_4 (10.0 equiv), 2-methyl-2-butene (excess), *t*BuOH/H_2O (4:1), 25 °C, 30 min, 70% over two steps; i) TBAF (1.0 M in THF, 5.0 equiv), THF, 25 °C, 15 h, 60%. NIS = *N*-iodosuccinimide, Teoc = 2-(trimethylsilyl)ethoxycarbonyl, NMP = *N*-methylpyrrolidinone.

72.1, 70.8, 65.0, 51.6, 36.6, 35.3, 34.8, 33.4, 32.2, 31.4, 29.6, 27.6, 16.1 ppm; HRMS (MALDI): calcd for $C_{22}H_{32}O_7Na^+$ [M+Na^+]: 431.2040; found: 431.2047.

32: $R_f = 0.39$ (silica gel, EtOAc/hexanes 1:2); $[\alpha]_D^{25} = +11.25$ (CH_2Cl_2, $c = 2.40$); IR (film): $\tilde{\nu}_{max} = 3463, 2930, 2856, 1743, 1458, 1368, 1242, 1069, 1021, 987, 961, 839\ cm^{-1}$; ^1H NMR (500 MHz, CD_2Cl_2): $\delta = 5.74$ (m, 1H), 5.68 (dt, $J = 10.5$, 1.0 Hz, 1H), 5.63 (dt, $J = 10.5$, 1.0 Hz, 1H), 5.43 (ddt, $J = 15.5$, 7.0, 1.0 Hz, 1H), 5.16 (d, $J = 3.0$ Hz, 2H), 4.78 (br s, 1H), 4.57 (d, $J = 14.0$ Hz, 1H), 4.51 (d, $J = 14.0$ Hz, 1H), 4.38 (t, $J = 5.5$ Hz, 1H), 4.23 (dt, $J = 9.0$, 5.5 Hz, 1H), 4.17 (br s, 1H), 4.03 (t, $J = 6.5$ Hz, 2H), 3.98 (br s, 1H), 3.93 (d, $J = 5.5$ Hz, 1H), 3.35 (d, $J = 5.5$ Hz, 1H), 3.11 (ddq, $J = 17.5$, 7.5, 4.0 Hz, 1H), 2.47 (ddt $J = 17.5$, 4.5, 2.5 Hz, 1H), 2.25 (dt, $J = 12.0$, 7.5 Hz, 1H), 2.15–2.07 (m, 5H), 2.05 (s, 3H), 2.01 (s, 3H), 1.98–1.90 (m, 3H), 1.88–1.83 (m, 1H), 1.79 (dd, $J = 13.0$, 6.5 Hz, 1H), 1.75–1.67 (m, 3H), 1.62 (dd, $J = 12.0$, 7.0 Hz, 2H), 1.42 (br s, 1H), 1.10 (d, $J = 7.0$ Hz, 3H), 0.92 (s, 9H), 0.91 (d, $J = 7.0$ Hz, 3H), 0.87 (d, $J = 7.0$ Hz, 3H), 0.06 (s, 3H), −0.01 ppm (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2): $\delta = 215.2$, 171.2, 170.7, 145.6, 132.0, 130.6, 128.6, 122.9, 113.9, 110.3, 106.0, 79.3, 78.9, 77.7, 77.5, 72.1, 71.1, 64.1, 64.1, 40.9, 37.0, 35.9, 35.7, 35.1, 34.1, 32.6, 31.7, 29.9, 29.0, 28.4, 26.0, 21.1, 19.4, 19.4, 18.5, 17.0, 16.3, −4.5, −5.0 ppm; HRMS (ESI-TOF): calcd for $C_{41}H_{66}O_{11}SiNa^+$ [M+Na^+]: 785.4266; found: 785.4245.

36: $R_f = 0.33$ (silica gel, EtOAc/hexanes 1:3); $[\alpha]_D^{25} = +2.4$ (CH_2Cl_2, $c = 0.9$); IR (film): $\tilde{\nu}_{max} = 3437, 2956, 2927, 2851, 1741, 1700, 1654, 1560, 1508, 1458, 1249, 1057, 837\ cm^{-1}$; ^1H NMR (600 MHz, CD_2Cl_2): $\delta = 5.75$–5.73 (m, 1H), 5.71–5.63 (m, 2H), 5.43 (dd, $J = 15.3$, 7.4 Hz, 1H), 5.18 (br s, 1H), 4.96 (br s, 1H), 4.79 (br s, 1H), 4.72 (m, 1H), 4.37–4.32 (m, 2H), 4.24 (d, $J = 4.9$ Hz, 1H), 4.20 (br s, 1H), 4.18–4.15 (m, 2H), 4.03 (t, $J = 6.6$ Hz, 2H), 4.02 (m, 1H), 3.92 (br s, 1H), 3.74 (br s, 1H), 3.73 (d, $J = 4.4$ Hz, 1H), 3.66 (d, $J = 14.0$ Hz, 1H), 3.20 (t, $J = 12.5$ Hz, 1H), 2.94–2.91 (m, 1H), 2.54–2.50 (m, 1H), 2.46 (m, 1H), 2.25 (dt, $J = 12.5$, 7.9, 1H), 2.15–2.08 (m, 7H), 2.01 (s, 3H), 1.99–1.95 (m, 2H), 1.94–1.92 (m, 1H), 1.90 (dd, $J = 8.8$, 4.8 Hz, 1H), 1.84 (m, 2H), 1.75–1.68 (m, 4H), 1.67–1.57 (m, 6H), 1.51 (q, $J = 13.2$ Hz, 2H), 1.40 (dt, $J = 13.6$, 5.2 Hz, 1H), 1.31 (q, $J = 12.2$ Hz, 2H), 1.04 (d, $J = 7.0$ Hz, 3H), 1.03–0.99 (m, 2H), 0.97 (d, $J = 7.0$ Hz, 3H), 0.92 (s, 9H), 0.91 (d, $J = 7.0$ Hz, 3H), 0.88 (d, $J = 6.1$ Hz, 3H), 0.82 (d, $J = 6.6$ Hz, 3H), 0.81 (d, $J = 6.1$ Hz, 3H), 0.04 (s, 9H), 0.03 (s, 3H), 0.00 ppm (s, 3H); ^{13}C NMR (125 MHz, CD_3OD):

δ = 215.3, 171.2, 156.3, 146.9, 132.0, 130.7, 128.6, 122.9, 114.5, 110.3, 106.0, 97.4, 96.9, 79.1, 78.8, 78.5, 78.0, 77.6, 74.0, 72.4, 71.3, 71.1, 64.2, 63.2, 49.1, 45.8, 40.8, 40.0, 39.5, 37.0, 35.1, 34.9, 34.8, 33.6, 32.6, 31.7, 31.7, 30.1, 29.9, 29.0, 28.4, 26.2, 26.1, 24.9, 23.2, 21.1, 19.7, 18.9, 18.6, 18.5, 18.2, 18.2, 16.7, 16.3, −1.4, −3.8, −4.9 ppm; HRMS (ESI-TOF): calcd for $C_{61}H_{101}NO_{14}Si_2Na^+$ [M+Na^+]: 1150.6652; found: 1150.6662.

37: R_f = 0.2 (silica gel, EtOAc:hexanes 2:1); $[\alpha]_D^{25} = -6.2$ (CH_3OH, c = 0.13); IR (film): $\tilde{\nu}_{max}$ = 3383, 2955, 2921, 2874, 1698, 1674, 1568, 1555, 1411, 1252, 1170, 1259, 837 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ = 5.76–5.70 (m, 2H), 5.62 (d, J = 10.5 Hz, 1H), 5.42 (dd, J = 15.5, 7.5 Hz, 1H), 5.21 (br s, 1H), 4.96 (br s, 1H), 4.79–4.77 (m, 2H), 4.59 (d, J = 3.0 Hz, 1H), 4.49–4.45 (m, 1H), 4.29 (br s, 1H), 4.23 (d, J = 6.0 Hz, 1H), 4.20 (dd, J = 10.5, 6.5 Hz, 1H), 4.16–4.15 (m, 1H), 4.10–4.04 (m, 1H), 3.88 (br s, 1H), 3.80 (d, J = 4.0 Hz, 1H), 3.79–3.77 (m, 1H), 3.71 (d, J = 13.0 Hz, 1H), 3.26 (d, J = 13.0 Hz, 1H), 2.79 (q, J = 7.0 Hz, 1H), 2.45 (m, 1H), 2.34–2.26 (m, 3H), 2.24–2.22 (m, 4H), 2.15–2.10 (m, 3H), 2.08–2.05 (m, 1H), 2.03–1.96 (m, 2H), 1.92 (dd, J = 12.1, 7.7 Hz, 1H), 1.86–1.83 (m, 1H), 1.82–1.78 (m, 1H), 1.76–1.69 (m, 3H), 1.68–1.63 (m, 2H), 1.62–1.52 (m, 3H), 1.44–1.34 (m, 2H), 1.33–1.28 (m, 4H), 1.05 (d, J = 6.6 Hz, 3H), 1.03 (ddd, J = 9.9, 6.2, 3.0 Hz, 2H), 0.99 (d, J = 7.0 Hz, 3H), 0.96 (t, J = 8.0 Hz, 9H), 0.94 (s, 9H), 0.93 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 6.2 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 5.9 Hz, 3H), 0.62 (q, J = 8.0 Hz, 6H), 0.06 (s, 9H), 0.05 (s, 3H), 0.02 ppm (s, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ = 215.6, 181.9, 157.6, 148.2, 133.9, 130.6, 129.4, 123.3, 115.3, 111.2, 107.1, 98.4, 97.8, 80.5, 80.2, 79.6, 78.8, 75.0, 73.4, 72.6, 72.1, 64.1, 50.0, 49.9, 47.0, 42.5, 41.7, 40.3, 38.7, 37.9, 37.6, 35.8, 35.4, 34.6, 34.5, 33.2, 32.9, 32.8, 32.5, 30.82, 30.78, 30.75, 30.5, 26.7, 25.8, 23.6, 20.9, 19.2, 19.1, 18.5, 16.8, 16.6, 7.2, 5.8, −1.3, −3.4, −4.7 ppm; HRMS (ESI-TOF): calcd for $C_{65}H_{111}NO_{14}Na^+$ [M+Na^+]: 1236.7204; found: 1236.7189.

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