Synthesis of the ABCD Ring System of Azaspiracid**

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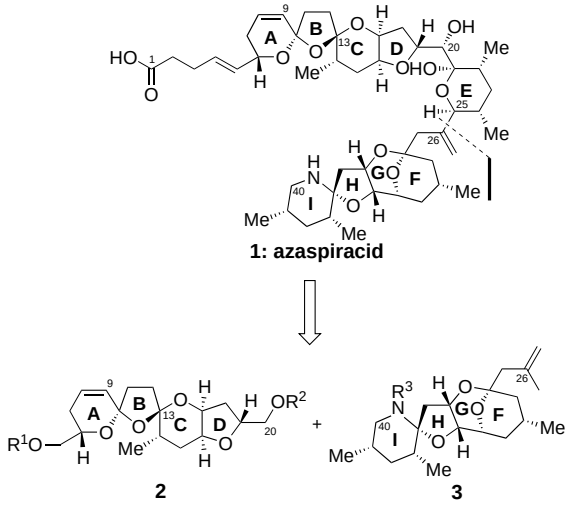
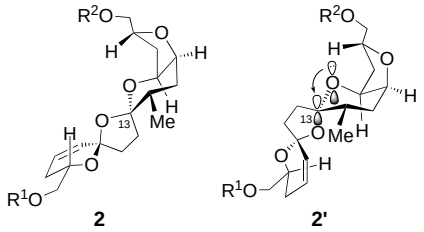
Azaspiracid (**1**, Scheme 1) is a marine biotoxin[1] whose structure and damaging effects on the environment and humans have recently stimulated considerable synthetic activities.[2] Justification of endeavors directed towards its total synthesis has been given elsewhere in a report that also included the construction of the FGHI ring system of this molecule.[3] Here we report the synthesis of the ABCD ring framework of azaspiracid (**1**) by a special strategy requiring a hydrogen bonding auxiliary group to establish the proper configuration of one of the spirocenters (C13).



Scheme 1. Structure of azaspiracid (**1**) and retrosynthetic analysis leading to the ABCD and FGHI fragments **2** and **3**.

According to our previously articulated retrosynthetic analysis,[3] azaspiracid (**1**) is disconnected by rupturing the C25–C26 bond leading to the ABCD and FGHI domains **2** and **3** as shown in Scheme 1. Considering that neither the absolute stereochemistry of **1** nor the relative stereochemistry of the two domains of this compound are known, we decided arbitrarily to develop routes to these systems which could be adaptable to either enantiomer. At the onset, it was clear that the anomeric effects[4] within structure **2** will favor the undesired 13*S* configuration, thus providing a thorny challenge regarding this stereochemical problem (see Scheme 2).



Scheme 2. Conformational arrangements of the ABCD ring system of azaspiracid (**2**, 13*R*, desired) and its C13 epimer (**2′**, 13*S*, undesired, favored by anomeric effect).

Indeed, a recent report[2d] by the Forsyth group in which an attempted spirocyclization of an open-chain precursor led exclusively to the unwanted C13 diastereomer whose epimerization to the correct C13 stereoisomer proved impossible, confirmed these suspicions.

Our approach to addressing this problem invoked the use of a stereocontrolling group at C9 capable of driving the spirocyclization reaction toward the desired 13*R* configuration through favorable intramolecular interactions. The first attempt to solve this problem was inspired by the work of Williams and co-workers who utilized an optically active sulfoxide as an auxiliary group to construct spiroketals.[5] The hypothesis to be tested was that a tolyl sulfoxide (ArSO) group installed at C9 might be influential in controlling the C13 stereochemistry at the spirocyclization step (see Scheme 4, **21** → **22**). Scheme 3 summarizes the synthesis of the first required building block for the projected synthesis of the ABCD ring system according to this plan. Thus, methyl ester **4**[6] reacted with the lithium anion of dimethyl methylphosphonate to furnish β-ketophosphonate **5** in 84% yield. Treatment of **5** with LiCl and $i\mathrm{Pr}_2\mathrm{NEt}$[7] followed by addition of aldehyde **6**[8] led to enone **7** in 86% yield. Chelation-controlled 1,2-reduction of **7** using Mori's method[9] (LiAlH_4, LiI, $-100\,^{\circ}\mathrm{C}$) afforded allylic alcohol **8** in 98% yield accompanied by only traces of the undesired epimeric alcohol. Acid-catalyzed removal of the acetonide group from **8** gave triol **9** in 97% yield which set the stage for the cyclization to ring D. To this end, **9** was exposed to NIS in the presence of NaHCO_3 to yield tetrahydrofuran derivative **10** in 70% yield with the desired 2,5-*trans* stereochemistry.[10] Selective protection of the primary hydroxy group in **10** was then accomplished by the use of TBDPSCl/Et_3N/4-DMAP (90%), and this was followed by protection of the secondary hydroxy group with TBSOTf/2,6-lutidine (100%) to furnish compound **12** via **11**. Reductive cleavage of the C–I bond in **12** with a suspension of Raney Ni in ethanol under a hydrogen

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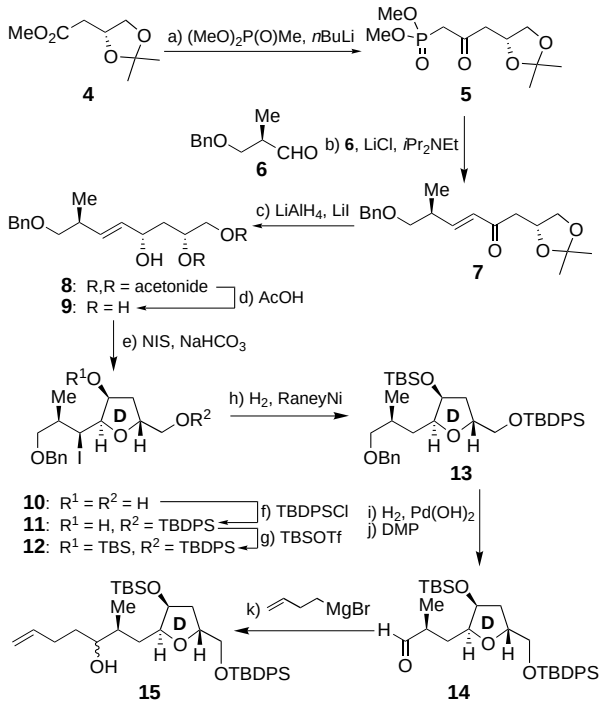
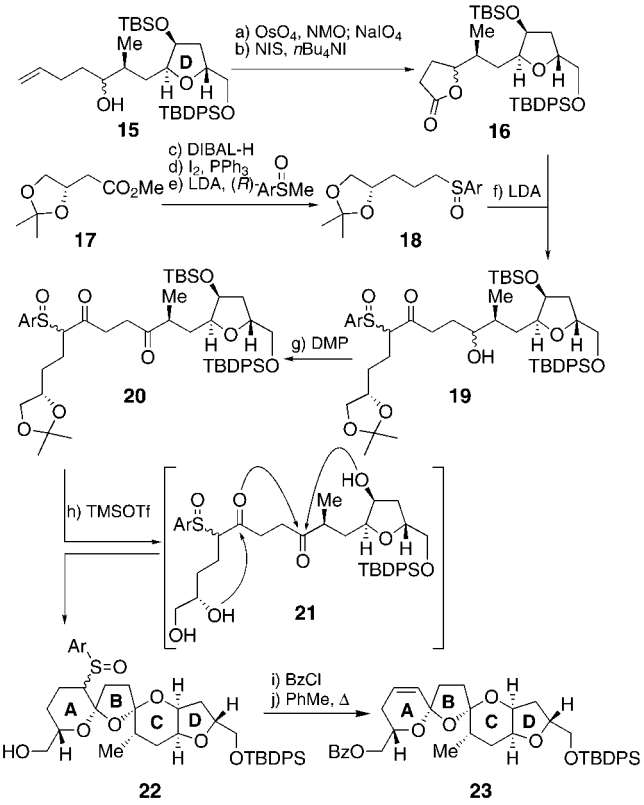


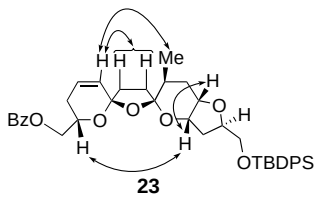
Scheme 3. Construction of key intermediate **15**: a) $(MeO)_2P(O)Me$ (2.2 equiv), *n*BuLi (1.6 M in hexanes, 2.2 equiv), THF, $-78\,^{\circ}C$, 1 h, 84%; b) **6** (0.67 equiv), LiCl (1.3 equiv), iPr_2NEt (1.0 equiv), CH_3CN, $25\,^{\circ}C$, 12 h, 86% based on **6**; c) $LiAlH_4$ (10.0 equiv), LiI (8.0 equiv), Et_2O, $-100\,^{\circ}C$, 30 min, 98%; d) $AcOH/H_2O$ (2:1), $25\,^{\circ}C$, 5 h, 97%; e) NIS (5.0 equiv), $NaHCO_3$ (10.0 equiv), THF, $0\,^{\circ}C$, 2.5 h, 70%; f) TBDPSCl (1.4 equiv), Et_3N (3.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, $-10\rightarrow0\,^{\circ}C$, 3 h, 90%; g) TBSOTf (1.6 equiv), 2,6-lutidine (4.0 equiv), CH_2Cl_2, $-10\,^{\circ}C$, 30 min, 100%; h) H_2, Raney Ni (100 equiv), EtOH, $25\,^{\circ}C$, 1 h, 99%; i) H_2, $Pd(OH)_2/C$ (10% by weight, 0.1 equiv), EtOH, $25\,^{\circ}C$, 3 h, 88%; j) DMP (2.0 equiv), CH_2Cl_2, $25\,^{\circ}C$, 2 h, 99%; k) 3-butenylmagnesium bromide (6.0 equiv), THF, $-78\rightarrow-10\,^{\circ}C$, 3 h, 87%. NIS = *N*-iodosuccinimide, TBDPS = *tert*-butyldiphenylsilyl, 4-DMAP = 4-(dimethylamino)pyridine, TBS = *tert*-butyldimethylsilyl, OTf = trifluoromethanesulfonate, DMP = Dess Martin periodinane.



Scheme 4. Preparation of the C13-epimeric ABCD ring system (**23**; for selected physical data, see Table 1) by the sulfoxide method: a) OsO_4 (0.03 equiv), NMO (2.0 equiv), *t*BuOH/THF/H_2O (10:2:1), $25\,^{\circ}C$, 12 h; then $NaIO_4$ (5.0 equiv), pH 7 buffer, $25\,^{\circ}C$, 5 h, 96%; b) NIS (5.0 equiv), nBu_4NI (2.0 equiv), CH_2Cl_2, $25\,^{\circ}C$, 1 h, 98%; c) DIBAL-H (1.0 M in CH_2Cl_2, 2.5 equiv), THF, $-78\rightarrow25\,^{\circ}C$, 1 h; d) I_2 (1.5 equiv), PPh_3 (1.5 equiv), imidazole (1.5 equiv), Et_2O, $25\,^{\circ}C$, 1 h, 99% over two steps; e) LDA (1.0 equiv), (*R*)-(+)-methyl-*para*-tolylsulfoxide (1.0 equiv), THF, $-78\,^{\circ}C$, 30 min, 83%; f) LDA (1.0 equiv), **16** (1.5 equiv), THF, $-78\,^{\circ}C$, 15 min, 87%; g) DMP (3.0 equiv), CH_2Cl_2, $25\,^{\circ}C$, 2 h, 92%; h) TMSOTf (3.0 equiv), CH_2Cl_2, $-78\,^{\circ}C$, 1 h; then $0\,^{\circ}C$, 10 min, 62%; i) BzCl (4.0 equiv), py (100 equiv), CH_2Cl_2, $25\,^{\circ}C$, 12 h, 96%; j) $P(OMe)_3$ (6.0 equiv), toluene, reflux, 45%. NMO = *N*-methylmorpholine *N*-oxide, DIBAL-H = diisobutylaluminum hydride, Ar = *para*-tolyl, LDA = lithium diisopropylamide, TMS = trimethylsilyl, Bz = benzoyl, py = pyridine.

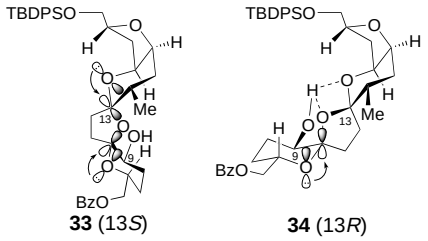
atmosphere produced compound **13** in 99% yield, while hydrogenolysis of the benzyl ether from the latter compound was facilitated by catalytic amounts of palladium hydroxide and hydrogen in ethanol (88%). The resulting primary alcohol was then oxidized with DMP leading to aldehyde **14** in 99% yield. Finally, treatment of **14** with excess 3-butenylmagnesium bromide afforded hydroxy olefin **15** in 87% yield as a mixture of diastereomers (ca. 1:1).

Scheme 4 summarizes the final drive toward the goal of this approach. Thus, dihydroxylation of the terminal olefin of **15** (NMO, cat. OsO_4) followed by cleavage of the resulting 1,2-diol ($NaIO_4$) gave the corresponding aldehyde–lactol mixture (96% overall yield) which was oxidized (NIS/nBu_4NI)[11] to afford the γ-lactone **16** in 98% yield (ca. 1:1 ratio of diastereomers). The fragment corresponding to azaspiracid's A ring was then introduced by using intermediate **18**, which also carried the required aryl sulfoxide moiety. This compound was constructed from **17** (*S* configuration)[6] by DIBAL-H reduction, iodination of the resulting alcohol (Ph_3P/I_2, 99% overall yield), and coupling of the iodide with the lithium derivative (LDA) of (*R*)-(+)-methyl-*p*-tolyl sulfoxide (83% yield). Generation of the anion from sulfoxide **18** with LDA followed by addition of lactone **16** gave coupling product **19** as a mixture of four diastereomers (ca. 1:1:1:1 ratio) and in 87% yield. Oxidation of the secondary hydroxy group in **19** with DMP furnished the coveted cyclization precursor, diketone **20**, in 92% yield (mixture of two diastereomers, ca. 1:1 ratio). Exposure of **20** to TMSOTf[12] removed the acetonide and TBS groups, presumably forming intermediate **21** whose anticipated cascade cyclization to a tetracyclic system (**22**) was concomitantly realized under the reaction conditions (62% overall yield). Determination of the C13 stereochemistry of the obtained ABCD ring system was postponed until further elaboration. Thus, benzoylation of the free hydroxy group in **22** (BzCl, py) furnished the corresponding benzoate in 96%



Scheme 5. Selected NOE enhancements observed for compound **23**.

yield (mixture of two sulfoxide diastereomers, ca. 1:1 ratio). Heating this sulfoxide mixture in refluxing toluene resulted in the formation of olefin **23** (45% yield) plus recovery of the equatorial sulfoxide (ca. 45%) which requires higher temperatures (refluxing xylenes) to eliminate and give the same olefin **23**. The spiroketal **23** was obtained as a single diastereomer; but, unfortunately, NMR analysis revealed (see Scheme 5 for NOEs) its incorrect stereochemistry at C13.

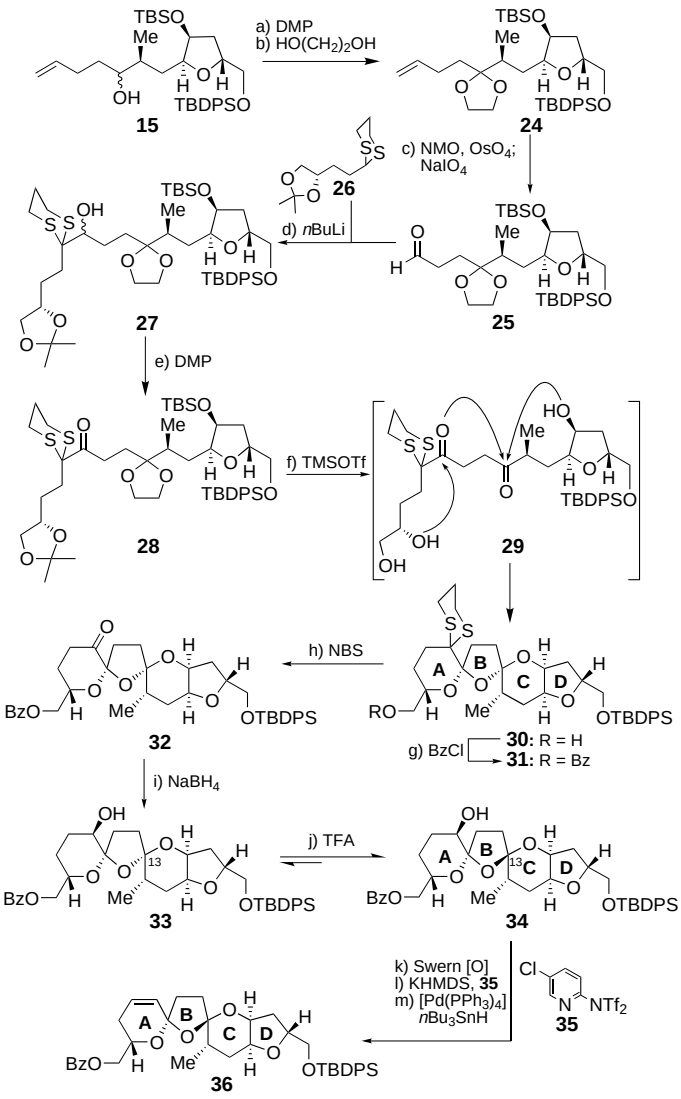


Scheme 6. Hydrogen bonding and anomeric effects in spiroketals **33** (13*S*, undesired) and **34** (13*R*, desired, favored by hydrogen bonding). For selected physical data of compounds **33** and **34**, see Table 1.

Apparently, the bulky tolyl sulfoxide group at C9 failed to overcome the anomeric effects forcing this spiroketal into the undesired configuration during the cyclization step (**20** → **21** → **22**). Furthermore, exposure of **23** to acid catalysis failed to change its stereochemistry, forcing us to seek an alternative approach to the desired 13*R* spiroketal fragment.

Based on a previous report,[13, 14] it was reasoned that an equatorial free hydroxy group at C9 might be capable, by virtue of its hydrogen bonding ability, to invert the 13*S* configuration of the double spiroketal system of the ABCD azaspiracid system to its natural 13*R* form. The rationale for this hypothesis is shown graphically in Scheme 6 which depicts both the desired (13*R*) and the undesired (13*S*) stereoisomers of the targeted ABCD ring framework. Armed with this argument, a new sequence for this compound was devised and followed as shown in Scheme 7. Thus, DMP oxidation of alcohol **15** followed by ketalization furnished ethylene ketal **24** in 93% overall yield. A two-step oxidative cleavage of the terminal olefin within **24** as described above led quantitatively to aldehyde **25** which was coupled with the anion derived from dithiane **26**[15] and *n*BuLi, to afford a diastereomeric mixture (ca. 1:1) of alcohols (**27**) in 87% yield. DMP oxidation of **27** led to ketone **28** (88% yield) whose cascade deprotection–cyclization reaction was induced by TMSOTf as described above for **20**, affording the double spiroketal **30** (85% yield), presumably via open chain precursor **29**. Benzoylation of **30** as before furnished benzoate **31** (93% yield), while exposure of the latter derivative (**31**) to NBS/2,6-lutidine in aqueous acetonitrile removed the dithiane group, leading to ketone **32** in 91% yield. Diastereoselective reduction of **32** with sodium borohydride in methanol furnished alcohol **33** (92% yield) in which the hydroxy group was found to reside in the desired equatorial position.

With tetracycle **33** at hand, we were now ready to attempt the crucial epimerization at C13 via acid catalysis. Gratifyingly, when **33** was exposed to TFA in CH_2Cl_2 at ambient temperature, an equilibrium mixture was soon reached from



Scheme 7. Synthesis of the ABCD ring system (**36**) of azaspiracid by the hydroxy auxiliary method: a) DMP (2.0 equiv), CH_2Cl_2, 25 °C, 3 h, 95%; b) $HO(CH_2)_2OH$ (7.0 equiv), triethyl orthoformate (3.0 equiv), *p*TsOH (cat.), 55 °C, 98%; c) OsO_4 (0.03 equiv), NMO (2.0 equiv), *t*BuOH/THF/H_2O (10:2:1), 25 °C, 14 h, then $NaIO_4$ (5.0 equiv), pH 7 buffer, 25 °C, 5 h, 100%; d) *n*BuLi (1.6 M in hexanes, 2.6 equiv), **26** (2.6 equiv), THF, −20 °C, 40 min, 87%; e) DMP (2.0 equiv), CH_2Cl_2, 25 °C, 1 h, 88%; f) TMSOTf (3.0 equiv), CH_2Cl_2, −78 → −30 °C, 1 h, 85%; g) BzCl (4.0 equiv), py, 25 °C, 2 h, 93%; h) NBS (8.0 equiv), 2,6-lutidine (16.0 equiv), aqueous CH_3CN, 25 °C, 2 h, 91%; i) $NaBH_4$ (1.0 equiv), MeOH, −5 °C, 5 min, 92%; j) TFA (3.0 equiv), CH_2Cl_2, 25 °C, 4 h, 56%; k) DMSO (20 equiv), $(COCl)_2$ (10 equiv), Et_3N (50 equiv), CH_2Cl_2, −78 °C, 1 h, 80%; l) **35** (10 equiv), KHMDS (0.5 M in toluene, 9.0 equiv), THF, −78 °C, 45 min, 83%; m) $[Pd(PPh_3)_4]$ (0.2 equiv), nBu_3SnH (10 equiv), THF, 25 °C, 45 min, 90%. *p*TsOH = *para*-toluene sulfonic acid, NBS = *N*-bromosuccinimide, DMSO = dimethylsulfoxide, KHMDS = potassium bis(trimethylsilyl)-amide.

which a 56% yield of a new compound (**34**, less polar on silica gel, hexanes/ethyl acetate 5:1) was isolated in addition to starting material (**33**, 44%). Recycling the starting material (**33**) twice raised the yield of **34** to 80%, making this step a practical method for obtaining the new isomer **34**. Even more delightful was the confirmation of the correct 13*R* configurations of **34** by NMR spectroscopy as shown by NOEs (see Scheme 8). Evident from these studies was also the stereo-

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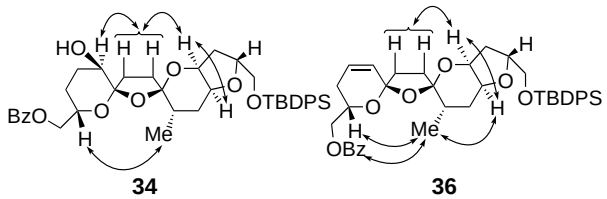
Table 1. Selected physical data for compounds **23**, **33**, **34**, and **36**.

23: Colorless oil; $R_f = 0.64$ (silica gel, hexanes/ethyl acetate, 2:1); $[\alpha]_D^{20} = -31.7$ ($CHCl_3$, $c = 0.30$); IR (film): $\tilde{\nu}_{max} = 2928$, 1724, 1462, 1378, 1272, 1113, 1070, 1032, 990, 710 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 8.07$ (br d, $J = 7.2$ Hz, 2H), 7.66 (m, 4H), 7.47 (t, $J = 7.2$ Hz, 1H), 7.43 – 7.35 (m, 8H), 5.97 (ddd, $J = 10.1$, 5.7, 1.3 Hz, 1H), 5.65 (d, $J = 10.1$ Hz, 1H), 4.39 (m, 3H), 4.30 (m, 2H), 3.84 (d, $J = 1.7$ Hz, 1H), 3.64 and 3.60 (dd-like AB system, $J = 10.6$, 4.8/3.9 Hz, 2H), 2.25 (m, 1H), 2.10 (m, 3H), 2.06 (m, 1H), 1.99 (m, 1H), 1.93 – 1.70 (m, 5H), 1.03 (s, 9H), 0.86 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.6$, 135.6, 133.6, 133.0, 130.1, 129.7, 129.6, 128.7, 128.4, 127.6, 126.5, 109.4, 104.9, 78.5, 76.5, 73.3, 67.5, 67.1, 66.3, 37.3, 35.9, 34.9, 31.1, 29.7, 26.8, 26.5, 19.3, 15.8; HRMS (MALDI): calcd for $C_{40}H_{48}O_7SiNa^+$ [M+Na^+]: 691.3061, found: 691.3044

33: Colorless oil; $R_f = 0.27$ (silica gel, hexanes/ethyl acetate, 2:1); $[\alpha]_D^{20} = -2.8$ ($CHCl_3$, $c = 0.68$); IR (film): $\tilde{\nu}_{max} = 3483$, 2929, 2856, 1722, 1453, 1273, 1112, 1070, 1028, 867, 710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.16$ (br d, $J = 8.4$ Hz, 2H), 7.77 – 7.71 (m, 4H), 7.59 – 7.54 (m, 1H), 7.52 – 7.42 (m, 8H), 4.43 (dd, $J = 11.0$, 3.7 Hz, 1H), 4.32 (d, $J = 11.0$ Hz, 1H), 4.39 – 4.25 (m, 3H), 4.01 – 3.98 (m, 1H), 3.74 and 3.68 (dd-like AB system, $J = 10.6$, 4.8/3.7 Hz, 2H), 3.62 (br dd, $J = 11.4$, 5.0 Hz, 1H), 2.38 – 2.31 (m, 1H), 2.27 – 2.04 (m, 5H), 1.99 (ddd, $J = 13.9$, 4.0, 2.2 Hz, 1H), 1.94 – 1.75 (m, 5H), 1.68 – 1.57 (m, 1H), 1.53 (d, $J = 11.4$ Hz, 1H), 1.12 (s, 9H), 1.02 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 166.5$, 135.60, 135.58, 133.6, 133.0, 130.1, 129.7, 129.6, 129.5, 128.3, 127.6, 110.1, 108.4, 78.6, 76.3, 73.6, 71.4, 69.5, 67.1, 66.2, 36.0, 34.7, 34.3, 31.3, 30.8, 29.1, 27.4, 26.8, 19.3, 16.6; HRMS (MALDI): calcd for $C_{40}H_{50}O_8SiNa^+$ [M+Na^+]: 709.3167, found: 709.3183

34: Colorless oil; $R_f = 0.39$ (silica gel, hexanes/ethyl acetate, 2:1); $[\alpha]_D^{20} = +13.9$ ($CHCl_3$, $c = 1.24$); IR (film): $\tilde{\nu}_{max} = 3507$, 2931, 1722, 1454, 1428, 1273, 1111, 997, 710 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 8.11$ (br d, $J = 8.4$ Hz, 2H), 7.78 – 7.71 (m, 4H), 7.66 – 7.61 (m, 1H), 7.53 – 7.43 (m, 8H), 4.53 – 4.46 (m, 1H), 4.36 (dd, $J = 11.0$, 3.3 Hz, 1H), 4.32 (d, $J = 11.0$ Hz, 1H), 4.33 – 4.26 (m, 1H), 4.26 – 4.22 (m, 1H), 3.98 – 3.94 (m, 1H), 3.86 and 3.72 (dd-like AB system, $J = 10.6$, 4.0/3.7 Hz, 2H), 3.61 – 3.52 (m, 1H), 3.01 (d, $J = 10.3$ Hz, 1H), 2.61 – 2.52 (m, 1H), 2.37 – 2.27 (m, 1H), 2.23 (ddd, $J = 13.2$, 9.2, 4.4 Hz, 1H), 2.17 (ddd, $J = 14.7$, 2.9, 2.9 Hz, 1H), 2.14 – 2.06 (m, 2H), 2.04 – 1.88 (m, 3H), 1.86 – 1.77 (m, 2H), 1.70 – 1.56 (m, 1H), 1.50 (ddd, $J = 14.7$, 13.2, 3.3 Hz, 1H), 1.12 (s, 9H), 0.99 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 166.4$, 135.60, 135.59, 133.5, 132.9, 130.1, 129.63, 129.60, 128.25, 127.64, 111.8, 108.7, 78.6, 76.6, 75.9, 68.9, 68.2, 67.2, 66.0, 36.1, 33.7, 31.2, 30.3, 29.7, 28.9, 26.9, 26.8, 19.3, 15.6; HRMS (MALDI): calcd for $C_{40}H_{50}O_8SiNa^+$ [M+Na^+]: 709.3167, found: 709.3191

36: Colorless oil; $R_f = 0.54$ (silica gel, hexanes/ethyl acetate, 2:1); $[\alpha]_D^{20} = -17.0$ ($CHCl_3$, $c = 0.50$); IR (film): $\tilde{\nu}_{max} = 2926$, 1723, 1454, 1379, 1272, 1112, 988, 824, 743, 710 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 8.04$ (d, $J = 7.5$ Hz, 2H), 7.67 (m, 4H), 7.56 (t, $J = 7.4$ Hz, 1H), 7.45 – 7.35 (m, 8H), 6.00 (ddd, $J = 10.1$, 5.7, 1.7 Hz, 1H), 5.75 (dd, $J = 10.1$, 1.3 Hz, 1H), 4.47 (m, 1H), 4.39 (m, 1H), 4.36 (m, 2H), 4.17 (m, 1H), 3.87 (d, $J = 2.2$ Hz, 1H), 3.76 and 3.64 (dd-like AB system, $J = 10.9$, 4.2/3.5 Hz, 2H), 2.22 (m, 1H), 2.17 – 1.98 (m, 9H), 1.42 (m, 1H), 1.03 (s, 9H), 0.88 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 166.5$, 135.60, 135.58, 133.6, 133.0, 130.0, 129.7, 129.6, 129.5, 128.2, 127.6, 127.3, 111.7, 104.0, 78.6, 76.5, 76.0, 67.0, 66.7, 66.2, 36.2, 35.8, 33.9, 30.8, 29.7, 26.8, 26.4, 19.3, 15.8; HRMS (MALDI): calcd for $C_{40}H_{48}O_7SiNa^+$ [M+Na^+]: 691.3061, found: 691.3062



Scheme 8. Selected NOE enhancements observed for compounds **34** and **36** (hydrogen bonding not shown). For selected physical data of comounds **34** and **36**, see Table 1.

chemical integrity of the epimerizable C14 methyl group in these systems. Having established the correct stereochemistry of the ABCD ring system, the facilitating (but superfluous) hydroxy group had to be excised, a task assumed to require nonacidic conditions for stereochemical safety purposes. This goal was accomplished by oxidation [$(COCl)_2$, DMSO, Et_3N, 80% yield], enol triflate formation (KHMDS, triflimide **35**, 83% yield) and reduction ($n$$Bu_3SnH$, cat. [$Pd(PPh_3)_4$], 90% yield) to furnish the desired ABCD azaspiracid fragment **36**. The structural assignment of this final product was also confirmed by observing the expected NOEs (see Scheme 8). The described chemistry provides a solution to one of the main obstacles remaining in the total synthesis of azaspiracid (**1**) and, as such, opens the way for the final drive toward this novel natural product.

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[15] Compound **26** was prepared from acetonide methyl ester **17** and 1,3-dithiane by a similar route to that used to prepare **18** (see Scheme 4).