Azaspiracid (2)

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Total Synthesis of (+)-Azaspiracid-1. Part II: Synthesis of the EFGHI Sulfone and Completion of the Synthesis**

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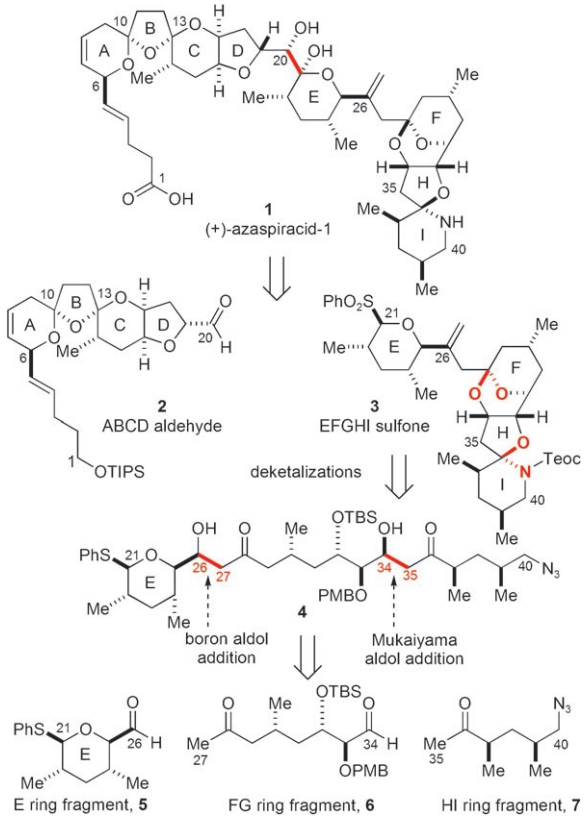
Dedicated to Professor Dieter Seebach on the occasion of his 70th birthday

With a practical synthesis of the ABCD aldehyde in hand (**2**, Scheme 1),[1] herein we describe our progress that culminated in the synthesis of (+)-azaspiracid-1 (**1**) in 26 linear steps and 2.7% overall yield.

As outlined in Scheme 1, the addition of an anomeric sulfone anion derived from **3** to a C20-electrophile, as represented by aldehyde **2**, could provide a highly convergent approach to the target. Since all nine rings of azaspiracid-1 (**1**) are formed prior to this final fragment coupling, the number of manipulations required after the coupling step would be minimal. Such anomeric sulfone anion additions have considerable precedent, both in the original investigations of anomeric sulfone anions derived from carbohydrates[2,3] and subsequently in advanced fragment couplings in total synthesis,[4–6] although the crucial sulfone anion addition of **3** to electrophiles such as aldehyde **2** would represent the most complex anomeric sulfone anion addition to date.

Conformational analysis of the HI spiroaminal portion of pentacyclic sulfone **3** (Figure 1) suggests, on the basis of anomeric stabilization and an analysis of steric effects, that this synthon exists in its favored configuration. Therefore, a number of ketalization events were incorporated into the assembly of **3**, in which the molecule is anticipated to spontaneously form the desired tetracyclic FGHI system under equilibrating conditions. The fragment couplings to construct intermediate **4** (Scheme 1) would involve a boron-mediated addition of the C27-methyl ketone of the FG ring fragment **6** to the E ring aldehyde **5**, while a chelate-controlled Mukaiyama aldol addition[7] of the enolsilane



Scheme 1. Retrosynthetic analysis of (+)-azaspiracid (**1**) and the EFGHI sulfone **3**. See Ref.[8] for abbreviations.

derived from the C35-methyl ketone of **7** to the aldehyde of **6** was anticipated to establish the stereocenter at C34.

By inspection, two *syn* 1,3-dimethyl synthons of the same configuration are embedded in the azaspiracid structure in the E and the I rings. We were attracted to the possibility of constructing both of these subunits from the common

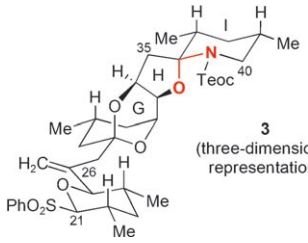


Figure 1. Three-dimensional representation of the EFGHI sulfone **3**.

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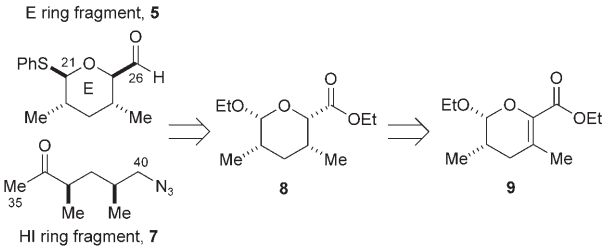
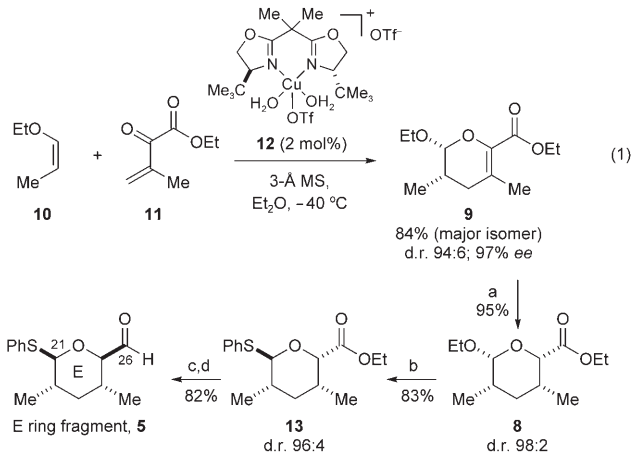
precursor **8** as outlined in Scheme 2. Tetrahydropyran **8** could potentially be accessible from dihydropyran **9**, which could be prepared using the catalytic enantioselective hetero-Diels–Alder reaction previously developed in our research group[9] for this particular target structure.



Scheme 2. Retrosynthetic analysis of the E and HI ring fragments.

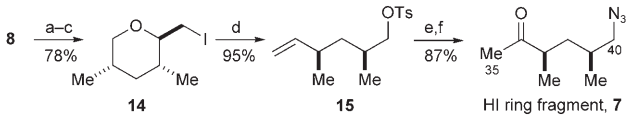
The hetero-Diels–Alder cycloaddition to construct **9** from **10**[10] and **11**[11] using the Cu^{2+} complex **12**[9] proved to be quite efficient. Optimization of the solvent and the reaction temperature afforded an enantio- and diastereoselective cycloaddition [97% *ee*, d.r. 94:6,[12] Eq. (1), Scheme 3]. The



Scheme 3. Synthesis of the E ring fragment. Reagents and conditions: a) H_2 (1 atm), Pd/C, EtOAc, 95% **8**; b) PhSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20 °C, d.r. 96:4, 83% **13**; c) *t*BuOK, THF, −50 °C, d.r. 96:4, 88%; d) DIBALH, toluene, −94 to −78 °C, 93%. See Ref. [8] for abbreviations.

desired major diastereomer **9** was routinely obtained on a 10–20 g scale in 84% yield of the isolated product. The subsequent hydrogenation of dihydropyran **9** proceeded in excellent yield and diastereoselectivity (H_2, Pd/C, EtOAc, d.r. 98:2, 95% of **8**, Scheme 3). Careful treatment of the tetrahydropyran **8** with one equivalent of thiophenol and a slight excess of $BF_3{\cdot}OEt_2$ provided lactol thioether **13** (d.r. 96:4, 83% of **13**) along with minor amounts of the acyclic dithiane as a by-product. Epimerization of the ester substituent to give a tetrahydropyran, with all four substituents occupying equatorial positions, proceeded readily with catalytic amounts of *t*BuOK (d.r. 96:4, 88% of major isomer). A final reduction to give the desired aldehyde **5** (DIBALH, 93%) proceeded smoothly. In summary, the synthesis of E ring fragment **5** was achieved in five steps and 54% overall yield.

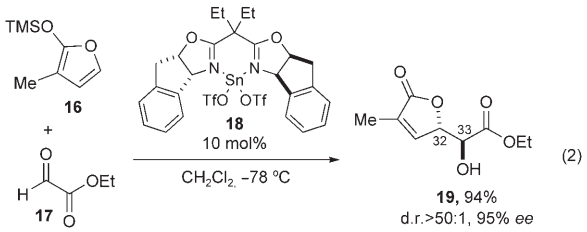
In the synthesis of the acyclic HI ring fragment **7** from the common tetrahydropyran **8**, a ring fragmentation reaction was alternatively incorporated into our synthesis plan (Scheme 4). Thus, **8** was converted into an appropriate



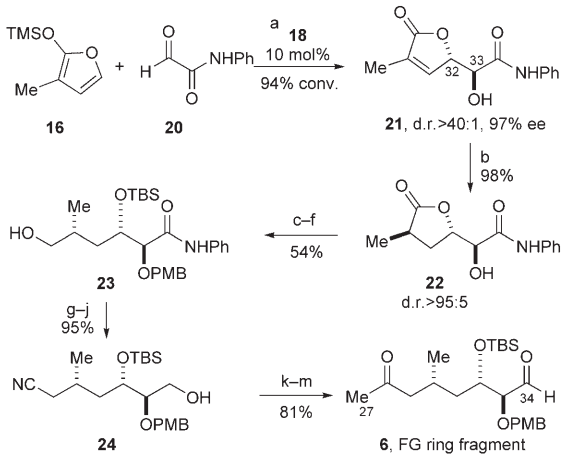
Scheme 4. Synthesis of the HI ring fragment. Reagents and conditions: a) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 91%; b) $LiAlH_4$, Et_2O, 0 °C, 91%; c) I_2, PPh_3, imidazole, CH_3CN/benzene, RT to 60 °C, 94%; d) *t*BuLi, THF, −78 °C, then TsCl, −78 to 0 °C, 95%; e) O_2, $PdCl_2$, CuCl, H_2O, DMF, 89%; f) NaN_3, DMSO, 50 °C, 98%. See Ref. [8] for abbreviations.

fragmentation precursor in a three-step sequence that involved acetal reduction (Et_3SiH, $BF_3{\cdot}OEt_2$, 91%), ester reduction ($LiAlH_4$, 91%), and conversion of the resulting primary alcohol into the corresponding iodide **14** (I_2, PPh_3, imidazole, 94%).[13] Subsequent metal-halogen exchange with *t*BuLi in THF resulted in a β elimination to give a lithium alkoxide, which was trapped in situ to give the tosylate **15** in 95% yield. This procedure obviated the need to handle the volatile primary alcohol. After Wacker oxidation under standard conditions (O_2, $PdCl_2$, CuCl, 89%), azide introduction (NaN_3, DMSO, 98%) concluded the synthesis of the HI ring fragment **7** in eight linear steps and 51% overall yield.

In the synthesis of the FG ring fragment **6** (Scheme 1), we envisioned that the C32–C33 *anti* diol array could be efficiently obtained in an enantioselective catalytic Mukaiyama aldol reaction of methyl-substituted siloxyfuran **16**[14] [Eq. (2)].



While we have previously demonstrated that unsubstituted siloxyfurans participate in Cu^{2+}-catalyzed aldol reactions,[15] the corresponding Sn^{2+}-catalyzed aldol reaction[16] with Sn^{2+} complex **18** afforded optimal results in the current transformation. Thus, the siloxyfuran **16** underwent stereoselective aldol addition with ethyl glyoxalate **17** to give the desired lactone **19** in excellent yield and selectivities (94%, 95% *ee*, d.r. > 50:1). An even more practical variant of this addition process using *N*-phenyl glyoxamide **20**[17] is shown in Scheme 5 and afforded adduct **21** (94% conversion, d.r. > 40:1, 97% *ee*) as a highly crystalline solid.



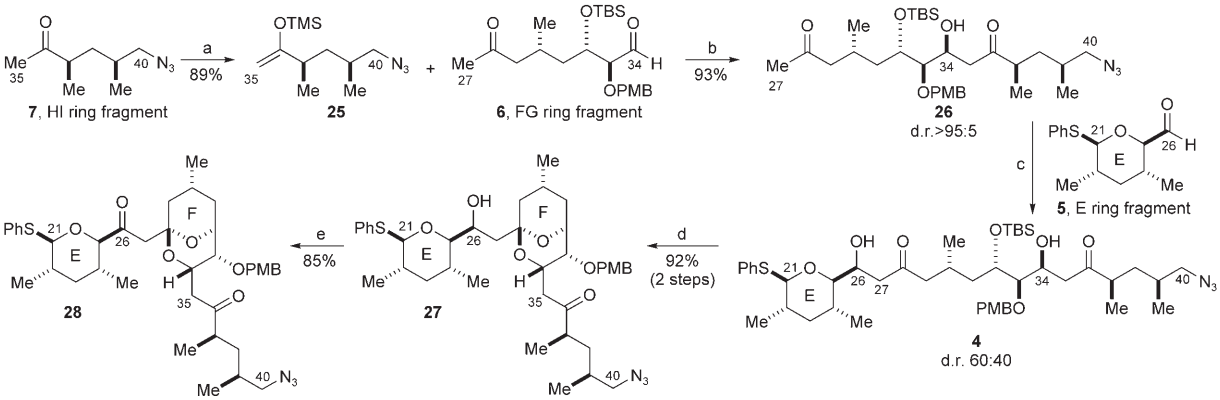
Scheme 5. Synthesis of the FG ring fragment. Reagents and conditions: a) 10 mol% **18**, CH_2Cl_2, −78 °C, 94% conversion, d.r. > 40:1, 97% *ee* (67% after recrystallization, > 99% *ee*); b) H_2 (1 atm), 2 mol% [(cod)Ir(PCy_3)(py)]PF_6, CH_2Cl_2, 98%, d.r. > 95:5; c) PMBBr, NaH, DMF, −40 to −20 °C, 67%; d) $KHBEt_3$, THF, 0 °C to RT, 94%; e) TBSCl, imidazole, DMF, 99%; f) HF·py, THF, −10 °C, 87%; g) TsCl, DMAP, py, 98%; h) NaCN, DMSO, 55 °C, 99%; i) Boc_2O, DMAP, CH_3CN, 99%; j) $LiBH_4$, H_2O, THF, 0 °C to RT, 99%; k) TMSCl, imidazole, CH_2Cl_2, 99%; l) MeLi, Et_2O, 0 °C, 84%; m) SO_3·py, DMSO, iPr_2NEt, CH_2Cl_2, −30 °C, 97%. See Ref. [8] for abbreviations.

The planned directed hydrogenation of **21** proved to be optimal with the Crabtree catalyst[18] to give lactone **22** as a single isomer (98%, d.r. > 95:5). Protection of the secondary alcohol as a PMB ether was sufficiently chemoselective under basic conditions (PMBBr, NaH, 67%) whereas a variety of acidic conditions led to both decomposition and epimerization of the newly set methyl stereocenter. A set of standard transformations was then employed: lactone reduction ($KHBEt_3$, 94%), silylation (TBSCl, 99%), and removal of the primary TBS group (HF·py, 87%) afforded alcohol **23**, followed by tosylation (TsCl, 98%) and cyanide substitution (NaCN, 99%). We elected to introduce C28 as a cyano function at this stage of the synthesis to provide maximal flexibility in the subsequent fragment couplings, because the nitrile could be converted into either an electrophile (an aldehyde) or a nucleophile (a methyl ketone). The *N*-phenyl amide functionality was reduced in a two-step sequence,[19] which involved Boc-activation (Boc_2O, 99%) and reduction ($LiBH_4$, 99%) to give alcohol **24**. After transient protection of the primary alcohol (TMSCl, 99%) to effect full conversion in the subsequent step, the nitrile was converted into the C27-methyl ketone (MeLi, 84%) with concomitant hydrolysis of the TMS group during the workup procedure. A final Parikh–Doering oxidation (97%) concluded the synthesis of the FG ring fragment **6** in 13 linear steps and 27% overall yield.

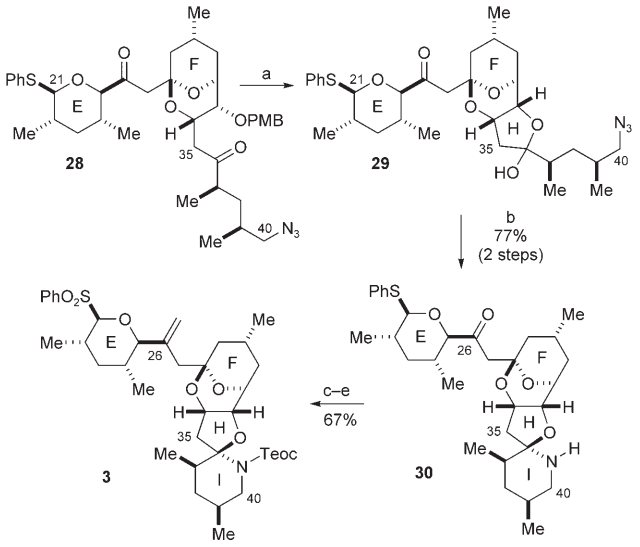
In the subsequent fragment couplings, the enolsilane **25** needed for the chelate-controlled Mukaiyama aldol addition was readily formed from methyl ketone **7** under standard conditions (LiHMDS, TMSCl, Et_3N, 89%, Scheme 6). A careful evaluation of a range of Lewis acids to effect this transformation established that freshly prepared solid $MgBr_2$·OEt_2[20] was superior to other Lewis acids such as $TiCl_2(OiPr)_2$, $TiCl_4$, $SnCl_4$, MgI_2, $MgBr_2$, $Mg(OTf)_2$, and commercial $MgBr_2$·OEt_2. Chelate-controlled addition of enolsilane **25** to aldehyde **6** thus proceeded in excellent yield to afford the desired aldol adduct **26** as a single diastereomer (93%, d.r. > 95:5).

The methyl ketone moiety at C27 in adduct **26** was then converted into its derived boron enolate. The excess Cy_2BCl used in this step was intended to function as a transient protecting group for the C34–C36 hydroxyketone moiety. When treated with a slight excess of E ring aldehyde **5**, the desired aldol adduct **4** was formed in near quantitative yield. On exposure to aqueous HF in acetonitrile, the TBS ether was cleaved and the molecule spontaneously cyclized to form the FG bicyclic ketal **27** as a mixture of C26-alcohol diastereomers (92%, 2 steps). The absence of any significant diastereoselectivity in the boron aldol addition was inconsequential as the stereocenter at C26 was subsequently oxidized to the corresponding ketone **28** with Dess–Martin periodinane (DMP)[21] (85%). The use of pyridine to buffer this latter oxidation was crucial to suppress overoxidation and subsequent loss of the C21-phenylsulfide moiety that was otherwise a prominent side reaction.

In the further elaboration of ketone **28**, the PMB moiety was oxidatively removed to afford a mixture of lactols **29** and open-chain tautomers (DDQ, pH 7 buffer, Scheme 7). Next, the azide was reduced, a step that induced the spontaneous



Scheme 6. Assembly of the EFGHI carbon skeleton and formation of the FG bicyclic ketal. Reagents and conditions: a) LiHMDS, TMSCl, Et_3N, THF, −78 °C, 89%; b) $MgBr_2$·OEt_2, CH_2Cl_2, 0 °C, 93%, d.r. > 95:5; c) Cy_2BCl (2.2 equiv), iPr_2NEt, CH_2Cl_2, −78 °C, then **5** (1.40 equiv), −78 to 0 °C; then H_2O_2, MeOH, pH 7 buffer, 0 °C to RT, d.r. 60:40; d) HF, H_2O, CH_3CN, 0 °C, 92% (2 steps); e) DMP, py, CH_2Cl_2, 85%. See Ref. [8] for abbreviations.



Scheme 7. Completion of the EFGHI sulfone **3**. Reagents and conditions: a) DDQ, pH 7 buffer, CH_2Cl_2, 0 °C; b) H_2 (1 atm), Pd/C, THF, 77% (2 steps); c) TeocCl,[25] iPr$_2$NEt, THF, 0 °C, 89%, d.r. > 97:3; d) Tebbe reagent,[23] py, toluene, −40 °C, 78%;[24] e) H_2O_2, py, [$(NH_4)_6Mo_7O_{24}$], tBuOH, 96%. See Ref. [8] for abbreviations.

formation of the thermodynamically favored HI spiroaminal **30** as a single diastereomer (H_2, Pd/C, 77%, 2 steps). Key NOE interactions that established the desired configuration of the spiroaminal **30** are shown in Figure 2.

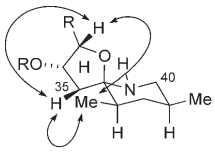
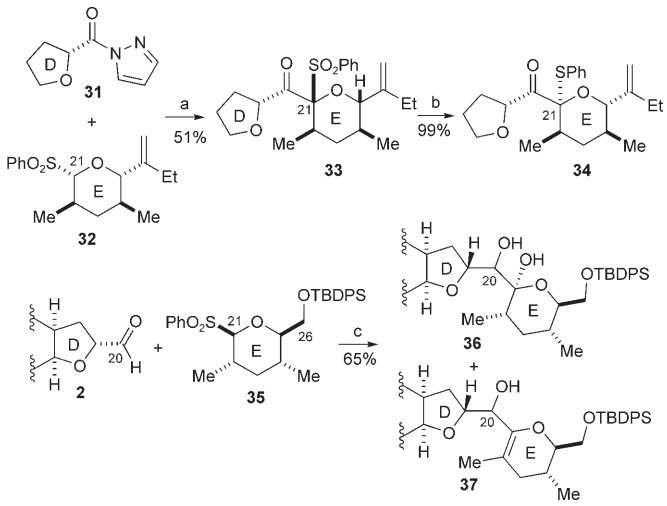


Figure 2. Key NOE interactions observed with spiroaminal **30** (C_6D_6, 500 MHz).

We then elected to protect the spiroaminal nitrogen of **30** as its Teoc derivative, a transformation which proceeded in excellent stereoselectivity when conducted in THF at high concentrations (TeocCl, 89%, d.r. > 97:3; Scheme 7). With all reactive functionalities in the molecule thus protected, the stage was set for the olefination of the C26-ketone. The Tebbe reagent,[22] buffered with pyridine to avoid any C36-epimerization, proved to be best in this transformation, and could conveniently be prepared in situ from Cp_2TiCl_2 and $AlMe_3$[23] to give the desired olefinated product in 78% overall yield.[24] The key NOE interactions of the spiroaminal portion remained unchanged from those depicted in Figure 2, thus verifying that no potential epimerization at C36 had taken place during these latter transformations. Finally, the oxidation to sulfone **3** proceeded in the presence of pyridine (H_2O_2, [$(NH_4)_6Mo_7O_{24}$], 96%) to avoid concomitant loss of the C21-sulfur substituent as was observed in initial unbuffered experiments. Altogether, the above sequence allowed the efficient synthesis of the EFGHI sulfone **3** in 22 linear steps and 10% overall yield.

With a practical route to the anomeric sulfone **3** in hand, we turned our attention to the final fragment coupling. To the best of our knowledge, the most related precedent for such a fragment coupling can be found in our altohyrtin synthesis, where an anomeric sulfone was added to an *N*-acylbenzotriazole as the electrophile.[4,5] In a simple azaspiracid model system, sulfone **32** could likewise be added to *N*-acylpyrazole **31** to give ketosulfone **33** that was subsequently transformed quantitatively into ketosulfide **34** (Scheme 8). Unfortunately, these transformations proved to be less promising on more



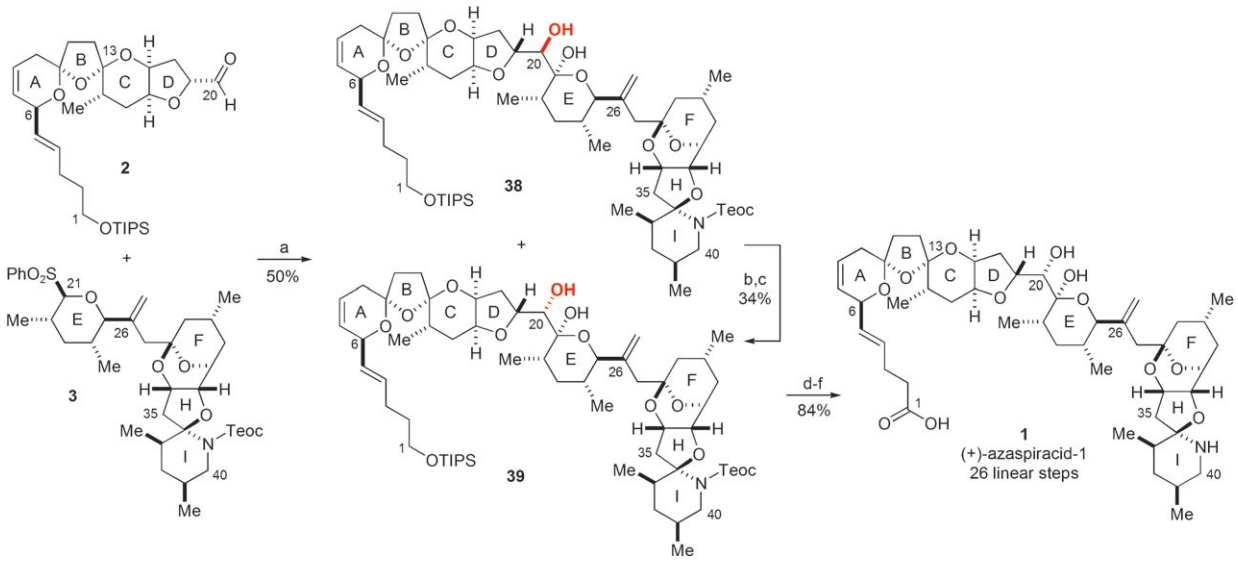
Scheme 8. Model studies of the final C20–C21-sulfone fragment coupling. Reagents and conditions: a) LDA, THF, −78 °C, d.r. (C21) 6:1, 51% **33**; b) PhSLi, Et_2O, −78 °C, 99%; c) nBuLi, THF, −78 °C, then sat. aq NH_4Cl, −78 °C to RT, 65%, 3:1 **36**/**37**. See Ref. [8] for abbreviations.

elaborate model systems.[26] A more rapid entry to the C21-lactol region of the azaspiracid skeleton would be to use aldehyde **2** directly, a strategy with some promising precedent in the literature.[6] The well-known competing side reaction in such a transformation is the elimination to the corresponding dihydropyran.[2,5] Encouragingly, when this reaction was carried out with aldehyde **2** and the simple model sulfone **35** followed by a quench with slightly acidic buffer at −78 °C, the desired lactols **36** were preferentially formed over dihydropyrans **37** (3:1, **36**/**37**).

Although unoptimized, this latter experiment provided a credible lead for the final coupling experiments and established that the C21-lactols **36** could indeed be accessed directly upon appropriate workup conditions in the sulfone fragment coupling.

In the actual coupling process, the sulfone anion derived from **3** was added to aldehyde **2** followed by a quench at −78 °C with pH 5 buffer to afford near equal amounts of the separable lactol diastereomers **38** and **39** in 50% overall yield (Scheme 9).[27] Interestingly, the undesired alcohol **38** was obtained as an inseparable mixture of the C21-lactol and the corresponding hydroxyketone, which suggests a lower configurational stability of this C20-diastereomer. This equilibrium complicated the oxidation of alcohol **38** to the corresponding C20-ketone that was best effected under Swern conditions (60%), followed by a diastereoselective reduction to give the desired C20-diastereomer **39** ($LiBH_4$, CH_2Cl_2, −40 °C, 56%, d.r. > 20:1).

Subsequently, the two silyl protecting groups were readily removed from **39** (TBAF, 93%) followed by a mild two-step oxidation of the C1 terminus. Interestingly, a Dess–Martin



Scheme 9. Final fragment coupling and completion of the synthesis. Reagents and conditions: a) **3** (2.2 equiv), *n*BuLi, −78 °C, then **2** (1.0 equiv), NaOAc/AcOH buffer, −78 °C to RT, 50% (27% **38**, 23% **39**); b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to −20 °C, 60%; c) $LiBH_4$, CH_2Cl_2, −40 °C, d.r. > 20:1, 56%; d) TBAF, THF, 0 °C, 93%; e) DMP, CH_2Cl_2, 0 °C; f) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, 2-methyl-2-butene, *t*BuOH, 90% (2 steps). See Ref. [8] for abbreviations.

oxidation at 0 °C cleanly afforded the desired C1-aldehyde, despite the fact that a large excess of Dess–Martin periodinane was required to reach a full conversion into the aldehyde. In contrast, the secondary C20-hydroxy group could readily be oxidized with DMP at room temperature. Finally, the C1-aldehyde was oxidized with $NaClO_2$ to the corresponding carboxylic acid[28] in the presence of 2-methyl-2-butene as a chlorine scavenger[29] (90%, 2 steps). This sequence concluded the total synthesis of (+)-azaspiracid-1 (**1**) and has allowed us to synthesize 75 mg of this complex structure. The spectroscopic data for (+)-azaspiracid-1 corresponded with those reported for (−)-azaspiracid (*ent*-**1**) apart from the optical rotation which was of equal magnitude but of opposite sign ((+)-azaspiracid-1 (**1**), $[\alpha]_D^{24} = +21.7$ ($c = 1.00$, MeOH); natural (−)-azaspiracid-1 (*ent*-**1**), $[\alpha]_D^{20} = -21$ ($c = 0.1$, MeOH),[30] synthetic (−)-azaspiracid-1 (*ent*-**1**), $[\alpha]_D^{33} = -19.0$ ($c = 0.07$, MeOH)[31]).

In summary, the total synthesis of (+)-azaspiracid-1 (**1**) was realized by a highly convergent approach in only 26 linear steps and 2.7% overall yield. The spirocyclic nature of this polyketide target was used in an approach that allowed the minimal use of protecting groups in the final stages of the synthesis. Additionally, the synthesis featured a diastereoselective chelate-controlled Mukaiyama aldol fragment coupling, a regioselective boron-mediated methyl ketone aldol addition in the presence of an unprotected hydroxyketone moiety, and a complex addition of an anomeric sulfone anion to an aldehyde. The latter transformation allowed for a rapid final assembly of (+)-azaspiracid-1 (**1**) with only three postcoupling transformations of the desired lactol **39**.

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[1] See the previous Communication: D. A. Evans, L. Kværnø, J. A. Mulder, B. Raymer, T. B. Dunn, A. Beauchemin, E. J. Olhava, M. Juhl, K. Kagechika, *Angew. Chem.* **2007**, *119*, 4777–4791; *Angew. Chem. Int. Ed.* **2007**, *46*, 4693–4697.

[2] a) S. V. Ley, B. Lygo, A. Wonnacott, *Tetrahedron Lett.* **1985**, *26*, 535–538; b) C. Greek, P. Grice, S. V. Ley, A. Wonnacott, *Tetrahedron Lett.* **1986**, *27*, 5277–5280.

[3] a) J. M. Beau, P. Sinaÿ, *Tetrahedron Lett.* **1985**, *26*, 6185–6188; b) J. M. Beau, P. Sinaÿ, *Tetrahedron Lett.* **1985**, *26*, 6189–6192; c) J. M. Beau, P. Sinaÿ, *Tetrahedron Lett.* **1985**, *26*, 6193–6196.

[4] a) D. A. Evans, P. J. Coleman, L. C. Dias, *Angew. Chem.* **1997**, *109*, 2951–2954; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2738–2741; b) D. A. Evans, B. W. Trotter, B. Cote, P. J. Coleman, *Angew. Chem.* **1997**, *109*, 2954–2957; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2741–2744; c) D. A. Evans, B. W. Trotter, B. Cote, P. J. Coleman, L. C. Dias, A. N. Tyler, *Angew. Chem.* **1997**, *109*, 2957–2961; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2744–2747.

[5] D. A. Evans, B. W. Trotter, P. J. Coleman, B. Cote, L. C. Dias, H. A. Rajapakse, A. N. Tyler, *Tetrahedron* **1999**, *55*, 8671–8726.

[6] a) D. A. Evans, P. H. Carter, E. M. Carreira, J. A. Prunet, A. B. Charette, M. Lautens, *Angew. Chem.* **1998**, *110*, 2526–2530; *Angew. Chem. Int. Ed.* **1998**, *37*, 2354–2359; b) D. A. Evans, P. H. Carter, E. M. Carreira, A. B. Charette, J. A. Prunet, M. Lautens, *J. Am. Chem. Soc.* **1999**, *121*, 7540–7552.

[7] a) T. Mukaiyama, K. Narasaka, K. Banno, *Chem. Lett.* **1973**, 1011–1014; b) T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509; c) T. Mukaiyama, *Angew. Chem.* **2004**, *116*, 5708–5733; *Angew. Chem. Int. Ed.* **2004**, *43*, 5590–5614.

[8] Abbreviations: Boc = *tert*-butyloxycarbonyl, cod = 1,5-cyclooctadiene, Cy = cyclohexyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIBALH = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, LDA = lithium diisopropylamide, LiHMDS = lithium hexamethyldisilazide, PMB = 4-methoxybenzyl, py = pyridine, TBAF = tetrabutylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, Tebbe reagent = (μ-chloro)(μ-methylene)bis(cyclo-

pentadienyl)(dimethylaluminum)titanium, Teoc = 2-(trimethylsilyl)ethoxycarbonyl, TES = triethylsilyl, Tf = trifluoromethanesulfonyl, TIPS = triisopropylsilyl, TMS = trimethylsilyl, Ts = *p*-toluenesulfonyl.

[9] a) D. A. Evans, E. J. Olhava, J. S. Johnson, J. M. Janey, *Angew. Chem.* **1998**, *110*, 3553 – 3557; *Angew. Chem. Int. Ed.* **1998**, *37*, 3372 – 3375; b) D. A. Evans, J. S. Johnson, E. J. Olhava, *J. Am. Chem. Soc.* **2000**, *122*, 1635 – 1649.

[10] E. Taskinen, R. Virtanen, *J. Org. Chem.* **1977**, *42*, 1443 – 1449.

[11] M. Rambaud, M. Bakasse, G. Duguay, J. Villieras, *Synthesis* **1988**, 564 – 566.

[12] The less-than-perfect *cis*/*trans* diastereomeric ratios (94:6) in the cycloaddition could arise from either a stepwise mechanism or from isomerization of either the propenyl ether **10** or the dihydropyran product **9** under the reaction conditions. Isomerization of either component was not observed in control experiments, thus suggesting a stepwise reaction pathway during the cycloaddition.

[13] a) P. J. Garegg, B. Samuelsson, *J. Chem. Soc. Perkin Trans. 1* **1980**, 2866 – 2869; b) P. J. Garegg, R. Johansson, C. Ortega, B. Samuelsson, *J. Chem. Soc. Perkin Trans. 1* **1982**, 681 – 683.

[14] a) E. Yoshii, T. Koizumi, E. Kitatsuji, T. Kawazoe, T. Kaneko, *Heterocycles* **1976**, *4*, 1663 – 1668; b) C. W. Jefford, A. W. Sledeski, J. C. Rossier, J. Boukouvalas, *Tetrahedron Lett.* **1990**, *31*, 5741 – 5744.

[15] a) D. A. Evans, J. A. Murry, M. C. Kozlowski, *J. Am. Chem. Soc.* **1996**, *118*, 5814 – 5815; b) D. A. Evans, M. C. Kozlowski, J. A. Murry, C. S. Burgey, K. R. Campos, B. T. Connell, R. J. Staples, *J. Am. Chem. Soc.* **1999**, *121*, 669 – 685.

[16] D. A. Evans, D. W. C. MacMillan, K. R. Campos, *J. Am. Chem. Soc.* **1997**, *119*, 10859 – 10860.

[17] D. A. Evans, J. Wu, *J. Am. Chem. Soc.* **2005**, *127*, 8006 – 8007.

[18] a) R. H. Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331 – 338; b) R. H. Crabtree, M. W. Davis, *Organometallics* **1983**, *2*, 681 – 682.

[19] a) D. L. Flynn, R. E. Zelle, P. A. Grieco, *J. Org. Chem.* **1983**, *48*, 2424 – 2426; b) D. A. Evans, P. H. Carter, C. J. Dinsmore, J. C. Barrow, J. L. Katz, D. W. Kung, *Tetrahedron Lett.* **1997**, *38*, 4535 – 4538.

[20] a) G. E. Keck, E. P. Boden, *Tetrahedron Lett.* **1984**, *25*, 265 – 268; b) G. E. Keck, E. P. Boden, *Tetrahedron Lett.* **1984**, *25*, 1879 – 1882; c) K. Takai, C. H. Heathcock, *J. Org. Chem.* **1985**, *50*, 3247 – 3251; d) R. Bernardi, D. Ghiringhelli, *J. Org. Chem.* **1987**, *52*, 5021 – 5022; e) L. M. Harwood, A. C. Manage, S. Robin, S. F. G. Hopes, D. J. Watkin, C. E. Williams, *Synlett* **1993**, 777 – 780.

[21] a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155 – 4156; b) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277 – 7287.

[22] F. N. Tebbe, G. W. Parshall, G. S. Reddy, *J. Am. Chem. Soc.* **1978**, *100*, 3611 – 3613.

[23] L. F. Cannizzo, R. H. Grubbs, *J. Org. Chem.* **1985**, *50*, 2386 – 2387.

[24] At −40 °C, the Tebbe reaction only proceeded to about 60 % conversion (55 % yield of isolated product) while the residual starting ketone could be reisolated in high yield. The overall reported yield of 78 % represents two recycling steps of the starting material. At higher temperatures, the conversions were higher but the decomposition of the starting ketone was also significant, thus giving an overall lower mass recovery.

[25] R. E. Shute, D. H. Rich, *Synthesis* **1987**, 346 – 349.

[26] A full account of these studies including the first-generation syntheses of the fragments will subsequently be reported.

[27] The majority of the sulfone **3** could be recovered as **3** and its C21-epimer (78 % combined recovery based on the 50 % yield from the coupling).

[28] B. O. Lindgren, T. Nilsson, *Acta Chem. Scand.* **1973**, *27*, 888 – 890.

[29] a) G. A. Kraus, M. J. Taschner, *J. Org. Chem.* **1980**, *45*, 1175 – 1176; b) G. A. Kraus, B. Roth, *J. Org. Chem.* **1980**, *45*, 4825 – 4830.

[30] M. Satake, K. Ofuji, H. Naoki, K. J. James, A. Furey, T. McMahon, J. Silke, T. Yasumoto, *J. Am. Chem. Soc.* **1998**, *120*, 9967 – 9968.

[31] a) K. C. Nicolaou, S. Vyskocil, T. V. Koftis, Y. M. A. Yamada, T. T. Ling, D. Y. K. Chen, W. J. Tang, G. Petrovic, M. O. Frederick, Y. W. Li, M. Satake, *Angew. Chem.* **2004**, *116*, 4412 – 4418; *Angew. Chem. Int. Ed.* **2004**, *43*, 4312 – 4318; b) K. C. Nicolaou, T. V. Koftis, S. Vyskocil, G. Petrovic, T. T. Ling, Y. M. A. Yamada, W. J. Tang, M. O. Frederick, *Angew. Chem.* **2004**, *116*, 4418 – 4424; *Angew. Chem. Int. Ed.* **2004**, *43*, 4318 – 4324; c) K. C. Nicolaou, T. V. Koftis, S. Vyskocil, G. Petrovic, W. J. Tang, M. O. Frederick, D. Y. K. Chen, Y. W. Li, T. T. Ling, Y. M. A. Yamada, *J. Am. Chem. Soc.* **2006**, *128*, 2859 – 2872.

