Azaspiracid (1)

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Total Synthesis of (+)-Azaspiracid-1. Part I: Synthesis of the Fully Elaborated ABCD Aldehyde**

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

(−)-Azaspiracid-1 (**2**, Figure 1) is a structurally complex marine neurotoxin that is implicated in seafood poisoning.

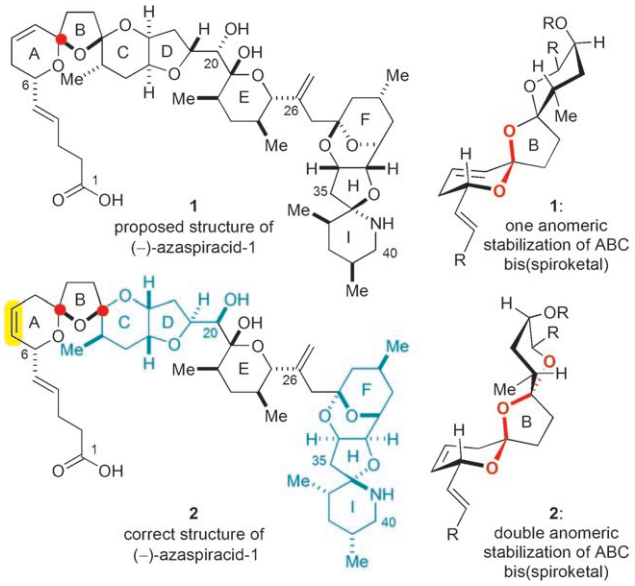
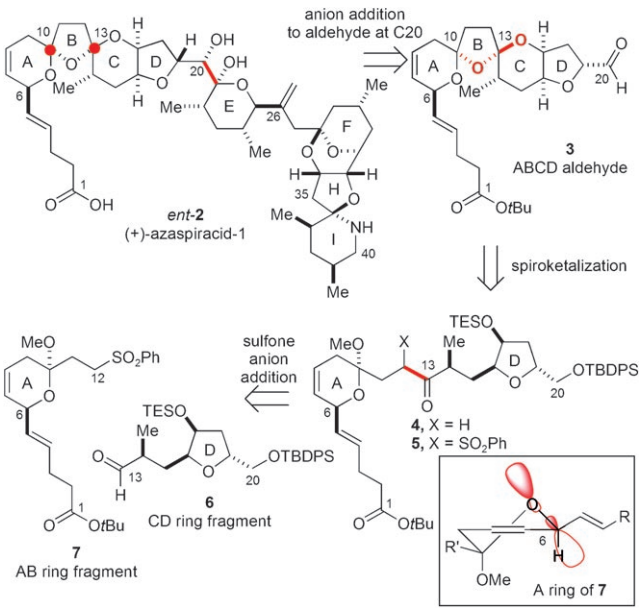


Figure 1. Originally proposed structure (**1**)[2] and correct structure of (−)-azaspiracid-1 (**2**).[5]

Outbreaks of azaspiracid poisoning were first reported in 1995[1] and in 1998 the causative toxin was isolated in minute amounts from blue mussels (*Mytilus edulis*). Extensive NMR spectroscopic studies resulted in the proposed structural assignment **1**, in which the relative configurations between the ABCDE and FGHI domains, as well as the absolute configuration, remained uncertain.[2] The intriguing chemical structure of azaspiracid-1, in combination with its scarcity in nature, has spurred considerable interest among the chemical community.[3] These efforts resulted in a synthesis of the proposed structure **1** in 2003 by the research group of Nicolaou with the finding that this structure did not match that of the natural product.[4] Subsequent efforts in the research group of Nicolaou involving numerous degradation studies and the synthesis of multiple diastereomers resulted in a significant structural revision that allowed the unambiguous structural assignment of (−)-azaspiracid-1 (**2**) in 2004.[5] Based on these impressive studies, an improved total synthesis of azaspiracid-1 in 39 linear steps was recently reported by Nicolaou and co-workers.[6]

Herein and in the following Communication,[7] we describe our efforts, which culminated in a synthesis of (+)-azaspiracid-1 (*ent*-**2**, Scheme 1). This target requires only minimal changes in our original synthesis plan that targeted the originally proposed structure **1** of (−)-azaspiracid-1, namely the design of a new AB ring fragment and the synthesis of the enantiomer of the E ring fragment. Herein we



Scheme 1. Retrosynthetic analysis of the ABCD aldehyde **3** of (+)-azaspiracid-1 (*ent*-**2**). See Ref.[9] for abbreviations.

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address the asymmetric syntheses of the AB and CD ring fragments and their assembly into the fully elaborated ABCD portion of this natural product.

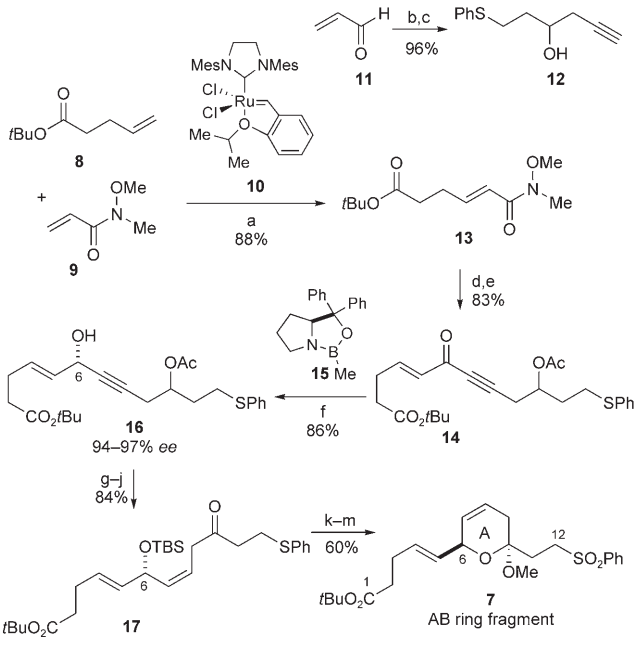
The corrected (−)-azaspiracid structure (**2**)[5] contains an ABC bis(spiroketal) synthon, now containing two stabilizing anomeric effects, that is presumed to be in its favored configuration (Figure 1). Accordingly, a thermodynamically controlled spiroketalization should be effective in controlling both the spiroketal stereocenters at C10 and C13. The plan for the deconstruction of the ABCD synthon **3** is outlined in Scheme 1 and affords fragments **6** and **7** of comparable complexity. The selection of the lactol methyl ether **7** rather than an equivalent acyclic divinylcarbinol synthon was made in response to the extreme lability of the hydroxy group at C6 in acyclic intermediates under a range of conditions.[8] It was reasoned that the inclusion of the hydroxy group at C6 as its corresponding lactol methyl ether **7** would influence its stability in a positive manner. As depicted in Scheme 1, the double bond in the ring is taken out of conjugation with the C–O bond at C6 in ketal **7**, thus eliminating the impact of this π bond toward hyperconjugative donation and chemical labilization.

To preserve the desired oxidation state of the carboxy terminus, the synthesis plan included the AB ring fragment **7** with the carboxylic acid protected as its *tert*-butyl ester (Scheme 2). The synthesis was initiated with the cross-metathesis[10] of alkene **8**[11] and unsaturated Weinreb amide **9**,[12] which proceeded smoothly in the presence of the Grubbs–Hoveyda catalyst **10**[13] to provide unsaturated Weinreb amide **13** (88%). The remaining six-carbon-atom fragment was introduced as the racemic alkyne **12**, which was readily prepared from acrolein (96%, 2 steps) and added chemoselectively as its dianion to the unsaturated Weinreb amide **13**. This alkyne addition required some experimentation before it was eventually found that transmetalation in the presence of $MgBr_2{\cdot}OEt_2$[14] as a mild Lewis acid, as well as the addition of THF at a late stage of the reaction, were both crucial in achieving the desired transformation. Thus, after acetylation of the unpurified mixture, ene-ynone **14** was obtained in 83% yield (2 steps).

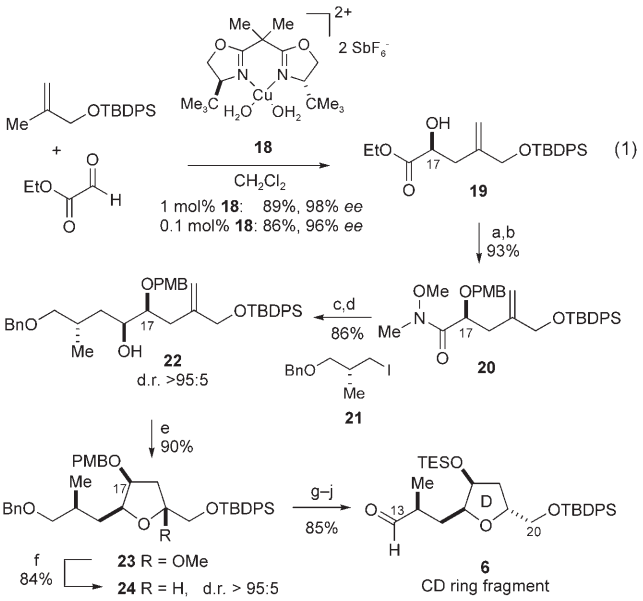
Introduction of the stereocenter at C6 was then effected in high yield and enantioselectivity using a stoichiometric CBS reduction[15] (**15**, $BH_3{\cdot}SMe_2$, 86%, 94–97% *ee*) to afford alcohol **16**. The subsequent semihydrogenation of the alkyne under Lindlar conditions proceeded readily, although the product was contaminated with 3–5% of the undesired alkane that was separated from the major product at a later stage. After protection of the alcohol as a TBS ether under standard conditions (92%, 2 steps), the acetate was removed (K_2CO_3, MeOH), and a subsequent Parikh–Doering oxidation[16] gave the bisallylic silyl ether **17** ($SO_3{\cdot}$py, DMSO, 91%, 2 steps). The crucial formation of the lactol was subsequently effected with HF·pyridine buffered with excess pyridine (74%). To our relief, this lactol was smoothly transformed into the desired lactol methyl ether in excellent yield (PPTS, MeOH, 92%), thus validating the anticipated stability of the lactol at C6 to acidic conditions (vide infra). Finally, the sulfide moiety was oxidized to the derived sulfone (H_2O_2, $[(NH_4)_6Mo_7O_{24}]$, 88%) to conclude the synthesis of the desired AB ring fragment **7** in 11 linear steps and 32% overall yield.

In the synthesis of the CD ring fragment **6**, the enantioselective Cu^{2+}-catalyzed glyoxylate-ene reaction reported by our research group[17] provided the first stereocenter at C17 [Eq. (1), Scheme 3]. This reaction could routinely be conducted on a 20 g scale in good yields and enantioselectivities using 1 mol% of the Cu^{2+} complex **18** (89% yield, 98% *ee*). In the presence of 0.1 mol% of **18**, almost identical results were obtained (86% yield, 96% *ee*) although the reaction times to reach full conversion in the latter case increased considerably (5 days compared with 12 h). Subsequently, the resultant hydroxy ester **19** was converted into the corresponding Weinreb amide[18] (MeNH(OMe)·HCl, Me_3Al, 98%) for which $A^{1,3}$ strain is presumed to allow for a PMB protection under standard basic conditions (PMBBr, NaH, 95%) with no detrimental epimerization of the stereocenter at C17 (Scheme 3).

Metalation of the known iodide **21**[19] with *t*BuLi[20] provided the remaining four-carbon-atom subunit (−78°C, 90%). The resulting α-alkoxyketone was reduced with L-Selectride with Felkin control to afford alcohol **22** as the only detectable diastereomer (96%, d.r. > 95:5). Careful ozonolysis of the 1,1-disubstituted olefin in the presence of Sudan III dye as an indicator[21] allowed for the selective oxidative cleavage of the olefin (O_3, −78°C, then Me_2S) without any



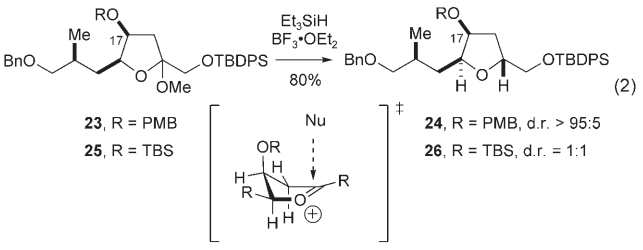
Scheme 2. Synthesis of the AB Ring Fragment **7**. Reagents and conditions: a) **10** (5 mol%), CH_2Cl_2, 40°C, 88%; b) PhSH, Et_3N, CH_2Cl_2; c) allenylMgBr, Et_2O, 0°C, 96% (2 steps); d) **12**, *n*BuLi, Et_2O, −78°C, then $MgBr_2{\cdot}OEt_2$, then **13**, −78 to 0°C, THF added, then RT; e) Ac_2O, DMAP, py, CH_2Cl_2, 83% (2 steps); f) **15** (2 equiv), $BH_3{\cdot}SMe_2$, THF, 0°C, 86%, 94–97% *ee*; g) H_2 (1 atm), $Pd/CaCO_3/Pb$ (5%), py, benzene; h) TBSCl, DMAP, imidazole, DMF, 92%, 3–5% alkane (2 steps); i) K_2CO_3, MeOH; j) $SO_3{\cdot}$py; DMSO, iPr_2NEt, CH_2Cl_2, −25°C, 91% (2 steps); k) HF·py, py, THF, 0°C, 74%; l) PPTS, $HC(OMe)_3$, MeOH, CH_2Cl_2, −10°C, 92%; m) H_2O_2, $[(NH_4)_6Mo_7O_{24}]$, MeOH, 0°C, 88%. See Ref. [9] for abbreviations.



Scheme 3. Synthesis of the CD ring fragment **6**. Reagents and conditions: a) MeNH(OMe)·HCl, Me_3Al, THF, 98%; b) PMBBr, NaH, DMF, 95%; c) **21**,[19] *t*BuLi, Et_2O, −78°C, 90%; d) L-Selectride, THF, −78°C, 96%; e) 1. O_3, py, CH_2Cl_2/MeOH (5:1 v/v), −78°C, then Me_2S, −78°C to RT; 2. PPTS, MeOH, 90%; f) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78°C, 84%; g) DDQ, CH_2Cl_2/pH 7 buffer, 0°C (9:1 v/v), 94%; h) TESCl, imidazole, DMF, 97%; i) LiDBB, THF, −78°C, 96%; j) $SO_3{\cdot}$py, DMSO, *i*Pr_2NEt, CH_2Cl_2, −30°C, 97%. See Ref. [9] for abbreviations.

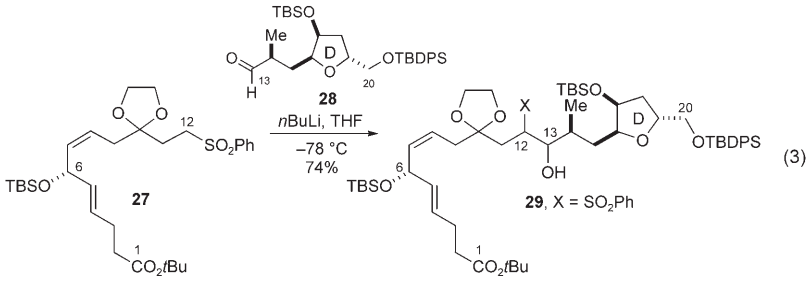
undesired oxidation of the benzylic ether protecting groups. Subsequent ketalization (PPTS, MeOH) afforded the methyl ketal **23** (90% yield, 2 steps). The desired trisubstituted tetrahydrofuran **24** could be readily obtained by stereoselective reduction with Et_3SiH mediated by $BF_3{\cdot}OEt_2$ (84% yield, d.r. > 95:5), with the primary by-product derived from an elimination reaction to the corresponding undesired furan.

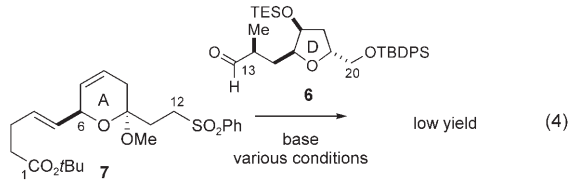
The observed diastereoselectivity in the reduction of the oxocarbenium ion of **23** to give **24** is in good agreement with the model for nucleophilic additions to five-membered cyclic oxocarbenium ions proposed by Woerpel and co-workers.[22] It is noteworthy that the analogous reduction of the methyl ketal **25** with TBS protection at O17 proceeded with no diastereoselectivity to give the tetrahydrofuran **26** [Eq. (2)], which suggests that steric factors also play a significant role for these sterically rather encumbered substrates.



As a silyl ether protecting group at C17 was required for the global synthesis plan, the next two transformations of tetrahydrofuran **24** (Scheme 3) comprised an oxidative removal of the PMB group (DDQ, 94%) and a silylation of the secondary alcohol at C17 (TESCl, 97%). Finally, the benzyl group was best removed under radical anion conditions (LiDBB,[23] 96%), followed by a Parikh–Doering oxidation[16] to give aldehyde **6** (97%). Altogether, this sequence efficiently provided the desired CD ring fragment **6** in 12 steps and 46% overall yield.

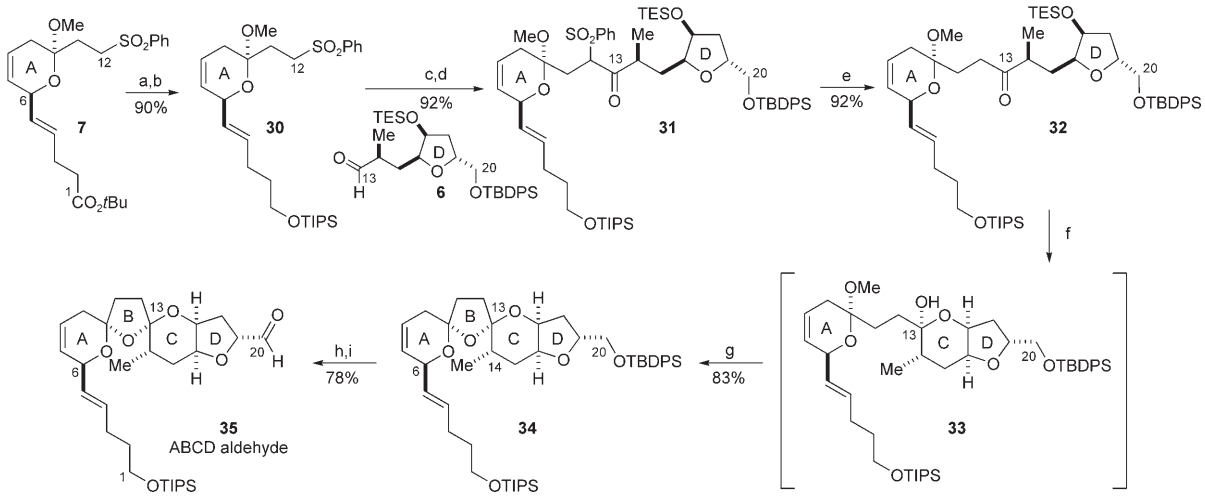
Although the α protons of the C1-ester and C12-sulfone termini of the AB ring fragment are of comparable thermodynamic acidity, we anticipated that a selective kinetic deprotonation α to the sulfone might be feasible under the appropriate experimental conditions. This expectation was indeed borne out by experiment in the selective addition of sulfone **27** to the TBS-protected aldehyde **28** [74% yield, Eq. (3)]. Unfortunately, adduct **29** proved too unstable to successfully participate in the subsequent derivatization into the ABCD bis(spiroketal) and was abandoned for further studies.[8] However, much to our surprise, the corresponding addition of the lactol derivative **7** to aldehyde **6** was very unselective for deprotonation at C12 under a variety of experimental conditions [Eq. (4)]. These findings thus suggest that although α deprotonation of the sulfone is generally kinetically favored, subtle steric differences may have a negative impact on the kinetics in such α deprotonations.





A solution to this obstacle was the reduction of the carboxy terminus of **7** and protection as its silyl ether **30**, as depicted in Scheme 4 ($LiAlH_4$, 92%; TIPSCl, 98%). Subsequent sulfone deprotonation with LDA and addition to aldehyde **6** readily proceeded to give the two C12-diastereomeric ketosulfones **31** after Dess–Martin oxidation[24] of the initial mixture of the four hydroxy sulfones (92% yield, 2 steps). Sodium amalgam excision of the sulfone moiety[25] then provided ketone **32** as a single diastereomer in excellent overall yield for the fragment coupling sequence (92%).

In the crucial spirocyclization event, optimal yields were obtained when the TES ether was selectively removed with



Scheme 4. Synthesis of the ABCD aldehyde **35**. Reagents and conditions: a) $LiAlH_4$, Et_2O, −20 °C, 92%; b) TIPSCl, imidazole, DMF, 98%; c) **6**, LDA, THF, −78 °C; d) DMP, py, CH_2Cl_2, 92% (2 steps); e) Na/Hg (5%), NaH_2PO_4, THF/MeOH, −10 °C, 92%; f) TBAF, THF, −20 °C (workup); g) PPTS, CH_2Cl_2, 0 °C (83%, 2 steps); h) TBAF, AcOH, DMF, 86%; i) SO_3·py; DMSO, iPr_2NEt, CH_2Cl_2, −30 °C, 91%. See Ref. [9] for abbreviations.

one equivalent of TBAF at low temperature to form the intermediary lactol **33**, followed by treatment of the unpurified mixture with PPTS in a nonpolar solvent such as CH_2Cl_2. Thus, the major and desired bis(spiroketal) isomer **34** was obtained in overall 83% yield (2 steps).[26] The desired bis(spiroketal) configuration of **34** was established by a key NOE interaction between H6 and the methyl group at C14, as also previously reported for analogous azaspiracid-derived bis(spiroketal) structures.[2,5] Finally, chemoselective removal of the TBDPS ether[27] (TBAF, AcOH, 86%) and subsequent Parikh–Doering oxidation[16] (91%) afforded the desired tetracyclic aldehyde **35**.

In summary, the convergent sequence afforded the fully elaborated ABCD aldehyde **35** in 20 linear steps and 16% overall yield. These advances led to the completion of the synthesis of (+)-azaspiracid-1 (*ent*-**2**) as detailed in the following Communication.[7]

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Keywords: ene reaction · natural products · nucleophilic addition · spiroketalization · total synthesis

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[7] See the following Communication: D. A. Evans, T. B. Dunn, L. Kværnø, A. Beauchemin, B. Raymer, E. J. Olhava, J. A. Mulder, M. Juhl, K. Kagechika, D. A. Favor, *Angew. Chem.* **2007**, *119*, 4782 – 4787; *Angew. Chem. Int. Ed.* **2007**, *46*, 4698 – 4703.

[8] A full account of these studies, including the first-generation syntheses of fragments, will subsequently be published.

[9] Abbreviations: Bn = benzyl, CBS = Corey–Bakshi–Shibata, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, DMP = Dess–Martin periodinane, DMSO = dimethylsulfoxide, LDA = lithium diisopropylamide, LiDBB = lithium di-*tert*-butyl biphenylide, Mes = 2,4,6-trimethylphenyl, Nu = nucleophile, PMB = 4-methoxybenzyl, PPTS = pyridinium *p*-toluenesulfonate, py = pyridine, TBAF = tetrabutylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TIPS = triisopropylsilyl.

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