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Synthesis of the ABCD and ABCDE ring systems of azaspiracid-1†‡

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Received (in Cambridge, UK) 5th July 2004, Accepted 2nd August 2004
First published as an Advance Article on the web 20th September 2004

The efficient syntheses of the ABCD ring system of the originally proposed structure of azaspiracid-1 and the ABCDE ring system of the revised structure of azaspiracid-1 containing the correct stereochemistry at C_6, C_{10}, C_{13}, C_{14}, C_{16}, C_{17}, C_{19}, C_{21}, C_{22}, C_{24} and C_{25} have been achieved.

Azaspiracid-1 (**1**) was discovered in 1995 when several individuals became ill after consuming mussels harvested from Killary Harbor in Ireland.[1] Yasumoto and co-workers soon concluded a new toxin, azaspiracid-1 (**1**), was the cause of the outbreak in Ireland (Fig. 1).[2] Subsequent to Yasumoto's original report, several derivatives **2**–**5** have been isolated from Ireland[3] and there is growing evidence of the spread of azaspiracid throughout other regions of Europe.[4] A recent report appears to link the presence of azaspiracid to an ubiquitous alga.[5] The toxic effects of azaspiracid have been shown to include serious injury to the digestive tracts, liver, pancreas, thymus and spleen in mice.[6] The significant effect of this toxin on the European shellfish industry[4] and its daunting structure garnered our attention[7] as well as the interest of several other laboratories.[8]

One particularly challenging portion of the azaspiracid architecture is the C_{10},C_{13} transoidal bisspiroketal moiety. This transoidal stereochemistry in **1** is proposed to exist with the C_{13} furan oxygen in an equatorial or "non-anomeric" orientation (Fig. 2). Given the fact that no external stabilizing force appears to be present, the non-anomeric orientation at this position has proven to be a demanding structural motif to construct. Our laboratory[7d–f] as well as the Nicolaou[8h] and Nishiyama[8m] laboratories have developed solutions to address this hurdle.

Recently, Nicolaou and co-workers revealed, in a series of impressive publications,[9] that azaspiracid-1 was actually misassigned. They initially proposed an alternate structure **6** involving the relocation of the $C_{8,9}$ alkene to the $C_{7,8}$ position and the enantiomer of C_{28}–C_{47} FGHI ring system (FGHI-*ent*).[9a,b] Nicolaou and co-workers asserted that movement of the alkene to the $C_{7,8}$ position might address their observation of two inseparable compounds (presumably due to the bisspiroketal) *versus* the one isomer observed by Yasumoto. While the data put forth by Nicolaou to justify his proposed structure **6** was clearly enticing, we were troubled by the complications created by the relocation of the $C_{8,9}$ olefin.[2] It was not apparent to us what stereochemical difference would be relayed to the bisspiroketal by movement of the $C_{8,9}$ alkene.

It was our belief that the major error(s) in structural assignment of azaspiracid lay in the CD ring system. We were intrigued by the possibility that the actual structure of azaspiracid might instead possess the epimeric C_{14} stereocenter (*e.g.* compound **8**). This modification would potentially allow the C_{13} spiroketal to return to its preferred anomeric conformation (Fig. 2). The differences in chemical shifts reported by Nicolaou[9a,b] at H_4–H_6 and H_8–H_9 might be explained by the significant difference in local environment caused by returning the C_{13} furan oxygen on the C ring to the anomeric conformation. Independent and concurrent to our efforts, the Nicolaou laboratory has revised their original proposal to include the epimeric C_{14} stereochemistry while establishing the correct structure of azaspiracid-1 (**7**).[9c,d] Herein, we describe our synthesis of the ABCD and ABCDE ring systems of azaspiracid. Our overall retrosynthetic strategy for compounds **1** and **8** is shown in Scheme 1.

Synthesis of the keto phosphonate **11** began from the commercially available Masamune auxiliary (Scheme 2).[10] Boron-mediated *anti*-aldol reaction[11] of 2-bromoacrolein with the norephedrine auxiliary produced the *anti* adduct in good diastereoselectivity. Subsequent protection of the C_{25} hydroxyl as

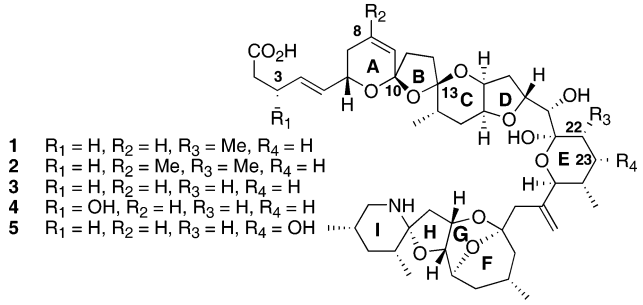


Fig. 1 Originally proposed structure assignments for azaspiracid-1 to azaspiracid-5.

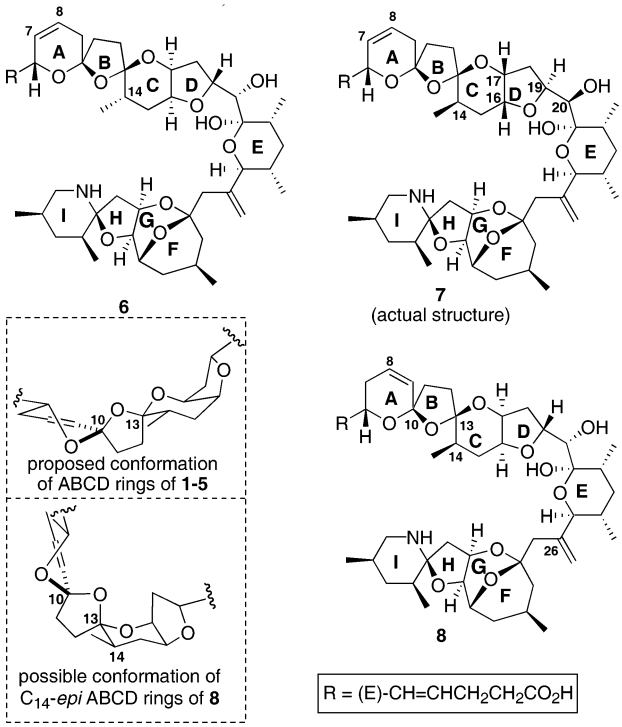
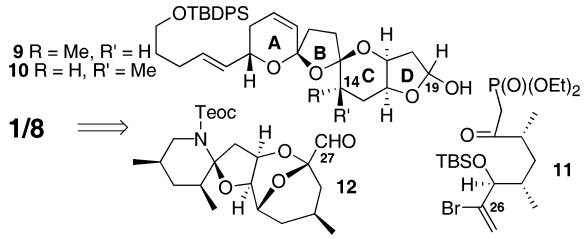


Fig. 2 Alternate proposed structures for azaspiracid-1.

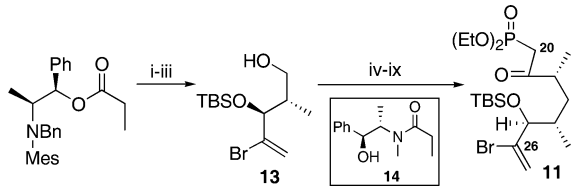
† Electronic Supplementary Information (ESI) available: Complete experimental procedures and ^1H and ^{13}C spectra are provided for all new compounds. See http://www.rsc.org/suppdata/cc/b4/b410092a/

‡ Dedicated to Professor Li-Xin Dai on the occasion of his 80th birthday.

DOI: 10.1039/b410092a



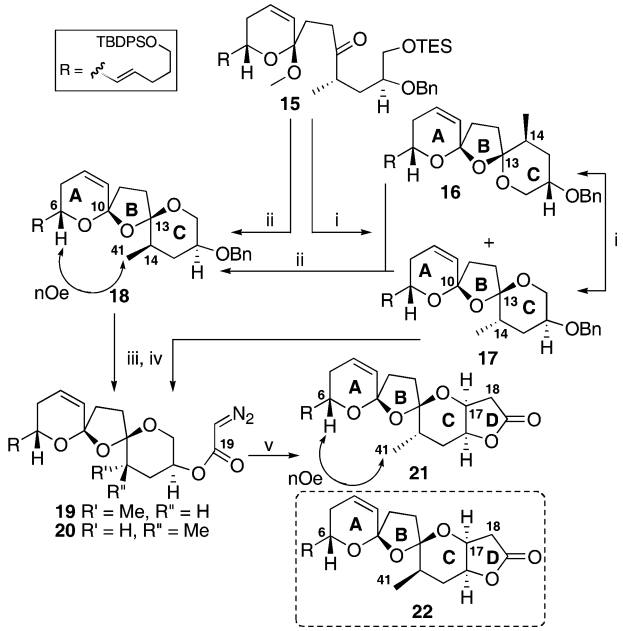
Scheme 1 Retrosynthetic plan for targets **1** and **8**.



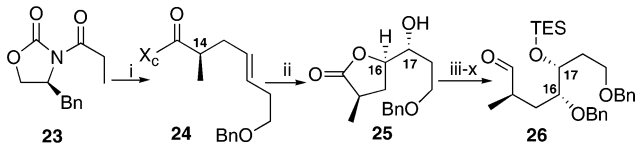
Scheme 2 (i) Cyx_2BOTf, Et_3N, 2-bromoacrolein, Et_2O, 92%, 93 : 7 d.r.; (ii) TBSOTf, Et_3N, DMAP, CH_2Cl_2, 62%; (iii) DIBAL-H, CH_2Cl_2, −78 °C, 86%; (iv) Ph_3P, imid., I_2, CH_2Cl_2, 88%; (v) LDA, LiCl, **14**, THF, 92%; (vi) LDA, $BH_3{\bullet}NH_3$, THF, 84%; (vii) TPAP, NMO, CH_2Cl_2, mol. sieves; (viii) $Me(O)P(OEt)_2$, *n*-BuLi, THF; (ix) PDC, DMF, mol. sieves, 53% over 3 steps.

its TBS ether followed by reduction yielded the alcohol **13**. Alteration to the corresponding iodide, Myers alkylation[12] and conversion to the keto phosphonate provided **11**.

The synthesis of the northern portion of azaspiracid commenced with previously reported ketone **15**[7e] (Scheme 3). Acid-catalyzed bisspirocyclization using PPTS in THF/H_2O yielded the two bisspiroketals **16** and **17** in near equal amounts (10 : 9). As observed previously, the unwanted cisoidal bisspiroketal **16** could be recycled to provide the transoidal bisspiroketal **17**. These conditions are an improvement on our original CSA, PhMe/*t*-BuOH conditions[7d–f] which provided a 5 : 3 ratio (**16** : **17**). Interestingly, treatment of the ketone **15** with CSA in hexanes led to formation of the C_{14}-*epi* transoidal compound **18**[13] as the major product (4.5 : 1 : 6 ratio for **16** : **17** : **18**). Unlike the bisspiroketals **16** and **17**, the C_{14}-*epi* compound **18** could *not* be re-equilibrated to the alternate spiroketals. It appears from this experiment that C_{14}-*epi* transoidal adduct **18** is the thermodynamic "sink" for the C_{16}-benzyloxy



Scheme 3 (i) PPTS, THF, H_2O, 40% **16**, 36% **17**; (ii) CSA, hexanes, 42% **18**, 32% **16**, 7% **17**; (iii) LiDBB, THF, −78 °C, 10 min; (iv) ClCOCH= N-NHTs, *N,N*-dimethylaniline, Et_3N, CH_2Cl_2, 60% **19** over 2 steps, 65% **20** over 2 steps; (v) $Rh_2(4S)$-(MPPIM)$_4$, CH_2Cl_2, reflux, 12% **21**.

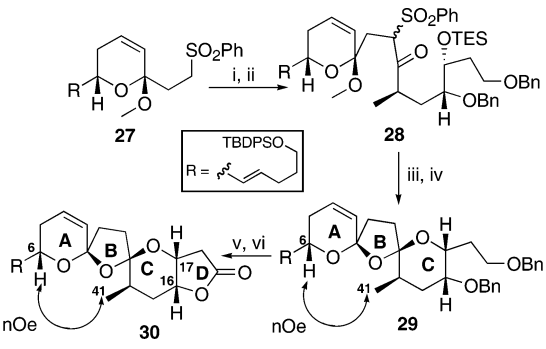


Scheme 4 (i) NaHMDS, $ICH_2CH{=}CHCH_2CH_2OBn$, THF, 92%; (ii) AD mix β*, $NaHCO_3$, *t*-BuOH, H_2O, r.t., 4 : 1 d.r., 55%; (iii) TIPSOTf, imid. DMF, 88%; (iv) $LiBH_4$, MeOH, THF, 99%; (v) PivCl, DMAP, Et_3N, CH_2Cl_2, 82%; (vi) BnBr, NaH, DMF; (vii) TBAF, THF, 24% over 2 steps; (viii) TESCl, DMAP, Et_3N, CH_2Cl_2, 99%; (ix) $LiBH_4$, MeOH, THF, 89%; (x) TPAP, NMO, CH_2Cl_2, mol. sieves, 95%.

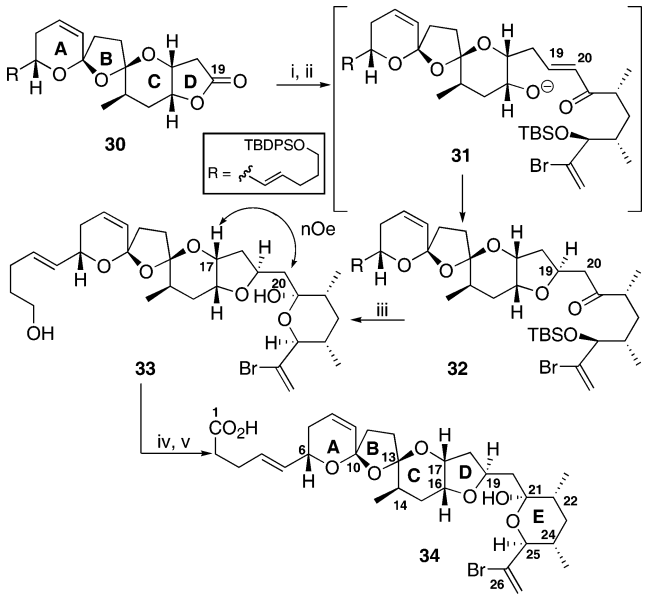
bisspiroketals. Working in parallel, removal of the C_{16} *O*-benzyl ether from **17** and **18** using LiDBB[14] followed by conversion to the diazoester yielded **19** and C_{14}-*epi* product **20**. Rhodium-catalyzed C–H insertion using traditional catalysts such as $Rh_2(OAc)_4$ performed poorly in our hands, yielding none of the desired lactone. Based on recent work by Doyle's[15] and Wee's[16] laboratories using the chiral catalyst $Rh_2[(4S)$-(MPPIM)$]_4$,[17] treatment of the diazo ester with 1 mol% of the rhodium catalyst in refluxing dichloromethane yielded the desired lactone in an unoptimized 12% yield for **21**. This compound proved to be *unstable* upon prolonged storage. The transoidal nature of the spiroketal **21** was confirmed by extensive 2D NMR. Unfortunately, the analogous C–H insertion with C_{14}-*epi* compound **20** appeared to provide only a trace of the presumed product **22**. Based on this result, synthesis of a C_{14} *epi*-variant of bisspirocyclization precursor **15**, which possessed C_{18} and C_{19} needed to be constructed.

Synthesis of the required aldehyde began with the readily available Evans alkylated product **24** (Scheme 4). We initially hypothesized that Sharpless dihydroxylation with AD mix β should provide the desired stereochemical combination at $C_{16,17}$. This stereochemical result would have been opposite of what would be predicted by the accepted Sharpless model;[18] however, we expected preferential π-stacking of the 1° *O*-benzyl ether[7a] with the AD mix ligands would reverse the selectivity. Subsequent functional group manipulation, in accord with our prior work,[7e,f] gave aldehyde **26**. After careful inspection of lactone **25** using Mosher ester analysis,[19] we discovered that our π-stacking hypothesis had proven to be in error. As the exact structure of azaspiracid-1 was still unknown at this point, we chose to pursue the bisspiroketalization with the aldehyde **26**.

Our standard Julia coupling approach[7c,f] with the previously prepared sulfone **27**[7a] followed by TPAP oxidation gave the keto sulfone **28** (Scheme 5). Na/Hg amalgam reduction and treatment with PPTS, THF/H_2O yielded the expected transoidal product **29** as the *sole* bisspiroketal. The formation of a single transoidal bisspiroketal coupled with the observed H_6-H_{41} NOE (also found in azaspiracid) led us to suspect that compound **29** possessed the correct stereochemistry present in the natural product. Finally, conversion of the lactone **30** was accomplished through LiDBB debenzylation and TPAP oxidation. Similar NOE correlations



Scheme 5 (i) **27**, LDA, THF, then **26**, −78 °C; (ii) TPAP, NMO, CH_2Cl_2, mol. sieves, 66% yield over 2 steps; (iii) Na/Hg, Na_2HPO_4, THF, H_2O, 82%; (iv) PPTS, THF, H_2O, 50%; (v) LiDBB, THF, −78 °C; (vi) TPAP, NMO, CH_2Cl_2, mol. sieves, 73% over 2 steps.



Scheme 6 (i) DIBAL-H, CH_2Cl_2, −78 °C, 78%; (ii) **11**, KHMDS, THF, −78 °C to r.t., 45%; (iii) TBAF, THF, 57%; (iv) TPAP, NMO, CH_2Cl_2, mol. sieves, 68%; (v) $NaClO_2$, *t*-BuOH, H_2O, 2-methyl-2-butene, 60%.

were again observed confirming the transoidal nature of both compounds.

With the synthesis of the lactone **30** complete, conversion to the ABCDE ring system was undertaken (Scheme 6). Reduction with DIBAL-H provided the lactol as a mixture of undetermined epimers. Subsequent Wadsworth–Emmons olefination with *in situ* cyclization[20] gave the coupled material **32** in reasonable (45%) yield. Finally, TBAF removal of the protecting groups and oxidation at C_1 gave the ABCDE ring system **34**.

Comparison of the NMR spectra of synthetic **33** and **34** and azaspiracid-1 in identical solvents (CD_3OD + 0.5% CD_3CO_2D) revealed some intriguing results. Large sections of the synthetic materials **33** and **34** were in good agreement with published data for azaspiracid-1.[2] Major points of divergence proved to be the $H_{8,9}$ alkene position and H_6 (^{1}H NMR: **33** H_6 = 4.36, **34** H_6 = 4.35, azaspiracid-1 H_6 = 4.81; **33** H_8 = 5.94, **34** H_8 = 5.95, azaspiracid-1 H_8 = 5.76). Given the results presented, we concluded that the relocation of the alkene to the $C_{7,8}$ position (*e.g.* compound **7**) was necessary for the actual structure of azaspiracid-1. Subsequent to this conclusion, Professor Nicolaou independently reported the confirmation of this assignment.[9d]

In summary, efficient approaches to the originally proposed ABCD ring system (17 steps from oxazolidinone *ent*-**23**) and the revised ABCDE ring system (21 steps from oxazolidinone **23**) of azaspiracid are presented. It is important to note that acid **34** contains the *correct* stereochemistry at C_6, C_{10}, C_{13}, C_{14}, C_{16}, C_{17}, C_{19}, C_{21}, C_{22}, C_{24} and C_{25} necessary for the actual structure of azaspiracid-1 (**7**).[9d] Key transformations include the Wadsworth–Emmons coupling to form the $C_{19,20}$ linkage and bisspiroketalization of the ketone **28** to provide a single *transoidal* bisspiroketal **29**. Further progress toward the total synthesis of the actual structure of azaspiracid-1 (**7**) will be reported in due course.

Financial support was provided by the National Institutes of Health (GM63723). We thank Professor Michael Doyle (University of Maryland) for his generous gift of the rhodium catalysts. The authors would also like to thank Professor Max Dienzer (OSU) and Dr. Jeff Morré (OSU) for mass spectral data, Roger Kohnert (OSU) for NMR assistance, Professor David A. Horne (OSU), Dr. Daniel P. Furkert (OSU) and Dr. Roger Hanselmann (Rib-X Pharmaceuticals) for their helpful discussions.

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