ORGANIC LETTERS

2000
Vol. 2, No. 24
3913−3916

Studies Directed toward the Total Synthesis of Azaspiracid: Stereoselective Construction of C_1–C_{12}, C_{13}–C_{19}, and C_{21}–C_{25} Fragments

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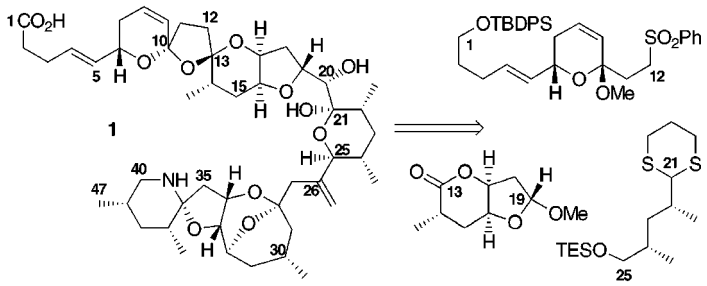
Received September 29, 2000

ABSTRACT



The efficient entry to the C_1–C_{12}, C_{13}–C_{19}, and C_{21}–C_{25} fragments of azaspiracid is outlined. The C_1–C_{12} portion is constructed using a key asymmetric allenyl borane addition to the corresponding α,β-unsaturated aldehyde. The synthesis of the C_{13}–C_{19} portion utilizes an Evans asymmetric alkylation followed by Sharpless asymmetric dihydroxylation. In addition, a novel solution to the mismatched effects of a neighboring chiral oxazolidinone during a Sharpless dihydroxylation is detailed.

Azaspiracid (**1**) was recently isolated in Killary Harbor, Ireland, from the mussel *Mytilus edulis*.[1] Two structurally similar derivatives, azaspiracid-2 (**2**) and azaspiracid-3 (**3**), were later discovered in the Arramore Island region of Donegal, Ireland.[2] Azaspiracids **1**−**3** have been shown to possess considerable toxicity in vitro with lethal doses in mice of 0.2, 0.11, and 0.14 mg/kg, respectively. The relative stereochemistries of **1**−**3** were determined by extensive NMR studies, but their absolute stereochemistry is, as yet, undetermined (Figure 1).

In addition, the origin of the azaspiracids remains a mystery. These compounds are believed to be dinoflagellate in nature, due to their highly oxygenated polyether structure; however, none of the known phytoplanktons were observed in the water samples. The low amounts isolated, as well as apparent seasonal occurrence, have hindered further investigation.

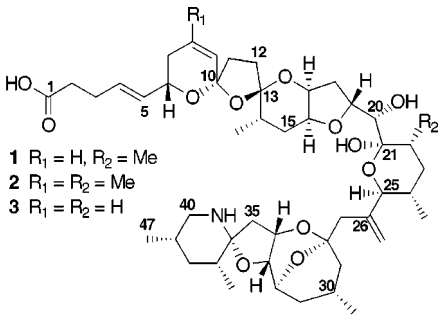


Figure 1. Azaspiracid and structural derivatives.

(1) (a) Satake, M.; Ofuji, K.; Naoki, H.; James, K. J.; Furey, A.; McMahon, T.; Silke, J.; Y.; Yasumoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 9967. (b) MacMahon, T.; Silke, J. *Harmful Algae News* **1996**, *14*, 2.

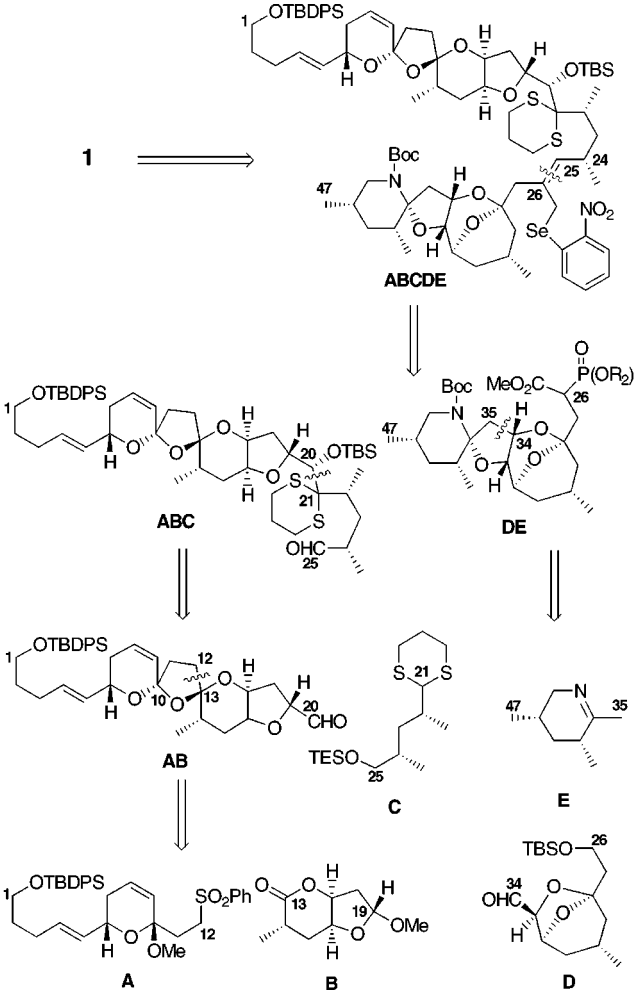
(2) Ofuji, K.; Satake, M.; McMahon, T.; Silke, J.; James, K. J.; Naoki, H.; Oshima, Y.; Yasumoto, T. *Nat. Toxins* **1999**, *7*, 99.

10.1021/ol006674w CCC: $19.00
Published on Web 11/07/2000

The structural architecture of spirocycle **1** possesses a challenging array of features: 47 carbons, 20 stereocenters, and 9 rings, including a unique azaspiro linkage fused to a [3.3.1] bicyclic nonane ring system. The formidable structural features of this molecule, in combination with the biological toxicity, make azaspiracid (**1**) an attractive synthetic target.[3] Other spirocyclic compounds, such as pinnatoxin A and okadaic acid, have also garnered considerable synthetic interest.[4]

Strategy. Because of the structural complexity and size of azaspiracid, it is imperative that any synthetic approach toward **1** be highly convergent. For this reason, **1** was broken down into five relatively equal fragments **A**−**E** (Scheme 1).

Scheme 1. Retrosynthetic Plan for Azaspiracid (**1**)

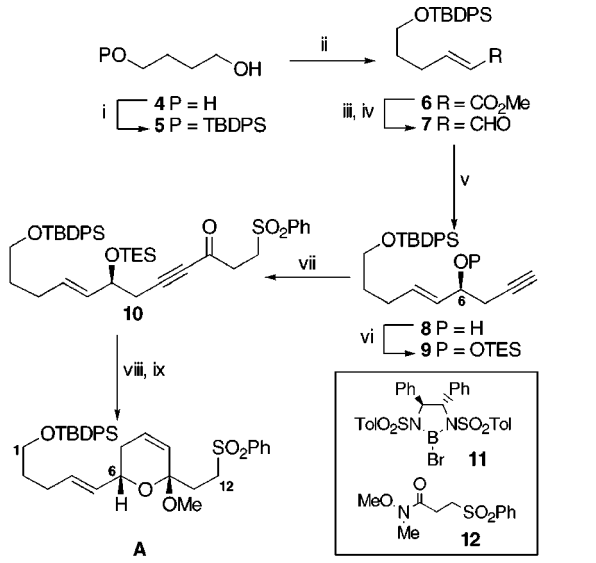


To construct the $C_{24,25}$ *anti*-configuration, we envision an oxidation of the aryl allylic selenide **ABCDE** with in situ [2,3]-sigmatropic rearrangement. Our laboratory has recently reported the first catalytic method for accomplishing this tandem reaction sequence.[5] The necessary $C_{25,26}$ alkene will be constructed using a Still−Gennari coupling[6] between aldehyde **ABC** and phosphonoester **DE**. The $C_{20,21}$ bond will be formed from a dithiane addition of **C** to the aldehyde **AB**, setting the C_{20} stereochemistry. Finally, the $C_{12,13}$ bond should be available via a sulfone ester coupling between fragments **A** and **B** followed by spirocyclization.

Fragment A. The critical C_6 ether linkage, embedded in the dihydropyran ring, represents the major challenge in the construction of fragment **A**. This stereocenter was envisioned to arise from a boron-mediated, asymmetric allenyl addition[7] to the α,β-unsaturated aldehyde. Successful examples of asymmetric propargyl or allenyl additions to unsaturated aldehydes are relatively rare,[8] in part to the decreased reactivity imparted by the alkene.[8a]

The construction of fragment **A** was accomplished in nine steps from commercially available 1,4-butanediol (**4**) (Scheme 2). Monoprotection of **4** as its TBDPS ether followed by

Scheme 2. Synthesis of the **A** Fragment[a]



[a] (i) TBDPSCl, DMAP, Et_3N, CH_2Cl_2; (ii) TPAP, NMO, molecular sieves, CH_2Cl_2; $Ph_3P{=}CHCO_2Me$, 78% (two steps); (iii) DIBAL-H, CH_2Cl_2, −78 to 0 °C, 99%; (iv) TPAP, NMO, molecular sieves, CH_2Cl_2, 89%; (v) triphenylpropargyl stannane **11**, CH_2Cl_2, −78 °C, 74%, 80% ee; (vi) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 85%; (vii) *n*-BuLi, $CeCl_3$ (1.3 equiv), THF; **12**, 63%; (viii) Lindlar's catalyst, H_2, quinoline, hexanes, 57%; (ix) $Et_3N{\cdot}HF$, MeOH, CH_2Cl_2, then PPTS, 64%.

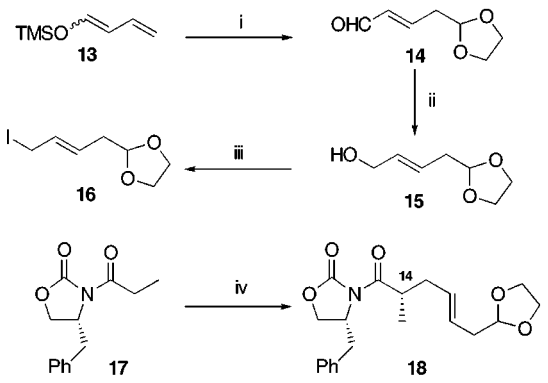
TPAP oxidation and in situ Wittig olefination provided the *trans*-ester **6** in 78% overall yield. DIBAL-H reduction of **6** with subsequent oxidation using TPAP proceeded without incident in 89% yield. Incorporation of the propargyl

(3) (a) Hao, J.; Aiguade, J.; Forsyth, C. *Abstracts of Papers*, 219th National Meeting of the American Chemical Society, San Francisco; American Chemical Society: Washington, DC, 2000; ORGN-767. (b) Aiguade, J.; Hao, J.; Forsyth, C. J. *Abstracts of Papers*, 219th National Meeting of the American Chemical Society, San Francisco; American Chemical Society: Washington, DC, 2000; ORGN-766. (c) Illig, A. M.; Aiguade, J.; Forsyth, C. J. *Abstracts of Papers*, 219th National Meeting of the American Chemical Society, San Francisco; American Chemical Society: Washington, DC, 2000; CHED-373. (d) Forsyth, C. J.; Aiguade-Bosch, J.; Dounay, A. B.; Hao, J. *Abstracts of Papers*, 218th National Meeting of the American Chemical Society, New Orleans; American Chemical Society: Washington, DC, 1999; ORGN-619.

functionality using Corey's bromoborane reagent **11** efficiently provided the desired alcohol **8** in 74% yield. The enantiomeric excess (ee) of 80% as well as the absolute configuration were determined via Mosher ester analysis.[9] Formation of the dianion of **8** followed by addition of the Weinreb amide **12** (prepared from the commercially available acid chloride) resulted in significant amounts of elimination of the β-phenyl sulfonyl group. For this reason, the 2° alcohol function was masked using TESOTf to provide the silyl ether **9**. Lithiation of the acetylene using *n*-BuLi, followed by addition to the amide **12**, in the presence of $CeCl_3$, yielded the desired acetylenic ketone **10** in 63% yield. Partial reduction using Lindlar's catalyst in the presence of quinoline incorporated the necessary *cis* alkene in 57% yield. Finally, after considerable experimentation, desilylation using $Et_3N\cdot HF$ followed by in situ ketalization using PPTS provided the desired fragment **A** in 64% yield.

Fragment B. Incorporation of the critical C_{14} stereocenter represented the first major hurdle in the construction of fragment **B**. Treatment of **13** with 2-methoxy-1,3-dioxolane in the presence of zinc chloride gave the desired enal **14** in 61% yield (Scheme 3).[10] Reduction of the aldehyde **14** using

Scheme 3. Construction of the C_{14} Stereocenter[a]

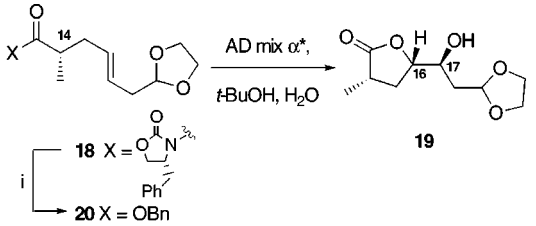


[a] (i) 2-methoxy-1,3-dioxolane, $ZnCl_2$, CH_2Cl_2, 61%; (ii) DIBAL-H, Et_2O, −78 to 25 °C, 76%; (iii) Ph_3P, I_2, imidazole, MeCN, Et_2O (1:3), 91%; (iv) NaHMDS, THF, −78 °C; **16**, −78 °C, 99%, >95% ds.

DIBAL-H provided the allylic alcohol **15**. The iodide **16** was initially constructed via the mesylate (Ms_2O, Et_3N, 0 °C, 92%); however, conversion to halide using sodium iodide in acetone proved to be capricious on amounts greater than 1 g. Ultimately, the iodide **16** was effectively synthesized using triphenylphosphine and iodide in the presence of a slight excess of imidazole in 91% yield. Finally, the key alkylation of the iodide **16** with the sodium enolate derived from commercially available oxazolidinone **17** was successfully accomplished in 99% yield with excellent diastereoselectivity (ds > 20:1).

Our interest now shifted to the critical dihydroxylation using the Sharpless asymmetric dihydroxylation methodology (Table 1).[11] The Sharpless mnemonic predicted that AD mix

Table 1. Selected Examples Sharpless Dihydroxylation Selectivity Based on Carbonyl Substitution[a]



entry	alkene	additive	yield (d.s.)
1	18	none	36% †
2	18	$NaHCO_3$	87% (2.5:1)
3	20	$NaHCO_3$	77% (10:1)

[a] i) LiOBn, BnOH, THF, 0 °C, 90%, 85% recovered auxiliary. † The d.s. was not determined due to impurities.

α should give the desired stereochemistry; however, it should be noted that Brimble and co-workers have recently observed a complete reversal in selectivity using the AD mixes on an Evans alkylated product.[12] Treatment of alkene **18** with AD mix α*[13] did induce dihydroxylation, with contaminant cyclization, to provide the desired lactone **19** in a disappointing 36% yield. The stereochemical outcome of the dihydroxylation was secured via X-ray crystal analysis of **19**. The yield of this transformation could be improved dramatically by buffering the solution with three equivalents of sodium bicarbonate; however, poor selectivity was observed (2.5:1).[14] One possible explanation for the poor selectivity in the dihydroxylation could be a mismatched interaction between the oxazolidinone and the chiral osmium species. To investigate this hypothesis, the alkene **18** was converted into its benzyl ester **20**. Subsequent dihydroxylation, with in situ lactonization, indeed did lead to improved selectivity (10:1) of **19** without a significant decrease in yield (77%). The major diastereomer could be easily recrystallized to greater than 20:1 selectivity in 68% isolated yield.

(4) For a recent review, see: Brimble, M. A.; Farés, F. A. *Tetrahedron* **1999**, *55*, 7661.
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(7) Corey, E. J.; Yu, C.-M.; Lee, D.-H. *J. Am. Chem. Soc.* **1990**, *112*, 878.
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(9) (a) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (c) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143.
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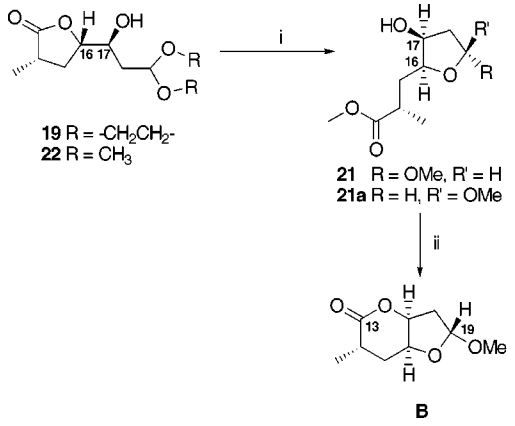
(11) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(12) Allen, P. A.; Brimble, M. A.; Prabaharan, H. *Synlett* **1999**, 295.
(13) AD mix α* = [$(DHQ)_2PHAL$ (154 mg), $K_2OsO_2\cdot 2H_2O$ (25.5 mg), K_2CO_3 (2.90 g), $K_3Fe(CN)_6$ (7.00 g)] Commercially available AD mix α proved to be slow and inefficient.
(14) The undesired diastereomer appears to be preferentially consumed in the dihydroxylation in the absence of $NaHCO_3$.
(15) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1987**, *109*, 2208−10.

With a viable route to the lactone **19**, the next challenge was the construction of the bicyclic methoxy acetal **B** (Scheme 4). This reorganization required the conversion of

Scheme 4. Completion of the **B** Fragment[a]

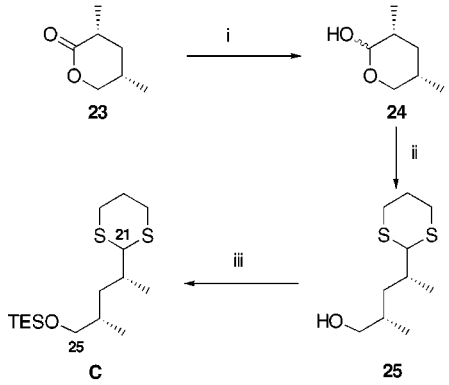


[a] (i) p-TsOH, MeOH, 64% (after three cycles); (ii) imidazole, MeCN, 90 °C, 97%.

the γ-lactone into the desired Δ-lactone and formation of the furan acetal via the C_{16} hydroxyl function. Initially, treatment of acetal **19** under aqueous acidic conditions did lead to removal of the C_{19} acetal; however, approximately 10% elimination of the β-hydroxyl function was also observed. Fortunately, treatment of **19** under methanolic acidic conditions led to conversion to desired furan acetal **21** in 64% yield after three cycles. The remaining mass balance consisted of the anomeric methoxy furan **21a** (12%) and the desired bicycle **B** (7%) as well as the dimethoxy acetal **22**. These products were easily separable, and resubmission of **22** and **21a** led to the same equilibrium mixture. Finally, lactonization of **21** with imidazole in acetonitrile[15] at reflux gave the desired fragment **B** in 97% yield. X-ray crystal analysis of the bicycle **B** allowed for the conclusive establishment of the C_{19} stereochemistry.

Fragment C. The synthesis of the dithiane fragment **C** was based on close analogy to literature precedent (Scheme 5).[16] Starting from the known lactone **23** (available in five

Scheme 5. Synthesis of Fragment **C**[a]



[a] (i) DIBAL-H, CH_2Cl_2, −60 °C, 95%; (ii) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 72%; (iii) TESCl, Et_3N, CH_2Cl_2, 84%.

steps from commercially available methyl (*R*)-(−)-3-hydroxy-2-methylpropionate), reduction to the lactol **24** was accomplished using DIBAL-H in 95% yield. Subsequent treatment of **24** with 1,3-propanedithiol in the presence of $BF_3{\cdot}Et_2O$ provided the thioacetal **25** in 72% yield. It should be noted that less than 5% epimerization at C_{22} was observed during this sequence. Finally, protection the 1° hydroxyl function as its TES ether provided fragment **C** in 84% yield.

The stereoselective construction of the C_1-C_{12}, $C_{13}-C_{19}$, and $C_{21}-C_{25}$ fragments of azaspiracid has been achieved in nine, eight, and eight steps, respectively. The synthesis of the C_1-C_{12} portion utilizes the Corey allenyl borane methodology as an effective method for asymmetric addition to a functionalized, α,β-unsaturated aldehyde. The $C_{13}-C_{19}$ fragment is constructed using an Evans alkylation followed by a Sharpless asymmetric dihydroxylation. A unique solution for increased diastereoselectivity in a mismatched system is reported. Our continued progress toward the total synthesis of **1** will be reported in due course.

Acknowledgment. The authors thank the University of Mississippi for their generous support of this work, Dr. Todd D. Williams (University of Kansas) for mass spectral data, and Dr. Walter E. Cleland, Jr. (University of Mississippi) for X-ray crystal data.

Supporting Information Available: Experimental procedures and spectral characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006674W

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