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Synthetic Studies toward the C5–C20 Domain of the Azaspiracids

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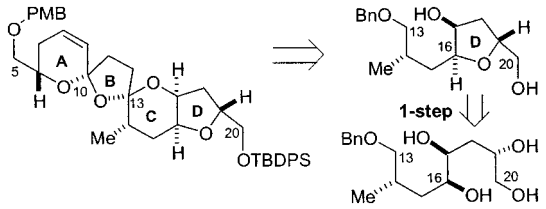
ABSTRACT



An approach toward the C5–C20 THF-fused trioxadispiroketal portion of the azaspiracids is reported. The highly substituted azaspiracid D ring (C16–C19) was prepared by the one-pot conversion of a tetraol into a tetrahydrofuran. Efforts to establish the C10 and C13 spiroketal centers via an oxonium-initiated bis-spiroketalization under both kinetic and thermodynamic conditions have yielded the (10*R*,13*S*)-trioxadispiroketal 19 as the major product, which is diastereomeric with the (10*R,13*R**) relative configuration assigned to the azaspiracids.**

The marine natural product azaspiracid (**1**, Figure 1) was isolated from the mussel *Mytilus edulis* and implicated as the causative toxin in human poisoning events beginning in The Netherlands in 1995.[1] Two closely related analogues of **1**, azaspiracid-2 (**2**) and azaspiracid-3 (**3**), have recently been reported as well.[2] The azaspiracids are structurally complex ω-amino acids that contain within their 40-carbon backbone an unprecedented array of polycyclic, spiro-fused ring systems.[3] The structural complexity, stereochemical ambiguity, biological activity, and scarcity of the azaspiracids have stimulated considerable interest in the synthesis of these natural products.[4] A growing need for authentic samples for environmental monitoring has emerged. Initial synthetic efforts toward the C5−C20 THF-fused bis-spiroketal-containing domain (**4**) of the azaspiracids are described herein.

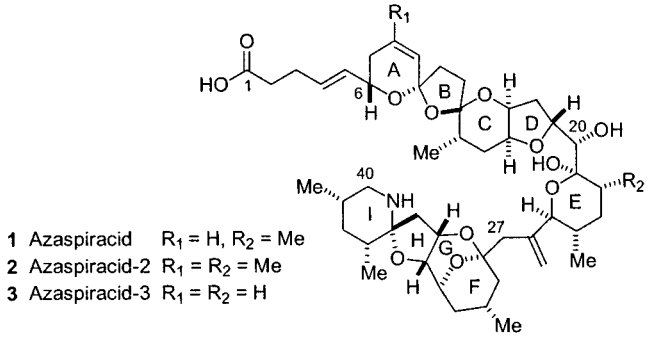


Figure 1. Azaspiracids.

Synthetic Design. The original strategy for assembly of the A−D ring system of azaspiracid relied upon the acid-catalyzed bis-spiroketalization of **5** to form the A and B rings

(1) Satake, M.; Ofuji, K.; Naoki, H.; James, K. J.; Furey, A.; McMahon, T.; Silke, J.; Yasumoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 9967.

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

(3) For a review of bis-spiroketal natural products and their syntheses see: (a) Brimble, M. A.; Farès, F. A. *Tetrahedron* **1999**, *55*, 7661. (b) McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647.

(4) (a) Carter, R. G.; Weldon, D. J. *Org. Lett.* **2000**, *2*, 3913. (b) Aiguade, J.; Hao, J.; Forsyth, C. J. *Tetrahedron Lett.* **2001**, *42*, 817. (c) Hao, J.; Aiguade, J.; Forsyth, C. J. *Tetrahedron Lett.* **2001**, *42*, 821. (d) Aiguade, J.; Hao, J.; Forsyth, C. J. *Org. Lett.* **2001**, *3*, 979.

(5) A similar acid-triggered spiroketalization was employed to install the dioxaspiro[4.5]nonane system of okadaic acid: Forsyth, C. J.; Sabes, S. F.; Urbanek, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 8381.

(6) Numbering corresponds to that of **1**−**3**.

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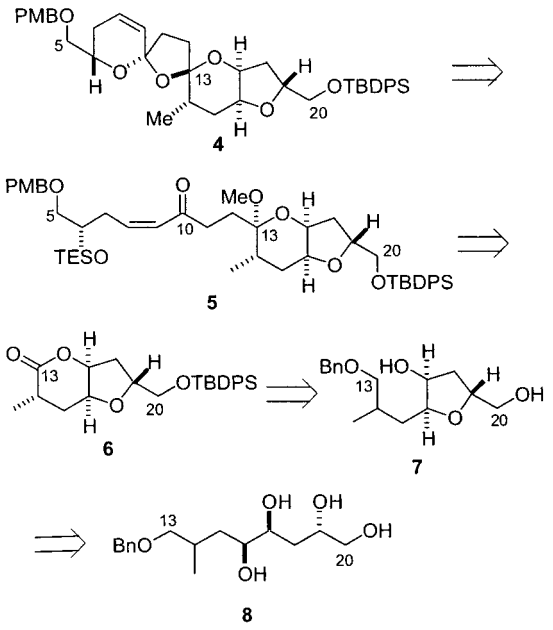
Scheme 1. Synthetic Strategy for the C5−C20 Domain of the Azaspiracids

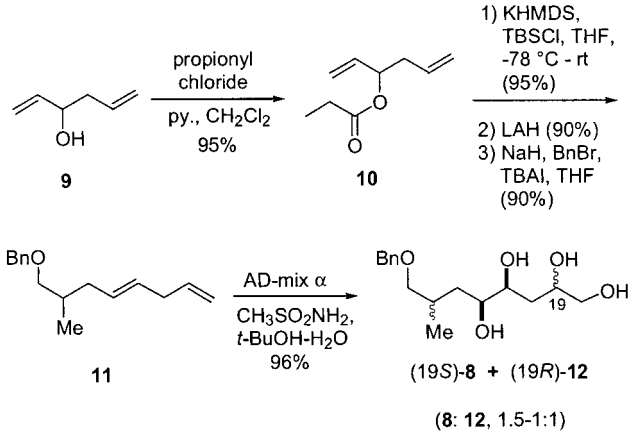


(Scheme 1).[5] Enone **5** would be derived from lactone **6**, which in turn could be obtained from diol **7** as a result of regioselective protection, debenzylation, and oxidation. The relative configuration at C14[6] would be established at the stage of lactone **6** as a result of equilibration of the methyl group to the anticipated thermodynamically favored equatorial position.

The synthesis of the highly functionalized tetrahydrofuran **7** would employ the use of a novel method for the one-pot conversion of a tetraol into a tetrahydrofuran. The envisioned conversion of tetraol **8** to tetrahydrofuran **7** would involve selective sulfonylation of the primary C20 hydroxyl group of **8**, followed by base-induced epoxide formation and intramolecular trans-etherification in a 5-*exo* mode to provide **7**. This concept is based on the earlier development of a one-pot conversion of vicinal diols into transient epoxides and the in situ nucleophilic opening of the epoxides under carbanionic conditions.[7] Tetraol **8** was expected to arise from a stereoselective bis-dihydroxylation of a diene using Sharpless asymmetric dihydroxylation (SAD) methodology.

Results and Discussion. Efforts toward the construction of the C5−C20 domain of azaspiracid began with the synthesis of the tetraol **8** (Scheme 2). The readily available

Scheme 2. Synthesis of C13−C20 Tetraol



allylic alcohol (±)-**9**[8] was acylated with propionyl chloride to provide allylic ester **10**. Conversion of **10** to its *tert*-butyldimethylsilyl ketene acetal followed by Ireland-Claisen rearrangement[9] gave the α-methyl TBS-silyl ester, which was hydrolyzed to the carboxylic acid upon workup. In the same manner, (*S*)-**10**[10] was treated with LDA followed by TMSCl in THF to give the corresponding (*R*)-α-methyl-carboxylic acid in 70% yield and 75% ee. However, the C14 stereocenter could ultimately be established more conveniently from (±)-**9** via epimerization at a later stage. Reduction of the carboxylic acid with $LiAlH_4$ followed by benzylation of the resultant primary alcohol yielded diene **11** in excellent overall yield.

Bis-dihydroxylation of diene **11** under standard SAD conditions[11] consistently provided a mixture of chromatographically separable tetraols **8** and **12** as the result of the highly diastereoselective dihydroxylation at the internal olefin and a surprisingly low diastereoselectivity of terminal olefin dihydroxylation.[12] Use of enantiomerically enriched **11** in the SAD reaction also gave rise to a mixture of C19 epimers. Attempts to optimize this stereorandom dihydroxylation with the use of other ligands[13] ($(DHQ)_2PYR$ and $(DHQ)_2AQN$) provided no improvements in diastereoselectivity. Nevertheless, the high overall yield and brevity of this approach allowed for easy synthetic access to tetraol **8**.

Tetraol **8** was employed in a study of a novel, one-pot conversion of a tetraol into a tetrahydrofuran via a dihydroxy-epoxide intermediate (Scheme 3). Base-induced trans-etherifications of hydroxy epoxides have been successfully employed in the construction of heterocycles toward the

(7) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 8122.

(8) Compound **9** is commercially available from Aldrich Chemical Co., or it can be synthesized via addition of allylmagnesium bromide to acrolein.

(9) (a) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III. *J. Org. Chem.* **1991**, *56*, 650. (b) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041. (c) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

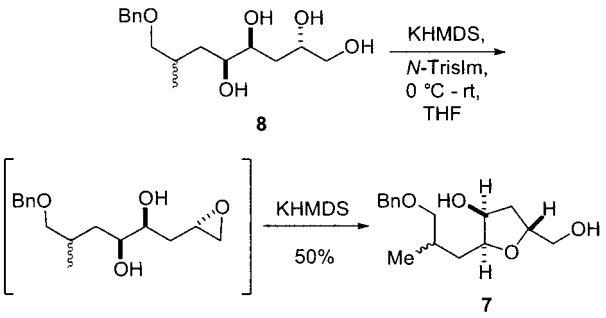
(10) Either enantiomer of **9** is available in high % ee from the enantioselective allylation of acrolein with the appropriate *B*-allyldiisopinocampheylborane; see: Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

(11) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L.; *J. Org. Chem.* **1992**, *57*, 2768. (b) For a review on Sharpless asymmetric dihydroxylation: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(12) The diol intermediate resulting from dihydroxylation of the terminal olefin prior to dihydroxylation of the 1,2-disubstituted olefin showed a ca. 1.5−1:1 dr by ^1H NMR spectroscopic analysis. This suggests that the poor diastereoselectivity does not simply result from intramolecular directing effects of the internal diol.

(13) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785.

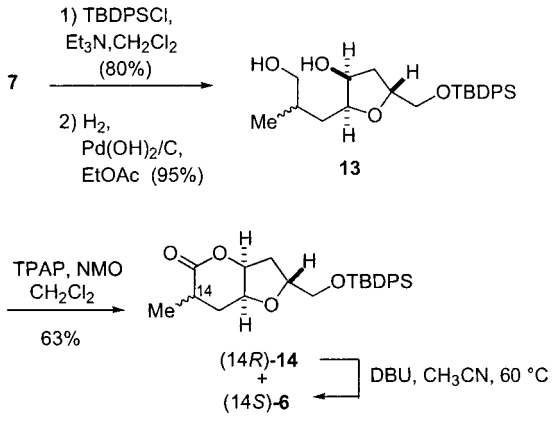
Scheme 3. Base-Induced Epoxidation and Tetrahydrofuran Formation from Tetraol



synthesis of complex polyether natural products.[14] However, the expediency and convenience of a one-pot conversion of a tetraol to a tetrahydrofuran without the intermediacy of an isolated hydroxy epoxide is synthetically advantageous. After extensive experimentation, it was found that treatment of the tetraol with 1 equiv of KHMDS followed by slow addition of 1 equiv of *N*-triisopropylsulfonylimidazole[15] allowed for selective sulfonylation of the primary alcohol. Subsequent treatment with an additional equivalent of base provided the diol-epoxide, which underwent base-induced tetrahydrofuran formation upon treatment with excess KHMDS and warming to room temperature. The one-pot protocol allowed for conversion of tetraol **8** to substituted tetrahydrofuran **7** in moderate yield.[16] This transformation represents a remarkably convenient and relatively efficient method for construction of highly substituted tetrahydrofurans.

A short sequence of standard transformations allowed for conversion of tetrahydrofuran **7** to lactone **6** (Scheme 4).

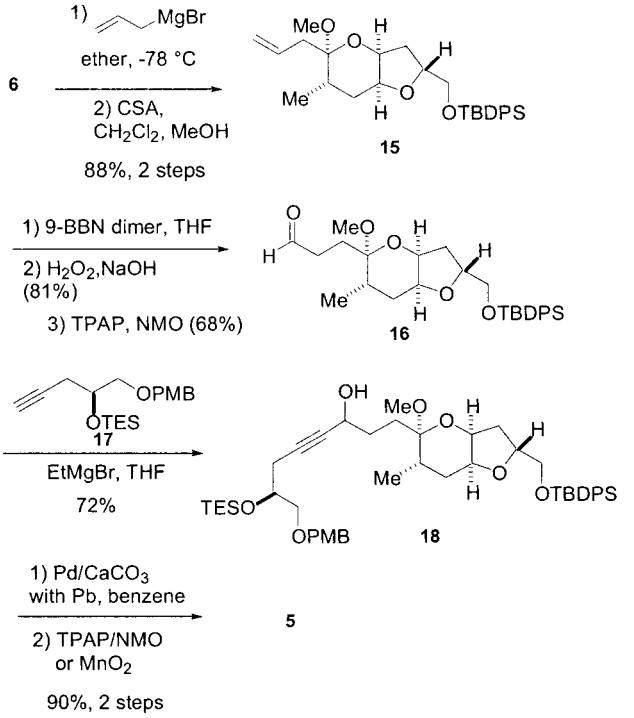
Scheme 4. Synthesis of C13−C20 Lactone



The primary alcohol of **7** was selectively protected as a TBDPS ether, and the benzyl ether was cleaved by hydrogenolysis to provide diol **13**. Oxidation using TPAP/NMO provided the chromatographically separable lactones **6** and **14** in moderate yield. Other oxidation conditions, including PCC and TEMPO, were explored, but these provided no enhancement in yield. The overall yield of **6** was improved by subsequent partial epimerization of **14** with DBU in CH_3CN at 60 °C for 48 h. At this stage, the relative stereochemistry between C16 and C19 was verified using NOE studies. Additionally, the configuration of the C14 methyl-bearing stereocenter in lactones **6** and **14** was determined on the basis of $^1H-^1H$ *J*-coupling values and NOE studies. X-ray crystallography of the diol obtained by $LiAlH_4$ reduction of **14** verified the stereochemical assignments.

Lactone **6** was elaborated into bis-spiroketalization precursor **5** (Scheme 5). Treatment of **6** with 1 equiv of allylmagnesium bromide cleanly provided the hemiketal, which was converted to mixed methyl ketal **15**. Hydroboration-oxidation of the olefin in **15** with 9-BBN/H_2O_2 gave the sensitive primary alcohol, and oxidation with TPAP/NMO yielded aldehyde **16**. Addition of the magnesium acetylide of alkyne **17**[17] to aldehyde **16** provided propargylic alcohol **18**. Lindlar reduction of propargylic alcohol **18** generated the (*Z*)-allylic alcohol, which was oxidized to enone **5** using TPAP/NMO or MnO_2.

Scheme 5. Synthesis of the C5−C20 Enone



(14) (a) Sasaki, M.; Inoue, M.; Takamatsu, K.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 9399. (b) Matsukura, H.; Morimoto, M.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 5545. (c) Hoye, T. R.; Witowski, N. E. *J. Am. Chem. Soc.* **1992**, *114*, 7291.

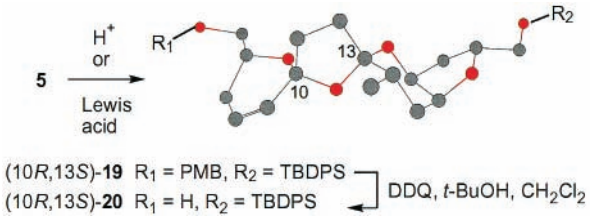
(15) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Lipshutz, B. *J. Am. Chem. Soc.* **1980**, *102*, 1439. Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974**, 203.

(16) For convenience on a multigram scale, the mixture of **8** and **12** was typically used directly in the THF-ring formation step, at which stage diol **7** was readily separated from its C19 epimer by column chromatography.

(17) Alkyne **17** was derived from commercially available (*R*)-(+)-glycidol in four steps: (i) PMBCl, NaH, TBAI, THF; (ii) trimethylsilylacetylene, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF; (iii) TBAF, THF; (iv) TESCl, Et_3N, DMAP, CH_2Cl_2.

Treatment of enone **5** under acidic conditions was expected to yield the derived trioxadispiroketal as a result of C13 oxonium formation and spiroketalization accompanied by loss of the TES group (Scheme 6). Exposure of enone **5** to

Scheme 6. Spiroketalization of the C5−C20 Enone



numerous Brönsted and Lewis acids (e.g., PPTS, CSA, BF_3·OEt_2, TMSOTf) with a variety of solvents (e.g., benzene, THF, acetonitrile, dichloromethane) and reaction temperatures consistently resulted in the formation of trioxadispiroketal **19** as the major product. Treatment of enone **5** with TMSOTf in CH_3CN at −40 °C provided **19** in 85% yield, without the generaton of diastereomeric spiroketals. Enone **5** was also treated with CSA in various solvents at room temperature to allow for equilibration to the thermodynamically favored trioxadispiroketal. Although **19** was the major product under all reaction conditions surveyed, a minor diastereomeric side product, **19***, was also formed under the CSA conditions.[18] The configurations at C10 and C13 of **19** were initially assigned on the basis of extensive NOE studies and were verified by X-ray crystallography of the derived alcohol **20**. Molecular mechanics calculations indicate that the (10*R*,13*S*)-configurational array within the C5−C20 trioxadispiroketal, which experiences a double anomeric stabilization due to the axial-type orientation of the B-ring oxygen atom with respect to both the A- and C-ring pyrans, is approximately 2−3 kcal/mol lower in energy than the corresponding (10*R*,13*R*)-trioxadispiroketal. Experimental results also suggest that **19** is kinetically more accessible than **4** from enone **5** under the reaction conditions surveyed. The observed kinetic selectivity for the (13*S*)-configuration of **19** may be explained by the stereoelectronically favored axial attack of the C10 keto-oxygen atom upon an initially formed oxonium species at C13.

Conclusions. A synthesis of trioxadispiroketal (10*R*,13*S*)-**19** has been developed that begins with a novel method for formation of the highly substituted tetrahydrofuran **7** and subsequent oxonium-initiated bis-spiroketalization. Continued studies will explore the scope and limitations of the polyol etherification cascade that led to **7** and its applicability to the synthesis of other cyclic ether-containing natural products. The tetrahydrofuran **7** was elaborated into bis-spiroketalization precursor **5**. Thereafter, formation of the trioxadispiroketal system by intramolecular trapping of an oxonium species generated at C13 gave the same major product [(10*R*,13*S*)-**19**] under thermodynamic and kinetic conditions. The corresponding (10*R*,13*R*)-intermediate **4**, which appears to represent a contra-thermodynamic configurational array, remains the target of ongoing synthetic studies.

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Supporting Information Available: Experimental procedures and spectral data for compounds **5**, **6**, **7**, **7a**, **7b**, **10**, **10a**, **10b**, **11**, **14**, **15**, **15a**, **16**, **18**, **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Studies are underway to fully characterize **19***. The ratio of **19**:**19*** obtained under various CSA conditions ranged from 4:1 (benzene, 24 h) to 7:3 (CH_3CN, 24−48 h).