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Synthesis of the ABC Ring System of Azaspiracid. 1. Effect of D Ring Truncation on Bis-spirocyclization†

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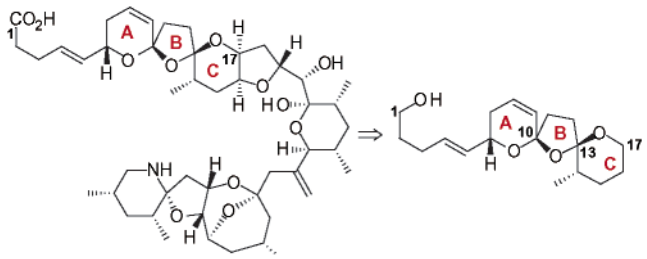
ABSTRACT



Synthesis of a spirocyclization precursor with a truncated D ring has been accomplished. Subsequent bis-spirocyclization induced the formation of equal amounts of the natural transoidal 10*R*,13*R* bis-spirocycle and its cisoidal 10*R*,13*S* epimer under an apparent thermodynamically controlled process.

A new class of toxins in shellfish, the azaspiracids, has been recently observed in mussels harvested in the surrounding waters of Europe (Scheme 1).[1] Azaspiracid (**1**)[2] and its related structures, azaspiracids 2−5 (**2**−**5**),[3,4] have been shown to induce serious injury to the digestive tracts, liver, pancreas, thymus, and spleen in mice. In addition to their significant biological properties, the azaspiracids represent a daunting synthetic challenge as the parent structure **1** possesses 20 stereocenters and three separate spirocyclic linkages. For these reasons, the azaspiracids have garnered significant recent attention in both the biological[1−5] and synthetic communities.[6−8] This paper discloses the successful construction of the C_1-C_{17} portion of azaspiracid including the crucial C_{10}, C_{13} transoidal bis-spirocyclic array.

Strategy. The major stumbling block in the synthesis of the northern portion of azaspiracid has been the effective

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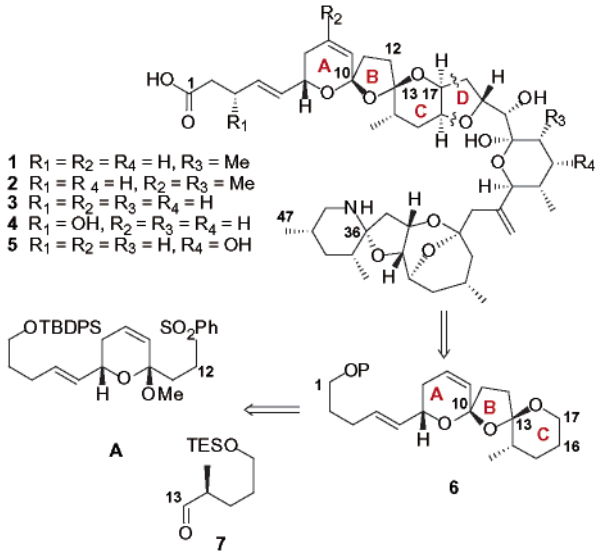
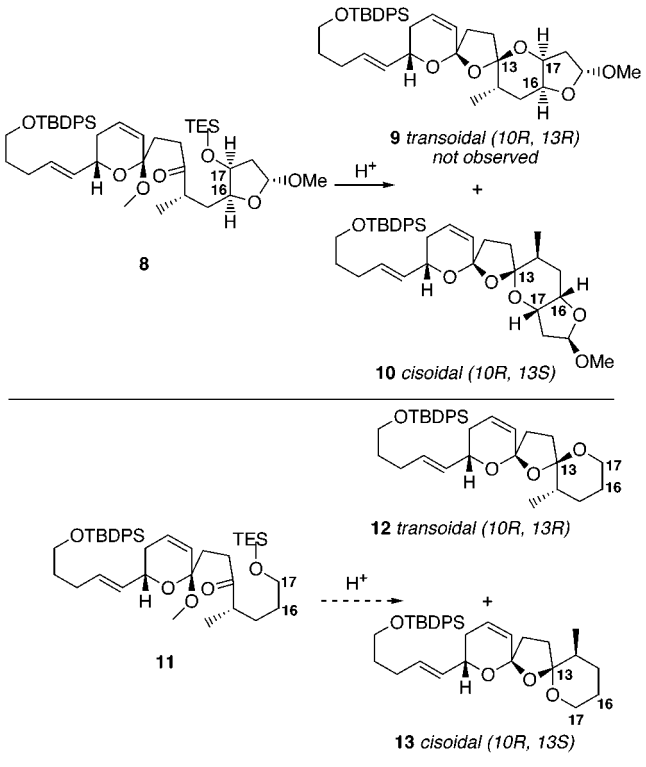
Scheme 1. Retrosynthetic Strategy for Truncation of D Ring in Bis-spirocyclization



construction of the natural transoidal bis-spirocycle at C_{10} and C_{13}.[8] Our laboratory[6b,c] as well as others[7c,g,8] have disclosed the apparent preference for the undesired cisoidal orientation of the spirocycles on systems possessing a fully functionalized surrounding architecture (Scheme 2). One possible solution for this problem would be the simplification of the surrounding functionality in order to facilitate the desired stereochemical array. Low-level molecular modeling

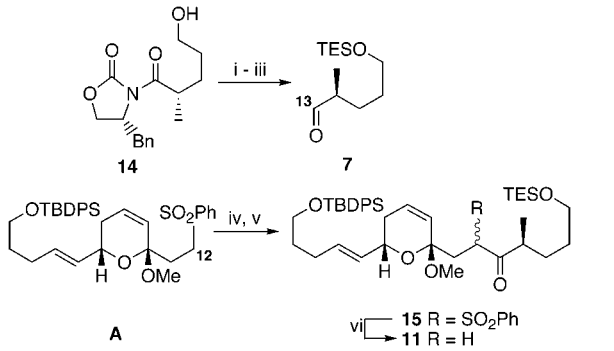
Scheme 2. Proposed Truncation of D Ring at C_{16} and C_{17}



calculations showed that truncation of the D ring allows for a significant narrowing of the energy difference between the cisoidal and transoidal stereochemical arrays. Based on these observations, we felt it was prudent to explore a strategy in which the furan D ring was included after spirocyclization. Access to the appropriate bis-spirocyclization precursor **11** should be available from our previously established Julia coupling strategy between sulfone **A** and aldehyde **7** (Scheme 1).[6]

Exploration of Simplified Model System. The Julia coupling of the previously synthesized sulfone **A**[6a] with the readily available aldehyde **7**[9] proceeded smoothly in 81% yield as a mixture of all four diastereomers (Scheme 3).

Scheme 3. Julia Coupling Strategy[a]



[a] Key: (i) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 86%; (ii) $LiBH_4$, MeOH, THF, 81%; (iii) TPAP, NMO, CH_2Cl_2, molecular sieves, 96%; (iv) LDA, THF, −78 °C, then add **7**, 81%; (v) TPAP, NMO, CH_2Cl_2, molecular sieves, 78%; (vi) Na/Hg, Na_2HPO_4, MeOH, THF, −10 °C.

Subsequent TPAP oxidation yielded the desired keto sulfone **15**. To construct the viable model system for the spirocyclization, the keto sulfone **15** was converted to the labile ketone **11**[10] using Na/Hg amalgam.[11]

A series of spirocyclization conditions were explored as shown in Table 1. Our optimum conditions (Table 1, entry 4) employed camphorsulfonic acid (CSA) in an equal mixture of toluene and *tert*-butyl alcohol to provide a separable 1:1 ratio of the desired *transoidal* spirocycle **12** and the undesired cisoidal spirocycle **13** in a 68% yield from **15**. Both compounds **12** and **13** were assigned via 2D NMR techniques ($CDCl_3$ for **12**, C_6D_6 for **13**). Two key NOEs (H_{12} to H_9 and H_{12} to H_{17}) allowed for the establishment of the *natural transoidal* 10*R*,13*R* spirocycle **12** over the alternate non-natural transoidal spirocycle that our laboratory has observed

(9) The aldehyde **7** is available in three steps from the known alcohol **14**. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(10) It is interesting to note that while the keto sulfones (such as **15**) can be stored indefinitely in the freezer, the desulfonylated carbonyl species (i.e., ketone **11**) are prone to elimination at $C_{10,11}$ to the corresponding enol ether. This elimination, however, is not at all detrimental to the subsequent bis-spirocyclization as the enol ether is the first observed intermediate in the TES deprotection/spirocyclization sequence.

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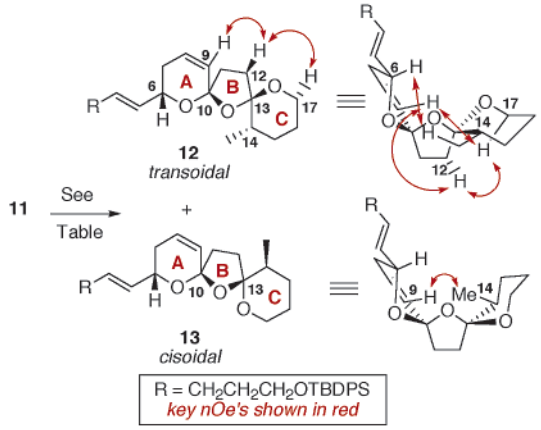
Table 1. Bis-spirocyclization with a Precursor Lacking Substitution at C_{16} and C_{17}

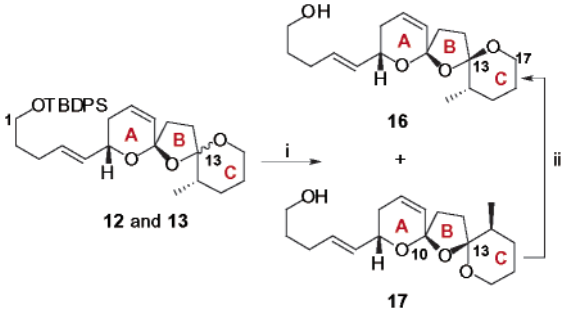


entry	conditions	ratio of **12**:**13**
1	CSA, MeCN	decomposition
2	CSA, PhMe	decomposition
3	PPTS, *t*-BuOH	1:2
4	CSA, 50% PhMe / 50% *t*-BuOH	1:1 (68% from **15**)

on D-ring-containing systems.[6c] These NOEs are *only* possible in the natural transoidal spirocycle as shown in structure **12**; the alternate non-natural transoidal bis-spirocycle would not provide this NOE pattern. Finally, the observed data support a "nonanomeric" C ring conformation, placing both the C_{13} oxygen and the C_{14} methyl in the equatorial positions. This hypothesis is also consistent with the proposed conformation for the natural product.[2] In addition, resubmission of the undesired cisoidal product **13** to the same reaction conditions (0.04 M CSA, *t*-BuOH/PhMe, 14−18 h) led to an *identical equilibrium mixture*. This result is in contrast to our previous work with substrates containing the D ring in which resubmission of the cisoidal product did not lead to formation of any further transoidal material.[6c]

While the cisoidal and transoidal spirocycles **12** and **13** could be separated by careful chromatography, the similarity in the two compounds' R_f's made this method impractical for the isolation of significant quantities of material. Removal of the C_1 silyl protecting group, however, facilitated straightforward separation of the two spirocycles **16** and **17** in an 86% overall yield (Scheme 4). We were also gratified to find that resubmission of the cisoidal spirocycle **17** to the identical spirocyclization conditions (0.04 M CSA, *t*-BuOH/PhMe, 14−18 h) led to a similar equilibrium mixture (9:11 for compounds **16**/**17**). Using one equilibration cycle, an overall 62% yield can be obtained of the desired transoidal bis-spirocycle **16**.

Scheme 4. Synthesis of C_1-C_{17} Azaspiracid Fragment[a]



[a] Key: (i) TBAF, THF, 43% of **16** and 43% of **17**; (ii) CSA, *t*-BuOH/PhMe (1:1), 44% of **16** and 50% of **17**.

The synthesis of the C_1-C_{17} fragment of azaspiracid has been accomplished. The *natural* configurations at the two key spiroketal linkages have been accessed by truncation of the D ring at C_{16} and C_{17}. The bis-spirocyclization appears to be the result of a thermodynamically controlled process. The equilibration of cisoidal bis-spirocycles **13** and **17** to their corresponding transoidal epimers **12** and **16** represent the *first* examples of equilibration of a properly functionalized ABC ring system possessing the $C_{8,9}$ alkene. Exploration into the bis-spirocyclization of precursors containing C_{16} and C_{17} substitution is disclosed in the following paper in this issue.[12]

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

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