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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 C₁–C₁₇ portion of azaspiracid including the crucial C₁₀, C₁₃ transoidal bis-spirocyclic array.

Strategy

The major stumbling block in the synthesis of the northern portion of azaspiracid has been the effective construction of the natural transoidal bis-spirocycle at C₁₀ and C₁₃.⁸ 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 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

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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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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). 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 (CDCl₃ for **12**, C₆D₆ for **13**). Two key NOEs (H₁₂ to H₉ and H₁₂ to H₁₇) 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 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 C₁₃ oxygen and the C₁₄ 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 C₁ 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**.

The synthesis of the C₁–C₁₇ 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 C₁₆ and C₁₇. 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 C₁₆ and C₁₇ substitution is disclosed in the following paper in this issue.¹²

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

Scheme 2.
Proposed Truncation of D Ring at C₁₆ and C₁₇

Scheme 3. Julia Coupling Strategy^a

^a Key: (i) TESOTf, 2,6-lutidine, CH₂Cl₂, -78 °C, 86%; (ii) LiBH₄, MeOH, THF, 81%; (iii) TPAP, NMO, CH₂Cl₂, molecular sieves, 96%; (iv) LDA, THF, -78 °C, then add 7, 81%; (v) TPAP, NMO, CH₂Cl₂, molecular sieves, 78%; (vi) Na/Hg, Na₂HPO₄, MeOH, THF, -10 °C.

Scheme 4. Synthesis of C₁-C₁₇ 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**.

Table 1Bis-spirocyclization with a Precursor Lacking Substitution at C₁₆ and C₁₇

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