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Synthesis of the ABC Ring System of Azaspiracid. 2. A Systematic Study into the Effect of C_{16} and C_{17} Substitution on Bis-spirocyclization†

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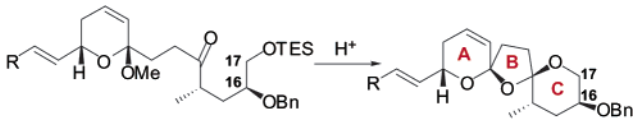
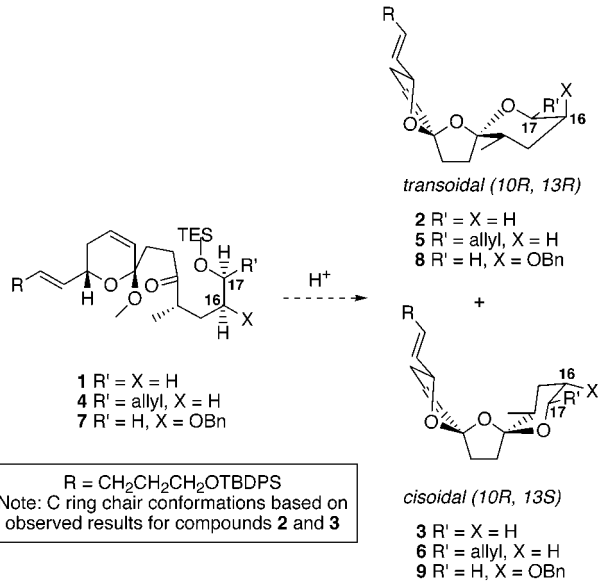
ABSTRACT



A systematic study into the effect of C_{16} and C_{17} substitution on the stereochemical outcome of bis-spirocyclization to form the ABC ring system of azaspiracid is disclosed. Successful construction of the natural 10*R*,13*R* bis-spirocyclic stereochemistry has been accomplished on the C_{16} benzyloxy-containing precursor.

The azaspiracids are an intriguing class of recently isolated natural products that possess a complex structural framework as well as considerable biological activity.[1−3] As discussed in the previous paper,[4] the D ring appears to exert considerable influence on the bis-spirocyclization. Based on these results, our efforts shifted toward the construction of selected substrates containing substitution at C_{16} or C_{17} (Scheme 1). The C_{17} series appeared more attractive as inspection of the potential chair conformations of bis-spiroketals **2** and **3**[4] revealed that the transoidal and the cisoidal structures were both capable of placing the C_{17} allyl substituent equatorial on the basis of the proposed conformation for bis-spiroketals **5** and **6**.

Scheme 1. Potential Combinations for Substitution Patterns at C_{16} and C_{17}



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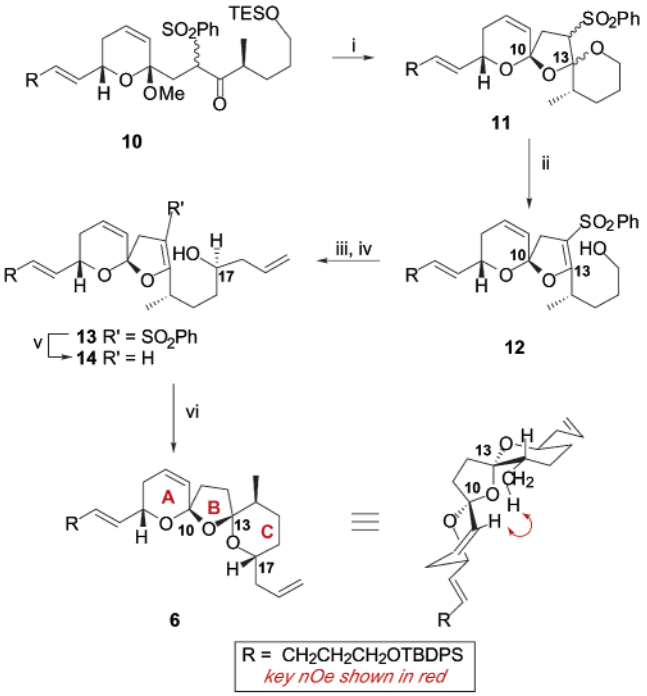
C_{17} Substitution. Spirocyclization of previously described keto sulfone **10**[4] using our preferred conditions for keto sulfone substrates (CSA, MeCN)[5] led to a mixture of stereoisomers (Scheme 2). Treatment of the spirocycle **11**

Scheme 2. Bis-spirocyclization of C_{17} Allyl Substrate[a]

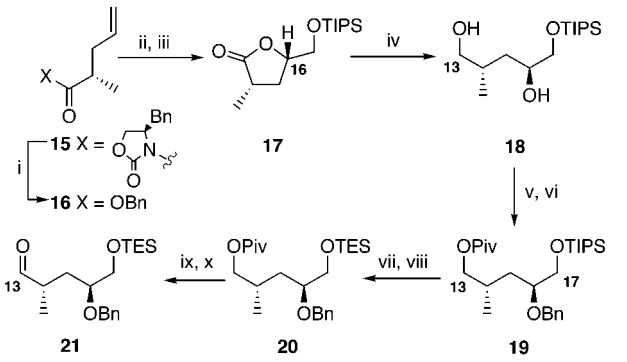


[a] Key: (i) CSA, MeCN, 90%; (ii) *n*-BuLi, THF, −78 °C, 70%; (iii) TPAP, NMO, CH_2Cl_2, mol. sieves, 96%; (iv) (+)-Ipc_2Ballyl, Et_2O, pentane, 70%, >20:1 d.s.; (v) 5% Na/Hg, Na_2HPO_4, MeOH, THF, −10 °C; (vi) CSA, *t*-BuOH, PhMe, 76% (over two steps).

with *n*-BuLi induced *β*-elimination to yield the elaborate enol ether **12** in 70% yield, along with 10% of the presumed C_{10} epimer. The strategy allowed for the protection of the C_{13} carbonyl function while selectively revealing the C_{17} hydroxyl group. Oxidation at C_{17} followed by Brown allylation[6] yielded the homoallylic alcohol **13** in greater than 20:1 d.s. Removal of the sulfone functionality revealed the highly labile enol ether **14**, which rapidly underwent spirocyclization under the standard conditions (0.04 M CSA, *t*-BuOH/PhMe, 14−18 h) to give the bis-spiroketal **6** as a single diastereomer. Unfortunately, NOESY and COSY NMR experiments ($CDCl_3$) confirmed the *cisoidal* 10*R*,13*S* relationship of the bis-spiroketal. While it is important to point out that the enol ether spirocyclization precursor **14** is structurally different than ketone **4**, previous work in our laboratory has shown that the C_{10} ketal is readily ionized under acidic conditions,[5] thereby ensuring formation of comparable spirocyclization intermediates from both precursors. It is interesting to note, however, that the sulfone moiety once again provided added stability,[7] as **13** was indefinitely stable in the freezer. Also, our ketalization/*β*-elimination/desulfonylation strategy represents, to the best of our knowledge, a unique strategy for the effective construction of highly labile enol ethers (e.g., **14**).

C_{16} Substitution. The synthesis of the required benzyloxy aldehyde **21** began with the known Evans alkylation product **15**[8] (Scheme 3). Conversion to its benzyl ester **16** followed

Scheme 3. Synthesis of the C_{16} Benzyloxy-Substituted Aldehyde[a]



[a] Key: (i) BnOLi, PMBOH, THF, 99%; (ii) AD mix α, $NaHCO_3$, *t*-BuOH, H_2O; (iii) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 66% overall yield from **16** (3:1 d.s.); (iv) $LiBH_4$, MeOH, THF, 0 °C, 99%; (v) PivCl, Et_3N, DMAP, CH_2Cl_2, 66%; (vi) NaH, BnBr, DMF, −50 °C to −10 °C; (vii) TBAF, THF, 79% (over two steps); (viii) TESCl, DMAP, Et_3N, CH_2Cl_2, 95%; (ix) $LiBH_4$, saturated aqueous NH_4Cl, THF, 0 °C to rt, 99%; (x) TPAP, NMO, CH_2Cl_2, molecular sieves, 87%.

by Sharpless asymmetric dihydroxylation,[9] in situ lactonization, and TIPS protection yielded the lactone **17**, in overall 66% yield from **16**, as a separable 3:1 ratio at C_{16} favoring the desired stereochemistry.[10] While the diastereomeric selectivity in the dihydroxylation is less than optimum (3:1 d.s.), direct dihydroxylation of the chiral oxazolidinone-containing alkene **15** provided inferior results (1.5:1 d.s.). This observation is consistent with our previous findings with other oxazolidinone-containing alkenes.[11] Subsequent reduction using $LiBH_4$ provided the diol **18**. Next, sequential protection at C_{13} and C_{16} produced the fragment **19**, along with a small amount of impurities derived from migration of the pivaloate and silyl protecting groups. Removal of the TIPS ether under standard conditions allowed for easy purification. The C_{17} hydroxyl was reprotected as its TES ether **20**. Cleavage of the C_{13} pivaloate protecting group did

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(7) We have consistently observed an increased stabilization in substrates containing the sulfone function versus their corresponding desulfonylated counterparts, which are prone to elimination at $C_{10,11}$ to the corresponding enol ether.
(8) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
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(10) A small, inseparable bi-product was present in **17**. Fleming and coworkers recently reported the presence of an *n*-propyl silyl impurity in selected TIPS protection protocols. As silylation as alternate silyl protecting groups (such as TBS or TES) did *not* lead to a similar impurity, it would appear that the *n*-propyl silyl species is a reasonable explanation. Barden, D. J.; Fleming, I. *Chem Commun.* **2001**, 2366.
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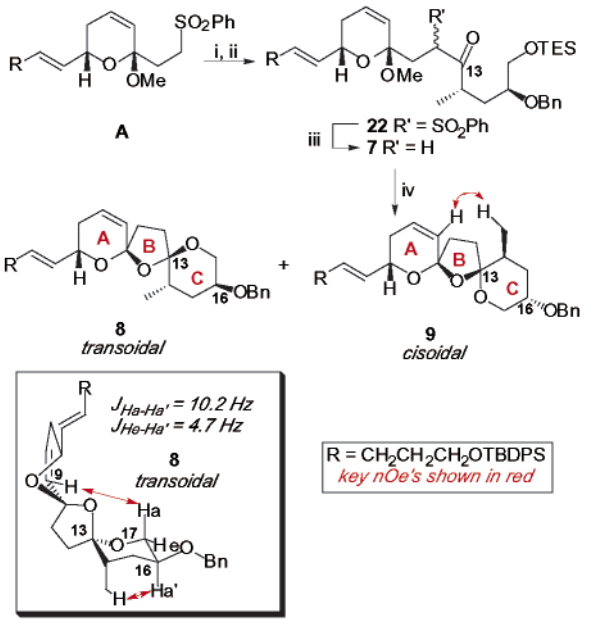
prove problematic with DIBAL-H;[12] however, the use of $LiBH_4$, in the presence of a small amount of saturated aqueous NH_4Cl, cleanly provided the desired alcohol in 99% yield. Finally, TPAP oxidation yielded the target aldehyde **21**.

Lithiation of sulfone **A** with LDA followed by addition of the aldehyde **21** provided the hydroxy sulfone adduct as a labile mixture[13] of all four diastereomers (Scheme 4).

Scheme 4. Bis-spirocyclization of C_{16} Benzyloxy Substrate[a]



[a] Key: (i) LDA, THF, −78 °C then **21**; (ii) TPAP, NMO, CH_2Cl_2, molecular sieves 60% (over two steps); (iii) 5% Na/Hg, Na_2HPO_4, MeOH, THF, −10 °C; (iv) CSA, PhMe/*t*-BuOH, 80%, 3:5 ratio (**8**/**9**).

Immediate oxidation to the ketone sulfone **22** was accomplished with TPAP in a 60% yield over two steps. Desulfurization under standard conditions followed by bis-spirocyclization (0.04 M CSA, *t*-BuOH/PhMe, 14−18 h) gave *two* spiroketals in a 3:5 ratio (**8**/**9**) in an overall 80% yield. After careful separation of the two isomers, the stereochemistry of the more polar isomer was determined to be the cisoidal ketal **9** (2D NMR, $CDCl_3$). We were gratified to find, however, that the less polar spirocycle **8** possessed the *natural transoidal* stereochemistry at C_{10} and C_{13} as established by ROESY and COSY correlations (C_6D_5N). While the NOE between the C_9 alkene to C_{17} hydrogen was previously observed in the transoidal product **2** from the D ring truncated series,[4] the NOE between the C_6 hydrogen and the methyl at C_{14} was *not* present. This lack of signal can be explained by the placement of the C_{13} furan oxygen and the C_{14} methyl substituents in *axial* orientations within the pyran C ring. Further NMR evidence supports this hypothesis: (1) a strong NOE is observed between the C_{14} methyl and the C_{16} hydrogen and (2) the coupling constants between the C_{16} and C_{17} hydrogens match the predicted data for the proposed C ring, chair conformation using the Karplus correlation.[14] Furthermore, the alternate chair conformer (with the C_{13} furan oxygen and the C_{14} methyl substituent in equatorial orientations) is significantly higher in energy (3.4 kcal/mol) using the B3LYP density functional and a 6-31G(d) basis set. It should also be noted that the observed NOE and coupling constant data would *not* be expected for the alternate non-natural transoidal bis-spirocycle.[5] Finally, the proposed conformation of transoidal spirocycle **8** is in contrast to the previously discussed transoidal spirocycle **2**, which appeared to place the C_{13} furan oxygen and the C_{14} methyl substituents in equatorial orientations.

To further study the nature of the bis-spiroketalization, the reaction with ketone **7** was performed at lower temperatures (−10 to +4 °C, 21 h) and reduced molarity of the acid catalyst (0.003 M) under otherwise identical reaction conditions (1:1 *t*-BuOH/PhMe). We were intrigued to discover that the predominate product was the *cisoidal* bis-spirocycle **9**. Gratifyingly, further warming of the reaction to room temperature for an additional 48 h resulted in the previously observed (3:5 ratio of **8**:**9**) equilibrium mixture.[15] It would appear from these observations that the cisoidal bis-spirocycle **9** is the result of *kinetic* control while the transoidal bis-spirocycle **8** can be accessed under *thermodynamic* conditions. With one equilibration cycle, a 50% overall yield of the desired transoidal bis-spirocycle **8** can be obtained. Finally, use of Nicolaou and co-workers' conditions[16] for equilibration of their cisoidal bis-spirocycle to the natural transoidal species (3 equiv of TFA, CH_2Cl_2) provided inferior results for the conversion of **9** to **8** (approximately 1:3 ratio for **8**:**9**).[17]

The *first* systematic study into the effect of substituents on the bis-spirocyclization of a series of precursors has been presented. The C_{16} oxygen substitution facilitated formation of a nearly equal mixture of the cisoidal and transoidal bis-spirocycles while C_{17} allyl substitution provided sole access to the cisoidal species. Our continuing progress toward the total synthesis will be reported in due course.

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(12) It is unclear at this juncture as to the exact nature of the problem; however, the experimental data is consistent with silyl migration of the C_{17} TES protecting group.

(13) The Julia adduct appeared to be prone to rapid spirocyclization of the C_{13} hydroxyl moiety onto a corresponding C_{10} oxonium ion. This problem could be easily circumvented by the immediate oxidation of the hydroxy sulfone intermediate (without purification or storage) to the corresponding keto sulfone **22**.

(14) Karplus, M. *J. Phys. Chem.* **1959**, *30*, 11.

(15) The same ratio (3:5, 92% overall yield) can also be observed by resubmission of the cisoidal bis-spirocycle **9** to the standard conditions (0.04 M CSA, *t*-BuOH/PhMe, 14−18 h).

(16) Nicolaou, K. C.; Qian, W.; Bernal, F.; Uesaka, N.; Pihko, P. M.; Hinrichs, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4068.

(17) While this protocol appeared to reach equilibrium in a similar time frame to Nicolaou and co-workers (4 h), the TFA/CH_2Cl_2 conditions led to a significantly more complex crude reaction mixture, presumably due to decomposition.

for mass spectral data. Finally, we thank Dr. Roger Hanselmann (Rib-X Pharmaceuticals) for his helpful discussions.

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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