Synthesis of the ABC Ring System of Azaspiracid. 2. A Systematic Study into the Effect of C₁₆ and C₁₇ Substitution on **Bis-spirocyclization**[†]

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ABSTRAC



A systematic study into the effect of C16 and C17 substitution on the stereochemical outcome of bis-spirocyclization to form the ABC ring system of azaspiracid is disclosed. Successful construction of the natural 10R,13R bis-spirocyclic stereochemistry has been accomplished on the C₁₆ 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.

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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



^{*a*} Key: (i) CSA, MeCN, 90%; (ii) *n*-BuLi, THF, -78 °C, 70%; (iii) TPAP, NMO, CH₂Cl₂, mol. sieves, 96%; (iv) (+)-Ipc₂Ballyl, Et₂O, pentane, 70%, >20:1 d.s.; (v) 5% Na/Hg, Na₂HPO₄, 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 C13 carbonyl function while selectively revealing the C₁₇ hydroxyl group. Oxidation at C17 followed by Brown allylation6 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 (CDCl₃) confirmed the cisoidal 10R,13S relationship of the bisspiroketal. 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 C₁₀ 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



^{*a*} Key: (i) BnOLi, PMBOH, THF, 99%; (ii) AD mix α, NaHCO₃, *t*-BuOH, H₂O; (iii) TIPSOTf, 2,6-lutidine, CH₂Cl₂, -78 °C, 66% overall yield from **16** (3:1 d.s.); (iv) LiBH₄, MeOH, THF, 0 °C, 99%; (v) PivCl, Et₃N, DMAP, CH₂Cl₂, 66%; (vi) NaH, BnBr, DMF, -50 °C to -10 °C; (vii) TBAF, THF, 79% (over two steps); (viii) TESCl, DMAP, Et₃N, CH₂Cl₂, 95%; (ix) LiBH₄, saturated aqueous NH₄Cl, THF, 0 °C to rt, 99%; (x) TPAP, NMO, CH₂Cl₂, 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 oxazolidinonecontaining 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 LiBH₄ 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 silvl protecting groups. Removal of the TIPS ether under standard conditions allowed for easy purification. The C₁₇ 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.

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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 LiBH₄, 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 mixture¹³ of all four diastereomers (Scheme 4).



^{*a*} Key: (i) LDA, THF, -78 °C then **21**; (ii) TPAP, NMO, CH₂Cl₂, molecular sieves 60% (over two steps); (iii) 5% Na/Hg, Na₂HPO₄, 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 bisspirocyclization (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, CDCl₃). We were gratified to find, however, that the less polar spirocycle **8** possessed the *natural transoidal* stereochemistry at C₁₀ and C₁₃ as established by ROESY and COSY correlations (C₆D₅N). While the NOE between the C₉ alkene to C₁₇ hydrogen was previously observed in the transoidal product **2** from the D ring truncated series,⁴ the NOE between the C₆ hydrogen and the methyl at C₁₄ was *not* present. This

lack of signal can be explained by the placement of the C13 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 C16 and C17 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 bisspirocycle.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 C₁₄ 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* bisspirocycle 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 bisspirocycle 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' conditions¹⁶ for equilibration of their cisoidal bis-spirocycle to the natural transoidal species (3 equiv of TFA, CH₂Cl₂) 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 bisspirocycles 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**.

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⁽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).

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⁽¹⁷⁾ While this protocol appeared to reach equilibrium in a similar time frame to Nicolaou and co-workers (4 h), the TFA/CH₂Cl₂ 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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