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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†

Rich G. Carter[*,‡], **David E. Graves**[§], **Melissa A. Gronemeyer**[§], and **Gregory S. Tschumper**[§]

‡*Department of Chemistry, Oregon State UniVersity, CorVallis, Oregon 97331*

§*Department of Chemistry and Biochemistry, UniVersity of Mississippi, UniVersity, Mississippi 38677*

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**.

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** 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

†This work was performed at the University of Mississippi.

rich.carter@oregonstate.edu.
The corresponding author's present address is Department of Chemistry, Oregon State University, Corvallis, OR 97331.

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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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 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 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). 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

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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.

Supplemental Materials

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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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 DJ, Fleming I. Chem Commun 2001:2366.
11. Carter RG, Weldon DJ. Org Lett 2000;2:3913. [PubMed: 11101452]
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 KC, Qian W, Bernal F, Uesaka N, Pihko PM, Hinrichs J. Angew Chem Int Ed 2001;40:4068.

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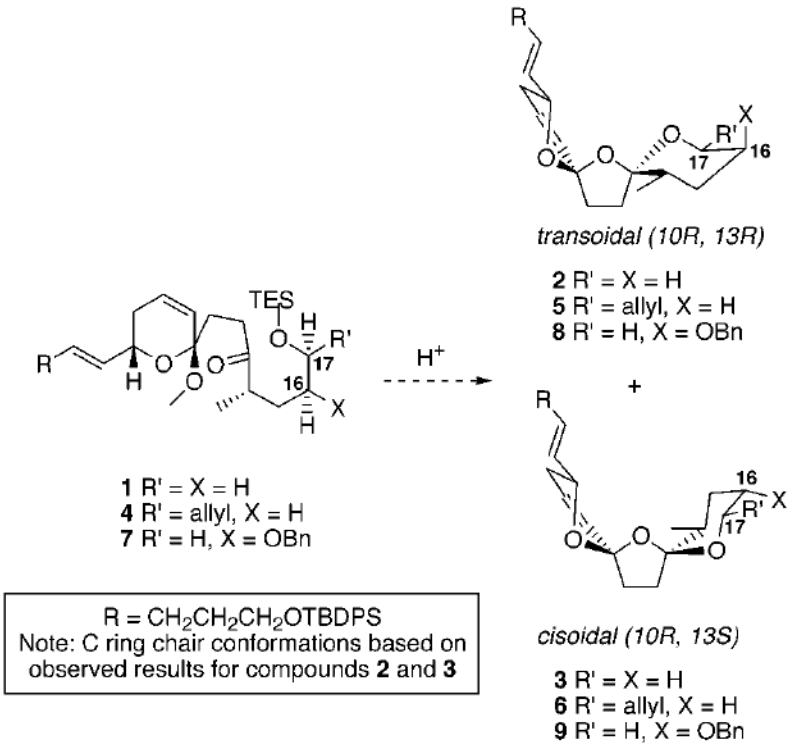
17. While this protocol appeared to reach equilibrium in a similar time frame to Nicolaou and co-workers (4 h), the TFA/CH_2C_{l2} conditions led to a significantly more complex crude reaction mixture, presumably due to decomposition.



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

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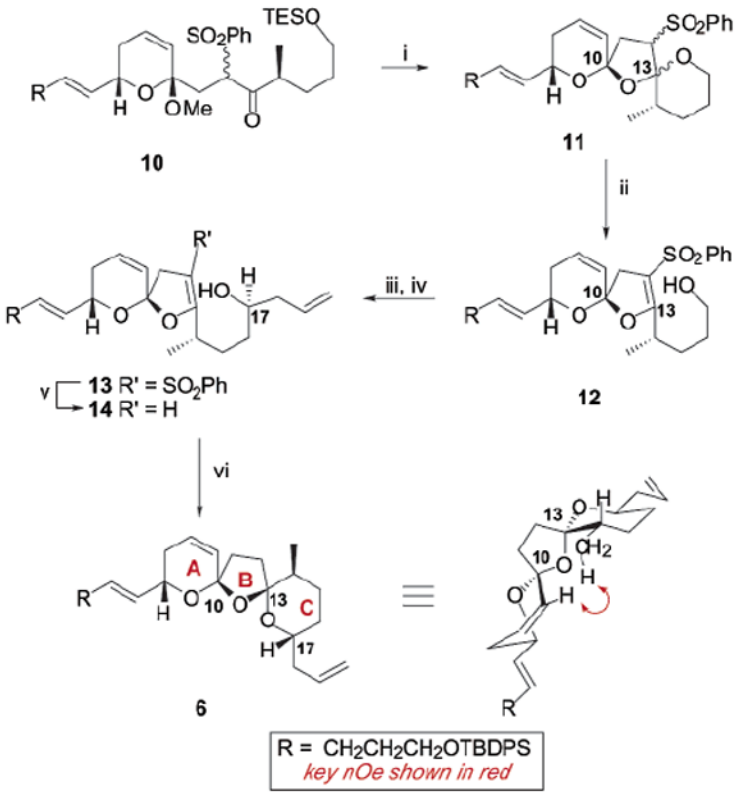
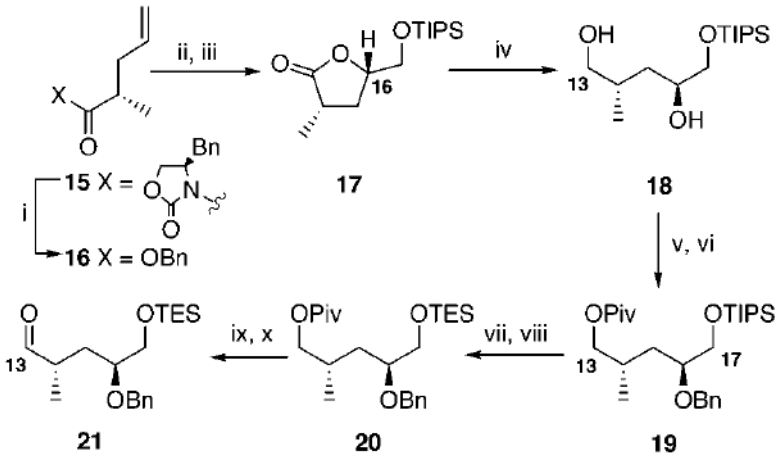


Scheme 2.

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).



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%.

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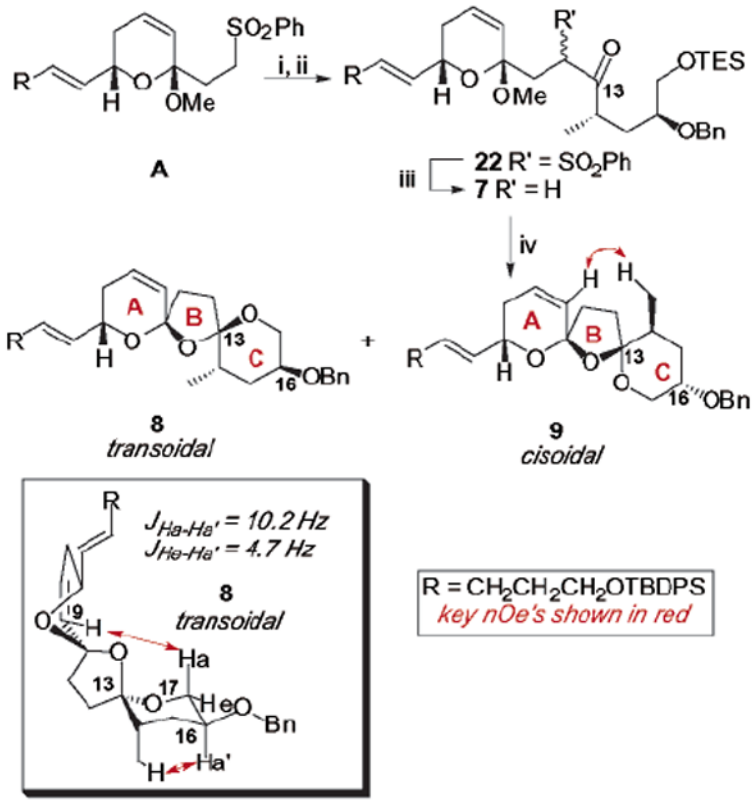

Scheme 4.

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**).