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Synthesis of the Azaspiracid-1 Trioxadispiroketal

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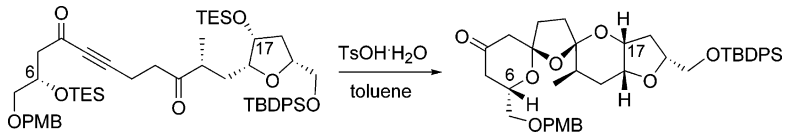
ABSTRACT



The de novo analysis, design, and synthesis of the azaspiracid-1 trioxadispiroketal system is described. A revised structural model was developed on the basis of an independent analysis of the NMR spectral data of the natural product that fit all of the data and the thermodynamically favored spiroketal paradigm. This model was then tested via synthesis using a novel trioxadispiroketalization process and supported by spectroscopic correlation.

The azaspiracids are remarkable natural products that combine a unique, complex structure with an acute and perhaps chronic human health hazard.[1−3] As such, these compounds have been the focus of intense study, including numerous synthetic reports. Among these are many that targeted the originally assigned relative stereochemistry of the A−D trioxadispiroketal system.[4] Most recently, however, the total synthesis and structural revision of AZA-1 (**1**) have been reported and correct three errors in the original assignment.[5] These corrections include the position of the A-ring alkene, and the relative stereochemistry of the face-fused C and D rings with respect to both the carbinol-linked E ring and the dispiro-fused A and B rings. Summarized herein are the de novo analysis, design, and synthesis of the long problematic A−D trioxadispiroketal via a new variant of the double intramolecular hetero-Michael addition (DIHMA).[6]

One of the most curious aspects of the structural assignments originally made to **1** was the relative configuration of the C13 spiroketal center, which would not benefit from anomeric effect stabilization.[1] An established paradigm in spiroketal natural products is that the combination of configurations and conformations generally reflects the most thermodynamically favored array, consistent with nonenzymatic ketalization processes.

There seemed to be no compelling reason to believe that the azaspiracids should violate this phylogenic profile. Thus, our initial work in this area involved probing the thermodynamic stability of the A−D ring system as it was originally

(1) Satake, M.; Ofuji, K.; Naoki, H.; James, K. J.; Furey, A.; McMahon, T.; Silke, J.; Yasumoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 9967−9968.

(2) James, K. J.; Lehane, M.; Moroney, C.; Fernandez-Puente, P.; Satake, M.; Yasumoto, T.; Furey, A. *Food Addit. Contam.* **2002**, *19*, 555−561.

(3) Ito, E.; Satake, M.; Ofuji, K.; Higashi, M.; Harigaya, K.; McMahon, T.; Yasumoto, T. *Toxicon* **2002,** *40*, 193−203.

(4) (a) Carter, R. G.; Weldon, D. J. *Org. Lett.* **2000**, *2*, 3913−3916. (b) Dounay, A. B.; Forsyth, C. J. *Org. Lett.* **2001**, *3*, 975−978. (c) Carter, R. G.; Graves, D. E. *Tetrahedron Lett.* **2001**, *42*, 6035−6039. (d) Nicolaou, K. C.; Qian, W.; Bernal, F.; Uesaka, N.; Pihko, P. M.; Hinrichs, J. *Angew. Chem., Int Ed.* **2001**, *40*, 4068−4071. (e) Carter, R. G.; Bourland, T. C.; Graves, D. E. *Org. Lett.* **2002**, *4*, 2177−2179. (f) Carter, R. G.; Graves, D. E.; Gronemeyer, M. A.; Tschumper, G. S. *Org. Lett.* **2002**, *4*, 2181−2184. (g) Carter, R. G.; Bourland, T. C.; Zhou, X.-T.; Gronemeyer, M. A. *Tetrahedron* **2003**, *59*, 8963−8974. (h) Nicolaou, K. C.; Li, Y.; Uesaka, N.; Koftis, T. V.; Vyskocil, S.; Ling, T.; Govindasamy, M.; Qian, W.; Bernal, F.; Chen, D. Y.-K. *Angew. Chem., Int Ed.* **2003**, *42*, 3643−3648. (i) Nicolaou, K. C.; Chen, D. Y.-K.; Li, Y.; Qian, W.; Ling, T.; Vyskocil, S.; Koftis, T. V.; Govindasamy, M. *Angew. Chem., Int Ed.* **2003**, *42*, 3649−3653. (j) Ishikawa, Y.; Nishiyama, S. *Heterocycles* **2004**, *63*, 539−565. (k) Ishikawa, Y.; Nishiyama, S. *Heterocycles* **2004**, *63*, 885−893. (l) Ishikawa, Y.; Nishiyama, S. *Tetrahedron Lett.* **2004**, *45*, 351−354. (m) Nicolaou, K. C.; Vyskocil, S.; Koftis, T. V.; Yamada, Y. M. A.; Ling, T.; Chen, D. Y.-K.; Tang, W.; Petrovic, G.; Frederick, M. O.; Li, Y.; Satake, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4312−4318.

(5) Nicolaou, K. C.; Koftis, T. V.; Vyskocil, S.; Petrovic, G.; Ling, T.; Yamada, Y. M. A.; Tang, W.; Frederick, M. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 4318−4324.

(6) (a) Forsyth, C. J.; Hao, J.; Aiguade, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3663−3667. (b) Aiguade, J.; Hao, J.; Forsyth, C. J. *Org. Lett.* **2001**, *3*, 979−982. (c) Hao, J.; Forsyth, C. J. *Tetrahedron Lett.* **2002**, *43*, 1−2.

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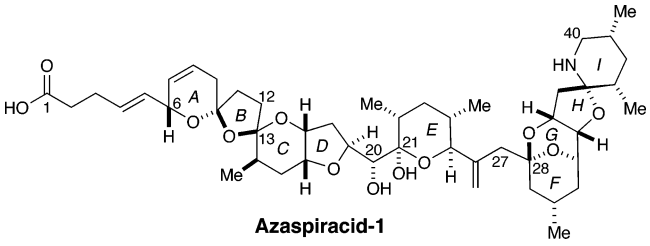


Figure 1. Corrected structure of azaspiracid-1 (**1**).[5]

assigned (Figure 2). This involved an oxonium ion-triggered bisspiroketalization followed by attempts at thermodynamic equilibration.[4b] These early experiments established both that the relative configurational array epimeric *only* at C13 to that of the original assignment[1] was overwhelmingly favored thermodynamically, and that this 13-epimer clearly did not match the corresponding spectral data of **1**. The Nicolaou group had subsequently reported that the originally assigned stereochemical array of the A−D system also did not match the natural product **1** via NMR spectral comparison of synthetic and authentic materials. Consequently, they had correctly proposed that the A-ring alkene be transposed from C8−9 to C7−8.[4i] We noted, however, that the allylic shift of the A-ring alkene alone would not be expected to significantly alter the trioxadispiroketal configurational thermodynamics due to the overriding energetic contribution of the anomeric effects.

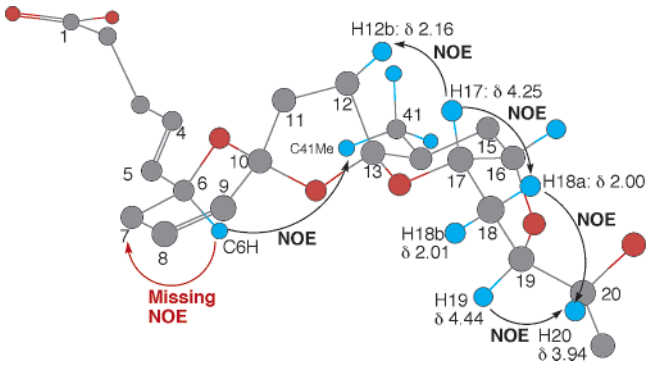


Figure 2. Original assignment of the (6*S**,10*R**,13*R**,14*S**,16*S**,17*S**,19*R**,20*S**)-A−D rings of AZA-1 and key NOEs.[1,8]

An independent analysis of the NMR spectral data of **1** led us to postulate that the A−D ring system with the A-ring alkene transposed to C7−8 *is also* epimeric at C6, C10, and C13 (Figure 3). In addition to fitting the NMR data for **1**, this $\Delta^{7,8}$-6,10,13-tris-epimer model also aligned with the thermodynamically driven natural product spiroketal paradigm. Simultaneously meeting both of these criteria made

(7) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983.

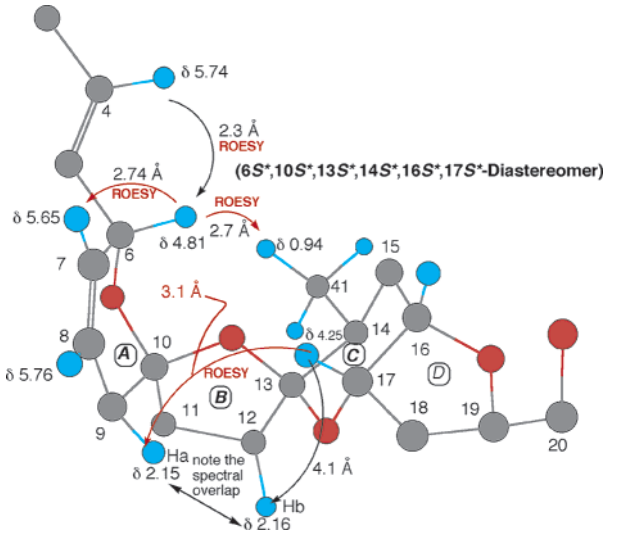


Figure 3. Minnesota structural model of the (6*S**,10*S**,13*S**,14*S**,16*S**,17*S**)-C3−C20 truncated domain of **1**.[8] The natural product has been assigned the enantiomeric configuration.[5]

this hypothesis compelling. It is based upon two specific sets of observations. First, there are conspicuous absences of ROESY correlations for **1** between the C6 methine proton and either of the A-ring methylene protons (δ 2.15 and 2.49), which were originally assigned to be at C7.[1] Instead, there is a ROESY correlation between C6H and the resonance at δ 5.65 originally assigned to the C9 alkene proton. This implies that C6H is spatially closer to the vinyl proton with the resonance that was originally assigned to C9 than it is to the A-ring methylene protons originally assigned to C7. Hence, the A-ring methylene was reassigned to C9 and the alkene to C7−8, as previously noted.[4i]

The second and more fundamentally important set of observations regards the original contrathermodynamic C13 configurational assignment that was apparently based *solely* upon a single ROESY correlation (Figure 2) between the C17 methine proton (δ 4.25) and a methylene proton resonance originally attributed to C12Hb (δ 2.16).[1] The chemical shift of C12Hb (δ 2.16) and the upfield A-ring methylene proton resonance at δ 2.15, now reassigned to C9Ha, are essentially *indistinguishable* from one another in the ROESY spectrum of **1**. Hence, the observed cross-peak could be attributed to C17H (δ 4.25) and either C12Hb (δ 2.16) *or* C9Ha (δ 2.15), or both. The allylic proton resonating at δ 2.15 (C9Ha) is about 3 Å from C17H in our model (Figure 3). This second set of observations suggested that the C13 configuration could well be epimeric to that of the original assignment with respect to the remaining centers about the C and D rings and hence benefit from the anomeric effect.[7]

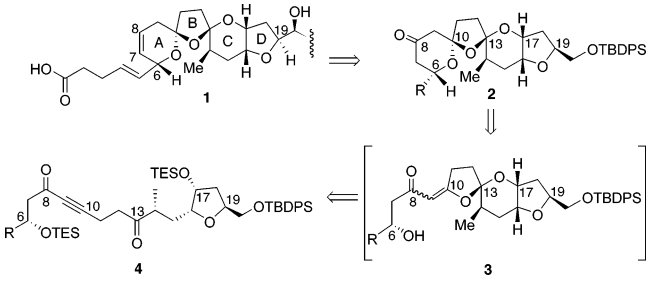
The relative configurations among carbons 14, 16, and 17 (14*S**,16*S**,17*S**) were originally well established by Satake

(8) This three-dimensional model was energetically minimized via iterative application of the MMFF94 force field (Spartan'02); any indicated interatomic distances are estimated on the basis of this model, whereas indicated NOEs (ROESYs) were experimentally observed.

et al. on the basis of vicinal ^{1}H-coupling constants. They also assigned the relative configurations among C6, C10, and C13 (6*S**,10*S**,13*S**), but on the basis of NOE studies (Figure 2).[1] The absence of an NOE between C6H and a C11 methylene proton guided the relative stereochemical assignment between C6 and C10, with C6H and C11 being trans about the A-ring oxygen. Similarly, the observation of an NOE between C17H and a methylene proton resonating at δ 2.15−2.16, originally ascribed to an axial C12Hb, but more likely due to C9Ha, led to the contrathermodynamic C13 configurational assignment. Finally, the relative stereochemistry of C10 and C13 was established by the observation of an NOE between C6H and the methyl group at C14. Thus, the two stereochemical triads, (6*R**,10*R**,13*R**) and (14*S**,16*S**,17*S**), giving rise to two C6−C17 diastereomers of the A−D system should have been considered: the contrathermodynamic original diastereomeric assignment[1] modified by transposition of the A-ring alkene, $\Delta^{7,8}$-(6*R**,10*R**,13*R**,14*S**,16*S**,17*S**), and the thermodynamically favored $\Delta^{7,8}$-(6*S**,10*S**,13*S**,14*S**,16*S**,17*S**)-diastereomer. Upon noting that all of the spectral data for **1** are consistent with the latter, thermodynamically favored $\Delta^{7,8}$-6,10,13-tris-epimer model (Figure 3), we targeted it for empirical verification.

Testing of the $\Delta^{7,8}$-(6*S**,10*S**,13*S**,14*S**,16*S**,17*S**)-model (Figure 3) began by targeting the (6*R*,10*R*,13*R*,14*R*,16*R*,17*R*)-A−D system of **1**[9] for synthesis using a previously unreported variation of the double intramolecular hetero-Michael addition (DIHMA) spiroketalization process (Scheme 1).[6] In this approach, the preinstalled configuration at C6

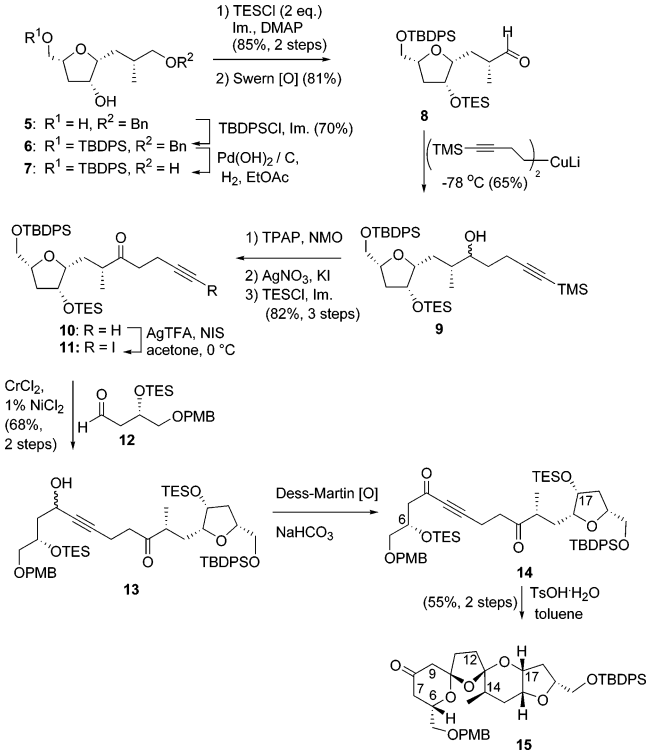
Scheme 1. Retrosynthesis of the AZA-1 A−D System



relative to the stereochemical triad at C14−17 in THF-ynedione **4** would drive the establishment of both C10 and C13 configurations via thermodynamic trioxadispiroketalization, as seen previously using the C6 epimer under C13 oxonium-initiated trioxadispiroketalization.[4b] Selective scission of the TES ethers in **4** would allow the liberated C17 oxygen to close the C-ring via hemiketalization and the exocyclic C13 oxygen to close the B-ring via a 5-exo-dig conjugate addition upon the C8−C10 ynone to generate enone **3**. Final closure of the A-ring by the addition of the C6 hydroxyl upon C10 would then result in trioxadispiroketal-ketone **2** upon thermodynamic equilibration. Thereafter, the residual ketone at C8 in **2** would facilitate the installation of the A-ring alkene of **1**.

The synthesis began with the functionalized THF ring **5** (Scheme 2), which was prepared in a fashion similar to that

Scheme 2. Synthesis of Trioxadispiroketal **15**



previously described.[10] Differential functionalization of the alcohol termini of **5** provided primary 1°−2° diol **7**, which was converted into aldehyde **8** directly from the corresponding bis-TES ether.[11] The B-ring carbons were then introduced via nucleophilic addition to the C13 aldehyde. Numerous attempts to add silylated 4-butynylmagnesium halides to **8** were unsuccessful.[12] Instead, the addition of the corresponding Gilman reagent[13] succeeded to satisfactorily provide secondary alcohols **9**. After alcohol oxidation to the C10 ketone, the TMS-substituted alkyne was converted into the terminal iodide **11**. Direct methods to convert the TMS-alkyne to the iodo-alkyne ($AgNO_3$/NIS/DMF)[14] failed. Also, removal of the TMS group with K_2CO_3 in methanol led to epimerization at C14. Better results were obtained with a stepwise procedure that involved initial removal of the TMS group with $AgNO_3$/KI[15] with partial cleavage of the second-

(9) Choice of absolute configuration was arbitrary but turned out to match that reported in ref 5 for natural **1**.

(10) Dounay, A. B.; Florence, G. J.; Saito, A.; Forsyth, C. J. *Tetrahedron* **2002**, *58*, 1868−1874. The C19 epimer was used here for convenience.

(11) Tolstikov, G. A.; Miftakhov, M. S.; Vostrikov, N. S.; Komissarova, N. G.; Adler, M. E.; Kuznetsov, O. M. *J. Org. Chem. USSR* **1988**, *24*, 202−203.

(12) Ashby, E. C.; Goel, A. B. *J. Am. Chem. Soc.* **1981**, *103*, 4983−4985.

(13) Eisch, J. J. *Organometallics* **2002**, *21*, 5439−5463.

(14) Speed, T. J.; Thamattoor, D. M. *Tetrahedron Lett.* **2002**, *43*, 367−370.

(15) Drouin, J.; Boaventura, M. A. *Tetrahedron Lett.* **1987**, *28*, 3923−3926.

ary silyl ether. Reformation of the TES ether and iodination of the alkyne using AgTFA/NIS[16] completed the synthesis of **11**.

A simple four-carbon aldehyde (**12**)[17] representing C5−C8 of **1** and bearing the C6 stereogenic center as a TES ether to match that at C17 was coupled with iodide **11** under an organochromium-mediated reaction[18] to yield propargylic alcohols **13** (Scheme 2). Oxidation to ynedione (6*S*,14*R*,16*R*,17*R*)-**14** completed the assembly of the trioxadispiroketal precursor. Selective cleavage of the C6 and C17 TES ethers and subsequent trioxadispiroketal formation was cleanly effected upon treating **14** with *p*-TsOH·H_2O in toluene at room temperature for 1−2 days. Ketone **15** was thus obtained in moderate yield as the only trioxadispiroketal observed under these prolonged, potentially equilibrating conditions (TLC and chromatographic isolation).

The structure of the resultant bisspiroketal **15** was firmly established on the basis of MS and extensive NMR analyses. In particular, the newly formed C10 stereogenic center was assigned relative to that at C13 in **15** by reciprocal NOEs observed between the C14 methyl group and the C6 methine proton (Figure 4). In addition, the presence of the C8 ketone

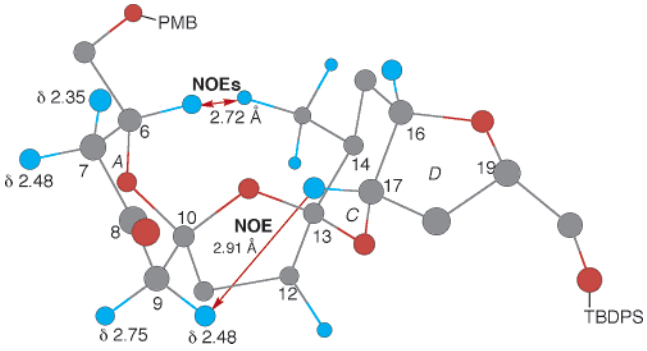


Figure 4. Key NOEs observed for trioxadispiroketal **15** and approximate interatomic distances (the enantiomer of **15** is depicted here).[8]

in the A-ring allowed the equatorial C9Heq (δ 2.48) to be spectroscopically differentiated from the B-ring protons and the determination of an NOE between the C17H methine proton and C9Heq, as postulated for **1** (Figures 3 and 4).[19] NOEs could not be discerned between either C17H and a C12H or between C6H and a C11H in **15**, suggesting that the configurations at C10 and C13 relative to those at C6 and C17 in the thermodynamic product (6*S*,10*R*,13*R*,14*R*,16*R*,17*R*)-**15** are as indicated.

The correlation of spectral data of trioxadispiroketal **15** with those of the corresponding domain of **1** supports the relative stereochemical identity of both compounds at C6−C17 and hence the validity of the structural model presented in Figure 3. This structural model has more recently been corroborated by the remarkable total synthesis of **1** reported by the Nicolaou group.[5] Hence, the de novo analysis and synthesis of the trioxadispiroketal system of **1** via a novel application of the DIHMA process has succeeded in providing an intermediate applicable to a concise total synthesis of the azaspiracids. Ongoing studies are directed at the regioselective installation of the A-ring alkene from the C8 ketone.

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Supporting Information Available: Experimentals and characterization data for key compounds and an annotated ROESY plot of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Bohner, T. V.; Beaudeguire, R.; Vasella, A. *Helv. Chim. Acta* **1999**, *82*, 143.
(17) Paterson, I.; Coster, M. J. *Tetrahedron Lett.* **2002**, *43*, 3285−3290.
(18) Kishi, Y. *Pure Appl. Chem.* **1992**, *64*, 342−350.
(19) Chemical shifts for the axial proton at C7 and the equatorial proton at C9 are coincident; however, the distance between C17H and C7Hax is >4 Å, whereas that between C17H and C9Heq is estimated to be <3 Å. Furthermore, the NOE observed at δ 2.48 appears to be due to a single proton (see Supporting Information).