Synthesis of the C1-C21 Domain of Azaspiracids-1 and -3

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ABSTRACT



An efficient synthesis of the C1–C21 fragment of azaspiracids-1 and –3 is described. This features a Nozaki–Hiyama–Kishi reaction to couple the AB and CD ring precursors and formation of the THF-fused ABCD trioxadispiroketal system under thermodynamic conditions.

The azaspiracids (Aza, Figure 1) are structurally complex marine toxins that display a range of human health related activities.^{1,2} Among the latter is inhibition of the hERG ion channel.³ Accordingly, the discovery of the azaspiracids has stimulated intense synthetic activity.⁴ The total synthesis of azaspiracids and non-natural analogs may uniquely contribute to immunodetection of the

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Figure 1. Azaspiracids.

azaspiracids^{4f} and definition of their molecular pharmacology.⁵ Notable total syntheses of Aza1 and cogeners by the Nicoloau group⁶ and a total synthesis of *ent*-Aza1 by the Evans group⁷ have been reported. Both successful approaches involved the joining of advanced C1–C19 and C20–C40 intermediates via the addition of C20 acyl anion equivalents to C19 carbonyls. To enahance the overall efficiency, an alternative fragment coupling approach involving a C22–C40 nucleophilic partner with a C1–C21 aldehyde was designed to deliver Aza1 and Aza3. Herein,

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we report an efficient and scalable synthesis of the requisite C1-C21 domain.

The present strategy to assemble the trioxadispiroketal of the C1–C21 domain 4 relied upon the acid-catalyzed bisspiroketalization of 5 (Scheme 1), a transketalization process related to the original approach toward the ABCD domain of Aza1^{4a} and a synthesis of okadaic acid.⁸ The C13 (Aza numbering) ketone 5 would be derived convergently from a Nozaki-Hiyama-Kishi (NHK) coupling⁹ of C1-C12 iodide 6 and C13-C21 aldehyde 7. The endocyclic alkene of 6 would be installed from the corresponding vinyl triflate.^{4c} Known glyceral acetonide derivative $\mathbf{8}^{10}$ provides carbons 5–10 of 6. The THF ring of 7 would be reductively $closed^{6a,11}$ from a hemiketal precursor obtained from a Mukaiyama aldol reaction.¹² The requisite silvl enol ether and aldehyde could be accessed from known building blocks 8, 9, and 10.13 Asymmetric dihydroxylation of 9 would install the vicinal C19-20stereochemistry.

The synthesis of the A-ring containing fragment commenced with hydroboration–oxidation¹⁴ of alkene 8^{10} (Scheme 2). The derived primary alcohol 11 was converted into aldehyde 12 under Swern conditions.¹⁵ Addition of lithium trimethylsilyl acetylide to 12 followed by oxidation¹⁶ gave ynone 13. Upon cleavage of the acetonide moiety with acidic methanol, cyclization occurred to close the A-ring as mixed ketal 14. Alcohol 14 was elaborated into NHK coupling partner 6 (Scheme 3). This began with Parikh–Doering oxidation to the corresponding aldehyde, followed by a highly stereoselective Takai olefination to

Scheme 1. Retrosynthetic Analysis of the C1-C21 Fragment



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yield vinyl iodide **15**.¹⁷ The E/Z ratio was greater than 15:1 using a 6:1 (v/v) mixture of 1,4-dioxane and THF as the Takai reaction solvent.¹⁸

The C1–C3 side chain was next installed efficiently through a Suzuki cross-coupling.¹⁹ This was preceded by hydroboration of allyl TBDPS ether, which then allowed Pd-mediated sp^3-sp^2 coupling with vinyl iodide **15** to give **16**. The C7 alkene was installed next. A Stille reduction²⁰ of a C7–C8 vinyl triflate was chosen for this task. Hence, the C7 *O*-PMB ether was selectively cleaved and the resultant alcohol was oxidized to ketone **17**. Treatment of **17** with KHMDS and Comins' reagent²¹ gave the anticipated kinetic enol triflate. This was smoothly reduced in the presence of the silyl-substituted alkyne under Stille conditions to complete installation of the A-ring alkene. Finally, a direct alkyne desilylation–iodination (AgOTf/NIS/ DMF)²² completed the preparation of alkynyl iodide **6**.

The synthesis of the C13-C21 CD-ring containing intermediate 7 featured a Mukaiyama aldol coupling of aldehyde 20 and silvl enol ether 23 (Scheme 4). The aldehyde was prepared via the known vicinal diol 10 (Scheme 1),¹³ which was converted into a benzylidene acetal then regioselectively opened with DIBAL to afford the primary alcohol. This was then oxidized to aldehyde 20. In parallel, the preparation of 23 commenced with a Sharpless asymmetric dihydroxylation²³ of ethyl crotonate **9** to generate diol **21** in 90% ee. The α -hydroxyl group was selectively silvlated, the ester moiety was reduced, and the resultant primary alcohol was acylated with pivaloyl chloride to yield 22. The residual C19 secondary alcohol was oxidized to the methyl ketone, which was then converted into silvl enol ether 23. The anticipated coupling of aldehyde 20 with latent nucleophile 23 was thus enabled.

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A chelation controlled Mukaiyama aldol reaction between 20 and 23 provided C13–C21 β -hydroxy ketone 24 (Scheme 4). Various Lewis acids and ligating C16 O-protective groups were screened to optimize this process. Among the combinations examined, the use of SnCl₄ and a C16 benzyl ether provided the best result with a 76% yield and 10:1 diastereoselectivity. The C17 hydroxyl group of 24 was then acetylated, and the C16 benzyl ether was cleaved to afford γ -hydroxy ketone 25 as an equilibrium mixture of hydroxy ketone and cyclic hemiketal. The azaspiracid tetrafuran D-ring was permanently closed with a Kishi reduction.^{11,6a} The standard conditions ($BF_3 \cdot OEt_2$ / Et₃SiH at -78 °C) afforded a significant amount of side products. The use of SnCl₄ proved to be the best of the Lewis acids tested for the reductive cyclization of 25. The observed exclusive trans-2,5-THF stereochemistry of

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Scheme 4. Synthesis of Aldehyde 7



the reductive cyclization was confirmed by NOE measurements and is consistent with that of similar systems.²⁴ The major THF product obtained from **25** was the C13 primary alcohol (60%) accompanied with the corresponding C13 *O*-TBS ether (25%), which was cleanly desilylated with TsOH in methanol. A final Parikh–Doering oxidation completed the synthesis of the C12 aldehyde **7**.

The A- and D-ring containing fragments **6** and **7**, respectively, were finally joined under NHK conditions⁹ to yield the advanced C1–C21 azaspiracid intermediate **26** in 78% yield as an epimeric mixture of propargylic alcohols (Scheme 5). A virtue of this type of organometallic couping is the chemoselectivity for aldehyde addition, which allows the incorporation of other potential electrophilic functionalities, exemplified by the D-ring acetate here. Carbinol oxidation¹⁶ followed by conjugated alkyne reduction²⁵ then transformed **26** into ketone **27** (Scheme 5).

Penultimate intermediate 5 (Scheme 1) was attained from mildly basic methanolysis of the C17 acetate of 27, which avoided significant epimerization of the α -keto C14

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Scheme 5. Synthesis of the C1-C21 Domain of Azaspiracid-3



stereogenic center. Finally, the A-ring ketal and C13 ketone were engaged in an acid-triggered transketalization using PPTs in CH₂Cl₂ to construct the B- and C-rings of trioxadispiroketal **4**. As had been originally noted in a similar context,^{4a} the thermodynamically favored configurations at the newly formed C10 and C13 spiroketals were unaccompanied by appreciable amounts of anomeric epimers. Thus, stereoselective establishment of the azaspiracid A–C-ring bisspiroketal domain under thermodynamic conditions again provides reliable access to the natural products' stereochemistry.

This convergent approach to the fully elaborated C1–C21 domain of Aza1 and Aza3 features both reliable access to core building blocks and enabling late-stage transformations. The latter include the NHK coupling of A- and D-ring bearing fragments,⁹ regioselective ynone reduction,²⁵ and thermodynamic transketalizations.^{4a,8} The generation of the C1–C21 intermediate **4** spans

18 steps in 5% overall yield in the longest linear sequence from the C5–C10 building block 8^{10} The synthesis of 4 will support ongoing efforts to highlight the utility of complex molecule synthesis in the context of generating azaspiracids and informative analogs for targeted pharmacological studies.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.