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

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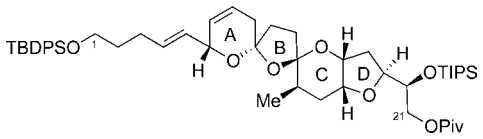
ABSTRACT



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 azaspiracids[4f] and definition of their molecular pharmacology.[5] Notable total syntheses of Aza1 and cogeners by the Nicoloau group[6] and a total synthesis of *ent*-Aza1 by the Evans group[7] 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,

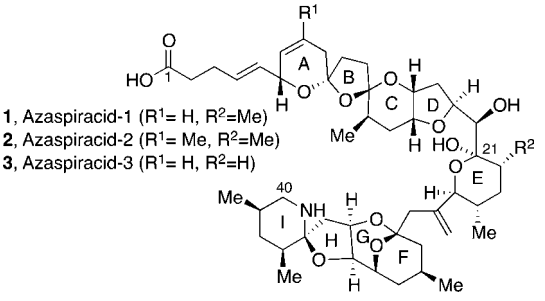


Figure 1. Azaspiracids.

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

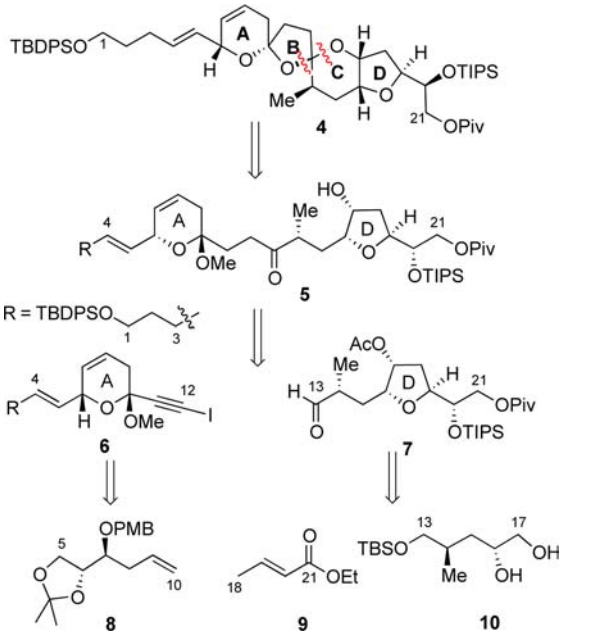
The present strategy to assemble the trioxadispiroketal of the C1−C21 domain **4** relied upon the acid-catalyzed bisspiroketalization of **5** (Scheme 1), a transketalization process related to the original approach toward the ABCD domain of Aza1[4a] and a synthesis of okadaic acid.[8] The C13 (Aza numbering) ketone **5** would be derived convergently from a Nozaki−Hiyama−Kishi (NHK) coupling[9] 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 **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 silyl enol ether and aldehyde could be accessed from known building blocks **8**, **9**, and **10**.[13] Asymmetric dihydroxylation of **9** would install the vicinal C19−20 stereochemistry.

The synthesis of the A-ring containing fragment commenced with hydroboration−oxidation[14] 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 oxidation[16] 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 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 reduction[20] 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' reagent[21] 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 silyl 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 dihydroxylation[23] of ethyl crotonate **9** to generate diol **21** in 90% ee. The α-hydroxyl group was selectively silylated, 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 silyl enol ether **23**. The anticipated coupling of aldehyde **20** with latent nucleophile **23** was thus enabled.

Scheme 1. Retrosynthetic Analysis of the C1−C21 Fragment



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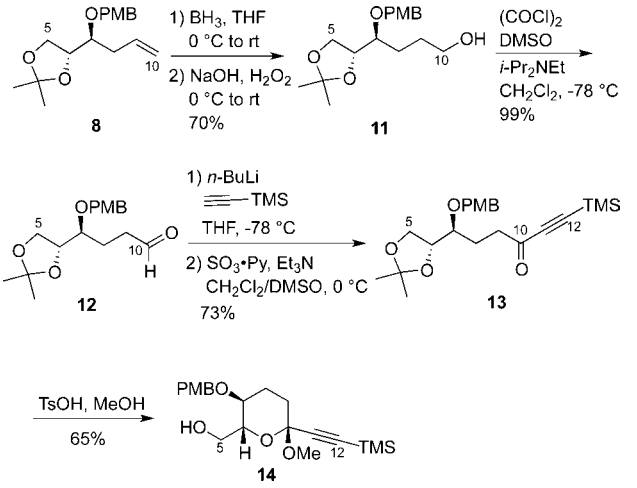
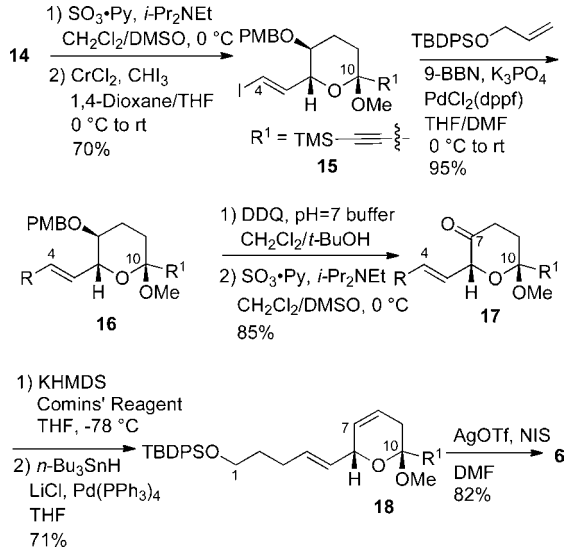
Scheme 2. A-Ring Assembly

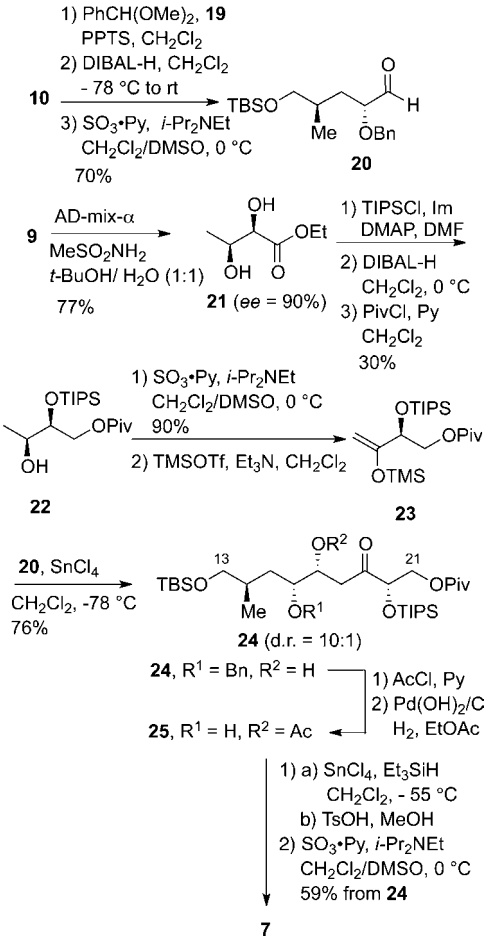


Scheme 3. Synthesis of Alkynyl Iodide **6**



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 $SnCl_4$ 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 ($BF_3 \cdot OEt_2$/Et_3SiH at −78 °C) afforded a significant amount of side products. The use of $SnCl_4$ 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

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 conditions[9] 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 oxidation[16] followed by conjugated alkyne reduction[25] 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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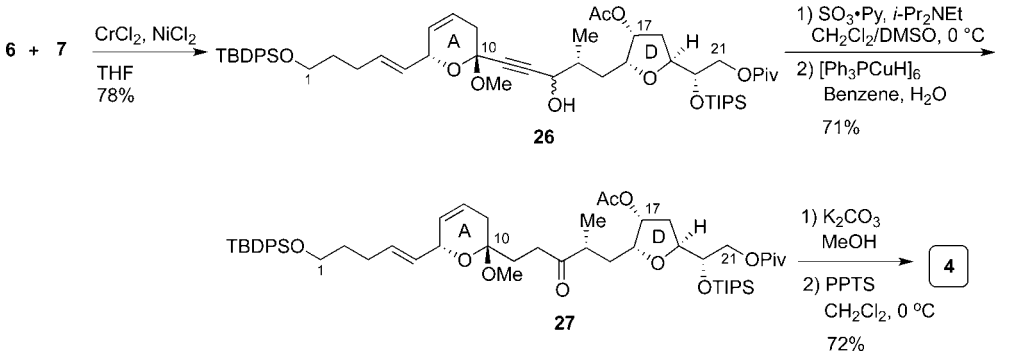
Scheme 5. Synthesis of the C1−C21 Domain of Azaspiracid-3



stereogenic center. Finally, the A-ring ketal and C13 ketone were engaged in an acid-triggered transketalization using PPTs in CH_2Cl_2 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.