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Synthesis of the C22−C40 Domain of the Azaspiracids

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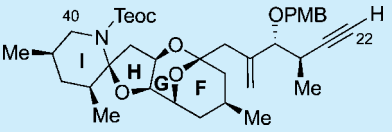
Supporting Information

ABSTRACT: An efficient synthesis of the C22−C40 domain of the azaspiracids is described. The synthetic route features a Nozaki−Hiyama−Kishi (NHK) coupling and chelation controlled Mukaiyama aldol reaction to access an acyclic intermediate and a double-intramolecular-hetero-Michael addition (DIHMA) to provide the FG-ring system bridged ketal.



The azaspiracids (Aza, Figure 1) comprise a class of lipophilic algal toxins isolated from the dinoflagellates

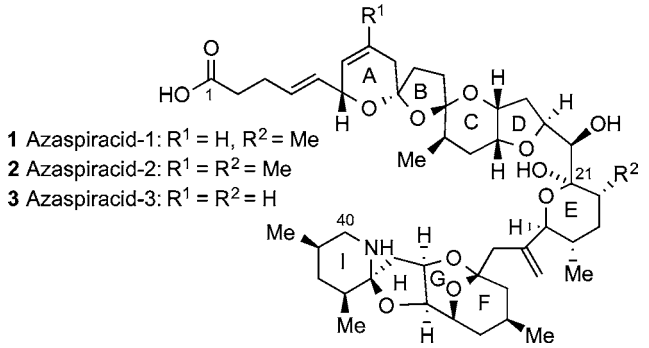


Figure 1. Structures of three principal azaspiracids.

Azadinium spinosum and *A. poporum*.[1] Shellfish accumulation and metabolism of the three primary azaspiracids (Aza1-3, **1**−**3**, respectively) is believed to be responsible for the generation of a large number of structural variants. Aza exposure elicits a range of biological responses in vertebrates.[2,3] Human consumption of Aza-contaminated shellfish may cause acute reactions, including classic symptoms of diarrhetic shellfish poisoning.[3] Notably, various Aza analogues induce distinct biological responses.[3d] The combination of unique structural architecture and potent biological activities of the azaspiracids has prompted considerable effort toward their laboratory syntheses.[4−8]

Seminal total syntheses of Aza1 and congeners by the Nicoloau group[4e,f,i−k] and a remarkable total synthesis of *ent*-Aza1 by the Evans group[5] highlight successes in this area. Nicoloau's syntheses of azaspiracids and analogs have also contributed to further definition of their molecular pharmacology and immunodetection.[9] Earlier targeted generation of synthetic haptens based upon the architecture of the structurally constant Aza FGHI-polycycic domain has enabled broad-specificity immuno-detection of the azaspiracids.[7h,k] The past total syntheses involved joining of advanced C1−C20 and C21−C40 intermediates via the addition of C21 acyl anion equivalents to C20 carbonyls.[4e,f,i−k,5] An alternative fragment coupling approach toward the azaspiracids that involves the pairing of a C22−C40 nucleophilic partner derived from terminal alkyne **6** (Scheme 1) with a C1−C21 aldehyde **5** is designed to enhance synthetic access, with an initial focus on Aza3. Among the azaspiracids lacking functionalization at C22 are azaspiracids-3, -4, -6, and -9, all of which in principle may readily derive from **6**. An assembly of aldehyde **5** was reported recently in support of this total synthesis coupling strategy.[7j] Described here is a synthesis of the complementary C22−C40 domain **6**.

It is anticipated that **3** may be derived from advanced intermediate **4** via four heteroatom deprotections and C1 oxidation (Scheme 1). In turn, **4** would be achieved from chemoselective reduction of an ynone obtained from a metallo-acetylide derived from **6** and aldehyde **5**. A significant departure from previous total syntheses efforts is that **5** contains the preinstalled correct stereochemistry at C20. Establishing the natural products' (20*R**)-configuration in previous total syntheses was costly in terms of additional late-stage synthetic steps and diminished yields.[4e,f,i−k,5]

Current access to the C22−C40 intermediate **6** adopts a previously developed approach to the FGHI ring system[7h] but incorporates optimized fragment couplings and resequencing of ring closures. The complex architecture of the FGHI polycycle-containing domain **6** would be derived from the acyclic hydroxy dione **7**. This is a highlight of the synthetic approach, embedding all of the functionality and stereochemistry in acyclic **7** to generate polycycle **6** via carefully sequenced and efficient heterocyclizations. This would involve an initial H ring closure followed by a double intramolecular-hetero-Michael addition (DIHMA)[7b] process to construct the FG ring bridged ketal. Due to the previously encountered instability of the HI ring spiroaminal moiety,[10] its assembly was deferred to the end of the synthetic sequence. Linear precursor **7** could be assembled convergently from three fragments, C22−C26 aldehyde **8**, C27−C34 alkyne **9**, and C35−C40 silyl enol ether **10**. The C26−C28 conjugated ynone moiety would derive from an NHK coupling[11] of **8** with an alkynyl iodide

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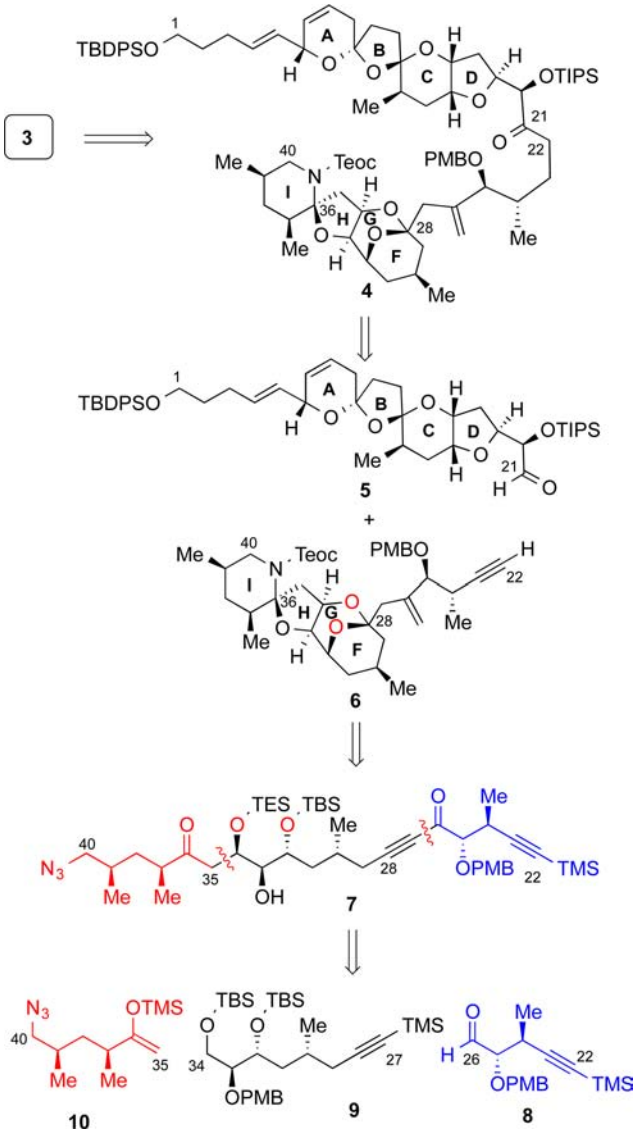
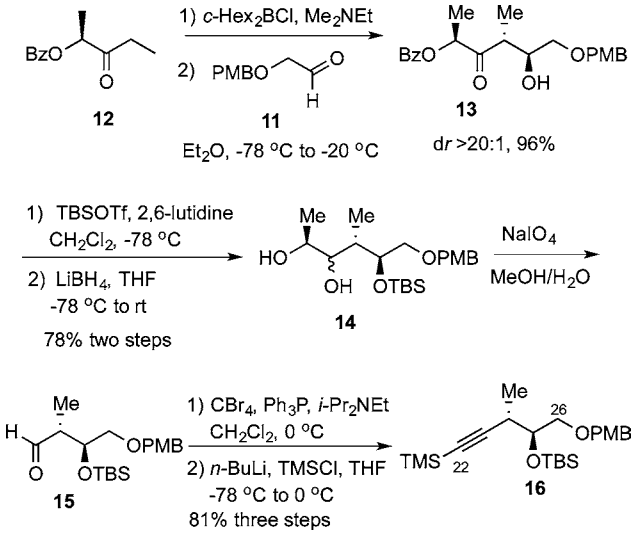
Scheme 1. Retrosynthetic Analysis of Aza-3 via the C22–C40 Fragment



Scheme 2. Synthesis of TMS Alkyne 16



derived from **9** followed by propargylic alcohol oxidation. A chelation-controlled Mukaiyama aldol reaction between **10** and a C34 aldehyde was recognized to yield the C34–C36 β-hydroxy ketone moiety.[12]

Because alkyne **9** and silyl enol ether **10** are established compounds,[7h] new synthetic efforts initially focused on the C22–C26 aldehyde **8** which would be obtained from masked diol **16** (Scheme 2). A Paterson *anti*-aldol reaction[13] between aldehyde **11** and (*S*)-lactate-derived ketone **12** produced the β-hydroxy ketone **13** with excellent diastereoselectivity. Alcohol **13** was protected as a silyl ether, and the keto-ester was reduced with $LiBH_4$ to afford an epimeric mixture of diols **14**. Oxidative cleavage of the diol with $NaIO_4$ yielded aldehyde **15**. A Corey–Fuchs reaction[14] followed by silylation then provided TMS-alkyne **16**.

A short reaction sequence was performed to prepare aldehyde **8** from differentially protected diol **16** (Scheme 3). The TBS protecting group was removed before the role of the C26-PMB protecting group was expanded to also engage the C25 hydroxyl group as epimeric acetals **18**.[15] Subsequent reduction with DIBAL provided primary alcohol **19** accompanied by **17**. Secondary alcohol **17** could be easily separated from the primary alcohol **19** for recycling. A Parikh–Doering oxidation[16] of **19** delivered aldehyde **8**.

The choice of a PMB protecting group at the C25 hydroxyl position was strategic. In initial synthetic exploration, a TBS ether at C25 led to consistently low yields during the TBAF mediated DIHMA process to close the FG rings. However, a simple protective group manipulation at this early stage allowed for dramatically improved efficiency in the FG ring closure.

Preparation of the functionally and stereochemically encoded acyclic intermediate **7** was accomplished as illustrated in Scheme 3. The TMS-alkyne **9**[7h] was converted into the iodo-alkyne **20** under silver catalysis. An efficient NHK reaction was employed to deliver propargylic alcohols **21**. The C34 silyl ether was selectively cleaved under HF·Py/Py conditions.[17] The resultant diols were then oxidized to keto-aldehyde **22**. A chelation-controlled Mukaiyama aldol reaction between **22** and the TMS enol ether **9**[7b,12] was then performed to deliver the β-hydroxy ketone efficiently with remarkably high diastereoselectivity. The resultant secondary alcohol was then protected as TES ether **23**. A carefully optimized DDQ-mediated reaction enabled the selective cleavage of the C33 PMB ether in the presence of the electron-deficient C25 PMB ether[18] to generate γ-hydroxy ketone **7**.

The polycyclizative assembly of the FGHI ring system began with **7**, in which 15 of the 19 backbone carbons are functionalized. Treatment of **7** with PPTs in methanol promoted closure of the H-ring to generate epimeric cyclic mixed methyl ketals **24** (Scheme 4). The FG bridged ketal **25** was next formed upon treatment of **24** with TBAF through a double intramolecular oxy-Michael reaction.[7b] Initial attempts to effect this nucleophilic ketalization[19] with substrates bearing a silyl ether at C25 provided yields in the 20% range under various basic fluoride conditions.[20] The low yields likely reflect electrostatic diminution of the Michael acceptor's electrophilicity upon alkoxide generation at C25.

Accordingly, a dramatic enhancement in nucleophilic ketalization efficiency was achieved with the use of a C25 PMB ether installed at the stage of **19** (Scheme 3).[21] A modified Staudinger reduction of azide **25** followed by *in situ* Teoc-protection provided the C40 Teoc-carbamate **25b** (Scheme 4). A Wittig olefination converted the C26 ketone

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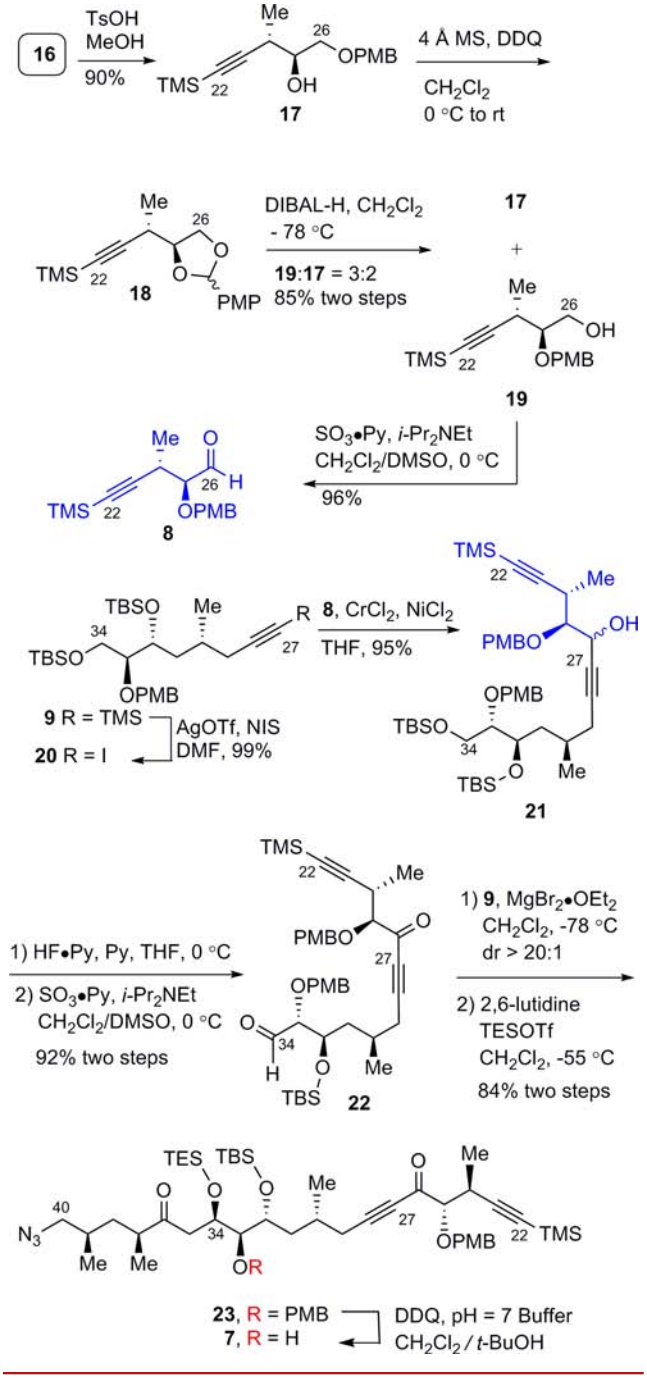
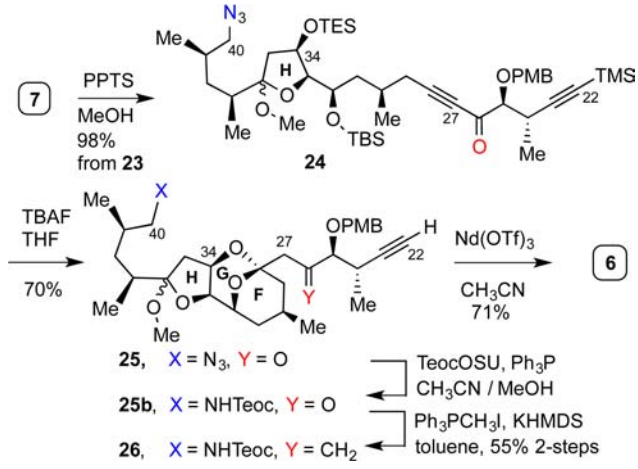
Scheme 3. Synthesis of Linear Precursor 7



into the natural products' alkene. The final namesake ring closure was accomplished with the lanthanide salt $Nd(OTf)_3$ to afford azaspiro-**6** under thermodynamically controlled conditions to favor the natural products' C36 configuration.[7b,4g,22] Only five steps were needed to convert functionally rich acyclic intermediate **7** into tetracycle **6**, which is poised for C22 alkyne activation toward nucleophilic addition to a complementary C21 aldehyde **5** (Scheme 1).

An efficient and scalable route to access the fully functionalized C22−C40 domain of the azaspiracids was detailed herein. Reliable NHK coupling and chelation-controlled Mukaiyama aldol reactions were employed to convergently assemble the advanced C22−C40 linear precursor **7**. Thereafter, successive cyclizations delivered an advanced intermediate

Scheme 4. Polycyclizative Assembly of 6



embodying the azaspiracid FGHI ring system that is appropriately functionalized to match the previously reported ABCD-ring containing coupling partner.[7j]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00557.

Experimental procedures and full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(20) (a) C25 *O*-TBS, C25 *O*-MTM, and C34 *O*-TBS protecting groups were also tested in a similar substrate. See ref 10. (b) TES protection of the C32 hydroxyl was also examined, but attempts at selective desilylation failed.

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(22) The use of $Yb(OTf)_3$ was initially reported for this transformation (ref 7b); however, extensive experimental studies by Nicolaou (ref 4g) identified $Nd(OTf)_3$ as a useful alternative.

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