Total Synthesis Hot Paper

International Edition: DOI: 10.1002/anie.201711006
German Edition: DOI: 10.1002/ange.201711006

Total Synthesis of (6*R*,10*R*,13*R*,14*R*,16*R*,17*R*,19*S*,20*R*,21*R*,24*S*,25*S*,28*S*,30*S*,32*R*,33*R*,34*R*,36*S*,37*S*,39*R*)-Azaspiracid-3 Reveals Non-Identity with the Natural Product

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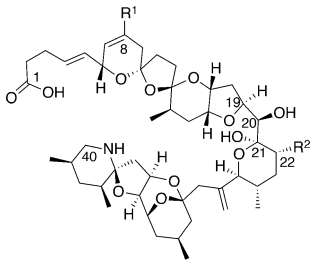
Dedicated to Professor Yoshito Kishi on the occasion of his 80th birthday

Abstract: *A convergent and stereoselective total synthesis of the previously assigned structure of azaspiracid-3 has been achieved by a late-stage Nozaki–Hiyama–Kishi coupling to form the C21−C22 bond with the C20 configuration unambiguously established from* L*-(+)-tartaric acid. Postcoupling steps involved oxidation to an ynone, modified Stryker reduction of the alkyne, global deprotection, and oxidation of the resulting C1 primary alcohol to the carboxylic acid. The synthetic product matched naturally occurring azaspiracid-3 by mass spectrometry, but differed both chromatographically and spectroscopically.*

The azaspiracids (AZAs) are lipophilic toxins produced by some marine dinoflagellates of the family Amphidomataceae (Figure 1).[1] Widespread AZA occurrence and concentration by filter-feeding bivalves serves as a conduit into human food chains.[2] Incidental human consumption of AZAs raises health concerns ranging from acute diarrheic shellfish poisoning to chronic cardiomyopathy and neurotoxicity.[3] These concerns have spurred extensive surveillance efforts to detect and quantify the AZA content in potential human food sources, and have motivated toxicological studies.[4]



1: AZA1 $R^1 = H$ $R^2 = CH_3$
2: AZA2 $R^1 = CH_3$ $R^2 = CH_3$
3: AZA3 $R^1 = H$ $R^2 = H$

Figure 1. Published structures of AZAs **1**–**3**.[9]

The structures of the AZAs are diverse because of the primary biosynthesis and subsequent bivalve metabolism. Mussels concentrate and convert primary AZAs into toxic AZA metabolites.[2,5] There are some 59 AZA structures recognized, and they warrant monitoring to reduce human poisonings. The provision of certified AZA reference standards of known structures is an important need.[6] Also, probing the toxicology of the AZAs benefits from synthetic inputs and

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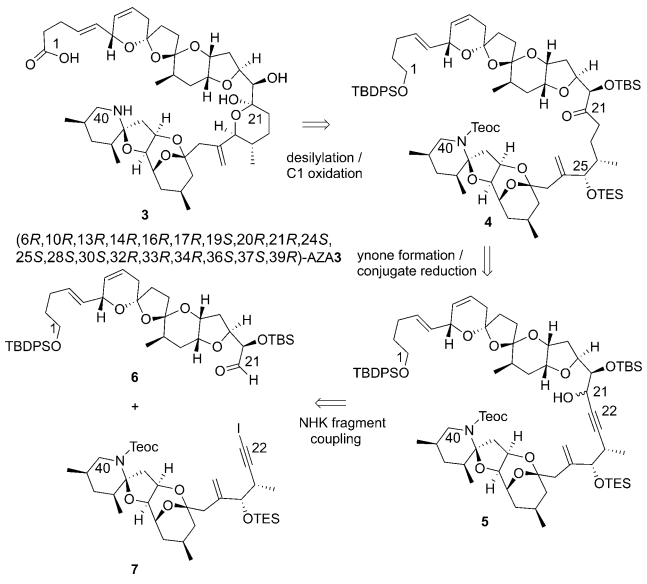
requires an accurate understanding of the relationship between chemical structure and function.

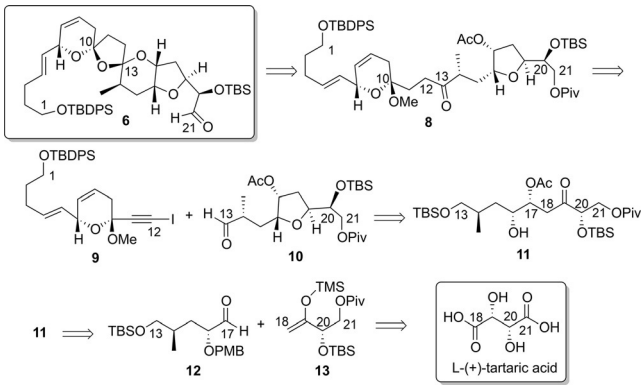
The structure of AZA1 was originally outlined by Yasumoto, Satake, and co-workers in 1998[1a] and refined by subsequent extensive efforts.[7] Nicolaou, Satake, and co-workers correlated oxidative degradation fragments of AZA1 with synthetic products to reduce the structural possibilities,[8] and it resulted in the total syntheses of AZA1-3, and seemed to complete the structural assignments.[9] AZA3 is accepted to be the C22-desmethyl variant of AZA1,[1b] with spectroscopic and synthetic data to support that otherwise AZA1–AZA3 share identical stereochemistry. In mussels, oxidation of the C22 methyl group of AZA1 may generate the C22 carboxylic acid AZA17, which, upon C22 decarboxylation, yields AZA3.[10] Reported herein is the total synthesis of the previously assigned structure of AZA3[1b,8b] and its direct comparison with naturally occurring AZA3.

Prior syntheses of AZA1–AZA3[9] and *ent*-AZA1[11] relied upon late-stage formation of the C20–C21 bond that installed the C20 stereogenic center by either ketone reductions or a poorly diastereoselective[11b,c] coupling reaction. In the present approach to AZA3, the key coupling is between C21 and C22 (**6** + **7** = **5**, Scheme 1). This coupling was to minimize postcoupling transformations and enhance mass throughput. It also provides the C20 carbinol configuration, which at the outset is known and unperturbed from that of L-(+)-tartaric acid. Thus, AZA3 was to arise from the C21 ketone **4** by global desilylation and C1 oxidation. The ketone **4** was to derive from the propargylic alcohol **5**, which would result from the convergent union of a C1–C21 aldehyde (**6**) and a C22–C40 alkyne (**7**) by an NHK reaction.[12]

The bis-spiroketal **6** would derive from the ketone **8** upon deacetylation and thermodynamically driven intramolecular transketalizations (Scheme 2). The ketone **8** derives from the known C1–C12 alkynyl iodide **9**[13] and C13–C21 aldehyde **10**.



Scheme 1. Retrosynthesis of **3**. NHK = Nozaki–Hiyama–Kishi,[12] TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, Teoc = 2-trimethyl(ethyloxy)carbonyl, TES = triethylsilyl.



Scheme 2. Genesis of the C1–21 domain. Ac = acetyl, Piv = pivaloyl, PMB = 4-methoxybenzyl.

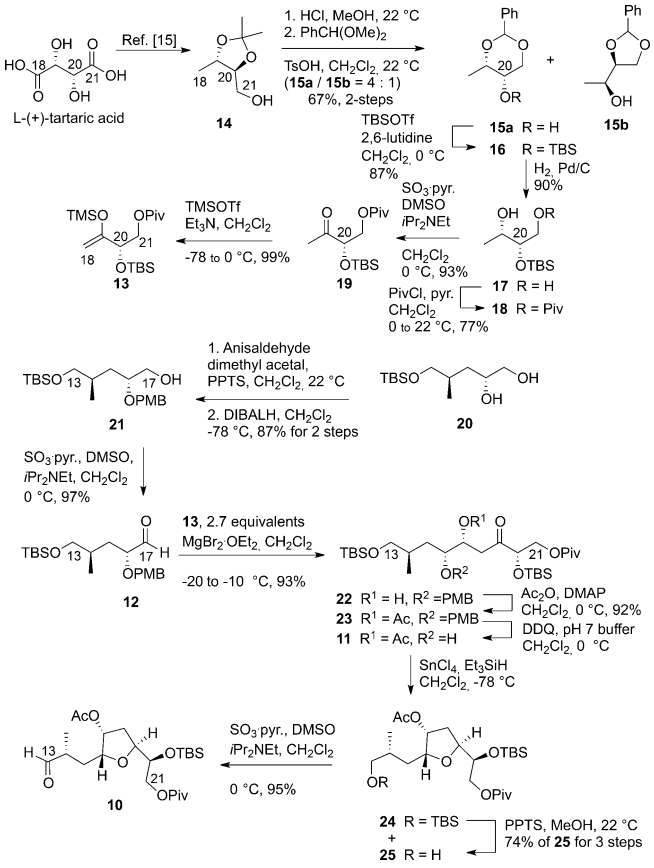
The latter derives from the acyclic keto-alcohol **11**. A chelation-controlled Mukaiyama aldol reaction[14] between the aldehyde **12** and L-(+)-tartrate-derived silyl enol ether **13** would predictably generate **11**.

Preparation of **10** is outlined in Scheme 3. The synthon **14** provided the C20 stereogenic center derived from L-(+)-tartaric acid.[15] The vicinal acetonide **14** was converted into benzylidenes **15a**/**15b**, and silylation of **15a** yielded the masked triol **16**, which was hydrogenated to diol **17**. Acylation of the primary alcohol and oxidation of the secondary alcohol gave the ketone **19**, which was converted into the silyl enol ether **13**. The partner aldehyde **12** was derived from diol **20**[16] via a PMB ether (**21**). An efficient Mukaiyama aldol reaction[14] between **12** and **13** generated the β-hydroxyl ketone **22**, and conversion into the γ-hydroxyl ketone **11** allowed reductive cyclization to stereoselectively generate the *trans*-THF **24**.[11,17] The aldehyde **10** was derived simply from **24**.

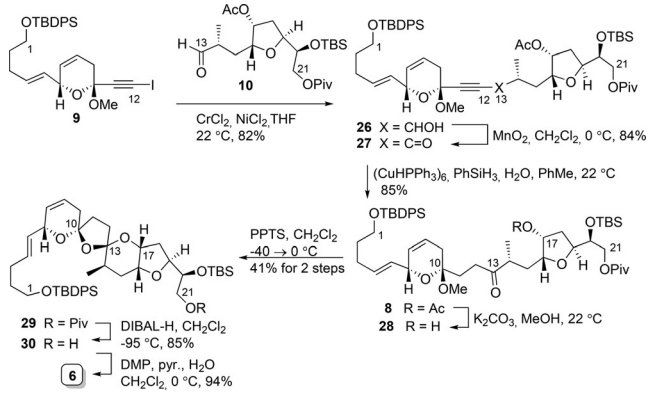
The aldehyde **10** was joined by an NHK reaction[12] to **9**[13] to generate epimeric propargylic alcohols (**26**) which were oxidized to the ynone **27** (Scheme 4). Conjugate reduction[18] afforded **8**. Deacetylation at C17 allowed acid-induced bis-spiroketalization,[11,19] and consolidated the ABCD-ring system in **29**. Selective deprotection and oxidation gave the C1–C21 aldehyde **6**.

The C22–C40 coupling partner **7** was obtained from the alkyne **31**[7b] (Scheme 5) by iodination and allylic ether modification. Prior installation of the iodine atom at C22 was critical to consistently obtaining high yields for oxidative scission of the PMB ether, as rapid decomposition resulted upon treatment of **31** with DDQ.

The carbon skeleton of **3** was obtained from **6** and **7** by an optimized NHK reaction (Scheme 6).[12] Key to the rapid success of this reaction was the use of 4-*tert*-butylpyridine as an additive.[20] This additive seems to solublize and activate the metal salts and buffer acidity, while also accelerating the reaction rate. In the absence of 4-*tert*-butylpyridine, **7** underwent decomposition under the NHK reaction conditions. The resultant epimeric propargylic alcohols **5** were oxidized to the ynone **34**, which was chemoselectively reduced to **4**. This modified Lipshutz–Stryker reduction also benefited from careful optimization: inclusion of 1,2-bis(diphenylphosphi-

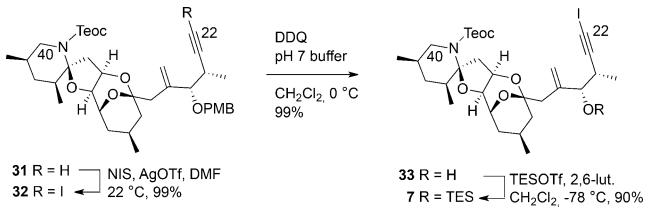


Scheme 3. C13–C21 Fragment assembly. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIBALH = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, DMSO = dimethylsulfoxide, PPTS = pyridinium 4-toluenesulfonate, pyr. = pyridine, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, TMS = trimethylsilyl, TMSOTf = trimethylsilyl trifluoromethanesulfonate, TsOH = 4-toluenesulfonic acid.

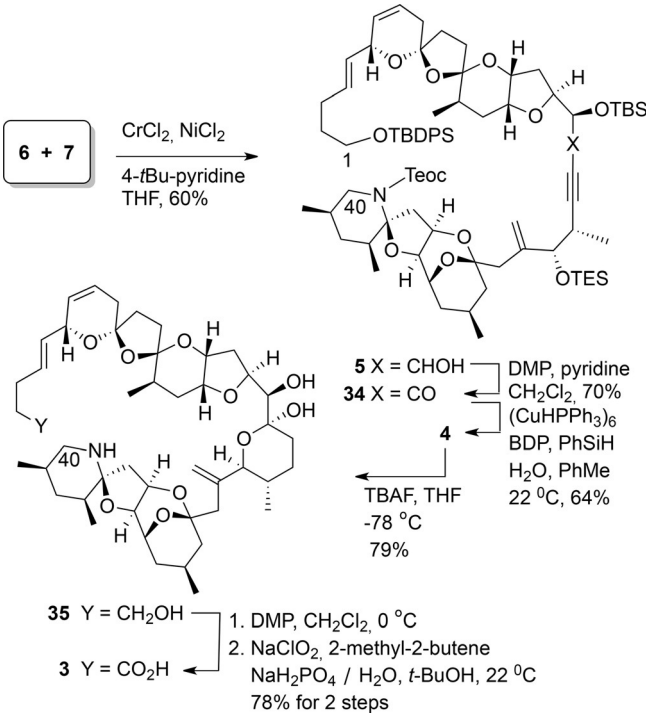


Scheme 4. Convergent assembly of the C1–C21 domain. DMP = Dess–Martin periodinane

no)benzene (BDP) was critical for success.[18] Global deprotection of **4** was achieved with a freshly prepared TBAF solution and provided the primary alcohol **35**. Two-step oxidation to the carboxylic acid completed the total synthesis of **3**. As observed by Evans et al.,[11b,c] the C20 alcohol was



Scheme 5. Elaboration of the C22–C40 domain. AgOTf = silver trifluoromethanesulfonate, DMF = *N*,*N*-dimethylformamide, 2,6-lut. = 2,6-dimethylpyridine, NIS = *N*-iodosuccinimide, TESOTf = triethylsilyl trifluoromethanesulfonate.



Scheme 6. Completion of the synthesis of **3**. BDP = 1,2-bis(diphenylphosphino)benzene, TBAF = tetra-n-butyl-ammonium fluoride.

largely inert towards oxidation using unbuffered Dess–Martin periodinane[21] conditions.

Comparative LC-MS analysis of **3** and an authentic sample of AZA3 showed nearly indistinguishable MS/MS spectra, but a different retention time was observed for each (Figure 2). Comparison of the ^{1}H and ^{13}C NMR spectroscopic data of synthetic **3** and AZA3 revealed significant differences in the appearance of the C19-H multiplet and the chemical shifts of the C20-H and C22-H axial multiplets.[22,23] The possibility that the stereochemistry at either C19 or C20 had been compromised en route to **3** was seriously considered. Subsequent experiments established with certainty, however, that the structure of synthetic **3** is as represented in Schemes 1 and 6.[24] It was thus concluded that synthetic (6*R*,10*R*,13*R*,14*R*,16*R*,17*R*,19*S*,20*R*,21*R*,24*S*,25*S*,28*S*,30*S*,32*R*,33*R*,34*R*,36*S*,37*S*,39*R*)-**3**, which corresponds to the previously accepted structure,[1b,8b] was an isomer of naturally occurring AZA3, and that the actual structure of AZA3 was yet unknown. These results prompted further investigations

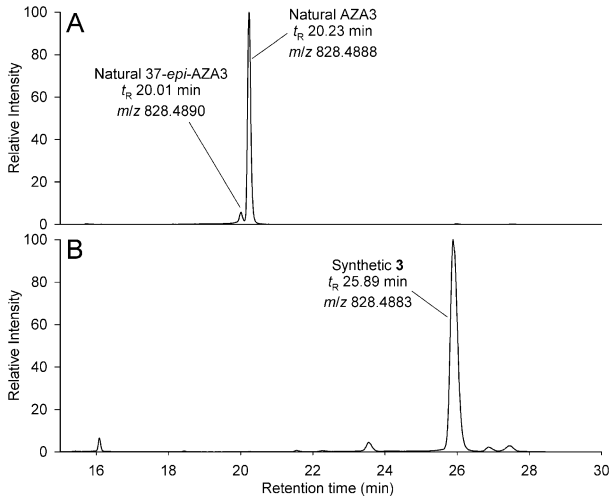


Figure 2. LC-HRMS chromatograms of A: natural AZA3 (t_R 20.23 min, m/z 828.4888), and B: synthetic **3** (t_R 25.89 min, m/z 828.4883) (LC-MS method 1; see the Supporting Information).

based upon this synthetic approach and direct comparision with natural AZA3 to determine the actual structure of AZA3.[24]

Experimental Section

Please see the Supporting Information for comprehensive experimental details.

Acknowledgements

This work was sponsored by the NIH (R01-ES10615), The Ohio State University (OSU), and the Forsyth Research Fund (CJF). We thank Dr. L. Xiao (OSU) for administrative assistance, and Prof. Dr. A. B. Dounay, and Drs. J. Aiguade-Bosch, J. Hao, L. K. Geisler, Y. Li, and F. Zhao for foundational research contributions. This work was supported by the First Call for Transnational Research Projects within the Marine Biotechnology ERA-NET; project number 604814. ("Enhanced Biorefining Methods for the Production of Marine Biotoxins and Microalgae Fish Feed"), and The Research Council of Norway is acknowledged for support through the Norwegian NMR Platform, NNP (226244/F50).

Conflict of interest

The authors declare no conflict of interest.

Keywords: azaspiracids · natural products · structure elucidation · total synthesis · toxins

How to cite: *Angew. Chem. Int. Ed.* **2018**, *57*, 805–809
Angew. Chem. **2018**, *130*, 813–817

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[22] The chemical shift of H-20 is variable and is probably at least partially controlled by the degree of protonation of the amino group.

[23] Comparative data are provided in the Supporting Information.

[24] Summation of this study is reported in the subsequent communication: see reference [7c].

Manuscript received: October 26, 2017
Revised manuscript received: November 16, 2017
Accepted manuscript online: November 28, 2017
Version of record online: December 13, 2017

