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

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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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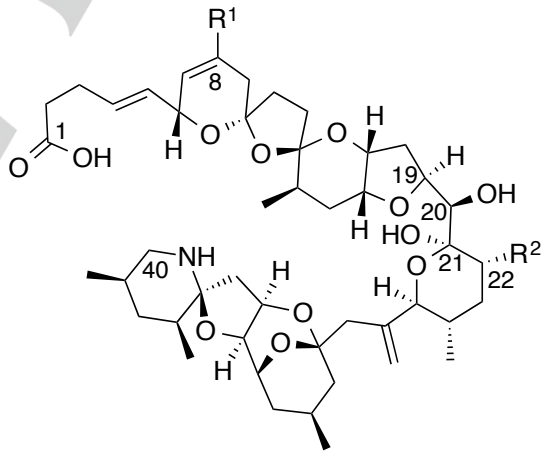
This work is dedicated to Professor Yoshito Kishi on the occasion of his 80th birthday.

Abstract: A convergent and stereoselective total synthesis of the previously assigned structure of azaspiracid-3 has been achieved via a late stage NHK coupling to form the C21–C22 bond with the C20 configuration unambiguously established from L-(+)-tartaric acid. Post-coupling steps involved oxidation to an ynone, modified Stryker reduction of the alkyne, global deprotection, and oxidation of the 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] This has spurred extensive surveillance efforts to detect and quantify AZA content in potential human food sources, and toxicological studies.[4]

The structures of the AZAs are diverse due to 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, that 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 requires an accurate understanding of the relationship between chemical structure and function.



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 structure of AZA1 was originally outlined by Yasumoto, Satake, and co-workers in 1998[1a] and refined by subsequent extensive efforts.[7] Nicolaou and Satake correlated oxidative degradation fragments of AZA1 with synthetic products to reduce the structural possibilities,[8] which resulted in 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 AZA1–3 otherwise share identical stereochemistry.

τ Co-authors contributed equally to the research described.
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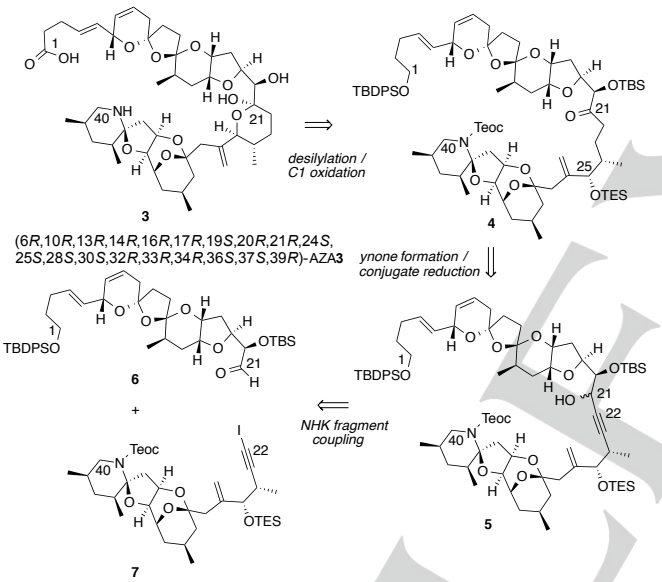
In mussels, oxidation of the C22 methyl group of AZA1 may generate the C22 carboxylic acid AZA17, which, upon C22 decarboxylation, yields AZA3.[10] Reported herein is the total synthesis of the previously assigned structure of AZA3[1b,8b] and its direct comparison with naturally occuring AZA3.

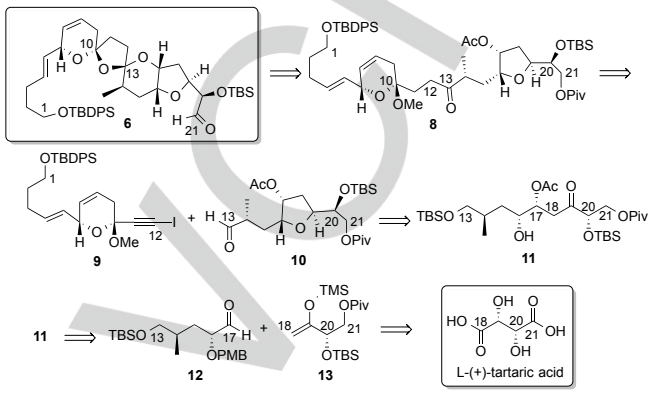
Prior syntheses of AZA1–3[9] and *ent*-AZA1[11] relied upon late-stage formation of the C20–C21 bond that installed the C20 stereogenic center via ketone reductions or a poorly diastereoselective[11b,c] coupling reaction. In the present approach to AZA3 the key coupling is between C21 and C22 (**6** + **7** = **5**, scheme 1). This was to minimize post-coupling transformations and enhance mass throughput. It also provides the C20 carbinol configuration at the outset knowingly and unperturbed from L-(+)-tartaric acid. Thus, AZA3 was to arise from C21 ketone **4** via global desilylation and C1 oxidation (scheme 1). Ketone **4** was to derive from propargylic alcohol **5**, that would result from the convergent union of a C1–C21 aldehyde (**6**) and a C22–C40 alkyne (**7**) via an NHK reaction.[12]



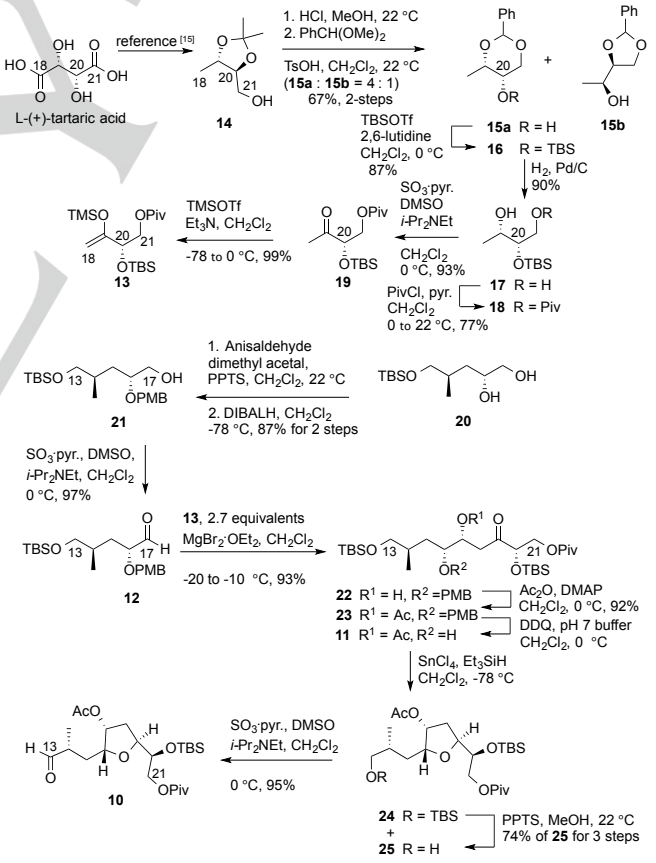
Scheme 1. Retrosynthesis of **3**. NHK = Nozaki-Hiyama-Kishi.[12] TBS = *tert*-butyldimethylsilyl. TBDPS = *tert*-butyldiphenylsilyl. Teoc = 2-trimethyl(ethyloxy)carbonyl. TES = triethylsilyl.

The bis-spiroketal **6** would derive from ketone **8** upon deacetylation and thermodynamically driven intramolecular transketalizations (scheme 2). Ketone **8** derives from the known C1–C12 alkynyl iodide **9**[13] and C13–C21 aldehyde **10**. The latter derives from acyclic keto-alcohol **11**. A chelation-controlled Mukaiyama aldol reaction[14] between aldehyde **12** and L-(+)-tartrate-derived silyl enol ether **13** would predictably generate **11**.

Preparation of the C13–C21 fragment **10** is outlined in scheme 3. Synthon **14** provided the C20 stereogenic center derived from L-(+)-tartaric acid.[15] Vicinal acetonide **14** was converted to benzylidenes **15a**/**15b**. Silylation of **15a** yielded masked triol **16**, which was hydrogenated to diol **17**. Acylation of the primary and oxidation of the secondary alcohol gave ketone **19**, which was converted to silyl enol ether **13**. Partner aldehyde **12** was derived from diol **20**[16] via PMB ether **21**. An efficient Mukaiyama aldol reaction[14] between **12** and **13** generated β-hydroxyl ketone **22**. Conversion to γ-hydroxyl ketone **11** allowed reductive cyclization to stereoselectively generate *trans*-THF **24**.[11,17] Aldehyde **10** was derived simply from **24**.



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



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.

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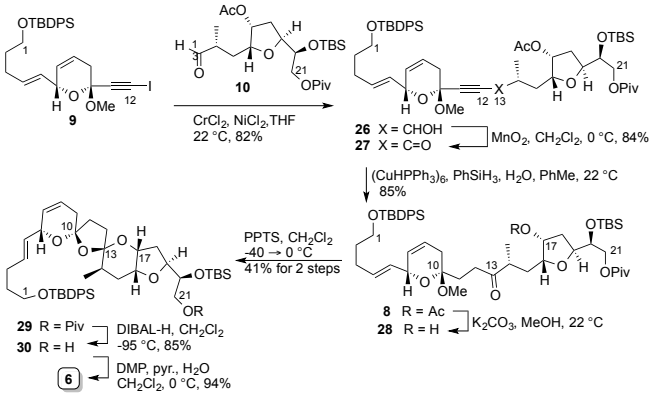
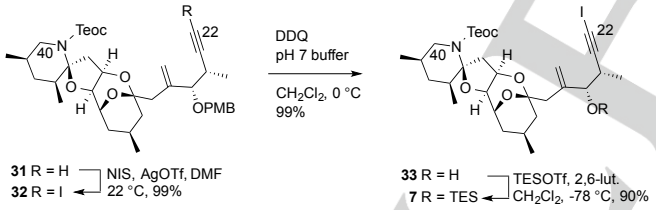
Aldehyde **10** was joined via an NHK reaction[12] with C1–C12 iodoalkyne **9**[13] to generate epimeric propargylic alcohols **26** that were oxidized to ynone **27** (scheme 4). Conjugate reduction[18] afforded ketone **8**. C17-*O*-Deacetylation allowed acid-induced bis-spiroketalization[11,19] to consolidate the ABCD-ring system in **29**. Selective deprotection and oxidation gave the C1–C21 aldehyde **6**.



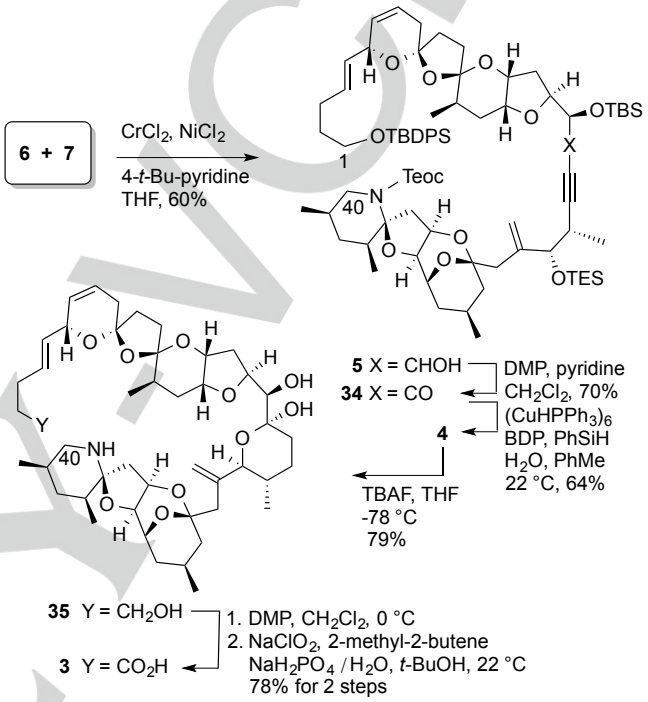
Scheme 4. Convergent assembly of the C1–C21 domain. DMP = Dess-Martin periodinane.

The C22–C40 coupling partner **7** was obtained from alkyne **31**[20] (scheme 5) via iodination and allylic ether modification. Prior installation of the C22 iodine atom was critical to consistently obtain high yields for oxidative scission of the PMB ether, as rapid decomposition resulted upon treatment of **31** with DDQ.



Scheme 5. Elaboration of the C22–C40 domain. AgOTf = silver trifluoromethanesulfonate. DMF = *N,N*-dimethylformamide. NIS = *N*-iodosuccinimide. PMB = 4-methoxybenzyl. TES = triethylsilyl. TESOTf = triethylsilyl trifluoromethanesulfonate. Teoc = 2-trimethyl(ethyloxy)carbonyl. 2,6-lut. = 2,6-dimethylpyridine.

The carbon skeleton of **3** was obtained from **6** and **7** via 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.[21] This 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 ynone **34**, which was chemoselectively reduced to ketone **4**. This modified Lipshutz-Stryker reduction also benefited from careful optimization: inclusion of 1,2-bis(diphenylphosphino)benzene (BDP) was critical for success.[18] Global deprotection of **4** was achieved with freshly prepared TBAF solution provided primary alcohol **35**. Two-step oxidation to the carboxylic acid completed the total synthesis of **3**. As observed by Evans,[11b,c] the C20 alcohol was largely inert towards oxidation using unbuffered Dess-Martin periodinane[22] conditions.



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

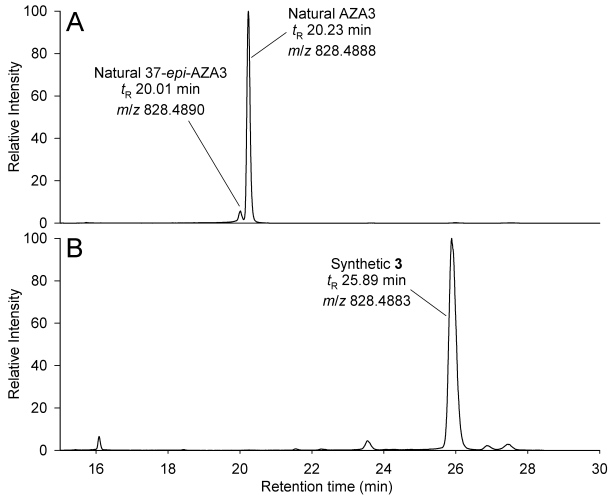


Figure 2. LC-HRMS chromatograms of **A**: natural AZA3 (t_R 20.23 min, *m/z* 828.4888), and **B**: synthetic **3** (t_R 25.89 min, *m/z* 828.4883) (LC-MS method 1; see SI).

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.[23,24] The possibility that the stereochemistry at 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.[25] 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 based upon this synthetic approach and direct comparision with natural AZA3 to determine the actual structure of AZA3.[25]

Experimental Section

Please see the Supporting Information for comprehensive experimental details.

Acknowledgements

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Keywords: azaspiracids • total synthesis • structure determination • natural products • toxins

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

[24] Comparative data are provided in the SI.

[25] Summation of this study is reported in the subsequent communication: N. Kenton, D. Adu-Ampratwum, A. A. Okumu, P. McCarron, J. Kilcoyne, F. Rise, A. L. Wilkins, C. O. Miles, C. J. Forsyth, *Angew. Chem. Int. Ed.* **2017**, xxx.

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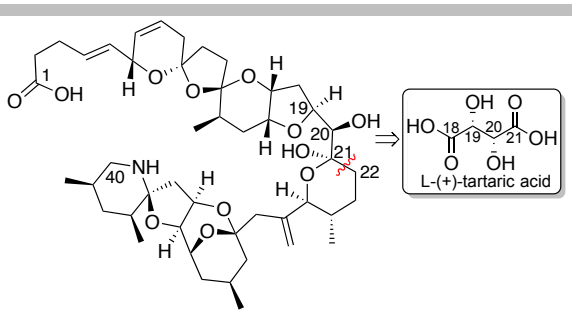
COMMUNICATION

A convergent and stereospecific total synthesis of the previously assigned structure of the marine neurotoxin azaspiracid-3 reveals non-identity and thus necessitates structural revision of the primary azaspiracids.



(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**

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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