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# Biomimetic studies towards the C28–C40 polycyclic domain of the azaspiracids

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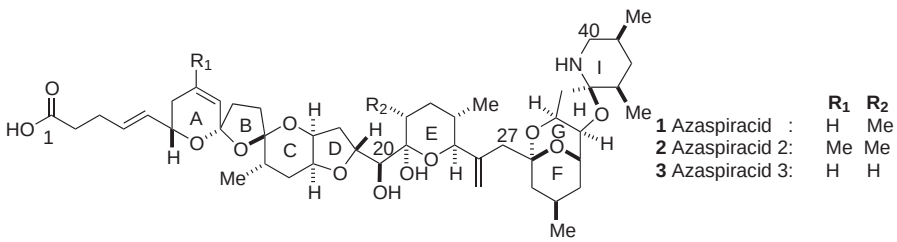
**Abstract**—An acyclic intermediate representing a putative biomimetic precursor of the C28–C40 domain of the novel marine toxin azaspiracid was constructed convergently from C28–C34 and C35–C40 fragments. In studying the assembly of the C28–C34 dioxabicyclo[3.3.1]nonane system via an intramolecular hetero-conjugate addition upon a C34–C36 enone, a stereoselective *C*-Michael addition intervened to provide a highly substituted cyclohexane. © 2001 Elsevier Science Ltd. All rights reserved.

Azaspiracid (**1**) is a marine natural product that was isolated from the blue mussel *Mytilus edulis* as the causative agent of human poisonings.[1] The symptoms resembled those of diarrhetic shellfish poisoning[2] (DSP) but the concentrations of the major DSP toxins such as okadaic acid[3] and dinophysistoxins[4] were very low in the contaminated mussels. Extensive bioassays performed on **1** have demonstrated that the effects of the toxin when administered to mice are distinct from those caused by other marine toxins.[5] Hence, azaspiracid poisoning (AZP) defines a new type of neurotoxicity associated with this environmental contaminant. Mass spectrometric and extensive NMR spectroscopic analysis revealed that azaspiracid is an ω-amino acid with a 40-carbon backbone bearing an unprecedented array of polycyclic, spiro-fused ring systems that terminate in a spiroaminal.[1]

Recently, two analogs of azaspiracid, azaspiracid-2 (**2**) and azaspiracid-3 (**3**), have been isolated from similar sources.[6] However, neither the absolute configurations nor the relative stereochemistries between their C1–C25 and C28–C40 domains of the azaspiracids have been reported. The intriguing structures, stereochemical ambiguities, distinct mechanism of action, and current scarcity combine to make the azaspiracids important synthetic targets. Reported here are preliminary studies aimed at a possible biomimetic preparation of the unique C28–C40 domain of the azaspiracids that resulted in a facile intramolecular *C*-Michael addition.

Assembly of the F–I ring system of **1**–**3** was envisioned to occur via a polycyclization cascade (Scheme 1). An α,β-unsaturated iminium species ***ii*** derived from the hypothetical acyclic amino–ketone ***i*** may trigger the formation of the F–G rings. Specifically, addition of an axial hemiketal oxygen upon the conjugated iminium ***iii***, a tautomer of ***ii***, would close the F–G ring system (***iv***). Final closure to the spiroaminal ***v*** by addition of the C33 alcohol upon the C36 iminium center would complete the sequence towards the polycyclic system ***v***. To test this approach, an acyclic keto–enone **4** (Scheme 2) was chosen as a surrogate for the postulated iminium species ***iii*** to initially study the viability of the hemiketal/hetero-Michael addition sequence. A convergent synthesis of **4** was developed from intermediates representing the C28–C34 (**5**) and C35–C40 (**6**) portions of **1**–**3**. Thereafter, closure of the 2,9-dioxabicyclo-[3.3.1]nonane system via an intramolecular conjugate addition of a cyclic C28 hemiketal upon a C34–C36 Michael acceptor could be examined.




| | R1 | R2 |
|---|---|---|
| **1** Azaspiracid : | H | Me |
| **2** Azaspiracid 2: | Me | Me |
| **3** Azaspiracid 3: | H | H |

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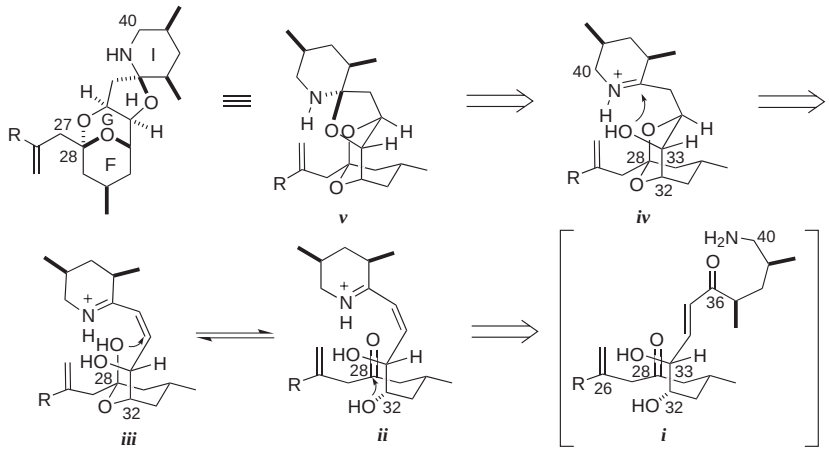
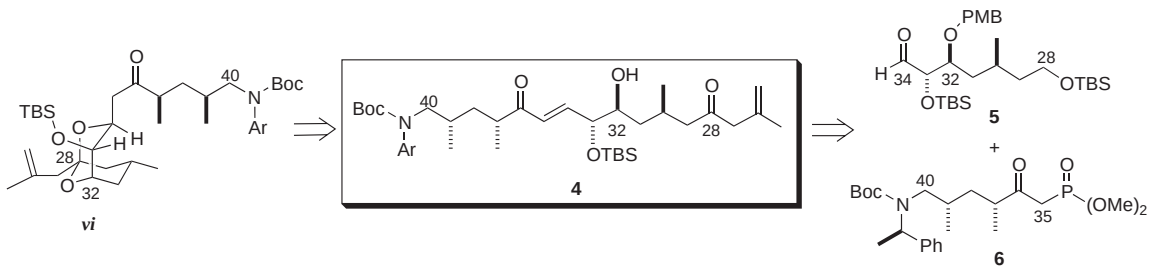


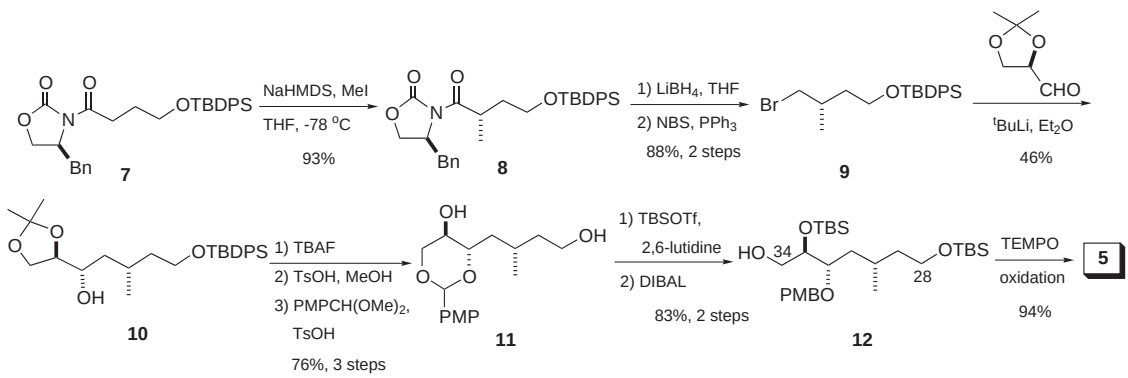
**Scheme 1.** Biosynthetic hypothesis for the C28–C40 domain of the azaspiracids.

The synthesis of aldehyde **5** began with oxazolidinone **7** (Scheme 3).[7] The stereochemistry of **5** was arbitrarily chosen to have the (30*R*,32*S*,33*R*)-absolute configuration.[8] Methylation afforded **8** as essentially a single diastereomer.[9] Reductive removal of the oxazolidinone with lithium borohydride[10] followed by treatment of the resulting alcohol with NBS and $Ph_3P$ gave bromide **9**. Addition of the lithium anion derived from **9** to (*R*)-glyceraldehyde acetonide provided alcohol **10** in moderate yield as the major diastereomer of a 4:1 mixture.[11] Compound **10** was assigned the (32*S*)-configuration by Mosher ester analysis. Attempts to improve the yield by changing temperature or reaction time, or using additives (TMEDA, HMPA) were unfruitful. Treatment of **10** with TBAF followed by acidic hydrolysis of the acetonide group afforded a tetraol, which was converted to the cyclic acetal **11**. Protection of both hydroxyl groups as TBS ethers followed by regioselective opening of the anisylidene with DIBAL gave primary alcohol **12**.[12] The regioselectivity of the acetal opening was high, but the yield was inconsistent, due mainly to cleavage of the silyl ethers.[13] Finally, oxidation of **12** with TEMPO[14] afforded aldehyde **5** in high yield.

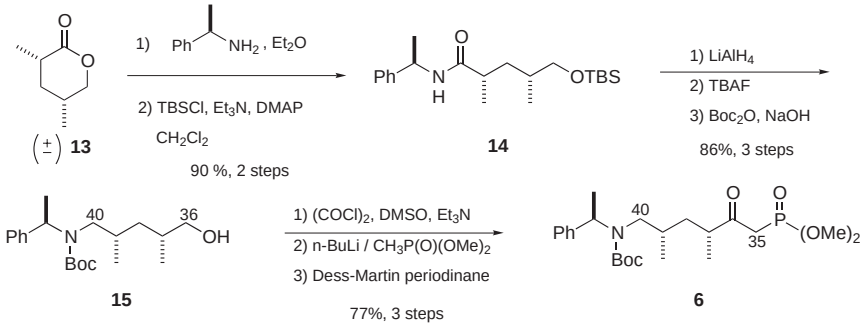
The synthesis of the complementary ketophosphonate **6** began with the known racemic lactone **13** (Scheme 4).[15] Ring opening with (*R*)-phenethylamine provided a 1:1 mixture of amide diastereomers that were chromatographically separated after conversion of the primary hydroxyl to the TBS ether **14**.[16] The desired diastereomer (37*R*,39*S*)-**14** was reduced to the corre-



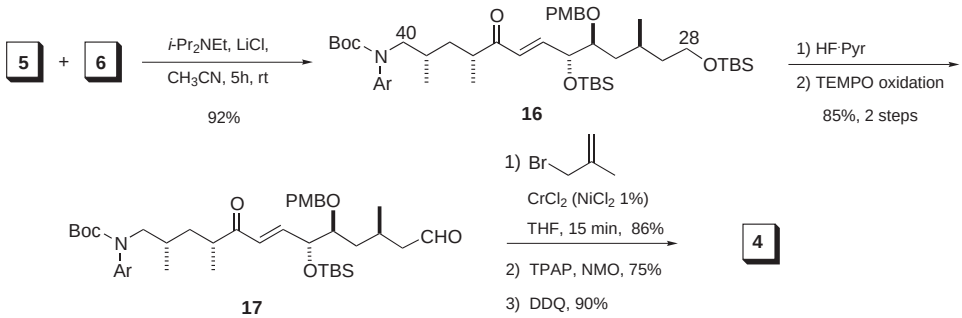
**Scheme 2.** Retrosynthesis of enone **4**.



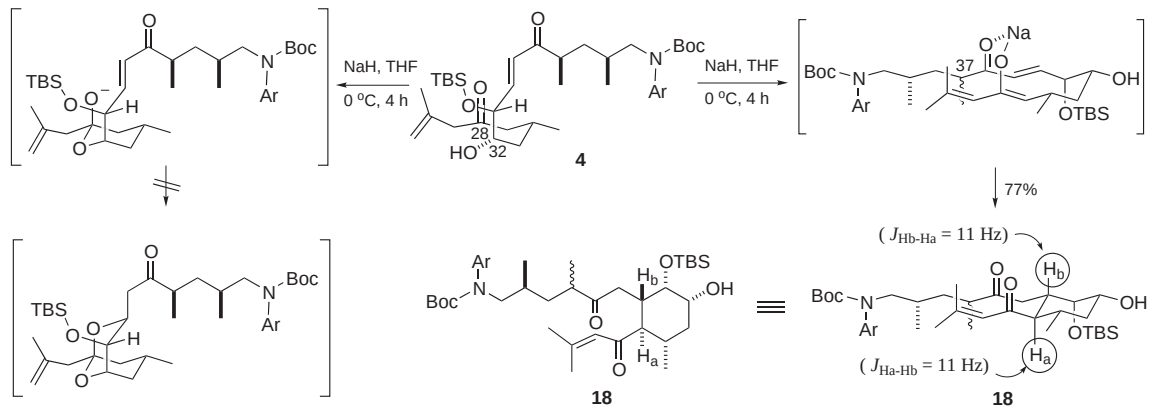
**Scheme 3.** Synthesis of intermediate **5**.




**Scheme 4.** Synthesis of the C35–C40 domain (**6**).




**Scheme 5.** Synthesis of intermediate **4**.




**Scheme 6.** Facile intramolecular *C*-Michael addition.

sponding amine. Subsequent desilylation and carbamate formation gave **15**. Swern oxidation of the alcohol provided the C36 aldehyde. Addition of the lithium anion of methyl dimethylphosphonate followed by oxidation with Dess–Martin periodinane[17] completed the synthesis of ketophosphonate **6**.

Aldehyde **5** and ketophosphonate **6** were advanced towards keto–enone **4** by coupling under Masamune–Roush conditions[18] to give (*E*)-**16** (Scheme 5). At this stage, an appropriate β,γ-unsaturated ketone needed to be installed at C28. Hence, the primary alcohol was selectively liberated with HF·pyridine and oxidized with TEMPO to afford aldehyde **17**. A $CrCl_2/NiCl_2$ mediated reaction[19] of methallyl bromide with **17** provided the corresponding homoallylic alcohol. Methallyl bromide was chosen as a simple substitute for the adjoining portion of the azaspiracids. Oxidation of the newly formed carbinol and subsequent cleavage of the PMB ether with DDQ provided the acyclic intermediate **4**.

With the initial goal of studying the assembly of the polycyclic domain of **1**–**3** in a stepwise fashion, keto–enone **4** was subjected to a variety of different basic conditions.[20] Simple treatment of **4** with NaH in THF at 0°C provided a mixture of cyclization products in 77% yield (Scheme 6). The major products were intramolecular *C*-Michael adducts **18** epimeric at C37 (3:1) instead of the anticipated 2,9-dioxabicyclo[3.3.1]nonane system of ***vi*** (Scheme 2). The stereochemistry of the two newly formed stereogenic centers on cyclohexane **18** was assigned on the basis of the observed large coupling constant ($J_{Ha,Hb}=11$ Hz) between the newly generated methine protons.

The generation of **18** can be explained by an intramolecular *C*-Michael addition reaction occurring in preference to *O*-Michael addition (cf. ***iii***→***iv***, Scheme 1). The observed carbocyclization may be promoted by a conformational predisposition of the tethered nucleophile–electrophile pair to undergo rapid bond formation via a chair-like transition state. Furthermore, the sodium cation of the enolate may be dually coordinated with the enolate and enone oxygens to enforce the reactive conformation and facilitate carbocyclization. Once enolized, the C28 ketone is inert to intramolecular attack by the C32 oxygen, thus preventing hemiketal formation that would be associated with hetero-Michael addition. Similar carbocyclization of **4** was observed upon treatment with KO$^t$Bu.

A putative acyclic precursor of the C28–C40 domain of the azaspiracids was constructed from C28–C34 (**5**) and C35–C40 (**6**) fragments. However, initial attempts to induce formation of the 2,9-dioxabicyclo[3.3.1]nonane system representing the F–G rings under basic conditions resulted instead in a facile *C*-Michael addition. The propensity of an acyclic keto–enone, with carbonyl and Michael acceptor separated by 6-carbons, to undergo stereoselective carbocyclization provides an efficient and perhaps general method to form a highly substituted cyclohexane. Alternative methods to induce the postulated biomimetic assembly of azaspiracids' unique F–I ring system are under study.

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