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Remarkably chemoselective indium-mediated coupling en route to the C21–C40 acyclic portion of the azaspiracids

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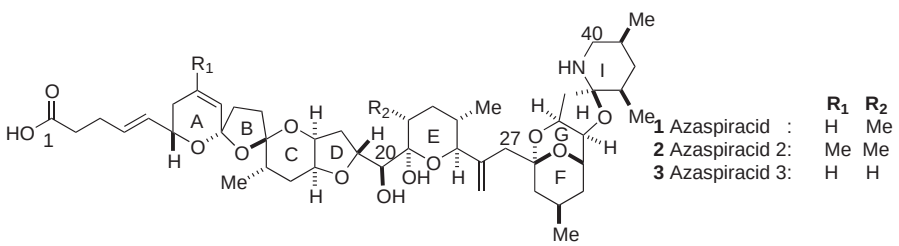
Abstract—A densely functionalized acyclic intermediate representing the C21–C40 portion of the novel marine natural product azaspiracid was prepared via a chemoselective indium-mediated coupling between C21–C27 and C28–C40 intermediates. Although the coupling partners contained aldehyde, azide, ketone, enone, and lactone functionalities, the C21–C27 allylic species added selectively to the aldehyde of a C28–C40 intermediate under aqueous indium-mediated conditions. The C21–C27 and C35–C40 fragments were prepared in a divergent fashion from a common *syn*-1,3-dimethyl synthon **9**.

The total synthesis of complex natural products often relies upon the chemoselective coupling of highly functionalized advanced intermediates under mild reaction conditions.[1] The exploration of a biomimetic-inspired approach to the C28–C40 polycyclic domain of the recently described azaspiracid marine toxins has highlighted the utility of the emerging organo-indium methodology for selective carbon–carbon bond formation in the context of complex molecule synthesis. The azaspiracids (**1**–**3**) have been identified as the causative agents of human poisoning following the consumption of contaminated mussels *Mytilus edulis*.[2,3] Azaspiracid poisoning (AZP) appears to differ toxicologically from previously characterized shellfish-induced intoxications, such as diarrhetic shellfish poisoning (DSP) and paralytic shellfish poisoning (PSP).[3,4] The unique toxicological profile of the azaspiracids is accompanied by novel structural features, including a 2,9-dioxabicyclo[3.3.1]nonane system fused to a terminal spiroaminal (F–I rings).

A postulated biomimetic approach to assemble the C28–C40 polycyclic domain of the azaspiracids involves the hetero-Michael addition of a C28 (azaspiracid numbering) hemiketal oxygen upon an α,β-unsaturated iminium species to form the dioxabicyclononane system (F–G rings), followed by spiroaminal closure via attack of the C33 hydroxy upon C36 to form the H–I rings.[5] To test the viability of this approach experimentally, an acyclic version of the C21–C40 domain was prepared.

The acyclic C21–C40 intermediate was to be derived from three fragments, the allylic bromide **8** representing C21–C27, the aldehyde **7**[6] corresponding to C28–C34, and the C35–C40 ketophosphonate **6** (Scheme 1). The pivotal β,γ-unsaturated C28 ketone could be installed via an organometallic-mediated coupling of allylic bromide **8** and a C28 aldehyde, followed by oxidation of the resultant homoallylic alcohol. Compounds **6** and **8** originated from a common synthon **9**, which is readily available on a multi-gram scale via an enzymatic



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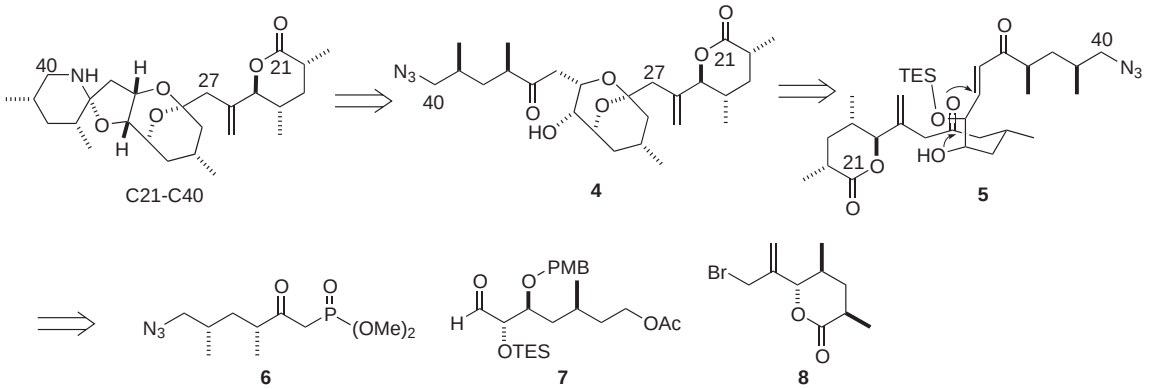
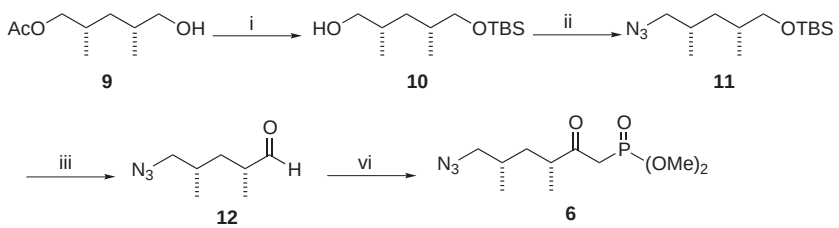


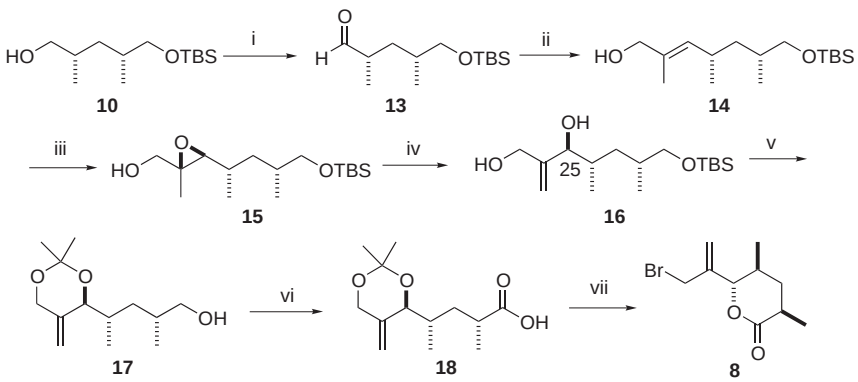
Scheme 1. Retrosynthesis of the C21–C40 domain of azaspiracid.

resolution of *meso syn*-2,4-dimethyl-1,5-pentanediol (Scheme 2).[7] Standard protecting group manipulations converted **9** into alcohol **10**, which was further transformed into azide **11** in 81% yield. The basis for choosing an azide as a latent primary amine was twofold. First, it eliminates tedious protective group manipulations, and second, reduction of an azide to an amine under appropriate conditions at a late stage may be relied upon to initiate spiroaminal formation to install the H and I rings. With **11** in hand, the TBS group was removed with TBAF. Swern oxidation of the resulting primary alcohol gave aldehyde **12**. Treatment of **12** with the lithium anion derived from methyl dimethylphosphonate, followed by Dess–Martin oxidation[8] provided β-ketophosphonate **6**.

The synthesis of bromide **8** began with the same intermediate **10** (Scheme 3). Aldehyde **13** was obtained by Swern oxidation of **10**. Subsequent Horner–Emmons reaction and DIBAL reduction of the resulting (*E*)-enone yielded allylic alcohol **14**. The C25 stereogenic center was installed by a Sharpless asymmetric epoxida-



Scheme 2. Synthesis of ketophosphonate **6**. (i) (a) TBSCl, NEt_3, DMAP, CH_2Cl_2, rt, 100%; (b) LAH, Et_2O, 0°C, 98%; (ii) $(PhO)_2P(O)N_3$, DEAD, Ph_3P, THF, rt, 81%; (iii) (a)TBAF, THF, rt, 87%; (b) Swern oxidation, 91%; (vi) (a) $LiCH_2P(O)(OMe)_2$, THF, −78°C; (b) Dess–Martin reagent, $NaHCO_3$, CH_2Cl_2, rt, 75% (two steps).



Scheme 3. Synthesis of allylic bromide **8**. (i) Swern oxidation 85%; (ii) (a) $EtOCOC(CH_3)PPh_3$, CH_2Cl_2, rt, 90%; (b) DIBAL, CH_2Cl_2, −78°C, 80%; (iii) (*L*)-DET, $Ti(O^iPr)_4$, ^{t}BuOOH, CH_2Cl_2, −25°C, 91%; (iv) LDA, THF, 0°C to rt, 86%; (v) (a) 2,2-dimethoxypropane, CSA, acetone, rt, 97%; (b) TBAF, THF, rt, 92%; (vi) TEMPO, $NaClO_2$, bleach, CH_3CN, pH 6.6 phosphate buffer, 35°C, 95%; (vii) (a) TsOH, wet CH_2Cl_2, rt, 89%; (b) Ph_3P, NBS, Et_2O/CH_3CN (v/v, 1:1), rt, 96%.

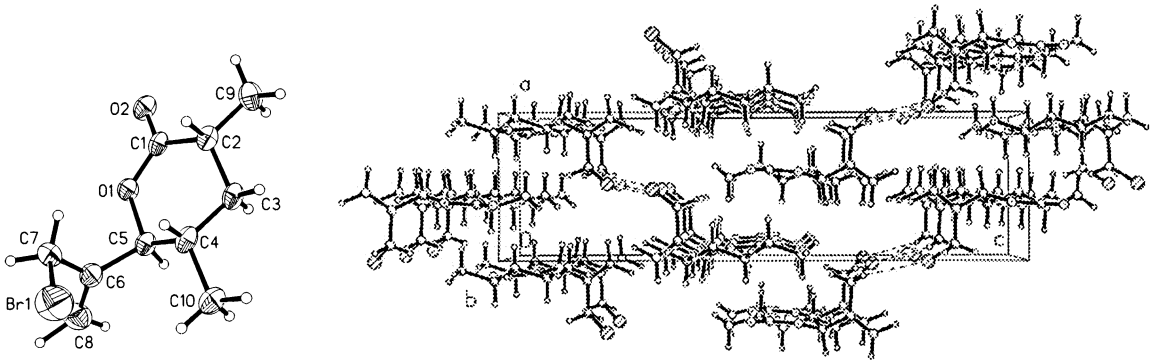
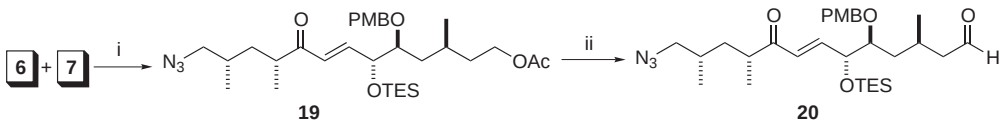
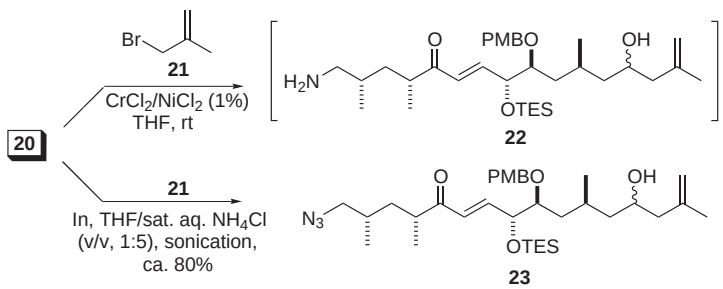


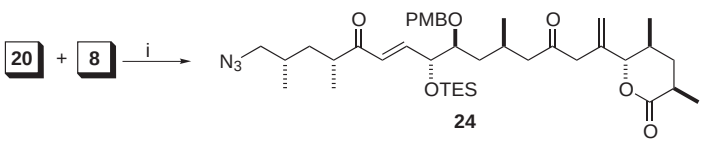
Figure 1. X-ray model of **8** and observed intermolecular hydrogen bonding.



Scheme 4. Synthesis of aldehyde **20**. (i) DIPEA, LiCl, CH_3CN, rt, 86%; (ii) (a) KCN, EtOH, rt, 75%; (b) Dess–Martin reagent, $NaHCO_3$, CH_2Cl_2, rt, 81%.



Scheme 5. Metal-mediated chemoselective allylation.



Scheme 6. Synthesis of the C21–C40 acyclic portion of azaspiracid (**24**). (i) (a) In, THF/sat. aq. NH_4Cl (v/v, 1:5), sonication; (b) Dess–Martin reagent, $NaHCO_3$, CH_2Cl_2, rt, 70% (two steps).

tion (SAE)/base-induced fragmentation sequence. Under standard SAE conditions hydroxy epoxide **15** was obtained in 91% yield,[9] which was then treated with LDA to provide bis-allylic alcohol **16** in 86% yield.[10] Simple manipulations gave alcohol **17**, which was oxidized in a single operation to carboxylic acid **18** via a TEMPO-catalyzed reaction.[11] Under carefully optimized acidic conditions, the desired six-membered hydroxy lactone was obtained in 89% yield as a single isomer from **18**, with no eight-membered lactone detected. Further treatment of the hydroxy lactone with PPh_3 and NBS provided the allylic bromide **8** representing the C21–C28 portion of azaspiracid. The structure of **8** was further secured by X-ray crystallographic analysis (Fig. 1). It is interesting to note that a weak intermolecular hydrogen bond was observed between the bromine atom and an adjacent methylene hydrogen atom in the crystal of **8**.

The ketophosphonate **6** was coupled with aldehyde **7** to provide the (*E*)-enone **19** under Masamune–Roush conditions[12] (Scheme 4). The primary acetate was removed with KCN in EtOH at ambient temperature, and Dess–Martin oxidation of the newly formed primary alcohol led to aldehyde **20** in good yield. At this stage, however, attempted coupling of **20** with a model allylic bromide **21** mediated by $CrCl_2/NiCl_2$[13] in THF proved to be problematic, probably due to the reduction of the azide by $CrCl_2$.[14] In contrast, an indium-mediated coupling in an aqueous system[15] provided the desired allylation product chemoselectively under a variety of reaction conditions (Scheme 5). These

involved varying the solvent system, such as water, THF/water, and the use of aqueous NH_4Cl (THF/saturated aq. NH_4Cl). Furthermore, ultrasonication dramatically accelerated the reaction. It is noteworthy that other potentially reactive functionalities, such as azide,[16] enone, and ketone, did not compete with the aldehyde for reaction with the in situ generated organo-indium intermediate under any of the reaction conditions examined.[17] Typically, the reaction mixture was continuously sonicated for 4 h before work-up, and the products were uniformly obtained in ~80% yield. The coupling of **20** with lactone **8** worked equally well under these conditions. Without further purification the crude allylic alcohol adducts were oxidized with Dess–Martin reagent to provide enone **24** (Scheme 6).

In summary, the highly functionalized product **24**, representing a putative acyclic form of the C21–C40 portion of azaspiracid, was prepared in a convergent fashion from key building blocks allylic bromide **8** and aldehyde **20**. A regioselective SAE/base induced-fragmentation sequence was employed in the construction of bromide **8**, and the 1,3-dimethyl containing intermediates **6** and **8** were prepared from the common synthon **9**. Notably, bromide **8** and aldehyde **20** were joined via a chemoselective indium-mediated reaction in the presence of lactone, ketone, enone, and azide functional groups. The resulting carbon chain, containing 15 functionalized carbons, will serve as a key platform to study the subsequent biomimetic assembly of azaspiracid's novel E–I ring systems.

Acknowledgements

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17. Typical procedure: To a mixture of aldehyde **20** (0.05 mmol) and allylic bromide **21** (0.1 mmol) in THF/saturated aq. NH_4Cl (1 mL, 1:5, v/v) was added indium pieces (0.1 mmol). The flask containing the resulting mixture was immersed in an aqueous sonication bath and sonicated continuously for 4 h. The water in the sonication bath was changed periodically to almost maintain ambient temperature. The reaction flask was then removed from the sonication bath, ethyl acetate was added, and the resulting mixture was stirred for 30 min before the standard extractive work-up. Silica gel column chromatography provided the homoallylic alcohol **23** (~0.04 mmol).