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Studies toward the total synthesis of azaspiracids: synthesis of the FGHI ring domain

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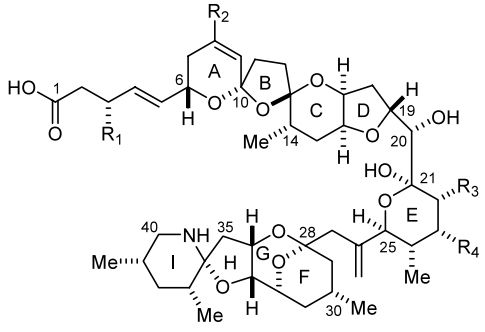
Abstract—Synthesis of the FGHI ring domain of azaspiracids, the causative agents for a new type of shellfish poisoning, azaspiracid poisoning (AZP), has been achieved. The synthesis features dithiane anion–epoxide coupling for convergent fragment assembly.

Azaspiracid poisoning (AZP) is a new type of shellfish poisoning prevailing in Europe since 1995.[1] Azaspiracid (**1**) and its congeners (**2**–**5**) were isolated as the causative toxins from the contaminated Irish mussels, *Mytilus edulis*, and their structures were elucidated by extensive NMR analysis and FAB collision-induced dissociation MS/MS experiments by Yasumoto and co-workers (Fig. 1).[2] These toxins are characterized by a bisspiroketal structure fused to a tetrahydrofuran ring and an unusual azaspiro ring fused with a 2,9-dioxabicyclo[3.3.1]nonane ring system. However, the relative configuration between C25 and C28, and the absolute stereochemistry remained to be determined. The unprecedented molecular architecture and intriguing biological activity of these natural toxins have attracted considerable interest among synthetic chemists.[3] As part of our efforts toward the total synthesis of azaspiracids, we describe herein the synthesis of the FGHI ring domain **6a**. Although the synthesis of *ent*-**6a** has been recently reported by the Nicolaou[3f] and Forsyth groups,[3g] our approach features dithiane-epoxide coupling for the C35–C36 bond construction.[4]

Our synthetic plan for the assembly of the C21–C40 domain **6b** of azaspiracids involved convergent coupling of the HI ring aldehyde **7** with the E ring allylstannane **8** followed by closure of the 2,9-bicyclo[3.3.1]nonane ring (Scheme 1).[5] The azaspiro ring system of **7** would, in turn, be accessible from an open-chain precursor **9**, which was envisioned to be obtained from coupling of the C36–C40 dithiane **10** and the C28–C35 epoxide **11**. The viability of the strategy was investigated by the synthesis of a more simple system **6a**.[3f,g]

The synthesis of dithiane **10** is summarized in Scheme 2. Desymmetrization of the known *meso*-diol **12**[7] by treatment with vinyl acetate and lipase AK provided the corresponding monoacetate **13**, $[\alpha]_D^{23}$ +10.8 (*c* 1.00, $CHCl_3$).[8] Protection as its *tert*-butyldimethylsilyl (TBS) ether followed by deacetylation gave alcohol **14**. Oxidation[9] to the aldehyde and subsequent treatment



1 azaspiracid (AZP): $R_1 = R_2 = H$, $R_3 = Me$, $R_4 = H$
2 azaspiracid-2: $R_1 = H$, $R_2 = R_3 = Me$, $R_4 = H$
3 azaspiracid-3: $R_1 = R_2 = R_3 = R_4 = H$
4 azaspiracid-4: $R_1 = OH$, $R_2 = R_3 = R_4 = H$
5 azaspiracid-5: $R_1 = R_2 = R_3 = H$, $R_4 = OH$

Figure 1. Structures of azaspiracid (**1**) and its analogues.

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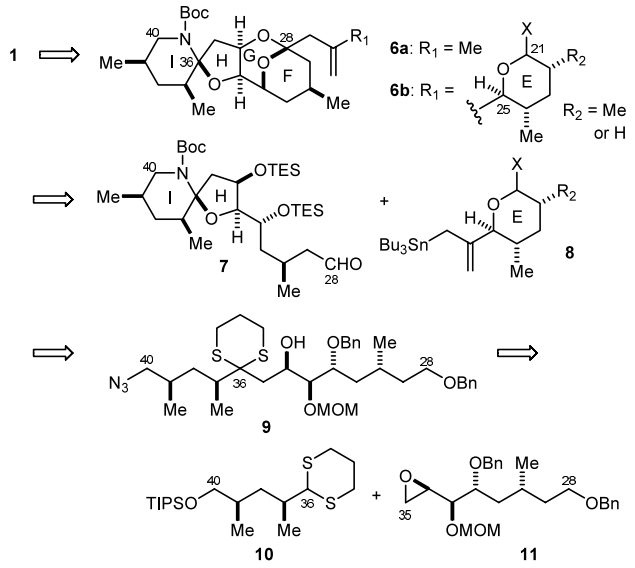
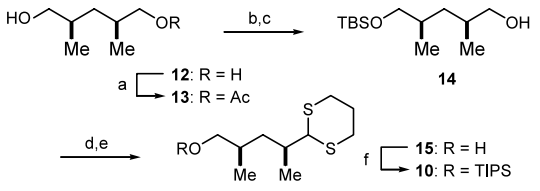


Scheme 1. Retrosynthetic analysis of the C21–C40 domain **6**.

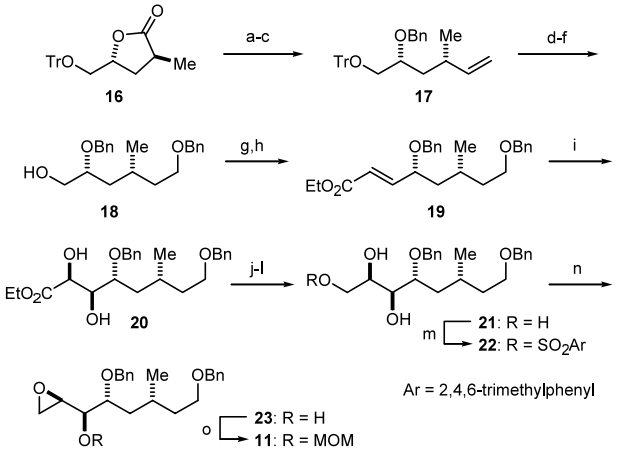


Scheme 2. *Reagents and conditions*: (a) CH_2=CHOAc, lipase AK, THF, 0°C, 47%; (b) TBDMSCl, imidazole, CH_2Cl_2, rt; (c) K_2CO_3, MeOH, rt, 86% (two steps); (d) IBX, DMSO, rt, 90%; (e) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C, 96%; (f) TIPSCl, imidazole, CH_2Cl_2, rt, 89%.

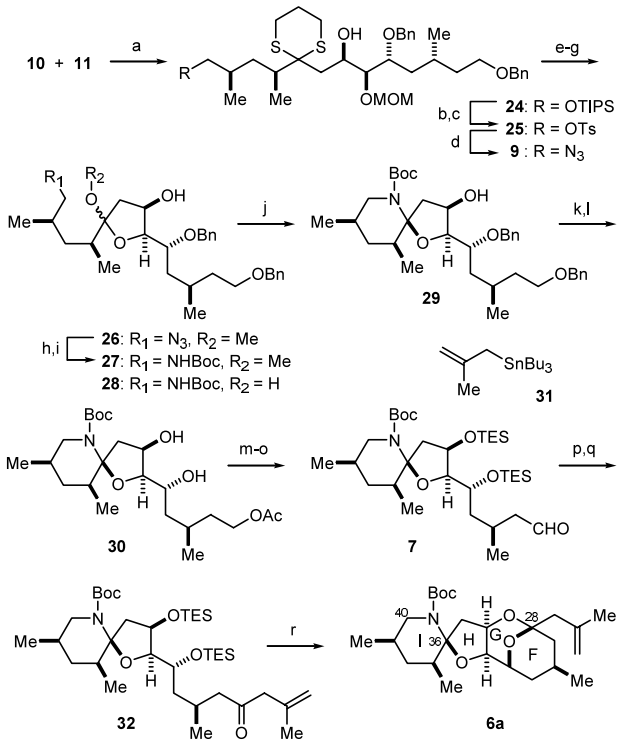
with propanedithiol and $BF_3{\cdot}OEt_2$ afforded dithiane alcohol **15**, which was reprotected as the TIPS ether to give **10**.

The synthesis of epoxide **11** began with lactone **16** ($[\alpha]_D^{25}$ −33.7 (*c* 0.89, $CHCl_3$)),[10] which was subjected to DIBALH reduction and Wittig methylenation to give, after benzylation, olefin **17** (Scheme 3). Hydroboration–oxidation followed by benzylation of the derived alcohol and removal of the trityl ether provided alcohol **18**, which was then oxidized to the aldehyde and homologated to enoate **19**. Dihydroxylation of **19** with OsO_4/NMO produced an approximately 3:1 diastereomeric mixture of diols (77% yield), with the desired **20** predominating as predicted by the empirical rule developed by Cha et al.[11] On the contrary, Sharpless asymmetric dihyroxylation with AD mix-β[12] afforded **20** with high selectivity (>20:1). Diol **20** was then converted to triol **21** by a three-step sequence. Selective sulfonylation of the primary hydroxyl group with 2,4,6-trimethylbenzenesulfonyl chloride followed by base treatment led to epoxide **23**, which was then protected as the MOM ether to provide **11**.

With the requisite fragments **10** and **11** in hand, we next focused on their coupling (Scheme 4). After some experiments, the best result was realized by generation of the anion of **10** with *n*-BuLi in THF at room temperature for 5 min followed by reaction with **11** at 0°C for 20 min. Thus, the desired coupling product **24** was obtained in 92% yield. Desilylation and tosylation gave **25**, which upon displacement with NaN_3 afforded azide **9**. After removal of the MOM group, treatment with $Hg(ClO_4)_2$ in the presence of $CaCO_3$ in THF/methanol gave a mixture of methyl ketal **26** and the corresponding hemiketal (ca. 1.3:1), which without separation was treated with PPTS in methanol to afford **26** in 74% yield from **9**. Reduction of the azide and protection of the resulting amine as the *tert*-butylcarbamate gave *N*-Boc derivative **27**. Subsequent spiroaminal formation was carried out according to the procedure described by Forsyth et al.[3g] Thus, treatment of **27** with $Yb(OTf)_3$ (0.01 equiv.) in CH_3CN at −20°C gave the desired spiroaminal **29** in 57% yield (73% based on recovered **27**). In this reaction, hemiketal **28** was obtained in 13% yield, but this could be readily converted into **27** by treatment with PPTS in methanol (77% yield) and recycled. Reductive debenzylation with lithium di-*tert*-butylbiphenilide (LiDBB)[13] and selective acetylation of the primary hydroxyl group gave monoacetate **30**. Protection of the diol as the TES ethers was followed by deacetylation and oxidation of the derived alcohol to give aldehyde **7**. Reaction with methallyltributylstannane **31** in the presence of $MgBr_2{\cdot}OEt_2$ and oxidation of the resulting secondary alcohol produced ketone **32**. Finally, treatment of **32** with HF·pyridine in pyridine/THF at room temperature effected formation of the 2,9-dioxabicy-



Scheme 3. *Reagents and conditions*: (a) DIBALH, CH_2Cl_2, −78°C; (b) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, 0°C, 53% (two steps); (c) NaH, BnBr, DMF, 0°C→rt; (d) 9-BBN, THF, rt, then $NaBO_3{\cdot}4H_2O$; (e) NaH, BnBr, DMF, 0°C→rt, 60% (three steps); (f) *p*-TsOH, MeOH/CH_2Cl_2 (1:1), rt, 70%; (g) IBX, DMSO, rt; (h) $(i\text{-PrO})_2P(O)CH_2CO_2Et$, KO*t*-Bu, THF, 0°C, 90% (two steps); (i) AD mix-β, $CH_3SO_2NH_2$, OsO_4 (0.05 equiv.), *t*-BuOH/H_2O (1:1), rt, 83% (>20:1); (j) $PhCH(OMe)_2$, CSA, CH_2Cl_2, rt; (k) $LiAlH_4$, THF, 0°C; (l) *p*-TsOH, MeOH, rt, 76% (three steps); (m) 2,4,6-Me_3PhSO_2Cl, Et_3N, DMAP, CH_2Cl_2, 0°C→rt; (n) K_2CO_3, EtOH, rt, 59% (two steps); (o) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 67%.



Scheme 4. *Reagents and conditions*: (a) **10**, *n*-BuLi, THF, rt, then **11**, 0°C, 92%; (b) TBAF, THF, rt, 81%; (c) *p*-TsCl, Et_3N, DMAP, CH_2Cl_2, rt; (d) NaN_3, DMF, 50°C, 94% (two steps); (e) $BF_3{\cdot}OEt_2$, Me_2S, CH_2Cl_2, 0°C, 87%; (f) $Hg(ClO_4)_2$, $CaCO_3$, THF/MeOH (4:1), 0°C; (g) PPTS, MeOH, rt, 85% (two steps); (h) Ph_3P, THF, then H_2O, rt; (i) Boc_2O, Et_3N, CH_2Cl_2, rt, quant. (two steps); (j) $Yb(OTf)_3$, CH_3CN, −20°C, 57%; (k) LiDBB, THF, −78°C, 92%; (l) AcCl, 2,4,6-collidine, CH_2Cl_2, −40°C, 79%; (m) TESOTf, 2,6-lutidine, CH_2Cl_2, −40°C, 86%; (n) DIBALH, CH_2Cl_2, −78°C, 88%; (o) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 91%; (p) **31**, $MgBr_2{\cdot}OEt_2$, CH_2Cl_2, −20°C→rt, 78%; (q) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 73%; (r) HF·pyr, pyr, THF, 0°C→rt, 30%.

clo[3.3.1]nonane ring system to complete the synthesis of the FGHI ring domain **6a**, $[\alpha]_D^{20}$ −3.7 (*c* 0.22, $CHCl_3$), in 30% yield (not optimized). The spectral data for **6a** were fully consistent with those reported previously.[3f]

In conclusion, we have developed a convergent synthetic route to the FGHI ring system **6a** of azaspiracids based on dithiane anion–epoxide coupling for the C35–C36 bond construction. Further studies toward the total synthesis of azaspiracids are currently underway and will be reported in due course.

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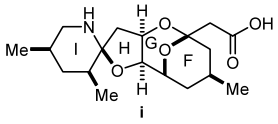

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