Natural Product Synthesis

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Synthesis of the Southern FGHI Ring System of Azaspiracid-1 and Investigation into the Controlling Elements of C28- and C36-Ketalization**

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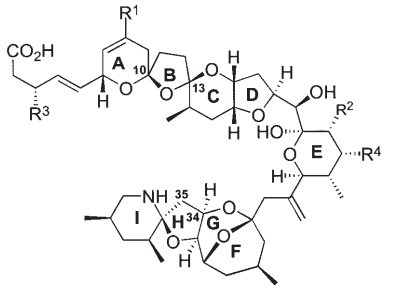
The azaspiracid family of natural products has stimulated significant interest in both the synthetic[1–3] and biological communities[4] due to their complex structural architecture and toxicity (Figure 1). We were initially drawn toward



azaspiracid-1 (**1**): R^1 = H, R^2 = Me, R^3 = R^4 = H
azaspiracid-2 (**2**): R^1 = R^2 = Me, R^3 = R^4 = H
azaspiracid-3 (**3**): R^1 = R^2 = R^3 = R^4 = H
azaspiracid-4 (**4**): R^1 = R^2 = H, R^3 = OH, R^4 = H
azaspiracid-5 (**5**): R^1 = R^2 = R^3 = H, R^4 = OH

Figure 1. The azaspiracids.

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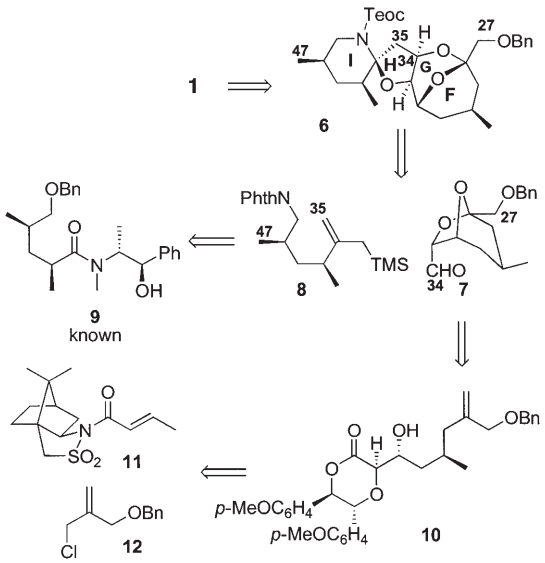
azaspiracid-1 (**1**) by the C10,C13-bis-spiroketal portion of the molecule. Our endeavors have led to a better understanding of the controlling elements behind this structural motif.[1] Herein, we detail our successful construction of the FGHI ring system present in the southern portion of azaspiracid.

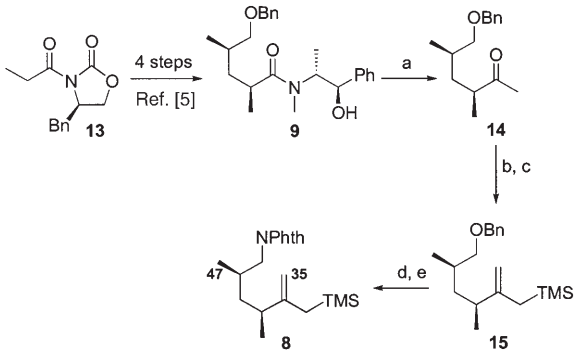
Our retrosynthetic strategy for the southern portion of azaspiracid disconnected FGHI ring system **6** at the C34–35 linkage to yield aldehyde **7** and allyl silane **8** (Scheme 1). To



Scheme 1. Retrosynthetic analysis of azaspiracid-1 (**1**). Teoc = 2-(trimethylsilyl)ethoxycarbonyl, Bn = benzyl, TMS = trimethylsilyl, PhthN = phthalimido.

establish the correct stereochemistry at C34, this key coupling would need to proceed via a Cram-chelated intermediate with aldehyde **7**. The allyl silane portion would be available from the known Myers alkylation product **9**.[5] The aldehyde **7** should be accessible from the Andrus aldol adduct **10**, which in turn could be constructed from the sultam **11** and the chloride **12**.

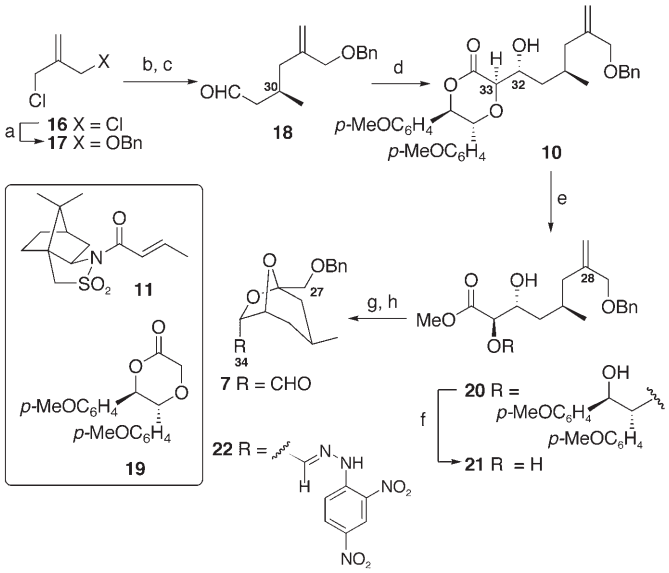
The synthesis of the allyl silane **8** is shown in Scheme 2. The Myers alkylation adduct **9** was prepared in four steps



Scheme 2. Synthesis of allyl silane **8**. Reagents and conditions: a) MeLi, Et_2O, 82%; b) KHMDS, Comins' reagent, THF, 91%; c) $[Pd(PPh_3)]_4$, LiCl, $TMSCH_2MgBr$, Et_2O, 77%; d) Na, naphthalene, THF, −78→−40°C, 72%; e) phthalimide, DEAD, PPh_3, THF, 96%. HMDS = hexamethyldisilazide, DEAD = diethyl azodicarboxylate.

from the commercially available oxazolidinone **13**.[5] Treatment of **9** with methyllithium yielded the methyl ketone **14**. Next, conversion of **14** into the enol triflate followed by palladium-catalyzed coupling gave the allyl silane **15**. Removal of the benzyl ether was accomplished by using sodium naphthalenide. Finally, Mitsunobu reaction gave the phthalimide **8**.

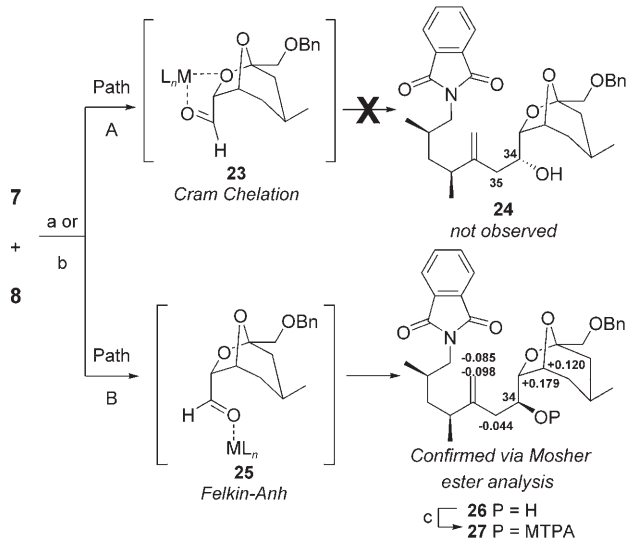
Synthesis of the aldehyde fragment **7**[6] was accomplished in eight steps (Scheme 3). After monobenzylation of the



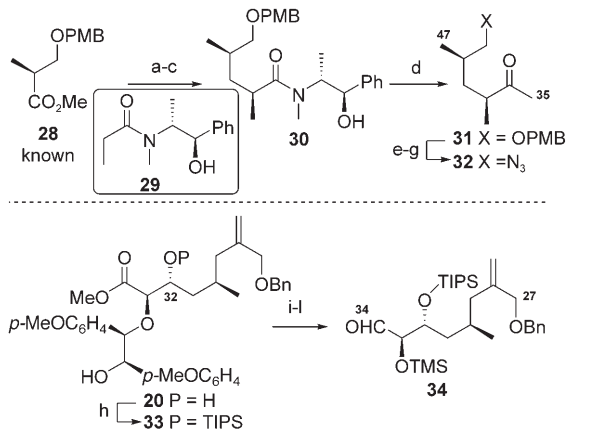
Scheme 3. Synthesis of bicyclic aldehyde **7**. Reagents and conditions: a) NaH, BnOH, THF, DMF, 77%; b) Mg, $BrCH_2CH_2Br$, CuBr·DMS, **11**, LiCl, TMSCl, THF, 90%; c) DIBAL-H, CH_2Cl_2, −78°C, 84%; d) **19**, $(c\text{-}C_6H_{11})_2BOTf$, Et_3N, CH_2Cl_2; −78→−20°C, 86%; e) NaOMe, MeOH, 0°C, 90%; f) CAN, MeCN/H_2O (9:1), 72%; g) O_3, CH_2Cl_2, DMS then Amberlyst-15, 80%; h) DIBAL-H, CH_2Cl_2, −78°C, 87%. DMF = *N*,*N*-dimethylformamide, DMS = dimethyl sulfide, DIBAL-H = diisobutylaluminum hydride, OTf = trifluoromethanesulfonate, CAN = ceric ammonium nitrate.

commercially available dichloride **16**, cuprate addition to the known sultam **11**, under similar conditions described by Paquette and Boulet,[7] led to generation of the stereocenter at C30 with excellent diastereoselectivity (d.r. > 20:1). Direct reduction of the product to the aldehyde **18** followed by boron-mediated aldol reaction with the Andrus dioxanone (**19**)[8] resulted in the adduct **10** again with excellent selectivity (d.r. > 10:1). Ring opening of the lactone **10** to its methyl ester **20** followed by CAN oxidative cleavage provided the diol **21**. The key [3.2.1] bicyclic ketal moiety could be constructed through ozonolysis of **21** with DMS workup, which induced spontaneous C28-ketal formation. This ketalization process could be driven to completion by the addition of Amberlyst-15. Finally, reduction with DIBAL-H proceeded cleanly to give the aldehyde **7**. The stereochemistry of aldehyde **7** was conclusively established through X-ray crystal structure assignment of the 2,4-dinitrohydrazone derivative **22**.[9]

With the two major subunits in hand, we shifted our focus to their combination (Scheme 4). Treatment of a precooled solution of aldehyde **7** with Lewis acids ($TiCl_4$ or $SnCl_4$)



Scheme 4. First-generation coupling. Reagents and conditions: a) $SnCl_4$, CH_2Cl_2, 54% (**26**); b) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 52% (**26**); c) (*R*)/(*S*)-Mosher acid chloride, DMAP, CH_2Cl_2, 45–51%. Representative data points for the difference in NMR chemical shift values [ppm], that is, $\delta(S)$-Mosher ester$-\delta(R)$-Mosher ester, are shown for ester **27** (400 MHz, $CDCl_3$). MTPA = α-methoxy-α-trifluoromethylphenylacetic acid (Mosher), DMAP = 4-(dimethylamino)pyridine.



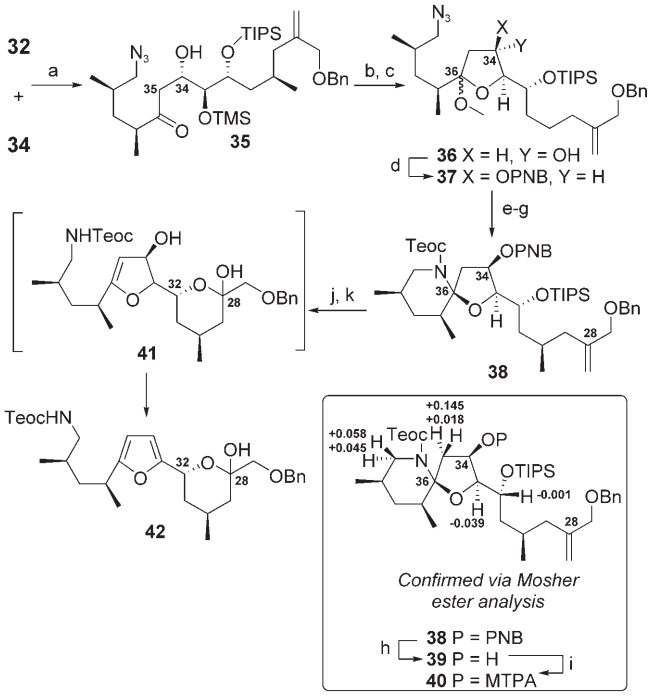
Scheme 5. Synthesis of revised coupling partners **32** and **34**. Reagents and conditions: a) $LiAlH_4$, Et_2O, 0°C, 99%; b) Ph_3P, I_2, imid., CH_2Cl_2, 86%; c) **29**, LDA, LiCl, THF, 90%; d) MeLi, Et_2O, 92%; e) DDQ, CH_2Cl_2, H_2O; f) TsCl, Et_3N, CH_2Cl_2, 64% (over 2 steps); g) NaN_3, DMF, 92%; h) TIPSOTf, 2,6-lut., CH_2Cl_2, −78°C, 83%; i) CAN, MeCN/H_2O (9:1), 98%; j) TMSOTf, 2,6-lut., CH_2Cl_2, −78°C, 86%; k) DIBAL-H, CH_2Cl_2, −78°C; l) DMP, CH_2Cl_2, 76% (over 2 steps). imid. = imidazole, LDA = lithium diisopropylamide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, Ts = *para*-toluenesulfonyl, TIPS = triisopropylsilyl, lut. = lutidine, DMP = Dess–Martin periodinane, PMB = *para*-methoxybenzyl.

followed by the addition of allyl silane **8** provided the coupled material as a single diastereomer at C34. We had hypothesized that chelating Lewis acids such as titanium or tin would proceed via the intermediate **23** to give the desired stereochemical outcome (**24**). We were surprised to find, upon conversion of the intermediate into its Mosher ester **27**,[10] that the C34 stereochemistry was in fact that of the undesired isomer. Further support for this assignment can be found in the fact that treatment of **7** with $BF_3{\cdot}Et_2O$ (a Lewis acid incapable of proceeding via intermediate **23**) also gave alcohol **26**, again as a single diastereomer. Despite our considerable efforts, we were unable to devise a viable route to invert the stereochemistry at C34.

It would appear from our efforts that the encumbered nature of alcohol **26** made it impossible to properly install the C34 stereogenic center. On the basis of this setback, we chose to revise our approach (Scheme 5). Starting from the known PMB-protected ester **28**,[11] DIBAL-H reduction, iodination, and Myers alkylation gave **30**. Conversion of **30** into the methyl ketone followed by DDQ deprotection and two-step azide incorporation gave **32**.

For the aldehyde component **34**, selective protection at C32 was required. Triisopropylsilylation of aldol adduct **10** did yield the corresponding silyl ether; however, methanolysis of the lactone proved unsuccessful. Fortunately, treatment of **20** with TIPSOTf and 2,6-lutidine at low temperature gave selectively the C32-OTIPS product **33**. None of the corresponding benzyl OTIPS ether was observed. Finally, deprotection with CAN, protection with TMS, and reduction produced the aldehyde **34**.

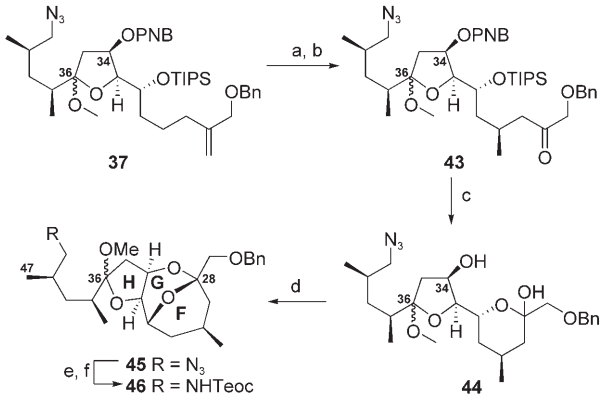
Next, our efforts returned to the combination of the subunits **32** and **34** (Scheme 6). Aldol reaction of ketone **32** and aldehyde **34** gave the coupled adduct **35** in excellent yield



Scheme 6. Formation of unwanted furan **42**. Reagents and conditions: a) LDA, THF, −78°C, 94%; b) TBAF, HOAc, THF, 99%; c) PPTS, MeOH, 94%; d) *p*-NO_2-$C_6H_4CO_2H$, DEAD, PPh_3, THF, 53%; e) PPh_3, THF, H_2O; f) Teoc-O-(C_6H_4-*p*-NO_2), Et_3N, EtOAc, 71% (over two steps); g) Yb(OTf)$_3$, MeCN, 78%; h) K_2CO_3, MeOH, 75%; i) (*R*)/(*S*)-Mosher acid chloride, DMAP, CH_2Cl_2, 68–72%; j) TBAF, THF, 81%; k) O_3, CH_2Cl_2, −78°C; DMS then Amberlyst-15, CH_2Cl_2. Representative data points for the difference in chemical shift values [ppm], that is, $\delta(S)$-Mosher ester$-\delta(R)$-Mosher ester, are shown for ester **40** (400 MHz, $CDCl_3$). TBAF = tetra-*n*-butylammonium fluoride, PPTS = pyridinium *para*-toluenesulfonate, PNB = *para*-nitrobenzoate.

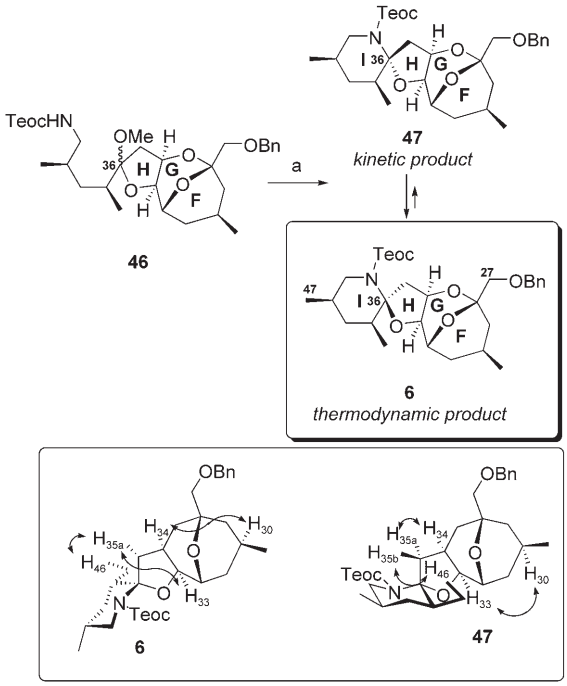
as a single diastereomer. On the basis of precedent from us and others,[2e,3e,g] we suspected that the C34 stereochemistry was once again incorrect. Fortunately, after removal of the TMS group at C33 and mixed ketal formation at C36, we were able to cleanly invert the C34 stereochemistry using Martin's modified Mitsunobu conditions.[12] Staudinger reduction of the azide followed by Teoc protection and cyclization[2e] using $Yb(OTf)_3$ gave the HI ring system in **38**. The desired stereochemistry at C34 was confirmed through modified Mosher ester analysis.[10] Treatment of **38** with TBAF in THF induced selective removal of the TIPS (C32) and PNB (C34) protecting groups in the presence of the Teoc moiety. With only alkene cleavage at C28 and [3.3.1] bicyclic ketal formation remaining, we believed that the completion of the FGHI ring system was within reach. We were surprised to find that despite considerable experimentation, we consistently observed degradation of the material during ozonolysis. Small amounts of a minor product could be isolated for which the spectral data was supportive of furan structure **42**, which presumably formed via the enol ether intermediate **41**.

Thwarted by the unexpected furan formation, we reexamined the ordering of cyclization events (Scheme 7). Starting from the C34 inversion product **37**, C28 alkene dihydroxylation and cleavage yielded the ketone **43**. Removal of the TIPS ether at C32 as well as the *p*-nitrobenzoate group at C34 with TBAF yielded the diol **44**. While non-alcoholic solvents proved problematic in the formation of the [3.3.1] bicyclic structure, use of methanol as a solvent cleanly led to formation of the desired FGH ring system of **45**. The use of a hydrogen-bonding solvent moderates the acidity of the system, thereby preventing formation of the destructive C35–36 enol ether. Finally, azide reduction and Teoc protection provided compound **46**.



Scheme 7. Incorporation of FGH ring system. Reagents and conditions: a) $K_2OsO_4 \cdot 2H_2O$, NMO, acetone, H_2O; b) $NaIO_4$, THF, H_2O, 87% (over two steps); c) TBAF, THF, 85%; d) CSA, MeOH, 79%; e) PPh_3, THF, H_2O; f) Teoc-O-(C_6H_4-*p*-NO_2), Et_3N, EtOAc, 86% (over two steps). NMO = *N*-methylmorpholine-*N*-oxide, CSA = camphorsulfonic acid.

With the FGH rings now in place, the final challenge remaining was the formation of the azaspiro HI ring system (Scheme 8). Initial attempts to form C36 azaspiroketal using



Scheme 8. Completion of the southern fragment. Reagents and conditions: a) $Yb(OTf)_3$, THF, 30 min, 74% (4:3 **6**/**47**). Key NOE interactions in **6** and **47** are indicated by double-ended arrows in the lower part of the scheme.

acidic media (e.g. CSA, MeOH) led to extensive decomposition. Interestingly, treatment of **46** with $Yb(OTf)_3$[2e,3e,g,p] in PhMe led to rapid formation (30 min, room temperature) of a single new product **47**. Careful analysis by 2D NMR spectroscopy revealed that **47** possessed the undesired stereochemistry at C36. Use of extended reaction times led to formation of a second compound, compound **6**; however, decomposition was a competitive pathway under these conditions. Fortunately, use of an alternate solvent (THF) at room temperature led to the desired C36 spiroaminal **6** as the major product (74% yield, **6**/**47** 4:3 ratio). The minor product **47** could be recycled by resubmission to identical reaction conditions to generate the same thermodynamic 4:3 ratio. As we have previously demonstrated in our synthesis of the C1–C26 northern portion of azaspiracid-1 (**1**),[1h] we are able to control the stereochemical outcome during ketalization through the proper choice of conditions. We did find the formation of the unwanted spiroaminal **47** as the kinetic product to be surprising, as the anomerically stabilized axial orientation is typically kinetically favored as a result of a presumed lower transition-state energy. We attribute this unusual behavior to a severe steric interaction between the NTeoc group and the fused GH ring system.

In summary, an efficient synthesis of the C27–C47 southern portion (**6**) has been achieved in 20 steps from commercially available dichloride **16**. The outlined approach represents the shortest route to the FGHI ring system reported to date.[2e,3e,g,p] In addition, we have demonstrated that careful selection of conditions for the ketalization steps allows control over the stereochemical outcome of the reaction.

Completion of the total synthesis of azaspiracid-1 (**1**) will be reported in due course.

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[9] See Supporting Information for the ORTEP representation of **22**. CCDC-605862 (**22**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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