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Total Synthesis and Structural Elucidation of Azaspiracid-1. Construction of Key Building Blocks for Originally Proposed Structure

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Abstract: Syntheses of the three key building blocks (**65**, **98**, and **100**) required for the total synthesis of the proposed structure of azaspiracid-1 (**1a**) are described. Key steps include a TMSOTf-induced ring-closing cascade to form the ABC rings of tetracycle **65**, a neodymium-catalyzed internal aminal formation for the construction of intermediate **98**, and a Nozaki−Hiyama−Kishi coupling to assemble the required carbon chain of fragment **100**. The synthesized fragments, obtained stereoselectively in both their enantiomeric forms, were expected to allow for the construction of all four stereoisomers proposed as possible structures of azaspiracid-1 (**1a**−**d**), thus allowing the determination of both the relative and absolute stereochemistry of the natural product.

Introduction

Among recently isolated marine biotoxins, none has created as much concern with regard to seafood poisoning and human health, or research interest with regard to its structure and chemical synthesis, as azaspiracid-1. Its story began in The Netherlands when, in 1995, an incident of human illness with diarrhetic shellfish poisoning (DSP)-like symptoms was reported and eventually traced to the consumption of mussels originating from Killary Harbour, Ireland.[1] A subsequent investigation of these mussels, belonging to the *Mytilus* edulis family, by Yasumoto, Satake, and co-workers led to the isolation and structural assignment of azaspiracid-1 as one of the four possible structures (**1a**−**d**) shown in Figure 1.[2] Its discovery and recognized health hazard led to the declaration of a new toxic syndrome, named azaspiracid poisoning (AZP), with a molecular structure and pathological effects sufficiently different from previously known DSP phenomena to warrant the new name. Known symptoms in humans include nausea, vomiting and severe diarrhea. Furthermore, azaspiracid-1 was shown to cause lung, liver, spleen, and lymphocyte damage as well as lung tumor formation in mice.[3]

The heroic isolation and structural elucidation investigations by the Yasumoto−Satake team yielded only small amounts of azaspiracid-1; nonetheless, they permitted extensive mass spectrometric and NMR (^{1}H, COSY, TOCSY, ROESY, HSQC, and HMBC) spectroscopic studies, leading to the proposal of structure **1a** or one of its stereoisomeric forms [*epi*-FGHI-**1a** (**1b**, the FGHI diastereomer of **1a**), *ent*-**1a** (**1c**, the enantiomer of **1a**), and *ent*-(*epi*-FGHI-**1a**) (**1d**, the enantiomer of **1b**)]. Containing no stereocenters, the two-carbon bridge separating the ABCDE and FGHI domains of the molecule ($C_{26}-C_{27}$) was apparently a sufficient barrier to prevent stereochemical correlation across the entire backbone of the structure. Nevertheless, these structural assignments revealed a unique and unprecedented molecular architecture that included in its $C_{47}H_{71}NO_{12}$ formula no less than 9 rings and 20 stereogenic centers. Among its most prominent structural motifs are a trioxadispiroacetal system fused onto a tetrahydrofuran ring, the entire framework comprising the molecule's ABCD domain, and an azaspiro ring system fused onto a 2,9-dioxabicyclo[3.3.1]nonane system, completing the structure of the tetracyclic FGHI framework. Given the secondary amino group of the azaspiro system and the C_1 carboxyl moiety that it also carries, azaspiracid-1 is an amino acid, a feature not to be overlooked, for it may play a role in the overall conformation and properties of the molecule. The assigned structure also boasted three sites of unsaturation in the form of carbon−carbon double bonds (C_4-C_5, C_8-C_9, and $C_{26}-C_{44}$), a hemiketal moiety (at C-21), and several stereocenters prone to epimerization (C-10, -13, -14, -21, -36, and -37) under acidic conditions. All in all, these structural features presented an appealing, but formidable, synthetic

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10.1021/ja0547477 CCC: $33.50

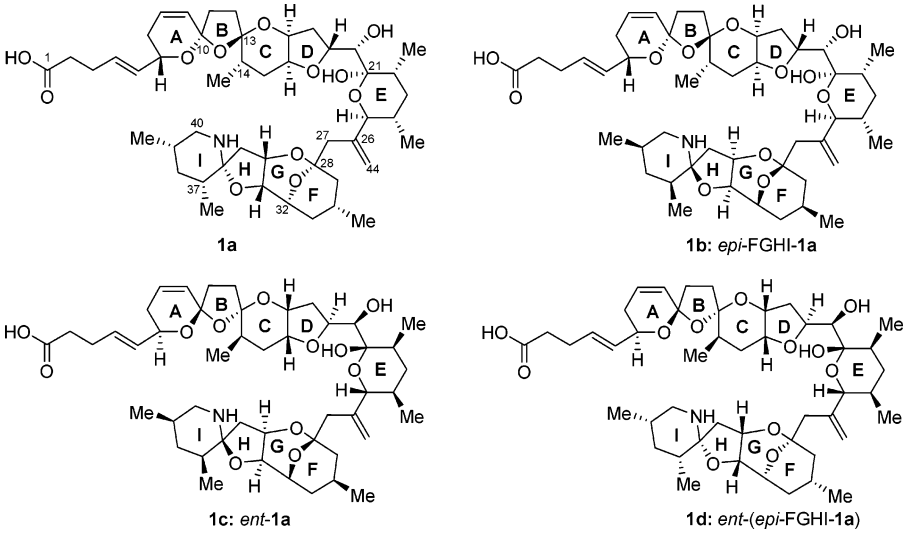

Figure 1. The four structures originally proposed for azaspiracid-1 (**1a**−**d**, Satake et al. 1998).

challenge which became even more pressing due to the extreme scarcity and hazardous nature of the molecule.

By virtue of its structural complexity, natural scarcity, and biological importance, azaspiracid-1 prompted many groups to pursue its total synthesis,[4] including ours.[5] It would be our team that reached the target in 2003,[6] only to prove, however, that the assigned structures (**1a**−**d**) were wrong. This finding spurred a collaborative effort with the Satake group to determine the true structure of the natural product through degradative work and chemical synthesis, which would culminate, in 2004, in the demystification of the structure of azaspiracid-1 and its first total synthesis.[7] In this and accompanying articles[8,9] in this series, we present the details of the total synthesis campaign that led to the revision of the structure of azaspiracid-1 and the establishment of its absolute stereochemistry as **1** (Figure 2). It should be noted that the developed synthetic technology for the total synthesis of azaspiracid-1 could, in principle, be suitably adopted to deliver its siblings, azaspiracids-2 through -11 (**2a**−**11a**, originally assigned structure; **2**−**11**, revised structures) shown in Figure 3.[10] We begin, in this paper, with the retrosynthetic analysis and construction of the defined key building blocks required for the total synthesis of the originally proposed structures of azaspiracid-1 (**1a**−**d**).

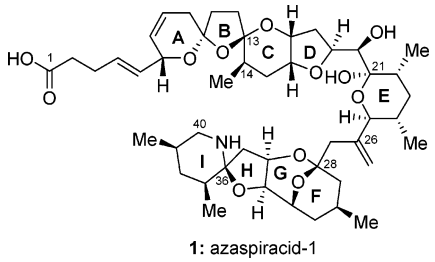

Figure 2. Revised structure of azaspiracid-1 (**1**).

Results and Discussion

1. Retrosynthetic Analysis. A brief inspection of the structure of azaspiracid-1 (e.g., **1a**) reveals a double spiroacetal (ABC ring junction), a hemiketal (E ring), an intramolecular bridged ketal (FG ring system), and a spiroaminal (HI ring junction) as interesting structural motifs that may need special attention from the synthetic point of view due to their stereochemical features and fragile nature. In addition, the astute observer may recognize a number of uniquely strategic bonds for retrosynthetic disconnection, as outlined in Figure 4. For optimum convergency, our first retrosynthetic analysis involved disconnections at the $C_{20}-C_{21}$ (dithiane technology)[11] and the $C_{25}-C_{26}$ (Nozaki−Hiyama−Kishi coupling)[12] bonds leading, upon suitable functional group manipulation, to aldehyde **13** (or an equivalent C_1-C_{20} fragment), dithiane aldehyde **12** (or an equivalent

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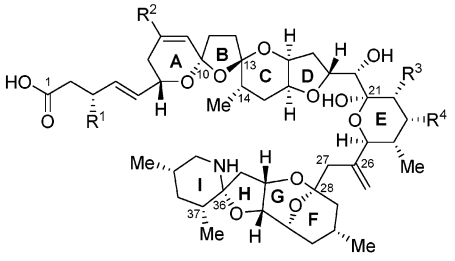
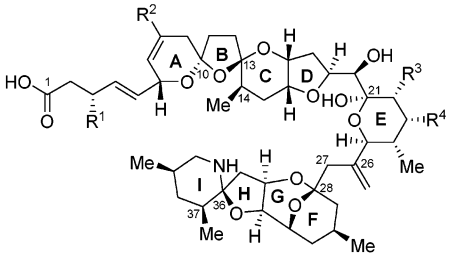
originally proposed structures



revised structures



	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
2a: azaspiracid-2	H	Me	Me	H	**2:** azaspiracid-2	H	Me	Me	H
3a: azaspiracid-3	H	H	H	H	**3:** azaspiracid-3	H	H	H	H
4a: azaspiracid-4	OH	H	H	H	**4:** azaspiracid-4	OH	H	H	H
5a: azaspiracid-5	H	H	H	OH	**5:** azaspiracid-5	H	H	H	OH
6a: azaspiracid-6	H	Me	H	H	**6:** azaspiracid-6	H	Me	H	H
7a: azaspiracid-7	OH	H	Me	H	**7:** azaspiracid-7	OH	H	Me	H
8a: azaspiracid-8	H	H	Me	OH	**8:** azaspiracid-8	H	H	Me	OH
9a: azaspiracid-9	OH	Me	H	H	**9:** azaspiracid-9	OH	Me	H	H
10a: azaspiracid-10	H	Me	H	OH	**10:** azaspiracid-10	H	Me	H	OH
11a: azaspiracid-11	OH	Me	Me	H	**11:** azaspiracid-11	OH	Me	Me	H

Figure 3. Originally proposed structures for azaspiracids-2 to -11 (**2a**−**11a**, left) and revised structures (**2**−**11**, right).

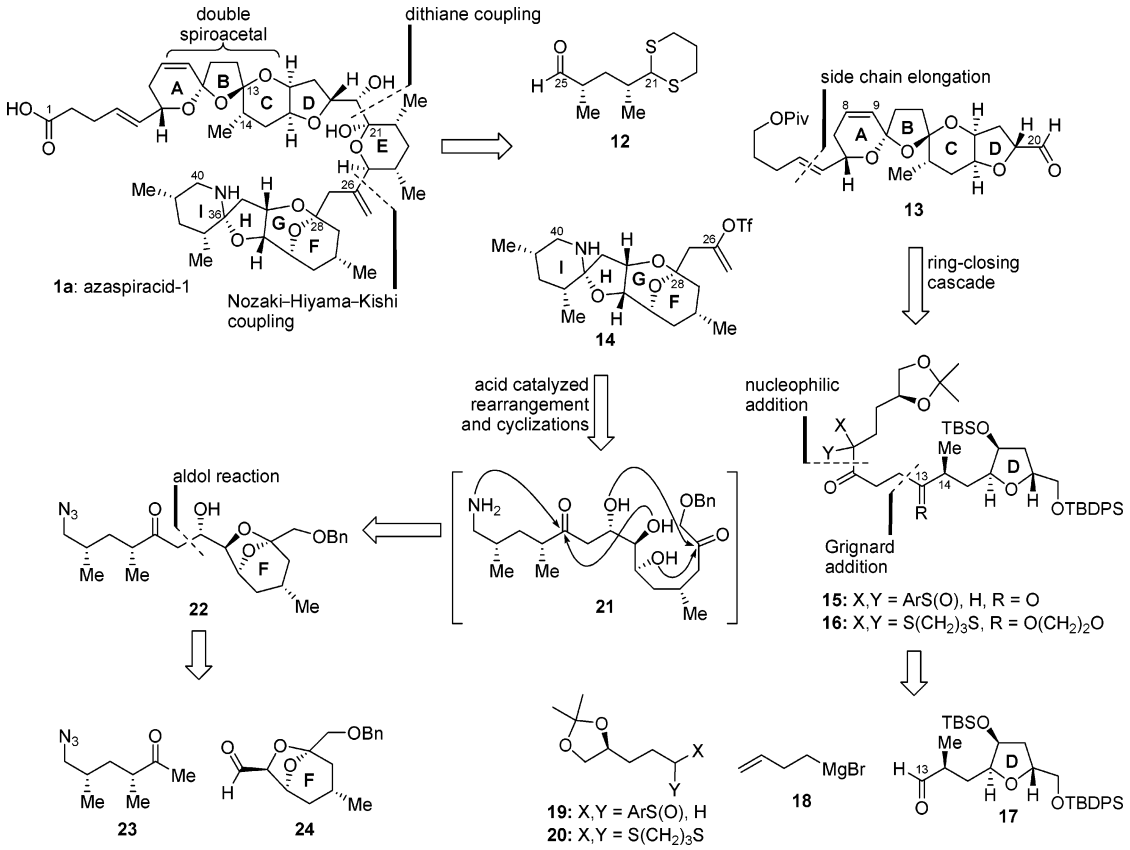


Figure 4. First-generation retrosynthetic analysis of the originally proposed structure of azaspiracid-1 (**1a**).

C_{21}−C_{25} fragment), and vinyl triflate **14** (or an equivalent C_{26}−C_{40} fragment) as potential key building blocks for the intended construction.

Side-chain detachment followed by dismantling of the double spiroacetal within **13** then led to appropriately protected monocyclic compounds **15** and **16** as plausible precursors of the desired polycycle. Equipped with a sulfoxide or a dithiane group, the latter compounds could then be disconnected through two carbon−carbon bond-forming reactions, a nucleophilic addition, and a Grignard addition, yielding fragments **19** (aryl sulfoxide) and **20** (dithiane), Grignard reagent **18**, and aldehyde **17** as reasonably accessible starting materials for the synthesis of the ABCD domain of the molecule. Similarly, the tetracyclic FGHI fragment **14** was traced back to open chain trihydroxy amino-diketone **21** as a potential progenitor, as shown in Figure 4. The latter intermediate was then disconnected to the potential starting material **22** (acetal formation) and then further disconnected to azido-ketone **23** and aldehyde **24** (aldol reaction). The strategy that emerged from this retrosynthetic analysis provided us, in addition to high convergency, the flexibility to construct both enantiomers of each key building block (**12**−**14**) so as to ensure the definition of the relative stereochemistry of the

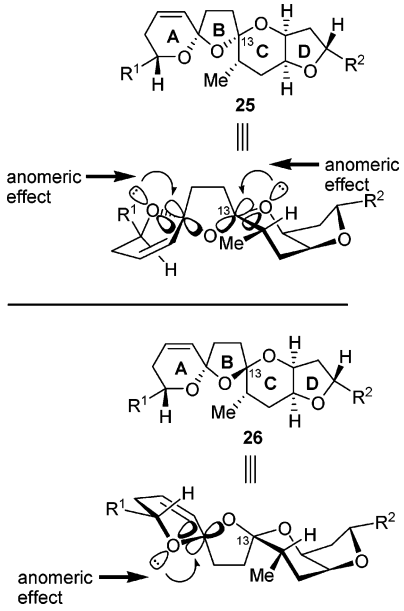


Figure 5. Anomeric effects providing stabilization for the two isomeric ABCD domains **25** (two anomeric effects, thermodynamically more stable) and **26** (one anomeric effect, thermodynamically less stable).

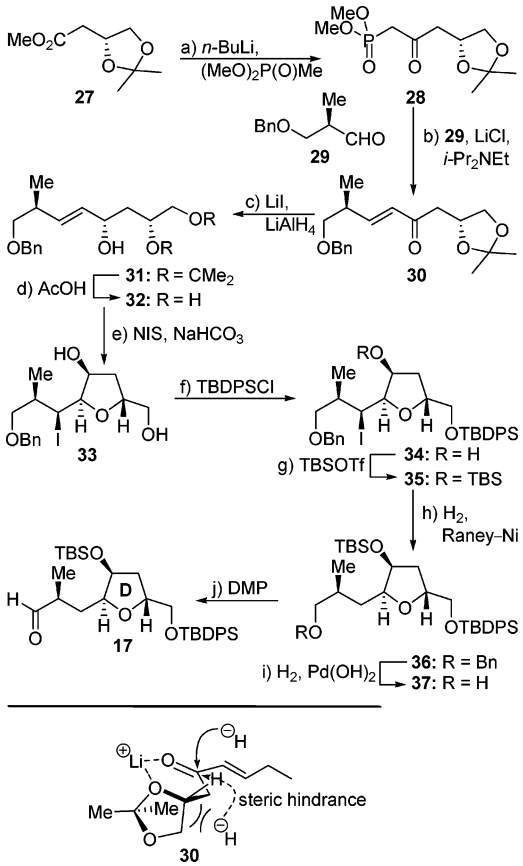
ABCDE and FGHI domains of azaspiracid-1, as well as its absolute stereochemistry.

2. Construction of the Undesired ABCD Ring System through a Chiral Sulfoxide. Upon inspection of the ABCD ring framework and some early modeling studies, it became clear to us that the reported stereochemical arrangement of the double spiroacetal moiety (ABC ring junction) represented the thermodynamically less favored structure (**26**, 13*R*) as compared to its C-13-epimer (**25**, 13*S*). Figure 5 depicts these epimeric compounds with the crucial anomeric effects that provided the reason for the expected higher thermodynamic stability for the undesired (**25**, 13*S*) structure. Indeed, timely disclosures by the Carter and Forsyth groups[4b,g] confirmed this postulate, as these researchers had synthesized suitable precursors of the ABCD framework of azaspiracid-1 and demonstrated its preference to fall, under thermodynamically controlled conditions, exclusively into the undesired structural motif (**25**, 13*S*). It was, therefore, abundantly evident at the time that a special strategy was necessary for the casting of the unfavored (**26**, 13*R*) ABCD stereoisomer.

Our first attempt to address this rather thorny problem involved the use of a chiral sulfoxide moiety, as had previously been described by Williams.[13] Thus, we reasoned that a bulky group adjacent to the C-13 stereocenter may provide enough steric bias to override the influence of the anomeric effect, thereby reversing the outcome of the ring-closing reaction. A group that would facilitate the construction of the precursor substrate as well as the required olefinic bond after the cyclization would be preferred. The *p*-tolylsulfoxide group fulfilled these criteria and, therefore, was chosen for incorporation into the intermediates of the sequence. Schemes 1−3 depict the results of our investigations employing the chiral sulfoxide strategy to control the C-13 spiroacetal cyclization.

The sequence began with enantiomerically pure acetonide methyl ester **27**,[14] whose reaction with the lithio anion derived

Scheme 1. Construction of Key Intermediate **17**[a]



[a] Reagents and conditions: (a) $(MeO)_2P(O)Me$ (2.2 equiv), *n*-BuLi (1.6 M in hexanes, 2.2 equiv), THF, −78 °C, 1 h, 84%; (b) **29** (0.67 equiv), LiCl (1.3 equiv), *i*-Pr_2NEt (1.0 equiv), MeCN, 25 °C, 12 h, 86% based on **29**; (c) $LiAlH_4$ (10 equiv), LiI (8.0 equiv), Et_2O, −100 °C, 30 min, 98%; (d) AcOH:H_2O (2:1), 40 °C, 5 h, 97%; (e) NIS (5.0 equiv), $NaHCO_3$ (10 equiv), THF, 0 °C, 36 h, 70%; (f) TBDPSCl (1.4 equiv), Et_3N (3.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 0 °C, 3 h, 90%; (g) TBSOTf (1.6 equiv), 2,6-lutidine (4.0 equiv), CH_2Cl_2, 0 °C, 30 min, 100%; (h) H_2, Raney-Ni (1:1 w/w), EtOH, 25 °C, 1 h, 99%; (i) H_2, 20% $Pd(OH)_2$/C (25% w/w), EtOH, 25 °C, 3 h, 88%; (j) DMP (2.0 equiv), CH_2Cl_2, 25 °C, 2 h, 99%. Abbreviations: THF, tetrahydrofuran; NIS, *N*-iodosuccinimide; TBDPS, *tert*-butyldiphenylsilyl; 4-DMAP, 4-(dimethylamino)pyridine; TBS, *tert*-butyldimethylsilyl; Tf, trifluoromethanesulfonate; DMP, Dess−Martin periodinane.

from dimethylmethylphosphonate and *n*-BuLi resulted in the formation of ketophosphonate **28** in 84% yield (Scheme 1). Reaction of an excess of this ketophosphonate with enantiomerically pure aldehyde **29**[15] in the presence of LiCl and *i*-Pr_2NEt then furnished the α,β-unsaturated ketone **30** in 86% yield.[16] Chelation-controlled reduction of the latter compound with $LiAlH_4$, orchestrated by LiI in ether at −100 °C,[17] pleasingly gave the desired secondary alcohol stereoisomer **31** in 98% yield and ≥98:2 diastereoselectivity. The acetonide group was then removed by exposure to AcOH from the latter compound, furnishing triol **32** in 97% yield. This substrate was then subjected to iodoetherification with NIS (for abbreviations of reagents and protecting groups, see the scheme footnotes) in

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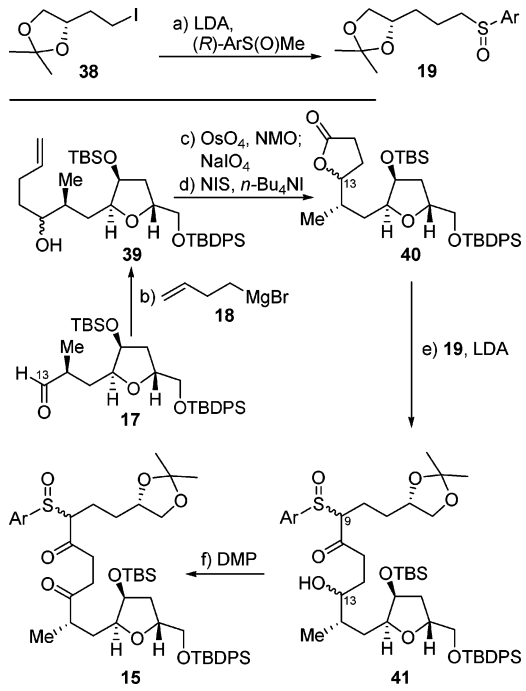
Scheme 2. Synthesis of Chiral Sulfoxide Cyclization Precursor **15**[a]

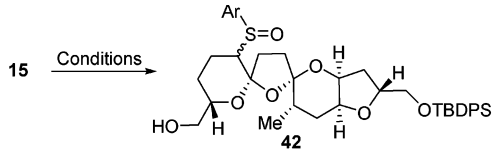


[a] Reagents and conditions: (a) LDA (1.0 equiv), (*R*)-methyl-*p*-tolylsulfoxide (1.0 equiv), THF, −78 °C, 30 min, 83%; (b) 3-butenylmagnesium bromide **18** (6.0 equiv), THF, −78 → −10 °C, 3 h, 87% (ca. 1:1 mixture of diastereomers); (c) OsO_4 (0.03 equiv), NMO (2.0 equiv), *t*-BuOH:THF:H_2O (10:2:1), 25 °C, 12 h; then $NaIO_4$ (5.0 equiv), pH 7 buffer, 25 °C, 5 h, 96%; (d) NIS (5.0 equiv), *n*-Bu_4I (2.0 equiv), CH_2Cl_2, 25 °C, 1 h, 98%; (e) LDA (1.0 equiv), **19** (1.5 equiv), THF, −78 °C, 15 min, 83%; (f) DMP (3.0 equiv), CH_2Cl_2, 25 °C, 2 h, 92%. Abbreviations: LDA, lithium diisopropylamide; NMO, *N*-methylmorpholine-*N*-oxide; Ar, *p*-tolyl.

THF in the presence of $NaHCO_3$ at 0 °C to afford the tetrahydrofuran system **33** in 70% yield as a single isomer.[18] The preference of this process for a single cyclic ether isomer is remarkable in that the reaction not only was ring-selective, but it was also highly stereoselective (≥98% de). The following step was also highly selective, leading from the resulting dihydroxy iodoether to the mono-TBDPS derivative **34** upon treatment with a slight excess of TBDPSCl and Et_3N in the presence of 4-DMAP (90% yield). Further silylation of this compound (**34**) under TBSOTf-2,6-lutidine conditions afforded bis-silyl ether **35** in quantitative yield. Reductive removal of the iodine residue from **35** (H_2, Raney-Ni) then gave the desired tetrahydrofuran system **36** in 99% yield. This compound (**36**) was then converted to aldehyde **17** by first hydrogenolyzing its benzyl ether off [H_2, $Pd(OH)_2$] to afford the primary alcohol (**37**, 88% yield) and then oxidizing the latter compound with DMP (99%).[19]

Scheme 2 shows the sequence through which aldehyde **17** was advanced to the next stage, namely cyclization precursor **15**. Thus, the Grignard reagent **18** generated from 4-bromo-1-butene was reacted with **17** in THF to afford olefinic secondary alcohol **39** in 87% yield as a mixture of diastereomers (ca. 1:1). Dihydroxylation of this compound with catalytic OsO_4 in the presence of NMO, followed by $NaIO_4$ cleavage of the resulting

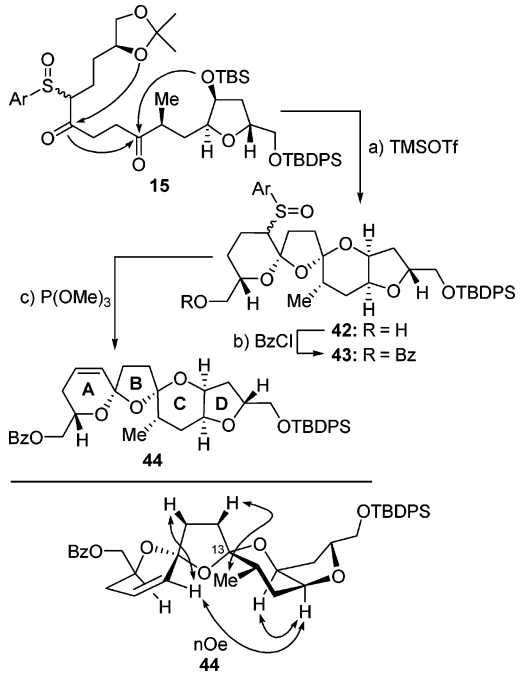
Table 1. Conditions for the Cyclization of Sulfoxide **15** to Tetracycle **42**



entry	conditions[a]	yield (%)
1	TFA (3.0 equiv), THF:H_2O (4:1), 0 → 25 °C, 48 h	25
2	CSA (1.0 equiv), PhH:MeOH:H_2O (10:2:1), 25 °C 24 h	nr
3	*p*-TsOH·H_2O (0.1 equiv), MeOH, 25 °C, 36 h	<10
4	BCl_3 (2.5 equiv), CH_2Cl_2, 25 °C, 3 min	0
5	AcOH:H_2O (4:1), 25 °C, 18 h	<10
6	TMSOTf (3.0 equiv), CH_2Cl_2, −78 → 0 °C, 3 h	62

[a] Reactions were carried out on 0.1 mmol scale. Abbreviations: TFA, trifluoroacetic acid; CSA, camphorsulfonic acid; TMS, trimethylsilyl; *p*-TsOH, *p*-toluenesulfonic acid; nr, no reaction.

Scheme 3. Synthesis of Undesired C_6-C_{20} Isomer **44** of the ABCD Domain[a]



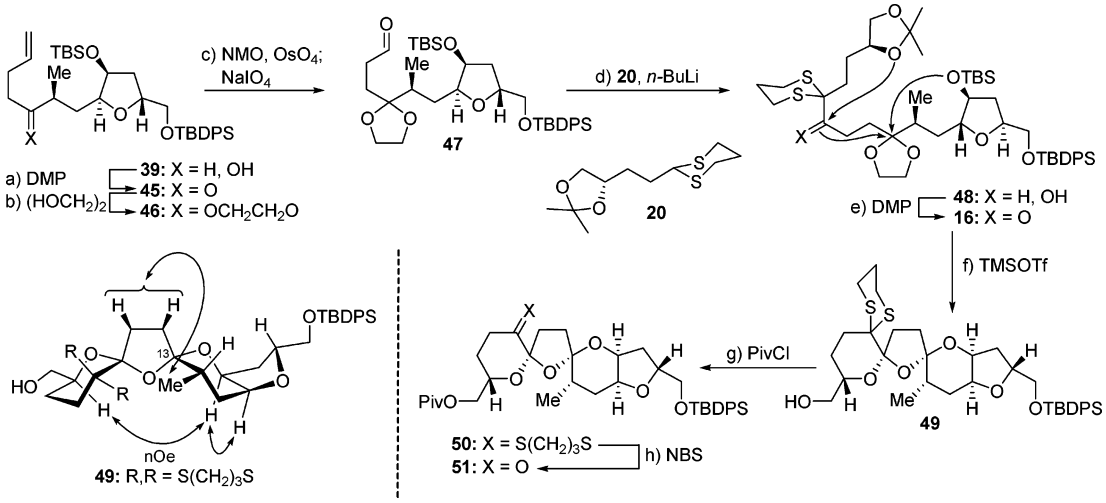
[a] Reagents and conditions: (a) TMSOTf (3.0 equiv), CH_2Cl_2, −78 °C, 1 h; then 0 °C, 10 min, 62%; (b) BzCl (4.0 equiv), py (100 equiv), CH_2Cl_2, 25 °C, 12 h, 96%; (c) $P(OMe)_3$ (6.0 equiv), toluene, reflux, 12 h, 45%. Abbreviations: Bz, benzoyl; py, pyridine.

1,2-diol, produced the corresponding lactol, which was then oxidized to the γ-lactone (**40**) by treatment with NIS and *n*-Bu_4NI, in 96% overall yield. Sulfoxide **19** (derived in one step from (*R*)-methyl-*p*-tolylsulfoxide and iodide **38**, Scheme 2)[20] was converted to its anion with LDA and then reacted with lactone **40** to afford the coupled product, hydroxy ketone sulfoxide **41**, as a mixture of four diastereomers, in 83% combined yield. Dess−Martin oxidation (92% yield) converted this mixture to the diketone sulfoxide **15**, setting the stage for the pending deprotection−cyclization cascade.

Indeed, upon brief experimentation (see Table 1), it was found that exposure of precursor **15** to TMSOTf [21] in CH_2Cl_2 at −78

(18) (a) Adinolfi, M.; Parrilli, M.; Barone, G.; Laonigro, G.; Mangoni, L. *Tetrahedron Lett.* **1976**, *16*, 3661. (b) Haaima, G.; Weavers, R. T. *Tetrahedron Lett.* **1988**, *29*, 1085.
(19) Dess, D. B.; Martin, J. C. *J. Org. Soc.* **1983**, *48*, 4155.
(20) Allingham, M. T.; Howard-Jones, A.; Murphy, P. J.; Thomas, D. A.; Caulkett, P. W. R. *Tetrahedron Lett.* **2003**, *44*, 8677.
(21) Bou, V.; Vilarrasa, J. *Tetrahedron Lett.* **1990**, *31*, 567.

Scheme 4. Synthesis of the Originally Proposed ABCD Ring System (**51**) of Azaspiracid-1[a]



[a] Reagents and conditions: (a) DMP (2.0 equiv), CH_2Cl_2, 25 °C, 3 h, 95%; (b) $HO(CH_2)_2OH$ (7.0 equiv), triethylorthoformate (3.0 equiv), *p*-TsOH (0.1 equiv), 55 °C, 2 h, 98%; (c) OsO_4 (0.03 equiv), NMO (2.0 equiv), *t*-BuOH:THF:H_2O (10:2:1), 25 °C, 14 h; $NaIO_4$ (5.0 equiv), pH 7 buffer, 25 °C, 5 h, 100%; (d) *n*-BuLi (1.6 M in hexanes, 2.6 equiv), **20** (2.6 equiv), THF, −20 °C, 3 h, 87%; (e) DMP (2.0 equiv), CH_2Cl_2, 25 °C, 1 h, 88%; (f) TMSOTf (3.0 equiv), CH_2Cl_2, −78 → −30 °C, 1 h, 85%; (g) PivCl (3.0 equiv), py (10 equiv), 4-DMAP (0.1 equiv), 25 °C, 3 h, 95%; (h) NBS (8.0 equiv), 2,6-lutidine (16 equiv), MeCN, 25 °C, 2 h, 91%. Abbreviations: Piv, trimethylacetyl; NBS, *N*-bromosuccinimide.

°C, followed by warming to 0 °C, induced selective cleavage of the acetonide and TBS groups, events that triggered three spontaneous ring closures, furnishing the anticipated ABCD fragment **42** as a mixture of two diastereomeric sulfoxides (62% combined yield, Scheme 3). This mixture of sulfoxides was benzoylated (BzCl, py, 96% yield) and then thermolyzed in refluxing toluene in the presence of $P(OMe)_3$, leading to olefinic benzoate **44** in 45% yield as a single compound. NMR spectroscopic analysis, however, revealed the undesired (13*S*) stereochemistry for the synthesized product (**44**), as indicated by the NOEs (nOes) shown in Scheme 3. Apparently, the influence of the aryl sulfoxide moiety was not sufficient to override the directing effect exerted by the double anomeric effect that drives the formation of the observed 13*S* diastereomer (**44**). Given the almost neutral conditions employed to convert **42** to **44**, it is unlikely that epimerization at C-13 occurred after the cyclization event. Furthermore, exposure of **44** to various Lewis and protic acids failed to change its stereochemistry, confirming the thermodynamically most stable nature of this isomer as compared to its *epi*-C-13 counterpart.

3. Synthesis of the Desired ABCD Ring System through an Intramolecular Hydrogen-Bonding Strategy. Having reached this roadblock in our drive toward the ABCD domain of azaspiracid-1, we adopted an alternate approach which was to rely on the stabilizing effect of a neighboring hydroxyl group exerted through hydrogen bonding, as shown in Figure 6. Specifically, it was reasoned that a hydroxyl group at C-9 occupying the equatorial position on ring A may be in a position to hydrogen-bond with both the ring B and ring C oxygens, thereby lowering the energy level of the desired 13*R* stereoisomer sufficiently to revert the equilibrium away from the undesired isomer. Beyond this rationale, we were also encouraged by previous work in the field in which such hydrogen-bonding effects decisively manifested themselves.[22] To set the

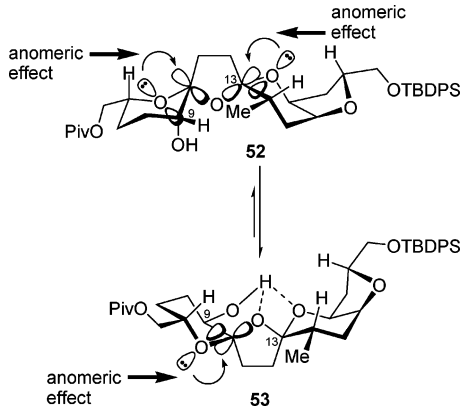


Figure 6. Rationale for the expectation that the 9-hydroxy ABCD domain will fold into the 13*R* isomer **53** as the thermodynamically favored isomer (stabilized by one anomeric effect and a hydrogen-bonding arrangement) over the 13*S* isomer **52** (stabilized by two anomeric effects).

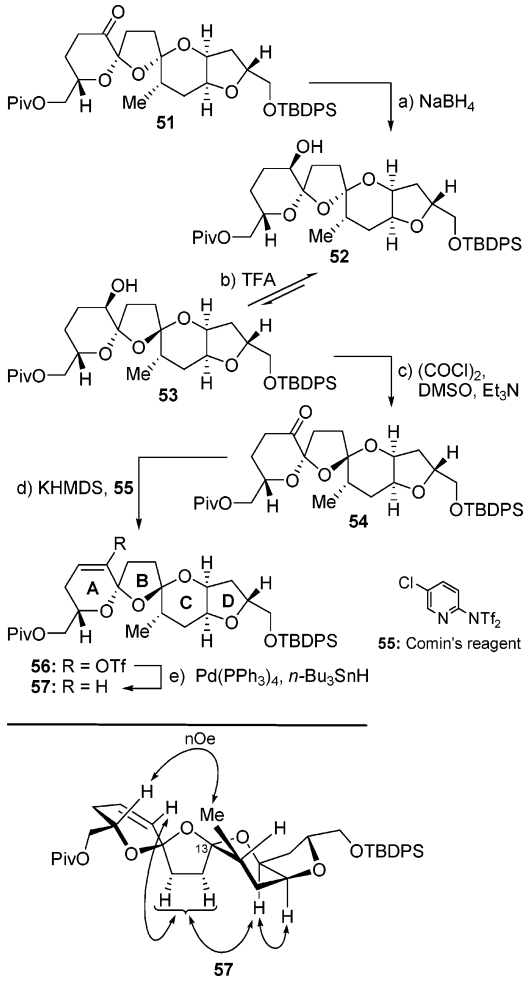
stage for testing this hypothesis, the ABCD ketone system **51** was targeted and synthesized as shown in Scheme 4. Thus, the mixture of diastereomeric alcohols **39** (see Schemes 1 and 2 for its preparation) was oxidized (DMP, 95% yield), and the resulting ketone (**45**) was transformed to its ethylene ketal (ethylene glycol, triethylorthoformate, *p*-TsOH, **46**, 98% yield). The terminal olefin of the latter compound (**46**) was then converted by a standard dihydroxylation/periodate cleavage procedure (OsO_4−NMO; $NaIO_4$)[23] to afford aldehyde **47** in quantitative yield. Addition of the lithio derivative derived from dithiane **20**[24] and *n*-BuLi to aldehyde **47** (87% yield), followed by DMP oxidation (88% yield), yielded ketone **16**, whose TMSOTf-induced polycyclization proceeded as expected to afford tetracycle **49** as the thermodynamically most stable system (in 85% yield). Pivaloate formation (PivCl, py, 4-DMAP, 95% yield) followed by dithiane removal (NBS, 2,6-lutidine, 91% yield)[25] resulted in the formation of the anticipated ketone **51** via dithiane pivaloate ester **50**. The 13*S* stereochemistry of

(22) (a) Ishihara, J.; Sugimoto, T.; Murai, A. *Synlett* **1998**, 603. (b) Paterson, I.; Wallace, D. J.; Gibson, K. R. *Tetrahedron Lett.* **1997**, *38*, 8911. (c) Claffey, M. M.; Hayes, C. J.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8267. (d) McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647.

(23) Pappo, R.; Allen, D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

(24) Jenkins, P. R.; Selim, M. M. R. *J. Chem. Res. Miniprint* **1992**, *3*, 701.

Scheme 5. Construction of Originally Proposed ABCD Domain (**57**) of Azaspiracid-1 through Trifluoroacetic Acid-Induced Epimerization[a]

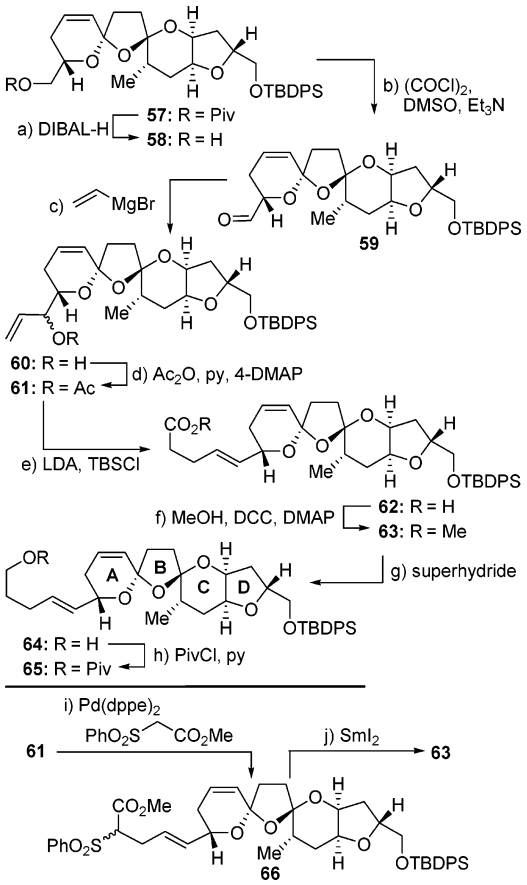


[a] Reagents and conditions: (a) $NaBH_4$ (1.0 equiv), MeOH, −5 °C, 5 min, 92%; (b) TFA (3.0 equiv), CH_2Cl_2, 25 °C, 4 h, 56% (40% recovered **52**); (c) $(COCl)_2$ (5.0 equiv), DMSO (11 equiv), CH_2Cl_2, −78 °C, 1 h; Et_3N (22 equiv), CH_2Cl_2, −78 → 0 °C, 1 h, 80%; (d) KHMDS (0.5 M in toluene, 4.5 equiv), **55** (5.0 equiv), THF, −78 °C, 45 min, 83%; (e) $[Pd(PPh_3)_4]$ (0.2 equiv), *n*-Bu_3SnH (10 equiv), THF, 25 °C, 45 min, 90%. Abbreviations: DMSO, dimethyl sulfoxide; KHMDS, potassium bis(trimethylsilyl)amide.

the last three compounds was evident from NOE studies carried out with **49** (see Scheme 4).

Scheme 5 summarizes the events that took ketone **51** to the next stage along the path toward the desired ABCD domain, intermediate **57**. Thus, reduction of **51** with $NaBH_4$ in MeOH at 0 °C furnished exclusively, and in 92% yield, the desired 9*R* (axial) alcohol **52**, ready for the intended equilibration experiments. Indeed, and much to our delight, upon exposure to TFA in CH_2Cl_2 at 0 °C, hydroxy spiroacetal **52** equilibrated to a mixture of C-13 isomers (**53**:**52**, ca. 2:1) which were conveniently separated by silica gel chromatography. Recycling of the recovered starting isomer (twice) brought the yield of the new product (**53**) to 84%, making the sequence into a practical process for accessing what was, at this stage, presumed to be the desired 13*R* spiroacetal stereoisomer. This assertion was proven beyond doubt by conversion of this compound (**53**) to

Scheme 6. Installation of the Side Chain of Azaspiracid-1 and Synthesis of the ABCD Fragment **65**[a]



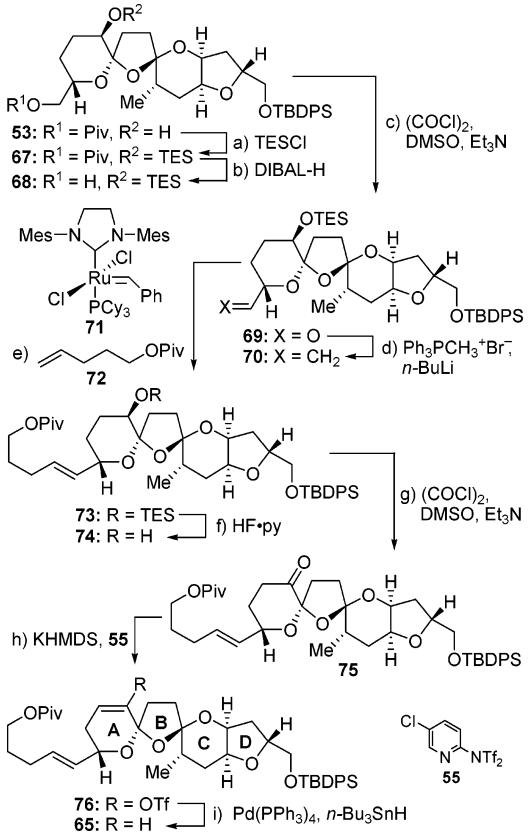
[a] Reagents and conditions: (a) DIBAL-H (1.0 M in toluene, 2.5 equiv), toluene, −78 °C, 20 min, 92%; (b) $(COCl)_2$ (5.0 equiv), DMSO (11 equiv), CH_2Cl_2, −78 °C, 1 h; −60 °C, 1 h; then Et_3N (22 equiv), −60 → −30 °C, 1 h, 92%; (c) vinylmagnesium bromide (1.0 M in THF, 1.6 equiv), Et_2O, 0 °C, 30 min, 78%; (d) Ac_2O (5.0 equiv), py (10 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 0 °C, 1 h, 94%; (e) LDA (1.5 equiv), TBSCl (1.5 equiv), HMPA (1.5 equiv), THF, −78 → 25 °C, 72 h, 82%; (f) MeOH (10 equiv), DCC (1.2 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 0 → 25 °C, 2 h, 86%; (g) superhydride (1.0 M in THF, 5.0 equiv), THF, −78 → 0 °C, 30 min, 96%; (h) PivCl (3.0 equiv), py (10 equiv), 4-DMAP (1.0 equiv), CH_2Cl_2, 0 → 25 °C, 12 h, 95%; (i) $Pd(dppe)_2$ (0.1 equiv), DBU (1.0 equiv), 1,4-dioxane, 25 °C, 18 h, 92%; (j) SmI_2 (2.0 equiv), MeOH:THF (1:1), −78 → 25 °C, 15 min, 95%. Abbreviations: DIBAL-H, diisobutylaluminum hydride; HMPA, hexamethylphosphoramide; DCC, 1,3-dicyclohexylcarbodiimide; superhydride, lithium triethylborohydride; dppe, 1,2-bis(diphenylphosphino)ethane; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene.

the next milestone intermediate (i.e., **57**) by Swern oxidation[26] of **53** to the corresponding ketone (80% yield), followed by enol triflate formation (KHMDS, Comin's reagent (**55**),[27] 83% yield) and reductive removal of the triflate group (*n*-Bu_3SnH, $Pd(PPh_3)_4$, 90% yield). The ^1H NMR data and NOE studies of the resulting product revealed the desired 13*R* stereochemistry (see NOEs on structure **57**, Scheme 5).

Having secured the targeted ABCD fragment **57**, it was time to extend its A ring chain by four carbons as required for the azaspiracid-1 structure. Three methods were developed for this task; the first two approaches are shown in Scheme 6. Thus, pivaloate ester **57** was reduced with DIBAL-H (92% yield), and the resulting alcohol (**58**) was oxidized under Swern conditions [$(COCl)_2$, DMSO, Et_3N] to afford aldehyde **59** (92% yield),

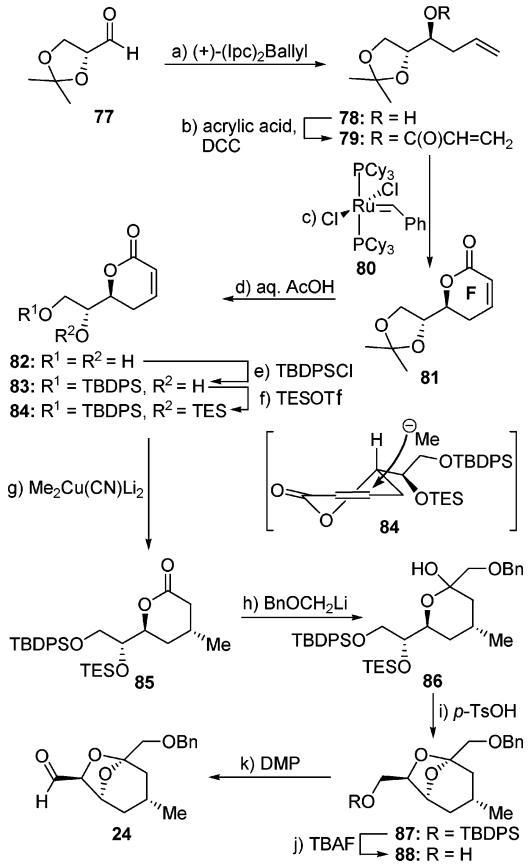
(25) Williams, D. R.; Jass, P. A.; Allan Tse, H.-L.; Gaston, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 4552.
(26) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957.
(27) Commins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

Scheme 7. Olefin Metathesis-Based Attachment of the C_1-C_5 Side Chain of Azaspiracid-1 To Afford **65**[a]



[a] Reagents and conditions: (a) TESCl (1.5 equiv), imidazole (3.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 0 °C, 10 h, 92%; (b) DIBAL-H (1.0 M in toluene, 3.0 equiv), CH_2Cl_2, −78 °C, 1 h, 87%; (c) $(COCl)_2$ (5.0 equiv), DMSO (10 equiv), CH_2Cl_2, −78 °C, 1 h; Et_3N (15 equiv), −78 → 0 °C, 1 h, 88%; (d) $Ph_3PCH_3^+Br^-$ (6.0 equiv), *n*-BuLi (1.6 M in THF, 5.0 equiv), THF, −78 → 0 °C, 1 h; then −78 °C; then **69**, −78 → 0 °C, 30 min, 81%; (e) **71** (0.1 equiv), **72** (3.0 equiv), CH_2Cl_2, 40 °C, 12 h, 65% (30% recovered **70**); (f) HF•py (10 equiv), THF:py (1:1), 0 °C, 2 h, 94%; (g) $(COCl)_2$ (5.0 equiv), DMSO (10 equiv), CH_2Cl_2, −78 °C, 1 h; Et_3N (15 equiv), −78 → 0 °C, 1 h, 95%; (h) KHMDS (0.5 M in toluene, 4.5 equiv), **55** (5.0 equiv), THF, −78 °C, 1 h, 94%; (i) $Pd(PPh_3)_4$ (0.2 equiv), *n*-Bu_3SnH (3.0 equiv), THF, 25 °C, 40 min, 96%. Abbreviations: TES, triethylsilyl; Mes, mesitylene; Cy, cyclohexane.

Scheme 8. Construction of Acetal Aldehyde **24**[a]



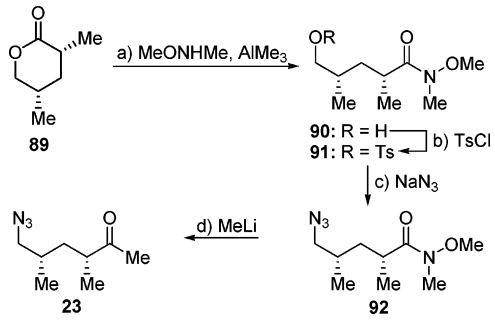
[a] Reagents and conditions: (a) (+)-$(Ipc)_2$Ballyl (2.0 equiv), Et_2O, −100 °C, 4 h, 88%; (b) acrylic acid (2.0 equiv), DCC (2.5 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 25 °C, 18 h, 73%; (c) **80** (0.1 equiv), CH_2Cl_2, 40 °C, 5 h, 95%; (d) H_2O:AcOH (1:2), 55 °C, 2 h; (e) TBDPSCl (1.4 equiv), Et_3N (3.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 0 → 25 °C, 4 h, 98% over two steps; (f) TESOTf (2.0 equiv), 2,6-lutidine (3.0 equiv), CH_2Cl_2, 0 °C, 88%; (g) $Me_2Cu(CN)Li_2$ (2.0 equiv), Et_2O, −78 °C, 1 h, 97% (ca. 10:1); (h) $BnOCH_2Li$ (2.0 equiv), THF, −78 → −40 °C, 1 h, 52% (ca. 1:1); (i) *p*-TsOH (0.03 equiv), CH_2Cl_2, 1 h, 25 °C, 90%; (j) TBAF (1.0 M in THF, 1.5 equiv), THF, 25 °C, 1 h, 93%; (k) DMP (2.0 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 25 °C, 3 h, 86%. Abbreviation: TBAF, tetra-*n*-butylammonium fluoride.

which was reacted with vinylmagnesium bromide, leading to allylic alcohol **60** (ca. 1:1 mixture of diastereomers, 78% combined yield). This mixture was acetylated (Ac_2O, py, 4-DMAP, 94% yield), and the acetates (**61**) so obtained were subjected to an Ireland−Claisen rearrangement (LDA, TBSCl, HMPA, −78 → 25 °C)[28] to afford the elongated carboxylic acid **62** in 82% yield. The latter compound was then converted to its methyl ester (**63**, MeOH, DCC, 4-DMAP, 86% yield) and then, through reduction (superhydride, −78 → 0 °C, **64**, 96% yield) and pivaloate ester formation (PivCl, py, 4-DMAP, 95% yield), to the targeted pivaloate−TBDPS derivative **65**. A second sequence to convert acetates **61** to methyl ester **63** relied on a coupling reaction employing methyl phenylsulfonyl acetate, $Pd(dppe)_2$, and DBU as a means to elongate the chain, affording intermediate **66** (92% yield), whose extraneous phenylsulfonyl group was reductively removed by treatment with SmI_2 (**63**, 95% yield) (Scheme 6).[29]

Finally, a more expedient sequence based on an olefin cross-metathesis reaction[30] was developed for the attachment of the side chain onto the ABCD domain (see Scheme 7). Thus, hydroxy pivaloate ester **53** was first converted to TES-protected ether terminal olefin **70** by a series of four steps [(i) TESCl, 4-DMAP, imidazole, **67**; (ii) DIBAL-H, **68**; (iii) $(COCl)_2$, DMSO; Et_3N, **69**; and (iv) $Ph_3PCH_2^+Br^-$, *n*-BuLi, **70** (57% over the four steps)]. Terminal olefin **70** was reacted with 3.0 equiv of olefin **72** in the presence of the Grubbs second-generation catalyst (**71**) to afford the desired C_1-C_{20} fragment **73** cleanly (65% yield, plus 30% recovered **70**) and as a single (*E*) geometrical isomer. Resubmitting the recovered starting material to the reaction conditions two more times led to 90% combined yield for this conversion (**70** → **73**). Selective desilylation of the secondary alcohol within **73** was cleanly effected by exposure to HF•py (94% yield); Swern oxidation [$(COCl)_2$, DMSO; Et_3N] of the resulting compound (**74**) then furnished ketone **75** in 95% yield. Sequential enolization (KHMDS) of this ketone **75**, followed by reaction with Comin's reagent (**55**), then gave enol triflate **76**, whose reductive cleavage [$Pd(PPh_3)_4$,

(28) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897.
(29) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.
(30) For a review on the use of Grubbs' catalyst in total synthesis, see: Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490.

Scheme 9. Synthesis of Azido-Ketone **23**[a]



[a] Reagents and conditions: (a) MeO(NHMe)·HCl (5.0 equiv), $AlMe_3$ (2.0 M in toluene, 5.1 equiv), THF, −15 °C, 2 h, 96%; (b) *p*-TsCl (1.5 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 25 °C, 18 h, 96%; (c) NaN_3 (2.0 equiv), DMF, 25 °C, 76 h, 96%; (d) MeLi (1.25 M in Et_2O, 1.0 equiv), THF, −78 °C, 40 min, 82%.

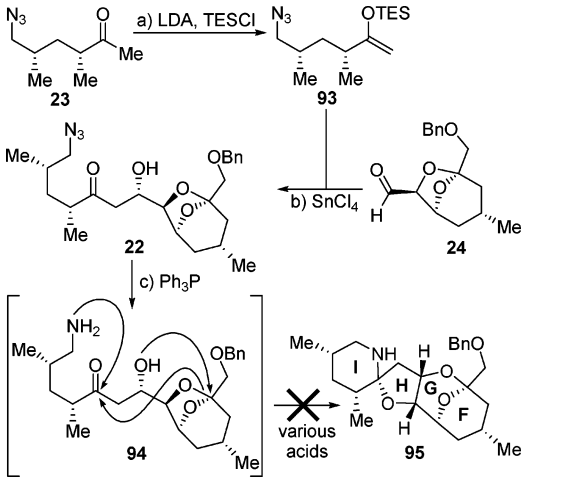
n-Bu_3SnH] led to the coveted segment **65** in 90% overall yield for the two steps.

4. First Attempt To Prepare the FGHI Domain of Azaspiracid-1. We now turn our attention to the construction of the FGHI ring system **14** as defined by the retrosynthetic analysis depicted in Figure 4. Our plan called for the intermediacy of the open-chain amino bis-carbonyl trihydroxy system **21** (Figure 4) or its equivalent, whose acid-catalyzed folding was expected, upon suitable elaboration, to furnish tetracycle **14** with the two spiro centers hopefully in the proper stereochemical arrangement. To test this hypothesis, we targeted azido acetal **22** (Figure 4) as a potential precursor to the desired compound (**14**).

Thus, and as shown in Scheme 8, Brown allylboration[31] of D-isopropylidene glyceraldehyde (**77**)[32] with (+)-$(Ipc)_2$Ballyl gave allylic alcohol **78** (ca. 96:4 mixture, 88% combined yield), whose reaction with acrylic acid in the presence of DCC gave acrylate ester **79** (73% yield). Ring-closing metathesis within **79** was initiated by the Grubbs first-generation catalyst (**80**), furnishing the α,β-unsaturated δ-lactone **81** in 95% yield, whose destination was to become ring F of the final target. At this stage, it was considered necessary to differentially protect the two hydroxyl groups of the growing molecule; to that end, the acetonide group was removed (AcOH−H_2O), and the resulting diol was sequentially and selectively engaged first with TBDPSCl−Et_3N (98% yield over two steps) and then with TESOTf−2,6-lutidine (88% yield), leading to intermediates **84** via **83** and **82**.

Biased by the side chain of the substrate, the 1,4-addition of $Me_2Cu(CN)Li_2$ to α,β-unsaturated lactone **84** (see Scheme 8) delivered, stereoselectively, methylated lactone **85** in 97% yield (ca. 10:1 mixture of isomers).[33] This compound (**85**) was then reacted with $BnOCH_2Li$[34] to afford the hemiacetal **86** (ca. 1:1 mixture of isomers, 52% combined yield). Exposure of the latter compound (**86**) to *p*-TsOH in refluxing benzene resulted in its conversion to intramolecular bridged ketal **87** (90% yield), whose casting proceeded spontaneously upon the expected departure of the TES group. Sequential removal of the TBDPS group from **87** with TBAF (93% yield), followed by oxidation of the resulting primary alcohol (**88**) with Dess−Martin periodinane, led to aldehyde **24** (86% yield).

Scheme 10. Failed Attempt To Construct the FGHI Ring Fragments of Azaspiracid-1 from Azido-Hydroxy Ketone **22** via **94**[a]



[a] Reagents and conditions: (a) LDA (1.5 equiv), TESCl (3.0 equiv), THF, −78 °C, 86%; (b) $SnCl_4$ (1.0 M in CH_2Cl_2, 1.0 equiv), CH_2Cl_2, −78 °C; then **93** (1.0 equiv), 1.5 h, 50%; (c) Ph_3P (3.0 equiv), THF:H_2O (10:1), 25 °C, 21 h.

The synthesis of aldol partner **23** commenced from known lactone **89**[35] and proceeded as shown in Scheme 9. Thus, treatment of **89** with MeONHMe·HCl and $AlMe_3$ afforded Weinreb amide **90** in 96% yield.[36] Subsequent tosylation of the liberated primary alcohol (*p*-TsCl, Et_3N, 96% yield) within **90**, followed by displacement of the newly formed tosylate (**91**) with NaN_3, afforded azide **92** in 96% yield. Finally, reaction of MeLi with **92** resulted in displacement of the amide moiety, leading to the desired azido-methyl ketone **23** (82% yield).

With both fragments **23** and **24** in hand, their coupling became the next task (see Scheme 10). To this end, a $SnCl_4$-catalyzed Mukaiyama aldol reaction[37] with TES enol ether **93** (obtained from methyl ketone **23**, LDA, and TESCl, in 86% yield) and aldehyde **24** was performed, furnishing the coveted azido-hydroxyketone **22** stereoselectively in 50% yield. Carrying all the carbon atoms required for the targeted FGHI ring system **95**, the latter compound was only two steps away from its final destination. Staudinger reaction[38] with **22** (Ph_3P, THF, H_2O) provided the desired intermediate, primary amine **94**, whose desired ring-opening/polycyclization, however, could not be achieved, as treatment with protic or Lewis acids led to either decomposition or a large number of products, none of which resembled the desired tetracycle **95**. Faced with this roadblock, we resorted to a new strategy.

5. Second-Generation Retrosynthetic Analysis of Azaspiracid-1 (1a). To circumvent the problems encountered in our first strategy toward the construction of the targeted azaspiracid-1 (**1a**), and having gathered enough intelligence regarding this challenge, we proceeded to develop a new strategy based on a second retrosynthetic analysis whose basic disconnections are shown in Figure 7. Thus, opening ring G of **1a** led, upon suitable modification, to hydroxy enol ether **96** as a potential precursor to the final target through a short sequence involving selective iodo-etherification/reductive de-iodination as a key

(31) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.
(32) Ahrendt, K. A.; Williams, R. M. *Org. Lett.* **2004**, *6*, 4539.
(33) Lipshutz, B. H. *Synthesis* **1987**, 325.
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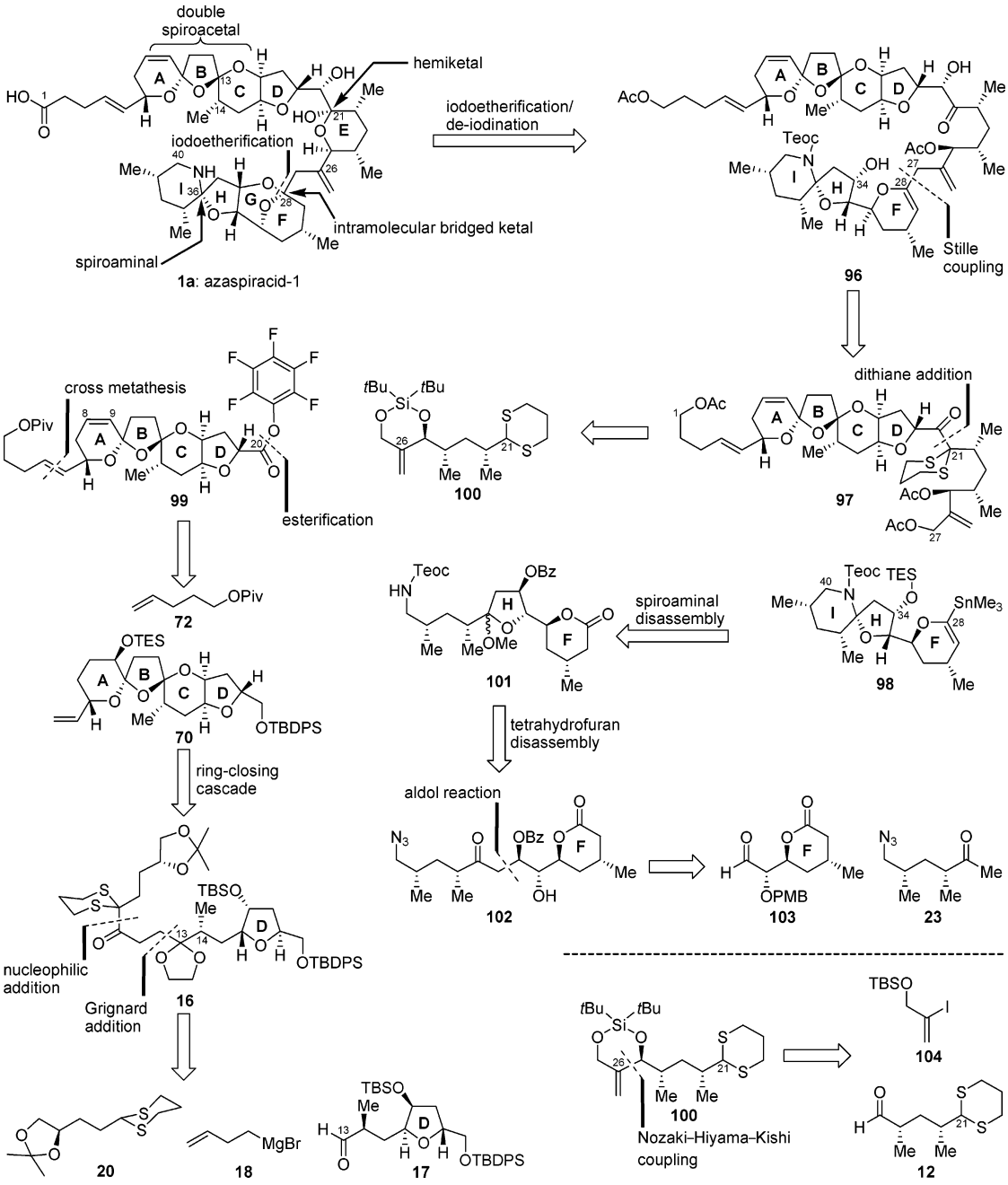

Figure 7. Second-generation retrosynthetic analysis of the originally proposed structure of azaspiracid-1 (**1a**).

protocol. The next disconnection was performed at the $C_{27}-C_{28}$ bond (in contrast to the first retrosynthetic analysis which involved disconnection of the $C_{25}-C_{26}$ bond), unraveling allylic acetate **97** and vinyl stannane **98** as potential precursors. In the synthetic direction, it was envisioned that a Stille coupling[39] would ensure the assembly of these fragments to form **96**. The C_1-C_{27} fragment **97** was then disconnected, employing a retro-dithiane addition reacting onto the activated ester **99** (note exchange of the acetate with the more robust pivaloate group), whose origin was traced to the truncated ABCD domain **70** via a retro cross-olefin metathesis reaction with terminal olefin **72** [the former intermediate could be envisioned to arise from key building blocks **17**, **18** (see also Figure 4), and **20**]. The FHI segment **98** was stepwise disassembled, first to bicycle **101** by rupturing ring I and then to δ-lactone **102** by opening ring H, as shown in Figure 7. Finally, a retro-aldol transform on **102** pointed to aldehyde **103** and azido-methyl ketone **23** as starting points for the construction of the FGHI domain of the target molecule.

The construction of the FHI stannane **98** (Figure 7) commenced with the (+)-diethyltartrate-derived PMP acetal **105**[40] and proceeded along the path delineated in Schemes 11−13. Thus, the diol **105** (Scheme 11) was monoprotected as a TBDPS ether (*n*-BuLi, TBDPSCl, 87% yield), and the resulting product (**106**) was subjected to a regioselective acetal opening with BH_3·THF, furnishing the PMB ether 1,2-diol **107** in 76% yield. Cleavage of the vicinal diol system within **107** with $NaIO_4$ gave

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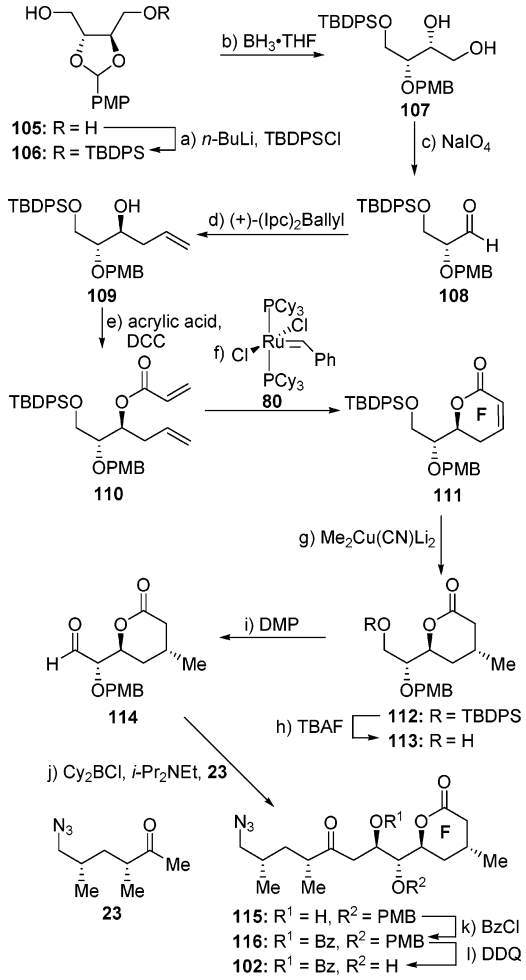
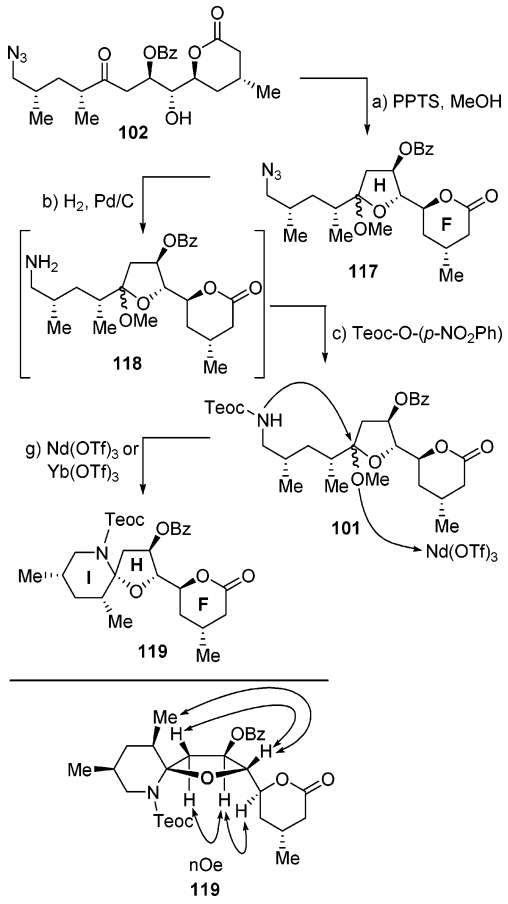
Scheme 11. Synthesis of Key Intermediate **102**[a]



[a] Reagents and conditions: (a) *n*-BuLi (1.6 M in THF, 1.1 equiv), TBDPSCl (1.1 equiv), THF, −78 → 0 °C, 18 h, 87%; (b) BH_3•THF, THF, 65 °C, 4 h, 76%; (c) $NaIO_4$ (4.0 equiv), THF:H_2O (3:2), 25 °C, 4 h, 88%; (d) (+)-$(Ipc)_2$Ballyl (2.0 equiv), Et_2O, −100 °C, 2 h, 100% (ca. 96:4); (e) acrylic acid (3.0 equiv), DCC (3.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2, 40 °C, 18 h, 78%; (f) **80** (0.1 equiv), CH_2Cl_2, 40 °C, 18 h, 91%; (g) $Me_2Cu(CN)Li_2$ (2.0 equiv), Et_2O, −78 °C, 1 h, 95%; (h) TBAF (1.0 M in THF, 1.5 equiv), THF, 25 °C, 30 min, 87%; (i) DMP (1.4 equiv), py (10 equiv), CH_2Cl_2, 25 °C, 92%; (j) **23** (1.1 equiv), Cy_2BCl (1.3 equiv), *i*-Pr_2NEt (1.5 equiv), CH_2Cl_2, 0 °C, 1.5 h; then **114** (1.0 equiv), −78 °C, 3.5 h, 93% (ca. 38:1); (k) BzCl (3.0 equiv), py, 0 °C, 4 h, 88%; (l) DDQ (1.5 equiv), CH_2Cl_2:H_2O (10:1), 0 °C, 3 h, 96%.

aldehyde **108**, whose reaction with (+)-$(Ipc)_2$Ballyl, according to Brown,[31] furnished allylic alcohol **109** as a 96:4 mixture with its stereoisomer (100% combined yield). Esterification of **109** with acrylic acid, as facilitated by DCC, yielded acrylate **110** (78% yield), which served admirably as a substrate for a ring-closing metathesis initiated by the Grubbs first-generation catalyst (**80**) to afford α,β-unsaturated lactone **111** in 91% yield. A conjugate addition to **111** by $Me_2Cu(CN)Li_2$ installed stereoselectively (see Scheme 8, structure **84** for a mechanistic rationale) the required methyl group, yielding compound **112** in 95% yield. Removal of the TBDPS group from **112** through the action of TBAF then gave alcohol **113** (87% yield), whose DMP oxidation (92% yield) led to aldehyde **114**. The latter compound (**114**) was then reacted with the boron enolate derived from methyl ketone **23** (Cy_2BCl, *i*-Pr_2NEt) according to the procedure of Patterson[41] to furnish stereoselectively the aldol product **115** (93% yield, ca. 38:1 ratio of isomers by ^1H NMR spectroscopy). This welcome result was then followed by protecting group exchanges, leading sequentially from alcohol **115** to benzoate **116** (BzCl, py, 88% yield) and then to secondary alcohol **102** (DDQ, 96% yield). The latter intermediate (**102**) contains, besides all required carbon atoms for the target FHI ring system **98**, the appropriately equipped functional groups for elaboration to the targeted model FGHI system (i.e., **130**, Scheme 14).

Scheme 12. Preparation of Tricycle **119**[a]



[a] Reagents and conditions: (a) PPTS (0.3 equiv), MeOH, 25 °C, 2 h, 93% (ca. 1:1); (b) H_2, 10% Pd/C (25% w/w), EtOAc, 25 °C, 7 h; (c) Teoc-*O*-(*p*-NO_2Ph) (3.0 equiv), Et_3N (4.0 equiv), EtOAc, 25 °C, 15 h, 80% over two steps; (d) $Nd(OTf)_3$ (0.1 equiv), MeCN, 25 °C, 15 min, 81%; or $Yb(OTf)_3$ (0.1 equiv), MeCN, 25 °C, 3 min, 72%. Abbreviation: PPTS, pyridinium *p*-toluenesulfonate.

Scheme 12 shows the advancement of intermediate **102** to the desired FHI ring system **119**. Thus, exposure of **102** to PPTS in methanol resulted in the formation of methoxyacetal **117** (ca. 1:1 mixture of stereoisomers, 93% combined yield) with the second required ring (H) in place. Subsequent reduction of the azido group within **117** with H_2−10% $Pd(OH)_2$, followed by treatment with Teoc−*O*-(*p*-NO_2Ph),[42] furnished the Teoc-protected amine **101** (80% yield over two steps) through in situ trapping of the incipient primary amine (**118**). Finally, exposure of this amino-acetal (**101**) to $Nd(OTf)_3$ in MeCN at 25 °C led to expulsion of the methoxy group and ring closure, generating the desired spiroaminal **119** in 81% yield as a single stereoisomer. The stereochemical arrangement within **119** was confirmed

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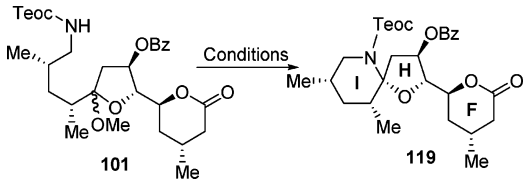
Table 2. Optimization of Ring I Cyclization



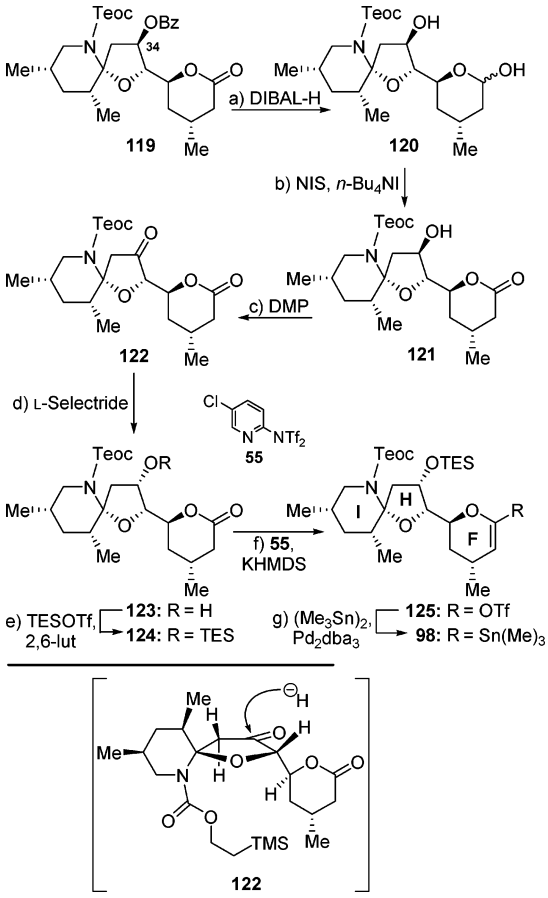
entry	conditions[a]	yield (%)[b]
1	*p*-TsOH (0.1 equiv), MeOH, 25 °C, 24 h	0
2	CSA (0.1 equiv), MeOH, 25 °C, 1 h	0
3	TfOH (0.1 equiv), CH_2Cl_2, 0 °C, 10 min	0
4	$BF_3{\cdot}Et_2O$ (0.1 equiv), CH_2Cl_2, 0 °C, 10 min	60
5	$Yb(OTf)_3$ (0.1 equiv), MeCN, 25 °C, 3 min	72
6	$Sn(OTf)_2$ (0.1 equiv), MeCN, 25 °C, 5 min	0
7	$Ag(OTf)_2$ (0.1 equiv), MeCN, 25 °C, 30 min	0
8	$Y(OTf)_3$ (0.1 equiv), MeCN, 25 °C, 10 min	22
9	$Nd(OTf)_3$ (0.1 equiv), MeCN, 25 °C, 15 min	81
10	$Eu(OTf)_3$ (0.1 equiv), MeCN, 25 °C, 15 min	65

[a] Reactions were carried out at 0.1−0.2 mmol scale. [b] Yields refer to isolated products, the desired isomer (**119**) being obtained as a single isomer.

by NOE studies (see Scheme 12). The use of $Nd(OTf)_3$ came about after a systematic study to optimize this ring closure, which proved nontrivial. Thus, and as shown in Table 2, initial attempts to employ protic acids (entries 1−3) failed to produce any of the desired product (**119**), leading, instead, to several unidentified products or decomposition. The first good results were obtained with the Lewis acid $BF_3{\cdot}Et_2O$ (entry 4) in CH_2Cl_2 at 0 °C, which led to ring-closed product **119** in 60% yield. The Forsyth group demonstrated the use of $Yb(OTf)_3$ as an effective catalyst in inducing such a ring closure in a similar system,[4f] and indeed the same conditions proved quite effective in converting **101** to **119** (72% yield, entry 5). Further experimentation with other species (entries 6−10) led to the discovery that $Nd(OTf)_3$ was an even more effective catalyst in closing ring I, producing **119** from **101** in 81% yield as already mentioned above.

At this juncture, it was necessary to invert the stereochemistry of the C-34 hydroxyl group within the last intermediate (**119**, Scheme 13), for it was all along opposite of that embedded within the natural product. Manual molecular modeling suggested that a simple oxidation−reduction sequence may suffice to accomplish the required inversion on the basis of steric hindrance alone (see structure **122** in Scheme 13). To this end, the benzoate group was cleaved from tricyclic compound **119** by DIBAL-H reduction, an operation which also reduced the lactone moiety to the corresponding lactol, leading to intermediate **120**. To recover the required dicarbonyl compound (i.e., **122**) for the intended elaboration, it was necessary to employ a two-step protocol, namely treatment with NIS and *n*-BuNI, to afford the intermediate hydroxy lactone **121** (70% yield from **119**), followed by oxidation with DMP (87% yield). Delightfully, the reduction of ketone **122** with L-selectride, a bulky reagent, furnished the desired 34*S*-hydroxy compound (**123**) in 79% yield. TES protection of this alcohol (**123**) (TESOTf, 2,6-lutidine, 93% yield) then furnished intermediate **124**, whose reaction with KHMDS and Comin's reagent (**55**) led to the expected vinyltriflate **125** (89% yield), from which the targeted FHI stannane **98** was finally generated in 98% yield by the action of $(SnMe_3)_2$ in the presence of $Pd_2(dba)_3$, TFP, and LiCl (see Scheme 13).

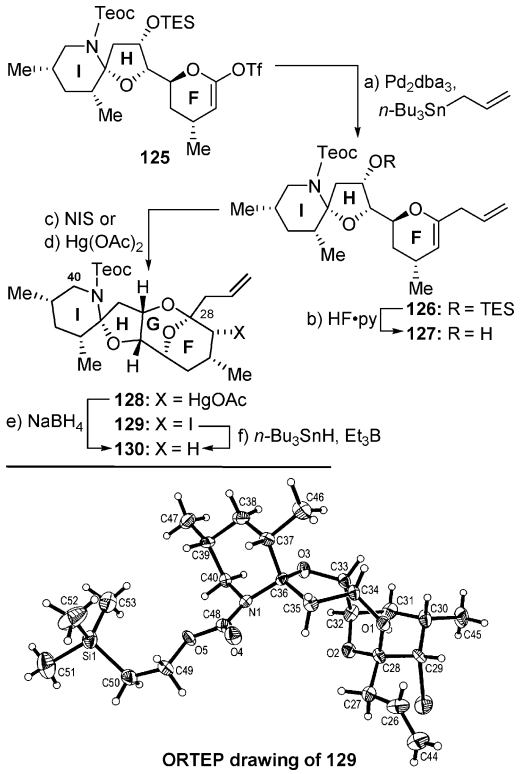
Scheme 13. Synthesis of Vinyl Stannane **98**[a]



[a] Reagents and conditions: (a) DIBAL-H (1.0 M in toluene, 4.0 equiv), toluene, −78 °C, 30 min; (b) NIS (10 equiv), *n*-Bu_4NI (2.0 equiv), CH_2Cl_2, 25 °C, 1 h, 70% over two steps; (c) DMP (1.4 equiv), py (10 equiv), CH_2Cl_2, 25 °C, 3 h, 87%; (d) L-selectride (1.0 M in THF, 2.0 equiv), THF, −78 °C, 20 min, 79%; (e) TESOTf (1.5 equiv), 2,6-lutidine (3.0 equiv), CH_2Cl_2, −78 °C, 10 min, 93%; (f) KHMDS (1.0 M in toluene, 4.0 equiv), **55** (5.0 equiv), THF, −78 °C, 45 min, 89%; (g) $(Me_3Sn)_2$ (10 equiv), TFP (0.5 equiv), LiCl (3.0 equiv), Pd_2dba_3 (0.1 equiv), THF, 25 °C, 1 h, 98%. Abbreviations: L-selectride, lithium tri-*sec*-butylborohydride; TFP, trifurylphosphine; dba, dibenzylidene acetone.

Having obtained both the vinyl triflate **125** and stannane **98** as described above, we were in a position to test their suitability as partners for the intended Stille coupling reaction and the subsequent ring G closure. Toward this end, the vinyl triflate **125** proved highly effective in coupling with allyl-tri-*n*-butyltin in the presence of Pd_2dba_3, TFP, and LiCl, furnishing diene **126** in 95% yield (Scheme 14). Removal of the TES group from the latter substance (**126**) with the aid of HF·py afforded the secondary alcohol **127** in 94% yield. A brief search for a suitable reagent to close ring G, employing hydroxy diene **127** as a substrate, revealed both $Hg(OAc)_2$ (75% yield) and NIS (77% yield) as equally effective (as it turned out, the mercuric acetate-based method would fail in the real system, leaving the NIS method as the procedure to be called upon in the end of the campaign to synthesize the targeted azaspiracid). Iodide **129**, obtained by exposure of **127** to NIS in the presence of $NaHCO_3$ in THF at 0 °C, crystallized nicely, allowing its X-ray crystallographic analysis (see ORTEP in Scheme 14), which confirmed its structure as the desired one. Reductive removal of the extraneous iodide residue from **129** was finally effected with *n*-Bu_3SnH:toluene (1:2) and Et_3B at 0 °C. The large excess

Scheme 14. Construction of Model FGHI Compound **130** and ORTEP Drawing of Compound **129**[a]

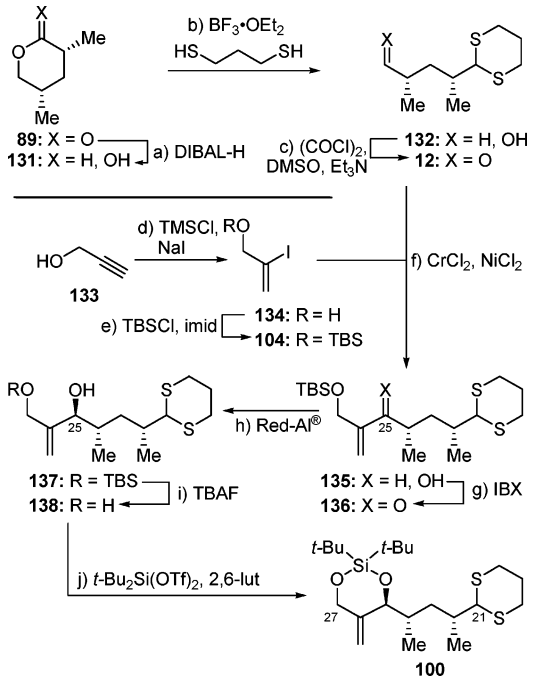


[a] Reagents and conditions: (a) allyltri-*n*-butyltin (10 equiv), TFP (0.5 equiv), LiCl (3.0 equiv), Pd_2dba_3 (0.1 equiv), THF, 25 °C, 1 h, 95%; (b) HF•py (5.0 equiv), THF:py (1:1), 0 → 25 °C, 2 h, 94%; (c) NIS (10 equiv), $NaHCO_3$ (30 equiv), THF, 0 °C, 12 h, 77% for **129**; (d) $Hg(OAc)_2$ (3.5 equiv), THF:H_2O (3:1), −5 °C, 20 min; (e) $NaBH_4$ (10 equiv), 75% from **127** via **128**; (f) Et_3B (1.0 M in hexanes, 3.0 equiv), *n*-Bu_3SnH:toluene (1:2), 0 °C, 5 min, 94%.

of *n*-Bu_3SnH was necessary in order to avoid ring closure of the initially formed carbon-centered radical onto the terminal olefin leading to a pentacyclic byproduct. The mercurial intermediate (**128**) could be converted to the same FGHI ring system **130** by reduction with $NaBH_4$ in THF:H_2O (3:1) at −5 °C (75% yield over two steps).

The last synthesis to be described herein is the construction of the C_{21}−C_{27} fragment corresponding to the E-ring of the targeted azaspiracid-1, as shown in Scheme 15, and starting with *δ*-lactone **89**. DIBAL-H reduction of **89**, followed by exposure of the resulting lactol (**131**) to 1,3-propanedithiol in the presence of BF_3•OEt_2, furnished hydroxydithiane **132** in 99% yield over two steps. Swern oxidation [$(COCl)_2$, DMSO; Et_3N] of the latter compound (**132**) then gave aldehyde **12** (94% yield), whose Nozaki−Hiyama−Kishi coupling with vinyl iodide **104** (obtained in 49% overall yield from propargyl alcohol **133** by reaction with NaI and TMSCl, followed by silylation of the resulting allylic alcohol **134** with TBSCl and imidazole, see Scheme 15) in the presence of $CrCl_2$ and $NiCl_2$ (cat.) yielded allylic alcohol **135** as a 1:1 mixture of C-25 diastereomers in 95% yield. Oxidation of this mixture with IBX in DMSO furnished ketone **136** (90% yield), whose reduction with Red-Al at −78 °C proceeded stereoselectively to afford the desired allylic alcohol **137** as a single stereoisomer in 80% yield. Desilylation of **137** (TBAF, 99% yield), followed by treatment of the resulting 1,3-diol (**138**) with *t*-$Bu_2Si(OTf)_2$ and 2,6-lutidine, gave the targeted cyclic silyl ether **100** in 75% yield.

Scheme 15. Construction of C_{21}-C_{27} Fragment **100**[a]



[a] Reagents and conditions: (a) DIBAL-H (1.0 M in CH_2Cl_2, 1.1 equiv), CH_2Cl_2, −78 °C, 1.5 h; (b) 1,3-propanedithiol (1.1 equiv), BF_3•Et_2O (1.5 equiv), CH_2Cl_2, 0 °C, 1 h, 99% over two steps; (c) $(COCl)_2$ (1.2 equiv), DMSO (2.4 equiv), CH_2Cl_2, −78 °C, 30 min; then Et_3N (5.0 equiv), −78 → −20 °C, 94%; (d) TMSCl (1.2 equiv), NaI (1.2 equiv), H_2O (0.6 equiv), MeCN, 0 → 25 °C, 1.5 h, 51%; (e) TBSCl (1.2 equiv), imidazole (2.5 equiv), DMF, 25 °C, 36 h, 96%; (f) $NiCl_2$ (0.02 equiv), $CrCl_2$ (4.0 equiv), DMF, 0 °C; then **12** (1.0 equiv), **104** (2.5 equiv), 0 → 25 °C, 15 h, 95%; (g) IBX (2.0 equiv), DMSO:THF (4:1), 25 °C, 2 h, 90%; (h) Red-Al (2.5 equiv), toluene, −78 °C, 1 h, 80%; (i) TBAF (2.2 equiv), THF, 25 °C, 1 h, 99%; (j) *t*-$Bu_2Si(OTf)_2$ (1.6 equiv), 2,6-lutidine (4.0 equiv), CH_2Cl_2, −30 °C, 30 min, 75%. Abbreviations: IBX, *o*-iodoxybenzoic acid; Red-Al, sodium bis(2-methoxyethoxy)aluminum hydride.

Conclusion

In this article, we described stereoselective constructions of all three key building blocks required for the total synthesis of the originally proposed structure of azaspiracid-1 (**1a**). The developed chemistry was applied to the synthesis of both enantiomers of these intermediates, in the event that they were needed in reaching the correct structure of the targeted molecule, since neither its relative (between the ABCDE and FGHI domains) nor its absolute stereochemistry was known at the time. Furthermore, within this paper we described synthetic technologies that could potentially be used to assemble the entire skeleton of what we believed was the structure of azaspiracid-1, including a method for connecting all fragments and casting ring G. In the following paper[8] we describe the application of these technologies to the construction of the targeted structures and our findings relating to the true identity of the natural substance.

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Supporting Information Available: Experimental procedures and compound characterization (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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