Total Synthesis of (±)-Azaspiracid-1. An Exhibition of the Intricacies of Complex Molecule Synthesis

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Abstract: The synthesis of the marine neurotoxin azaspiracid-1 has been accomplished. The individual fragments were synthesized by catalytic enantioselective processes: A hetero-Diels–Alder reaction to afford the E- and HI-ring fragments, a carbonyl-ene reaction to furnish the CD-ring fragment, and a Mukaiyama aldol reaction to deliver the FG-ring fragment. The subsequent fragment couplings were accomplished by aldol and sulfone anion methodologies. All ketalization events to form the nonacyclic target were accomplished under equilibrating conditions utilizing the imbedded configurations of the molecule to adopt one favored conformation. A final fragment coupling of the anomeric EFGHI-sulfone anion to the ABCD-aldehyde completed the convergent synthesis of (±)-azaspiracid-1.

Introduction

Background. Azaspiracid poisoning is a recent toxic syndrome first reported in 1995. On this occasion, at least 8 people in The Netherlands became ill after consuming blue mussels (*Mytilus edulis*) harvested in Killary Harbor, Ireland. Subsequently, intoxications related to azaspiracid poisoning have been reported in several countries including the U.K., Norway, Spain, France, and Italy as well as Morocco. An active search for the causative toxin provided the motivation for its isolation by the Satake group in 1998. Only minute amounts of the active toxin (2 mg) were obtained as an amorphous solid from 20 kg of mussel meat collected at Killary Harbor. Extensive NMR studies of this material resulted in the proposed structural assignment of azaspiracid-1 (Figure 1). In this nonacyclic structure, the absolute configuration remained uncertain. In addition, the flexible methylene bridge at C27 prevented an unambiguous determination of the relative configurations between the ABCDE- and FGHI-domains. All remaining stereochemistries such as the dense acyclic C19–C21 junction between the D- and the E-rings were assigned based on an analysis of NOE interactions. A total of 11 azaspiracid analogues differing slightly in their methylation and hydroxylation patterns have subsequently been described; five of these analogues were isolated and characterized by NMR spectroscopy while the remaining analogues were identified by tandem mass spectrometry.

The origin of these toxins has been proposed to be a marine dinoflagellate, and their occurrence has subsequently been reported in multiple shellfish species including mussels, oysters, scallops, clams, and cockles. Extensive studies of the azaspiracids continue.

Figure 1. Originally proposed structure (1) and correct structure of (−)-azaspiracid-1 (2).
racids have revealed a number of toxic effects such as cytoxicity in mammalian cell lines,\textsuperscript{10} teratogenic effects in fish,\textsuperscript{11} perturbation of cell adhesion,\textsuperscript{12} disorganization of the Actin cytoskeleton,\textsuperscript{13} and inhibition of the electrical activity of neuronal networks,\textsuperscript{14} although the specific modes of all such actions of azaspiracids yet remain unclear. The scarcity of azaspiracids from natural sources serves as a further complication in mechanistic elucidations aiming to better understand their toxicity and ultimately prevent their hazards to human health.

The intriguing structure of this toxin has furthermore served to stimulate interest in the chemical community, in particular by the research groups of Nicolaou,\textsuperscript{16} Carter,\textsuperscript{17,18} Forsyth,\textsuperscript{19} and others.\textsuperscript{20} The Nicolaou group reported a successful synthesis of the proposed structure 1 in 2003, only to clearly reveal its nonidentity to the isolated natural product.\textsuperscript{21} Subsequent impressive efforts in the Nicolaou group using a combination of degradation studies and the synthesis of multiple diastereomers resulted in a significant structural revision of azaspiracid 1 by total synthesis. These landmark studies allowed the unambiguous structural assignment of (−)-azaspiracid-1 (2) in 2004.\textsuperscript{22} As highlighted in Figure 1, the position of the A-ring olefin (yellow) was different, and the relative configurations of the CD- and FGHI-domains (green) were opposite in the correctly assigned natural product 2 compared to the originally proposed structure 1. On the basis of these findings, an improved synthesis of (−)-azaspiracid-1 (2) was recently reported by the Nicolaou group.\textsuperscript{23}

**Synthesis Plan.** Conformational analysis of azaspiracid-1 suggests that each of the multiple ketals exists in their thermodynamically favored configuration on the basis of anomic stabilization and steric effects (Figure 2). Accordingly, a number of thermodynamically controlled ketalization events were incorporated into the synthesis plan under the assumption that the desired configurations would be achieved under equilibrating conditions. Notably, whereas the ABC-bis(spiroketal) portion of the originally proposed structure 1\textsuperscript{b} contained only one anomic effect (not shown), the ABC-moieties of the corrected (−)-azaspiracid-1 structure (2)\textsuperscript{22} incorporates two stabilizing anomic effects and is presumed to be in its favored configuration. Thus, a thermodynamically controlled spiroketalization should be effective in controlling both spiroketal stereocenters at C10 and C13. We also anticipated that the FG-ring bicyclic ketal might also be constructed by an acid-catalyzed ketalization. Finally, we suspected that the HI-ring spiroaminal would spontaneously cyclize to provide the desired configuration at the C36 ring junction from an acyclic precursor with an unprotected C40 amino group.

![Figure 2. 3D-representation of (−)-azaspiracid-1 (2) highlighting stabilizing anomic effects in the molecule.](image)

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Scheme 1. Retrosynthetic Analysis of (+)-Azaspiracid-1 (ent-2)

**See ref 31 for abbreviations.**

In our own studies,\(^\text{24}\) we elected to pursue the synthesis of (+)-azaspiracid-1 (ent-2, Scheme 1). This target required only minimal changes in our original synthesis plan designed to pursue the initially proposed structure 1 of (−)-azaspiracid-1. Thus, the design of a new AB-ring fragment and the synthesis of the enantiomer of the E-ring fragment were required while all other regions of the molecule remain unaltered.

Our principal disconnections in the deconstruction of (+)-azaspiracid-1 (ent-2) are outlined in Scheme 1. In the final fragment coupling, the C21-anion of the anomeric EFGHI-sulfone 4 was envisioned to be a C20 electrophile such as +4 to give the intermediary ketone 5. After retrosynthetic installation of a sulfone moiety at C12, an addition of this C12-sulfone anion could provide AB-ring fragment 7 and CD-ring fragment 8 of comparable structural complexity. In the assembly of the EFGHI-sulfone 4, ketalization events under equilibrating conditions were likewise incorporated to give intermediate 9. The illustrated fragment couplings to construct the C21−C40 chain of 9 would be two aldol addition events: a boron-mediated aldol addition to form the C26−C27 bond and a chelate-controlled Mukaiyama aldol addition\(^\text{30}\) to form the C34−C35 bond. Thus, the three fragments 10, 11, and 12 of equal complexity would represent our initial targets in the synthesis of the fully elaborated EFGHI-sulfone 4.

The integration of catalytic enantioselective processes into our synthesis projects has been an ongoing objective in our research program. In this regard, the Cu-catalyzed heterodiels–Alder reaction to give methyl-substituted dihydroxypropanes

\[(\text{31})\] Abbreviations: Ac = acetyl, Bn = benzyl, Boc = tert-butyloxycarbonyl, CB5 = Corey-Bakshi-Shibata, COD = 1,5-cyclooctadiene, m-CPBA = m-chloroperoxybenzoic acid, Cy = cyclohexyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, Dess−Martin periodinane = 1,1,1-tris(2-furyl)tris(trifluoromethyl)methane, DIBALH = diisobutylaluminiumhydride, DMAF = dimethylaminomethylene phosphinimide, DMF = N,N-dimethylformamide, DMSO = dimethyl sulfoxide, HMPA = hexamethylenephosphoramidate, HPLC = high pressure liquid chromatography, LDA = lithium diisopropylamide, LiDBB = lithium di-tert-butylphosphinidate, LiHMDS = lithium hexamethyldisilazide, Mes = 2,4,6-trimethylphenyl, pMDP = p-methoxyphenylthionitrobenzenesulfonate, RanNi = Raney Nickel, RT = room temperature, S−Selectride = lithium tri-sec-butyllithium, TBAF = tetrabutylammonium fluoride, TBAI = tetrabutylammonium iodide, TBPDS = tert-butylphenylsulfoxide, TBS = tert-butyldimethylsilyl, TBPS = tert-butyldiphenylsilyl, TBS = tert-butyldimethylsilyl, Tebbe reagent = \((\mu\text{-chloro})(\mu\text{-methylen})\text{-bis(cyclopetadienyl)}(\text{dimethylaluminum})\text{tititanium}, \text{Teoc} = 2-(trimethylsilyl)ethoxy carbonyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-butyldiphenylsilyl, TES = tert-b
Results and Discussion

Synthesis of the AB-Ring Fragment 7. In the design of the azaspiracid AB-ring fragment, the major obstacle was anticipated to be the transposed A-ring olefin in the revised azaspiracid-1 structure (2), thus creating a labile C6 divinylcarbinol stereocenter. In order to suppress the lability of this stereocenter, we selected the C10 lactol methyl ether 7, which includes the C6 divinylcarbinol in the keto formation, as our targeted AB-ring fragment. As depicted in Figure 3, the endocyclic double bond is taken out of conjugation with the C6 C-aromatic orbital. This eliminates the impact of this π-bond toward hyperconjugative donation, thus influencing the stability of the C6 divinylcarbinol stereocenter in a sufficiently positive manner.

In order to preserve the desired oxidation state of the C1 carboxyl terminus, we incorporated the C1 carboxylic acid as its derived t-Bu ester into our synthesis plan (Scheme 2). While attempted cross metathesis was low yielding with the Grubbs second-generation catalyst (10%–35% yield), the more stable Grubbs-Hoveyda catalyst was considerably more efficient, affording Weinreb amide in excellent yield (88%). The C7–C12 fragment was introduced as the racemic acetylene, readily prepared from acrolein by conjugate addition of thiophenol, followed by addition of the allenyl Grignard reagent (96% yield, 2 steps). The two fragments were coupled by the selective 1,2-addition of the dianion derived from acetylene to the unsaturated Weinreb amide. After considerable experimentation, optimum conditions involved the conversion of acetylene to its derived Weinreb reagent by deprotonation with n-butyllithium and transmetalation with MgBr2·OEt2 followed by the addition of THF at a late stage of the reaction to facilitate solubilization. Since the product of the alkyne addition proved somewhat unstable, direct acetylation of the unpurified mixture provided the C1–C12 ene-ynone in 83% overall yield for the 2 steps.

On the basis of literature precedents for the enantioselective reduction of ene-yrones, the C6-stereocenter was introduced with high enantioselectivity in a supra-stoichiometric CBS-reduction using 2 equiv of oxazaborolidone and BH3·SMe2 to afford the desired alcohol (86%, 94–97% ee, Scheme 2).


Scheme 3. Synthesis of the AB-Ring Fragment 7^4  

Reagents and conditions: (a) 32 (equiv), BH$_3$·SM$_2$, THF, 0 °C, 86%, 94−97% ee; (b) H$_2$ (1 atm), Pd/CaCO$_3$·Ph (5%), pyr, benzene; (c) TBSCI, DMAP, imidazole, DMF, 92%, 3−5% C4−C5 alkene (2 steps); (d) K$_2$CO$_3$, MeOH; (e) SO$_3$·pyr, DMSO, i-Pr$_2$NET, CH$_2$Cl$_2$, −25 °C, 91% (2 steps); (f) HF·pyr, pyr, THF, 0 °C, 74%; (g) PPTS, HC(OMe)$_3$, MeOH, CH$_2$Cl$_2$, −10 °C, 92%; (h) H$_2$O$_2$, (NH$_4$)$_6$Mo$_7$O$_24$, MeOH, 0 °C, 88%; (i) LiAlH$_4$, Et$_2$O, −20 °C, 92%; (j) TIPSCI, imidazole, DMF, 98%. See ref 31 for abbreviations.  

3). Initial attempts to use a catalytic amount of oxazaborolidine 32 were detrimental both for the yield and the observed enantioselectivity in this transformation. Semihydrogenation of the alkyne under Lindlar conditions proceeded in high yield, although the product was contaminated with 3−5% of the undesired C4−C5 alkane that was separated from the major product by MPLC at a later stage. Subsequent TBS-protection (92% desired product over two steps) was followed by removal of the acetate moiety (K$_2$CO$_3$, MeOH). In the oxidation to the β,γ-unsaturated ketone 34, Dess-Martin periodinane also oxidized the phenylsulfide to the corresponding sulfone. A Parikh-Doering oxidation using Et$_3$N as the base afforded the product 34 accompanied by approximately 20% of the undesired α,β-unsaturated ketone resulting from base-induced olefin migration. This undesired side reaction was suppressed using the sterically hindered i-Pr$_2$NET as the base to give the desired β,γ-unsaturated ketone 34 in good yield (SO$_3$·pyr, DMSO, i-Pr$_2$NET, 91%, 2 steps).

The stage was now set for the crucial lactol formation of the C6 alcohol. This was best effected with HF·pyr buffered with pyridine at 0 °C to give primarily the desired lactol (74%) accompanied by 20−25% of the undesired conjugated trienone resulting from elimination of the C6 silyl ether substituent. To our relief, this lactol was smoothly transformed into the desired C6 divinylcarbinol moiety in good yield (SO$_3$·pyr, DMSO, i-Pr$_2$NET, 91%, 2 steps). In a later variation on the synthesis plan, the oxidation of the carboxyl terminus needed to be altered (vide supra). Accordingly, the ester terminus of this synthesis was reduced and protected as its silyl ether (LiAlH$_4$, 92%; TIPSCI, 98%), thus concluding the synthesis of the desired AB-ring fragment 7 and its carbonate analogue 34 in 13 linear steps from 25.

Synthesis of the CD-Ring Fragment 8. Initial Synthesis via a Stereoselective C14-Methylation. The first of two syntheses of this fragment is illustrated in Scheme 4. In our synthesis of this synthon, we envisioned that the enantioselective Cu$_{2+}$-catalyzed glyoxylate-ene reaction developed in these laboratories could provide the initial C17-stereocenter (eq 3). Further studies with these substrates proved that the reaction could routinely be conducted on a 20-g scale in good yields and enantioselectivities using 1 mol% of the bis(aquo)Cu$_{2+}$ complex 19 (89% yield, 98% ee, Scheme 4). In addition, the Cu$_{2+}$-catalyst was sufficiently Lewis acidic that commercial ethyl glyoxalate could be used directly in its polymerized form without prior distillation to afford the monomeric aldehyde. Whereas the substrate concentration in these experiments (0.27 M) was governed by the limited solubility of complex 19 in CH$_2$Cl$_2$, concomitant lowering of the catalyst loading and an increase of the substrate concentration (0.89 M) allowed for the use of only 0.1 mol % of catalyst 19. Almost identical results were obtained (86% yield, 96% ee) although the reaction times to reach full conversion in the latter case increased considerably (12 h versus 5 days, respectively).

34 Reagents and conditions: (a) NaH, BnBr, CH$_2$Cl$_2$, 0 °C to RT, 99%; (b) DIBALH, toluene, −94 °C; (c) K$_2$CO$_3$, MeOH, CH$_2$Cl$_2$, −78 °C, then Me$_2$S, RT, 79%; (d) Et$_3$SiH, BF$_3$·OEt$_2$, CH$_2$Cl$_2$, −78 °C, 82%, dr 90:10. See ref 31 for abbreviations.
The resultant α-hydroxy ester 20 was subsequently benzylated (NaH, Br, 99%) and reduced to the corresponding aldehyde 35 (DIBALH, −94 °C) that was used directly without purification in the next step. The zinc homoenolate of siloxycyclopropane 36 was then prepared in situ and added stereoselectively to aldehyde 35 according to the Kuwajima procedure. In accordance with presumed chelate control exerted by the Zn2+ Lewis acid, the resulting protected syn-diol 37 was obtained in high diastereoselectivity (59%, dr 93:7, two steps). Ozonolysis of the olefin in the presence of methanol directly afforded the C19 lactol methyl ethers 38 in 79% yield. The C19 stereocenter was then established in a stereoselective reduction with Et3SiH mediated by BF3·Et2O to afford the desired trisubstituted tetrahydrofuran 39 (82%, dr 90:10). The observed diastereoselectivity in this reduction is in good agreement with the stereoelectronic model 40 for nucleophilic additions to 5-membered cyclic oxocarbenium ions proposed by Woerpel.49

At this stage, our strategy for the stereoselective introduction of the C14-methyl substituent was influenced by a report by Narasaka that acyclic α-hydroxy esters 41 can be alkylated with high stereoselectivity (eq 4). The presence of HMPA was proven to be critical for the observed stereoselectivity as silyl-trapping experiments afforded silyl enol ethers of opposite stereochemistry in the absence and presence of HMPA, respectively. An 8-membered internal chelate 42 in the presence of HMPA was invoked as a possibility for explaining the observed high stereoselectivity.50

Prior to the actual methylation event, ethyl ester 39 was converted into its derived amide 44 with the magnesium amide of morpholine 51 (82%, Scheme 5). It was assumed that A1,3 strain in amide 44 would prevent bis(alkylation), thus allowing the use of excess external base to achieve full conversion in the methylation. The subsequent C14-methylation thus proceeded in excellent yield and moderately good diastereoselectivity to afford the alkylated product 45 (LiHMDS, 96%, dr 86:14).

Improved Synthesis of the CD-Ring Fragment 8 via a Direct Introduction of a C14-Methylated Fragment. While the above findings afforded us a workable route to the CD-ring fragment, we decided to investigate a modified approach to the orthogonally protected CD-fragment 8 (Scheme 1) which would involve the direct introduction of a fragment incorporating the

C14 methyl group (Scheme 6). In this regard, the hydroxy ester 20 derived from the carbonyl ene reaction (Scheme 4) was converted into the corresponding Weinreb amide 52 (MeNH-(OMe)-HCl, MeAl, THF, 98%); (b) PMBBr, NaH, DMF, 0 °C, 95%; (c) 47, 90%-BuLi, Et3O, −78 °C, then 46, 90%; (d) L-Selectride, THF, −78 °C, 96%, dr >95:5; (i) O3, pyridine, CH2Cl2/MeOH (5:1 v/v), −78 °C, then Me2S, −78 °C to RT; (ii) PPTS, MeOH, 90%; (f) Et3SiH, BF3·Et2O, CH2Cl2, −78 °C, 84%, dr >95:5; (g) DDQ, CH2Cl2/pH 7 buffer (9:1 v/v), 0 °C, 94%; (h) TESCl, imidazole, DMF, 97%; (i) LiDBB, THF, −78 °C, 96%; (j) SO3·Pyr, DMSO, i-Pr2NEt, CH2Cl2, −30 °C, 97%. See ref 31 for abbreviations.

**Scheme 6.** Second Synthesis of the CD-Ring Fragment 8

**Scheme 5.** C14-Methylation

**Improve Synthesis of the CD-Ring Fragment 8 via a Direct Introduction of a C14-Methylated Fragment.** While the above findings afforded us a workable route to the CD-ring fragment, we decided to investigate a modified approach to the orthogonally protected CD-fragment 8 (Scheme 1) which would involve the direct introduction of a fragment incorporating the
any accompanying oxidation of the benzylic ether protecting groups. Subsequent ketalization (PPTS, MeOH) afforded the methyl ketal 49 (90%, 2 steps). In analogy to the reduction to give 39 described in Scheme 4, stereoselective reduction with Et3SiH mediated by BF3·OEt2 then provided the desired trisubstituted tetrahydrofuran 50 (84%, dr > 95:5) with the primary byproduct being derived from elimination to the corresponding undesired furan.

Whereas the observed diastereoselectivity in the 49→50 oxocarbenium ion reduction (dr > 95:5) is in agreement with the stereoelectronic model 40 proposed by Woerpel,49 it is noteworthy that the analogous reduction of the O17-TBS protected methyl ketal 51 proceeded with no diastereoselectivity to give tetrahydrofuran 52 (dr 1:1, eq 5). This result suggests that steric factors also play a significant role for these sterically encumbered substrates.

Since a labile C17-silyl ether was required for the projected ketalization events, the PMB group was exchanged for a TES ether by oxidative cleavage with DDQ (94%) and reprotection under standard conditions (TESCl, 97%, Scheme 6). As this TES ether proved to be labile to standard palladium-catalyzed hydrogenolysis conditions, the terminal benzyl ether was removed under radical anion conditions (LiDBB,57 96%). Finally, a Parikh-Doering oxidation45 afforded aldehyde 8 in 97% yield. Altogether, this second-generation sequence obviates the need for any diastereomer separation and efficiently provided the desired CD-ring fragment 8.

Assembly of the ABCD-Aldehyde 3. A simple solution to the above obstacle was realized using the AB-ring fragment 7 with

\[ \text{C12-sulfone} \text{ under the appropriate experimental conditions in the presence of a C1 t-Bu ester, although the } \alpha\text{-protons of esters and sulfones are of comparable thermodynamic acidity. This expectation was born out by initial investigations using the sulfone 53, prepared by essentially the same sequence58 as previously described for AB-ring fragment 7, for which the C6 divinylcarbinol moiety was masked only as its acyclic silyl ether. Thus, selective addition of sulfone 53 to the C17-TBS-protected aldehyde 54 proceeded to give a mixture of diastereomeric hydroxysulfones 55 (74% yield, eq 6).}

Unfortunately, as eluded to earlier in our discussion of Figure 3, adducts 55 incorporating acyclic C6-divinylcarbinol moieties proved to be too unstable to successfully participate in the subsequent derivatization into the ABCD-bis(spiroketal) under a variety of conditions and were abandoned for further studies. However, much to our surprise, the corresponding addition of the superficially similar sulfone 56 to C17-TBS-protected aldehyde 8 was nonselective for C12 deprotonation under a variety of experimental conditions (eq 7). These findings suggest that although \(\alpha\)-deprotonation of the C12 sulfone moiety may be kinetically favored over enolization of the C1 ester, subtle steric differences may have a negative impact on the kinetics in such desired \(\alpha\)-deprotonations.

Union of the AB- and CD-Ring Fragments. With the AB- and CD-ring fragments in hand, we proceeded to investigate their coupling and further elaboration into the ABCD-bis(spiroketal). In the initial synthesis plan, we anticipated that a selective kinetic deprotonation of the AB-ring fragment might be feasible \(\alpha\) to the
the C1 terminus protected as its silyl ether (Scheme 7). With this pattern of orthogonal functionalities, sulfone deprotonation could readily be effected with LDA as also reported for structurally similar sulfone anion additions, a base which in previous experiments had displayed inferior kinetic selectivity for the sulfone moiety (eqs 6 and 7). The addition of the sulfonyl carbanion derived from 7 (1.6 equiv) to aldehyde 8 proceeded to give an initial mixture of four C12–C13 hydroxysulfones mixed with excess sulfone 7. Subsequent Dess-Martin oxidation afforded the two C12-diastereomeric ketosulfones 6 in 92% yield for the 2 steps. Subsequent recovery of unreacted sulfone 7 was achieved in 76% yield. The yield in this step is based on the limiting aldehyde reaction component. Sodium amalgam excision of the sulfone moiety under mild conditions (Na/Hg, NaH2PO4) then provided ketone 5 as a single diastereomer in 92% yield.

In the spirocyclization event, the TES ether was selectively removed with 1 equiv of TBAF at low temperature to form the intermediary lactol 57. This step was followed by treatment of the unpurified mixture with PPTS in a nonhydroxylic solvent such as CH2Cl2. Under these conditions, the desired bis(spiroketal) isomer was obtained in 83% yield (2 steps). Finally, the C20 terminus was elaborated by the selective removal of the TBDPS ether followed by a Parikh-Doering oxidation affording the two C12-diastereomeric ketosulfones 6 in 92% yield as a single isomer on a 10 g scale. Since neither propenyl ether nor dihydroxyran 60 were observed to isomerize in control experiments, we believe the less than perfect diastereomeric ratios in the cycloaddition could potentially be explained by a stepwise reaction pathway under these Lewis acid catalyzed conditions. In the subsequent hydrogenation of the tetrasubstituted olefin, EtOAc proved to be superior to alcoholic solvents, giving rise to tetrahydroxypyr, DMSO, 70 °C, 70%; (b) 2-propanoylMgBr, THF/EtOAc, −78 °C, 80%; (c) 15 (2 mol%), 3 Å MS, EtOAc, −40 °C, dr 94:6, 97% ee, 84% yield as a single isomer on a 10–20 g scale. Since neither propenyl ether 62 nor dihydroxyran 60 were observed to isomerize in control experiments, we believe the less than perfect diastereomeric ratios in the cycloaddition could potentially be explained by a stepwise reaction pathway under these Lewis acid catalyzed conditions. In the subsequent hydrogenation of the tetrasubstituted olefin, EtOAc proved to be superior to alcoholic solvents, giving rise to tetrahydroxypyr 59 in excellent yield and diastereoregularity (H2, Pd/C, EtOAc, dr 98:2, 95% of 59).

The two components of the hetero-Diels–Alder reaction, 62 and 64, were readily prepared on multigram scales using slight modifications of reported literature procedures (Scheme 9). The subsequent cycloaddition proceeded readily using low loadings of the bench-stable hydrated copper complex 15 (2 mol %), provided it was dehydrated with molecular sieves prior to use. In contrast to the related cycloadditions reported previously for which THF was identified as the optimal solvent, these conditions gave rise to a mixture of cis and trans diastereomers of dihydroxyran 60. Diethyl ether proved to be the optimal solvent for this particular hetero-Diels–Alder reaction (97% ee, dr 94:6), and the desired product 60 could be isolated in 84% yield as a single isomer on a 10–20 g scale. Since neither propenyl ether 62 nor dihydroxyran 60 were observed to isomerize in control experiments, we believe the less than perfect diastereomeric ratios in the cycloaddition could potentially be explained by a stepwise reaction pathway under these Lewis acid catalyzed conditions. In the subsequent hydrogenation of the tetrasubstituted olefin, EtOAc proved to be superior to alcoholic solvents, giving rise to tetrahydroxypyr 59 in excellent yield and diastereoregularity (H2, Pd/C, EtOAc, dr 98:2, 95% of 59).

Chelate-Controlled Vinylmetal Addition to Form the Central C20–C21 Bond. With the syn-1,3-dimethyl motif of the E-ring thus in hand, we turned our attention to the elaboration of tetrahydroxypyr 59 into an appropriate E-ring intermediate that would allow us to establish the crucial C20–C21 bond. These studies would identify in which order the remaining EFGHI-region of the molecule should be as-

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(61) The selective TES-removal was accompanied by minor loss of the C1 TIPS protecting group. Since the crude mixture of 60 was subjected directly to the PPTS-mediated spirocyclization, 76% of 61 was obtained directly in the spirocyclization event while additional 7% of 61 was obtained after reinstallation of the C1 TIPS substituent.
(64) Rambaud, M.; Bakasse, M.; Duguay, G.; Villieras, J. Synthesis 1988, 564–566.
assembled. One possible option we investigated as a viable C20–C21 fragment coupling was a chelate-controlled vinyl-lithium addition\(^\text{(65,66)}\) to a D-ring aldehyde synthon\(^\text{(65 eq 10)}\). As facile elaboration of the C21-1,1-disubstituted olefin was thought to be incompatible with the two olefins contained in the AB-ring fragment\(^7\), this C20–C21 bond construction to join the CD- and the E-ring fragments was investigated prior to the introduction of the AB-ring fragment.

Scheme 10. Synthesis of the E-Ring Vinyl Iodide 71\(^*\)

![Scheme 10](image)

\(\text{Reagents and conditions: (a) } \text{t-BuOK, THF, } -50^\circ\text{C, quant.; (b) } 1,3\)-propanedithiol, BF\(_3\)·OEt\(_2\), CH\(_2\)Cl\(_2\), 95% (2 steps); (c) LiBH\(_4\), THF, quant; (d) 2,2-dimethoxypropane, PPTS, CH\(_2\)Cl\(_2\), 98%; (e) -BuLi, HMPA, THF, -78 °C, then MeI, 92%; (f) Hg(ClO\(_4\))\(_2\), CaCO\(_3\), H\(_2\)O, THF, 88%; (g) trisilylhydrazine, THF, 93%; (h) -BuLi, THF, -78 to 0 °C, then I\(_2\), -78 °C, 86%. See ref 31 for abbreviations.\)

Synthesis of the E-Ring Vinyl Iodide 71. In order to arrive at an appropriately protected vinyl iodide fragment\(^66\), the ester substituent of tetrahydropyran\(^59\) was epimerized to its equatorial diastereomer (t-BuOK, THF, -50 °C, Scheme 10) prior to pyran ring opening to give the dithiane\(^68\) (1,3-propanedithiol, BF\(_3\)·OEt\(_2\), 95%, 2 steps). Subsequent ester reduction (LiBH\(_4\)) and acetonide protection proceeded uneventfully in excellent yields (Me\(_2\)C(OMe)\(_2\), PPTS, 98%, 2 steps). In the dithiane methylation,\(^69\) it was found that a 5-min deprotonation time of the intermediary dithiane at -78 °C was optimal. This afforded dithiane\(^69\) in good yield (MeL, t-BuLi, HMPA/THF, 92%). Longer deprotonation times or higher temperatures afforded substantial amounts of addition of the reactive dithiane anion to HMPA as the electrophile. Oxidative removal of the dithiane moiety under mild conditions revealed the methyl ketone (Hg(ClO\(_4\))\(_2\), 2,2-dimethoxypropane, THF, 98%). Finally, the desired vinyl iodide was conveniently installed in a Shapiro reaction\(^69\) via an intermediate trisilylhydrazine.\(^70\) Thus, the methyl ketone was converted into the intermediate trisilylhydrazine\(^70\) (trisilyl-drazine, 93%) which proved slightly unstable in solution but could be stored neat in the freezer for weeks without any detectable decomposition. Metalation with t-BuLi followed by warming to 0 °C generated the intermediate vinyl anion before an iodine quench at -78 °C furnished vinyl iodide in 86% overall yield. In summary, this sequence provided the desired E-ring vinyl iodide in 10 linear steps from the hetero-Diels–Alder precursors\(^62/64\).

Chelate-Controlled Vinylmetal Addition and Elaboration into the ABCDE-Region 77. In preparation for the subsequent chelate-controlled vinyl iodide addition to stereoselectively form the C20–C21 bond, the CD-ring tetrahydrofuran\(^50\) was desilylated (TBAF, AcOH, 97%) and converted in a Parikh-Doering oxidation\(^8\) to the corresponding D-ring aldehyde 72 (SO\(_3\)·pyr, DMSO, t-Pr\(_2\)NEt, CH\(_2\)Cl\(_2\), -30 °C, 94%; (c) 71 (2 equiv), t-BuLi, Et\(_2\)O, -78 °C, then MgBr\(_2\)·OEt\(_2\), CH\(_2\)Cl\(_2\), -20 °C, 80%, dr > 99:1; (d) Ac\(_2\)O, DMAP, Et\(_3\)N, CH\(_2\)Cl\(_2\), 96%; (e) O\(_3\), MeOH, CH\(_2\)Cl\(_2\), -78 °C, then Me\(_2\)S; (ii) MeOH, HC(OMe)\(_3\), PPTS, 75% (2 steps); (f) TBDPSCl, imidazole, CH\(_2\)Cl\(_2\); (g) DDQ, CH\(_2\)Cl\(_2\)/pH 7 buffer (9:1 v/v), 0 °C, 78% (2 steps); (h) TESCl, imidazole, CH\(_2\)Cl\(_2\), 90%; (i) H\(_2\), RanI (W-2), EtOH, 93%; (j) SO\(_3\)·Pyr, DMSO, t-Pr\(_2\)NEt, CH\(_2\)Cl\(_2\), -30 °C, 75%. See ref 31 for abbreviations.

Scheme 11. Synthesis of the ABCDE-region 77\(^*\)

![Scheme 11](image)

\(\text{Reagents and conditions: (a) } \text{TBAF, AcOH, THF 97%; (b) } \text{SO}_3\cdot\text{Pyr, DMSO, t-Pr}_2\text{NEt, CH}_2\text{Cl}_2, -30 ^\circ\text{C, 94%; (c) } 71 \text{ (2 equiv), } \text{t-BuLi, Et}_2\text{O, -78 °C, then } \text{MgBr}_2\cdot\text{OEt}_2, \text{CH}_2\text{Cl}_2, -20 °\text{C, 80%, dr > 99:1; (d) } \text{Ac}_2\text{O, DMAP, Et}_3\text{N, CH}_2\text{Cl}_2, 96%; (e) } \text{O}_3, \text{MeOH, CH}_2\text{Cl}_2, -78 °\text{C, then } \text{Me}_2\text{S}; (f) \text{TBDPSCl, imidazole, CH}_2\text{Cl}_2; (g) \text{DDQ, CH}_2\text{Cl}_2/pH 7 \text{ buffer (9:1 v/v), 0 °C, 78% (2 steps); (h) TESCl, imidazole, CH}_2\text{Cl}_2, 90%; (i) } \text{H}_2, \text{RanI (W-2), EtOH, 93%; (j) } \text{SO}_3\cdot\text{Pyr, DMSO, t-Pr}_2\text{NEt, CH}_2\text{Cl}_2, -30 °\text{C, 75%. See ref 31 for abbreviations.}\)


vinyl iodide 71 could additionally be recovered by a final I2 quench, thus emphasizing the stability of the vinylmetal species in CH2Cl2.

Subsequently, the coupled product was acetylated under standard conditions to give 73 (Ac2O, 96%). Careful ozonolysis of the 1,1-disubstituted olefin in the presence of Sudan III as a color indicator26 allowed for an almost completely selective cleavage of the olefin accompanied by only trace amounts of undesired oxidation of the benzyl ether protecting groups. Subsequent ketalization in the presence of a mild acid allowed for the formation of lactol methyl ether 74 (PPTS, MeOH, 75% of 74, 2 steps). Intermediates observed during investigations of this ketalization procedure suggested that the product was partially dehydrated to give the E-ring C21-dihydropyran which in the presence of strong acids such as p-TsOH could be more rapidly ketalized to give the desired C21 methyl lactol ether, albeit in only moderate overall yields upon scale-up. A subsequent series of standard protecting group manipulations involved TBDPS-protection (TBDPSCI, imidazole), PMB-removal (DDQ, 78%, 2 steps), and C17 TES installation (TESCl, imidazole, 90%). The final debenzylization in the presence of the TES silyl ether proceeded readily using W-2 RaNi71 (H2, RaNi, EtOH, 93%) followed by a Parikh-Doering oxidation25 to give the C13 aldehyde 75 (SO3·pyr, DMSO, 75%). In preliminary experiments, aldehyde 75 could be readily elaborated in a five-step sequence analogous to the one already discussed in Scheme 7 to give access to the ABCDE-region 77 of azaspiracid-1.

C20–C21 Bond via an Anomeric Sulfone Anion Addition. Although we had thus established a viable route to form the C20–C21 bond of azaspiracid-1 as our initial fragment coupling, we remained attracted to the possibility of performing this crucial C20–C21 bond formation last. This would constitute a more convergent approach to azaspiracid-1 since all 9 rings of the final target would be formed prior to such an ultimate fragment coupling as briefly outlined in Scheme 1.

Synthesis of Cyclic E-ring Fragments Containing a C21 Sulfide Moiety. We began these investigations by synthesizing several E-ring fragments containing a C21-sulfide substituent and different electrophiles at C26 (Scheme 12). Treatment of tetrahydropyran 59 with one equivalent of thiophenol and a slight excess of BF3·OEt2 provided thyioglycoside 78 (dr 96.4, 83% of 78) accompanied by minor amounts of the acyclic dithioacetal as a byproduct. We believe the diastereoselectivity observed in this reaction is the result of initial formation of the axial thyioglycoside, followed by Lewis acid induced isomerization to the more stable equatorial isomer 78. In support of this hypothesis, the observed diastereoselectivity at C21 was inferior when stoichiometric amounts of BF3·OEt2 were employed. Subsequent epimerization of the ester substituent to give the tetrahydropyran 79 with all four substituents occupying equatorial positions proceeded readily with catalytic amounts of t-BuOK in THF at low temperature (dr 96.4, 88% of 79). The only major byproduct in this reaction was the corresponding t-Bu ester, and its formation was minimized by using only 5 % of t-BuOK. Ester 79 could then alternatively be converted to Weinreb amide 80 (Me(OMe)NH·HCl, i-PrMgCl, 93%) or reduced directly to aldehyde 10 (DIBALH, 93%). In summary, this sequence provided the E-ring fragment 10 in 5 steps (54% yield) from the hetero-Diels–Alder precursors 62/64.

Model Experiments To Form The C20–C21 Bond by an Anomeric Sulfone Anion Addition. At this stage, we decided to test the viability of the final anomeric sulfone anion addition to form the C20–C21 bond of azaspiracid-1 using less elaborate model systems. To the best of our knowledge, the most related literature precedent for such a fragment coupling can be found in our altohyrtin synthesis where an anomeric sulfone anion was added to an N-acetylbenzotriazole as the electrophile.27,28 In a simple azaspiracid model system, the anion of sulfone 81 could likewise be added to a host of simple activated esters and amides as exemplified by the N-acrylpyrazole 82 (Scheme 13). Although the yields of these additions to give the slightly unstable C21-β ketosulfone 83 were only moderate at this stage, we were more concerned with the identification of sufficiently mild conditions for the subsequent anomeric sulfone excision to arrive at the desired C21-lactol moiety. Very little is reported about such anomeric sulfone derivatizations apart from the single altohyrtin precedent that required forcing conditions for converting one of the anomeric sulfone anomers,27,28 conditions which were judged to be too harsh in the present azaspiracid case.

Initially, it was found that the transformation of ketosulfone 83 into ketosulfide 84 could be effected with PhSH in the presence of MgBr2·OEt2 and i-Pr2NEt in relatively nonpolar solvents (CH2Cl2 or Et2O, −20 °C, >80% yield). Subsequently, we discovered that the same transformation could be effected in quantitative yield under very mild conditions (PhSLi, Et2O,

The well-known competing side reaction in such a reaction is an interesting transformation that proceeds with complete inversion at the C21 stereocenter. The resulting ketosulfide 84 could be stereoselectively reduced to afford either C20 alcohol diastereomer utilizing a simple change of solvent (KHBEt3 in THF or CH2Cl2, d 5–6:1 or 1:10, respectively). Finally, the phenylsulfide moieties could be readily converted with aqueous HgCl2 into the lactols 85 and 86 for which the C21 hydroxyl spontaneously occupied an axial position. This mild reaction sequence was judged to be viable for our more functionalized azaspiracid target.

As may be noted, the above investigations were performed with the enantiomer of the Weinreb amide E-ring fragment (ent-80) since they were part of our early studies targeting the originally proposed structure of azaspiracid-1 (1). By similar approaches as depicted in Scheme 13, we additionally synthesized the C19-epimers of lactols 85 and 86, thus providing access to all four diastereomers of the C19–C20 junction. Comparison of 1H NMR data for these four C19–C20 diastereomeric lactols with the published 1H NMR spectrum of azaspiracid-1 clearly suggested that the acyclic C19–C20 junction between the ABCD- and the E-rings was one likely region to have been originally miss-assigned. This assumption was confirmed by Nicolaou in 2004 with the structural revision of azaspiracid-1 (2).

Unfortunately, more elaborate model systems in the correct enantiomeric series of the D-ring that comprised activated esters and amides derived either from CD-ring aldehyde 72 (Scheme 11) or ABCD-aldehyde 3 (Scheme 7) and the addition of the anion of E-ring sulfone 87 (Scheme 14) proved significantly less promising under a variety of conditions, also in the subsequent transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown). As an alternative, a significantly more rapid entry to the C21-lactol subsequently transformation with PhSLi (not shown).

In Scheme 15, we have designed a strategy with some promising precedent in the literature, a goal yet to be achieved, and did not improve the ratio of desired lactols 88 to dihydropyran 89. Although by no means optimal, this coupling experiment depicted in Scheme 15 still provided a credible lead for the final C20–C21 coupling experiments and established that the C21 lactols 88 could indeed be accessed directly from ABCD-aldehyde 3 upon appropriate work up conditions. With this result in hand, a decision was made to embark on the synthesis of the fully elaborated EFGHI-sulfone 4 (Scheme 1) as will be discussed in the following sections.

Synthesis of the FG-Ring Fragment 11. In the synthesis of the FG-ring fragment 11, we envisioned that the C32–C33 antidiol array could be efficiently obtained by an extension of our enantioselective catalytic Mukaiyama aldol reaction of siloxy-furan 21 and (benzyloxy)acetaldehyde 22 (eq 9, entry A).

In contrast to the original studies where hydrated complex 23 was formed in situ with CuCl2·2H2O,34 further investigations revealed that bis(aquo) complex 23 could conveniently be isolated and stored as a bench-stable solid prior to use. The inclusion of CF3CH2OH as a silicon-scavenging reagent further increased the observed stereoselectivities and was readily amenable to reliable large-scale preparations of the desired product 24 (entry B, 79%, dr 93:7, 97% ee), thus suggesting the suppression of a racemic silicon-catalyzed background reaction. However, much inferior stereoselectivities were ob-

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tained in preliminary experiments with the corresponding methyl-substituted siloxyfuran 90\(^\text{76}\) (entry C, dr 80:20, 43% ee), thus prompting us to investigate alternative conditions for this particular transformation.

Further studies revealed that the corresponding Sn(2+-)-catalyzed aldol reaction\(^\text{77}\) with Sn(2+-)-complex 93 alternatively afforded optimal results in the desired transformation. Thus, methyl-substituted siloxyfuran 90 underwent stereoselective aldol addition with ethyl glyoxalate (92) to give the desired lactone 94 in excellent yield and selectivities (94%, 95% ee, dr >50:1, eq 10). During these investigations, it was found that the ethyl substituents on the chiral ligand were important for obtaining high stereoselectivities, for reasons that remain unclear.

Another practical variant of this addition process using N-phenyl glyoxamide 96,\(^\text{78}\) readily prepared by ozonolysis of olefin 95 and dehydration of the intermediary glyoxamide hydrate by vacuum sublimation, is depicted in Scheme 15 and afforded adduct 97 (94% conversion, dr >40:1, 97% ee) as a highly crystalline solid. In this transformation, it was found that the highest stereoselectivities were observed using a sequential addition of the reagents in 0.1 equiv increments rather than a slow addition of either reagent. The resulting lactone 97 could readily be recrystallized to enantiopurity prior to the subsequent transformations (99% ee, 67%). Another benefit of the N-phenyl amide functionality was reduced in a two-step sequence involving Boc-activation and reduction with lithium borohydride to give alcohol 98 (97% yield, 2 steps). At the other terminus of the molecule, the N-phenyl amide functionality was reduced under the same range of hydrolysis conditions (PMBBr, NaH, 60 °C, 93%) whereas a variety of acidic conditions afforded both decomposition and epimerization of the newly set methyl stereocenter.

The lactone 98 was next reduced to the diol (KHBEt, 94%), persilylated (TBSCI, 99%), and converted into the corresponding primary alcohol by selective desilylation (HF-pyr, 87%). We elected to introduce C28 as a cyano function at this stage of the synthesis to provide maximal flexibility in subsequent fragment couplings since the nitrite could be either converted into an electrophile (an aldehyde) or a nucleophile (a methyl ketone). This was accomplished in high yield by tosylation of the primary alcohol and displacement with sodium cyanide to give nitrile 99 (97% yield, 2 steps). At the other terminus of the molecule, the N-phenyl amide functionality was reduced in a two-step sequence involving Boc-activation and reduction with lithium borohydride to give alcohol 100 in 98% yield for the two steps. Preliminary investigations of our various fragment coupling strategies revealed that a C27-methyl ketone was the most desirable for coupling the FG-ring fragment to the E-ring fragment 10. The methyl ketone was therefore accessed by a methyllithium addition to the nitrite in a step that required transient protection of the primary alcohol to effect full conversion (TMSCI, 99%). Thus, the nitrite was converted into the C27 methyl ketone with methyllithium with concomitant TMS ether hydrolysis during the workup procedure (84%). Finally, a Parikh-Doering oxidation\(^\text{45}\) (SO3-pyr, DMSO, 97%) concluded the synthesis of the FG-ring ketoaldehyde 11.

Synthesis of the HI-Ring Fragment 12. Chiral Auxiliary Approach via Known Intermediate 104. In our initial efforts aimed at gaining access to the HI-ring fragment 12 for further studies, we utilized the known hydroxy ester 104 (Scheme 16). This intermediate is readily available in 8 steps\(^\text{81}\) based on a double stereodifferentiating directed hydrogenation\(^\text{80}\) of the homoallylic olefin 103 synthesized via a chiral auxiliary-based diastereoselective aldol reaction.\(^\text{83}\) The remaining four transformations comprised ester reduction, selective tosylation of the primary alcohol by selective desilylation (HF-pyr, 98%, dr >95:5). Subsequently, PMB-protection of the secondary alcohol to give 99 was sufficiently chemoselective under basic conditions (PBMBr, NaH, 67%) whereas a variety of acidic conditions afforded both decomposition and epimerization of the newly set methyl stereocenter.


primary alcohol to give 105, azide substitution, and finally a Swern oxidation\(^8\) (80%, 4 steps) to deliver the desired keto azide 12.

**Catalytic Enantioselective Approach via Hetero-Diels–Alder Intermediate 59.** Alternatively, we envisioned that our 1,3-syn-dimethyl substituted tetrahydropyran 59 generated in the enantioselective hetero-Diels–Alder reaction could likewise be utilized to synthesize the acyclic HI-ring fragment 12 by incorporation of a ring fragmentation. Thus, ester 109 was converted to alcohol 106 by sequential acetal and ester reduction (Et3SiH, BF3·OEt2·LiAlH4, 81% yield), followed by iodine installation (Scheme 17). Whereas initial investigations of the latter transformation were frustrated by the lack of reactivity of intermediate sulfonate esters derived from the primary alcohol 106, the iodide 107 was smoothly obtained by heating of the intermediate phosphonium salt derived from alcohol 106 to 60 °C (I2, PPh3, imidazole, 85 94%). Although the fragmentation of iodide 107 could be accomplished under a number of conditions (Zn, MeOH or n-BuLi, Et2O), the resultant primary alcohol was too volatile for convenient manipulation. As a solution, the intermediary lithium alkoxide was formed in THF and trapped in situ with TsCl to give 108 in 95% yield. The terminal olefin was smoothly oxidized to the methyl ketone under standard Wacker conditions (O2, PdCl2, CuCl, DMF, 89%), with the remainder of the material consisting of olefin isomers. Finally, an azide introduction (NaN₃, DMSO, 60 °C, 97%) concluded this catalytic asymmetric synthesis of the HI-ring fragment 12.

**Synthesis of the EFGHI-Sulfone 4, Assembly of the EFGHI Carbon Skeleton and Formation of the FG Bicyclic Ketal 115.** With the required E-, FG-, and HI-ring fragments in hand as described above, we proceeded to investigate their assembly to the pancyclical EFCHI-sulfone 4. We first formed the C34–C35 bond to unite the FG- and the HI-ring fragments in a chelate-controlled Mukaiyama aldol reaction.\(^3\) The required enolslane 109 was readily formed from methyl ketone 12 under standard conditions (LiHMDS, TMSCl, Et3N, Scheme 18). A careful evaluation of a range of Lewis acids to effect this transformation established that freshly prepared solid MgBr2·OEt2\(^8\) \(^\text{was superior to other Lewis acids such as TiCl4·(O-i-Pr)2·TiCl4·SnCl4·MgI2·MgBr2·Mg(OOTf)2·SnCl4}}\) and commercial MgBr2·OEt2. In addition, a high concentration (0.4 M) was crucial for obtaining a complete conversion with this mild and selective Lewis acid. Consequently, the desired chelate-controlled addition of enolslane 109 to aldehyde 110 proceeded in excellent yield to afford the desired aldol adduct 110 as a single diastereomer (93%, dr > 95:5). Subsequent model studies on adduct 110 revealed that treatment with aqueous HF in acetonitrile\(^8\) smoothly effected the formation of the desired FG bicyclic ketal 112 in 92% yield.

The aldol addition to form the C26–C27 bond was implemented with Cy3BCl (2.4 equiv, i-P2NET) due to its excellent regioselectivity in the enolization of methyl ketones (Scheme 19).\(^8\) The excess Cy3BCl is presumed to function as a transient protecting group for the C34–C35 hydroxyketone moiety and prevent any retroaldol reactions from taking place as depicted in the proposed intermediate 113. When treated with a slight excess of E-ring aldehyde 10, the desired aldol adduct 9 was formed in near quantitative yield (dr 60:40). When adduct 9 was subsequently exposed to aqueous HF in acetonitrile, the lone TBS ether was cleaved and the molecule spontaneously cyclized to form the desired FG bicyclic ketal 114 in excellent yield (92%, 2 steps). It is noteworthy that the analogous cyclization of the O34-TBS-protected aldol adduct 111 afforded a multitude of products.

The lack of diastereoselectivity in the boron aldol addition was inconsequential since the C26 secondary alcohols 114 were subsequently oxidized to the corresponding keto 115 with Dess-Martin periodinane\(^9\) (85%). Pyridine was crucial to buffer

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**Scheme 17. Catalytic Enantioselective Synthesis of the HI-Ring Fragment 12**

- Reagents and conditions: (a) Et3SiH, BF3·OEt2·CH2Cl2, 0 °C, 91%; (b) LiAlH4·EtO, 0 °C, 91%; (c) I2·PPh3·imidazole, CH3CN/benzene, RT to 60 °C, 94%; (d) n-BuLi·THF, −78 °C, then TsCl, −78 to 0 °C, 95%; (e) O3·PdCl2·CuCl·H2O·DMF, 89%; (f) NaN3, DMSO, 60 °C, 97%. See ref 31 for abbreviations.

**Scheme 18. Chelate-Controlled Mukaiyama Aldol Reaction and Initial Investigations of FG-Ketalization**

- Reagents and conditions: (a) LiHMDS·TMSCl·Et3N·THF, −78 °C, 89%; (b) MgBr2·OEt2·CH2Cl2, 0 °C, 93%, dr > 95:5; (c) HF·H2O·CH3CN, 0 °C, 92%; (d) TBSCl·imidazole·DMF, 99%. See ref 31 for abbreviations.

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The desired configuration of the spiroaminal 117 was verified by the key NOE interactions depicted in Figure 4.

To mask all reactive functionalities in the molecule, we then elected to protect the spiroaminal nitrogen of 117a as its Teoc derivative. This transformation proceeded in excellent selectivity when conducted in THF at high concentrations (TeocCl, 89%, >97:3 mixture of isomers). Somewhat surprisingly, all Teoc-protected intermediates proved to be slightly unstable to acidic conditions while their purification was readily executed using silica gel buffered with organic bases. The stage was now set for the olefination of the C26 ketone. We had deliberately postponed this transformation until after the closure of the FG bicyclic ketal in our synthesis plan to avoid any intermediates containing an \( \beta,\gamma \)-unsaturated ketone prone to isomerization.

After initial experiments using relatively nonbasic methylene-dianion equivalents such as the Takai-Nozaki reagent, the Tebbe reagent\(^{92}\) buffered with pyridine to avoid any C36-epimerization proved superior in this transformation. The Tebbe reagent could conveniently be prepared in situ from Cp2TiCl2 and AlMe3\(^{90}\) and afforded the desired olefinated product in 58% yield along with 41% of the recovered ketone.\(^{91}\) The yield for this step could be elevated to 78% after two recycles. The key NOE interactions of the spiroaminal portion remained unchanged from those depicted in Figure 4, thus verifying that the C36 spiroaminal had not epimerized during these latter transformations.

Finally, the oxidation of the C21-phenylsulfide moiety to sulfone 4 proceeded readily \( (\text{H}_2\text{O}_2, (\text{NH}_4)_6\text{Mo}_7\text{O}_{24}, 96\%) \) in analogy to the Dess-Martin oxidation described above, buffering of the reaction mixture with pyridine was crucial to suppress concomitant loss of the C21-sulfur substituent as an undesired side reaction. In summary, the above sequence allowed the efficient synthesis of the EFGHI-sulfone 4.

**Sulfone Coupling and Completion.** With the desired ABCD-aldehyde 3 and EFGHI-sulfone 4 in hand, we proceeded to the final fragment coupling to form the C20–C21 bond of azaspiracid utilizing the reaction conditions developed during our model studies (Scheme 14). Thus, the sulfone anion derived from 4 was generated with \( \text{BuLi} \) and added to aldehyde 3 followed by a quench at \(-78 \, ^{\circ}\text{C}\) with \( \text{H}_2\text{O} \) buffer. Gratifyingly, this procedure afforded a 50% overall yield of the readily separable lactol diastereomers 118 and 119 in nearly equal amounts (Scheme 21).\(^{94}\) Interestingly, the undesired alcohol 118

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**References:**

(91) At \(-40 \, ^{\circ}\text{C}\), the Tebbe reaction only proceeded to \( \sim60\% \) conversion (55% isolated yield) while the residual starting ketone could be reisolated in high yield. The combined 78% reported yield represents two recyclings of starting material. At higher temperatures, the conversions were higher but the amount of decomposition of the starting ketone was also significant, thus giving an overall lower mass recovery.
(94) The majority of the sulfone 4 could be recovered (78% based on the 50% coupling yield) as a mixture of 4 and its C21 epimer.
Scheme 21. Final Fragment Coupling and Completion of the Synthesis<sup>a</sup>

Reagents and conditions: (a) 4 (2.2 equiv), n-BuLi, −78 °C, then 3 (1.0 equiv), then NaOAc/AcOH buffer, −78 °C to RT, 50% (27% 118, 23% 119); (b) (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, −78 to −20 °C, 63%; (c) LiBH<sub>4</sub>(THF), CH<sub>2</sub>Cl<sub>2</sub>, 40 °C, dr > 20:1, 56%; (d) TBAF, THF, 0 °C, 93%; (e) Dess–Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (f) NaClO<sub>2</sub>, NaH<sub>2</sub>PO<sub>4</sub>, 78 °C to RT, 50% (27% 118, 23% 119). See ref 31 for abbreviations.

was obtained as an inseparable mixture of the C21-lactol and the corresponding hydroxyketone, thus suggesting a lower configurational stability of this C20 diastereomer. Next, the undesired lactol 118 was converted into the desired lactol 119 by an oxidation/reduction sequence. Oxidation to the corresponding C20 ketone was best effected under Swern conditions (oxalyl chloride, DMSO, Et<sub>3</sub>N, 63%), a transformation some-

mg of the target molecule. The spectroscopic data for (+)-azaspiracid-1 corresponded with those reported for (−)-azaspiracid (2) apart from the optical rotation which was of equal magnitude but of opposite sign ([α]<sup>21</sup>D +21.7 (c = 1.00, MeOH), natural (−)-azaspiracid-1 (2), [α]<sup>20</sup>D −21 (c = 0.1, MeOH),<sup>6</sup> synthetic (−)-azaspiracid-1 (2), [α]<sup>10</sup>D −19.0 (c = 0.07, MeOH)<sup>22</sup>).

Conclusions

In projects of this level of complexity, the casual reader is rarely informed of the intricacies associated with developing a viable synthesis. For structures such as azaspiracid, assembled from a number of complex subunits, once the viability of the successful route has been established, we routinely reanalyze the individual synths as a collection of “new targets”. If more aggressive approaches to the syntheses of these individual subunits can be perceived, the “first-generation” route to that subunit is re-evaluated as far as the final publication is concerned. In this article, we have attempted to reveal some of the hidden complexity associated with the reported synthesis of azaspiracid.

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Supporting Information Available: Experimental details and analytical data including copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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