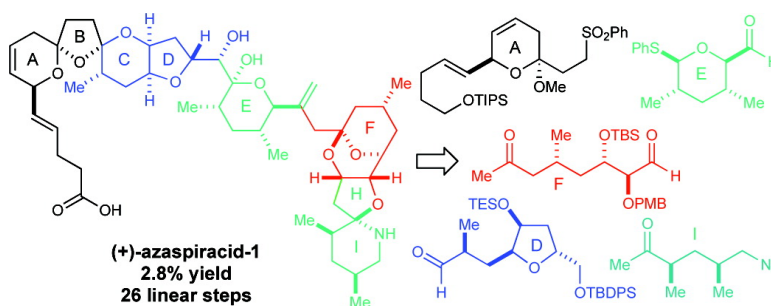Article

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

David A. Evans, Lisbet Kværnø, Travis B. Dunn, Andre# Beauchemin, Brian Raymer,
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(+)-azaspiracid-1
2.8% yield
26 linear steps

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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.[1] Subsequently, intoxications related to azaspiracid poisoning have been reported in several countries including the U.K., Norway,[2] Spain, France,[3] and Italy[4] as well as Morocco.[5] An active search for the causative toxin provided the motivation for its isolation by the Satake group in 1998.[6] 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 **1** 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.[6] 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 spectro-
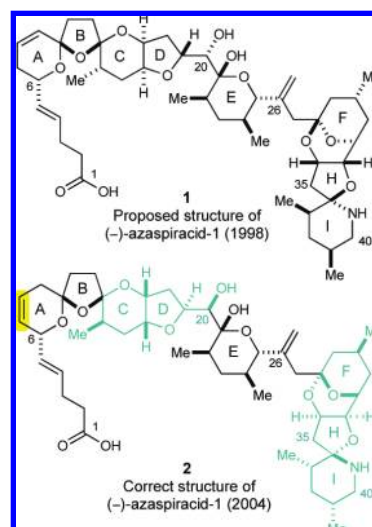

Figure 1. Originally proposed structure (**1**)[6] and correct structure of (−)-azaspiracid-1 (**2**).[22]

scopy[6,7] while the remaining analogues were identified by tandem mass spectrometry.[8]

The origin of these toxins has been proposed to be a marine dinoflagellate,[4] and their occurrence has subsequently been reported in multiple shellfish species including mussels, oysters, scallops, clams, and cockles.[9] Extensive studies of the azaspi-

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racids have revealed a number of toxic effects such as cytoxicity in mammalian cell lines,[10] teratogenic effects in finfish,[11] pertubation of cell adhesion,[12] disorganization of the Actin cytoskeleton,[13] and inhibition of the electrical activity of neuronal networks,[14] although the specific modes of all such actions of azaspiracids yet remain unclear.[15] 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,[16] Carter,[17,18] Forsyth,[19] and others.[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.[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
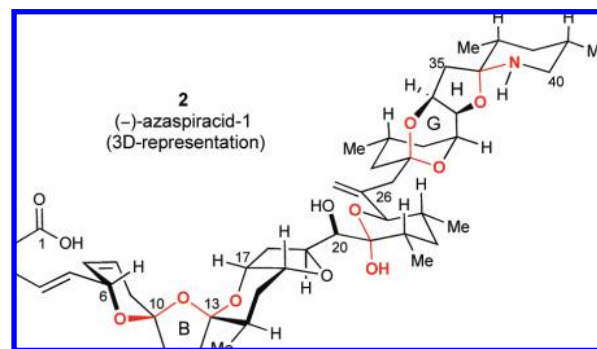

Figure 2. 3D-representation of (−)-azaspiracid-1 (**2**) highlighting stabilizing anomeric effects in the molecule.

structural assignment of (−)-azaspiracid-1 (**2**) in 2004.[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.[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 anomeric stabilization and steric effects (**2**, 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**[6] contained only one anomeric effect (not shown), the ABC-moiety of the corrected (−)-azaspiracid-1 structure (**2**)[22] incorporates two stabilizing anomeric 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.

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Scheme 1. Retrosynthetic Analysis of (+)-Azaspiracid-1 (*ent*-**2**)[a]
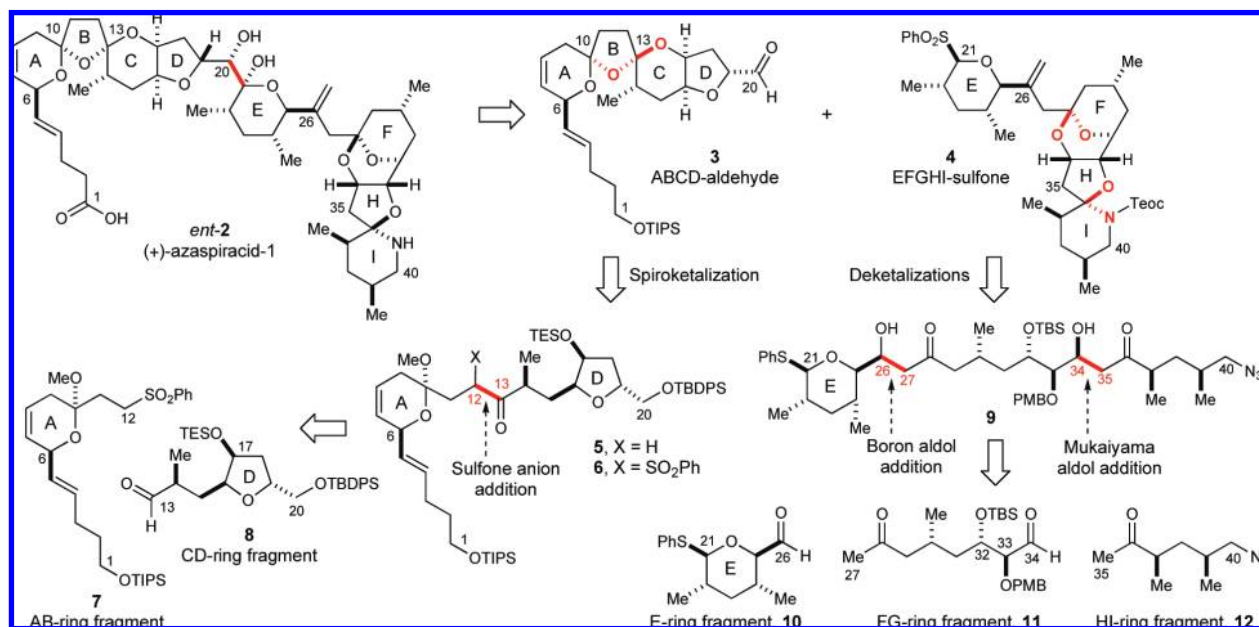
[a] See ref 31 for abbreviations.

In our own studies,[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 aldehyde **3**. This strategy could provide a convergent approach to (+)-azaspiracid-1 since all 9 rings are formed prior to this final sulfone anion addition. Related sulfonyl carbanion additions have substantial literature precedents, both in the original investigations from the carbohydrate field[25,26] and subsequently in several advanced fragment couplings in some of our previous total synthesis projects.[27−29]

The plan for the deconstruction of the ABCD synthon **3** involves a thermodynamically controlled spiroketalization event

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 assemblage 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[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**.
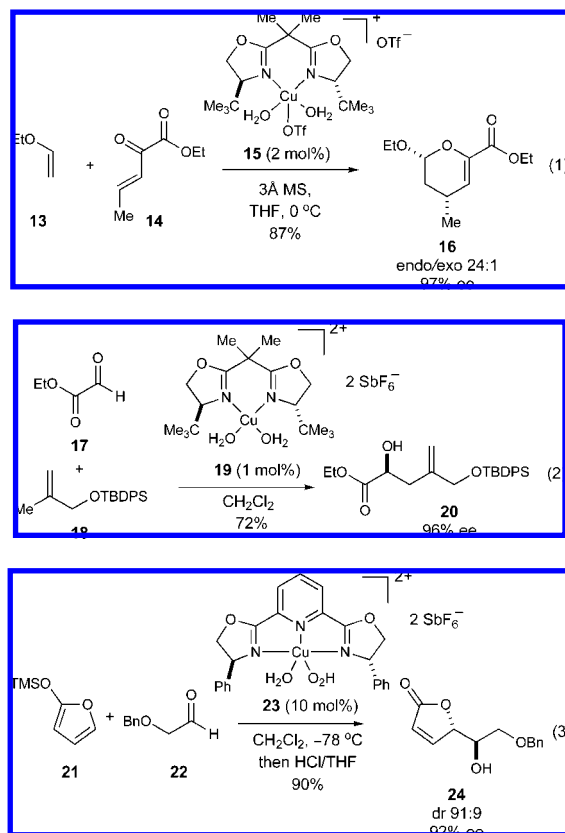
The integration of catalytic enantioselective processes into our synthesis projects has been an ongoing objective in our research program. In this regard, the Cu-catalyzed hetero-Diels−Alder reaction to give methyl-substituted dihydropyrans

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(31) Abbreviations: Ac = acetyl, Bn = benzyl, Boc = *t*-butyloxycarbonyl, CBS = Corey-Bakshi-Shibata, COD = 1,5-cyclooctadiene, *m*-CPBA = *m*-chlorperbenzoic acid, Cy = cyclohexyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, Dess-Martin periodinane = 1,1,1-tris(acetoxy)1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one, DIBALH = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, HMPA = hexamethylphosphoramide, HPLC = high pressure liquid chromatography, LDA = lithium diisopropylamide, LiDBB = lithium di-*tert*-butyl biphenylide, LiHMDS = lithium hexamethyldisilazide, Mes = 2,4,6-trimethylphenyl, pyr = pyridine, PG = protecting group, PMB = 4-methoxybenzyl, PPTS = pyridinium *p*-toluenesulfonate, RaNi = Raney Nickel, RT = room temperature, *L*-Selectride = lithium tri-*sec*-butylborohydride, TBAF = tetrabutylammonium fluoride, TBAI = tetrabutylammonium iodide, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, Tebbe reagent = (*μ*-chloro)(*μ*-methylene)-bis(cyclopentadienyl)(dimethylaluminum)titanium, Teoc = 2-(trimethylsilyl)ethoxycarbonyl, TES = triethylsilyl, TIPS = triisopropylsilyl, TMS = trimethylsilyl, Tr = trityl (triphenylmethyl), trisyl = 2,4,6-trisisopropylbenzenesulfonyl, Ts = *p*-toluenesulfonyl.

(eq 3)[32] was specifically developed for the synthesis of the azaspiracid E-ring fragment **10**. Independently, the glyoxylate-ene reaction to afford α-hydroxy-γ,δ-unsaturated esters (eq 3)[33] could be used to form the C17 stereocenter of the CD-ring fragment **8** while the Mukaiyama aldol reaction to furnish unsaturated lactones featuring 1,2-anti diol arrays (eq 3)[34] could be explored to construct the C32−C33 motif of the FG-ring fragment **11**.

Figure 3. Depiction of C6 CO*-orbital in AB-ring fragment **7**.

Scheme 2. Synthesis of the C1−C12 Chain of the AB-Ring Fragment[a]

[a] Reagents and conditions: (a) **27** (5 mol%), CH₂Cl₂, 40 °C, 88%; (b) PhSH, Et₃N, CH₂Cl₂; (c) allenylMgBr, Et₂O, 0 °C, 96% (2 steps); (d) **29**, *n*-BuLi, Et₂O, −78 °C, then MgBr₂·OEt₂, then **30**, −78 to 0 °C, THF added, then RT; (e) Ac₂O, DMAP, pyr, CH₂Cl₂, 83% (2 steps). See ref 31 for abbreviations.

attempted cross metathesis[35] between alkene **25**[36] and acrylate **26**[37] was low yielding with the Grubbs second-generation catalyst[38] (10−35% yield), the more stable Grubbs-Hoveyda catalyst **27**[39] was considerably more efficient, affording Weinreb amide **30** in excellent yield (88%). The C7−C12 fragment was introduced as the racemic acetylene **29**, 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 **29** to the unsaturated Weinreb amide **30**. After considerable experimentation, optimum conditions involved the conversion of acetylene **29** to its derived Grignard reagent by deprotonation with *n*-butyllithium and transmetalation with MgBr₂·OEt₂[40] 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 **31** in 83% overall yield for the 2 steps.

On the basis of literature precedents for the enantioselective reduction of ene-ynones,[41] the C6-stereocenter was introduced with high enantioselectivity in a supra-stoichiometric CBS-reduction[42] using 2 equiv of oxazaborolidone **32** and BH₃·SMe₂ to afford the desired alcohol **33** (86%, 94−97% ee, Scheme

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 ketal 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−O bond in ketal **7**. 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
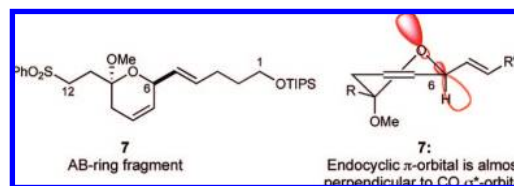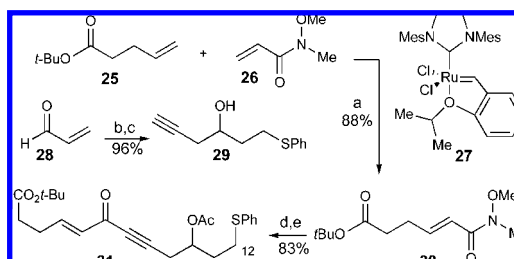
(32) (a) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3372–3375. (b) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635–1649.

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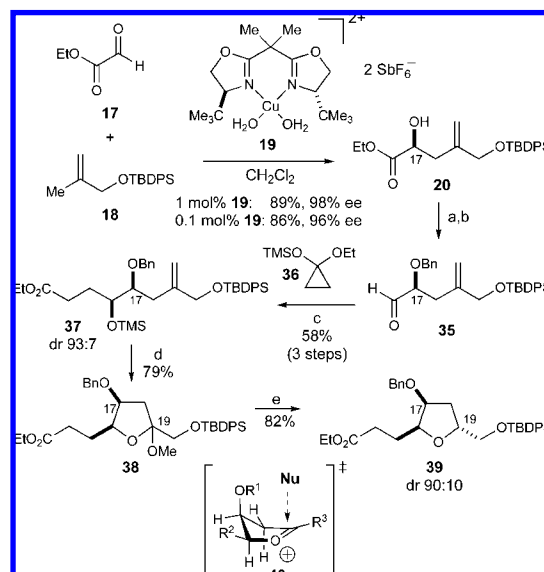
(35) (a) Choi, T. L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277–1279. (b) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923.

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(41) (a) Garcia, J.; Lopez, M.; Romeu, J. *Synlett* **1999**, 429–431. (b) Garcia, J.; Lopez, M.; Romeu, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2617–2626. (c) Yun, H. D.; Danishefsky, S. J. *J. Org. Chem.* **2003**, *68*, 4519–4522.

Scheme 3. Synthesis of the AB-Ring Fragment 7[a]
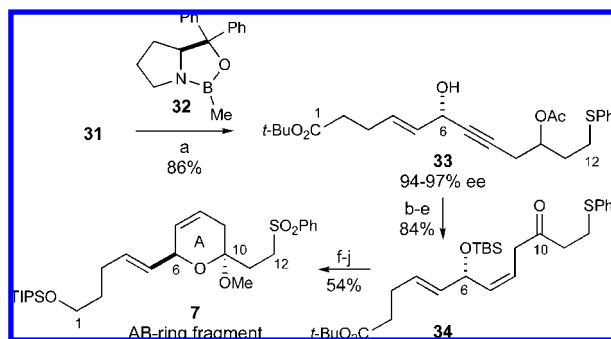
[a] Reagents and conditions: (a) **32** (2 equiv), BH$_3$·SMe$_2$, THF, 0 °C, 86%, 94−97% ee; (b) H$_2$ (1 atm), Pd/CaCO$_3$/Pb (5%), pyr, benzene; (c) TBSCl, DMAP, imidazole, DMF, 92%, 3−5% C4−C5 alkane (2 steps); (d) K$_2$CO$_3$, MeOH; (e) SO$_3$·Pyr, DMSO, i-Pr$_2$NEt, CH$_2$Cl$_2$, −25 °C, 91% (2 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) TIPSCl, imidazole, DMF, 98%. See ref 31 for abbreviations.

3).[43] Initial attempts to use a catalytic amount of oxazaborolidone **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 sulfoxide.[44] A Parikh-Doering oxidation[45] 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 excess 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 lactol methyl ether in excellent yield (PPTS, MeOH, 92%). This was the first time among various substrates investigated that the C6 divinylcarbinol moiety proved stable to acidic conditions, thus validating the anticipated stability of the C6-lactol (Figure 3) and providing us with a credible lead for the anticipated spiroketalization. Finally, the sulfide moiety was oxidized to

(42) (a) Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc., Chem. Commun.* **1981**, 315–317. (b) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun.* **1983**, 469–470. (c) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553. (d) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926. (e) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1987–2012.
(43) After silylation of the C6-alcohol, the four diastereomers formed in the reduction step were separable by HPLC and allowed for the determination of the enantiomeric excess.
(44) Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett.* **2003**, *5*, 575–578.
(45) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

Scheme 4. Initial Synthesis of the CD-Ring Fragment[a]

[a] Reagents and conditions: (a) NaH, BnBr, CH$_2$Cl$_2$, 0 °C to RT, 99%; (b) DIBALH, toluene, −94 °C; (c) ZnCl$_2$, **36**, 59% (2 steps), dr 93:7; (d) O$_3$, MeOH, CH$_2$Cl$_2$, −78 °C, then Me$_2$S, RT, 79%; (e) Et$_3$SiH, BF$_3$·OEt$_2$, CH$_2$Cl$_2$, −78 °C, 82%, dr 90:10. See ref 31 for abbreviations.

the derived sulfone (H$_2$O$_2$, (NH$_4$)$_6$Mo$_7$O$_{24}$, 88%). 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 synthon was reduced and protected as its silyl ether (LiAlH$_4$, 92%; TIPSCl, 98%), thus concluding the synthesis of the desired AB-ring fragment **7** and its carboxylate analogue **34** in 13 linear steps from **25**.
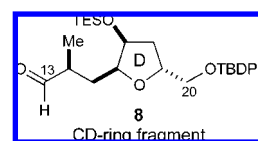
Synthesis of the CD-Ring Fragment 8. Initial Synthesis via a Stereoselective C14-Methylation. The first of two syntheses of this fragment is illustrated in Scheme 4. In our synthesis of this synthon, we envisioned that the enantioselective Cu^{2+}-catalyzed glyoxylate-ene reaction developed in these laboratories could provide the initial C17-stereocenter (eq 3).[33] 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**[46] (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).

(46) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541–4544.

The resultant α-hydroxy ester **20** was subsequently benzylated (NaH, BnBr, 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**[47] was then prepared in situ and added stereoselectively to aldehyde **35** according to the Kuwajima procedure.[48] In accordance with presumed chelate control exerted by the Zn^{2+} 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 Et_3SiH mediated by $BF_3 \cdot OEt_2$ to afford the desired trisubstituted tetrahydrofuran **39** (82%, dr 90:10). The observed diastereolectivity 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 δ-hydroxy esters such as **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]
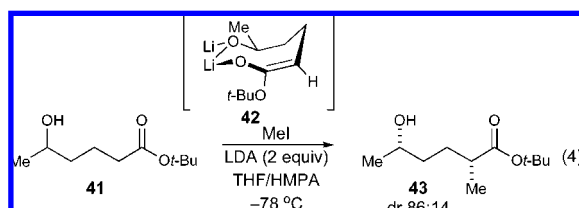
Prior to the actual methylation event, ethyl ester **39** was converted into its derived amide **44** with the magnesium amide of morpholine[51] (82%, Scheme 5). It was assumed that $A^{1,3}$ strain in amide **44** would prevent bis(alkylation), thus allowing the use of excess external base to achieve 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).

Scheme 5. C14-Methylation[a]
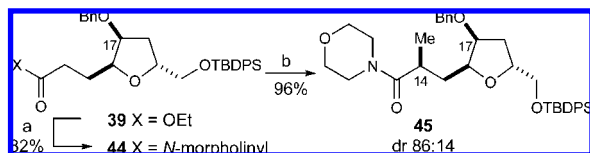
[a] Reagents and conditions: (a) *i*-PrMgCl, morpholine, THF, −78 to −20 °C, 82%; (b) LiHMDS, MeI, THF, −78 °C, 96%, dr 86:14. See ref 31 for abbreviations.

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

**Scheme 6.** Second Synthesis of the CD-Ring Fragment **8**[a]
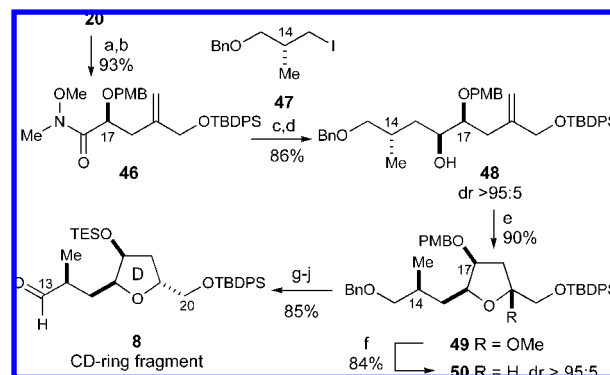
[a] Reagents and conditions: (a) MeNH(OMe)·HCl, Me₃Al, THF, 98%; (b) PMBBr, NaH, DMF, 0 °C, 95%; (c) **47**,[53] *t*-BuLi, Et₂O, −78 °C, then **46**, 90%; (d) *L*-Selectride, THF, −78 °C, 96%, dr >95:5; (e) (i) O₃, pyridine, CH₂Cl₂/MeOH (5:1 v/v), −78 °C, then Me₂S, −78 °C to RT; (ii) PPTS, MeOH, 90%; (f) Et₃SiH, BF₃·OEt₂, 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.

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, Me₃Al, 98%). The C17 hydroxy group was then protected as its derived PMB ether **46** under standard basic conditions with no epimerization of the lone stereocenter (PMBBr, NaH, DMF, 95%), presumably prevented by $A^{1,3}$ strain of the Weinreb amide.

Metalation of the readily available iodide **47**[53] with *t*-BuLi[54] followed by addition of Weinreb amide **46** then introduced the remaining 4-carbon subunit (−78 °C, 90%). Notably, optimal results were obtained when 1.5 equiv of *t*-BuLi relative to the iodide **47** were used, while 2 equiv of *t*-BuLi afforded substantial amounts of the undesired *t*-Bu-ketone. The resulting α-alkoxyketone was then reduced with *L*-Selectride to afford alcohol **48** as the only detectable diastereomer (96%, dr >95:5). This stereoselective reduction, presumably the result of Felkin control, was confirmed by advanced Mosher's ester analysis.[55] Careful ozonolysis of the 1,1-disubstituted olefin in the presence of Sudan III dye as an indicator[56] allowed for the selective oxidative cleavage of the olefin (O₃, −78 °C, then Me₂S) without

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(51) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461–5464.
(52) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989–993.
(53) (a) Vong, B. G.; Abraham, S.; Xiang, A. X.; Theodorakis, E. A. *Org. Lett.* **2003**, *5*, 1617–1620. (b) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216.
(54) (a) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404–5406. (b) Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406–5409.
(55) (a) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
(56) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807–810.

Scheme 7. Synthesis of the ABCD-aldehyde **3**[a]
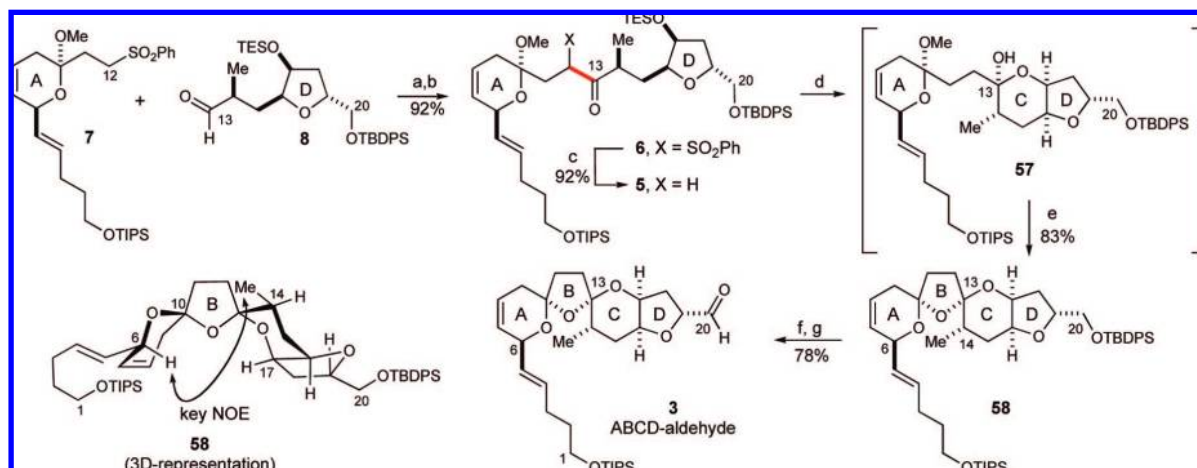
[a] Reagents and conditions: (a) **7** (1.6 equiv), LDA, THF, −78 °C; then **8** (1.0 equiv); (b) Dess-Martin periodinane, pyr, CH$_2$Cl$_2$, 92% (2 steps); (c) Na/Hg (5%), NaH$_2$PO$_4$, THF/MeOH, −10 °C, 92%; (d) TBAF, THF, −20 °C (workup); (e) PPTS, CH$_2$Cl$_2$, 0 °C (83%, 2 steps); (f) TBAF, AcOH, DMF, 86%; (g) SO$_3$·Pyr, DMSO, *i*-Pr$_2$NEt, CH$_2$Cl$_2$, −30 °C, 91%. See ref 31 for abbreviations.

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 Et$_3$SiH mediated by BF$_3$·OEt$_2$ 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.
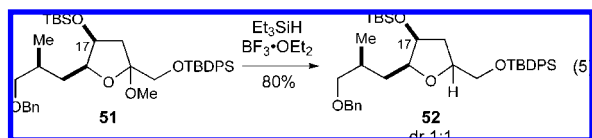
Since a labile C17-silyl ether was required for the projected ketalization events, the PMB group was exchanged for a TES ether by oxidative cleavage with DDQ (94%) and reprotection under standard conditions (TESCl, 97%, Scheme 6). As this TES ether proved to be labile to standard palladium-catalyzed hydrogenolysis conditions, the terminal benzyl ether was removed under radical anion conditions (LiDBB,[57] 96%). Finally, a Parikh-Doering oxidation[45] 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**.

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 α to the
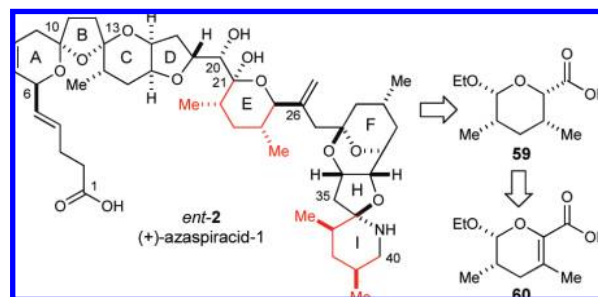
(57) (a) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924–1930. (b) Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854–860.

C12-sulfone under the appropriate experimental conditions in the presence of a C1 *t*-Bu ester, although the α-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 sequence[58] 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).
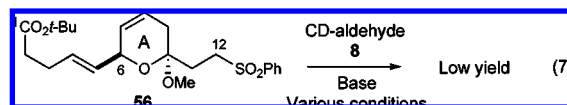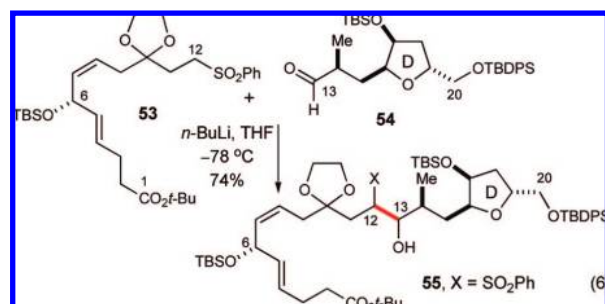
Unfortunately, as eluded to earlier in our discussion of Figure 3, adducts **55** incorporating acyclic C6-divinylcarbinol moieties proved to be too unstable to successfully participate in the subsequent derivatization into the ABCD-bis(spiroketal) under a variety of conditions and were abandoned for further studies. However, much to our surprise, the corresponding addition of the superficially similar sulfone **56** to C17-TES-protected aldehyde **8** was nonselective for C12 deprotonation under a variety of experimental conditions (eq 7). These findings suggest that although α-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 α-deprotonations.

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

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,[18] 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[59] 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, NaH$_2$PO$_4$)[60] 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 CH$_2$Cl$_2$. Under these conditions, the desired bis-(spiroketal) isomer **58** was obtained in 83% yield (2 steps).[61] The inclusion of a hydroxylic solvent such as MeOH led to the undesired formation of significant amounts of dimethylketals under otherwise identical spirocyclization conditions. The desired, thermodynamically favored bis(spiroketal) configuration in **58** was established by an NOE interaction between H6 and the methyl group at C14 (see 3D-depiction of **58**) as also previously reported for analogous azaspiracid-derived bis-(spiroketal) structures.[6,22] Finally, the C20 terminus was elaborated by the selective removal of the TBDPS ether[62] (TBAF, AcOH, 86%) followed by a Parikh-Doering oxidation[45] (SO$_3$·pyr, DMSO, 91%) to furnish the desired aldehyde **3**. In summary, the above convergent sequence afforded the fully elaborated ABCD-aldehyde.

Enantioselective Hetero-Diels−Alder Approach to the syn-1,3-Dimethyl Synthons of Azaspiracid-1. With a viable route to the ABCD-portion of azaspiracid-1 established, we turned our attention to the remaining EFGHI-region of the molecule. Initially, we focused on synthesizing the E-ring fragment to investigate potential strategies to form the central C20−C21 bond as will be discussed in the following sections. By inspection, two syn 1,3-dimethyl synthons of the same configuration are embedded in the E- and the I-rings of azaspiracid-1 (Scheme 8). We were particularly attracted to the possibility of constructing both of these subunits from the common precursor **59**. Tetrahydropyran **59** could potentially be accessible from dihydropyran **60**, which could be prepared using the hetero-Diels−Alder reaction previously developed in our laboratories (eq 3)[32] for this particular target structure.

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(59) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
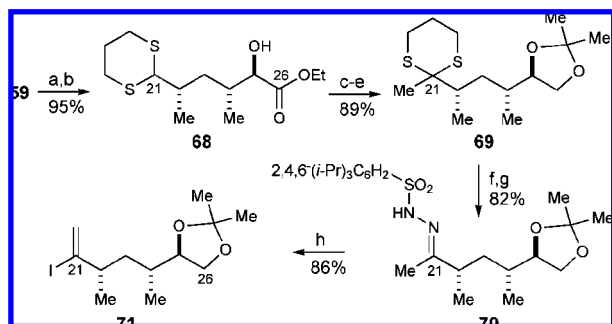(60) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477–3478.
(61) The selective TES-removal was accompanied by minor loss of the C1 TIPS protecting group. Since the crude mixture of **60** was subjected directly to the PPTS-mediated spirocyclization, 76% of **61** was obtained directly in the spirocyclization event while additional 7% of **61** was obtained after reinstallation of the C1 TIPS substituent.
(62) Crouch, R. D. *Tetrahedron* **2004**, *60*, 5833–5871.

Scheme 8. syn-1,3-Dimethyl Synthons Embedded in Azaspiracid-1

Scheme 9. Synthesis of the Tetrahydropyran **59**[a]
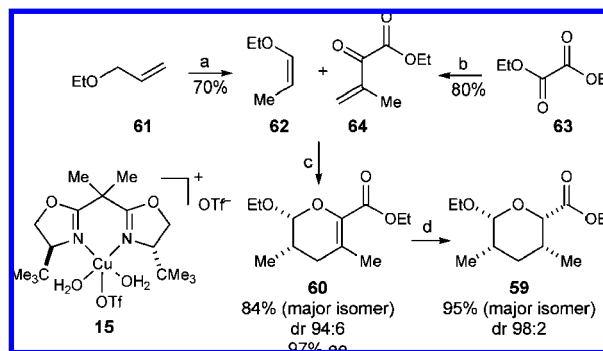
[a] Reagents and conditions: (a) KO*t*-Bu, DMSO, 70 °C, 70%; (b) 2-propenylMgBr, THF/Et$_2$O, −78 °C, 80%; (c) **15** (2 mol%), 3Å MS, Et$_2$O, −40 °C, dr 94:6, 97% ee, 84% **60**; (d) H$_2$ (1 atm), Pd/C (5 mol%), EtOAc, dr 98:2, 95% **59**. See ref 31 for abbreviations.

The two components of the hetero-Diels−Alder reaction, **62**[63] and **64**,[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,[32] these conditions gave rise to a mixture of *cis* and *trans* diastereomers of dihydropyran **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 dihydropyran **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 tetrahydropyran **59** in excellent yield and diastereoselectivity (H$_2$, 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 tetrahydroparan **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-

(63) Taskinen, E.; Virtanen, R. *J. Org. Chem.* **1977**, *42*, 1443–1449.
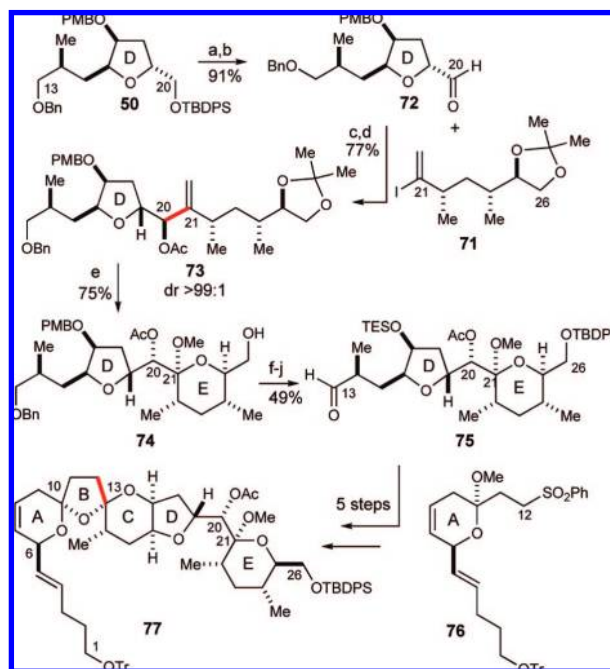(64) Rambaud, M.; Bakasse, M.; Duguay, G.; Villieras, J. *Synthesis* **1988**, 564–566.

Scheme 10. Synthesis of the E-Ring Vinyl Iodide 71[a]

[a] Reagents and conditions: (a) *t*-BuOK, THF, −50 °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) *t*-BuLi, HMPA, THF, −78 °C, then MeI, 92%; (f) Hg(ClO$_4$)$_2$, CaCO$_3$, H$_2$O, THF, 88%; (g) trisylhydrazine, THF, 93%; (h) *t*-BuLi, THF, −78 to 0 °C, then I$_2$, −78 °C, 86%. See ref 31 for abbreviations.

sembled. One possible option we investigated as a viable C20−C21 fragment coupling was a chelate-controlled vinyl-lithium addition[65,66] to a D-ring aldehyde synthon **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.
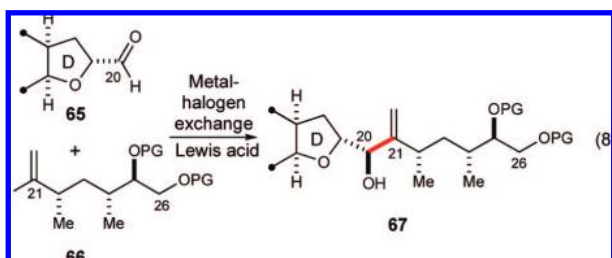
Synthesis of the E-Ring Vinyl Iodide 71. In order to arrive at an appropriately protected vinyl iodide fragment **66**, the ester substituent of tetrahydropyran **59** was epimerized to its equatorial diastereomer (*t*-BuOK, THF, −50 °C, Scheme 10) prior to pyran ring opening to give the dithiane **68** (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,[67] 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 (MeI, *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$_4$)$_2$, CaCO$_3$,[68] 88%). Finally, the desired vinyl iodide

(65) Peterson, S. L. Ph. D. Thesis, Harvard University, Cambridge, 2006.
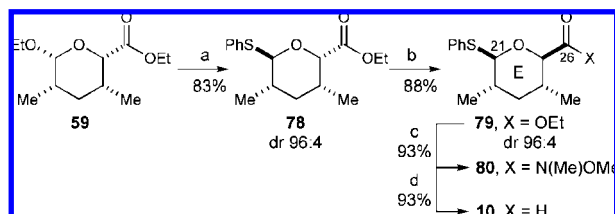(66) (a) Hayward, M. M.; Roth, R. M.; Duffy, K. J.; Dalko, P. I.; Stevens, K. L.; Guo, J. S.; Kishi, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 192–196. (b) Heathcock, C. H.; McLaughlin, M.; Medina, J.; Hubbs, J. L.; Wallace, G. A.; Scott, R.; Claffey, M. M.; Hayes, C. J.; Ott, G. R. *J. Am. Chem. Soc.* **2003**, *125*, 12844–12849.
(67) (a) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231–237. (b) Smith, A. B.; Condon, S. M.; McCauley, J. A.; Leazer, J. L.; Leahy, J. W.; Maleczka, R. E. *J. Am. Chem. Soc.* **1997**, *119*, 947–961.
(68) Bernardi, R.; Ghiringhelli, D. *J. Org. Chem.* **1987**, *52*, 5021–5022.

Scheme 11. Synthesis of the ABCDE-region 77[a]

[a] Reagents and conditions: (a) TBAF, AcOH, THF 97%; (b) SO$_3$·Pyr, DMSO, *i*-Pr$_2$NEt, CH$_2$Cl$_2$, −30 °C, 94%; (c) **71** (2 equiv), *t*-BuLi, Et$_2$O, −78 °C, then **72**, MgBr$_2$·OEt$_2$,[40] CH$_2$Cl$_2$, −20 °C, 80%, dr >99:1; (d) Ac$_2$O, DMAP, Et$_3$N, CH$_2$Cl$_2$, 96%; (e) (i) 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),[71] EtOH, 93%; (j) SO$_3$·Pyr, DMSO, *i*-Pr$_2$NEt, CH$_2$Cl$_2$, −30 °C, 75%. See ref 31 for abbreviations.

was conveniently installed in a Shapiro reaction[69] via an intermediate trisylhydrazone.[70] Thus, the methyl ketone was converted into the intermediate trisylhydrazone **70** (trisylhydrazine, 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 **71** in 86% overall yield. In summary, this sequence provided the desired E-ring vinyl iodide **71** 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[45] to the corresponding D-ring aldehyde **72** (SO$_3$·pyr, DMSO, 94%, Scheme 11). Metal-halogen exchange of the vinyl iodide fragment **71** was then effected with *t*-BuLi in Et$_2$O at −78 °C followed by cannulation of this vinyllithium solution into a solution of the aldehyde **72** precomplexed to MgBr$_2$·OEt$_2$ (prepared in an Et$_2$O/toluene solution[40]) in CH$_2$Cl$_2$. The observed diastereoselectivity was excellent at temperatures ranging from −78 to 0 °C while the best yields were obtained at −20 °C (80%, dr >99:1). With 2 equiv of vinyl iodide **71** relative to the aldehyde **72**, on the order of 0.6−0.7 equiv of

(69) Shapiro, R. H.; Heath, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5734–5735.
(70) (a) Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147–154. (b) Chamberlin, A. R.; Bloom, S. H. *Org. React.* **1991**, *45*, 1–84.
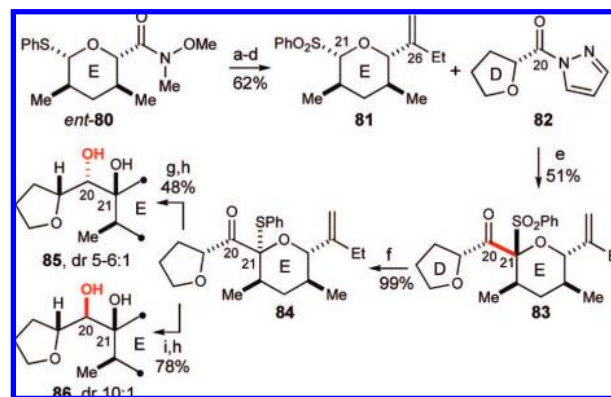
Scheme 12. Synthesis of Cyclic E-Ring Fragments.[a]

[a] Reagents and conditions: (a) PhSH, BF$_3$·OEt$_2$, CH$_2$Cl$_2$, −20 °C, dr 96:4, 83% **78**; (b) *t*-BuOK, THF, −50 °C, dr 96:4, 88% **79**; (c) Me(OMe)NH·HCl, *i*-PrMgCl,[51] THF, −78 to −20 °C, 93%; (d) **79**, DIBALH, toluene, −94 to −78 °C, 93%. See ref 31 for abbreviations.

Scheme 13. Model Studies of Final C20−C21 Sulfone Fragment Coupling and Product Elaboration[a]

[a] Reagents and conditions: (a) EtMgBr, THF, −78 °C, 99%; (b) TMSCH$_2$Li, THF, −78 °C, 70%; (c) KH, THF, 99%; (d) H$_2$O$_2$, Na$_2$WO$_4$·2H$_2$O,[72] MeOH, 91%; (e) **81** (1 equiv), LDA (1.2 equiv), THF, then **82** (1.5 equiv), −78 °C, dr(C21): 6:1, 51% **83**; (f) PhSLi, Et$_2$O, −78 °C, 99%; (g) KHBEt$_3$, THF, −78 to −20 °C, dr 5-6:1, 56% major isomer; (h) HgCl$_2$, pH 7 buffer, MeCN/THF, 0 °C, 86%; (i) KHBEt$_3$, CH$_2$Cl$_2$, −78 to −20 °C, dr 10:1, 91% major isomer. See ref 31 for abbreviations.

vinyl iodide **71** could additionally be recovered by a final I$_2$-quench, thus emphasizing the stability of the vinylmetal species in CH$_2$Cl$_2$.

Subsequently, the coupled product was acetylated under standard conditions to give **73** (Ac$_2$O, 96%). Careful ozonolysis of the 1,1-disubstituted olefin in the presence of Sudan III as a color indicator[56] 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 ketalyzed 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 (TBDPSCl, imidazole), PMB-removal (DDQ, 78%, 2 steps), and C17 TES installation (TESCl, imidazole, 90%). The final debenzylation in the presence of the TES silyl ether proceeded readily using W-2 RaNi[71] (H$_2$, RaNi, EtOH, 93%) followed by a Parikh-Doering oxidation[45] to give the C13 aldehyde **75** (SO$_3$·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 BF$_3$·OEt$_2$ provided thioglycoside **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 thioglycoside, 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 substoichiometric amounts of BF$_3$·OEt$_2$ 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 mol % 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*-acylbenzotriazole 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*-acylpyrazole **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 MgBr$_2$·OEt$_2$ and *i*-Pr$_2$NEt in relatively nonpolar solvents (CH$_2$Cl$_2$ or Et$_2$O, −20 °C, >80% yield). Subsequently, we discovered that the same transformation could be effected in quantitative yield under very mild conditions (PhSLi, Et$_2$O,

(71) Mozingo, R. *Org. Synth.* **1955**, *3*, 181–183.

(72) Blacklock, T. J.; Butcher, J. W.; Sohar, P.; Lamanec, T. R.; Grabowski, E. J. J. *J. Org. Chem.* **1989**, *54*, 3907–3913.
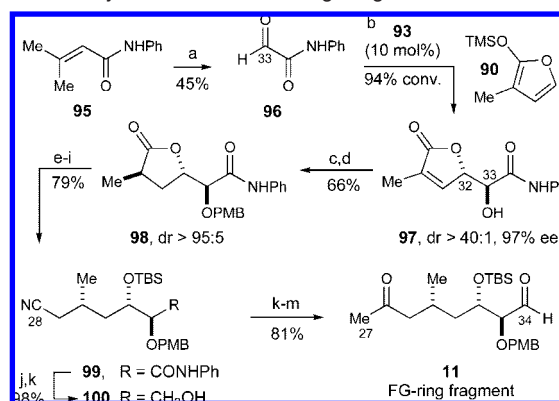
Scheme 14. Model Studies of Final C20–C21 Sulfone Fragment Coupling via the C20-Aldehyde **3**[a]
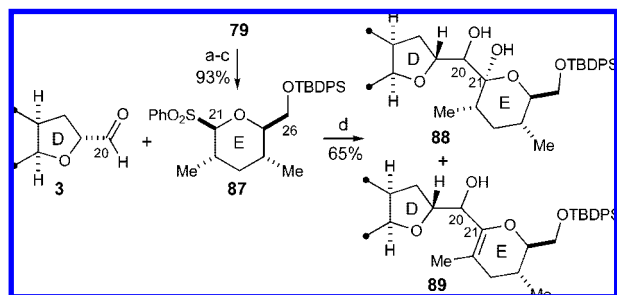
[a] Reagents and conditions: (a) LiAlH$_4$, Et$_2$O, −20 °C; (b) TBDPSCl, imidazole, DMF, 99% (2 steps); (c) *m*-CPBA, NaHCO$_3$, CH$_2$Cl$_2$, 94%; (d) **87** (2.3 equiv), *n*-BuLi, THF, −78 °C, then **3** (1.0 equiv), then sat. aq. NH$_4$Cl, −78 °C to RT, 65%, 3:1 **88**:**89**. See ref 31 for abbreviations.

Scheme 15. Synthesis of the FG-Ring Fragment **11**[a]

[a] Reagents and conditions: (a) O$_3$, MeOH, CH$_2$Cl$_2$, −78 °C, then Me$_2$S, 61%; then vacuum sublimation, 73%; (b) 10 mol% **93**, CH$_2$Cl$_2$, −78 °C, 94% conversion, dr >40:1, 97% ee (67% after recrystallization, >99% ee); (c) H$_2$ (1 atm), 2 mol% [(COD)Ir(PCy$_3$)(py)]PF$_6$, CH$_2$Cl$_2$, 98%, dr >95:5; (d) PMBBr, NaH, DMF, −40 to −20 °C, 67%; (e) KHBEt$_3$, THF, 0 °C to RT, 94%; (f) TBSCl, imidazole, DMF, 99%; (g) HF·pyr, THF, −10 °C, 87%; (h) TsCl, imidazole, DMAP, pyridine, 98%; (i) NaCN, DMSO, 55 °C, 99%; (j) Boc$_2$O, DMAP, CH$_3$CN, 99%; (k) LiBH$_4$, H$_2$O, THF, 0 °C to RT, 99%; (l) TMSCl, imidazole, CH$_2$Cl$_2$, 99%; (m) MeLi, Et$_2$O, 0 °C, 84%; (n) SO$_3$·Pyr; DMSO, *i*-Pr$_2$NEt, CH$_2$Cl$_2$, −30 °C, 99%. See ref 31 for abbreviations.

−78 °C, 99%) in 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 (KHBEt$_3$ in THF or CH$_2$Cl$_2$, dr 5–6:1 or 1:10, respectively). Finally, the phenylsulfide moieties could be readily converted with aqueous HgCl$_2$ 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 ^{1}H NMR data for these four C19–C20 diastereomeric lactols with the published ^{1}H NMR spectrum of azaspiracid-1[6] 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**).[22]

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 region of the azaspiracid skeleton would be to utilize aldehyde **3** directly, a strategy with some promising precedent in the literature.[29] The well-known competing side reaction in such a transformation is the sulfinate elimination to the corresponding C21-dihydropyran.[25,28] Nevertheless, when this reaction was carried out with aldehyde **3** and the E-ring model sulfone **87** followed by a quench with slightly acidic buffer at −78 °C, the desired lactols **88** were preferentially formed over dihydropyrans **89** (3:1 ratio, 65% combined yield). The desired lactols **88** could subsequently be interconverted by an oxidation/ reduction sequence of the C20 moiety to give either C20 alcohol in high stereoselectivty. A limited number of subsequent studies with several bases (*n*BuLi, LDA), additives (HMPA, MgBr$_2$·OEt$_2$), solvents (THF, Et$_2$O, and CH$_2$Cl$_2$ for precom-

plexation of the aldehyde), and different quenching buffers all failed to provide a full conversion of aldehyde **3**, a goal yet to be achieved, and did not improve the ratio of desired lactols **88** to dihydropyrans **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.
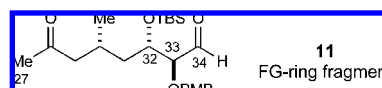

Synthesis of the FG-Ring Fragment 11. In the synthesis of the FG-ring fragment **11**, we envisioned that the C32–C33 anti diol array could be efficiently obtained by an extension of our enantioselective catalytic Mukaiyama aldol reaction of siloxy-furan **21**[73] and (benzyloxy)acetaldehyde **22**[74] (eq 9, entry A).[34] In contrast to the original studies where hydrated complex **23** was formed in situ with CuCl$_2$·2H$_2$O,[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 CF$_3$CH$_2$OH as a silicon-scavenging reagent[75] 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-

(73) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607–626.

(74) (a) Danishefsky, S. J.; Deninno, M. P. *J. Org. Chem.* **1986**, *51*, 2615–2617. (b) Garner, P.; Park, J. M. *Synth. Commun.* **1987**, *17*, 189–194.

(75) (a) Kitajima, H.; Katsuki, T. *Synlett* **1997**, 568–570. (b) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595–598. (c) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134–9142. (d) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480–4491.

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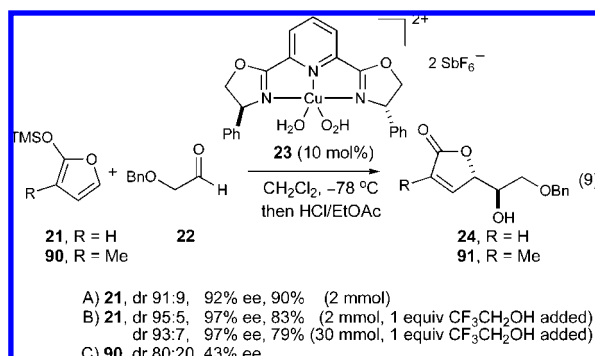

Further studies revealed that the corresponding Sn(2+)-catalyzed aldol reaction[77] with Sn(2+)-complex **93** alternatively afforded optimal results in the desired transformation. Thus, methyl-substituted siloxyfuran **90** underwent stereoselective aldol addition with ethyl glyoxalate (**92**) to give 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.
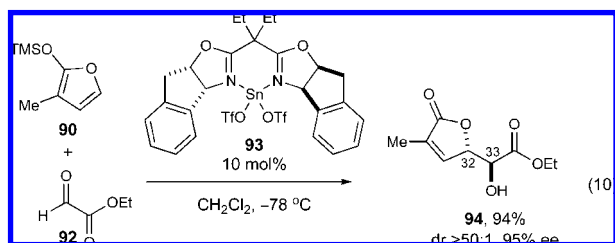
Another practical variant of this addition process using *N*-phenyl glyoxamide **96**,[78] readily prepared by ozonolysis of olefin **95** and dehydration of the intermediary glyoxamide hydrate by vacuum sublimation, is depicted in Scheme 15 and afforded adduct **97** (94% conversion, dr >40:1, 97% ee) 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 **97** was its propensity to undergo highly diastereoselective directed hydrogenations to install the methyl-bearing stereocenter, a goal that was not successfully achieved with the corresponding ethyl ester **94** under the same range of hydrogenation conditions. The directed hydrogenation of **97** proved to be optimal with Crabtree's catalyst[79] that afforded the resulting lactone as a single isomer (H₂, [(COD)Ir-

Scheme 16. Auxiliary-Based Synthesis of the HI-Ring Fragment **12**[a]
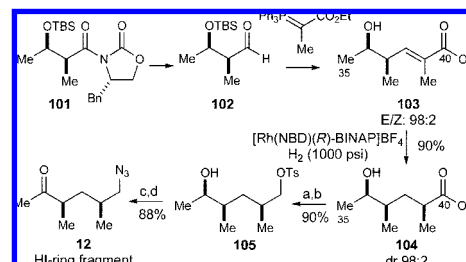
[a] Reagents and conditions: (a) **104**, LiAlH₄, THF, 0 °C, 95%; (b) TsCl, Et₃N, CH₂Cl₂, 0 °C to RT, 95%; (c) NaN₃, TBAI, DMF, 60 °C, 93%; (d) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, −78 °C to RT, 95%. See ref 31 for abbreviations.

(PCy₃)(py)]PF₆, 98%, dr >95:5). Subsequently, PMB-protection of the secondary alcohol to give **98** was sufficiently chemoselective under basic conditions (PMBBr, NaH, 67%) 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 (KHBEt₃, 94%), persilylated (TBSCl, 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 nitrile 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 nitrile in a step that required transient protection of the primary alcohol to effect full conversion (TMSCl, 99%). Thus, the nitrile was converted into the C27 methyl ketone with methyllithium with concomitant TMS ether hydrolysis during the workup procedure (84%). Finally, a Parikh-Doering oxidation[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[81] based on a double stereodifferentiating directed hydrogenation[82] of the homoallylic olefin **103** synthesized via a chiral auxiliary-based diastereoselective aldol reaction.[83] The remaining four transformations comprised ester reduction, selective tosylation of the

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**Scheme 17.** Catalytic Enantioselective Synthesis of the HI-Ring Fragment **12**[a]
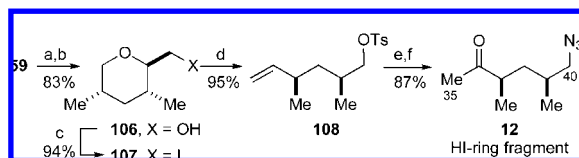
[a] Reagents and conditions: (a) Et$_3$SiH, BF$_3$·OEt$_2$, CH$_2$Cl$_2$, 0 °C, 91%; (b) LiAlH$_4$, Et$_2$O, 0 °C, 91%; (c) I$_2$, PPh$_3$, imidazole, CH$_3$CN/benzene, RT to 60 °C, 94%; (d) *t*-BuLi, THF, −78 °C, then TsCl, −78 to 0 °C, 95%; (e) O$_2$, PdCl$_2$, CuCl, H$_2$O, DMF, 89%; (f) NaN$_3$, DMSO, 60 °C, 97%. See ref 31 for abbreviations.

primary alcohol to give **105**, azide substitution, and finally a Swern oxidation[84] (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 **59** was converted to alcohol **106** by sequential acetal and ester reduction (Et$_3$SiH, BF$_3$·OEt$_2$; LiAlH$_4$, 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 (I$_2$, PPh$_3$, imidazole,[85] 94%). Although the fragmentation of iodide **107** could be accomplished under a number of conditions (Zn, MeOH or *n*-BuLi, Et$_2$O), 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 (O$_2$, PdCl$_2$, CuCl, DMF, 89%), with the remainder of the material consisting of olefin isomers. Finally, an azide introduction (NaN$_3$, DMSO, 60 °C, 97%) concluded this catalytic asymmetric synthesis of the HI-ring fragment **12**.
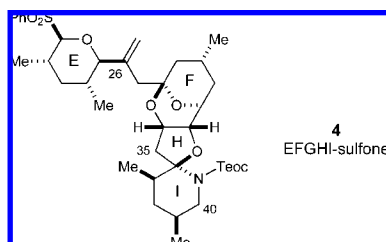
Synthesis of the EFGHI-Sulfone 4. Assembly of the EFGHI Carbon Skeleton and Formation of the FG Bicyclic Ketal 115. With the required E-, FG-, and HI-ring fragments in hand as described above, we proceeded to investigate their assembly to the pentacyclic EFGHI-sulfone **4**. We first formed the C34−C35 bond to unite the FG- and the HI-ring fragments in a chelate-

Scheme 18. Chelate-Controlled Mukaiyama Aldol Reaction and Initial Investigations of FG-Ketalization[a]
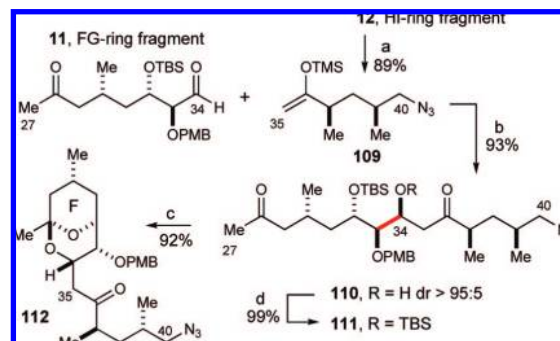
[a] Reagents and conditions: (a) LiHMDS, TMSCl, Et$_3$N, THF, −78 °C, 89%; (b) MgBr$_2$·OEt$_2$, CH$_2$Cl$_2$, 0 °C, 93%, dr >95:5; (c) HF, H$_2$O, CH$_3$CN, 0 °C, 92%; (d) TBSCl, imidazole, DMF, 99%. See ref 31 for abbreviations.

controlled Mukaiyama aldol reaction.[30] The required enolsilane **109** was readily formed from methyl ketone **12** under standard conditions (LiHMDS, TMSCl, Et$_3$N, 89%, Scheme 18). A careful evaluation of a range of Lewis acids to effect this transformation established that freshly prepared solid MgBr$_2$·OEt$_2$[68,87] was superior to other Lewis acids such as TiCl$_2$(O*i*-Pr)$_2$, TiCl$_4$, SnCl$_4$, MgI$_2$, MgBr$_2$, Mg(OTf)$_2$, and commercial MgBr$_2$·OEt$_2$. 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 enolsilane **109** to aldehyde **11** 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[86] 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 Cy$_2$BCl (2.4 equiv, *i*-Pr$_2$NEt) due to its excellent regioselectivity in the enolization of methyl ketones (Scheme 19).[88] The excess Cy$_2$BCl is presumed to function as a transient protecting group for the C34−C36 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 diastereoselectively in the boron aldol addition was inconsequential since the C26 secondary alcohols **114** were subsequently oxidized to the corresponding ketone **115** with Dess-Martin periodinane[59] (85%). Pyridine was crucial to buffer

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Scheme 19. Assembly of the EFGHI Carbon Skeleton and Formation of the FG Bicyclic Ketal 115[a]
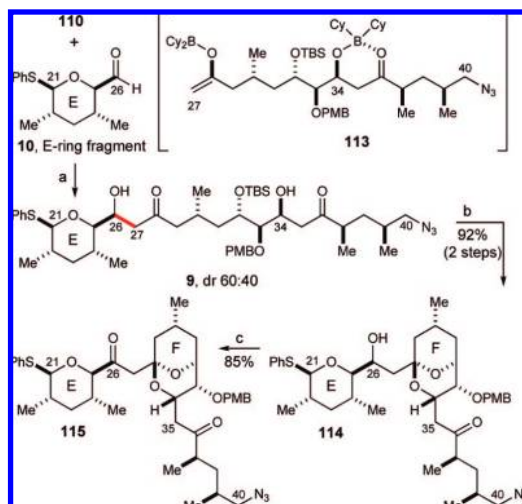
[a] Reagents and conditions: (a) Cy$_2$BCl (2.4 equiv), *i*-Pr$_2$NEt, CH$_2$Cl$_2$, −78 °C, then 10 (1.4 equiv), −78 to 0 °C; then H$_2$O$_2$, MeOH, pH 7 buffer, 0 °C to RT, dr 60:40; (b) HF, H$_2$O, CH$_3$CN, 0 °C, 92% (2 steps); (c) Dess-Martin periodinane, pyr, CH$_2$Cl$_2$, 85%. See ref 31 for abbreviations.

Scheme 20. Completion of the EFGHI-Sulfone 4[a]
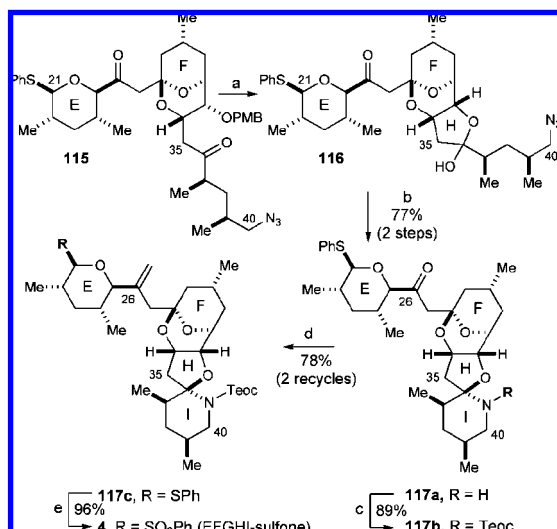
[a] Reagents and conditions: (a) DDQ, pH 7 buffer, CH$_2$Cl$_2$, 0 °C; (b) H$_2$ (1 atm), Pd/C, THF, dr >95:5, 77% (2 steps); (c) TeocCl,[89] *i*-Pr$_2$NEt, THF, 0 °C, 89%, dr >97:3; (d) Tebbe reagent,[90] pyr, toluene, −40 °C, 55%;[91] (41% recovered ketone); (e) H$_2$O$_2$, pyr, (NH$_4$)$_6$Mo$_7$O$_{24}$, *t*-BuOH, 96%. See ref 31 for abbreviations.

this latter oxidation step in order to suppress any overoxidation and subsequent loss of the C21-phenylsulfide moiety, a prominent side reaction observed in initial unbuffered experiments.

Completion of the EFGHI-Sulfone 4. Subsequently, the PMB ether in ketone 115 was oxidatively removed to afford an equilibrium mixture of lactols 116 and open-chain tautomers (DDQ, pH 7 buffer, Scheme 20). Decomposition of this intermediate upon exposure to silica gel was readily circumvented by buffering of the silica gel with Et$_3$N. With two of the three functional groups of the HI spiroaminal unmasked, the terminal azide was reduced to the primary amine. Whereas Staudinger conditions provided a mixture of isomers, hydrogenation under standard conditions induced the spontaneous formation of the thermodynamically favored HI-spiroaminal 117 as a single diastereomer (H$_2$, Pd/C, 77%, dr >95:5, 2 steps).
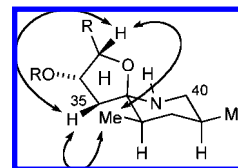
Figure 4. Key NOEs for spiroaminal 117 (C$_6$D$_6$, 500 MHz).

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 β,γ-unsaturated ketone prone to isomerization. After initial experiments using relatively nonbasic methylene-dianion equivalents such as the Takai-Nozaki reagent,[92] the Tebbe reagent[93] buffered with pyridine to avoid any C36-epimerization proved superior in this transformation. The Tebbe reagent could conveniently be prepared in situ from Cp$_2$TiCl$_2$ and AlMe$_3$[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 (H$_2$O$_2$, (NH$_4$)$_6$Mo$_7$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 *n*BuLi and added to aldehyde 3 followed by a quench at −78 °C with pH 5 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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(91) At−40 °C, the Tebbe reaction only proceeded to ∼60% 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.
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(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[a]
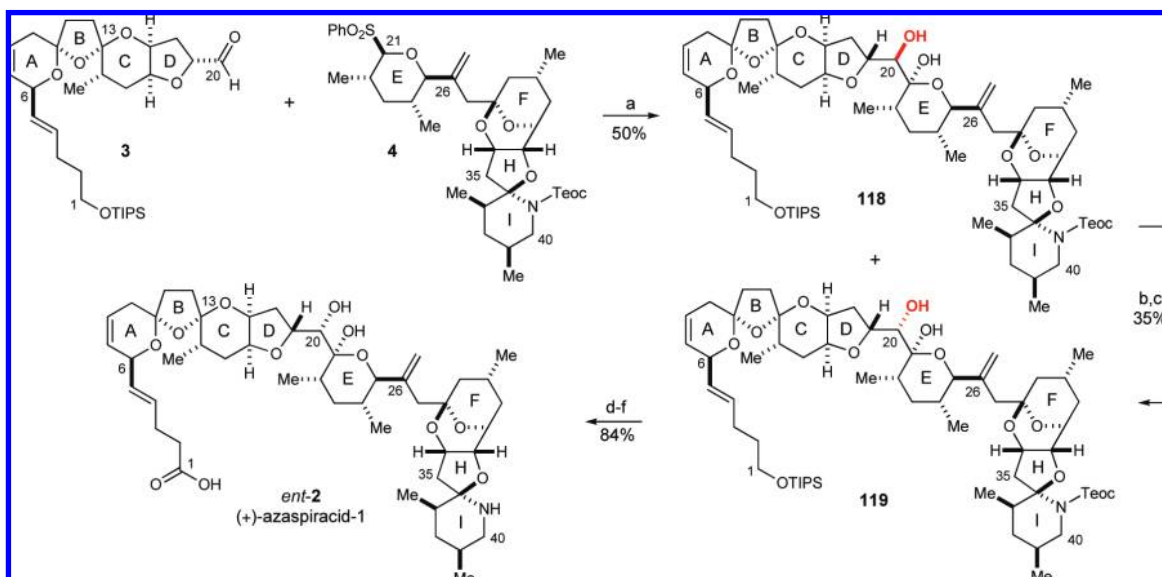
[a] Reagents and conditions: (a) **4** (2.2 equiv), *n*-BuLi, −78 °C, then **3** (1.0 equiv), then NaOAc/AcOH buffer, −78 °C to RT, 50% (27% **118**, 23% **119**); (b) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, −78 to −20 °C, 63%; (c) LiBH₄(THF), CH₂Cl₂, −40 °C, dr >20:1, 56%; (d) TBAF, THF, 0 °C, 93%; (e) Dess-Martin periodinane, CH₂Cl₂, 0 °C; (f) NaClO₂, NaH₂PO₄·H₂O, 2-methyl-2-butene, *t*-BuOH, 90% (2 steps). 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, Et₃N, 63%), a transformation somewhat complicated by the equilibrium between the C21 lactol and the hydroxyketone, since the latter is oxidized to the corresponding undesired diketone during the course of the reaction. A variety of reduction conditions were then evaluated in the diastereoselective reduction of the C20 ketone to test both traditional chelation and Felkin control, but unfortunately most reducing agents selectively provided the undesired lactol **118**. However, LiBH₄ in CH₂Cl₂ at −40 °C exclusively afforded the desired C20 diastereomer **119**, although in moderate yield (56%, dr >20:1).

With the desired lactol **119** thus prepared, only a few steps remained to complete the synthesis. Thus, the two silyl protecting groups were readily removed with TBAF (93% yield). Next, the C1 terminus was oxidized in a mild two-step sequence since initial experiments using TEMPO-type oxidations proved too harsh for the remainder of the molecule. Interestingly, a Dess-Martin oxidation at 0 °C chemoselectively afforded the desired C1 aldehyde even though a large excess of Dess-Martin periodinane was required to reach a full conversion into the aldehyde. In contrast, the C20 secondary alcohol of lactol **119** could rapidly be oxidized with Dess-Martin periodinane at room temperature. Finally, the resulting C1-aldehyde was cleanly oxidized with NaClO₂ to the corresponding carboxylic acid[95] in the presence of 2-methyl-2-butene as a chlorine scavenger[96] (90%, 2 steps). This sequence concluded the total synthesis of (+)-azaspiracid-1 (*ent*-**2**) and has allowed us to synthesize 75

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 ((+)-azaspiracid-1 (*ent*-**2**), $[\alpha]^{24}_D$ +21.7 (*c* = 1.00, MeOH), natural (−)-azaspiracid-1 (**2**), $[\alpha]^{20}_D$ −21 (*c* = 0.1, MeOH),[6] synthetic (−)-azaspiracid-1 (**2**), $[\alpha]^{33}_D$ −19.0 (*c* = 0.07, MeOH)[22]).

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 synthons 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.

Supporting Information Available: Experimental details and analytical data including copies of ¹H and ¹³C 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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