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Synthesis of the C1–C26 Northern Portion of Azaspiracid-1: Kinetic versus Thermodynamic Control of the Formation of the Bis-spiroketal**

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Keywords

azaspiracid-1; fused-ring systems; natural products; spiro compounds

Azaspiracid-1, a toxin found in European shellfish, was first observed in the mid-1990s when several individuals became ill from eating mussels harvested off the coast of Western Ireland. Considerable synthetic attention has been directed toward this compound by our group[1] and others.[2] Additional excitement was generated by the revelation that the initial structure of azaspiracid-1 (**1**) had been misassigned (Figure 1).[3] The genesis of the error was believed to be in the ABCDE northern portion of the molecule. Recently, the revised structure **2** was determined in an impressive series of publications by Nicolaou et al.[4] Independently and concurrently, we also converged on the same stereochemical conclusion.[5] Herein, we disclose our successful synthesis of the C1–C26 northern portion of the revised structure of azaspiracid-1 (**2**).

Our retrosynthetic analysis, as shown in Scheme 1, involved disconnection of **3** at the C19−20 linkage to provide the tetracycle **5** and the previously reported keto-phosphonate **6**.[5] The bis-spiroketal could be accessed from the ketone **7**, which would, in turn, be available from the sulfone 8 and the known aldehyde **9**.[5] It is important to note that the revised structure of azaspiracid **2** contains a new challenge in its synthetic architecture: the bisallylic carbon–oxygen bond at C6. We hypothesized that attempted formation of the bisspiroketal in the presence of this labile functionality might prove problematic, particularly under acidic conditions. On the basis of this assumption, care was taken not to incorporate both alkenes in this region until the bis-spiroketal had been formed.

Synthesis of the sulfone fragment commenced with the commercially available maleic acid **10** (Scheme 2). Following a known four-step protocol,[6] the *cis*-unsaturated ester **11** was constructed. Subsequent reduction of the carbonyl moiety followed by conversion into the allylic bromide provided **12**. Coupling of this electrophile with the readily available sulfone **14** (synthesized from the commercially available sodium salt of benzenesulfinic acid,

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Dedicated to Professor James D. White on the occasion of his 70th birthday

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thiophenol, and 1,3-dibromopropane (**13**)) and deprotection of the acetal gave the diol **15** as a mixture of stereoisomers at C10. Sequential protection at C4 and C6 provided the bis-silyl species **16**. After careful optimization, we found that the sulfone **16** could be cleanly converted into the β,γ-unsaturated ketone **17** using sodium hexamethyldisilizane and bis(trimethylsilyl) peroxide.[7] Despite our fears of the possible instability of **17**, this compound proved to be remarkably robust (stable to chromatography and prolonged storage in the freezer). Subsequent conversion into the methoxy ketal followed by oxidation of the sulfone[8] using Ley's TPAP reagent[9] yielded the coupling partner **8**.

With the sulfone subunit **8** in hand, we embarked on the combination of the subunits **8** and **9** (Scheme 3). Julia coupling of **8** and **9** with LDA proved problematic; however, use of the more hindered lithium base derived from 2,2,6,6-tetramethylpiperidine nicely addressed this issue. Subsequent oxidation with TPAP provided the ketosulfone species **18** in excellent yield (92%) over the two steps. Desulfonylation of **18** using Na/Hg amalgam followed by the formation of the bisspiroketal of **7** under our second-generation conditions (PPTS, THF/H_2O)[5] led cleanly to the desired transoidal bisspiroketal **19** with the corresponding cisoidal bis-spiroketal **20** as the minor product (2.5:1 **19**/**20**). This result is in stark contrast to the C8−9 series in which ketone **23** gave solely the transoidal bis-spiroketal **24**.[5] Interestingly, resubmission of the cisoidal bis-spiroketal **20** to the same reaction conditions did not lead to formation of any transoidal bis-spiroketal **19**. On the basis of these results, the location of the alkene in the A ring at the C8−9 position (allylic to C10) appears to be a catalyst for the unraveling and subsequent equilibration at C10. Even more intriguing, treatment of the TBDPS-protected cisoidal bis-spiroketal **20** under our first-generation conditions (CSA, *t*BuOH/PhMe)[1d–f] led to complete equilibration to the transoidal bis-spiroketal **19**. It would appear from these experiments that the use of PPTS in THF/H_2O leads to formation of the bis-spiroketal under kinetic control, whereas with CSA in *t*BuOH/PhMe the reaction proceeds under thermodynamic control. Additional support for this conclusion can be found in the exclusive formation of transoidal bis-spiroketal **19** from **7** upon treatment with CSA in *t*BuOH/PhMe. Note that decomposition appears to be a significant contributor to the low yield (20−30%) in the formation of the spiroketal from **7** using the first-generation conditions. The second-generation conditions were optimal for the initial formation of the bis-spiroketal of **7**, whereas the first-generation conditions were preferred for the equilibration of **20**.

Removal of the C4-silyl protecting group on **20** revealed additional information (Scheme 4). Treatment of **21** under the first-generation conditions once again leads to complete conversion into the transoidal bis-spiroketal **22**. Interestingly, use of our second-generation conditions also led to slow formation of the transoidal bis-spiroketal **22** (1:1 ratio of bis-spiroketals **21**/**22** after 72 h). Decomposition became a competitive pathway upon extended reaction times, making complete conversion of **21** into **22** under the second-generation conditions not feasible. The hydroxy group at C4 would appear to assist in the ionization of the bis-spiroketals, presumably through increasing the acidity of the local environment and/or a hydrogen-bonding interaction. Finally, debenzylation and oxidation/reduction at C19 provided the tetracycle **5** (Scheme 4).

Completion of the northern portion of azaspiracid-1 (**2**) is shown in Scheme 5. Wadsworth–Emmons coupling of **5** and **6** using KHMDS with in situ, intramolecular hetero-Michael addition yielded **27** with single stereochemistry at C19 of the furan D ring. Deprotonation using NaHMDS followed by a large excess of the Davis oxaziridine provided the hydroxyketone **29** as a single stereoisomer. Mosher ester analysis[10] confirmed that **30** displayed the undesired α stereochemistry. The stereochemical outcome in the hydroxylation can be explained through chelation of the sodium *Z*-enolate **28** to the oxygen atom of the furan D ring. Initial attempts to invert the stereochemistry at C20 using Mitsunobu-type conditions proved unsuccessful. Fortunately, triflation followed by displacement using the potassium salt of *p*-nitrobenzoic acid in DMF cleanly provided the desired β stereochemistry. The stereochemistry

of **31** was once again confirmed by means of Mosher ester analysis. Desilylation using CSA followed selenation, and oxidation/elimination using TPAP yielded the reactive bisallylic pyran **34**. To the best of our knowledge, the TPAP-mediated oxidation of selenium has not been previously reported.[11] Attempted oxidation of the selenide using traditional conditions (e.g. H_2O_2, THF)[12] led to multiple products. Finally, selective olefin metathesis with **35** using the second-generation Grubbs catalyst[13] gave the target **3**.

In summary, an efficient approach to the entire C1–C26 northern portion of azaspiracid-1 has been described (27 steps from known ester **12**). We have unearthed novel controlling factors for formation of the bis-spiroketal under kinetic versus thermodynamic control. The proper choice of substitution patterns and acidic media allows for the tuning of the equilibration of the bis-spiroketal. In addition, key steps in this synthetic sequence include the oxidation of a sulfone at C10 to form the β,γ-unsaturated ketone, tandem Wadsworth–Emmons/intramolecular hetero-Michael addition to construct ring D, Davis oxidation to incorporate the hydroxy moiety at C20, and selective olefin metathesis to incorporate the sidearm at C5. Application of this strategy to the total synthesis of azaspiracid-1 will be reported in due course.

References

1. a Carter RG, Weldon DJ. Org. Lett 2000;2:3913–3916. [PubMed: 11101452]Carter, RG.; Weldon, DJ.; Bourland, TC. 221st National ACS Meeting; San Diego. 2001; p. ORG-479. c Carter RG, Graves DE. Tetrahedron Lett 2001;42:6035–6039. d Carter RG, Bourland TC, Graves DE. Org. Lett 2002;4:2177–2179. [PubMed: 12074661] e Carter RG, Graves DE, Gronemeyer MA, Tschumper GS. Org. Lett 2002;4:2181–2184. [PubMed: 12074662] f Carter RG, Bourland TC, Zhou X-T, Gronemeyer MA. Tetrahedron 2003;59:8963–8974.
2. a Dounay AB, Forsyth CJ. Org. Lett 2001;3:975–978. [PubMed: 11277773] b Aiguade J, Hao J, Forsyth CJ. Org. Lett 2001;3:979–982. [PubMed: 11277774] c Aiguade J, Hao J, Forsyth CJ. Tetrahedron Lett 2001;42:817–820. d Hao J, Aiguade J, Forsyth CJ. Tetrahedron Lett 2001;42:821–824. e Nicolaou KC, Pihko PM, Diedrichs N, Zou N, Bernal F. Angew. Chem 2001;113:1302–1305.Angew. Chem. Int. Ed 2001;40:1262–1265.Buszek, KR. 221st National ACS Meeting; San Diego. 2001; p. ORGN-570. g Forsyth CJ, Hao J, Aiguade J. Angew. Chem 2001;113:3775–3779.Angew. Chem. Int. Ed 2001;40:3663–3667. h Nicolaou KC, Qian W, Bernal F, Uesaka N, Pihko PM, Hinrichs J. Angew. Chem 2001;113:4192–4195.Angew. Chem. Int. Ed 2001;40:4068–4071. i Sasaki M, Iwamuro Y, Nemoto J, Oikawa M. Tetrahedron Lett 2003;44:6199–6201.Buszek, KR.; Gibson, TS.; Reinhardt, BC.; Sunde, JR. 226th ACS National Meeting; New York. 2003; p. ORGN-179. k Ishikawa Y, Nishiyama S. Tetrahedron Lett 2004;45:351–354. l Ishikawa Y, Nishiyama S. Heterocycles 2004;63:539–565. m Ishikawa Y, Nishiyama S. Heterocycles 2004;63:885–893. n Geisler LK, Nguyen S, Forsyth CJ. Org. Lett 2004;6:4159–4162. [PubMed: 15524432]
3. a Nicolaou KC, Li Y, Uesaka N, Koftis TV, Vyskocil S, Ling T, Govindasamy M, Qian W, Bernal F, Chen DY-K. Angew. Chem 2003;115:3771–3776.Angew. Chem. Int. Ed 2003;42:3643–3648. b Nicolaou KC, Chen DY-K, Li Y, Qian W, Ling T, Vyskocil S, Koftis TV, Govindasamy M, Uesaka N. Angew. Chem 2003;115:3777–3781.Angew. Chem. Int. Ed 2003;42:3649–3653.
4. a Nicolaou KC, Vyskocil S, Koftis TV, Yamada YMA, Ling T, Chen DY-K, Tang W, Petrovic G, Frederick MO, Satake YM. Angew. Chem 2004;116:4412–4418.Angew. Chem. Int. Ed 2004;43:4312–4318. b Nicolaou KC, Koftis TV, Vyskocil S, Petrovic G, Ling T, Yamada YMA, Tang W, Frederick MO. Angew. Chem 2004;116:4418–4424.Angew. Chem. Int. Ed 2004;43:4318–4324.
5. Zhou X-T, Carter RG. Chem. Commun 2004:2138–2140.
6. a Flögel O, Amombo MGO, Reißig H-U, Zahn G, Brödgam I, Hartl H. Chem. Eur. J 2003;9:1405–1415. b Herradon B. Tetrahedron: Asymmetry 1991;2:191–194.
7. Hwu JR. J. Org. Chem 1983;48:4432–4433.
8. Guertin KR, Kende AS. Tetrahedron Lett 1993;34:5369–5372.
9. Ley SV, Norman J, Griffith WP, Marsden SP. Synthesis 1994:639–666.

10. a Ohtani I, Kusumi T, Kashman Y, Kakisawa H. J. Am. Chem. Soc 1991;113:4092–4096. b Dale JA, Mosher HS. J. Am. Chem. Soc 1973;95:512–519. c Sullivan GR, Dale JA, Mosher HS. J. Org. Chem 1973;38:2143–2147.

11. For the first example of a metal-catalyzed oxidation of aryl allylic selenides, see: a Carter RG, Bourland TC. Chem. Commun 2000:2031–2032. b Bourland TC, Carter RG, Yokochi AFT. Org. Biomol. Chem 2004;2:1315–1329. [PubMed: 15105922]

12. Grieco PA, Gilman S, Nishizawa M. J. Org. Chem 1976;41:1485–1486.

13. Chatterjee AK, Choi T-L, Sanders DP, Grubbs RH. J. Am. Chem. Soc 2003;125:11 360–11 370.

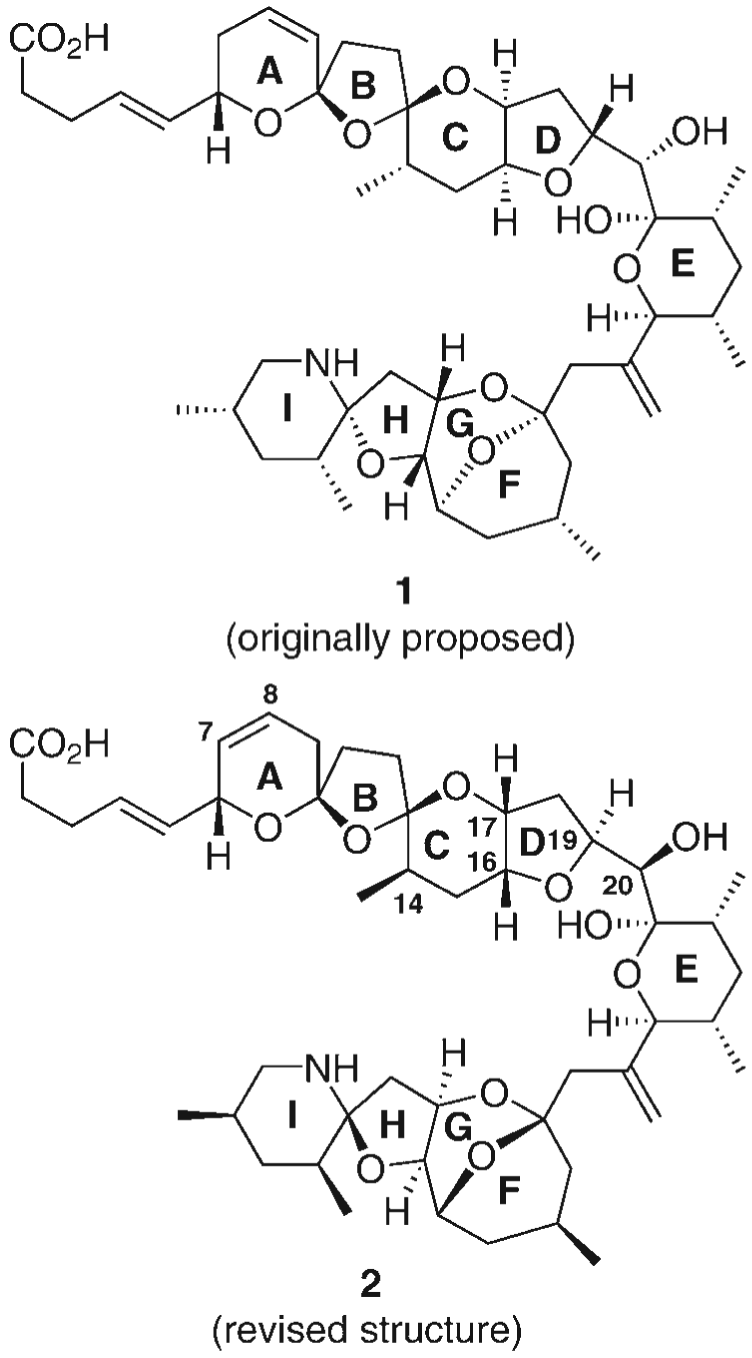
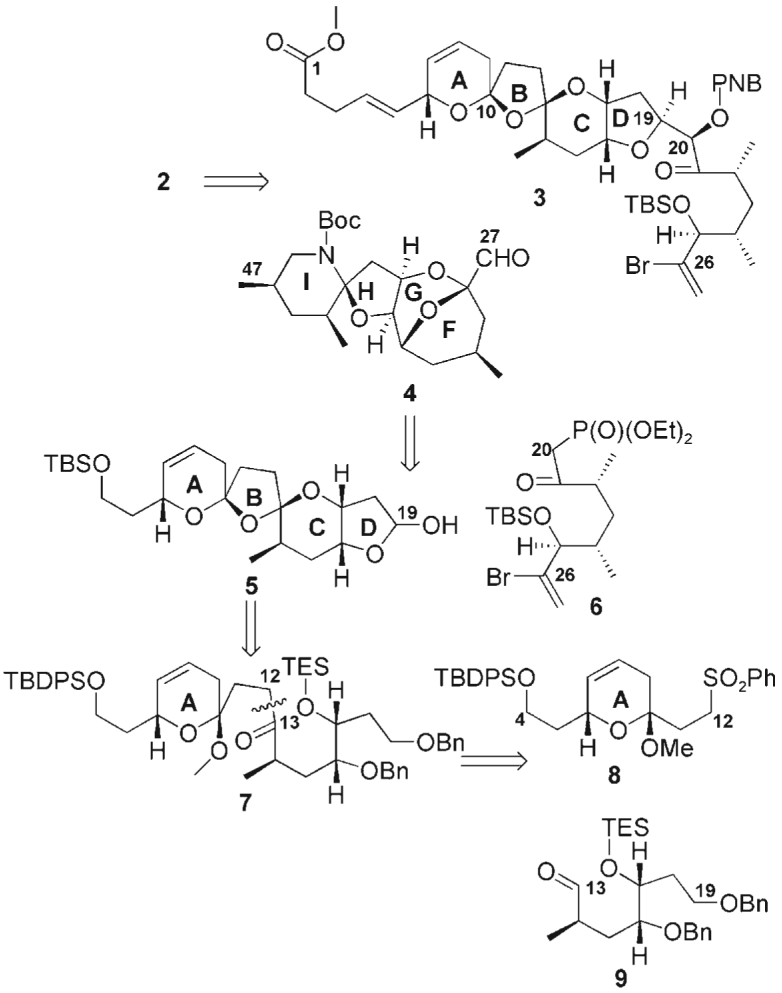
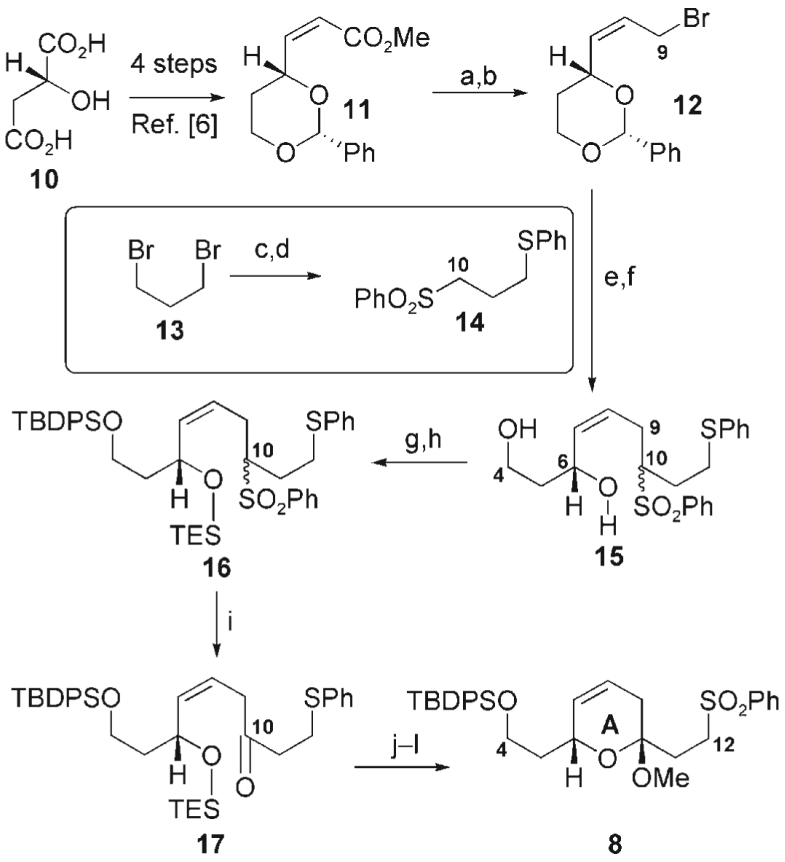


Figure 1.
Original **(1)** and revised **(2)** structures of azaspiracid-1.



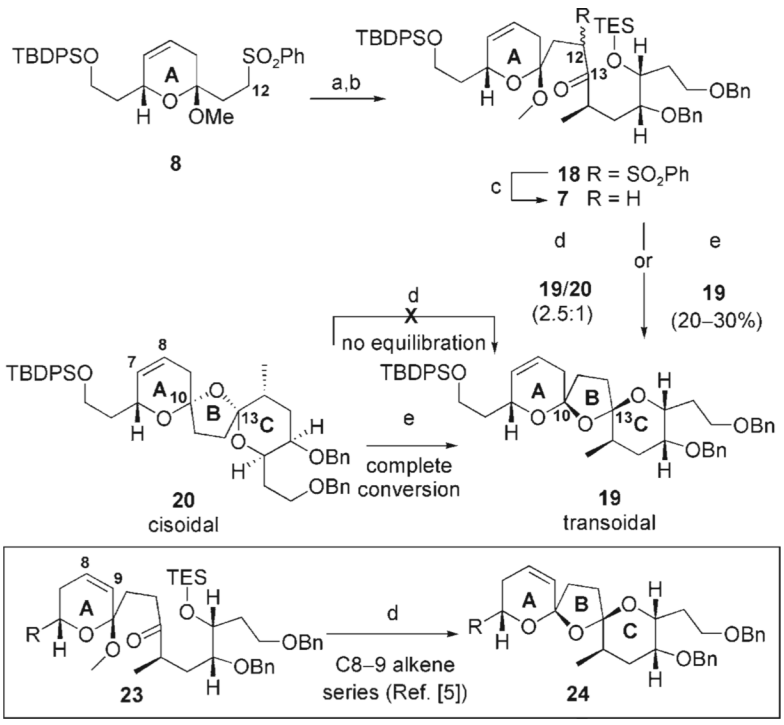
Scheme 1.

Retrosynthetic analysis of azaspiracid-1 **(2)**. PNB = *paranitrobenzoate*; TBS = *tert*-butyldimethylsilyl; Boc = *tert*-butyloxycarbonyl; TBDPS = *tert*-butyldiphenylsilyl; TES = triethylsilyl; Bn = benzyl.



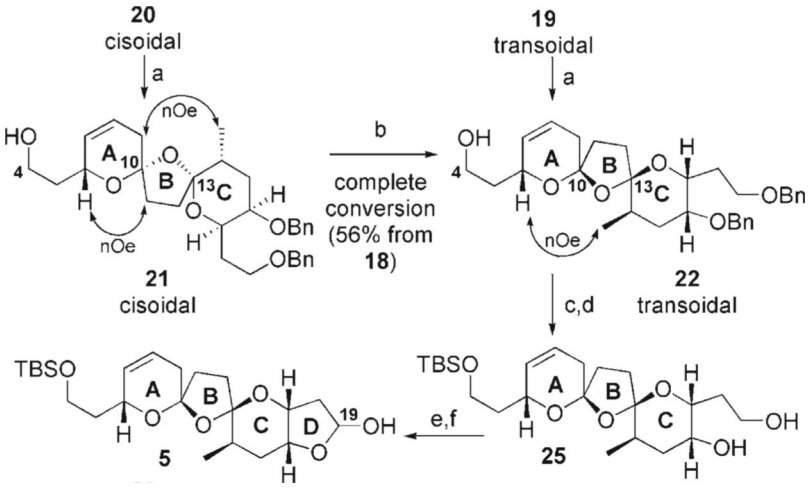
Scheme 2.

Synthesis of the sulfone. Reagents and conditions: a) DIBAL-H, CH_2Cl_2, 78°C, 98%; b) Ph_3P, CBr_4, MeCN, 92%; c) NaH, PhSH, DMF, 0°C, 73%; d) $NaSO_2Ph$, DMF, 86%; e) *n*BuLi, **14** (2.6 equiv), THF, 78°C; f) 2 N HCl, MeCN, 58% (over two steps); g) TBDPSCl, imid., CH_2Cl_2, 92%; h) TESOTf, 2,6-lutidine, CH_2Cl_2, 95%; i) NaHMDS, THF then $(TMSO)_2$, 72% (BORSM); j) NH_4F, MeOH/CH_2Cl_2 (4:1); k) PPTS, MeOH, 68% (over two steps, BORSM); l) TPAP, NMO, MeCN, 40°C, 88%. DIBAL-H = diisobutylaluminum hydride; DMF = *N*,*N*-dimethylformamide; imid = imidazole; TESOTf = triethylsilyl triflate; HMDS = hexamethyldisilazide; TMS = trimethylsilyl; PPTS = pyridinium *p*-toluenesulfonate; TPAP = tetra-*n*-propylammonium perruthenate; NMO = *N*-methylmorpholine-*N*-oxide. BORSM = based on recovered starting material.



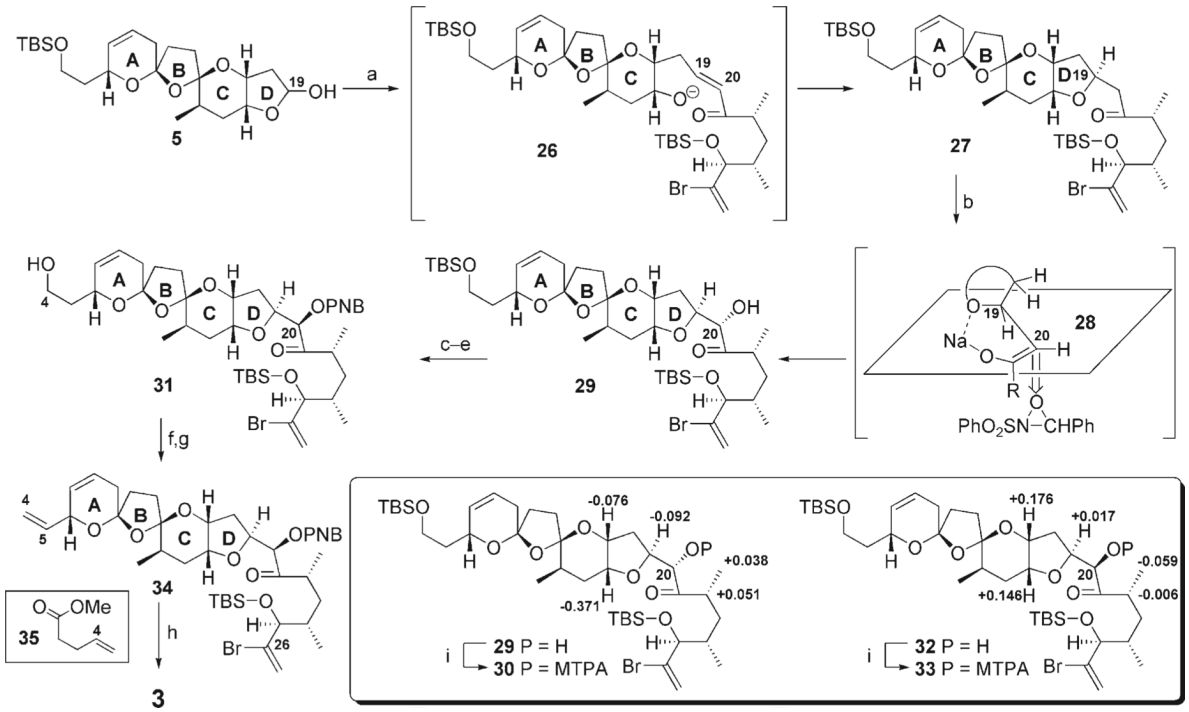
Scheme 3.

Synthesis and equilibration of bis-spiroketals. Reagents and conditions: a) 2,2,6,6-tetramethylpiperidine, *n*BuLi, THF then **9**; b) TPAP, NMO, CH_2Cl_2, M.S., 92% over two steps; c) Na/Hg, Na_2HPO_4, THF, H_2O, 86%; d) PPTS, THF/H_2O (4:1), 18 h; e) CSA, *t*BuOH/PhMe (1:1), 18 h. M.S. = molecular sieves; CSA = camphorsulfonic acid.



Scheme 4.

Equilibration of C4-hydroxy bis-spiroketals. Reagents and conditions: a) TBAF, THF; b) CSA, *t*BuOH/PhMe (1:1), 18 h; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 78°C, 99%; d) LiDBB, THF, −78° C, 95%; e) TPAP, NMO, CH_2Cl_2, M.S.; 67%; f) DIBAL-H, CH_2Cl_2, 90%. TBAF = tetra-*n*-butylammonium fluoride; DBB = lithium 4,4–di-*tert*-butylbiphenylide.



Scheme 5.

Completion of the northern portion of azaspiracid-1 (**2**). Reagents and conditions: a) **6**, KHMDS, THF, −78°C→RT, 84%; b) NaHMDS, THF, then Davis oxaziridine, 70%, > 20:1 d.r.; c) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78°C, 88%; d) KO_2C-*p*-NO_2-C_6H_4 (20 equiv), DMF, 90%; e) CSA, MeOH/CH_2Cl_2, 93%; f) *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF 93%; g) TPAP, NMO, Et_3N, CH_2Cl_2, 66%; h) second-generation Grubbs catalyst, **35**, CH_2Cl_2, 95% (BORSM), > 10:1 *E*/*Z*; i)(*R*)/(*S*)-Mosher acid chloride, DMAP, CH_2Cl_2. MTPA = α-methoxy-α-trifluoromethylphenylacetic acid (Mosher); DMAP = 4-(dimethylamino)pyridine. The stereochemistry at C20 was confirmed by Mosher ester analysis. Representative data points for the difference in the chemical shift values [(*S*)-Mosher ester (*R*)-Mosher ester (in ppm); $CDCl_3$, 300 or 400 MHz] are shown for structures **30** and **33**.