ammonia on the sample was performed at room temperature; the subsequent removal of ammonia was carried out at 120 °C for 1 h in flowing pure nitrogen.

Catalytic reactions: Two catalytic reactions were used to characterize the catalytic performance of the prepared materials, and analyses of the catalytic products were carried out using GC-8A and GC-17A (Shimazu Co.) instruments equipped with TCD and FID detectors. Catalytic cracking of 1,3,5-triisopropylbenzene was performed by the pulse method. Samples were calcined at 600 °C for 5 h to burn off any residual organic template. The catalytic testing was performed according to the following standard conditions: catalyst mass: 0.051 g; reaction temperatures in the range of 250–320 °C (no thermal cracking); the ratio of catalyst to 1,3,5-triisopropylbenzene or isopropylbenzene at 0.4 μL per 0.051 g. Nitrogen was used as carrier gas; flow rate 0.92 mL s^{-1}.

The catalytic alkylation of isobutane with butene was investigated at 2 MPa by using a stainless-steel apparatus equipped with a one-through stainless-steel flow reactor. Typical reactions were carried out with 0.5 g of catalyst and an isobutane/butene ratio of 12:1, and a 1-butene/2-butene ratio of 8:1; the WHSV was 9 h^{-1} at a reaction temperature of 25–100 °C.

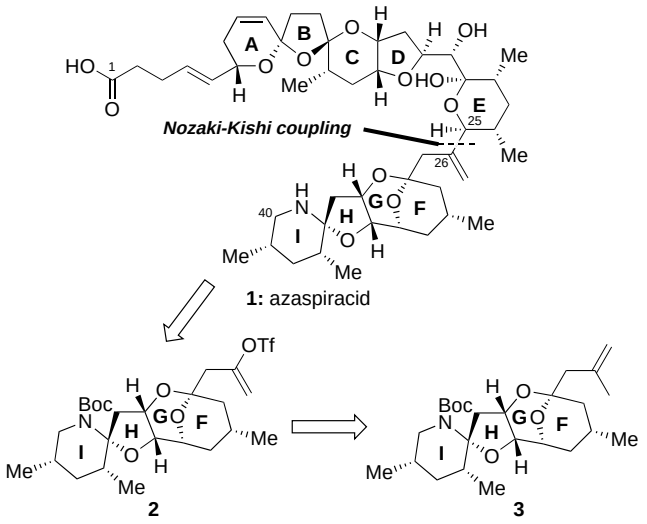
Received: November 28, 2000
Revised: January 4, 2001 [Z16188]

[1] A. Corma, *Chem. Rev.* **1997**, *97*, 2373.
[2] C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, J. S. Beck, *Nature* **1992**, *352*, 710.
[3] D. Zhao, J. Feng, Q. Huo, N. Melosh, G. H. Fredrickson, B. F. Chmelka, G. D. Stucky, *Science* **1998**, *279*, 548.
[4] S. S. Kim, W. Zhang, T. J. Pinnavaia, *Science* **1998**, *282*, 1032.
[5] R. Ryoo, J. M. Kim, C. H. Shin, *J. Phys. Chem.* **1996**, *100*, 17718.
[6] R. Ryoo, S. Jun, J. M. Kim, M. J. Jim, *Chem. Commun.* **1997**, 2225.
[7] R. Mokaya, W. Jones, *Chem. Commun.* **1997**, 2185; R. Mokaya, W. Jones, *Chem. Commun.* **1998**, 1839.
[8] R. Mokaya, *Angew. Chem.* **1999**, *111*, 3079; *Angew. Chem. Int. Ed.* **1999**, *38*, 2930.
[9] Q. S. Huo, D. Margolese, U. Ciesla, P. Feng, T. E. Gier, P. Sieger, R. Leon, P. M. Petroff, F. Schüth, G. D. Stucky, *Nature* **1994**, *368*, 317.
[10] P. D.Yang, D. Y. Zhao, D. I. Margolese, B. F. Chmelka, G. D. Stucky, *Nature* **1998**, *396*, 152.
[11] D. M. Antonelli, J. Y. Ying, *Curr. Opin. Coll. Interf. Sci.* **1996**, *1*, 523; T. Sun, J. Y. Ying, *Nature* **1997**, *389*, 704.
[12] C. Chen, H. Li, M. E. Davis, *Microporous Materials* **1993**, *2*, 17.
[13] D. Khushalani, A. Kuperman, N. Coombs, G. A. Ozin, *Chem. Mater.* **1996**, *8*, 2188.
[14] X. S. Zhao, G. Q. Lu, *J. Phys. Chem. B* **1998**, *102*, 1556.
[15] J. M. Kim, S. Jun, R. Ryoo, *J. Phys. Chem. B* **1999**, *103*, 6200.
[16] A. Karlsson, M. Stoker, R. Schmidt, *Microporous Mesoporous Materials* **1999**, *27*, 181–192.
[17] P. E. A. de Moor, T. P. M. Beelen, R. A. van Santen, T. Tsuji, M. E. Davis, *Chem. Mater.* **1999**, *11*, 36; P. E. A. de Moor, T. P. M. Beelen, R. A. van Santen, *J. Phys. Chem. B* **1999**, *103*, 1639.
[18] H. Robson, *ACS Symp. Ser.* **1989**, 398, 436.
[19] Q. Zhou, W. Pang, S. Qiu, M. Jia, CN Patent, ZL931 17593.3, **1996**; Q. Zhou, B. Li, S. Qiu, W. Pang, *Chem. J. Chin. Univ.* **1999**, *20*, 693.
[20] *Zeolite Molecular Sieves* (Ed.: D. W. Breck), Wiley, New York, **1974**; P. A. Jabobs, E. G. Derouane, J. Weitkamp, *J. Chem. Soc. Chem. Commun.* **1981**, 591.
[21] C. Li, G. Xiong, Q. Xin, J. K. Liu, P. Ying, Z. C. Feng, J. Li, W.-B. Yang, Y.-Z. Wang, G. R. Wang, X. Liu, M. Liu, X.-Q. Wang, E.-Z. Min, *Angew. Chem.* **1999**, *111*, 2358; *Angew. Chem. Int. Ed.* **1999**, *38*, 2220.
[22] M. J. Annen, M. E. Davis, *Microporous Materials* **1993**, *1*, 57.
[23] S. Biz, M. L. Occelli, *Catal. Rev. Sci. Eng.* **1998**, *40*, 329.

Synthesis of the FGHI Ring System of Azaspiracid**

K. C. Nicolaou,* Petri M. Pihko, Nicole Diedrichs, Ning Zou, and Federico Bernal

Azaspiracid (**1**, Scheme 1), a novel marine toxin isolated from the mussel *Mytilus edulis* in Killary Harbor, Ireland, represents a new class of marine metabolites unrelated to any



Scheme 1. Structure of azaspiracid (**1**) and retrosynthetic analysis leading to FGHI ring framework **3** via key intermediate **2**.

previously known agents of diarrhetic shellfish poisoning.[1] This seasonally occurring toxin displays an unusually complex molecular assembly – it harbors a total of nine rings, eight of which are part of acetal or ketal structures – namely, an azaspiro ring system fused to a 2,9-dioxacyclo[3.3.1]nonane ring and a trioxadispiroketal fused to a tetrahydrofuran ring. Adding to the serious challenge posed by such a molecular framework, the absolute stereochemistry of the molecule and the relative stereochemistry between the ABCDE and the

[*] Prof. Dr. K. C. Nicolaou, Dr. P. M. Pihko, Dr. N. Diedrichs, Dr. N. Zou, F. Bernal
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2469
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)
E-mail: kcn@scripps.edu

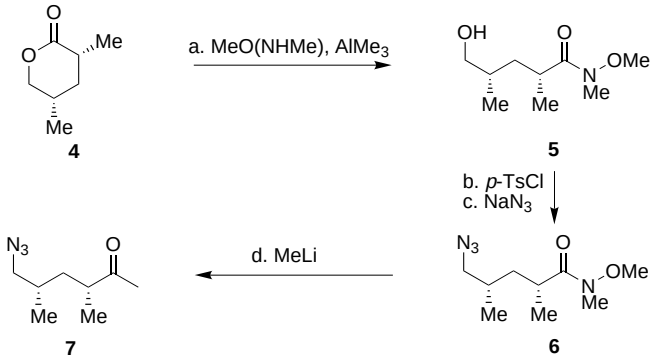
[**] We thank Dr. D. H. Huang and Dr. G. Siuzdak for NMR spectroscopic and mass spectrometric assistance, respectively. Financial support for this work was provided by The Skaggs Institute for Chemical Biology, the National Institutes of Health (USA), a predoctoral fellowship from Bristol–Myers Squibb (F.B.), postdoctoral fellowships from the Academy of Finland, the Ella and Georg Ehrnrooth Foundation, and the Tauno Tönning Foundation (all to P.M.P.), ArrayBiopharma (N.Z.), and Bayer AG (N.D.), and grants from Abbott, Amgen, ArrayBiopharma, Boehringer-Ingelheim, Glaxo, Hoffmann–La Roche, DuPont, Merck, Novartis, Pfizer, and Schering Plough.

  1433-7851/01/4007-1262 $ 17.50+.50/0

FGHI domains remain unknown. Azaspiracid (**1**) is a potent toxin in vivo, and exhibits mouse lethality at 0.2 mg kg^{-1}. The biological basis of the toxicity, however, also remains a mystery. These intriguing questions posed by the chemistry and biology of azaspiracid should be addressable through chemical synthesis.[2] Herein we report the first synthesis of the C26–C40 tetracyclic FGHI domain of azaspiracid by a novel strategy that affords the protected ring system in an enantiomerically pure form.

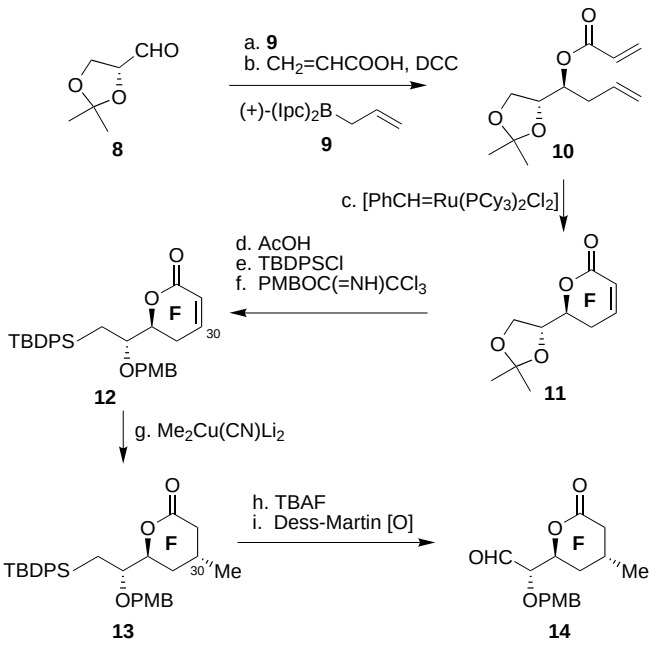
As shown in Scheme 1, azaspiracid (**1**) can be retrosynthetically dissected at the C25–C26 bond, thus dividing the molecule into the ABCDE and the FGHI domains. The synthetic rationale for this strategic disconnection arises not only from issues of convergency, but also from the need to synthesize the ABCDE and the FGHI ring systems separately in a manner that allows access to both enantiomers of each subunit. Thus, a Nozaki–Kishi disconnection led to triflate **2**, which is accessible, in principle, from olefin **3** by ozonolysis and formation of an enol triflate.

Scheme 2 outlines the synthesis of the I-ring precursor, ketone **7**. Starting from the known[3] lactone **4**, ring opening with $AlMe_3$ and MeO(NHMe) gave the Weinreb amide **5** in 96% yield.[4] Tosylation of the primary alcohol, followed by azide displacement afforded azide **6** in 92% overall yield. Finally, treatment of the latter compound (**6**) with MeLi resulted in a clean conversion into ketone **7** (82%).



Scheme 2. Preparation of azidoketone **7**: a) MeO(NHMe)·HCl (5.0 equiv), $AlMe_3$ (2.0 M in toluene, 5.1 equiv), THF, −15 °C, 2 h, 96%; b) *p*-TsCl (1.5 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 25 °C, 18 h, 96%; c) NaN_3 (2.0 equiv), DMF, 25 °C, 76 h, 96%; d) MeLi (1.25 M in Et_2O, 1.0 equiv), THF, −78 °C, 40 min, 82%. *p*-TsCl = *para*-toluenesulfonyl chloride.

The synthesis of the F-ring aldehyde is presented in Scheme 3. Allylboration of D-isopropylidene glyceraldehyde[5] (**8**) with the Brown chiral allylborane **9**[6] proceeded in 88% yield and 97:3 diastereoselectivity. Acylation of the resulting alcohol with acrylic acid and 1,3-dicyclohexylcarbodiimide (DCC) smoothly yielded acrylate **10** (73%). A remarkably efficient ring-closing metathesis reaction[7] within **10** then afforded unsaturated lactone **11** in 95% yield. Acid-catalyzed deprotection of the acetonide, selective silylation of the primary alcohol with *tert*-butyldiphenylsilyl chloride (TBDPSCl) and protection of the secondary hydroxy group as the 4-methoxybenzyl (PMB) ether[8] furnished lactone **12** in 76% yield over three steps. Methylcupration with $Me_2Cu(CN)Li_2$ served as an excellent method to install the C30



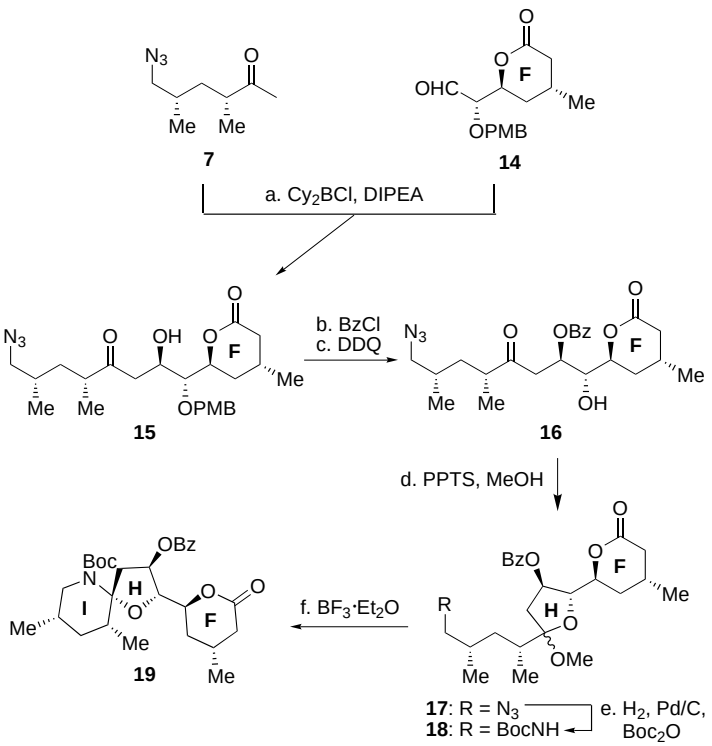
Scheme 3. Synthesis of the F ring aldehyde **14**: a) **9** (2.0 equiv), Et_2O, −100 °C, 6 h, 88% (97:3 selectivity); b) acrylic acid (1.8 equiv), DCC (2.0 equiv), 4-DMAP (0.08 equiv), CH_2Cl_2, 25 °C, 40 h, 73%; c) $[PhCH{=}Ru(PCy_3)_2Cl_2]$ (0.05 equiv), CH_2Cl_2, reflux, 4 h, 95%; d) AcOH/H_2O (3/1), 65 °C, 2 h; e) TBDPSCl (1.5 equiv), Et_3N (3.0 equiv), 4-DMAP (0.08 equiv), CH_2Cl_2, 0→25 °C, 5 h; f) PMBOC(=NH)CCl_3 (2.0 equiv), $TrBF_4$ (0.025 equiv), Et_2O, 0 °C, 20 min, 76% over three steps; g) $Me_2Cu(CN)Li_2$ (1.5 equiv), Et_2O, −78 °C, 10 min, 97%; h) TBAF (1.0 M in THF, 1.25 equiv), THF, 25 °C, 3 h, 89%; i) Dess–Martin periodinane (1.4 equiv), pyridine (10.0 equiv), CH_2Cl_2, 0 °C, 2 h, 95%. Ipc = isopinocampheyl, 4-DMAP = 4-(dimethylamino)pyridine, $TrBF_4$ = triphenylcarbenium tetrafluoroborate.

methyl group in a highly diastereoselective fashion to afford **13** in 97% yield as the only detectable stereoisomer.[9] The synthesis of aldehyde **14** was completed by a tetra-*n*-butylammonium fluoride (TBAF) mediated cleavage of the *tert*-butyldiphenylsilyl (TBDPS) group (89%) followed by oxidation of the liberated hydroxy group with Dess–Martin periodinane (95%).

With both building blocks **7** and **14** in hand, our next task was the aldol-facilitated union of the two fragments. Efforts to utilize a chelation-controlled Mukaiyama aldol process under the conditions of Reetz and Kesseler ($SnCl_4$, −78 °C)[10] resulted only in extensive decomposition of the aldehyde. We then turned to boron-mediated aldol reactions as mild alternatives. Thus, enolization of ketone **7** with $(Cy)_2BCl$ (Cy = cyclohexyl) and *N*,*N*-diisopropylethylamine (DIPEA)[11] followed by reaction with aldehyde **14** gave aldol **15** in 82% yield as a single isomer (Scheme 4). The aldol product in this case represented the undesired *anti* diastereoisomer (corresponding to the Felkin product).[12] However, we were confident that the stereochemistry at this newly formed chiral center could be corrected after the formation of the spirocycle as long as we could obtain the correct spiro stereochemistry.

Although a few methods for the construction of azaoxaspirane junctions are known,[13] our goal was to develop a method that would allow the direct synthesis of the spirocycle

  1433-7851/01/4007-1263 $ 17.50+.50/0

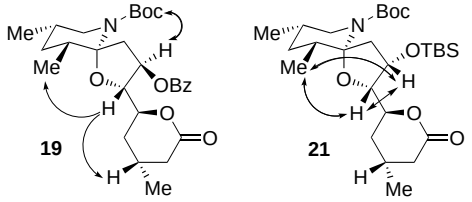


Scheme 4. Synthesis of azaspiro compound **19**: a) Cy_2BCl (1.3 equiv), DIPEA (1.5 equiv), CH_2Cl_2, $-78 \rightarrow -40\,^{\circ}C$, 5 h, 82% (>30:1 diastereoselectivity); b) BzCl (3.0 equiv), pyridine, 0 °C, 2 h, 96%; c) DDQ (1.5 equiv), CH_2Cl_2/H_2O (10/1), 0 °C, 8 h, 98%; d) PPTS (0.2 equiv), MeOH, 25 °C, 1.5 h; e) H_2, 10% Pd/C (20% by weight), Boc_2O (4.0 equiv), EtOAc, 25 °C, 3.5 h, 76% over two steps; f) $BF_3 \cdot Et_2O$ (0.1 equiv), CH_2Cl_2, 0 °C, 10 min, 60%. Bz = benzoyl, Boc = *tert*-butoxycarbonyl.

Table 1. Selected data for compounds **19** and **3**.

19: $R_f = 0.78$ (silica gel, ethyl acetate:hexanes 1:1); $[\alpha]_D^{20} = -13.1^{\circ}$ ($CHCl_3$, $c = 1.14$); IR (film) $\tilde{\nu}_{max} = 2959, 2924, 1720, 1365, 1274, 1159, 1110, 1068, 858, 713\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.00$ (dd, $J = 8.4$, 1.4 Hz, 2H), 7.56 (tt, $J = 7.5$, 1.1 Hz, 1H), 7.43 (t, $J = 7.9$ Hz, 2H), 5.67 (dt, $J = 7.3$, 2.2 Hz, 1H), 4.49 (dt, $J = 8.1$, 4.8 Hz, 1H), 4.27 (dd, $J = 8.1$, 1.8 Hz, 1H), 3.71 (ddd, $J = 13.2$, 4.0, 1.8 Hz, 1H), 3.32 (dd, $J = 16.2$, 7.4 Hz, 1H), 2.93 (dd, $J = 13.2$, 11.3 Hz, 1H), 2.62 (dd, $J = 16.5$, 5.7 Hz, 1H), 2.54 (dd, $J = 15.8$, 2.2 Hz, 1H), 2.24 (m, 1H), 2.15 (dd, $J = 16.5$, 9.2 Hz, 1H), 2.01 (ddd, $J = 13.9$, 7.7, 6.2 Hz, 1H), 1.99 (ddq, $J = 10.2$, 6.6, 3.7 Hz, 1H), 1.73 (ddd, $J = 13.9$, 6.6, 4.4 Hz, 1H), 1.61 (m, 1H), 1.57 (m, 1H), 1.46 (s, 9H), 1.30 (m, 1H), 1.11 (d, $J = 7.0$ Hz, 3H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.85 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 171.0$, 165.8, 155.7, 133.1, 129.9, 129.6, 128.4, 99.3, 85.8, 80.3, 76.6, 75.9, 50.7, 41.0, 38.4, 37.7, 31.8, 30.9, 30.3, 28.4, 23.4, 21.2, 18.8, 17.2; HR-MS (Matrix-assisted laser desorption/ionization (MALDI)): calcd for $C_{28}H_{39}NO_7Na^+$ [M+Na^+]: 524.2619, found 524.2613

3: $R_f = 0.56$ (silica gel, ethyl acetate:hexanes 4:1); $[\alpha]_D^{20} = +4.6^{\circ}$ (CH_2Cl_2, $c = 0.22$); IR (film) $\tilde{\nu}_{max} = 2925, 1591, 1492, 1446, 1373, 1225, 1190, 1115, 928, 747\ cm^{-1}$; ^1H NMR (500 MHz, [D_6]acetone): $\delta = 4.77$ (m, 1H), 4.73 (dt, $J = 5.1$, 2.4 Hz, 1H), 4.69 (m, 1H), 4.19 (br d, $J = 4.9$ Hz, 1H), 3.82 (dd, $J = 5.1$, 0.9 Hz, 1H), 3.68 (m, 1H), 3.64 (m, 1H), 3.19 (dd, $J = 13.2$, 11.8 Hz, 1H), 2.21 (AB, $J = 13.2$ Hz, $\nu_{ab} = 20.8$ Hz, 2H), 2.17 (dd, $J = 14.7$, 5.1 Hz, 1H), 2.16 (m, 1H), 2.00 (ddq, $J = 11.0$, 6.2, 4.1 Hz, 1H), 1.77 (t, $J = 0.7$ Hz, 3H), 1.77–1.72 (m, 2H), 1.60–1.50 (m, 2H), 1.42 (s, 9H), 1.37 (dt, $J = 12.6$, 5.3 Hz, 1H), 1.29 (m, 1H), 1.24 (dd, $J = 13.6$, 12.5 Hz, 1H), 0.88 (d, $J = 6.2$ Hz, 3H), 0.81 (d, $J = 6.6$ Hz, 3H), 0.79 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN): $\delta = 156.1$, 143.3, 114.9, 97.6, 97.1, 79.3, 78.8, 74.2, 72.3, 51.3, 50.2, 42.5, 40.9, 39.9, 37.4, 35.8, 32.3, 28.7, 25.1, 24.4, 23.2, 19.0, 16.8; HR-MS (MALDI): calcd for $C_{25}H_{41}NO_5Na^+$ [M+Na^+]: 458.2877, found 458.2864



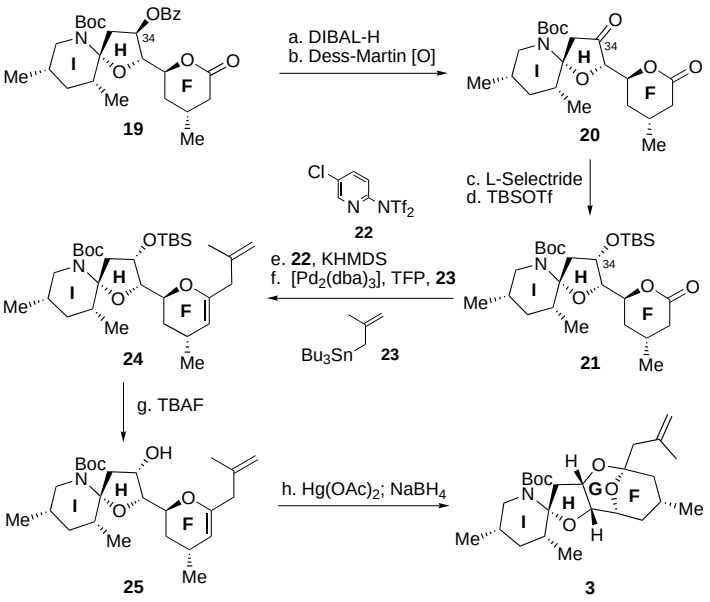
Scheme 5. Selected NOE interactions observed in intermediates **19** and **21**.

in a protected form, which would facilitate handling and purification. We projected that the acid-catalyzed construction of the azaoxaspiro system would require relatively harsh conditions because of the basic character of the nitrogen atom. However, we envisaged that by suitable protection of the nitrogen atom, cyclization with relatively mild acids or Lewis acids might become feasible. As shown in Scheme 4, we began with the protection of **15** as a benzoate (96%). Subsequent deprotection of the PMB ether with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave keto alcohol **16** in 98% yield. This compound was then further activated towards cyclization by formation of the mixed methyl ketal **17** with pyridinium *para*-toluenesulfonate (PPTS) in MeOH (ketal **17** was isolated as a 2:1 mixture of anomers). Hydrogenolysis of the azide in the presence of di-*tert*-butyl dicarbonate (Boc_2O),[14] afforded carbamate **18** in 76% yield over two steps. The stage was now set for the crucial spirocyclization. Although the use of protic acids to effect this transformation led mostly to decomposition of the starting material, we were gratified to observe that exposure of **18** to a catalytic amount of $BF_3 \cdot Et_2O$ at 0 °C resulted in the rapid formation of the desired spirocycle **19** in 60% yield (Table 1).[15] NOE studies of **19** confirmed the formation of the correct spiro stereochemistry (Scheme 5).

The remaining tasks consisted of the inversion of the stereochemistry at C34, the attachment of the methallyl side chain, and final cyclization to close ring G. An oxidation-reduction sequence accomplished the inversion task (Scheme 6). Thus, simultaneous reduction of the benzoate group and of the lactone with diisobutyl aluminum hydride (DIBAL-H) and oxidation of the resulting hydroxy groups with Dess–Martin periodinane gave ketone **20** (66% over two steps). A highly selective reduction of **20** with lithium tri-*sec*-butylborohydride (L-Selectride) gave an intermediate alcohol as a single isomer (84%). Protection of the resulting alcohol with *tert*-butyldimethyl trifluoromethanesulfonate (TBSOTf) furnished **21** in 68% yield.[16] Diagnostic NOE enhancements observed in the NMR spectra of **21** (Scheme 5) confirmed the illustrated stereochemistry.

For the installation of the methallyl side chain, functionalization of the lactone as the ketene acetal triflate[17] or phosphate[18] and subsequent Stille coupling with methallyl-*n*-tributyltin (**23**) appeared particularly attractive, since the resulting enol ether could readily be engaged in the formation of the final ketal under mild conditions. Towards this end, treatment of lactone **21** with potassium bis(trimethylsilyl)-amide (KHMDS) and **22** gave the intermediate ketene acetal triflate in 75% yield. Stille coupling (**23**, $[Pd_2(dba)_3] \cdot CHCl_3$ (dba = *trans*,*trans*-dibenzylideneacetone), tri-2-furylphosphine (TFP))[19] effected the smooth displacement of the

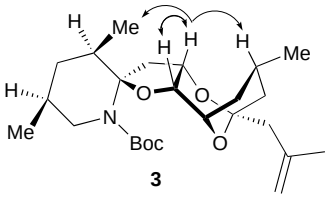
  1433-7851/01/4007-1264 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **2001**, *40*, No. 7



Scheme 6. Synthesis of the FGHI ring system **3**: a) DIBAL-H (1.0 M in CH_2Cl_2, 4.0 equiv), toluene, −78 °C, 10 min; b) Dess–Martin periodinane (3.0 equiv), pyridine (20 equiv), CH_2Cl_2, 0→25 °C, 1 h, 66% over two steps; c) L-Selectride, (1.0 M in THF, 2.0 equiv), THF, −78 °C, 20 min, 84%; d) TBSOTf (1.1 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2, −78 °C, 15 min, 68%; e) **23** (15 equiv), KHMDS (0.5 M in toluene, 10.0 equiv), THF, −20→0 °C, 30 min, 75%; f) LiCl (3.0 equiv), $[Pd_2(dba)_3]\cdot CHCl_3$ (0.05 equiv), tri-2-furylphosphine (0.43 equiv), methallyltributylstannane (5.0 equiv), THF, 25 °C, 10 h, 86%; g) TBAF (1.0 M in THF, 3.0 equiv), THF, 25 °C, 2 h, 93%; h) $Hg(OAc)_2$ (3.5 equiv), THF:H_2O (3:1), −5 °C, 20 min, then $NaBH_4$ (excess), 65% based on 75% conversion. DIBAL-H = diisobutylaluminum hydride, TBS = *tert*-butyldimethylsilyl.

triflate group (OTf) with the methallyl side chain to afford enol ether **24** in 86% yield. Finally, desilylation with TBAF gave the alcohol **25** in 93% yield, thus setting the stage for the final ring closure.

Our initial attempts at intramolecular ketalization with PPTS were not very encouraging. Although the desired FGHI spiro ring system **3** was indeed formed in 68% yield (based on 68% conversion), the product was obtained as an inseparable mixture of spiro isomers. We then turned our attention to other electrophiles. In spite of the presence of the potentially reactive methallyl side chain, we felt that the higher reactivity of the enol ether should allow a chemoselective reaction to take place at the enol double bond. Fortunately, exposure of **25** to $Hg(OAc)_2$ in THF/H_2O (3:1) at −5 °C followed by quenching with $NaBH_4$[20] effected a smooth cyclization into the desired FGHI ring system **3** in 65% yield (based on 75% conversion), with none of the undesired spiroisomer observed (Table 1). Remarkably, this mild mercurocyclization reaction also left the methallyl side chain intact. Scheme 7 displays the three-dimensional shape of **3** with the observed NOE effects, which confirm the assigned stereochemistry.



Scheme 7. Three-dimensional representation of **3** and representative NOE interactions confirming the indicated stereochemistry.

In conclusion, the synthesis of the protected FGHI domain of azaspiracid (**1**) has been achieved in 23 linear steps from known starting materials. The unusual nature of this intricately carved portion of the molecule necessitated the search for novel conditions to effect the required key cyclizations. The power of $BF_3\cdot Et_2O$ to catalyze the expedient formation of the HI spirocycle and the effectiveness of $Hg(OAc)_2$-mediated intramolecular ketalization have ultimately resulted in the first successful synthesis of the FGHI ring system of this novel target in a protected and enantiomerically pure form. Significantly, as both enantiomers of the starting materials utilized in this synthesis are readily available, the route described herein can provide material for continuing efforts toward the total synthesis of azaspiracid (**1**), determination of its absolute and relative stereochemistries, and for chemical biology studies.

Received: December 15, 2000 [Z16281]

[1] M. Satake, K. Ofuji, H. Naoki, K. J. James, A. Furey, T. McMahon, J. Silke, T. Yasumoto, *J. Am. Chem. Soc.* **1998**, *120*, 9967–9968. Two analogues of azaspiracid have also been isolated from *M. edulis*, see K. Ofuji, M. Satake, T. McMahon, J. Silke, K. J. James, H. Naoki, Y. Oshima, T. Yasumoto, *Nat. Toxins* **1999**, *7*, 99–102.

[2] For another approach towards the synthesis of azaspiracid, see R. G. Carter, D. J. Weldon, *Org. Lett.* **2000**, *2*, 3913–3916.

[3] D. B. Collum, J. H. McDonald, W. C. Still, *J. Am. Chem. Soc.* **1980**, *102*, 2118–2120.

[4] A. Basha, M. Lipton, S. M. Weinreb, *Tetrahedron Lett.* **1977**, 4171–4174.

[5] C. R. Schmid, J. D. Bryant, *Org. Synth.* **1995**, *72*, 6–13.

[6] U. S. Racherla, H. C. Brown, *J. Org. Chem.* **1991**, *56*, 401–404.

[7] For a similar cyclization, see A. K. Ghosh, J. Cappiello, D. Shin, *Tetrahedron Lett.* **1998**, *39*, 4651–4654. In our case, the use of $[Ti(O\mathit{i}Pr)_4]$ as a co-catalyst was not necessary.

[8] N. Nakajima, K. Horita, R. Abe, O. Yonemitsu, *Tetrahedron Lett.* **1988**, *33*, 4139–4142.

[9] For a literature precedent, see W. H. Pirkle, P. E. Adams, *J. Org. Chem.* **1980**, *45*, 4117–4121.

[10] M. T. Reetz, K. Kesseler, *J. Org. Chem.* **1985**, *50*, 5436–5438. A triethylsilyl enol ether derived from **7** was used for these Mukaiyama aldol experiments.

[11] K. Ganesan, H. C. Brown, *J. Org. Chem.* **1993**, *58*, 7162–7169.

[12] For a discussion of the numerous factors influencing the stereochemical outcome of boron-mediated aldol reactions, see C. J. Cowden, I. Paterson, *Org. React.* **1997**, *51*, 1–200.

[13] a) F. C. Uhle, *J. Am. Chem. Soc.* **1961**, *83*, 1460–1472; b) K. Schreiber, G. Adams, *Liebigs Ann. Chem.* **1963**, *666*, 155–176; c) G. Adams, H. Th. Huong, *J. Prakt. Chem.* **1981**, *323*, 839–842.

[14] S. Saito, H. Nakajima, M. Inaba, T. Moriwake, *Tetrahedron Lett.* **1989**, *30*, 837–838.

[15] For an example of the use of $BF_3\cdot Et_2O$, see A. M. P. Koskinen, L. A. Otsomaa, *Tetrahedron* **1997**, *53*, 6473–6484.

[16] The corresponding silyl ketene acetal, which results from enolization of the lactone and subsequent silylation, was also isolated in 20% yield from this reaction. This material can be recycled to the starting material in 95% yield with tetra-*n*-butylammonium flouride.

[17] K. Tsushima, K. Araki, A. Murai, *Chem. Lett.* **1989**, 1313–1316.

[18] a) K. C. Nicolaou, G.-Q. Shi, J. L. Gunzner, P. Gärtner, Z. Yang, *J. Am. Chem. Soc.* **1997**, *119*, 5467–5468; b) K. C. Nicolaou, G.-Q. Shi, K. Namoto, F. Bernal, *Chem. Commun.* **1998**, 1757–1758.

[19] V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.

[20] H. C. Brown, P. J. Geoghegan, *J. Org. Chem.* **1970**, *35*, 1844–1850. For a similar cyclization, see S. J. Danishefsky, W. H. Pearson, *J. Org. Chem.* **1983**, *48*, 3865–3866.

  1433-7851/01/4007-1265 $ 17.50+.50/0