molecular architectures in electronic devices in which the well-defined character of π-conjugated oligomers is combined with the material properties of polymers

*Experimental Section*

BOPVUP: Under an argon atmosphere, diisocytosine compound **2** (0.03 g, 0.07 mmol) was dissolved in anhydrous pyridine (5 mL) and heated to 90 °C. A solution of OPV-isocyanate **1** (0.20 g, 0.15 mmol) in anhydrous pyridine (10 mL) was added and the reaction mixture was stirred overnight at 90 °C. The solution was subsequently cooled to room temperature and the pyridine was removed by evaporation under vacuum. The residue was purified by column chromatography (silica gel, ethyl acetate then $CH_2Cl_2$ to remove impurities and finally $CH_2Cl_2$/MeOH (97/3, v/v) to collect the desired product) to afford BOPVUP as an orange solid (95 mg; 45 % yield). UV/Vis ($CHCl_3$): $\lambda_{max}$ ($\varepsilon$) = 432 nm (258000 $M^{-1}cm^{-1}$); $^1H$ NMR (400 MHz, [D]$CHCl_3$, 25 °C): $\delta$ = 13.04 (s, 2H), 12.04 (s, 2H), 10.88 (s, 2H), 7.51 – 7.36 (m, 14H), 7.18 – 7.01 (m, 14H), 6.74 (s, 4H), 5.82 (s, 2H), 4.46 (br s, 4H), 4.02 – 3.85 (m, 32H), 2.42 (br. t, 4H), 2.11 – 1.27 (m, 160H), 1.10 (s, 24H), 1.00 (s, 24H), 0.87 (br t, 18H); $^{13}C$-{$^1H$} NMR (400 MHz, [D]$CHCl_3$, 25 °C): $\delta$ = 173.4, 157.1, 154.8, 153.5, 152.8, 151.5, 151.4, 151.3, 151.2, 138.3, 137.2, 133.5, 128.8, 128.6, 127.9, 127.8, 127.7, 127.0, 128.9, 123.5, 122.8, 122.7, 11.0, 110.7, 110.1, 109.8, 106.1, 105,3, 74.7, 74.7, 74.4, 74.3, 73.8, 69.3, 43.5, 35.4, 35.3, 35.2, 32.9, 32.2, 32.1, 30.6, 30.0, 29.9, 29.7, 29.6, 29.4, 29.3, 29.2, 27.2, 26.6, 26.4, 22.9, 17.1, 17.0, 14.4, 11.8, 11.7, 11.6; IR (UATR): $\tilde{\nu}$ = 2957 $cm^{-1}$(m), 2922 (s), 2852 (s), 1695 (m), 1656 (m), 1583 (s), 1503 (s), 1465 (m), 1422 (s), 1386 (w), 1340 (m), 1253 (s), 1200 (s), 1115 (s), 1042 (m), 963 (s), 916 (w), 850 (m); MALDI-TOF MS ($M_r$ = 3062.62) *m*/*z*: 3063.29; elemental analysis calcd (%) for $C_{196}H_{306}N_8O_{18}$ ($M_r$ = 3062.62): C 75.9, H 10.1, N 3.7; found: C 75.1, H 10.0, N 3.3.

Received: June 20, 2001 [Z17322]


[1] For examples see: J. H. Bourroughes, D. D. C. Bradley, A. R. Brown, R. N. Marks, K. MacKay, R. H. Friend, P. L. Burns, A. B. Holmes, *Nature* **1990**, *347*, 539; A. Kraft, A. C. Grimsdale, A. B. Holmes, *Angew. Chem.* **1998**, *110*, 416; *Angew. Chem. Int. Ed.* **1998**, *37*, 402; U. Mitschke, P. Bäuerle, *J. Mater. Chem.* **2000**, *10*, 1471.

[2] For examples see: A. R. Brown, A. Pomp, C. M. Hart, D. M. de Leeuw, *Science* **1995**, *270*, 972; G. Horowitz, *Adv. Mater.* **1998**, *10*, 365; H. Sirringhaus, P. J. Brown, R. H. Friend, M. M. Nielsen, K Bechgaard, B. M. W. Langeveld-Voss, A. J. H. Spiering, R. A. J. Janssen, E. W. Meijer, P. Herwig, D. M. de Leeuw, *Nature* **1999**, *401*, 685; D. Philp, J. F. Stoddart, *Angew. Chem.* **1996**, *108*, 1242; *Angew. Chem. Int. Ed.* **1996**, *35*, 1154; D. L. Pearson, L. Jones, J. S. Schumm, J. M. Tour, *Synth. Met.* **1997**, *84*, 303.

[3] For examples see: N. S. Sariciftci, L. Smilowitz, A. J. Heeger, *Science* **1992**, *258*, 1474; G. Yu, J. Gao, J. C. Hummelen, F. Wudl, A. J. Heeger, *Science* **1995**, *270*, 1789; J. J. M. Halls, C. A. Walsh, N. C. Greenham, E. A. Marseglia, R. H. Friend, *Nature* **1995**, *376*, 498.

[4] R. E. Martin, F. Diederich, *Angew. Chem.* **1999**, *111*, 1440; *Angew. Chem. Int. Ed.* **1999**, *38*, 1350; J. M. Tour, *Chem. Rev.* **1996**, 96, 303.

[5] S. H. M. Söntjens, R. P. Sijbesma, M. H. P. van Genderen, E. W. Meijer, *J. Am. Chem. Soc.* **2000**, *122*, 7487.

[6] R. P. Sijbesma, F. H. Beijer, L. Brunsveld, B. J. B. Folmer, J. H. K. K. Hirschberg, R. F. M. Lange, J. K. L. Lowe, E. W. Meijer, *Science* **1997**, 278, 1601.

[7] B. J. B. Folmer, R. P. Sijbesma, R. M. Versteegen, J. A. J. van der Rijt, E. W. Meijer, *Adv. Mater.* **2000**, *12*, 874.

[8] F. S. Schoonbeek, J. H. van Esch, B. Wegewijs, D. B. A. Rep, M. P. de Haas, T. M. Klapwijk, R. M. Kellog, B. L. Feringa, *Angew. Chem.* **1999**, *111*, 1486; *Angew. Chem. Int. Ed.* **1999**, *38*, 1393.

[9] A. P. H. J. Schenning, P. Jonkheijm, E. Peeters, E. W. Meijer, *J. Am. Chem. Soc.* **2001**, *123*, 409.

[10] A. El-ghayoury, E. Peeters, A. P. H. J. Schenning, E. W. Meijer, *Chem. Commun.* **2000**, 1601.

[11] S. H. M. Söntjens, R. P. Sijbesma, M. H. P. van Genderen, E. W. Meijer, unpublished results.

[12] E. Peeters, P. A. van Hal, J. Knol, C. J. Barbec, N. S. Sariciftci, J. C. Hummelen, R. A. J. Janssen, *J. Phys. Chem. B* **2000**, *104*, 10174.

[13] For examples see: L. Ouali, V. V. Krasnikov, U. Stalmach, G. Hadziioannou *Adv. Mater.* **1999**, *11*, 1515; J.-F Nierengarten, J.-F Eckert, J.-F Nicoud, L. Ouali, V. V. Krasnikov, G. Hadziioannou *Chem. Commun.* **1999**, 617.

[14] T. Q. Nguyen, I. B. Martini, J. Liu, B. J. Schwartz, *J. Phys. Chem. B* **2000**, *104*, 237.

[15] L. S. Roman, M. R. Andersson, T. Yohannes, O. Inganäs, *Adv. Mater.* **1997**, *9*, 1164; H. Mattoussi, M. F. Rubner, F. Zhou, J. Kumar, S. K. Tripathy, L. Y. Chiang, *Appl. Phys. Lett.* **2000**, *77*, 1540.


## Synthesis of the (+)-C26 – C40 Domain of the Azaspiracids by a Novel Double Intramolecular Hetero-Michael Addition Strategy**

Craig J. Forsyth,* Junliang Hao, and Josep Aiguade

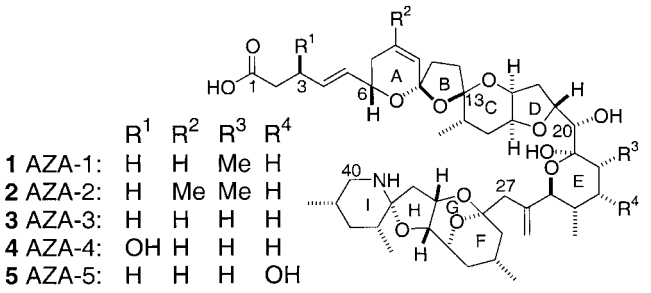
The azaspiracid natural products (AZA **1** – **5**, ) are causative agents of human poisonings associated with the consumption of shellfish that were first recognized in the Netherlands in 1995.[1] Originally isolated from the mussel *Mytilus edulis* cultivated in Killary Harbor, Ireland, the azaspiracids have since been detected in a growing range of aquatic organisms and geographical locations. Physiological aspects of azaspiracid poisoning (AZP) are distinct from those of other known shellfish intoxications. These include delayed onset and prolonged duration of acute symptoms, and necrosis of the intestine, thymus, and liver. Hence, the azaspiracids represent an emerging new class of environmental toxins with serious economic and human health consequences. As a result there is an urgent need of authentic samples for continued environmental monitoring.

Structurally, the azaspiracids are complex $\omega$-amino acids that contain within their 40-carbon backbone an unprecedented array of polycyclic, spiro-fused ring systems. Among the members of this class reported to date, minor variations in skeletal substitution occur within the C1 – C25 domain, but the C26 – C40 portion remains constant. The relative stereochemistries within the C6 – C25 and C28 – C40 domains of the azaspiracids have been assigned, but neither the stereochemical relationship between these two regions, nor the absolute stereochemistry of either has been established. These factors

[*] Prof. Dr. C. J. Forsyth, J. Hao, J. Aiguade
Department of Chemistry
Institute of Technology
University of Minnesota
Minneapolis, MN 55455 (USA)
Fax: (+1) 612-626-7541
E-mail: forsyth@chem.umn.edu

[**] This work was supported by the United States National Institute of Environmental Health Sciences (NIEHS; grant number ES10615), NIH, and by Bristol-Myers Squibb (CJF). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIEHS, NIH, or BMS. We thank Dr. A. B. Dounay and Dr. G. Florence for critical reading of the manuscript.

combine to make the azaspiracids premier, yet daunting targets of laboratory synthesis.[2] Each major domain embodies a wealth of heterocyclic ensembles that transcends the direct application of conventional synthetic methods for their

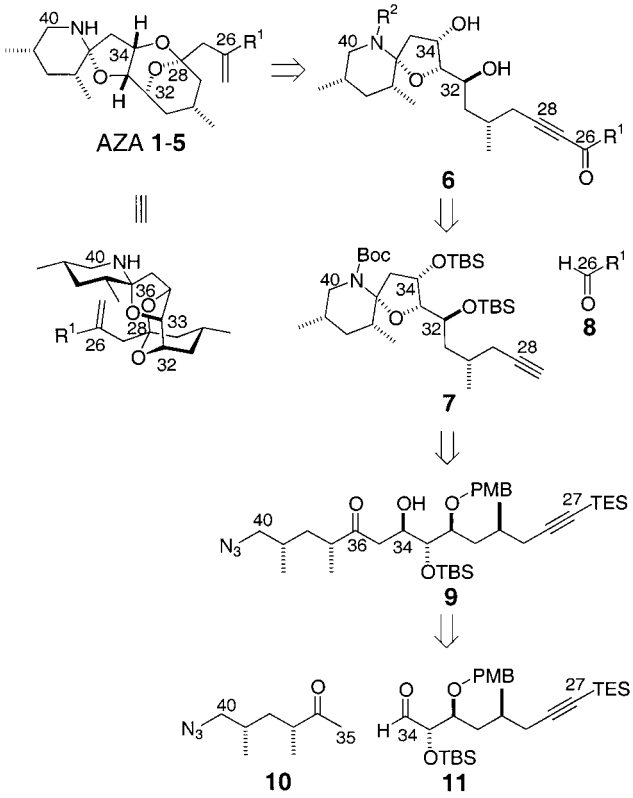


| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| **1** AZA-1: | H | H | Me | H |
| **2** AZA-2: | H | Me | Me | H |
| **3** AZA-3: | H | H | H | H |
| **4** AZA-4: | OH | H | H | H |
| **5** AZA-5: | H | H | H | OH |

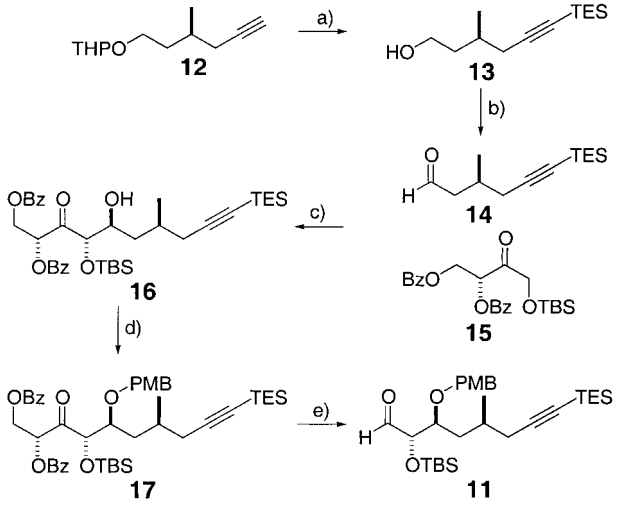
assembly. Of particular challenge is control over the natural products' relative configuration at C13[2e] of the ABCD polyether and the stereoselective construction of the unprecedented spiroaminal-fused dioxabicyclo[3.3.1]nonane system comprising the FGHI rings. Nicolaou and co-workers recently reported the first successful accomplishment of the latter task.[2b] Summarized here is an alternative enantioselective assembly of the C26–C40 domain of the azaspiracids that features the implementation of novel heterocycle formation methods recently developed in our laboratories for this purpose.

The synthetic plan for the assembly of the azaspiracid C26–C40 domain involved the sequential formation of the HI and FG ring systems, with an intermediary convergent attachment of the adjacent E ring containing fragment through C26–C27 bond formation (Scheme 1). A novel double intramolecular hetero-Michael addition (DIHMA)[2f, 3] was designed to form the FG system of the azaspiracids (**1**–**5**) from dihydroxy ynone **6**. The ynone would be derived from the convergent coupling of a C27–C40 acetylide (**7**) with a C26 aldehyde (**8**). The latter may represent the entire C1–C26 portion of the azaspiracids, or a subfragment thereof. The availability of exceedingly mild and chemoselective methods for acetylide additions to aldehydes[4] would support a late stage connection of the entire azaspiracid carbon chain through C26–C27 bond formation. Hence, the DIHMA-based heterocycle formation strategy proceeding through a C26–C28 ynone provides a strategic approach for major fragment coupling. To demonstrate the feasibility of this general strategy, access to the HI spiroaminal-containing alkyne **7** was required. This would be obtained from keto-azide **9** by cyclization of a derived primary amino functionality. The $\beta$-hydroxy ketone moiety of **9** logically implies an early aldol junction of a C35–C40 methyl ketone (**10**)[5] and a C27–C34 aldehyde (**11**).

The synthesis of aldehyde **11** began with the known alkyne **12**[6] bearing the single C30 stereogenic center (Scheme 2). Sequential protection of the alkyne terminus and hydroxyl liberation provided primary alcohol intermediate **13**. The derived aldehyde **14** underwent a substrate controlled boron-mediated *anti*-aldol reaction with chiral ketone **15** to establish the correct relative configurations at C32 and C33.[7] The newly generated C32 hydroxyl group of **16** was converted into the *p*-methoxybenzyl ether **17**. Thereafter, the dibenzoyl




Scheme 1. Retrosynthesis of **1**–**5**.



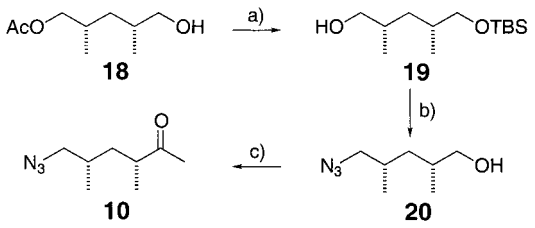

Scheme 2. Synthesis of the C27–C34 aldehyde **11**. a) 1) *n*BuLi, TESCl, THF, −78 °C, 2) PPTS, MeOH, RT, 74% (two steps); b) TPAP, NMO, 4 Å MS, $CH_2Cl_2$, RT; c) $Cy_2BCl$, $NEt_3$, $Et_2O$, 72% (two steps); d) PMBOC(=NH)$CCl_3$, $BF_3 \cdot OEt_2$, $CH_2Cl_2$, RT, 87%; e) 1) $NaBH_4$, MeOH, RT, 98%, 2) EtMgBr, THF, 0 °C, 3) $NaIO_4$, MeOH/$H_2O$ (2:1, v/v), RT, 70% (two steps). TESCl = chlorotriethylsilane, PPTS = pyridinium *p*-toluenesulfonate, TPAP = tetra-*n*-propylammonium perruthenate-(VII), NMO = 4-methylmorpholine *N*-oxide, Cy = cyclohexyl, PMB = *p*-methoxybenzyl.

ketone was transformed into a triol that was oxidatively cleaved with $NaIO_4$ to afford aldehyde **11**.

The complementary C35–C40 methyl ketone **10** was obtained conveniently from the known alcohol **18** (Scheme 3).[2d] Alternative manipulation of the terminally

  1433-7851/01/4019-3664 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **2001**, *40*, No. 19

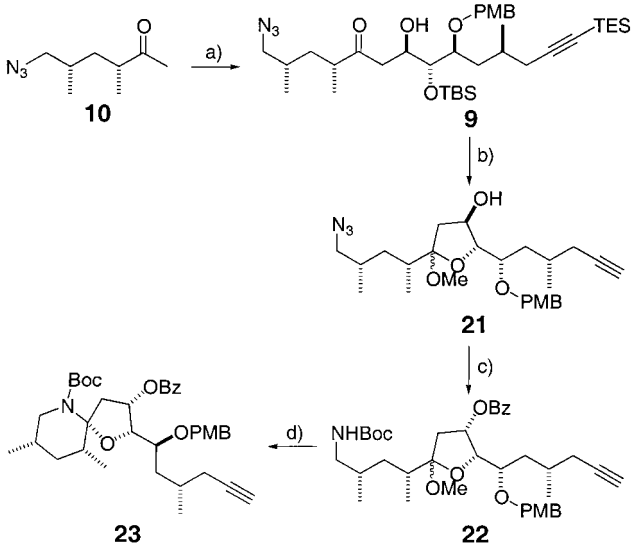
differentiated 1,3-dimethyl building block **18** may allow access to either enantiomer of the C35–C40 methyl ketone. To match the configuration of aldehyde **11**, alcohol **18** was




Scheme 3. Synthesis of the C35–C40 methyl ketone **10**. a) 1) TBSCl, $Et_3N$, $CH_2Cl_2$, RT, 2) $LiAlH_4$, $Et_2O$, 0 °C; b) 1) $Ph_3P$, $(PhO)_2P(=O)N_3$, DEAD, THF, RT, 2) TBAF, THF, RT, 69% (four steps); c) 1) DMSO, ClCOCOCl, $CH_2Cl_2$, −78 °C, $Et_3N$, RT; 2) MeMgBr, THF, 0 °C, 3) DMSO, ClCOCOCl, $CH_2Cl_2$, −78 °C, $Et_3N$, RT; 62% (three steps). TBAF = tetra-*n*-butylammonium fluoride, TBSCl = *tert*-butyldimethylchlorosilane, DEAD = diethyl azodicarboxylate, DMSO = dimethyl sulfoxide.

converted into monosilyl ether **19**. Installation of the latent terminal amino functionality of the azaspiracids was effected by treatment of alcohol **19** with DEAD and $(PhO)_2P(O)N_3$ to yield the corresponding azide **20**.[8] The methyl ketone moiety was then incorporated at the opposite terminus to complete the preparation of **10**.

With synthetic access to C27–C34 and C35–C40 aldol partners applicable to either enantiomeric series, construction of the polycyclic F–I system could be thoroughly addressed. The Felkin aldol product **9** was obtained in > 19:1 diastereoselectivity by treatment of ketone **10** with LDA followed by the addition of aldehyde **11** (Scheme 4). The *anti*-selectivity necessitated an inversion of configuration at the newly generated C34 stereogenic center. This was accomplished effectively within the context of the tetrahydrofuran H ring.




Scheme 4. Spiroaminal formation with $Yb[OTf]_3$. a) 1) LDA, THF, −78 °C, then **11**, 78%; b) 1) TBAF/AcOH (5:1), THF, RT, 2) PPTS, MeOH, RT, 82% (two steps); c) 1) $Ph_3P$, DEAD, BzOH, THF, RT, 62%, 2) $Bu_3P$, BocON, toluene, −20 °C to RT, 82%; d) $Yb[OTf]_3$, $CH_3CN$, RT, 72%. Tf = trifluromethanesulfonyl, LDA = lithium diisopropylamide, BzOH = benzoic acid, Boc = *tert*-butoxycarbonyl, BocON = 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile.

To this end, desilylation of **9** followed by mixed ketal formation afforded the cyclic intermediate **21**. The C34 configuration was then inverted by a Mitsunobu reaction. Spiroanulation of the terminal piperidine ring upon the H ring was preceded by reduction of the azide and *tert*-butylcarbamate formation using a convenient one-pot procedure.[9] Upon screening a variety of Lewis acid and solvent combinations to effect spiroaminal formation from the *tert*-butylcarbamate/mixed ketal **22**,[10] optimal results were achieved by using $Yb[OTf]_3$ in $CH_3CN$ at room temperature.[11, 12] This afforded rapid conversion to spiroaminal **23** as essentially a single diastereoisomer. The relative configuration of the newly formed C36 stereogenic center was assigned by NOE studies (Figure 1) to correspond to the azaspiracid natural

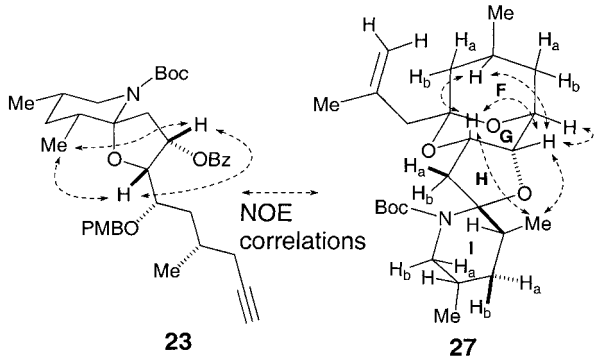



Figure 1. Observed NOEs in **23** and **27**.[14]

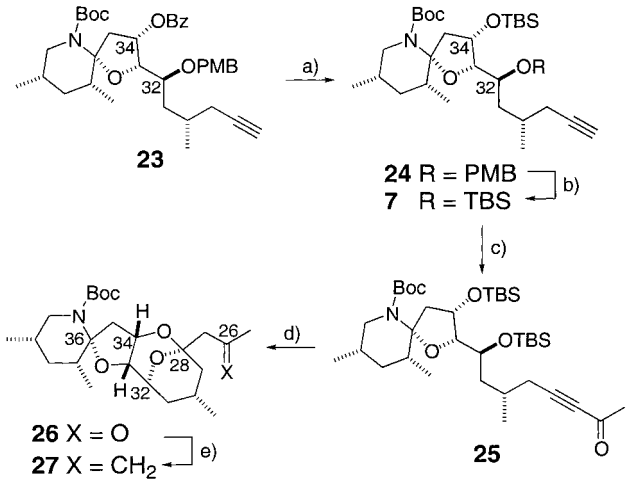
products. As anticipated, this places the C37 and C39 methyl groups equatorially and the C36 oxygen atom axially about the chair of the piperidine I-ring in **23**. The elaborated HI ring system **23** was thus prepared in six steps from aldol partners **10** and **11**.

Spiroaminal **23** bears a terminal alkyne set for coupling with the C1–C26 portion of the azaspiracids, as well as a latent C32,34-diol for formation of the F–G ring system. To facilitate a direct DIHMA process[2f] for F–G ring formation, the differentially protected C32,34-diol was converted into the corresponding bis-silyl ether prior to C26–C27 bond formation (Scheme 5). The C34 benzoate of **23** was readily cleaved with CsOH and the resulting alcohol was silylated with TBSOTf to provide mono-silyl ether **24**. It was observed that the HI ring spiro[5.4]aminal was susceptible to acid-induced isomerization to the corresponding piperidine–tetrahydropyran spiro[5.5]aminal when the C32 hydroxyl group was free to participate in *trans*-ketalization. Therefore, a pH 9 buffer was used in a DDQ-mediated oxidative cleavage of the C32 *p*-methoxybenzyl ether to attenuate the acidity of the reaction medium. Subsequent silylation gave the bis-TBS ether to complete the preparation of the convergent coupling intermediate **7**. With the intact HI spiroaminal incorporated into **7**, elaboration into the THF-fused dioxabicyclo[3.3.1]nonane ring system could be explored by electrophilic activation of the C28 alkynyl carbon atom by conjugation to a C26 ketone. The viability of this strategy was demonstrated with methyl ketone **25** (Scheme 5). For this, the magnesium

  1433-7851/01/4019-3665 $ 17.50+.50/0 

acetylide derived from **7** was added to acetaldehyde and the resultant propargylic alcohol was oxidized with $MnO_2$ to afford ynone **25**.

Formation of a simple 2,9-dioxabicyclo[3.3.1]nonane system had been accomplished previously from a masked 7,9-




Scheme 5. Formation of the F–G ring system by DIHMA. a) 1) CsOH, MeOH, RT, 2) TBSOTf, 2,6-lutidine, 0 °C, 98 % (two steps); b) 1) DDQ, *t*BuOH, pH 9 buffer, sonication, 2) TBSOTf, 2,6-lutidine, 0 °C, 82 % (two steps); c) 1) EtMgBr, acetaldehyde, THF, −78 °C, 98 %, 2) $MnO_2$, hexanes, RT, 78 %; d) TBAF, THF, RT, 85 %; e) $Ph_3PCH_3Br$, *n*BuLi, THF, 0 °C to RT, 72 %. DIHMA = double intramolecular hetero-Michael addition, TBSOTf = *tert*-butyldimethylsilyltrifluoromethanesulfonate, DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone.

dihydroxy-ynone under acidic reaction conditions.[2f] However, the previously noted lability of the HI spiroaminal system towards intramolecular transketaliztion in the presence of a free C32 hydroxyl group prompted the examination of alternative reaction conditions for the key DIHMA process. In a remarkably facile operation, treatment of ynone **25** with TBAF in THF at room temperature promoted silyl ether cleavage and bis-conjugate addition of the liberated C32 and C34 oxygen atoms upon C28 to provide the targeted FG ring system **26** in high yield (Scheme 5). The relative stereochemistry of the isobutenyl-substituted polycycle **27**[13] was confirmed by extensive NOE studies (Figure 2)[14] after methylenation of the residual ketone of **26**. Hence, the complete F–I polycyclic system was formed bearing the complete relative configurations found in the azaspiracid natural products. The C28 configuration obtained in the bis-conjugate addition likely results from initial F ring formation by attack of the proximal C32 oxygen atom upon the $\beta$-carbon atom of the ynone followed by a geometrically constrained addition of the C34 oxygen atom upon the resultant enone to close the G ring. By avoiding acidic conditions for the cyclization, the integrity of the piperidine–THF spiroaminal was maintained throughout the TBAF-initiated DIHMA process.

In summary, a stereocontrolled assembly of the substituted FGHI ring system of the azaspiracids that exploits novel methods for heterocycle synthesis has been developed. The sequence featured formation of an alkynyl-substituted H–I ring spiroaminal, generation of a latent 7,9-dihydroxy-ynone, and bis-heteroconjugate addition to close the F–G rings. The utility of $Yb[OTf]_3$ for efficient *N*-Boc spiroaminal formation was demonstrated in the formation of the H–I ring system. The C27–C40 alkynyl intermediate **7** containing the intact HI system was designed to allow a highly convergent, chemoselective, and late-stage fragment coupling with a C26 aldehyde en route to the natural products. The effectiveness of the DIHMA strategy for the synthesis of the fully functionalized 2,9-dioxabicyclo[3.3.1]nonane system representing the substituted F and G rings of the azaspiracids was established by using a TBAF-induced in situ desilylation–bis-conjugate addition sequence. This stereoselective intramolecular dihydroxy-ynone isomerization directly provided a $\beta$-keto-ketal that allowed the simple introduction of the C26 alkene of the azaspiracids. Finally, the synthetic sequence is amenable to the generation of either enantiomer of the C28–C40 domain. Hence, this work complements previous studies[2] to serve as a platform for continued research aimed at the development and application of organic synthesis to meet the needs and opportunities associated with the recent discovery of the azaspiracid class of natural products.

Received: July 6, 2001 [Z 17439]


[1] a) M. Satake, K. Ofuji, H. Naoki, K. J. James, A. Furey, T. McMahon, J. Silke, T. Yasumoto, *J. Am. Chem. Soc.* **1998**, *120*, 9967; b) K. Ofuji, M. Satake, T. McMahon, J. Silke, K. J. James, H. Naoki, Y. Oshima, T. Yasumoto, *Nat. Toxins* **1999**, *7*, 99; c) E. Ito, M. Satake, K. Ofuji, N. Kurita, T. McMahon, K. James, T. Yasumoto, *Toxicon* **2000**, *38*, 917; d) K. Ofuji, M. Satake, T. McMahon, K. J. James, H. Naoki, Y. Oshima, T. Yasumoto, *Biosci. Biotechnol. Biochem.* **2001**, *65*, 740.

[2] a) R. G. Carter, D. J. Weldon, *Org. Lett.* **2000**, *2*, 3913; b) K. C. Nicolaou, P. M. Pihko, N. Diedrichs, N. Zou, F. Bernal, *Angew. Chem.* **2001**, *113*, 1302; *Angew. Chem. Int. Ed.* **2001**, *40*, 1262; corrigendum: K. C. Nicolaou, P. M. Pihko, N. Diedrichs, N. Zou, F. Bernal, *Angew. Chem.* **2001**, *113*, 1621; *Angew. Chem. Int. Ed.* **2001**, *40*, 1573; c) J. Aiguade, J. Hao, C. J. Forsyth, *Tetrahedron Lett.* **2001**, *42*, 817; d) J. Hao, J. Aiguade, C. J. Forsyth, *Tetrahedron Lett.* **2001**, *42*, 821; e) A. B. Dounay, C. J. Forsyth, *Org. Lett.* **2001**, *3*, 975; f) J. Aiguade, J. Hao, C. J. Forsyth, *Org. Lett.* **2001**, *3*, 979.

[3] For examples of double intermolecular hetero-Michael additions see: D. T. MacPherson, H. K. Rami, *Comprehensive Organic Functional Group Transformations*, *Vol. 4* (Ed.: G. W. Kirby), Pergamon, New York, **1995**, pp. 159.

[4] a) K. Takai, T. Kuroda, S. Nakatsukasa, K. Oshima, H. Nozaki, *Tetrahedron Lett.* **1985**, *26*, 5585; b) A. Fürstner, *Chem. Rev.* **1999**, *99*, 991.

[5] Compound **10** was similarly used in the seminal synthesis of the FGHI system of the azaspiracids.[2b]

[6] O. Dirat, C. Kouklovsky, Y. Langlois, *J. Org. Chem.* **1998**, *63*, 6634.

[7] For a thorough description of relevant boron-mediated aldol reactions, see: a) C. J. Cowden, I. Paterson, *Org. React.* **1997**, *51*, 1–200; b) I. Paterson, D. J. Wallace, S. M. Velazquez, *Tetrahedron Lett.* **1994**, *48*, 9083; c) I. Paterson, D. J. Wallace, *Tetrahedron Lett.* **1994**, *48*, 9087; both enantiomers of aldol partner **15** are readily available: M. Carda, E. Falomir, J. Murgo, E. Castillo, F. Gonzalez, J. A. Marco, *Tetrahedron Lett.* **1999**, *40*, 6845.

[8] B. Lal, B. N. Pramanik, M. S. Manhas, A. K. Bose, *Tetrahedron Lett.* **1977**, 1977.

[9] X. Ariza, F. Urpi, C. Viladomat, J. Vilarrasa, *Tetrahedron Lett.* **1998**, *39*, 9101.

[10] It was reported that although protic acids were generally unproductive in a similar system, the Lewis acid borontrifluoride etherate was effective.[2b] Treatment of **22** with borontrifluoride etherate gave **23** in


  1433-7851/01/4019-3666 $ 17.50+.50/0 

< 50 % yield at − 20 °C, whereas Yb[Otf]$_3$ provided **23** in 72 % yield at room temperature.
[11] For a review on Yb[OTf]$_3$ in synthesis see: S. Kobayashi, *Synlett* **1993**, 689.
[12] For a thorough review on spiroaminal formation see: W. Rasshofer, *Methoden Org. Chem. (Houben-Weyl)*, *4th ed. 1952*-, Vol. E14a/2, **1991**, pp. 1 – 200.
[13] Compound **27** was previously described by Nicolaou et al.[2b] The spectral data obtained for **27** here ($[\alpha]_D^{23} = +5.0$ ($c = 0.26$, $CHCl_3$), IR, $^1$H and $^{13}$C NMR, HRMS) are fully consistent with those reported in reference [2b].
[14] For the assignment of methylene protons, the higher field proton was suffixed by a (e.g., $H_a$), while the lower field proton was suffixed by b (e.g., $H_b$).

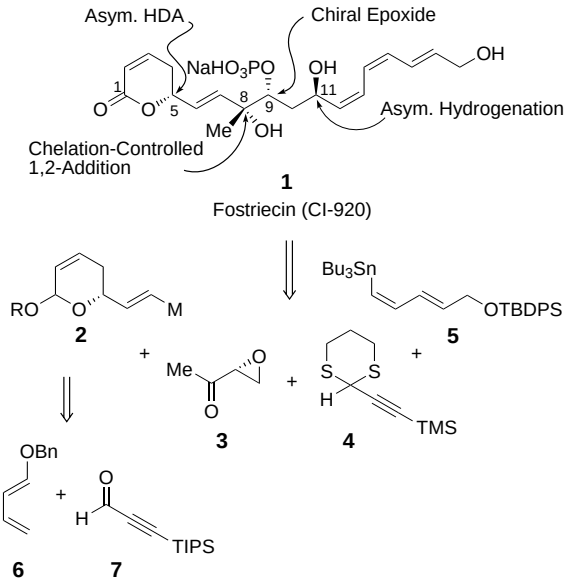
## Total Synthesis of Fostriecin (CI-920)**

David E. Chavez and Eric N. Jacobsen*

Fostriecin (CI-920, **1**; see Scheme 1) is a structurally interesting antitumor agent that was first isolated in 1983 by scientists at Warner Lambert-Parke Davis.[1] It displays in vitro activity against a broad range of cancerous cell lines as well as in vivo antitumor activity,[2] and it appears to operate by a novel mechanism involving inhibition of the mitotic entry checkpoint.[3] In this context, fostriecin is a potent inhibitor of protein serine/threonine phosphatases, and it is in fact the most selective protein phosphatase inhibitor identified to date ($10^4$ times greater affinity for the protein phosphatases PP2A and PP4 versus PP1).[4]

It was not until 1997 that a correct and complete stereochemical assignment of fostriecin was made by Boger and coworkers,[5] and that was followed very recently by a report of the first total synthesis from the same group.[6] Certainly, the development of a practical synthetic route to fostriecin is warranted based on its interesting biological properties. In addition, clinical trials carried out at the National Cancer Institute were halted early in Phase I over concerns about the stability and purity of the natural material.[7] A flexible synthetic route to **1** could serve as a basis for the discovery of analogues with similar biological but more desirable physical properties. In addition, the structure of fostriecin poses an assortment of interesting challenges to an efficient synthetic design, including the presence of the unsaturated lactone,[8] the C8 – C11 triol monophosphate component, and the conjugated *Z*,*Z*,*E*-trienol unit. Herein we report a new total synthesis of fostriecin. Our approach integrates highly effective asymmetric catalytic reactions to generate key chiral building blocks, and efficient coupling reactions to enable their convergent assembly.

The synthetic plan involves assembly of four fragments (**2** – **5**) of similar complexity (Scheme 1). Epoxyketone **3** plays a central role in our strategy, serving not only as the source of the C9 stereocenter, but also as a lynchpin for joining the left-hand vinyl lactone unit **2** and the right-hand triene diol fragment. We anticipated applying the [(salen)Co]-catalyzed hydrolytic kinetic resolution (HKR) reaction to the preparation of enantioenriched **3**, encouraged by the remarkable generality displayed by this method for the preparation of highly enantioenriched terminal epoxides.[9] However, while racemic **3** was prepared easily from inexpensive methyl vinyl ketone,[10] its HKR proved particularly challenging. Under standard conditions ((*S*,*S*)-**8**, 0.2 – 2 mol %, 0.55 equiv $H_2O$), precipitation of catalyst as the reduced [(salen)Co$^{II}$] complex was observed with low substrate conversion.[11] Fortunately, this problem proved relatively easy to circumvent. When the reaction was carried out under an atmosphere of $O_2$ instead of $N_2$ or air, reduction of catalyst was avoided and the HKR proceeded to completion affording **3** in > 99 % *ee* and 40 % yield (Scheme 2; possible yield = 50 %).




Scheme 1. Retrosynthetic analysis of **1**. TBDPS = *tert*-butyldimethylsilyl; TIPS = triisopropylsilyl

With an effective route to (*R*)-**3** in hand, the next key consideration in the synthesis was the diastereoselective addition of a vinyl organometallic such as **2** to the carbonyl group of **3** to assemble the two left-hand fragments and set the C8 tertiary alcohol stereocenter. While addition of Grignard reagents to **3** proceeded in THF with exclusive reaction at the ketone functionality, only modest diastereoselectivity (ca. 4:1)

[*] Prof. E. N. Jacobsen, D. E. Chavez
Department of Chemistry and Chemical Biology
Harvard University
Cambridge, MA 02138 (USA)
Fax: (+1) 617-496-1880
E-mail: jacobsen@chemistry.harvard.edu

[**] We thank Professor Andrew G. Myers and Scott E. Schaus for helpful discussions, and Dr. Alexandra E. Gould and Isabel K. Reichardt for important preliminary experimental work. We also thank Dr. Robert J. Schultz of the Drug Synthesis and Chemistry Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer institute, for a sample of natural fostriecin. This work was supported by the NIH (GM-59316), and by Beinecke Memorial and NSF predoctoral fellowships to D.E.C.

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

  1433-7851/01/4019-3667 $ 17.50+.50/0 