ORGANIC LETTERS

2001
Vol. 3, No. 7
979−982

Synthesis of a 2,9-Dioxabicyclo[3.3.1]nonane via Double Intramolecular Hetero-Michael Addition: Entry to the F–G Ring System of the Azaspiracids

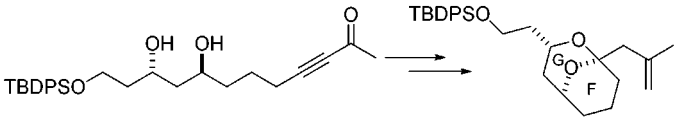
Josep Aiguade, Junliang Hao, and Craig J. Forsyth*

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota, Minnesota 55455

forsyth@chem.umn.edu.

Received January 15, 2001

ABSTRACT



An effective approach to form a 1,3-disubstituted 2,9-dioxabicyclo[3.3.1]nonane system representing the core of the F and G rings (C28–C34) of the azaspiracid natural products has been developed. The double intramolecular hetero-Michael addition (DIHMA) of a diol upon an ynone generated the bicyclic ketal in a highly diastereoselective fashion.

The azaspiracids are architecturally intriguing natural products that present a human health hazard due to their recurring contamination of edible shellfish.[1−3] The structural novelty, undefined stereochemistry,[1] distinct toxicology,[3] and inaccessibility of authentic samples make the azaspiracids important synthetic targets.[4] The unique structures of the azaspiracids (**1**−**3**, Figure 1)[1,2] include in their terminal domain a 2,9-dioxabicyclo[3.3.1]nonane system (F−G rings) fused to a THF−piperidine spiroaminal (H−I rings).

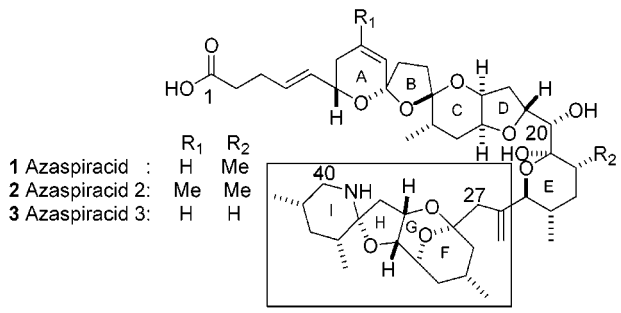
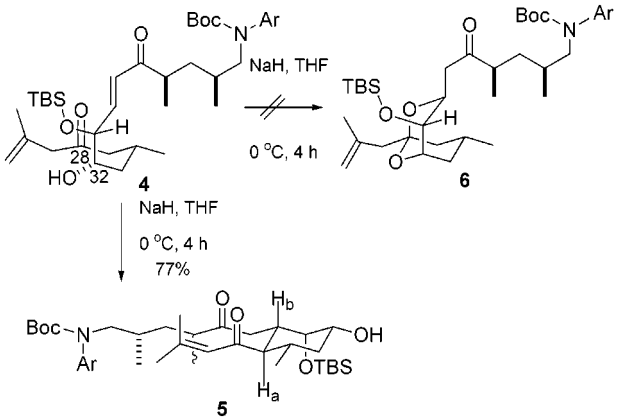


Figure 1. Azaspiracids.

One approach toward the synthesis of the F−I polycyclic system has focused on the development of a biomimetic hemiketal hetero-Michael addition (HHMA) to form the F−G ring system (Scheme 1).[4a] However, upon treatment under basic conditions, acyclic intermediate **4** underwent a facile intramolecular *C*-Michael reaction to give **5** in preference

Scheme 1. Carbon- vs Oxygen-Michael Addition

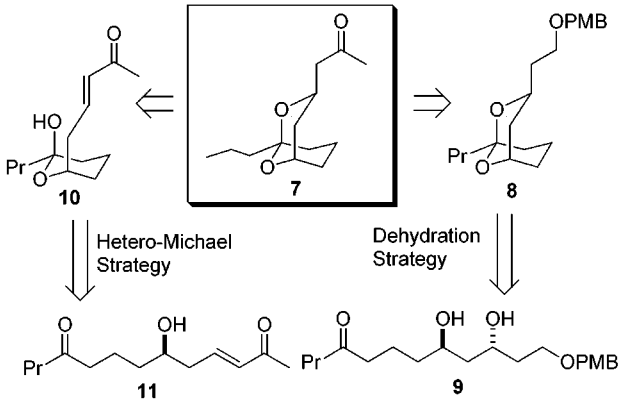


10.1021/ol015556l CCC: $20.00
Published on Web 03/16/2001

to 2,9-dioxabicyclo[3.3.1]nonane (F−G ring) formation which would have yielded **6**.[4a] Also, the 1,1-disubstituted alkene in **4**, representing that at C26[5] of **1**−**3**, readily isomerized to give a trisubstituted alkene. Reported here are the results of further studies that have led to an alternative strategy toward the F−G bicyclic system of the azaspiracids. The revised approach avoids previous complications and provides an efficient and reliable method to construct a substituted 2,9-dioxabicyclo[3.3.1]nonane.

To thoroughly examine the HHMA approach toward the construction of azaspiracids' F−G rings, a simple system containing only the essential functionalities was sought (Scheme 2). Furthermore, a synthesis of an authentic sample

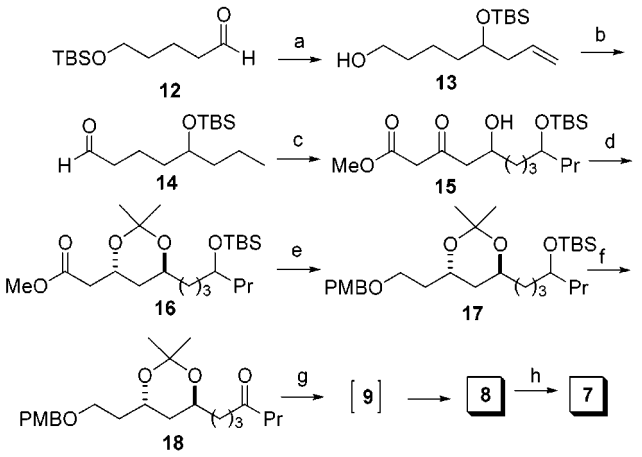
Scheme 2. HHMA vs Dehydrative Approaches to **7**



of the 1,3-disubstituted 2,9-dioxabicyclo[3.3.1]nonane core (**7**) was developed opn the basis of a classic dihydroxy ketone dehydration strategy[6] to facilitate rapid screening of potential biomimetic cascade reaction conditions.

Bicycloketal **7** was initially synthesized via dihydroxy ketone **9** (Scheme 2). Zinc-mediated allylation[7] of aldehyde **12** followed by protection of the resulting secondary alcohol as its TBS ether and selective cleavage of the primary TBS group provided alcohol **13** (Scheme 3). The terminal alkene was saturated. Subsequent Swern oxidation followed by addition of acetoacetate dianion afforded the corresponding *β*-ketoester **15**. Hydroxyl-directed selective *anti* reduction[8] of the ketone and protection of the resulting diol as an acetonide gave ester **16**. Reduction of **16** with $LiAlH_4$ followed by *p*-methoxybenzyl (PMB) ether formation yielded **17**. Following removal of the TBS group with TBAF, the secondary alcohol was oxidized to ketone **18**. After considerable optimization, it was found that diol liberation was best effected by treatment of **18** with CSA in CH_2Cl_2:MeOH (5:1, v/v) to yield crude **9**. Removal of the solvent followed by dissolution of the residue in benzene and stirring at room

Scheme 3. Synthesis of **7** via Dehydration[a]

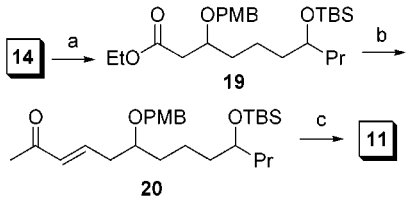


[a] (a) (i) allyl bromide, Zn powder, DMF, 51%; (ii) TBSCl, Et_3N, CH_2Cl_2, 70%; (iii) HF·pyr, THF, 77%; (b) (i) Pd/C, H_2, EtOAc; (ii) Swern oxidation, 85% (two steps); (c) acetoacetate dianion, THF, −78 °C, 71%; (d) (i) $Me_4NBH(OAc)_3$; (ii) 2,2-dimethoxypropane, PPTS, 79% (two steps); (e) (i) $LiAlH_4$, Et_2O; (ii) PMBCl, KH, THF, 91% (two steps); (f) (i) TBAF, THF, 86%; (ii) TPAP, NMO, CH_2Cl_2, 99%; (g) CSA, CH_2Cl_2 : MeOH (5:1, v/v), 82%; (h) (i) DDQ, CH_2Cl_2, 55%; (ii) TPAP, NMO, CH_2Cl_2; (iii) MeMgBr, THF; (iv) TPAP, NMO, CH_2Cl_2, 34% (three steps).

temperature completed the conversion into ketal **8** in 82% overall yield from **18**.[9] The terminal ether was transformed into a methyl ketone in four additional steps. These included removal of the PMB group, oxidation of the resultant alcohol to the corresponding aldehyde, addition of MeMgBr, and final oxidation to ketone **7**.

With an authentic sample of **7** in hand, attention was directed toward the preparation of **11**, a simple substrate with which to thoroughly study the HHMA approach to the targeted bicyclic ketal (Scheme 4). Conveniently, aldehyde

Scheme 4. Synthesis of HHMA Precursor **11**[a]



[a] (a) (i) LDA, EtOAc, THF, 88%; (ii) PMBOC(=NH)CCl_3, BF_3·OEt_2, CH_2Cl_2, 86%; (b) (i) DIBAL, toluene, 87%; (ii) dimethyl (2-oxopropyl)-phosphonate, DIPEA, LiCl, MeCN, 82%; (c) (i) CSA, MeOH, 90%; (ii) Dess−Martin oxidation; (iii) DDQ, CH_2Cl_2, 52% (two steps).

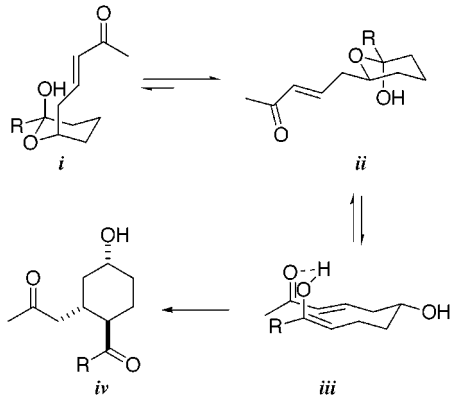
14 served as the starting point toward **11**. Subjection of **14** to the enolate derived from ethyl acetate and capping of the resultant *β*-hydroxy ester as its PMB ether yielded **19**. Reduction of **19** directly to the corresponding aldehyde was

(1) Satake, M.; Ofuji, K.; Naoki, H.; James, K. J.; Furey, A.; McMahon, T.; Silke, J.; Yasumoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 9967.
(2) Ofuji, K.; Satake, M.; McMahon, T.; Silke, J.; James, K. J.; Naoki, H.; Oshima, Y.; Yasumoto, T. *Nat. Toxins* **1999**, *7*, 99.
(3) Ito, E.; Satake, M.; Ofuji, K.; Kurita, N.; McMahon, T.; James, K.; Yasumoto, T. *Toxicon* **2000**, *38*, 917.

followed by condensation with dimethyl (2-oxopropyl)-phosphonate to afford enone **20**. Thereafter, the resident silyl ether was converted into a ketone via desilylation and oxidation. Finally, the homoallylic hydroxyl was unmasked with DDQ to provide the potential HHMA precursor **11**.

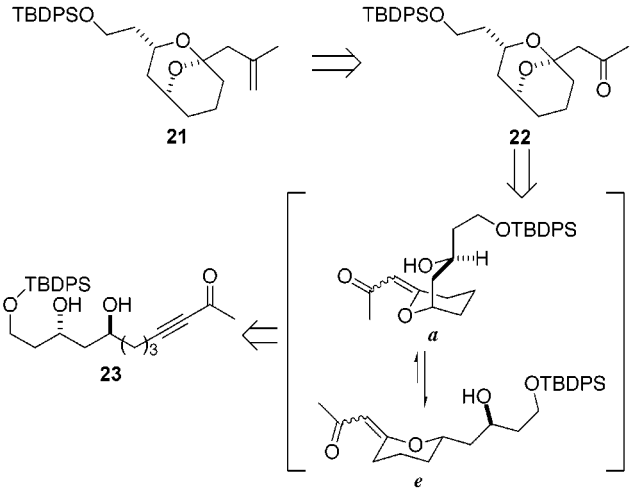
Previously, the proposed hemiketal hetero-Michael reaction sequence was plagued by undesired side reactions under *basic* conditions. These included enolization-induced *C*-Michael addition and C26 alkene migration.[4a] With access to both compounds **7** and **11**, alternative reaction conditions to effect formation of a 2,9-dioxabicyclo[3.3.1]nonane system were rapidly surveyed. These included subjection of **11** to a wide variety of Brönsted and Lewis acids (e.g., CSA, $BF_3 \cdot OEt_2$, TMSOTf, $MgBr_2$, $LiClO_4$, $TiCl_4$, $Sc(OTf)_3$, $Yb(OTf)_3$, $ZrCl_4$) and additional basic conditions (e.g., TBAF and DBU) with a variety of solvents (e.g., hexanes, benzene, CH_2Cl_2, THF, acetonitrile, nitromethane, methanol, and H_2O) and reaction temperatures. Under all conditions surveyed, there was no detectable conversion of **11** to **7** (TLC), although in most cases **11** was consumed.[10] Even though hemiketalization is facile, as evidenced by trapping as the mixed methyl ketal in methanol, the potential Michael acceptor side chain may not adopt a conformationally productive axial orientation (***i***) in preference to alternative conformers (e.g., ***ii***) or isomers (e.g., ***iii***) leading to side reactions (Scheme 5).

Scheme 5. Competitive Isomerizations



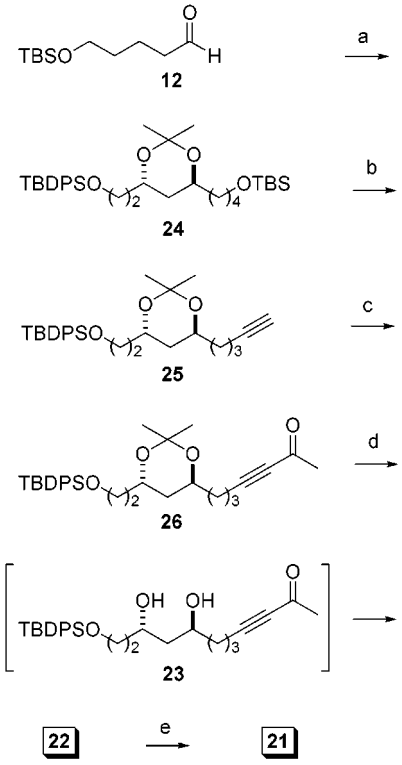
To overcome the problems associated with the HHMA approach, an alternative strategy was devised (Scheme 6). This involves a double intramolecular hetero-Michael addition (DIHMA) of a 7,9-diol upon a 1,3-ynone system (**23** → **22**).[11] Potential advantages here include the facility and stereoselectivity of sequential conjugate addition of both secondary hydroxyls to the unsaturated ketone and avoidance of C26 alkene isomerization because the latter is installed after ketal formation. The conformational equilibrium between the anticipated enol ether intermediates is expected to favor the equatorial one (***e***). However, trapping of the reactive axial conformer (***a***) via a second conjugate addition should shift the conformational equilibrium (***e*** → ***a***) and provide the geometrically accessible product (**22**).

Scheme 6. DIHMA Approach to **21**



To test the DIHMA strategy, dihydroxy ynone **23** was prepared (Scheme 7). For this, addition of acetoacetate dianion to aldehyde **12**, followed by hydroxyl-directed

Scheme 7. Synthesis of Bicyclic **21** via DIHMA[a]



[a] (a) (i) acetoacetate dianion, THF, −78 °C, 58%; (ii) $Me_4NBH(OAc)_3$; (iii) 2,2-dimethoxypropane, PPTS, 47% (two steps); (iv) $LiAlH_4$, Et_2O; (v) TBDPSCl, Et_3N, CH_2Cl_2, 80% (2 steps); (b) (i) HF·pyr, THF, 74%; (ii) Swern oxidation, 89%; (iii) dimethyl-1-diazo-2-oxopropyl-phosphonate,[12] MeOH, 84%; (c) (i) *n*-BuLi, acetaldehyde; (ii) MnO_2, 86%; (d) CSA, CH_2Cl_2:MeOH (5:1, v/v), then TsOH, benzene, 90%;[9] (e) Ph_3PCH_2Br, *n*-BuLi, 95%.

selective reduction,[8] installed the *anti*-1,3-diol. Acetonide formation and conversion of the ester into a TBDPS ether provided **24**. The TBS silyl ether terminus was converted into alkyne **25** in three additional steps. Treatment of **25** with *n*-BuLi followed by addition of acetaldehyde yielded a propargylic alcohol, which was oxidized with MnO_2 to deliver ynone **26**. The acetonide was removed by treatment of **26** with CSA in CH_2Cl_2:MeOH (5:1, v/v) to provide crude **23**. In a fashion similar to the ketalization of **9** leading to **8** (Scheme 3), diol **23** was induced to undergo the DIHMA process upon switching the solvent to benzene in the presence of CSA to afford the 1,3-disubstituted 2,9-dioxabicyclo[3.3.1]-nonane **22** as a single diastereomer in excellent yield (90% from **26**). It was found that addition of TsOH to the reaction mixture in benzene dramatically accelerated the DIHMA process. Ketone **22** was methylenated under standard Wittig reaction conditions to install the 1,1-disubstituted alkene representative of that at C26 of **1**−**3** and complete the synthesis of **21**.

In conclusion, an effective new approach toward the bicyclic system (F−G rings) of the azaspiracids has been developed. This DIHMA-based strategy overcomes two problems encountered in the biomimetic HHMA approach, *C*-Michael addition and migration of the alkene at C26. The classic dehydration of a dihydroxy ketone to form the allylic alkene-substituted 2,9-dioxabicyclo[3.3.1]nonane system of the azaspiracids may also be accompanied by migration of the alkene of a β,γ-unsaturated enone at C26−C28 into conjugation. In addition to avoiding these complications, the intermediacy of a terminal alkyne (e.g., **25**) en route to the dihydroxy ynone required for the DIHMA process provides a convenient synthetic handle for the convergent attachment of more elaborate ketone moieties. Application of this intramolecular nondehydrative ketalization method toward the construction of the complete C21−C40 polycyclic domain of the azaspiracids is in progress. Furthermore, the DIHMA sequence may find application in the construction of a variety of bicyclic ketal systems.

Acknowledgment. This publication was made possible by Grant ES10615 from the National Institute of Environmental Health Sciences (NIEHS), NIH, and generous unrestricted grant support from Bristol-Myers Squibb. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIEHS, NIH.

Supporting Information Available: Detailed experimental procedures and characterization data for **7**, **8**, **11**, **13**, **15**−**22**, and **24**−**26**. This material is available free of charge via Internet at http://pubs.acs.org.

OL015556L

(4) (a) Aiguade, J.; Hao, J.; Forsyth, C. J. *Tetrahedron Lett.* **2001**, *42*, 817. (b) Hao, J.; Aiguade, J.; Forsyth, C. J. *Tetrahedron Lett.* **2001**, *42*, 821. (c) Dounay, A. B.; Forsyth, C. J. *Org. Lett.* **2001**, *3*, 975. (d) Carter, R. G.; Weldon, D. J. *Org. Lett.* **2000**, *2*, 3913.

(5) Carbon numbering corresponds to that of **1**−**3**.

(6) The dehydration of dihydroxy ketones has been used previously to access 2,9-dioxabicyclo[3.3.1]nonane systems. See: Shimshock, S.; Watermire, R. E.; DeShong, P. *J. Am. Chem. Soc.* **1991**, *113*, 8791 and references therein.

(7) Shono, K.; Ishifune, M.; Kashimura, S. *Chem. Lett.* **1990**, 449.

(8) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(9) See Supporting Information for full experimental details.

(10) A (*Z*)-enone analogue of **4** also failed to provide an HHMA product, presumably due to competitive hemiketalization of the enone carbonyl with the δ-hydroxyl group.

(11) For a recent example of a double *C*-Michael addition upon an ynone, see: Grossman, R. B.; Varner, M. A.; Skaggs, A. J. *J. Org. Chem.* **1999**, *64*, 340.

(12) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.