ORGANIC LETTERS

2005
Vol. 7, No. 16
3497−3500

Synthesis of the Bis-spiroacetal Moiety of Spirolides B and D

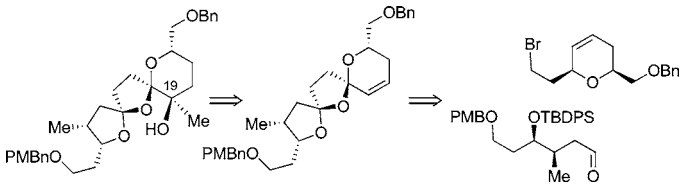
Kai Meilert and Margaret A. Brimble*

Department of Chemistry, University of Auckland, 23 Symonds Street, Auckland, New Zealand

m.brimble@auckland.ac.nz

Received May 29, 2005

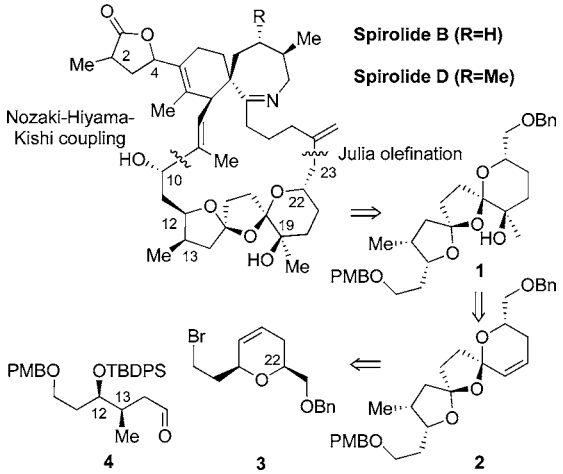
ABSTRACT



An enantioselective synthesis of the bis-spiroacetal fragment of spirolides B and D is reported. The carbon framework was constructed via Barbier reaction of dihydropyran 3 with aldehyde 4, followed by a double oxidative radical cyclization to construct the bis-spiroacetal. A silyl-modified Prins cyclization and enantioselective crotylation successfully installed the stereocenters in the cyclization precursor. The initial unsaturated bis-spiroacetals 2a–d underwent equilibration during epoxidation to *trans*-epoxide 14 that was converted to a tertiary alcohol.

The spirolides,[1] (Scheme 1) structurally related to the pinnatoxins,[2] gymnodimines,[3] and pteriatoxins,[4] are a family of marine toxins isolated from mussels (*Mytilus edulis*) and scallops (*Placopecten magellanicus*) from the eastern coast of Nova Scotia, Canada. The spirolides have been determined to be metabolites of the marine dinoflagellate *Alexandrium ostenfeldii*[5] that induce characteristic symptoms in the mouse bioassay (LD_{100} 250 μg/kg ip) and are weak activators of L-type transmembrane Ca^{2+} channels. The complete relative and absolute stereochemistry of the spirolides has not been established to date, but a tentative assignment based on NMR studies and molecular modeling has been reported.[6] The absolute stereochemistry at C2 and C4 remains uncertain, except for their syn relationship, but is predicted to be similar to that of pinnatoxin.[7] In common with the pinnatoxins, the

Scheme 1. Synthetic Strategy for the C10EnDash−C23 Fragment of Spirolides B and D



(1) (a) Hu, T.; Curtis, J. M.; Oshima, Y.; Walter, J. A.; Watson-Wright, W. M.; Wright, J. L. C. *J. Chem. Soc., Chem. Commun.* **1995**, 2159. (b) Aasen, J.; MacKinnon, S. L.; LeBlanc, P.; Walter, J. A.; Hovgaard, P.; Aune, T.; Quilliam, M. A. *Chem. Res. Toxicol.* **2005**, *18*, 509.

(2) (a) Uemura, D.; Chou, T.; Haino, T.; Nagatsu, A.; Fukuzawa, S.; Zheng, S.; Chen, H. *J. Am. Chem. Soc.* **1995**, *117*, 1155. (b) Chou, T.; Kamo, O.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 4023. (c) Chou, T.; Haino, T.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 4027. (d) Takada, N.; Uemura, N.; Suenaga, K.; Chou, T.; Nagatsu, A.; Haino, T.; Yamada, K.; Uemura, D. *Tetrahedron Lett.* **2001**, *42*, 3491.

(3) (a) Seki, T.; Satake, M.; Mackenzie, L.; Kaspar, H. F.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 7093. (b) Stewart, M.; Blunt, J. W.; Munro, M. H. G.; Robinson, W. T.; Hannah, D. J. *Tetrahedron Lett.* **1997**, *38*, 4889. (c) Miles, C. O.; Wilkins, A. L.; Stirling, D. J.; MacKenzie, A. L. *J. Agric. Food Chem.* **2000**, *48*, 1373.

(4) Takada, N.; Umemura, N.; Suenaga, K.; Uemura, D. *Tetrahedron Lett.* **2001**, *42*, 3495.

(5) Cembella, A. D.; Bauder, A. G.; Lewis, N. I.; Quilliam, M. A. *J. Plankton Res.* **2001**, *12*, 1413.

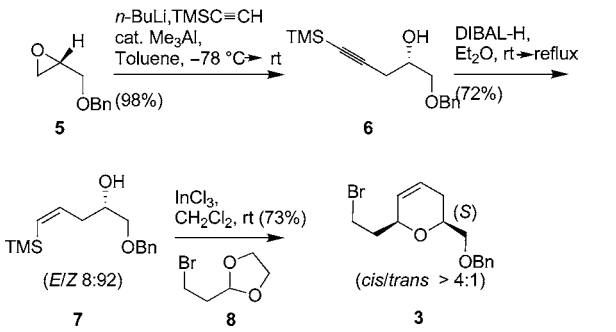
10.1021/ol051260u CCC: $30.25
Published on Web 07/01/2005

spirolides possess a seven-membered spirolinked cyclic imine together with a novel bis-spiroacetal ring system. Initial reports into the structure−activity relationship of these macrolides indicated that the spirocyclic imine is the key pharmacophore.[8] The total synthesis of the spirolides has not been reported to date; however, a synthesis of the bis-spiroacetal moiety via an acid-catalyzed cyclization has recently been reported.[9]

In addition to our work on the synthesis of model spiroimines[10] related to the spirolides, we have previously also reported the synthesis of a C10−C22 bis-spiroacetal fragment that lacked the C19 tertiary alcohol group using a double oxidative radical cyclization.[11] However, problems were encountered during the introduction of functionality at C19 and extension of the carbon framework at C22, thus prompting adoption of a modified synthetic plan in which disconnection of the C23−C24 bond rather than the C22−C23 bond was a pivotal step. The results of this revised strategy are presented herein, providing rapid access to the fully functionalized C10−C23 bis-spiroacetal fragment of spirolides B and D that is homologous to our previous fragment. This new approach relies on a silyl-modified Prins cyclization[12] to access dihydropyran **3** with the required (*S*)-configuration at C22 (Scheme 1). The two spiroacetal centers are then formed by oxidative radical cyclization of the alcohol resulting from the Barbier coupling of this dihydropyran with aldehyde **4**. The syn stereochemistry in aldehyde **4** is available from an enantioselective crotylation. The alkene in bis-spiroacetal **2** provides functionality for subsequent installation of the tertiary alcohol. It is also envisaged that the *cis* stereochemistry between the terminal rings of the bis-spiroacetal will be established by equilibration after incorporation into the macrocyclic ring. Thus, initial synthesis of *trans*-bis-spirocetals **1** and **2** was required.

The synthesis of the dihydropyran fragment **3** was carried out in three steps (51% overall yield), starting from enantiomerically pure *O*-benzyl-protected[13] (*R*)-(+)-glycidol (Scheme 2). Ring opening of epoxide **5** with lithium trimethylsilylacetylide in the presence of a catalytic amount of trimethylaluminum[14] afforded homopropargyl alcohol **6** in higher yield than when using a stoichiometric amount of boron trifluoride diethyl etherate.[15] Vinylsilane **7** was initially

Scheme 2. Synthesis of the C16−C23 Dihydropyran Fragment



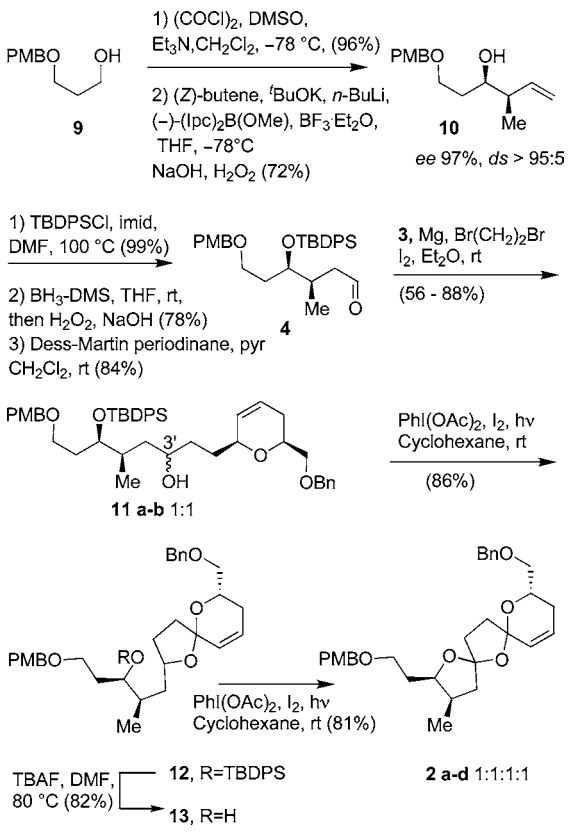
prepared by semihydrogenation of the corresponding acetylene **6** in the presence of a poisoned catalyst. Use of the Rosenmund catalyst ($Pd/BaSO_4$)[16] gave moderate *E*/*Z* selectivities and poor yields, while Lindlar's catalyst ($Pd/CaCO_3$/Pb)[17] gave variable selectivities.[18] Similar selectivity problems have been observed by others for alkynes bearing a trimethylsilyl substituent.[19]

Eventually, hydroalumination of **6** in ether[12a] using DIBAL-H (1 M in hexane) gave the desired olefin **7** with high (*Z*)-selectivity (92:8). The desired 1,3-cis (cis/trans > 4:1) dihydropyran **3** was then prepared using a silyl-modified Prins cyclization of vinylsilane **7** with acetal **8** catalyzed by either indium trichloride (72%)[12c,d] or iron trichloride (52%).[12e]

Aldehyde **4** was synthesized in five steps (44% overall yield) from monoprotected 1,3-propanediol **9**[20] (Scheme 3). Swern oxidation[21] followed by reagent-controlled enantioselective crotylation[22] gave the desired (3*R*,4*R*)-allylic alcohol[23] **10** in 97% optical purity and dr > 95:5.[24] After protection as a *tert*-butyldiphenylsilyl ether, hydroboration with borane dimethyl sulfide afforded an alcohol that was oxidized with Dess−Martin periodinane[25] to give the required aldehyde **4**. Use of Barbier conditions[26a] to couple aldehyde **4** with bromide **3** proved to be more efficient than use of standard

(6) Falk, M.; Burton, I. W.; Hu, T.; Walter, J. A.; Wright, J. L. C. *Tetrahedron* **2001**, *57*, 8659.
(7) McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647.
(8) Hu, T.; Curtis, J. M.; Walter, J. A.; Wright, J. L. C. *Tetrahedron Lett.* **1996**, *37*, 7671.
(9) Ishihara, J.; Ishizaka, T.; Suzuki, T.; Hatakeyama, S. *Tetrahedron Lett.* **2004**, *45*, 7855.
(10) Brimble, M. A.; Trzoss, M. *Tetrahedron* **2004**, *60*, 5613.
(11) Brimble, M. A.; Furkert, D. P. *Org. Biomol. Chem.* **2004**, *2*, 3573.
(12) Silyl-modified Prins cyclization and the silyl-modified Sakurai cyclization are in fact the same reaction, and the name silyl Prins is adopted herein. See: (a) Marko, I. E.; Bayston, D. J. *Tetrahedron* **1994**, *50*, 7141. (b) Marko, I. E.; Mekhalfia, A.; Bayston, D. J.; Adams, H. *J. Org. Chem.* **1992**, *57*, 2211. (c) Dobbs, A. P.; Martinovic, S. *Tetrahedron Lett.* **2002**, *43*, 7055. (d) Dobbs, A. P.; Guesne, S. J. J.; Martinovic, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003**, *68*, 7880. (e) Miranda, P. O.; Diaz, D. D.; Padron, J. I.; Bermejo, J.; Martin, V. S. *Org. Lett.* **2003**, *5*, 1979.
(13) Lai, M. T.; Oh, E.; Shih, Y.; Liu, H.-W. *J. Org. Chem.* **1992**, *57*, 2471.
(14) For method, see: Ooi, T.; Kagoshima, N.; Ichikawa, H.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 3328.
(15) For method, see: Ichikawa, Y.; Isobe, M.; Bai, D.-L.; Goto, T. *Tetrahedron* **1987**, *43*, 4737.
(16) Rosenmund, K. W. *Chem. Ber.* **1918**, *51*, 686.
(17) (a) Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446. (b) Kurihara, M.; Ishii, K.; Kasahara, Y.; Miyata, N. *Tetrahedron Lett.* **1999**, *40*, 3183.
(18) Optimum solvent was THF, affording 85:15 selectivity in favor of the desired (*Z*)-**7** (69%). The (*Z*)-configuration of **7** is crucial for the formation of dihydropyran **3**, as elimination of the trimethylsilyl group from the resultant six-membered ring formed from the (*E*)-isomer is very slow (<10% conversion after 12 h).
(19) (a) Soderquist, J. A.; Santiago, B. *Tetrahedron Lett.* **1990**, *31*, 5113. (b) McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4823. (c) Trost, B. M.; Braslau, R. *Tetrahedron Lett.* **1989**, *30*, 4657. (d) Kini, A. D.; Nadkarni, D. V.; Fry, J. L. *Tetrahedron Lett.* **1994**, *35*, 1507.
(20) Coelho, F.; Diaz, G. *Tetrahedron* **2002**, *58*, 1647. For a two-step procedure, see: Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889.
(21) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(22) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.
(23) Absolute configuration of *ent*-**10** has been assigned by X-ray diffraction of the derived camphanic ester; see: Meilert, K. T.; Clark, G. R.; Groutso, T.; Brimble, M. A. *Acta Crystallogr. Sect. E* **2005**, *E61*, O6.
(24) Enantiomeric excess was measured by ^{19}F NMR after formation of the Mosher ester.
(25) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

Scheme 3. Synthesis of the C10−C15 Aldehyde Fragment and Bis-spiroacetal Formation



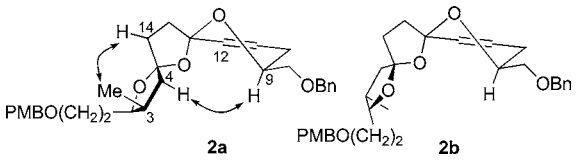
Grignard[26b] conditions. The coupled product **11** was isolated in 88% yield as a ∼1:1 mixture of diastereomers at C3′ (Scheme 3). The two diastereomers were easily separated by flash chromatography, but the mixture was used throughout the synthesis, as equilibration of the bis-spiroacetals **2a**−**d** was required at a later stage.

With alcohol **12** in hand, attention was turned to the iterative oxidative radical cyclization steps (Scheme 3).[11] Irradiation of **11a**,**b** with a 60 W desk lamp in the presence of iodobenzene diacetate and iodine in cyclohexane gave the spiroacetal **12** in 86% yield. The *tert*-butyldiphenylsilyl ether was then deprotected, and the bis-spiroacetal core structure was formed upon execution of a second oxidative radical cyclization providing bis-spiroacetals **2a**−**d** in 81% yield as a 1:1:1:1 mixture of diastereomers.

Acid-catalyzed equilibration of the 1:1:1:1 mixture of bis-spiroacetals **2a**−**d** gave a ∼4:1 mixture of two major isomers (**2a** and **2b**) together with trace quantities (<5%) of two other minor isomers (Table 1). Interestingly, use of indium trichloride gave better results than the more commonly used reagents such as HF·Pyr, PPTS, $ZnBr_2$ or $ZnCl_2$, affording an 87:13 mixture of the thermodynamically favored isomers **2a** and **2b** (Table 1, entry 5). The absolute configuration at C5 and C7 in isomer **2a** was assigned unambiguously using

(26) (a) Barbier P. *Compt. Rend.* **1899**, *128*, 110. (b) Grignard, V. *Compt. Rend.* **1890**, *130*, 1322.

Table 1. Equilibration of Bis-spiroacetals **2a** and **2b**

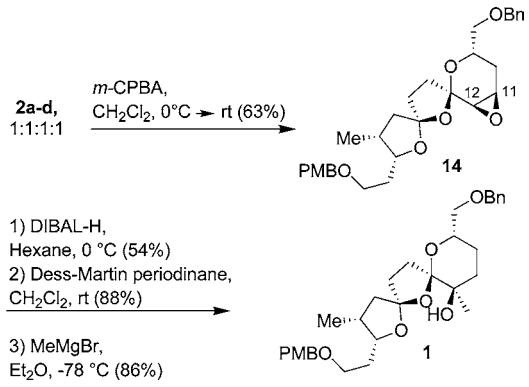


entry	conditions	**2a/2b** (yield)
1	HF·Pyr, MeCN, rt, 12 h	76:24 (81%)
2	PPTS (0.2 equiv), MeCN, rt, 18 h	∼81:19 (89%)
3	$ZnBr_2$ (0.2 equiv), CH_2Cl_2, rt, 19 h	76:24 (95%)
4	$ZnCl_2$ (0.2 equiv), CH_2Cl_2, rt, 24 h	∼83:17 (88%)
5	$InCl_3$ (0.2 equiv), MeCN, rt, 1 h	87:13 (85%)

two-dimensional NMR NOESY experiments,[27] which showed clear correlations between H-9 and H-4 and between 3-CH_3 and H-14, respectively (Table 1).

Initially, introduction of the tertiary alcohol onto the unsaturated bis-spiroacetal **2** was achieved using a hydroboration−oxidation sequence. Use of BH_3·SMe_2 or BH_3·THF afforded low yields of the undesired C11 ketone after Dess−Martin oxidation of the resultant alcohol, together with olefin-containing side products. Direct introduction of the ketone by Wacker oxidation[28] was also unsuccessful in that oxypalladation seemed to be directed toward formation of the undesired C11 ketone. Finally, treatment of the 1:1:1:1 mixture of bis-spiroacetals **2a**−**d** with *m*-CPBA afforded the *β*-epoxide **14** as a single diastereomer (Scheme 4). Remark-

Scheme 4. Equilibration and Introduction of the Tertiary Alcohol



ably, the presence of *meta*-chlorobenzoic acid and water in the *m*-CPBA[29] effected equilibration of the mixture of bis-spiroacetals **2a**−**d** to the most thermodynamically favored

(27) Use of a 600 MHz spectrometer was necessary in order to see splitting of the signals.

(28) For examples of heteroatom-directed Wacker oxidations see: (a) Tsuji, J. *Synthesis* **1984**, *5*, 369. (b) Kang, S. K.; Jung, K. Y.; Chung, J. U.; Namkoong, E. Y.; Kim, T. H. *J. Org. Chem.* **1995**, *60*, 4678. (c) Lai, J. Y.; Shi, X. X.; Dai, L. X. *J. Org. Chem.* **1992**, *57*, 3485.

(29) *m*CPBA purchased from Fluka contains ∼10% *m*-chlorobenzoic acid and ∼20% H_2O.

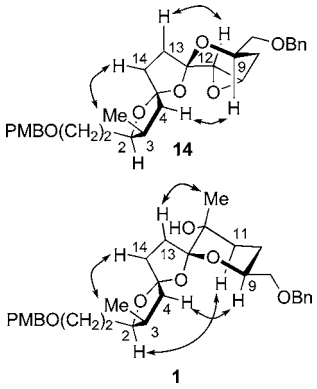


Figure 1. Characteristic NOESY correlations for the assignment of the absolute configuration of **14** and **1**.

isomer **2a**, which then underwent stereoselective epoxidation from the β-face, presumably due to hydrogen bonding effects. Epoxide **14** underwent regioselective reductive opening with DIBAL-H, and the resultant alcohol was oxidized upon treatment with Dess−Martin periodinane.[25] Analogous to the observations reported by Ishihara et al.,[9] stereoselective axial addition of methylmagnesium bromide to the ketone afforded the desired tertiary alcohol **15** with the same stereochemistry as that present in the spirolides.

The stereochemistry of epoxide **14** and tertiary alcohol **1** was assigned unambiguously by two-dimensional NMR NOESY experiments[27] (Figure 1). For epoxide **14**, correlations between H9 and H4, between H12 and H13, and between 3-CH_3 and H14 established the stereochemistry as indicated. No correlations were observed between H9 and H11 or H12 as would be expected if epoxidation had taken place from the α face. For tertiary alcohol **1**, clear correlations between H9 and H4 and between H2 and H11 clearly established the *trans* arrangement of the oxygen atoms about the central ring. The absolute configuration of the CH_3 at C12 was assigned by the observed correlation with H13. The *trans* stereochemistry adopted by tertiary alcohol **1** represents the thermodynamically favored isomer,[9] and it is envisaged that reequilibration of the bis-spiroacetal to the desired *cis* stereochemistry as found in the spirolides will take place upon incorporation of this moiety into the macrocyclic system.

The present work demonstrates the efficient construction of the bis-spiroacetal ring system present in the spirolides using an iterative oxidative radical cyclization strategy. Use of $InCl_3$ and *m*-CPBA to effect equilibration of the 6,5,5-bis-spiroacetal ring system provides further examples of reagents to effect spiroacetalizations in a stereoselective fashion. Furthermore, the use of a silyl-modified Prins cyclization provides an efficient entry to the dihydropyran unit of the cyclization precursor.

Acknowledgment. We would like to thank the Swiss National Science Foundation and the Royal Society of New Zealand Marsden Fund for financial support, Michael Walker for helpful discussions concerning NMR experiments, and L. Ravi Sumoreeah for preliminary experimentation on the silyl-modified Prins cyclization.

Supporting Information Available: Experimental procedures and spectral data for compounds **2**, **14**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051260U