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Synthesis of the C10–C22 Bis-spiroacetal Domain of Spirolides B and D via Iterative Oxidative Radical Cyclization

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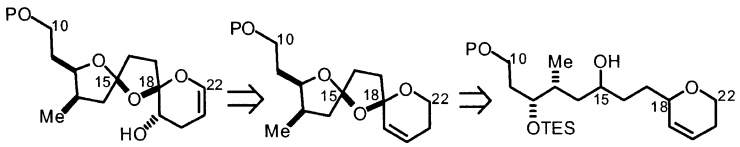
ABSTRACT



A synthetic approach to the novel bis-spiroacetal moiety of spirolides B and D is reported. The strategy hinges upon successive formation of the spirocenters at C15 and C18 by radical oxidative cyclization, followed by base-induced rearrangement of a C19–20 α-epoxide to introduce the C19 hydroxyl group.

Spirolides B and D (**1** and **2**, Figure 1) are members of a novel family of marine macrolides isolated from mussels (*Mytilus edulis*) and scallops (*Placopecten magellanicus*) during routine monitoring for diarrhetic shellfish toxins in Nova Scotia, Canada, in 1995.[1] They induce characteristic symptoms in the mouse bioassay (LD_{100} 250μg/kg ip) possibly through muscarinic acetylcholine receptor antagonism and are weak activators of L-type transmembrane Ca^{2+} channels. The relative and absolute stereochemistry has not been established to date, but a tentative assignment based on NMR studies has been reported.[2] The spirolides are metabolites of the marine dinoflagellate *Alexandrium ostenfeldii*[3] and exhibit much structural homology with macrolides of similar origin, including gymnodimine,[4] the pteriotoxins,[5] and most notably the pinnatoxins.[6] In common with the pinnatoxins, the spirolides possess a seven-membered spiro-linked cyclic imine together with a novel bis-spiroacetal ring system. The 1,7,9-trioxadispiro[4.1.5.2]tetradecane moiety present in the spirolides has yet to be synthesized and forms the focus of the current studies.[7]

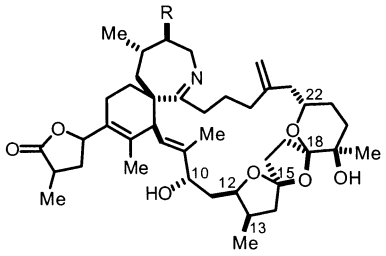


Figure 1. Spirolides B (**1**, R = H) and D (**2**, R = Me). Stereochemistry as assigned by Falk et al.[2]

Synthetic Strategy. The bis-spiroacetal moiety is present in several classes of natural products and represents a unique synthetic challenge. Most reported syntheses have proceeded

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(3) Cembella, A. D.; Bauder, A. G.; Lewis, N. I.; Quilliam, M. A. *J. Plankton Res.* **2001**, *12*, 1413.
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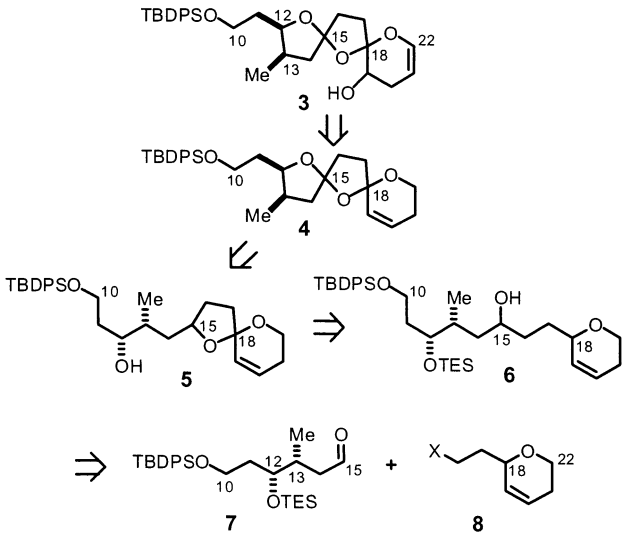
via acid-catalyzed cyclization of a suitably functionalized dihydroxy diketone precursor to furnish the corresponding tricyclic bis-spiroacetal.[8] The present study demonstrates the viability of the construction of bis-spiroacetals using an iterative oxidative radical cyclization strategy (Scheme 1).

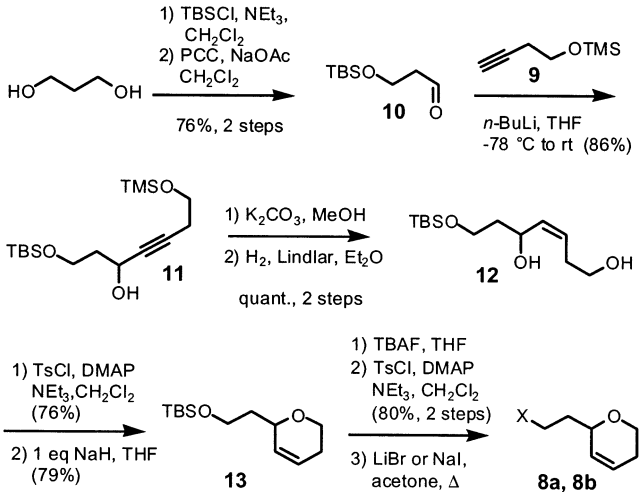
Scheme 1. Synthetic Strategy for the C10−C22 Domain of the Spirolides



Homoallylic alcohol **3** is a key intermediate for the synthesis of spirolides B and D because it contains the 1,7,9-trioxadispiro[4.1.5.2]tetradecane ring system and a glycal-like functionality that may be readily hydrated to provide a suitable electrophile for coupling with allylstannane derivatives.[9] Homoallylic alcohol **3** would be derived from epoxidation and base-induced rearrangement of bis-spiroacetal **4**, for which precedent has been established on a simpler bis-spiroacetal system.[10] The two spiroacetal centers in **4** would be formed by successive oxidative radical cyclization of precursors **5** and **6** mediated by hypervalent iodine.[8,11] Dihydropyran **6** in turn would be assembled from aldehyde **7** and an organometallic derivative of **8**, enabling flexible introduction of stereochemistry at C12 and C13 in order to aid the assignment of the natural product. The thermodynamically preferred configurations of bis-spiroacetals **3** and **4** are difficult to predict, due to the subtle interplay of steric and electronic effects. Recent work on the synthesis of azaspiracid and the pinnatoxins has demonstrated that the stereochemistry of bis-spiroacetals obtained upon equilibration is dependent on the nature of the substituents present on the ring system.[12a−d]

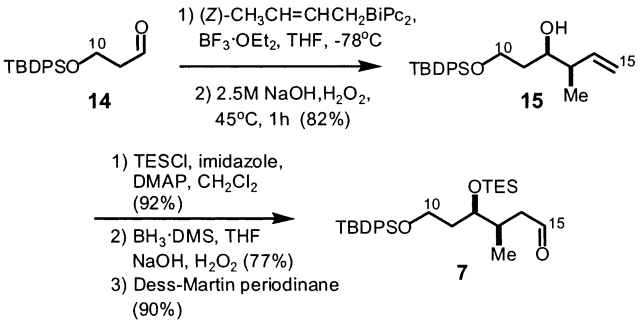
The most practical preparative route to the C16−C22 dihydropyran **8** (Scheme 2) involved addition of the lithium

Scheme 2. Synthesis of C16−C22 Dihydropyran. (**8a**, X = Br; **8b**, X = I)



acetylide of **9** to aldehyde **10**, available in two steps from propane-1,3-diol. The TMS ether in **11** was selectively cleaved by catalytic K_2CO_3 in methanol followed by Lindlar reduction of the acetylene to give (*Z*)-alkene **12** in high yield. Tosylation of the primary alcohol followed by treatment with 1 equiv of sodium hydride in THF afforded dihydropyran **13**, which after cleavage of the silyl ether using TBAF was converted to halide **8** via displacement of the corresponding tosylate. Preparation of aldehyde **7** (Scheme 3) began with

Scheme 3. Synthesis of C10−C15 Aldehyde



stereocontrolled crotylmetallation of aldehyde **14** to give (12*R*,13*R*)-**15** in 82% yield and >32:1 dr.[13] The 12*R*,13*R* configuration was selected both by analogy with pinnatoxin A[14] and the relative stereochemistry of the spirolides proposed by Falk et al.[2] Homoallylic alcohol **15** was then

(8) Brimble, M. A.; Fares, F. A. *Tetrahedron* **1999**, *55*, 7661.
(9) Brimble, M. A.; Fares, F. A.; Turner, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, *4*, 677.
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(12) (a) Nicolaou, K. C.; Qian, W.; Bernal, F.; Uesaka, N.; Pihko, P. M.; Hinrichs, J. *Angew. Chem., Int. Ed.* **2001**, *21*, 4068. (b) Sugimoto, T.; Ishihara, J.; Murai, A. *Synlett* **1999**, *5*, 541. (c) Carter, R. G.; Bourland, T. C.; Graves, D. E. *Org. Lett.* **2002**, *13*, 2177. (d) Carter, R. G.; Graves, D. E.; Gronemeyer, M. A.; Tschumper, G. S. *Org. Lett.* **2002**, *13*, 2181.
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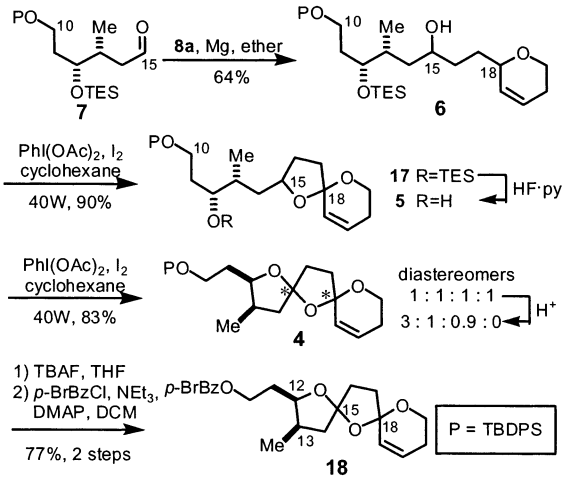
(14) Uemura, D.; Chou, T.; Haino, T.; Nagatsu, A.; Fukuzawa, S.; Zeng, S. Z.; Chen, H. S. *J. Am. Chem. Soc.* **1995**, *117*, 1155.

Scheme 4. Bis-spiroacetal Formation via Radical Cyclization



converted into aldehyde **7** in good yield using standard transformations.

Coupling of **7** and **8** (Scheme 4) proved to be somewhat problematic. Standard Grignard reaction conditions failed to yield the desired product, and only mediocre yields were obtained using an organolithium species derived from iodide **8b**. Alcohol **6** was finally prepared reproducibly in 64% yield using Barbier conditions in diethyl ether, together with the undesired Wurtz coupling product of **8a**.

Cyclization of **6** in the presence of $PhI(OAc)_2$ and iodine under irradiation cleanly gave spiroacetal **17** in 90% yield. The TES ether of **17** was then selectively cleaved in THF by portionwise addition of HF·pyridine over several hours. Finally, the resultant hydroxy spiroacetal **5** underwent smooth cyclization to **4** upon treatment with $PhI(OAc)_2$ and iodine. Prolonged stirring of the initial 1:1:1:1 product mixture with a catalytic quantity of *p*-toluenesulfonic acid in dichloromethane gave a 3:1:0.9 mixture (**4a**:**4b**:**4c**, Figure 2) of three of the four possible C15,C18 configurational isomers that were separable by careful chromatography. Deprotection of the TBDPS ether with TBAF followed by esterification under standard conditions led to bromobenzoate **18**, which upon equilibration with *p*-toluenesulfonic acid in dichloromethane formed a mixture of the *same three isomers in approximately the same ratio* (**18a**:**18b**:**18c**, Figure 2). Disappointingly, none of the bromobenzoate derivatives yielded crystals suitable for X-ray analysis.

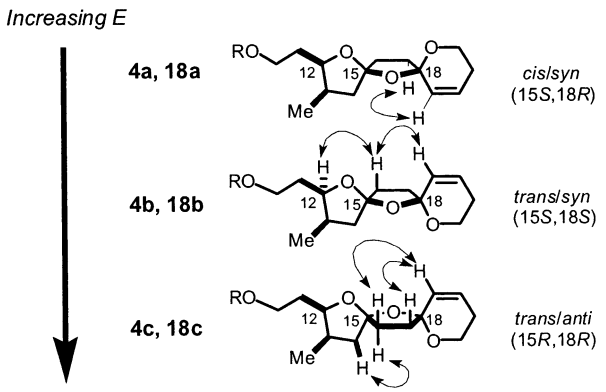
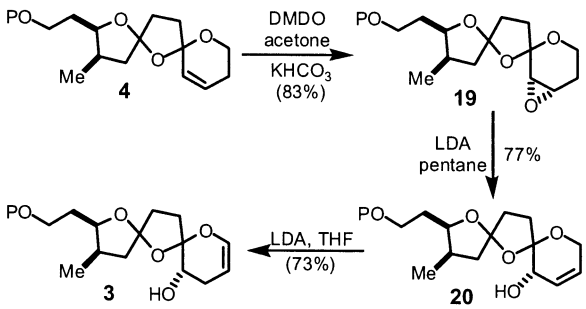


Figure 2. Putative assignments for **4a**−**c** and **18a**−**c** showing selected NOESY correlations.

Epoxidation of the major isomer of **4** (Scheme 5) was then effected using dimethyldioxirane in acetone to give **19** as a single diastereomer in 83% yield. Disappointingly, however, base-induced rearrangement with excess LDA in THF did not proceed at any temperature from −78 °C to reflux. This difficulty was circumvented by the use of pentane or hexane as the solvent, which allowed more effective coordination of LDA to the epoxide oxygen, affording allylic alcohol **20** by syn β-deprotonation. Rearrangement to the thermodynamically more stable homoallylic alcohol **3** was then effected by further treatment with excess LDA in THF. Interestingly, when rearrangement of epoxide **19** was performed in hexane with lithium pyrrolidinyl amide, a 2:1 ratio of **20**:**3** resulted, indicating that the nature of the base also influences the extent of homoallylic alcohol formation.[15]

Scheme 5. Epoxidation and Rearrangement of the C19−C20 Olefin



In an effort to clarify the stereochemistry of the thermodynamically preferred isomers of the 1,7,9-trioxadispiro[4.1.5.2]tetradecane ring system (Figure 2), computer modeling was carried out for **4** (TBDPS replaced by TMS for calculations), bromobenzoate **18**, and the parent alcohol (R = H). Relative energies were calculated at the ab initio level (Hartree−Fock, 3-21G* basis set), using semiempirical optimized geometries (AM1) for all molecular mechanics conformers (MMFF94) within 3 kcal/mol of the global minimum. In all cases, the calculated energies follow the trend cis/syn < trans/syn < trans/anti ≪ cis/anti, where cis/trans refers to the arrangement of oxygens across the central ring and syn/anti to the central oxygen and the alkyl substituent at C12. Extensive two-dimensional NMR studies support tentative assignments of **4a**−**c** and **18a**−**c** (Figure 2) in agreement with calculation.

In summary, a synthetic route to the novel 1,7,9-trioxadispiro[4.1.5.2]tetradecane ring system of spirolides B and D has been developed using an iterative oxidative radical

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cyclization strategy to form the C15 and C18 spirocenters. Bis-spiroacetal **4** was prepared as a separable 3:1:1 thermodynamic mixture of diastereomers for which the stereochemistry has been assigned on the basis of two-dimensional NMR and ab initio molecular modeling.

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