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Stereoselective Synthesis of the Lituarine Tricyclic Spiroacetal

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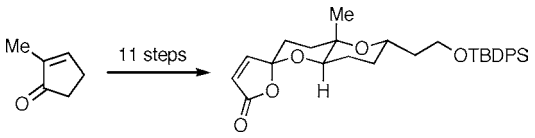
ABSTRACT

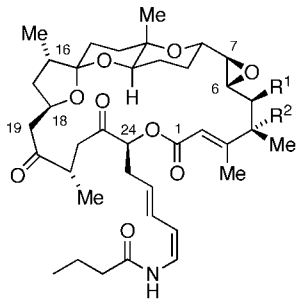


Oxidative cyclizations of 2-(4-hydroxybutyl)furan derivatives provide spirobutenolide acetals directly; on the basis of this methodology, we describe an asymmetric synthesis of a tricyclic spirobutenolide precursor to the C(7–18) fragment common to lituarines A–C.

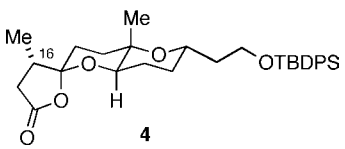
In the accompanying paper,[1] we introduced our strategy for the synthesis of lituarines A−C (**1**−**3**, Scheme 1), a small class of cytotoxic, antifungal marine natural products isolated from *Lituaria australasiae*,[2] and described a route to the C(1−6) and C(19−24) fragments of the natural products. Prior to this report, Smith's highly efficient synthesis of the C(7−19) tricyclic spiroacetal domain, starting from antipodal glycidyl ethers, stood as the only published synthetic work in this area.[3]

In this Letter, we describe a conceptually very different route to the lituarine C(7−18) spiroacetal, in which the absolute stereochemistry originates in an oxazaborolidine-mediated asymmetric reduction of 2-methylcyclopentenone. In our original analysis of the synthesis,[4] we were concerned that the C(16) stereogenic center would be prone to epimerization under the equilibrating acidic conditions typically employed for spiroacetal formation by ketodiol condensation, and this classical approach was rejected. Instead, we realized that a variant of the peracid oxidation of 2,5-disubstituted furans to give enediones[5] could be used as the key step in a direct synthesis of spirobutenolide **6** (Scheme 2) from which the C(16) methyl group could be introduced under kinetic

Scheme 1. Synthetic Analysis of Lituarines A−C



1, lituarine A; $R^1 = R^2 = H$
2, lituarine B; $R^1 = OAc$, $R^2 = OH$
3, lituarine C; $R^1 = R^2 = OH$



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(1) Robertson, J.; Dallimore, J. W. P.; Meo, P. *Org. Lett.* **2004**, *6*, 3857−3860.

(2) Vidal, J.-P.; Escale, R.; Girard, J.-P.; Rossi, J.-C.; Chantraine, J.-M.; Aumelas, A. *J. Org. Chem.* **1992**, *57*, 5857−5860.

(3) (a) Smith, A. B., III.; Frohn, M. *Org. Lett.* **2001**, *3*, 3979−3982. (b) Smith, A. B., III; Frohn, M. *Org. Lett.* **2002**, *4*, 4183 (correction).

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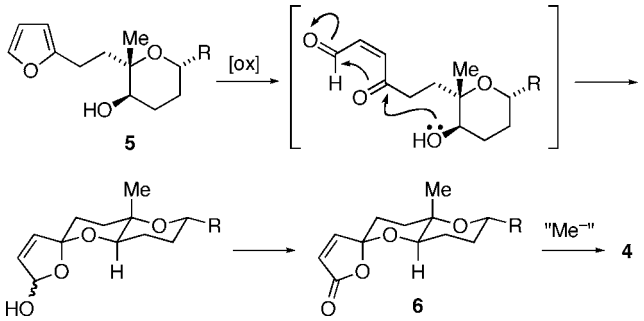
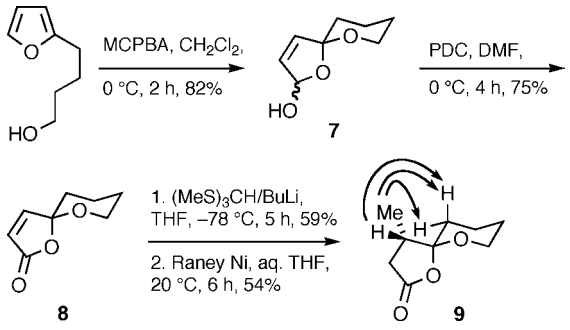
Scheme 2. Route to Tricycle **4** Based on Furan Oxidation



conditions by conjugate addition. This proposal[6] required stereocontrolled access to functionalized 2-(4-hydroxybutyl)-furan precursors of general structure **5**; before embarking on that synthesis, a model study was undertaken in order to establish the viability of the methodology.

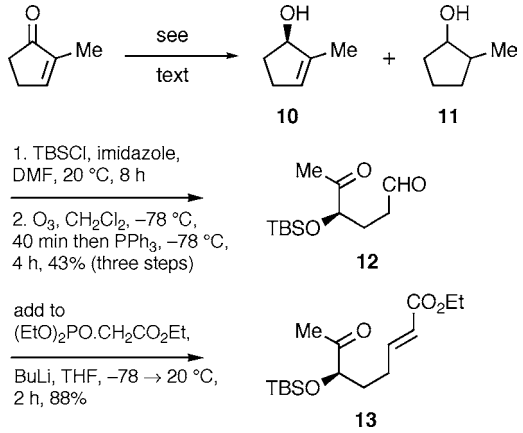
Treatment of 2-(4-hydroxybutyl)furan[7] with MCPBA in dichloromethane for 2 h at 0 °C provided spirolactol **7** (82%), which was oxidized without complication to give multigram quantities of the spirobutenolide **8**[8] (75%). Butenolide **8** could be obtained directly from the furan in comparable overall yield (65%) using 2.0 equiv of MCPBA at 20 °C. Pleasingly, subsequent 1,4-addition[9] of $(MeS)_3CLi$ afforded the conjugate adduct as essentially one diastereomer.[10] Raney nickel desulfurization of this adduct gave spirolactone **9**, the stereochemistry (dr = 19:1) being established by NOE experiments (Scheme 3).[11] We also briefly investigated

Scheme 3. Oxidative Spiroacetalization and Stereoselective Conjugate Addition; Diagnostic NOE Data for **9**



Yamamoto's system[12] for delivery of methyl in a conjugate sense; under the recommended conditions (Me_2CuLi·TMSCl, CH_2Cl_2, 0 → 20 °C), 1,4-addition proceeded cleanly, but the adduct was obtained as a roughly equimolar mixture of diastereomers.

Scheme 4. Asymmetric Reduction and Elaboration



Following this success, the synthesis of the more complex oxidation precursor **5** (R = $CH_2CH_2OTBDPS$) was undertaken, beginning with asymmetric reduction[13] of 2-methylcyclopentenone (Scheme 4). Use of BH_3·THF in this reduction[14] provided an 85:15 mixture of inseparable alcohols **10** and **11** in mediocre yield and with only a moderate ee (82%).[15] In contrast, application of Corey's modification,[16] using catecholborane at low temperature, resulted in an improved ee (92%)[15] and avoided competing over-reduction.[17] Later work showed that the most reproducible results (90% yield, 94% ee) could be obtained using a stoichiometric quantity of (*S*)-2-methyl-CBS-oxazaborolidine·BH_3 complex.[18]

The crude alcohol (**10**) was immediately protected and the alkene cleaved to provide keto aldehyde **12**. Interestingly, the intermediate ozonide[19] precursor to keto aldehyde **12** proved to be relatively stable in the presence of a large excess of dimethyl sulfide and was isolated after silica gel chromatography. Fortunately, triphenylphosphine effected complete reduction of this ozonide at −78 °C. Selective Horner−Wadsworth−Emmons olefination of aldehyde **12** proceeded in good yield at low temperature[20] with high (*E*)-stereoselectivity and with no significant loss of stereochemical

(5) (a) First report: Clauson-Kaas, N.; Fakstorp, J. *Acta Chem. Scand.* **1947**, *1*, 415−421. (b) For an early synthetic application: Williams, P. D.; LeGoff, E. *J. Org. Chem.* **1981**, *46*, 4143−4147.

(6) Recently, Nelson reported such a process during a study of the Sharpless kinetic resolution of difuryl diols: (a) Harding, M.; Hodgson, R.; Nelson, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2403−2413. (b) Bartlett, S.; Hodgson, R.; Holland, J. M.; Jones, M.; Kilner, C.; Nelson, A.; Warriner, S. *Org. Biomol. Chem.* **2003**, *1*, 2393−2402.

(7) Sun, M.; Deng, Y.; Batyreva, E.; Sha, W.; Salomon, R. G. *J. Org. Chem.* **2002**, *67*, 3575−3584.

(8) Fukuda, H.; Takeda, M.; Sato, Y.; Mitsunobu, O. *Synthesis* **1979**, 368−370.

(9) Damon, R. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1976**, 1561−1564.

(10) Cf.: Reed, A. D.; Hegedus, L. S. *J. Org. Chem.* **1995**, *60*, 3787−3794.

(11) This was confirmed by X-ray crystallography, details of which will be provided in a full description of this work.

(12) Asao, N.; Lee, S.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 4265−4266.

(13) (a) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475−1504. (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37* (7), 1986−2012.

(14) Corey, E. J.; Gavai, A. V. *Tetrahedron Lett.* **1988**, *29*, 3201−3204.

(15) Enantiomeric excess was determined by Mosher's ester derivatization.

(16) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611−614.

(17) On the basis of the ^1H NMR spectrum of the crude material.

(18) Simpson, A. F.; Szeto, P.; Lathbury, D. C.; Gallagher, T. *Tetrahedron: Asymmetry* **1997**, *8*, 673−676.

(19) Bunnelle, W. H.; Isbell, T. A. *J. Org. Chem.* **1992**, *57*, 729−740.

(20) Hammond, G. B.; Cox M. B.; Wiemer D. F. *J. Org. Chem.* **1990**, *55*, 128−132.

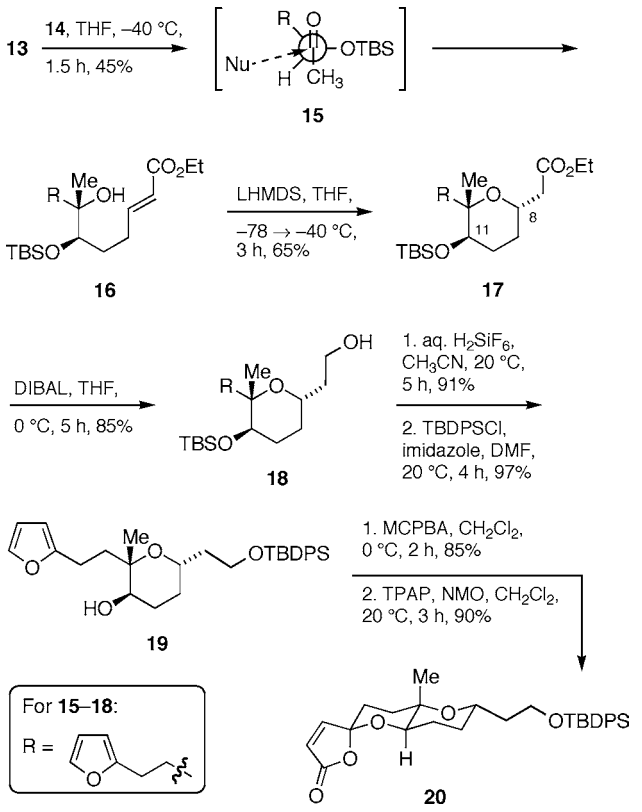
integrity at C(11), as inferred by Mosher's ester analysis at a later stage (compound **18**).

Two key aspects of stereocontrol then had to be faced: (1) the level of stereochemical induction during addition of a furan-containing organometallic to the α-(silyloxy)ketone and (2) the level and sense of stereoselectivity during conjugate cyclization to form the tetrahydropyran ring.[21] A screen of unfunctionalized organometallic reagents soon showed Grignard reagents to be preferential; addition of 2-(2-furyl)ethylmagnesium bromide (**14**)[22] to ketone **13** proceeded in moderate yield (→ **16**) and with good (10:1) stereocontrol in accord with a nonchelated Felkin−Anh approach (**15**). This Grignard reaction was particularly sensitive to oxidation, careful degassing of the solvents[23] being necessary in order to obtain consistent results.

Anticipating the stereochemical outcome of the tetrahydropyran ring closure, we expected the desired product (**17**) to be the more stable of the two diastereomers, but predicting the outcome under kinetic conditions was difficult given the absence of a close literature precedent.[24] Therefore, a small range of bases was screened in this reaction (full details will be reported elsewhere) and it was found that the diastereoselectivity was influenced by the reaction temperature as well as the nature of the metal counterion; with LHMDS as the base, and maintaining the reaction temperature below −40 °C, the desired diastereomer **17** was obtained exclusively, albeit with some recovery of starting material (Scheme 5). In the ^{1}H NMR spectrum of this compound, both C*H*OR resonances exhibited a coupling constant of a magnitude consistent with a diaxial relationship between the vicinal protons in support of the desired relative stereochemistry.

To prevent competitive addition of the nucleophilic methyl equivalent later in the synthesis, and to set up a double-deprotection/double-elimination sequence prior to eventual ring-closing metathesis,[1] the ester in **17** was reduced and the primary hydroxyl protected (→ **19**). The furan oxidation

Scheme 5. Assembly of the C(8−12) Tetrahydropyran Ring and Oxidative Spirocyclization



method worked particularly well in this case, and spirobutenolide **20** was obtained as a single diastereomer in 77% overall yield.

Investigations of the conjugate addition chemistry of spirobutenolide **20** and its elaboration toward the lituarines are currently underway.

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Supporting Information Available: Experimental procedures and spectroscopic characterization are provided for compounds **8**, **9**, **12**, **13**, and **16**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) For a discussion of the origins of stereocontrol in related cyclizations, see: (a) Betancort, J. M.; Martín, V. S.; Padrón, J. M.; Palazón, J. M.; Ramírez, M. A.; Soler, M. A. *J. Org. Chem.* **1997**, *62*, 4570−4583. (b) Ramírez, M. A.; Padrón J. M.; Palazón, J. M.; Martín, V. S. *J. Org. Chem.* **1997**, *62*, 4584−4590.

(22) Grignard reagent was generated from 2-(2-bromoethyl)furan, prepared in a three-step sequence from furan in 87% overall yield: (a) BuLi, ethylene oxide, THF; (b) MsCl, Et_3N, Et_2O; (c) LiBr, THF; see: Jung, M. E.; Miller, S. J. *Heterocycles* **1990**, *30*, 839−853.

(23) Cf.: Sperry, J. B.; Whitehead, C. R.; Ghiviriga, I.; Walczak, R. M.; Wright, D. L. *J. Org. Chem.* **2004**, *69*, 3726−3734.

(24) For a related example of cyclization of a 3°-alkoxide, see: Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E. *J. Am. Chem. Soc.* **1989**, *111*, 6682−6690.