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Progress in the Synthesis of the Lituarines: Stereocontrol in Sequential C–C Bond Formation on a Spirobutenolide Template

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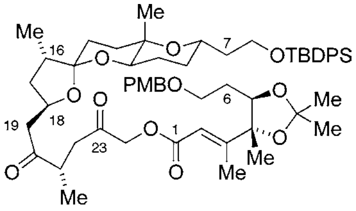
ABSTRACT



We describe elaboration of a tricyclic spirobutenolide corresponding to the C(7–18) tricyclic substructure common to lituarines A–C. Conjugate addition, to install the C(16) methyl, is followed by construction of the crucial C(18–19) bond by silyl enol ether addition to the derived spiroacetal C(18)–O oxonium ion. Esterification with a C(1–6) acid, and selective ozonolysis to release the C(23) carbonyl, complete the assembly of all the carbons present in the lituarine macrocyclic core.

We recently reported[1] the preparation of two major structural fragments of the lituarines, a group of cytotoxic, antifungal spiroacetal macrolides isolated from *Lituaria australasiae*.[2] Our plan for the union of these fragments and continuation to the natural products is shown retrosynthetically in Scheme 1. Introduction of a C(19−24) hydroxydiketone equivalent (**4**) at C(18) of tricycle **3**, esterification with a C(1−6) acid (**5** or **6**), release and elimination of the two protected primary hydroxyl groups, olefin metathesis to close the macrocycle at the C(6−7) bond, and epoxidation were expected to provide the macrocyclic core; further studies would then determine at which point in the route the C(24) *N*-acyldienamine side chain would be installed. In parallel studies, Smith's group has described a fundamentally different synthesis of a C(7−19) fragment[3] and its elaboration by Horner−Wadsworth−Emmons extension at C(7) and subsequent regioselective oxidation.[4] In the Smith approach, it is likely that macrocyclization will be achieved by esterification after incorporation of a C(20−24) unit at C(19).

In this paper, we focus on the introduction of the two new C−C bonds at C(16) and C(18) in the tetrahydrofuran ring since these are defining steps within the overall plan. Work on the first of these goals was set to follow from our model study in which we showed that conjugate addition of $(MeS)_3CLi$ to spirobutenolide **7** (Scheme 2) proceeded cleanly with high *anti* stereoselectivity (95:5 dr) with respect to the tetrahydropyran ring oxygen;[1b,5] furthermore, subse-

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[1] (a) Robertson, J.; Dallimore, J. W. P.; Meo, P. *Org. Lett.* **2004**, *6*, 3857. (b) Robertson, J.; Meo, P.; Dallimore, J. W. P.; Doyle, B. M.; Hoarau, C. *Org. Lett.* **2004**, *6*, 3861.

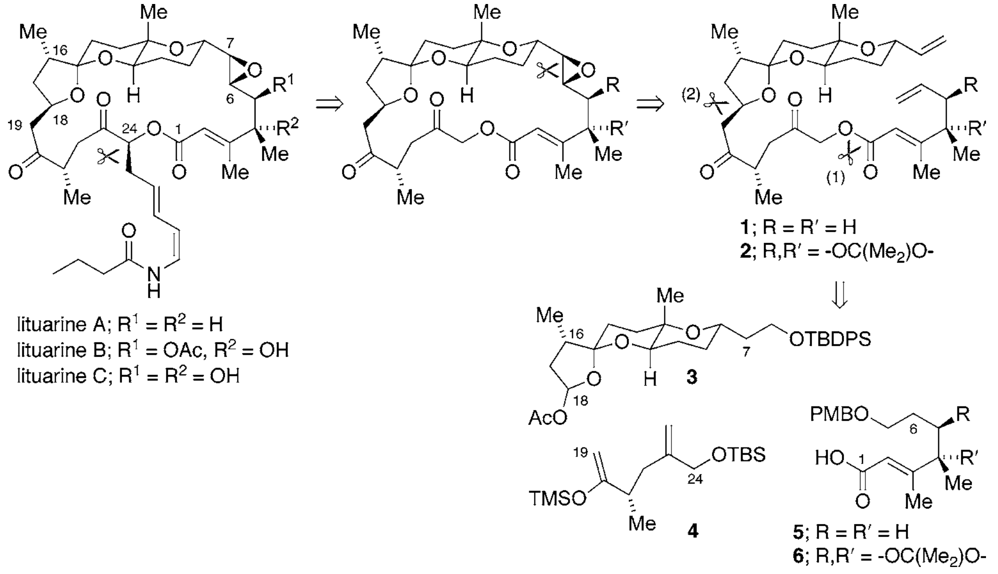
[2] Vidal, J.-P.; Escale, R.; Girard, J.-P.; Rossi, J.-C.; Chantraine, J.-M.; Aumelas, A. *J. Org. Chem.* **1992**, *57*, 5857.

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

[4] Smith, A. B., III; Walsh, S. P.; Frohn, M.; Duffey, M. O. *Org. Lett.* **2005**, *7*, 139.

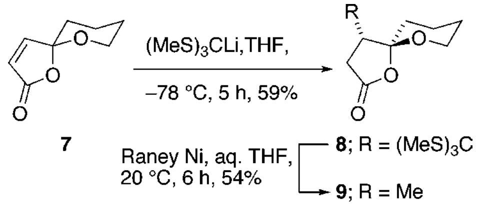
10.1021/ol0520018 CCC: $30.25

Scheme 1. Lituarine Synthetic Strategy



quent Raney nickel desulfurization of adduct **8** did not compromise this relative stereochemistry.

Scheme 2. Conjugate Addition Model Study[1b]



With this result secured, attention turned to modeling the formation of the C(18−19) bond since we were unable to find an appropriate precedent for this step which we intended to achieve through lactone reduction, acetylation, and subsequent trapping of the derived oxonium ion (**10**) with a silyl enol ether (Figure 1). While such bond constructions are well-known in the carbohydrate literature,[6] the application of such a method to the elaboration of spiroacetals has not been described, to the best of our knowledge. In fact, the use in synthesis of spirocyclic oxonium ions of this type is surprisingly uncommon; for example, Mead[7] and Brimble[8] have described allylation of 1,7-dioxaspiro[5.5]undecanes, and Hegedus has shown that 2-acetoxy-5-ethoxy tetrahydrofuran derivatives undergo Lewis acid-mediated substitution at the 2-position selectively with a variety of nucleophiles.[9] Against this was evidence that these reactions could be problematic with functionalized nucleophiles,[10] and it was with some trepidation that we embarked on the model study.

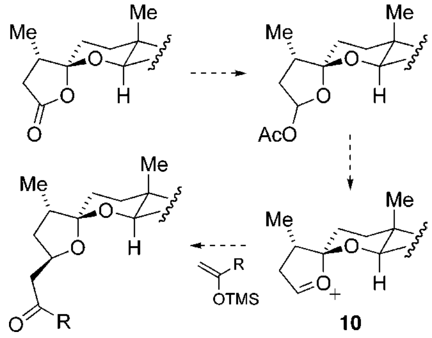
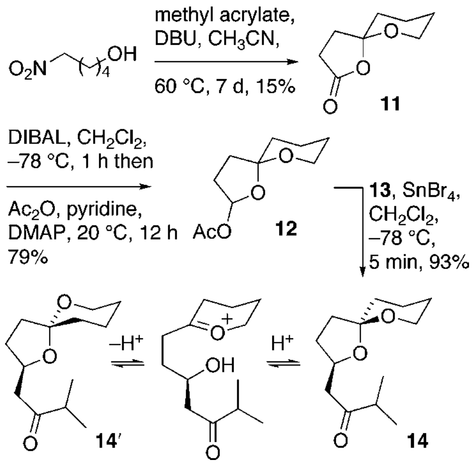


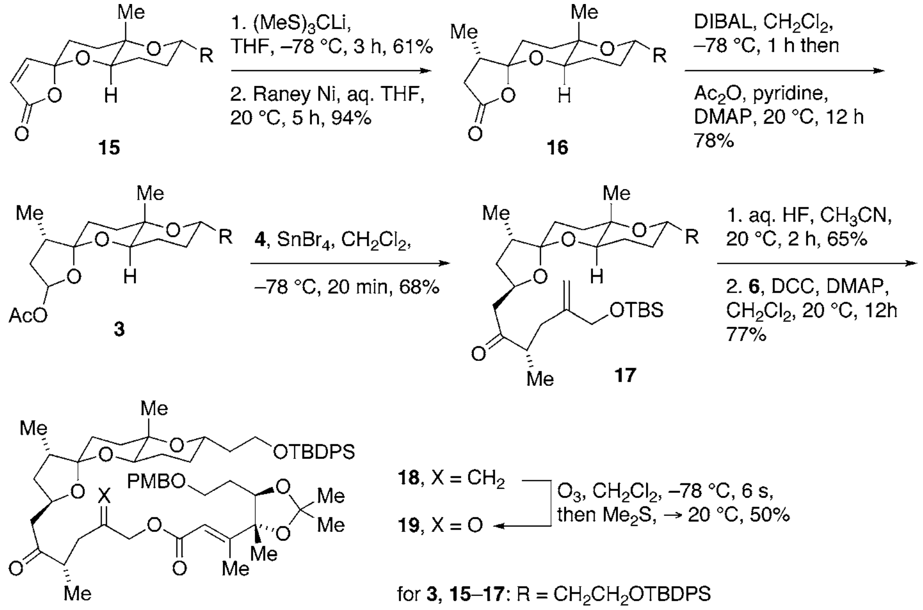
Figure 1. Proposed construction of the C(18−19) bond.

To work with a stereochemically simple system we chose spirobutyrolactone **11**[11] (Scheme 3) as the starting point which was prepared in a single step from 5-nitropentanol[12] in an unoptimized cascade conjugate addition−Nef−cyclization sequence.[13] Treatment of the derived acetoxy spiroacetal **12** with 3-methyl-2-(trimethylsilanyl)oxybutene (**13**)[14] in the

Scheme 3. C(18−19) Bond Formation Model Study



Scheme 4. Elaboration of Butenolide 15 to an Advanced Lituarine B,C Intermediate



presence of $SnBr_4$ resulted in the formation of a single compound, which we were delighted to find was the desired ketone **14** obtained as an approximately 1:1 mixture of diastereomers. Although we had not expected significant diastereocontrol in this reaction, we were not able to rule out the possibility that the addition *had* taken place to give predominantly one stereoisomer and that loss of stereochemical information had occurred subsequently by epimerisation at the acetal center, e.g., by protic acid catalysis as illustrated in Scheme 3. Since this mode of equilibration would be accompanied by loss of anomeric stabilization in the (rigid) lituarine system, we were confident that the results of high stereocontrol in the analogous reaction in that system would be retained during workup and purification.

The results of these model studies were then brought to bear on the total synthesis. The chemistry from tricyclic butenolide **15**[15] (Scheme 4) proved to be reliable and the sequence was followed without incident to give intermediate **17** with a fully functionalized tetrahydrofuran ring. Both of the key C−C bond-forming steps proceeded with high stereocontrol. The C(16) stereochemistry, arising from the conjugate addition, was established after complete assignment of the ^{1}H and ^{13}C NMR spectra; from this, NOESY correlations were established between the C(16) methyl and both C(14) protons, and between H(16) and the C(12) methyl, as illustrated in Figure 2. Second, in the reaction to form adduct **17**, the ^{1}H NMR spectrum of the crude product indicated the presence of a single diastereomer only. Assignment of the newly formed stereogenic center at C(18) followed from a NOESY correlation between the C(16) methyl and H(18), and the absence of a correlation between H(16) and H(18).

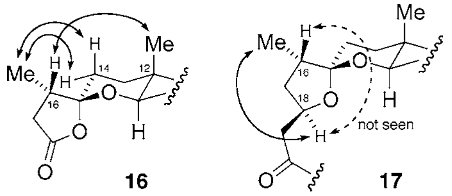


Figure 2. Diagnostic NOESY correlations.

The sense of stereoselectivity in the formation of adduct **17** is accommodated by Woerpel's "inside attack" model[16]

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(5) Our working hypothesis is that a stabilizing interaction of the incoming nucleophile, and then the forming C−C bond, with the tetrahydropyran [C(15)−O]σ^* acts cooperatively with electrostatic and solvation effects to favor attack *anti* to the six-membered ring oxygen. Cf. Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063.

(6) Ogawa, T.; Pernet, A. G.; Hanessian, S. G. *Tetrahedron Lett.* **1973**, 3543.

(7) (a) Mead, K. T.; Zemribo, R. *Synlett* **1996**, 1063. (b) Zemribo, R.; Mead, K. T. *Synlett* **2000**, 1569.

(8) Brimble, M. A.; Fares, F. A.; Turner, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 677.

(9) Umbricht, G.; Hellman, M. D.; Hegedus, L. S. *J. Org. Chem.* **1998**, *63*, 3, 5173.

(10) Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Org. Biomol. Chem.* **2003**, 104.

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

(12) Brewster, K.; Harrison, J. M.; Inch, T. D.; Williams, N. *J. Chem. Soc., Perkin Trans. 1* **1987**, 21.

(13) Cf. (a) Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D. *Synthesis* **2002**, 2725. (b) Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D. *Synthesis* **2003**, 316 (correction).

(14) Prepared in a standard procedure from methyl isopropyl ketone, LDA, and TMSCl. Cf. Beutelman, H. P.; Xie, L.; Saunders, W. H., Jr. *J. Org. Chem.* **1989**, *54*, 1703.

(15) Prepared on a multigram scale in a variant of the synthesis reported in ref 1b; in particular, the absolute stereochemistry was established by kinetic resolution through Sharpless epoxidation of (±)-2-methylhepta-1,6-dien-3-ol.

in which, discounting the influence of the counterion, the oxonium ion is trapped, under stereoelectronic control, from the upper face of envelope conformation **A** in preference to the lower face of conformation **B** (Figure 3). This reaction provides a further illustration[17] of the importance of a C(3) methyl substituent (furan numbering) in dictating the stereochemical course of additions to C(5)−O oxonium ions in these systems.

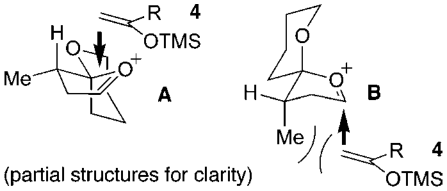

Figure 3. Rationalization of stereocontrol in the addition of silyl enol ether **4** to form **17**.

From this point, we have progressed the synthesis following the route established by our earlier study,[1a] essentially without modification. Some care was needed in the selective desilylation of compound **17** in order to avoid epimerisation, for example at C(21), and we prevented over-oxidation during the ozonolysis of the methylene group in **18** by keeping the reaction time down to an absolute minimum (6 s) in exposing the C(23) carbonyl group. These last three steps remain unoptimized pending the production of more material prior to completion of the synthesis as described in the introductory paragraph.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0520018

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(16) Larsen, C. H.; Ridgeway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208.

(17) For a survey of the stereoselectivity of silyl enol ether additions to isomeric methyl γ-lactols in the presence of a variety of Lewis acids, see: Schmitt, A.; Reiβig, H.-U. *Eur. J. Org. Chem.* **2001**, 1169.