ORGANIC LETTERS

2004
Vol. 6, No. 21
3857−3859

Syntheses of the C(1–6) and C(19–24) Fragments of Lituarines A, B, and C

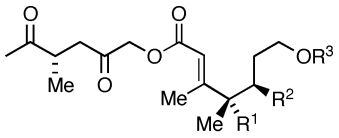
Jeremy Robertson,* Jonathan W. P. Dallimore, and Paul Meo

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, UK

jeremy.robertson@chem.ox.ac.uk

Received August 12, 2004

ABSTRACT



26, $R^1 = R^2 = H$; R^3 = TBDPS
27, R^1, $R^2 = OCMe_2O$; R^3 = PMB

Lituarines A–C are marine natural products comprising a tricyclic spiroacetal bridged at C(8) and C(18) by a functionalized ester linkage conceptually obtained from a C(19–24) alcohol and a C(1–6) carboxylic acid whose oxidation level varies at C(4) and C(5). Stereoselective routes are described to compounds 26 and 27, fully functionalized ester fragments of lituarine A and lituarines B and C, respectively.

Lituarines A−C (**1**−**3**) were isolated from the New Caledonian sea pen, *Lituaria australasiae*, by Vidal and coworkers in 1992.[1] These compounds were found to inhibit the growth of certain fungi and showed significant cytotoxicity toward KB cells (**1**, IC_{50} = 3.7−5.0 ng mL^{-1}; **2**, IC_{50} = 1.0−2.0 ng mL^{-1}; **3**, IC_{50} = 5.0−6.0 ng mL^{-1}). Because the lituarines could not be obtained in a crystalline form, their complex structures were determined mainly through extensive NMR investigations and their absolute configurations remain unknown.

The synthetic challenge defined by the assemblage of bis(tetrahydropyran), spiroacetal, epoxide, and *N*-acyldien-amine functionality, within a macrolactone ring, is not inconsiderable, and, to date, only a single description of a synthetic approach has been forthcoming.[2] Our approach to the macrolactone core, lacking the C(24) side-chain (Scheme 1), is founded on key C−C bond-forming reactions at C(18−19) and C(6−7). Thus, it is intended that esters formed by hypothetical condensation of alcohol **5** with acids **6** will be linked to tricyclic fragment **4** by nucleophilic addition of a C(19−20) enolate equivalent to a C(18)−O oxonium ion,[3] and ring-closing metathesis will furnish the macrocycle. In this Letter, we describe concise, stereoselective syntheses of fully functionalized ester intermediates **26** and **27**; our approach to tricyclic lactone **4** is described in the accompanying paper.[4]

In our first approach (Scheme 2) to alcohol **5** (R = H), a terminal acetylene was chosen as a masked form of the α-hydroxy ketone functionality. Pseudoephedrine amide **7** was alkylated under Myers' optimized conditions[5] with trimethylsilylpropargyl iodide[6] to give hexynone derivative **8** in good yield after treatment of the intermediate amide with methyllithium. The trialkylsilyl group was found not to interfere in Tamura's protocol[7] for oxidation of the triple bond; however, the product obtained was not the expected alcohol **5** (nor a cyclized variant thereof) but the trifluoro-

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

(2) (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).

(3) Woerpel has developed a model for relative stereocontrol in nucleophilic additions to five-membered cyclic oxonium ions that predicts a 2,4-anti relationship in related cases: Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208−12209.

(4) Robertson, J.; Meo, P.; Dallimore, J. W. P.; Doyle, B. M.; Hoarau, C. *Org. Lett.* **2004**, *6*, 3861−3864.

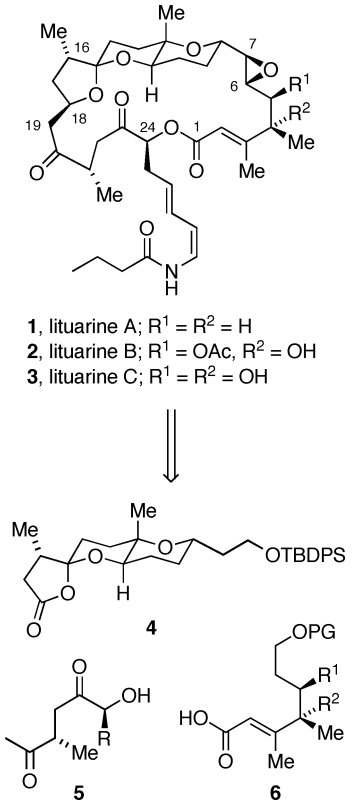
(5) (a) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511. (b) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361−9362.

(6) Rigby, J. H.; Cuisat, S. V. *J. Org. Chem.* **1993**, *58*, 6286−6291.

(7) Tamura, Y.; Yakura, T.; Haruta, J.-i.; Kita, Y. *Tetrahedron Lett.* **1985**, *26*, 3837−3840.

10.1021/ol048396x CCC: $27.50
Published on Web 09/22/2004

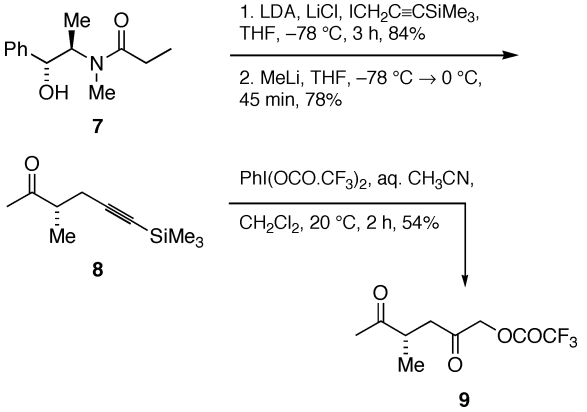
Scheme 1. Synthetic Analysis of Lituarines A−C



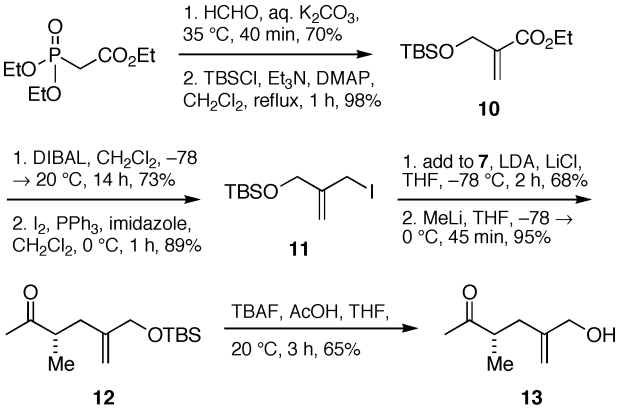
acetate derivative (**9**), a compound that proved to be surprisingly stable and which could be passed through a silica gel chromatography column without decomposition. Attempts to hydrolyze this ester to the corresponding alcohol resulted in complex product mixtures, and this route was discarded.

Identifying the C(23) (lituarine numbering) carbonyl group as the most likely cause of problems in this route, we opted for an alternative strategy in which this carbonyl would be present in latent form as an alkene. To this end, iodide **11** was prepared[8] in four efficient steps from triethyl phosphonoacetate (Scheme 3) and used to alkylate the enolate derived

Scheme 2. Attempted Synthesis of Alcohol **5** (R = H)

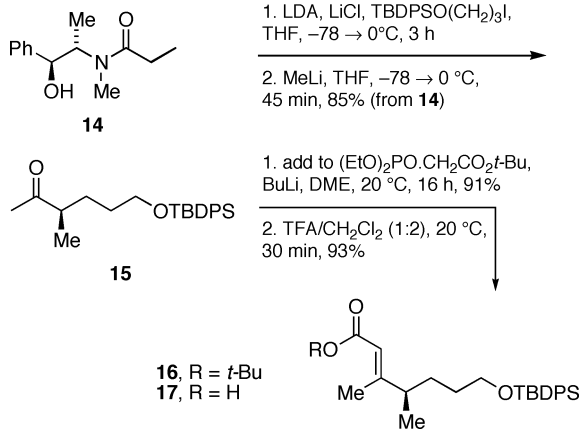


Scheme 3. Synthesis of Alcohol **5** (R = H) in Latent Form



from amide **7**. Ketone **12** could be deprotected without racemization under buffered TBAF conditions when the reaction time was kept to a minimum (≤3 h) in which case some residual starting material remained. The ee of this alcohol (91%) was determined on the basis of ^{1}H NMR analysis of its (*R*)-Mosher's ester derivative.

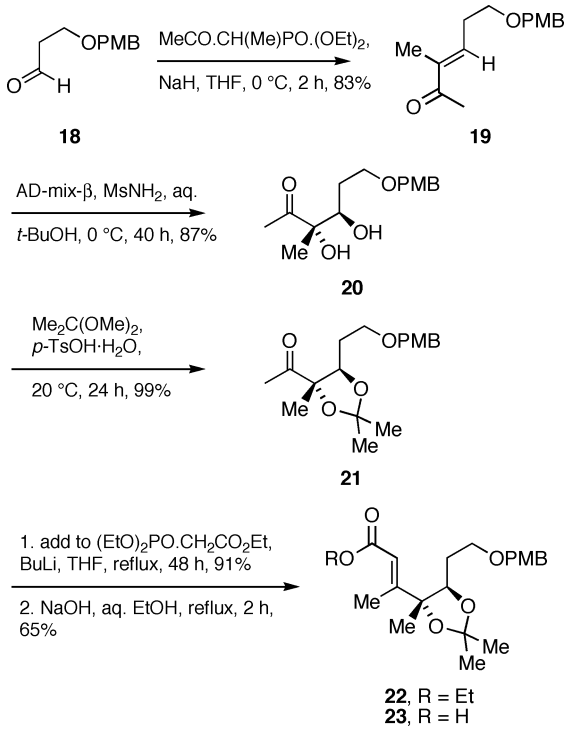
Scheme 4. Synthesis of Acid **17** (cf. **6**, $R^1 = R^2 = H$)



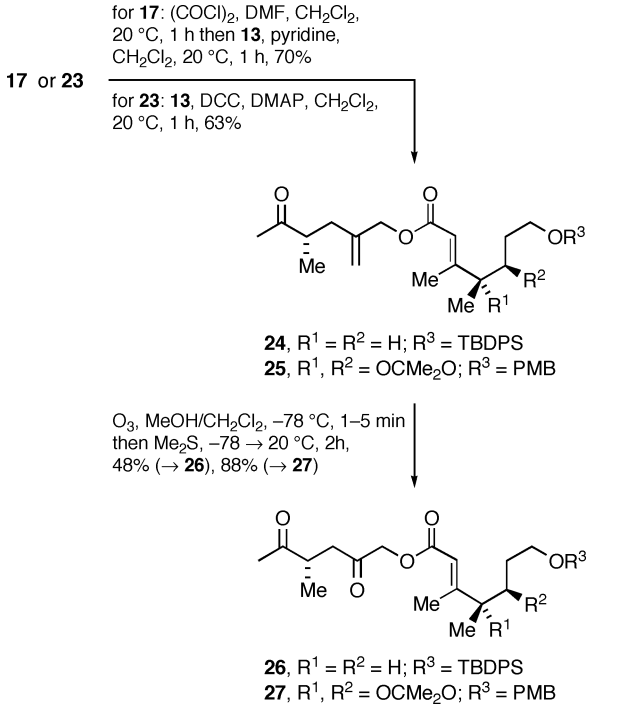
Separate routes (Schemes 4 and 5) to the variants of carboxylic acid **6** were developed for the lituarine A synthesis ($R^1 = R^2 = H$) and for the syntheses of lituarines B and C (R^1 = OAc or OH, R^2 = OH). In the simpler case, the single stereogenic center at C(4) was introduced, as before, using Myers' pseudoephedrine amide chemistry, this time in the enantiomeric series. Thus, amide **14** was converted in two high-yielding steps into ketone **15** and this ketone elaborated by Horner−Wadsworth−Emmons olefination into ester **16**, obtained solely as the (*E*)-isomer as judged by ^{1}H NMR. Release of the free carboxylic acid **17** was achieved under standard conditions and the ee (90%) assayed after reduction ($LiAlH_4$, Et_2O) to the allylic alcohol and conversion to its (*R*)-Mosher's ester. Some loss of stereochemical integrity

(8) (a) Villieras, J.; Rambaud, M. *Org. Synth.* **1988**, *66*, 220−224. (b) Danishefsky, S. J.; Mantlo, N. *J. Am. Chem. Soc.* **1988**, *110*, 8129−8133.

Scheme 5. Synthesis of Acid **23** (cf. **6**, R^1, R^2 = $OCMe_2O$)



Scheme 6. Completion of Lituarine A−C Ester Linkages



in this sequence may be attributable to the olefination reaction that proved to be rather slow (16 h), even at ambient temperature.

The more highly oxygenated analogues were prepared by Sharpless asymmetric dihydroxylation. Aldehyde **18**[9] was olefinated[10] to give enone **19** in good yield and with high diastereocontrol in favor of the (*E*)-isomer (19:1; *E*- established on basis of NOE data). Subjecting this compound to standard AD conditions afforded diol **20**, which was protected as the acetonide **21**. The ee at this stage was established as 94% after deprotection (DDQ) and esterification with (*R*)-Mosher's acid. From ketone **21**, Horner−Wadsworth−Emmons reaction afforded (*E*)-ester **22** as a single diastereomer, and saponification completed the route to acid **23** (Scheme 5).

To provide the complete ester linkages present in the lituarines, alcohol **13** was condensed with acid **17** (as its acid chloride) and the product (**24**) isolated as a single diastereomer in reasonable yield. Pleasingly, selective ozonolysis of the methylene group provided diketoester **26**; competitive cleavage of the trisubstituted alkene was minimized by keeping the reaction time within ca. 30−60 s. Following a similar route, ester **27** was generated in two steps from acid **23**, the dioxolane providing an increased steric impediment and electronic deactivation toward competitive cleavage of the enoate double bond (Scheme 6).

In our projected total synthesis of lituarines A−C, fragments **4** and **5** will be united prior to esterification with acid **6**; our progress on this coupling, subsequent macrocyclization, epoxidation, and incorporation of the C(24) side chain will be reported in due course.

Acknowledgment. We thank the EPSRC and the University of Oxford for funding (Grants GR/R25842/01, GR/P01397/01). We are grateful to Ms. Jenna C. Jamal for preliminary investigations.

Supporting Information Available: Experimental procedures and spectroscopic characterization for compounds **11**−**13**, **15**−**17**, and **19**−**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048396X

(9) Prepared in two steps from propane-1,3-diol by monoalkylation and subsequent Swern oxidation: Oka, T.; Murai, A. *Tetrahedron* **1998**, *54*, 1−20.

(10) Corbel, B.; Medinger, L.; Haelters, J.-P.; Sturtz, G. *Synthesis* **1985**, 1048−1051.