ORGANIC LETTERS

2001
Vol. 3, No. 24
3979−3982

Lituarine Synthetic Studies. An Efficient, Stereocontrolled Construction of the Common C(7–19) Tricyclic Spiroketal Fragment

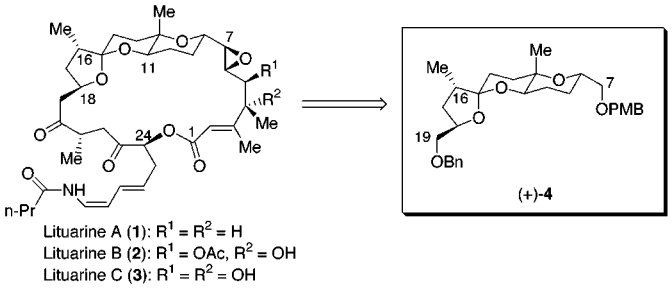
Amos B. Smith, III* and Michael Frohn

Department of Chemistry, Monell Chemical Senses Center and Laboratory for Research on the Structure of Matter, University of Pennsylvania, Philadelphia, Pennsylvania 19104

smithab@sas.upenn.edu

Received October 22, 2001

ABSTRACT



A highly efficient, stereocontrolled synthesis of (+)-4, the common C(7–19) tricyclic spiroketal fragment of the lituarines A, B, and C (1–3), has been achieved. Highlights of the synthesis include a remarkably facile 6-endo cyclization to access the C(8–12) pyran ring and a kinetically controlled acid-catalyzed spiroketalization.

In 1992 Vidal and co-workers reported the isolation, structural elucidation, and biological activity of the lituarines A, B, and C (**1**−**3**), architecturally complex natural products, isolated from the sea pen *Lituaria australasaie* endemic to the western region of the New Caledonian Lagoon near the "Baie de St. Vincent".[1] The connectivity and relative stereochemistry were secured via a combination of multidimensional NMR techniques and chemical correlation; the absolute configurations remain unknown.[1] Importantly, the lituarines displayed significant cytotoxicity toward KB cells [**1**, IC_{50} = 5.5−7.5 nmol; **2**, IC_{50} = 1−3 nmol; **3**, IC_{50} = 7−9 nmol[1]].

The unusual C(8−18) tricyclic core, consisting of a [6,5] spiroketal and trans-fused tetrahydropyran rings,[2] in conjunction with the C(1−7) fragment possessing four contiguous stereogenic centers for lituarines B and C (**2** and **3**), and a rare example of an acyclic conjugated dienamide, conspire to make the synthesis of the lituarines a significant challenge.[3] Given the structural complexity and potent cytotoxicities of the lituarines, combined with their scarcity (12.5 kg of sea pen furnished less than 25 mg of each congener) and our continuing interest in the synthesis of architecturally complex spiroketals having important bioregulatory properties,[4] we recently launched a program to construct these targets in a stereocontrolled manner. In this Letter, we report

(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) Okadaic acid contains a similar tricyclic fragment but is devoid of the methyl substituents at C(12) and C(16), see: Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Engen, D. V.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. *J. Am. Chem. Soc.* **1981**, *103*, 2469−2471.

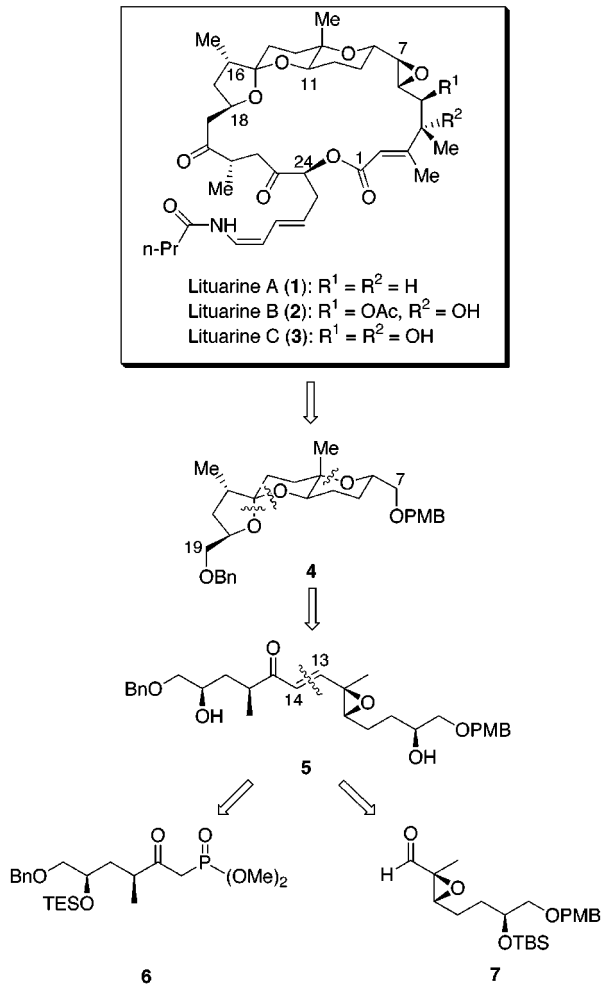
(3) For the construction of dienamides, see: (a) Oppolzer, W.; Frostl, W. *Helv. Chim. Acta* **1975**, *58*, 587−589. (b) Overman, L. E.; Clizbe, L. A. *J. Am. Chem. Soc.* **1976**, *98*, 2352−2354. (c) Overman, L. E.; Taylor, G. F.; Jessup, P. J. *Tetrahedron Lett.* **1976**, 3089−3092. (d) Katritzky, A. R.; Ignatchenko, A. V.; Lang, H.; *J. Org. Chem.* **1995**, *60*, 4002−4005.

10.1021/ol016948v CCC: $20.00
Published on Web 11/09/2001

an efficient, stereocontrolled synthesis of the common C(7−19) tricyclic spiroketal fragment (+)-**4**.

From the retrosynthetic perspective, we envisioned **4** to arise via an acid-catalyzed 6-endo cyclization of an epoxy-ketone (**5**) to assemble the C(8−12) tetrahydropyran with the required relative stereochemistry (Scheme 1); subsequent

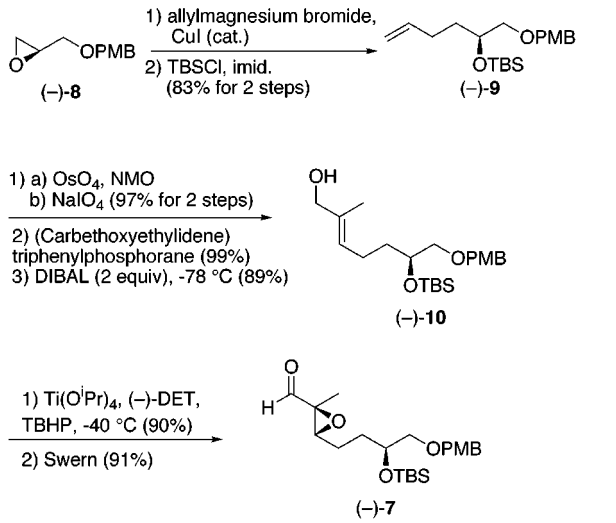
Scheme 1



reduction of the olefin and stereoselective spiroketalization would then complete the tricyclic fragment.[5] To overcome the inherent stereoelectronic constraints of the initial tetrahydropyran construction (i.e., 6-endo vs 5-exo cyclization),[6] we recognized the need for cationic stabilization adjacent to the epoxide. Thus, unsaturation at C(13,14), as introduced by Nicolaou,[7] would serve to maximize the regioselectivity in the ring formation. Reduction of the olefin would then be followed by stereoselective spiroketalization; the requisite stereogenicity of the C(15) spiroketal was anticipated on the basis of the anomeric effect[8] and previous experience in our laboratory.[4] Control of the relative configuration of the C(16) methyl substituent however was far less certain.[9] With this as rationale, α,*β*-unsaturated ketone **5** was selected to be the precursor for **4**. Continuing with this analysis, ketone **5** would arise via a Horner−Wadsworth−Emmons (HWE) condensation between phosphonate **6** and epoxy-aldehyde **7**, followed by removal of the silyl protecting groups.

Our point of departure for the construction of **5** entailed assembly of epoxy-aldehyde **7** (Scheme 2). Addition of

Scheme 2



allylmagnesium bromide to (*R*)-4-methoxybenzylglycidyl ether[10] catalyzed by CuI, followed by TBS protection of the derived alcohol, readily furnished (−)-**9** in 83% yield for the two steps.[11] Oxidative cleavage of the terminal olefin, Wittig olefination with (carbethoxyethylidene)triphenylphosphorane, and DIBAL reduction of the resulting ester then

(4) (a) Smith, A. B., III; Hale, K. J.; Vaccaro, H. A.; Rivero, R. A. *J. Am. Chem. Soc.* **1991**, *113*, 2112−2122 (b) Smith, A. B., III; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Salvatore, B. A.; Spoors, P. G.; Duan, J. J.-W. *J. Am. Chem. Soc.* **1999**, *121*, 10468−10477. (c) Smith, A. B., III; Doughty, V. A.; Lin, Q.; Zhuang, L.; McBriar, M. D.; Boldi, A. M.; Moser, W. H.; Murase, N.; Nakayama, K.; Sobukawa, M. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 191−195. (d) Smith, A. B., III; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Kerns, J. K.; Brook, C. S.; Murase, N.; Nakayama, K. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 196−199.

(5) For other methods for the construction of the fused tetrahydropyrans, see: (a) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380−1386 and references therein. (b) Sakamoto, Y.; Matsuo, G.; Matsukura, H.; Nakata, T. *Org. Lett.* **2001**, *3*, 2749−2752.

(6) In general, 5-exo cyclization is favored geometrically over 6-endo cyclization. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−736.

(7) (a) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K.; Somers, P. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1359−1362. (b) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330−5334.

(8) For reviews of the anomeric effect, see: (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, 1983. (b) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983.

(9) Monte Carlo conformational searches using the MM2 force field predicted the spiroketal epimeric to **4** at C(16) (i.e., *β*) to be more stable by 0.99 kcal/mol (1.49:1 ratio at equilibrium). Both methyl isomers epimeric at C(15) were predicted to be considerably less stable (ca. 7.7 kcal/mol).

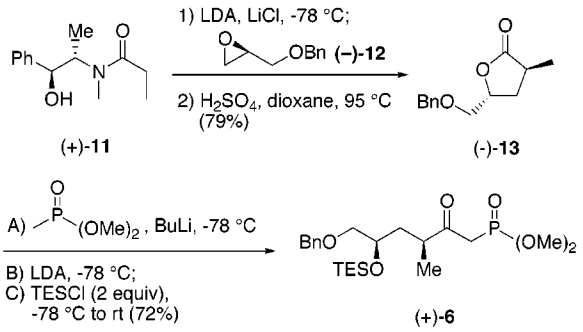
(10) Smith, A. B., III; Zhuang, L.; Brook, C. S.; Boldi, A. M.; McBriar, M. D.; Moser, W. H.; Murase, N.; Nakayama, K.; Verhoest, P. R.; Lin, Q. *Tetrahedron Lett.* **1997**, *38*, 8667−8670.

(11) Interestingly, minor amounts (<10%) of regioisomeric products were also observed.

led to the *E* allylic alcohol (−)-**10** in nearly quantitative yield. Subsequent Sharpless asymmetric epoxidation[12] proceeded both in high yield and with excellent diastereoselectivity (90% yield, >20:1 dr). Completion of (−)-**7** was achieved by Swern oxidation;[13] the overall yield for the seven-step sequence was 58%.

Construction of the HWE coupling partner, β-ketophosphonate **7**, began with the alkylation of (*S*,*S*)-pseudoephedrine amide **11** employing (*S*)-benzylglycidyl ether[14] according to the Myers protocol[15] to furnish, after acid-mediated cyclization, lactone (−)-**13**[15] (Scheme 3). Treatment of the

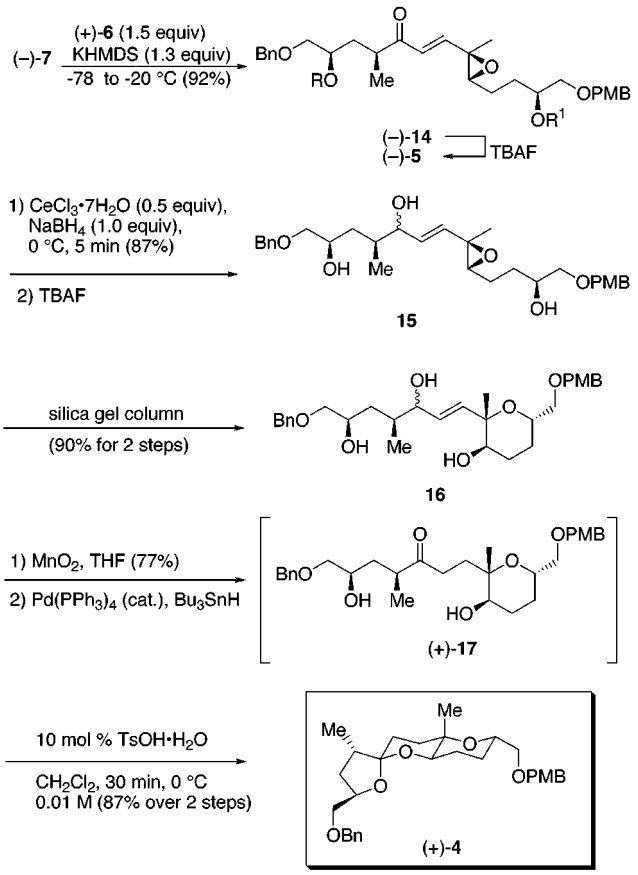
Scheme 3



latter with the lithium anion derived from dimethyl methylphosphonate, followed by in situ protection as the triethylsilyl ether,[16] rapidly furnished (+)-**6**. The overall yield for the three-step sequence was 57%.

Union of fragments (+)-**6** and (−)-**7** was next achieved in excellent yield (92%) with exclusive *E*-selectivity (Scheme 4).[17] Unfortunately, all attempts to effect cyclization of the derived diol **5** (TBAF) proceeded with low regioselectivity, presumably due to the electron poor nature of the olefin.[18] We therefore explored conditions to effect 1,2-reduction of the α,β-unsaturated ketone. Luche reduction[19] employing 0.5 equiv of $CeCl_3 \cdot 7H_2O$ at 0 °C in methanol furnished the desired allylic alcohol in high yield, albeit as a mixture of diastereomers (1:1). Removal of the silyl protecting groups (TBAF) then led to **15**, our second generation cyclization precursor. Pleasingly, this mixture of triols displayed a high propensity to undergo cyclization upon purification with silica gel. Additional experimentation revealed that slow elution of the mixture through silica gel consistently resulted in triols **16** in high yield (90% yield; i.e., TBAF followed

Scheme 4



by elution through silica gel). To the best of our knowledge this is the first regioselective cyclization of a vinyl epoxide reported to proceed by simple elution through silica gel.

Turning next to the requisite spiroketalization, selective oxidation of **16** with manganese(IV) oxide, followed by palladium(0)-catalyzed 1,4-reduction utilizing tributyltin hydride as the stoichiometric reductant, proceeded to give saturated ketone (+)-**17**,[20] accompanied by minor amounts of two cyclic hemiketals (ca. 10%). Unable to remove completely all traces of tin impurities after single elution through silica gel, the mixture of ketone (+)-**17** and cyclic hemiketals was used directly in the spiroketalization.

Of considerable risk vis-à-vis the prospective spiroketalization was loss of the C(16) stereogenicity.[9] Notwithstanding this concern, we were delighted to find that treatment of the mixture of ketone and the cyclic hemiketals with a catalytic amount of toluenesulfonic acid in CH_2Cl_2 at 0 °C (i.e., kinetic conditions) furnished tricyclic spiroketal (+)-**4** both in excellent yield (87%) and with high stereochemical control at the C(15) and C(16) stereogenic centers [C(15) > 18:1; C(16) > 20:1]. The relative configurations at C(15) and C(16), coinciding with those of the lituarines, were initially confirmed by extensive 2D NOESY NMR experiments (Figure 1).[21] Single-crystal X-ray analysis of (+)-**20**, the dibromobenzoate derived from (+)-**4**, confirmed this analy-

(12) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.
(13) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651−1660.
(14) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 6776−6777.
(15) (a) Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428−2440. (b) Myers, A. G.; Yang, B. H. *Org. Synth.* **1999**, *47*, 22−28.
(16) Ditrich, K.; Hoffmann, R. W. *Tetrahedron Lett.* **1985**, *26*, 6325−6328.
(17) Ley, S. V.; Meek, G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1125−1133.
(18) A mixture (ca. 1:1) of 6-endo/5-exo products was obtained in poor yield.
(19) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459.
(20) Keinan, E.; Gleize, P. A. *Tetrahedron Lett.* **1982**, *23*, 477−480.

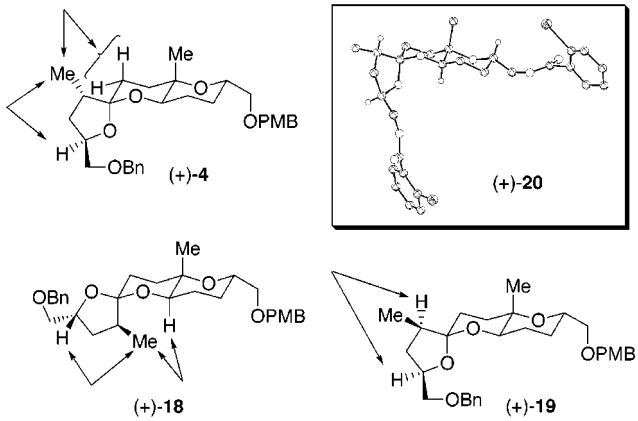


Figure 1. 2D NOESY correlations for (+)-**4**, (+)-**18**, and (+)-**19** and the ORTEP for (+)-**20**.

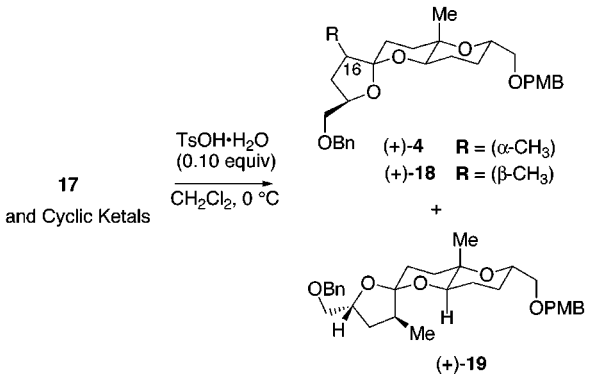
sis. When the spiroketalization was carried out on larger scale (ca. 200 mg), a second spiroketal, (+)-**19**, was isolated (10% yield), having the nonanomerically stabilized structure (Table 1, entry 1). Best results were obtained when the spiroketalization was carried out at higher concentration (0.3 M) and for a shorter reaction time (25 min) [83% yield, >20:1 dr at C(16); entry 2]. Longer reaction times (60 min) significantly erode the stereochemical integrity at C(16) (entry 3).

Aware of the possible future need for acidic protocols as the lituarine synthetic venture unfolds, we thought it prudent to define the minimal conditions that would lead to equilibration at C(16). To this end, treatment of (+)-**4** with a catalytic amount of toluenesulfonic acid, this time at room temperature over a 15 h period, yielded a mixture of tricycles (+)-**4** and (+)-**18**, now with the undesired C(16) congener (+)-**18** as the major component (ca. 1.4:1; Figure 1).[9] On the basis of our MM2 calculations,[9] this result presumably represents the equilibrium mixture.

In summary, a highly efficient, stereocontrolled synthesis of (+)-**4**, the C(7−19) tricyclic spiroketal fragment of the

(21) Tricycle (+)-**4** has been characterized by ^{1}H, ^{13}C, DEPT; 2D COSY, NOESY, HMQC, and HMBC NMR.

Table 1. Spiroketalization Study



entry	concentration (M)	time (min)	[(+)-**4**:(+)-**18**] [dr at C(16)]	(+)-**19** (%)
1	0.01	30	78 (18:1)	10
2	0.3	25	83 (>20:1)	<5
3	0.3	60	83 (2.5:1)	0

lituarines A, B, and C (**1**−**3**), has been achieved. The cornerstone of the construction entailed a remarkably facile 6-endo cyclization of an epoxy-alcohol upon elution through silica gel followed by a kinetically controlled, stereoselective spiroketalization. Further progress toward the total syntheses of the lituarines will be reported in due course.

Acknowledgment. Support was provided by the National Institutes of Health (National Cancer Institute) through Grant CA-19033. An American Cancer Society Postdoctoral Fellowship to M.F. is also gratefully acknowledged.

Supporting Information Available: Spectroscopic and analytical data for compounds (+)-**4**, (+)-**6**, (−)-**7**, (−)-**9**, (−)-**10**, and (−)-**14** through (+)-**17** and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016948V