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Diversity-Oriented Synthesis of Polyketide Natural Products via Iterative Chemo- and Stereoselective Functionalization of Polyenoates: Development of a Unified Approach for the C(1–19) Segments of Lituarines A–C

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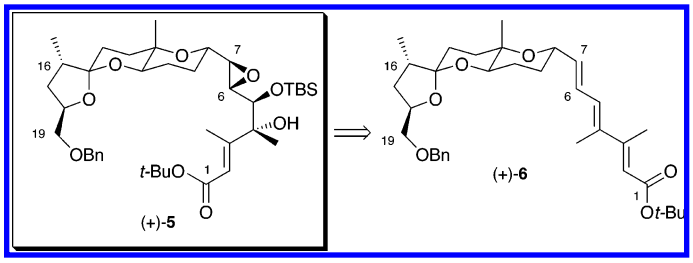
ABSTRACT



A unified, stereocontrolled synthesis of the C(1–19) segments of the lituarines A–C (1–3) has been achieved, highlighted by application of an iterative chemo- and stereoselective trienoate functionalization protocol, a strategy that holds considerable promise for the diversity oriented synthesis of polyketides.

In 1992, Vidal and co-workers reported the isolation, structural elucidation, and biological activity of the lituarines A−C (**1**−**3**, Scheme 1), 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 connectivities and relative stereochemistries were secured via a combination of multidimensional NMR techniques and chemical correlation; their absolute configurations remain unknown.[1] From the biomedical perspective, the lituarines display significant cytotoxicity toward KB cells [(**1**): $IC_{50} = 5.5-7.5$ nM; (**2**): $IC_{50} = 1-3$ nM; (**3**): $IC_{50} = 7-9$ nM].[1]

The unique C(8−18) tricyclic core, consisting of a [6,5]-spiroketal and trans-fused tetrahydropyran rings, in conjunction with the highly functionalized 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.

Given the structural complexity and biological activities 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, we recently initiated a program to construct these targets in a stereocontrolled manner.[2] An early achievement in this area entailed the design and execution of an efficient,

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

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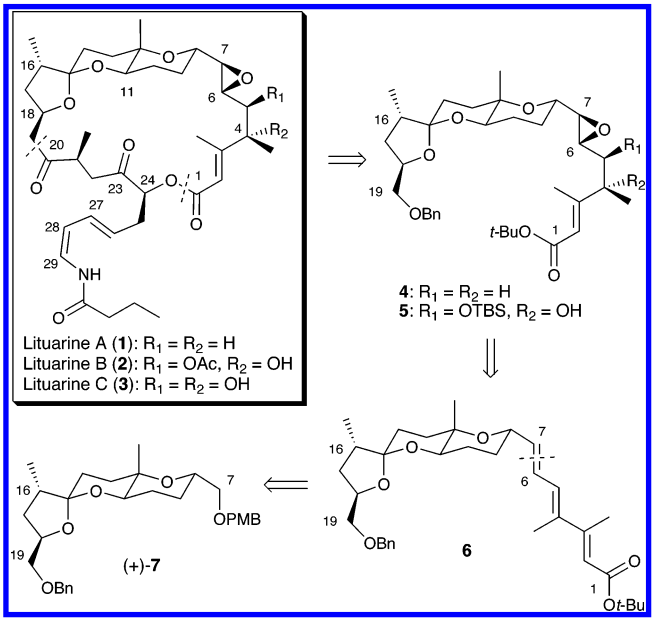
Scheme 1



stereocontrolled synthesis of the common C(7−19) tricyclic spiroketal fragment (+)-**7**, highlighted by a stereoselective kinetic spiroketalization to establish the requisite C(16) stereocenter.[3,4] Herein we report the synthesis of the C(1−19) segment of lituarines B and C (**5**), fully functionalized for elaboration to the natural products, as well as the synthesis of the remaining segment (**17**) bearing the requisite C(1−19) stereocenters present in lituarine A.

In keeping with our longstanding interest in the development of unified strategies, we selected a flexible approach exploiting a seldom employed tactic: the iterative chemo- and stereoselective functionalization of a polyenoate (**6**, Scheme 1),[5,6] a protocol that we believe holds considerable potential for diversity oriented synthesis of polyketides. Toward this end, disconnection at the macrolactone and the C(19−20) bonds of the lituarines provides two C(1−19) subtargets (Scheme 1): **4** corresponding to lituarine A and **5** corresponding to lituarines B and C, which we envisioned to arise from a common C(1−19) trienoate. Iterative chemo- and stereoselective oxidation, directed in each case to the most electron rich olefin (i.e., distal to the ester), employing reagent control, would install the requisite C(6,7) *trans*-epoxide and C(4,5) functionality in a highly stereocontrolled fashion, as required for any successful approach to the lituarines. From the perspective of diversity-oriented synthesis, extension of this iterative strategy, simply by varying the chiral auxiliary required for each oxidation and/or reduction step, would not only permit a unified approach to both **4** and **5** but also provide access to a small library of stereochemically diverse congeners at C(4−7).

The iterative chemoselective epoxidation of a polyene possessing a terminal electron-withdrawing group appears to have been first exploited in complex molecule synthesis by Pattenden and co-workers[5] as a biomimetic approach for the construction of the natural products aurovertin and citreoveridinol. Shortly thereafter, Sharpless and co-workers[7] reported high chemo- and enantioselectivities in the dihydroxylation of unfunctionalized dieneoates and trieneoates. O'Doherty and co-workers[6] later exploited the utility of the Sharpless iterative chemo- and enantioselective dihydroxylations for the elaboration of a simple trienoate in their synthesis of colletodiol. Finally, Shi and co-workers, during their development of chiral dioxiranes, demonstrated the feasibility of electronically directed chemo- and enantioselectivity in the enantioselective epoxidation of simple diene systems.[8]

Of considerable risk for the lituarine program was the requisite chemoselectivity required for epoxidation of the C(6,7)-disubstituted olefin [allylic to the C(8)-ether] versus the trisubstituted C(4,5) olefin, as well as the effect that a chiral substrate might exert on a reagent controlled process.[9] Thus, the effect of reagent control (i.e., use of chiral reagents) versus substrate control as a prospective tactic for future diversity-oriented synthesis employing polyenoates was of particular interest.

We began construction of **5** with removal of the PMB moiety in spiroketal (+)-**7**, followed in turn by oxidation and treatment of the resultant aldehyde (+)-**8** with the sodium ylide derived from dienyl phosphonate **9**.[10] A mixture of trienes **6** (*E*/*Z* 2.5:1) at the C(6,7) olefin resulted (Scheme 2). Equilibration with catalytic iodine furnished the desired all *E*-triene (>10:1 *E*/*Z*). Two methods were then explored for installation of the C(6,7) epoxide.[11] Application of the Shi protocol[8] to (+)-**6**, employing (−)-**10** as catalyst,

(2) (a) Smith, A. B., III; Thompson, A. S. *J. Org. Chem.* **1984**, *49*, 1469. (b) Smith, A. B., III; Fukui, M. *J. Am. Chem. Soc.* **1987**, *109*, 1269. (c) Smith, A. B., III; Fukui, M.; Vaccaro, H. A.; Empfield, J. R. *J. Am. Chem. Soc.* **1991**, *113*, 2071. (d) Smith, A. B., III; Rivero, R. A.; Hale, K. J.; Vaccaro, H. A. *J. Am. Chem. Soc.* **1991**, *113*, 2092. (e) Smith, A. B., III; Hale, K. J.; Vaccaro, H. A.; Rivero, R. A. *J. Am. Chem. Soc.* **1991**, *113*, 2112. (f) Smith, A. B., III; Empfield, J. R.; Rivero, R. A.; Vaccaro, H. A. *J. Am. Chem. Soc.* **1991**, *113*, 4037. (g) Smith, A. B., III; Friestad, G. K.; Duan, J. J.-W.; Barbosa, J.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Bertounesque, E.; Spoors, P. G.; Salvatore, B. A. *J. Org. Chem.* **1998**, *63*, 7596. (h) 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. (i) 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.* **2001**, *40*, 191. (j) 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.* **2001**, *40*, 196 and references therein.

(3) Smith, A. B., III; Frohn, M. *Org. Lett.* **2001**, *3*, 3974; *Org. Lett.* **2002**, *4*, 4183.

(4) For an alternative approach to the lituarines, see: (a) Robertson, J.; Meo, P.; Dallimore, J. W. P.; Doyle, B.; Hoarau, C. *Org. Lett.* **2004**, *6*, 3861. (b) Robertson, J.; Dallimore, J. W. P.; Meo, P. *Org. Lett.* **2004**, *6*, 3857.

(5) (a)Pattenden, G.; Forbes, J. *Tetrahedron Lett.* **1987**, *28*, 2771. (b) Ebenezer, W.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 4053.

(6) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 4447.

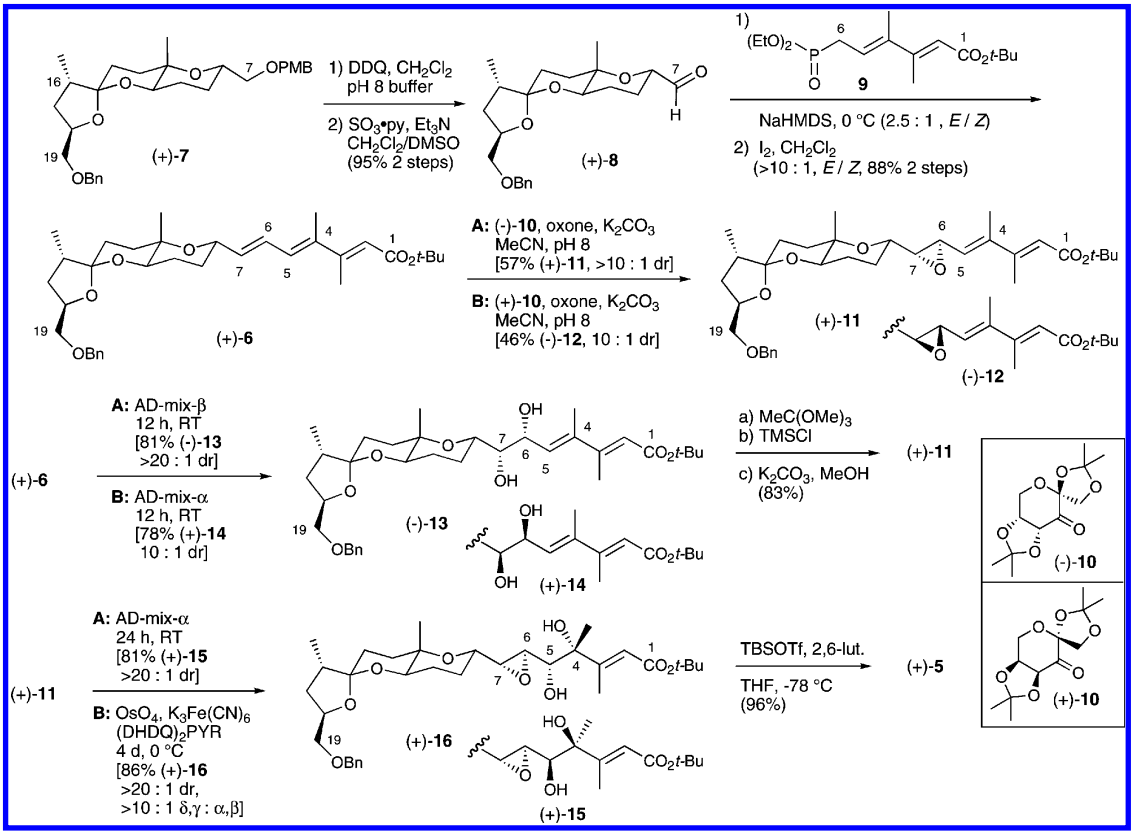
(7) (a) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570. (b) Becker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345.

(8) (a) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (b) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979. (c) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488. (d) Frohn, M.; Dalkeiwicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948.

(9) For an investigation into substrate effects on the dihydroxylation including a dieneoate system which favors reaction at the α,β-position, see: Hermitage, S. A.; Murphy, A.; Nielsen, P.; Roberts, S. M. *Tetrahedron* **1998**, *54*, 13185.

(10) For the synthesis of phosphonate **9**, see the Supporting Information.

Scheme 2

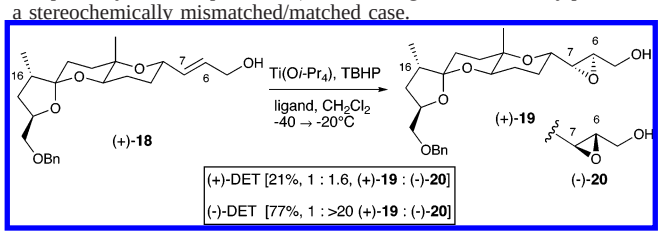


provided the desired (6*R*,7*S*)-epoxide (+)-**11** in moderate yield (57%) with excellent diastereoselectivity (>10:1), accompanied by formation of the C(4,5)-epoxide (ca. 5%) and over oxidation products (ca. 12%). The antipode (+)-**10** furnished a similar product mixture, featuring formation of the diastereomeric epoxide (−)-**12** (10:1 dr). Alternatively, Sharpless dihydroxylation exploiting the AD-mix-β[12] furnished the (6*R*,7*R*)-diol (−)-**13** as a single diastereomer in good yield; the alternate AD-mix-α provided the diastereomer (+)-**14** as the sole product. Epoxide formation by the method of Sharpless[13] converted diol (−)-**13** to the same epoxide [(+)-**11**] as obtained via the Shi protocol employing ketone (−)-**10** (67%; two steps). Dihydroxylation of the C(4,5) olefin in (+)-**11**, the second electrophilic oxidation required to functionalize the C(1−7) triene, proceeded smoothly with AD-mix-α to install the (4*S*,5*S*)-diol from the face opposite to the C(6,7) epoxide [(+)-**15**]. For the lituarines (B and C), however, we require installation of the diol on the same face as the proximal epoxide.[9]

We therefore turned to the use of AD-mix-β; a mixture of α,β and δ,γ diols (1:5) resulted, albeit the reaction proved sluggish. Screening a series of ligands led to $(DHDQ)_2PYR$; at 0 °C the desired (4*R*,5*R*)-diol (+)-**16** was obtained in high yield with excellent chemo- and diastereoselectivity. Completion of the C(1−19) fragment for lituarines B and C then only required protection of (+)-**16** as the TBS-ether. Of particular note in this synthetic sequence are the high chemo- and diastereoselectivities obtained for both antipodes of the chiral reagents. Assuming the generality of this synthetic tactic, the iterative chemo- and diastereoselective functionalization of polyenoates featuring a terminal electron-withdrawing group should hold considerable promise for diversity oriented synthesis.

To install the C(4) stereochemistry necessary for construction of fragment **4** required for lituarine A, we explored an alternative iterative tactic (Scheme 3). Initially, direct reduction of the C(6,7)-epoxide (+)-**11** proved problematic due to low chemo- and diastereoselectivity, as well as over-reduction. We reasoned that the C(6) hydroxyl might direct both the chemo- and diastereoselectivity for the required reduction; a variety of conditions were therefore explored. Optimized conditions proved to be catalytic hydrogenation employing the Lindlar catalyst; diol (−)-**17**, precursor to the

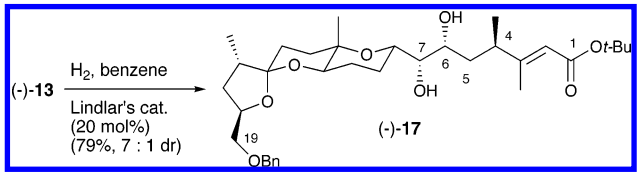
(11) In an effort to correlate the stereochemistry of the C(6,7) epoxide early in our program we discovered that a more conventional approach (i.e., Sharpless asymmetric epoxidation) for installing this functionality presented a stereochemically mismatched/matched case.



(12) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(13) Kolb, H. C.; Sharpless, K. B *Tetrahedron* **1992**, *48*, 10515.

Scheme 3



C(6,7) epoxide for lituarine A, was obtained in 79% yield (7:1 dr).[14]

In summary, we have developed the iterative chemo- and stereocontrolled functionalization of a trienoate substrate for the unified construction of the C(1−19) segments for lituarines A−C. High chemo- and stereoselectivities were observed for both the Shi asymmetric epoxidation and Sharpless asymmetric dihydroxylation protocols with a variety of chiral substrates. Importantly, the stereogenicity and functionality installed in the first iteration could be employed to direct the second chemo- and diastereoselective reduction in the absence of a chiral reagent. Progress toward the total synthesis of the lituarines, as well as additional applications of this iterative chemo- and stereocontrolled polyenoate functionalization tactic for the diversity-oriented synthesis of natural products and their stereochemical congeners, will be reported in due course.

(14) The stereochemistry of the C(4)-methyl group has been established via chemical correlation. For full details see the Supporting Information.

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Supporting Information Available: Spectroscopic data as well as experimental procedures for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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