ORGANIC LETTERS

2000
Vol. 2, No. 17
2683−2686

Total Synthesis of the Supposed Structure of (−)-Sclerophytin A and an Improved Route to (−)-7-Deacetoxyalcyonin Acetate

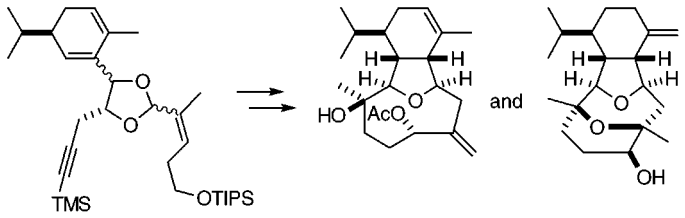
Larry E. Overman* and Lewis D. Pennington

Department of Chemistry, 516 Rowland Hall, University of California, Irvine, California 92697-2025

leoverma@uci.edu

Received June 21, 2000

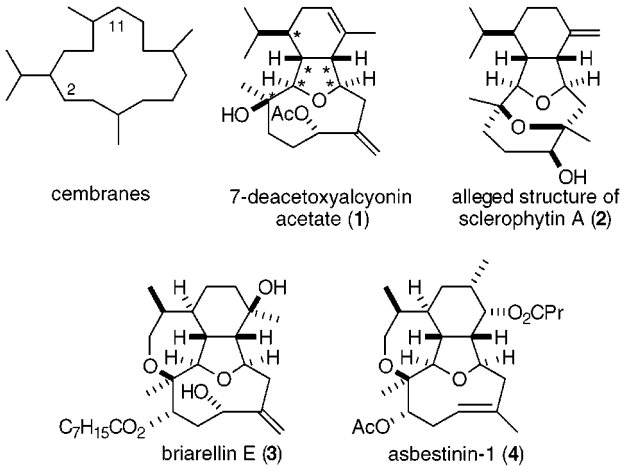
ABSTRACT



Stereoselective acid-catalyzed rearrangement of 15 → 16 is the central step in total syntheses of (−)-7-deacetoxyalcyonin acetate (1) and the compound with the alleged structure of sclerophytin A (2). Since tetracyclic diether 2 is not identical to sclerophytin A, the structure of this antineoplastic marine diterpene must be revised. The conversion of 15 → 16 demonstrates for the first time that tetrahydrofurans containing (*Z*)-1-methylalkenyl side chains can be prepared by Prins−pinacol rearrangements.

Marine invertebrates are a rich source of structurally novel oxacyclic diterpenes.[1] One large family is derived from cembrane precursors by C2−C11 bond formation and includes the cladiellins (e.g., **1** and **2**), the briarellins (e.g., **3**), the asbestinins (e.g., **4**) and the sarcodictyins, (e.g., eleuthrobin). The cladiellins, briarellins, and asbestinins have in common a rare oxatricyclic ring system composed of hydroisobenzofuran (2-oxabicyclo[4.3.0]-nonane) and oxacyclononane units as well as the six stereogenic centers indicated by asterisks in structure **1**.[1]

In 1995, we reported an enantioselective total synthesis of (−)-7-deacetoxyalcyonin acetate (**1**), which was the first total synthesis of a 2,11-cyclized cembranoid ether.[2] The



central step in this synthesis was condensation of (*S*)-carvone-derived dienyl diol **5** with a *trans*-α,β-unsaturated aldehyde,

(1) For recent reviews, see: (a) Coll, J. C. *Chem. Rev.* **1992**, *92*, 613−631. (b) Wahlberg, I.; Eklund, A.-M. In *Progress in the Chemistry of Organic Natural Products*; Springer-Verlag: New York, 1992; Vol. 60, pp 1−141. (c) Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531−556.

(2) (a) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391−10392. (b) MacMillan, D. W. C. Ph.D. Dissertation, University of California, Irvine, CA, 1996.

(3) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354−5365.

10.1021/ol006236p CCC: $19.00 © 2000 American Chemical Society
Published on Web 08/01/2000

(*E*)-**6**, to generate the hexahydroisobenzofuran ring and five stereogenic centers of (*E*)-**9** (Figure 1). A potentially valuable

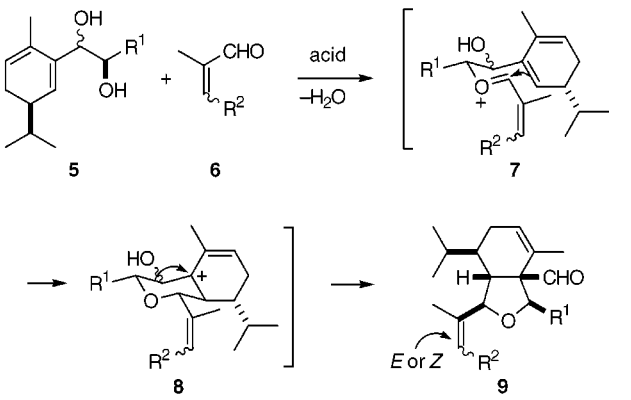
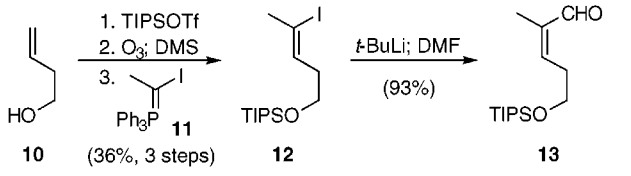


Figure 1.

extension of this strategy, which we anticipated might be of particular utility in addressing the additional structural complexity of the asbestinins and briarellins, would be realized if bicyclic ethers **9** containing a (*Z*)-1-methylalkenyl side chain could be prepared from condensation of **5** and (*Z*)-α,*β*-unsaturated aldehydes. It was unclear at the outset of this investigation whether such an extension could be achieved, since conjugated oxocarbenium ion **7**, a presumed intermediate in this Prins cyclization−pinacol rearrangement sequence,[3] might undergo ready stereomutation. We chose to first pursue this issue in the context of a total synthesis of sclerophytin A, a marine diterpene whose structure, although depicted with some ambiguity in the original accounts,[4] was most reasonably construed to be **2**.[5] This cladiellin was chosen since it was reported to exhibit notable in vitro toxicity against the L1210 leukemia cell line (0.001 μg mL^{-1}).[4a] Moreover, selection of this target would provide an opportunity for us to demonstrate that our total synthesis strategy could readily address natural products of this group that contain exocyclic as well as endocyclic unsaturation in the cyclohexane ring.[6]

Our studies began with the synthesis of (*Z*)-α,*β*-unsaturated aldehyde **13** (Scheme 1). Silylation of commercially available

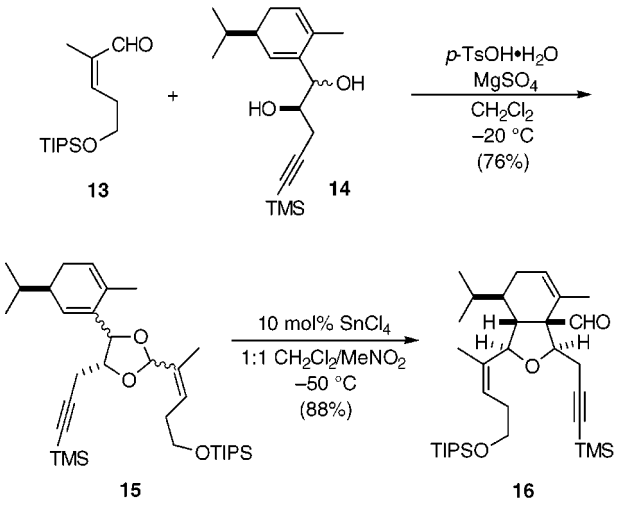
Scheme 1



3-buten-1-ol (**10**) followed by ozonolysis and stereoselective Wittig olefination of the derived aldehyde with phosphonium ylide **11**[7] furnished isomerically pure *Z* iodide **12**, after removal of a trace of the *E* stereoisomer by flash column chromatography on $AgNO_3$-impregnated silica gel. Conversion of **12** to the corresponding vinyllithium species followed by formylation with DMF provided isomerically pure **13**.

A two-step procedure for combining enal **13** and dienyl diol **14**[2] to produce hexahydroisobenzofuran **16** was developed (Scheme 2). Condensation of **13** with **14** under carefully

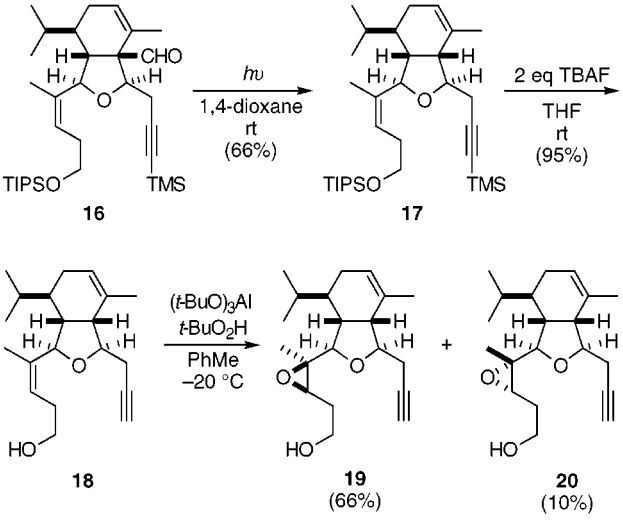
Scheme 2



optimized conditions generated acetal **15** as a mixture of diastereomers in 76% yield. Prins−pinacol rearrangement of **15** proceeded efficiently in the presence of catalytic $SnCl_4$ to give **16** in 88% yield. Salient features of the pivotal transformation of **13** and **14** to **16** are as follows: no stereomutation of the alkene substituent is observed and all of the carbon atoms of the target molecule are installed.

The extraneous carbon and protecting groups were removed from **16**, and the tertiary hydroxyl group was installed stereoselectively as outlined in Scheme 3. Photolytic deformylation[8] of **16** furnished hexahydroisobenzofuran **17** in

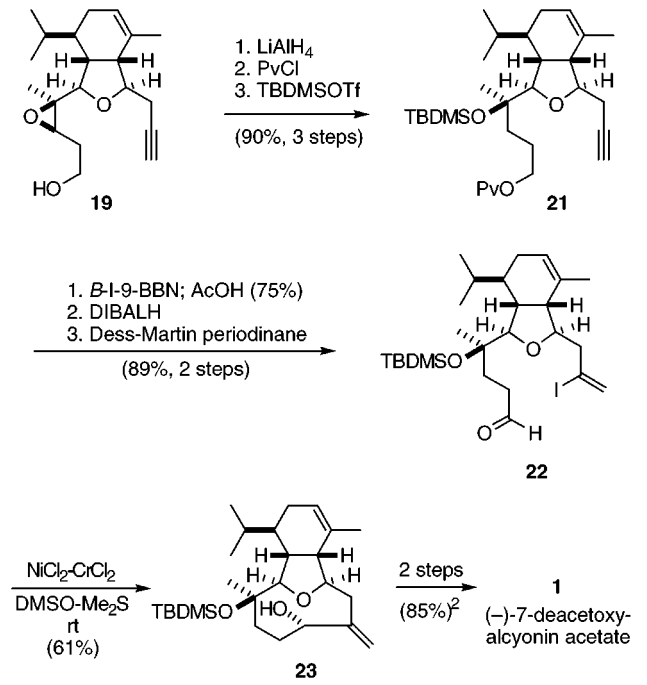
Scheme 3



66% yield after removal of ~10% of the $\Delta^{1,12a}$-tetrasubstituted alkene regioisomer by medium-pressure liquid chromatography. Bis-desilylation of **17**, followed by homoallylic alcohol-directed epoxidation of **18** with $(t\text{-BuO})_3\text{Al}/t\text{-BuO}_2\text{H}$,[9] provided a separable 7:1 mixture of epoxides **19** and **20** in good yield.

A series of transformations to elaborate the side chains of **19** set the stage for the formation of the oxonane ring (Scheme 4). Regioselective opening of epoxide **19** with

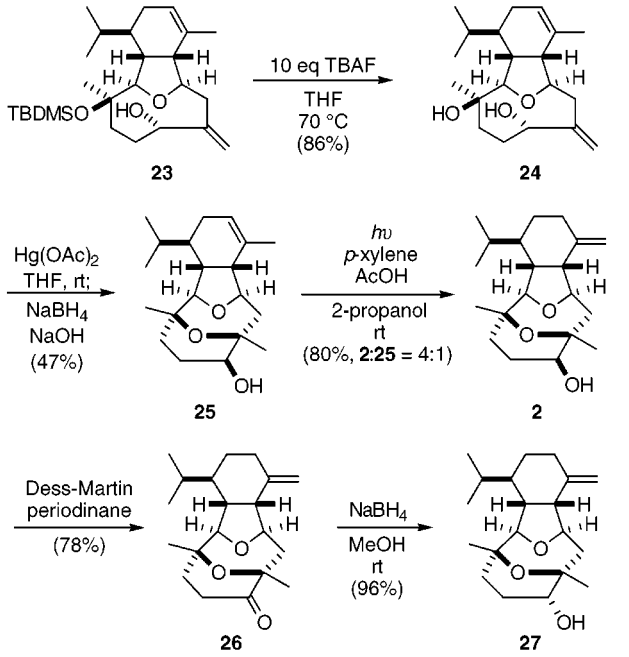
Scheme 4



$LiAlH_4$ followed by differential protection of the primary and tertiary alcohols produced **21**. Selective iodoboration of the alkyne moiety of **21** with *B*-iodo-9-borabicyclo[3.3.1]-nonane[10] (*B*-I-9-BBN) and subsequent cleavage of the pivaloyl group and oxidation of the resulting primary alcohol generated the known iodoaldehyde **22**.[2] As previously demonstrated,[2] Nozaki–Hiyama–Kishi cyclization[11] of **22** proceeded with high stereoselectivity to deliver **23** in good yield. This latter intermediate had been converted previously in two high-yielding steps to crystallographically characterized (−)-7-deacetoxyalcyonin acetate (**1**).[2]

Completion of the synthesis of the presumed structure of sclerophytin A (**2**) required formation of the bridging tetrahydropyran ring (Scheme 5). Desilylation of **23** provided

Scheme 5



diol **24**,[2b] which upon sequential treatment with $Hg(OAc)_2$ and $NaBH_4$ furnished the single tetracyclic diether **25** in 47% yield (66% based upon consumed **24**).[12] At short irradiation times in the presence of acetic acid, light-induced isomerization of **25** was realized in high yield to give **2** and **25** in a 4:1 ratio.[6,13] Spectral data for **2** did not match those reported for sclerophytin A.[4] To pursue the possibility that sclerophytin A was the alcohol epimer, **2** was oxidized to ketone **26**,[14] which underwent reduction from the less-hindered β-face with high selectivity to generate **27**. NMR data for this product were again distinctly different from those reported for sclerophytin A. Our results are in accord with independent investigations of Paquette and co-workers,[15] who after reinvestigating the natural isolate have proposed a revised structure for sclerophytin A.[16]

In conclusion, these studies demonstrate that (*Z*)-α,*β*-unsaturated aldehydes are viable reaction partners in the Prins–pinacol synthesis of cyclic ethers. Using this approach, a formal total synthesis (−)-7-deacetoxyalcyonin acetate (**1**),

(4) (a) Sharma, P.; Alam, M.*J. Chem. Soc., Perkin Trans. 1* **1988**, 2537–2540. (b) Alam, M.; Sharma, P.; Zektzer, A. S.; Martin, G. E.; Ji, X.; van der Helm, D. *J. Org. Chem.* **1989**, *54*, 1896–1900.

(5) Hochlowshi, J. E.; Faulkner, D. J. *Tetrahedron Lett.* **1980**, *21*, 4055–4056.

(6) Kropp, P. J. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1979; Vol. 4, pp 1–142.

(7) Wang, J. C. T.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 2827–2828.

(8) Baggiolini, E.; Hamlow, H. P.; Schaffner, K. *J. Am. Chem. Soc.* **1970**, *92*, 4906–4921.

(9) Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 1657–1660.

(10) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731–734.

(11) (a) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048–6050. (b) Kress, M. H.; Ruel, R.; Miller, L. W. H.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 5999–6002.

(12) Bordwell, F. G.; Douglass, M. L. *J. Am. Chem. Soc.* **1966**, *88*, 993–999.

(13) Marshall, J. A.; Hochstetler, A. R. *J. Am. Chem. Soc.* **1969**, *91*, 648–657.

(14) The minor endocyclic alkene isomer was easily removed at this stage by flash chromatography.

(15) Paquette, L. A.; Moradei, O. M.; Bernardelli, P.; Lange, T. *Org. Lett.* **2000**, *2*, 1875–1878.

(16) Friedrich, D.; Doskotch, R. W.; Paquette, L. A. *Org. Lett.* **2000**, *2*, 1879–1882.

which is two steps shorter than our original route,[2] was achieved and an enantioselective total synthesis of the alleged structure **2** of (−)-sclerophytin A was accomplished. The synthesis of **2** was realized in 15 steps and 3% overall yield from (*Z*)-α,*β*-unsaturated aldehyde **13** and dienyl diol **14**.

Acknowledgment. This research was financed by NIH Grant NS-12389, while L.D.P. was supported in part by a Pharmacia & Upjohn Graduate Fellowship in Synthetic Organic Chemistry. The authors thank Dr. John Greaves and Dr. John Mudd for mass spectrometric analyses. NMR and mass spectra were obtained at UCI using instrumentation acquired with the assistance of NSF and NIH Shared Instrumentation programs. We are grateful to Professor Leo A. Paquette for exchange of information regarding the actual and supposed structures of (−)-sclerophytin A.

Supporting Information Available: Experimental procedures and characterization data for the preparation of compounds **15**, **16**, **19**, **25**, and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006236P