ORGANIC LETTERS

2003
Vol. 5, No. 9
1543−1546

Total Synthesis of the Reputed Structure of Alcyonin and Reassignment of Its Structure†

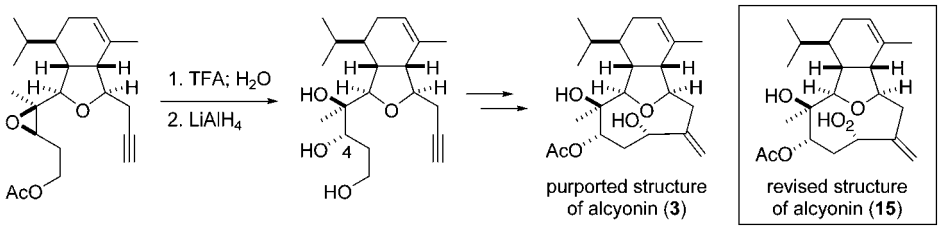
Olivier Corminboeuf, Larry E. Overman,* and Lewis D. Pennington‡

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

leoverma@uci.edu

Received March 5, 2003

ABSTRACT



Introduction of the C4 hydroxyl group by an epoxy ester rearrangement is a pivotal step in the first total synthesis of the purported structure of alcyonin. As the spectral data for diol acetate 3 do not match those reported for alcyonin, the structure of this marine diterpene must be revised. Reexamination of NMR spectra, MS data, and chemical transformations of natural alcyonin suggests that the structure of this marine metabolite is allylic peroxide 15.

A variety of structurally novel diterpene cyclic ethers, some with interesting biological activities, have been isolated from marine invertebrates.[1,2] A recent report from our laboratories described a versatile strategy for enantioselective total synthesis of members of the cladiellin subgroup of these diterpenes exemplified by 6-acetoxycladiell-7(16),11-dien-3-ol (**1**) and sclerophytin A (**2**).[3] In our approach, the condensation of a carvone-derived dienyl diol with an α,*β*-unsaturated aldehyde assembles the hexahydroisobenzofuran core and five of the six invariant stereocenters of these marine metabolites.[3,4] Three cladiellin diterpenes and most briarellin and asbestinin diterpenes (e.g., **4** and **5**)[2,5] contain oxygen substitution at C4 of the bridging oxacyclononane ring (Figure 1). Alcyonin, which was isolated by Kakisawa and co-workers in 1988 from the Okinawan soft coral *Sinularia flexibilis* and assigned structure **3**,[6] was chosen as a good target to first explore stereoselective introduction of this additional oxidation. We report herein the initial total synthesis of **3**, which necessitates reassignment of the structure of alcyonin.

The starting point for the total synthesis of **3**, the putative structure of alcyonin, was the known epoxide **6**.[7] Using our third-generation strategy, this intermediate is available in 9 steps and 14% overall yield from (*S*)-dihydrocarvone (Scheme 1).[3,7] Conventional acetylation of **6** provided the correspond-

† This paper is dedicated to the memory of John Faulkner, a pioneer in marine natural products chemistry.

‡ Current address: Array BioPharma, 2620 Trade Center Avenue, Longmont, CO 80501.

(1) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1−48.

(2) For recent reviews of cladiellin, briarellin, and asbestinin diterpenes, see: (a) Sung, P.-J.; Chen, M.-C. *Heterocycles* **2002**, *57*, 1705−1715. (b) Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531−556.

(3) MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033−9044.

(4) For an alternative approach to the total synthesis of **2**, see: Bernardelli, P.; Moradei, O. M.; Friedrich, D.; Yang, J.; Gallou, F.; Dyck, B. P.; Doskotch, R. W.; Lange, T.; Paquette, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 9021−9032.

(5) (a) Rodríguez, A. D.; Cóbar, O. M. *Tetrahedron* **1995**, *51*, 6869−6880. (b) Rodríguez, A. D.; Cóbar, O. M. *Chem. Pharm. Bull.* **1995**, *43*, 1853−1858. (c) Stierle, D. B.; Carté, B.; Faulkner, D. J.; Tagle, B.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 5088−5092. (d) Selover, S. J.; Crews, P.; Tagle, B.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 964−970.

(6) Kusumi, T.; Uchida, H.; Ishitsuka, M. O.; Yamamoto, H.; Kakisawa, H. *Chem. Lett.* **1988**, 1077−1078.

(7) Overman, L. E.; Pennington, L. D. *Org. Lett.* **2000**, *2*, 2683−2686.

10.1021/ol034384k CCC: $25.00
Published on Web 04/04/2003

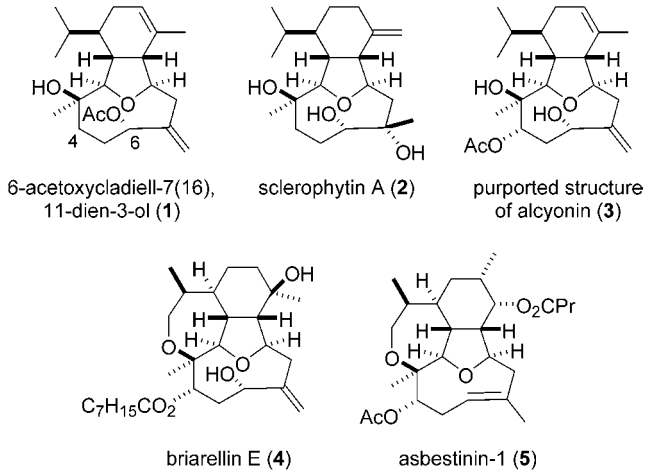
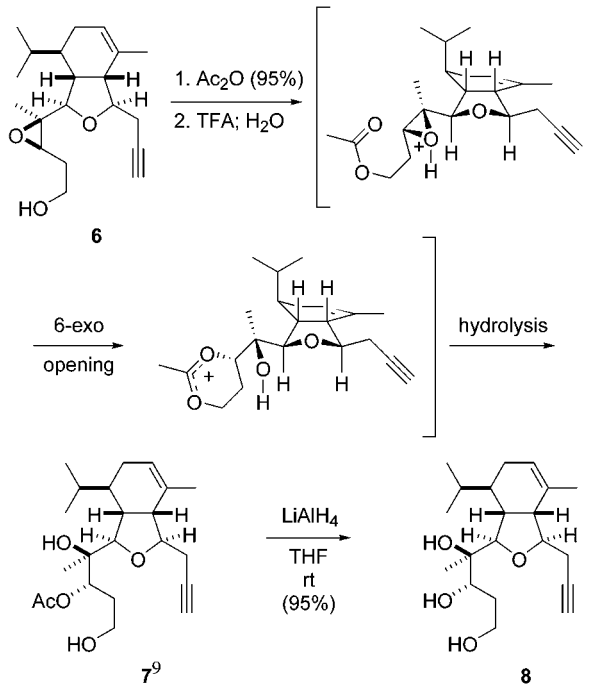


Figure 1. Representative cladiellin, briarellin, and asbestinin diterpenes.

ing acetate. Following the prescriptions of Giner and co-workers,[8] this epoxy acetate was transformed to diol acetate **7**[9] by sequential exposure to trifluoroacetic acid (1 equiv) and H_2O at room temperature. Reduction of **7** with $LiAlH_4$ delivered triol **8** in 90% overall yield from **6**. Ring opening of the epoxide functionality took place with high regio- and stereoselectivity; no trace of an isomer was seen by ^1H NMR analysis of the crude reduction product. The assigned orientation of the secondary hydroxyl group of **8** was initially based upon precedent and the mechanistic considerations depicted in Scheme 1.[8]

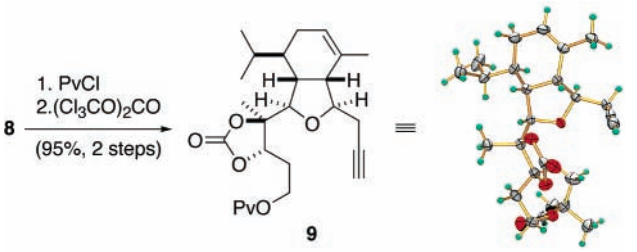
To confirm the configurational assignment for **8**, this triol was transformed to the crystalline carbonate derivative **9**,

Scheme 1



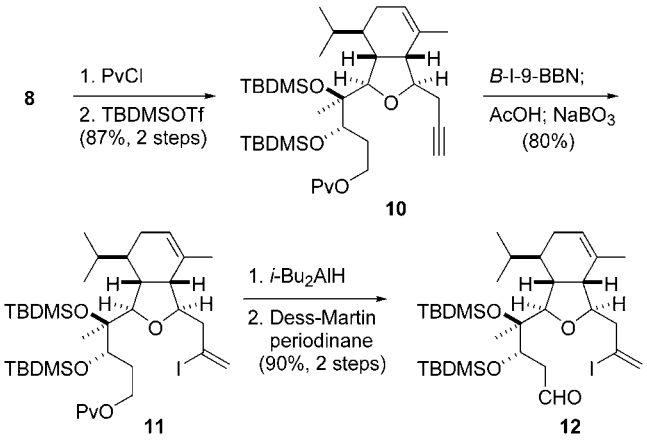
the structure of which was established by single-crystal X-ray analysis (Scheme 2). At the outset we had envisioned cyclic carbonate **9** as a late stage precursor of the vicinal C3 hydroxy and C4 acetoxy substituents of **3**;[10] however, the instability of intermediates derived from **9** ultimately forced us to adopt an alternate, more lengthy, approach.

Scheme 2



To set the stage for closure of the bridging nine-membered ring, triol **8** was protected by sequential reaction with pivaloyl chloride and TBDMSOTf to yield **10** (Scheme 3). Elabora-

Scheme 3



tion of the terminal propargyl side chain of this intermediate to a 2-iodo-2-propenyl fragment was accomplished by using a modification of the procedure we had employed previously for similar transformations.[3,11] Thus, treatment of **10** with *B*-iodo-9-borabicyclo[3.3.1]nonane (*B*-I-9-BBN),[12] in situ protonolysis of the resulting vinyl borane at −78 °C with acetic acid, and oxidative workup with sodium perborate[13]

(8) (a) Giner, J.-L.; Faraldos, J. A. *J. Org. Chem.* **2002**, *67*, 2717−2720. (b) Giner, J.-L.; Faraldos, J. A. *J. Org. Chem.* **2002**, *67*, 4659−4666.

(9) The crude product **7** from the epoxy ester rearrangement−hydrolysis sequence was an inconsequential mixture of primary and secondary acetates.

(10) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. *J. Chem. Soc., Chem. Commun.* **1994**, 295−296.

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

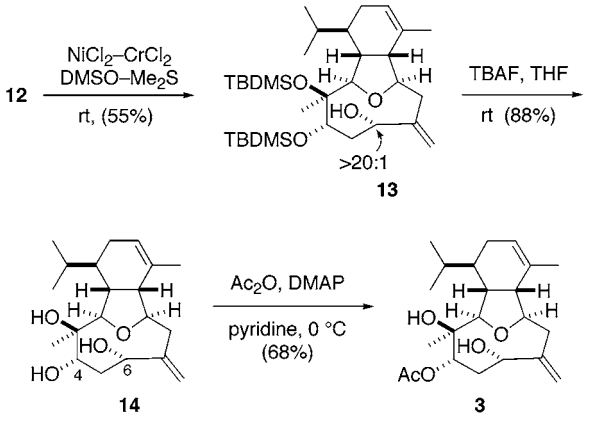
(12) Brown, H. C.; Kulkarni, S. U. *J. Organomet. Chem.* **1979**, *168*, 281−293.

(13) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930−5933.

gave **11** in 80% yield. Removal of the pivaloyl protecting group and oxidation of the resulting primary alcohol with Dess−Martin periodinane[14] provided vinyl iodide aldehyde **12** in 63% overall yield from triol **8**.

As in our previous syntheses of cladiellin diterpenes lacking oxidation at C4, the oxacyclononane ring of **3** was formed by Nozaki−Hiyama−Kishi cyclization (Scheme 4).[15] Using conditions similar to those employed in our synthesis of sclerophytin A,[3] **12** was transformed to oxatricyclic intermediate **13** in 55% yield. This cyclization took place with high stereoselection as only one allylic alcohol epimer was observed by ^{1}H NMR analysis of the crude product. The silyl protecting groups of **13** were removed by reaction with TBAF at room temperature, a conversion that was facilitated by migration of the TBDMS group from O3 to O4. Acetylation of the C4 secondary alcohol of **14** under carefully controlled conditions provided **3** in 68% yield. The position of the acetate substituent was apparent from diagnostic ^{1}H NMR chemical shifts of the C4 (δ 4.99) and C6 (δ 4.17) methine hydrogens.

Scheme 4



The structure of **3** was evident from NMR and mass spectral data, as well as comparisons of NMR data to those of **1** and related cladiellin natural products.[16] However, NMR data for **3** did not match those reported for alcyonin.[6] From the published data it appeared unlikely that the acetate functionality of alcyonin resided at C6.[6] Nonetheless, this supposition was confirmed by preparing the C6 acetate derivative of **14** by sequential reaction of **13** with Ac_2O (DMAP-pyridine) and TBAF; ^{1}H NMR data of this isomer also did not match data reported for alcyonin. It was clear at this point that the structure of alcyonin must be reconsidered.[5d,17]

Although a sample of natural alcyonin is no longer available,[18] reexamination of NMR data of natural alcyonin reveals that the signal at δ 4.76 assigned to H6 of the *Sinularia flexibili*s isolate is downfield by 0.3−0.4 ppm from signals for this hydrogen in other cladiell-7(16),11-dien-3,6-diols as is the absorption for C6.[16,18] Moreover, no signal for the allylic hydroxyl hydrogen was reported, nor is such a signal apparent in ^{1}H NMR spectra of natural alcyonin. However, a signal corresponding to one hydrogen, which was not mentioned in the original work,[6] is clearly visible at δ 8.0 (Figure 2).

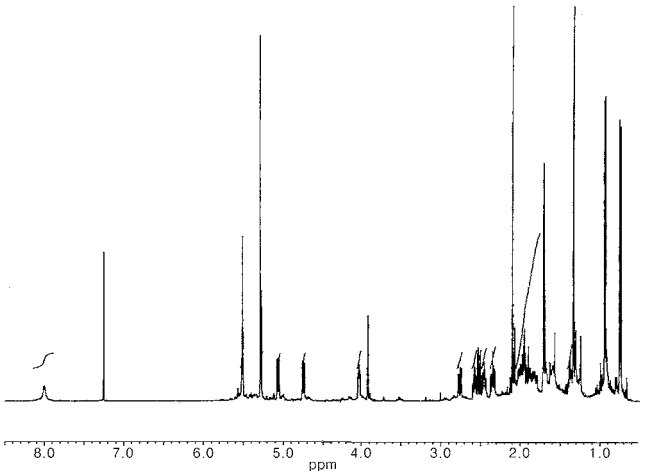


Figure 2. ^{1}H NMR spectrum of natural alcyonin.[6]

We conclude that alcyonin is the allylic hydroperoxide congener **15** of the originally proposed structure (Figure 3). This proposal gains strong support from the ^{1}H and ^{13}C NMR data reported for cladiellaperoxide (**16**)[19] and cladiellisin (**17**).[16a,19] Although the mass spectral data initially reported for natural alcyonin (*m/e* 376.2261) are consistent with its originally proposed constitution, these data are not inconsistent with the proposed hydroperoxide structure as it is

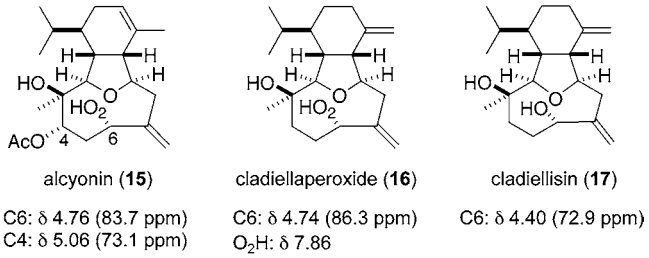


Figure 3. Proposed structure of alcyonin and structures and NMR data for cladiellaperoxide and cladiellisin.

(14) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

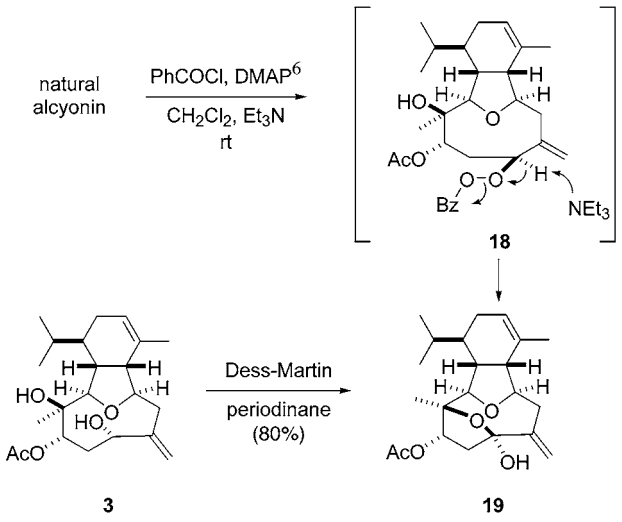
(15) For a recent review, see: Fürstner, A. *Chem. Rev.* **1999**, *99*, 991−1045.

(16) (a) Cladiellisin: δ 4.40 (H6), δ 72.6 (C6; 72.9 is reported in ref 19): Liu, J.; Zeng, L.; Wu, D. *Chin. Sci. Bull.* **1992**, *37*, 1627−1630. (b) Cladiell-7(16),11(17)-dien-3,6-diol: δ 4.40 (H6), δ 77.5 (C6): Sreenivasa Rao, D.; Sreedhara, C.; Venkata Rao, D.; Bheemasankara Rao, C. *Ind. J. Chem., Sect. B* **1994**, *33B*, 198−199. (c) 3-Acetoxycladiell-7(16),11(17)-dien-6-ol: δ 4.39 (H6), δ 72.2 (C6): Bheemasankara Rao, C.; Sreenivasa Rao, D.; Satyanarayana, C.; Benkata Rao, D.; Kassühlke, K. E.; Faulkner, D. J. *J. Nat. Prod.* **1994**, *57*, 574−580. (d) Palmonine F: δ 4.29 (H6), δ 73.7 (C6): Ortega, M. J.; Zubía, E.; Salvá, J. *J. Nat. Prod.* **1994**, *57*, 1584−1586.

likely that the ionization method employed produced a fragment ion of *m*/*e* 376.[20]

Moreover, the chemical properties reported for natural alcyonin are more in accord with the revised allylic hydroperoxide structure **15** than the putative allylic alcohol constitution **3**. For example, it was reported that benzoylation of alcyonin yields the tetracyclic hemiacetal **19** rather than the expected C6 benzoate (Scheme 5), a result ascribed to

Scheme 5



air oxidation of the allylic alcohol.[6] Yet there are numerous reports of the successful acylation of 6-hydroxy cladiell-7(16),11-dienes.[3,21] Furthermore, we have never observed air oxidation of **3** or related structures.[3] However, the formation of **19** upon attempted benzoylation is the anticipated outcome if alcyonin were hydroperoxide **15**, because benzoyl peroxide intermediate **18** would be expected to fragment to the 6 keto derivative in the presence of triethylamine. The constitutional relationship of our synthetic product **3** and natural alcyonin was confirmed by Dess−Martin oxidation[14] of **3** to form hemiacetal **19**. The NMR and mass spectrometric data of this product were indistinguishable from those of **19** derived from natural alcyonin.

In conclusion, the enantioselective total synthesis of the proposed structure **3** of alcyonin was accomplished in 11 steps and 18% overall yield from intermediate **6** (1.5% overall yield from (*S*)-carvone). Reexamination of NMR and MS data as well as chemical transformations reported for natural alcyonin show that the structure of this marine metabolite should be revised to allylic peroxide **15**. The approach employed here for introducing the C4 hydroxyl group of **3** should also be useful in total synthesis endeavors targeting the briarellin and asbestinin diterpenes.

Acknowledgment. We are grateful to Professor T. Kusumi of Tokushima University, Japan, for providing copies of NMR data for natural alcyonin and derivative **19**, and Professor José-Luis Giner of SUNY-ESF, New York, for helpful discussions. This research was supported by the NIH Neurological Disorders & Stroke Institute (NS-12389); fellowship support for O.C. from the Swiss National Science Foundation and L.D.P. from a Pharmacia & Upjohn Graduate Fellowship in Synthetic Organic Chemistry are gratefully acknowledged. NMR and mass spectra were obtained at UC Irvine, using instrumentation acquired with the assistance of NSF and NIH Shared Instrumentation programs.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for compounds **3**, **6**, and **8**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034384K

(17) To explore the possibility that alcyonin was the allylic alcohol epimer of **3**, this stereoisomer was prepared by a closely precedented oxidation−reduction sequence.[5d] ^{1}H NMR data for 6-*epi*-**3** also were different from those reported for alcyonin.

(18) Natural alcyonin is no longer available as Professor Kakisawa retired 10 years ago. We are grateful to Prof. T. Kusumi of Tokushima University, Japan, for providing copies of ^{1}H NMR and ^{13}C NMR spectra of natural alcyonin.

(19) (a) Yamada, K.; Ogata, N.; Ryu, K.; Miyamoto, T.; Komori, T.; Higuchi, R. *J. Nat. Prod.* **1997**, *60*, 393−396. (b) These authors showed that **17** is produced from reduction of **16** with $NaBH_4$.

(20) FAB or electrospray ionization, two methods not widely used in 1988, are often required to see the molecular ion of a hydroperoxide, see: (a) Schwarz, H.; Schiebel, H. M. In *The Chemistry of Peroxides;* Patai, S., Ed.; Wiley: New York, 1983; p 279. (b) Yu-Feng, H.; Wang, R.; Liu, Y.; Chang, Y.; Wang, Y.; Xia, C.; Suo, J. *J. Mol. Catal. A: Chem.* **2000**, *159*, 109−113.

(21) See, inter alia: (a) Miyamoto, T.; Yamada, K.; Ikeda, N.; Komori, T.; Higuchi, R. *J. Nat. Prod.* **1994**, *57*, 1212−1219. (b) Ochi, M.; Yamada, K.; Futatsugi, K.; Kotsuki, H.; Shibata, K. *Heterocycles* **1991**, *32*, 29−32. (c) In our hands, **3** was readily acetylated.