ORGANIC LETTERS

2000
Vol. 2, No. 13
1875−1878

Synthesis of the Alleged Structure of Sclerophytin A. The Setting of Two Oxygen Bridges within the Fused Cyclodecanol B Ring Is Not Nature's Way

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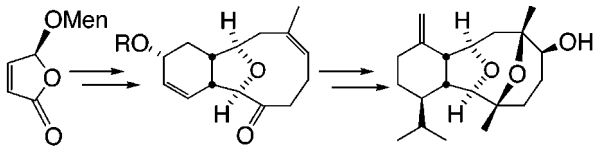
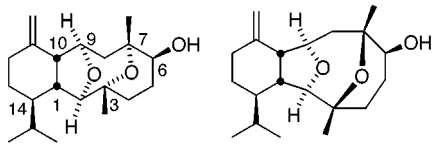
Received April 14, 2000

ABSTRACT



The structure attributed to sclerophytin A, a cytotoxic soft coral metabolite, was synthesized in an enantioselective manner from (5*S*)-5-(*d*-menthyloxy)-2(5*H*)-furanone. The spectral properties and polarity of the synthetic product require that the structural assignment to the natural material be revised.

The 2,11-cyclized cembranoids produced by octocorals,[1] encompassing more than 60 members in four classes, constitute a growing subset of biologically active compounds possessing interesting structural features.[2] In 1988, Sharma and Alam reported the isolation from *Sclerophytum capitalis* and characterization of sclerophytin A.[3] Bioassays revealed that this substance exhibits significant in vitro toxicity against the L1210 cell line at a concentration of 0.001 μg mL^{-1}. The tetracyclic ring system defined by this diterpenoid, assigned as **1** on the basis of NMR spectroscopic measurements, is new and intrinsically interesting. Particularly enigmatic to us was the manner in which the isolation group depicted the configuration at C-3 in their formulation. Unfortunately, the intentions behind the use of an "inverted carbon" symbolism here will never be known.[3] In addition, C-6 and C-7 are sufficiently remote as to introduce uncertainties in their configurational



1 **2**

depiction as well. Some directly relevant and reliable information is available however. X-ray crystallographic studies[4] and CD measurements,[5] as well as a recent synthesis of (−)-7-deacetoxyalcyonin acetate,[6] have made clear the

(1) Review: Coll, J. C. *Chem. Rev.* **1992**, *92*, 613.

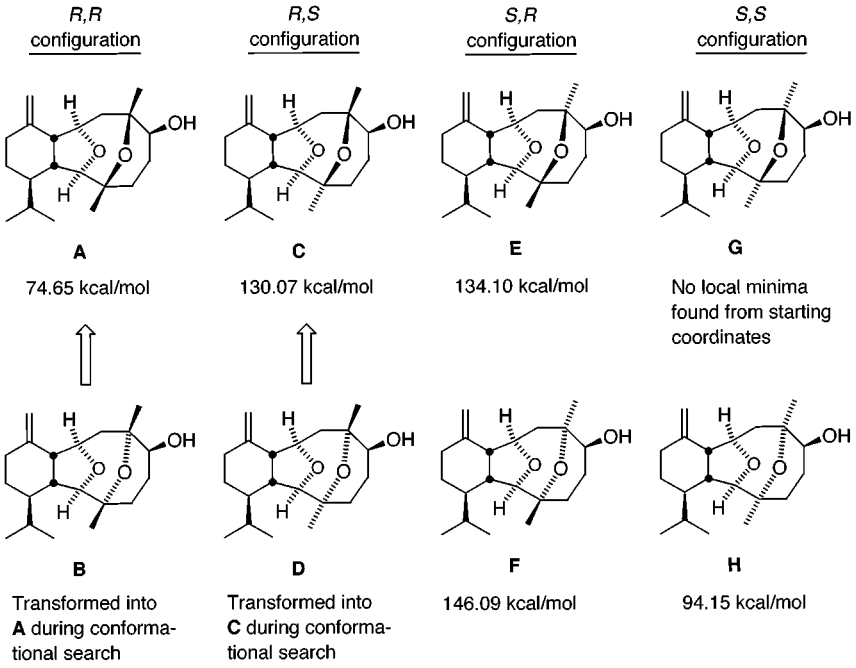
(2) (a) Wahlberg, I.; Eklund, A.-M. In *Progress in the Chemistry of Organic Natural Products*; Springer-Verlag: New York, 1992; Vol. 60, pp 1 ff. (b) Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531.

(3) Professor Alam met an untimely death on March 6, 1999 prior to the time that our queries were directed to him.

(4) (a) Kennard, O.; Watson, D. G.; Riva di Sanseverino, L.; Tursch, B.; Bosmans, R.; Djerassi, C. *Tetrahedron Lett.* **1968**, 2879. (b) Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Schönholzer, P. *Tetrahedron Lett.* **1977**, 4643. (c) Alam, M.; Sharma, P.; Zektzer, A. S.; Martin, G. E.; Ji, X.; van der Helm, D. *J. Org. Chem.* **1989**, *54*, 1896. (d) Su, J.; Zheng, Y.; Pordesimo, E. O.; Schmitz, F. J.; Hossain, M. B.; van der Helm, D. *J. Nat. Prod.* **1993**, *56*, 1601. (e) Uchio, Y.; Nakatani, M.; Hase, T.; Kodama, M.; Usui, S.; Fukazawa, Y. *Tetrahedron Lett.* **1989**, *30*, 3331.

10.1021/ol000083o CCC: $19.00
Published on Web 06/07/2000

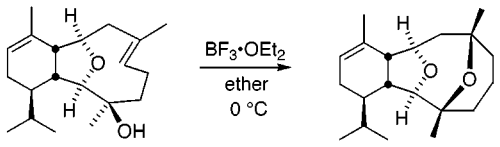
Table 1. Relative Strain Energies for the Diastereomers of Alleged Sclerophytin A[a]



[a] The stereodescriptors pertain to C-7 and C-3, respectively. Each vertical pair represents two conformers of the same stereoisomer.

fact that the resident stereocenters C-1, C-2, C-9, C-10, and C-14 generally possess the *R* configuration in common.[7]

The published data can be construed to be equally compatible with the 7*R* configuration as in **2**. An appreciation of the conformational energetics and relative thermodynamic stabilities of the four possible C-3/C-7 diastereomers of sclerophytin A has been derived from MM3 calculations (Table 1). It is noteworthy that "oxygen-up" conformations are favored for three of the isomer pairs, with **A** serving as the least strained standard. These results do not speak to the possible existence of kinetically stable atropisomers, but did focus our attention on preparing **2**(=**A**). This epimeric formulation conforms additionally to the low-temperature boron trifluoride-catalyzed cyclization of cladiellin **3** to **4**



3 **4**

previously delineated by Hochlowski and Faulkner.[8] Herein we illustrate a potentially generic protocol for accessing these marine metabolites.

The convergent assembly began with (5*S*)-5-(*d*-menthyloxy)-2(5*H*)-furanone (**5**), an enantiopure unsaturated lactone[9] previously recognized for its useful dienophilic properties.[10] Heating of **5** with the Danishefsky diene in toluene gave a sensitive (4 + 2) cycloadduct, which could be efficiently transformed into the cyclohexenone **6** by Vorndam's protocol.[11] Conventional Luche reduction[12] followed (Scheme 1). These three steps gave **7a** in 71% overall yield. After initial attempts to convert **7b** into the C-allylated bicyclic lactone **8** met with difficulties,[13] the discovery was made that hydrolysis to the γ-hydroxy-γ-lactone and Barbier-type condensation with the allylindium reagent under aqueous conditions proceeded with high diastereoselection for the *R* isomer **9** (NOE analysis). The stereochemical course of this important carbon−carbon bond-forming step is attributed to operation of a chelated transition state involving the neighboring carboxyl group.[14]

To set the stage for the tandem Tebbe-Claisen ring expansion,[15] we next undertook stereocontrolled installation

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(9) High quality **5** was routinely obtained by crystallization-induced epimerization of the diastereomeric mixture with CSA in CH_2Cl_2. Details will be provided in the full paper.

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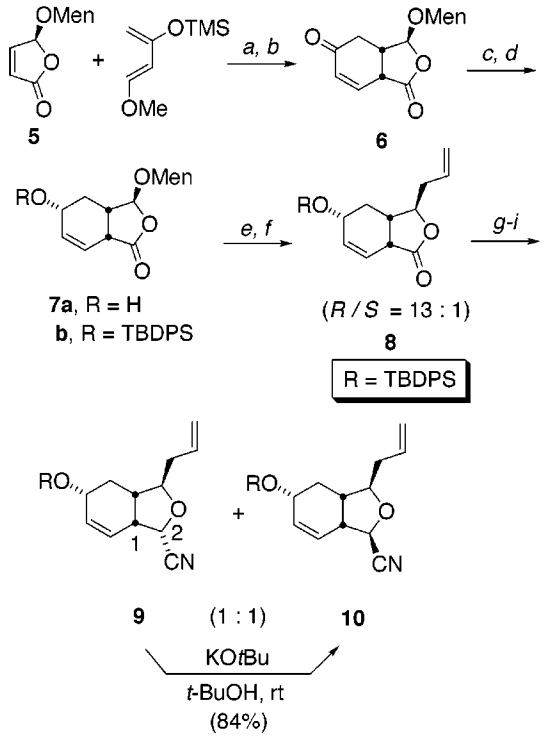
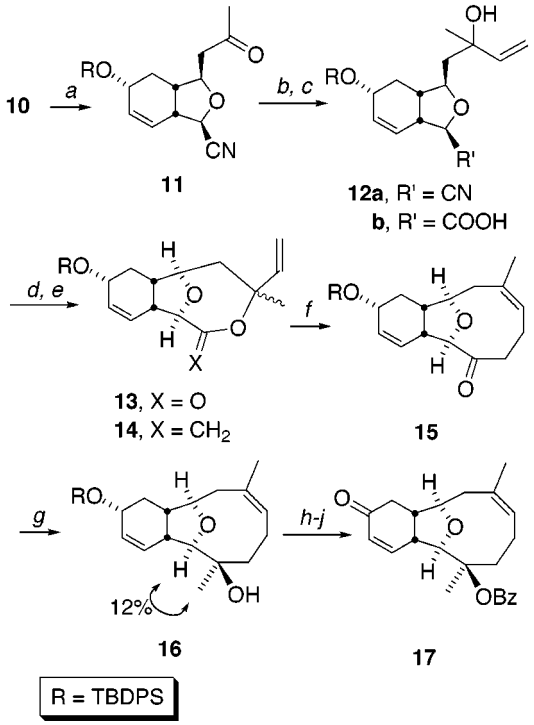
Scheme 1



[a] Toluene, Δ. [b] TMSOTf, lutidine, CH_2Cl_2, -78 °C. [c] $NaBH_4$, $CeCl_3$, MeOH, -78 °C (71% for 3 steps). [d] TBDPSCl, imid, DMF (100%). [e] Py·CSA, CH_3CN, H_2O, 80 °C (63%). [f] Br, In, Bu_4N^+ Br^-, THF, H_2O (84%). [g] Dibal-H, CH_2Cl_2, -78 °C. [h] Ac_2O, Et_3N, CH_2Cl_2, -78 °C → rt. [i] TMSCN, BF_3·OEt_2, CH_2Cl_2, -10 °C (93% for 3 steps).

Scheme 2



[a] O_2, $PdCl_2$, CuCl, DMF, H_2O (86%). [b] MgBr, $CeCl_3$, THF (87%). [c] NaOMe, MeOH; H_3O^+; LiOH, H_2O, MeOH. [d] $Cl_3C_6H_2COCl$, Et_3N, DMAP (72% for 4 steps). [e] $Cp_2Ti(Cl)CH_2AlMe_2$, THF, -50 °C (67%). [f] $NaBF_4$, toluene, Δ (80%). [g] CH_3Li, $NaBF_4$, THF (79%). [h] KH, BzCl, THF (91%). [i] TBAF, THF (100%). [j] TPAP, NMO, 4 Å MS, CH_2Cl_2 (95%).

of the β-cyano functionality as in **10**. Following the reduction of **8** with DIBAL-H, the resulting lactol was acetylated in advance of exposure to trimethylsilyl cyanide and BF_3·OEt_2 in CH_2Cl_2 at −78 °C. The prior acylation proved critical to the acquisition of a 1:1 mixture of **9** and **10** in 89% yield for the three steps.[16] The intense (9.8%) NOE interaction between H-1 and H-2 in **9** identified it as the α-isomer. As a result of the ease with which **9** could be epimerized to **10**, the nonstereoselective nature of the cyanation step was of little consequence. Following Wacker oxidation[17] of **10** to generate ketone **11** (Scheme 2), a vinyl group was introduced chemoselectively in advance of conversion to **12b**. Mild conditions were required for the nitrile hydrolysis, and this hurdle was conveniently overcome by conversion to the imino ether[18] in advance of gentle acidic treatment.[19] Submission of **12b** to the Yonemitsu modification[20] of the Yamaguchi macrocyclization gave rise efficiently to a separable mixture of **13** and its epimer. These intermediates were independently subjected to Tebbe methylenation[21] and thermal activation. When temperatures in excess of 130 °C in *p*-cymene were found to give only incomplete conversion and result in the onset of decomposition, recourse was made to promoting the sigmatropic shift with $NaBF_4$ in refluxing toluene.[22] Both epimers of **14** are transformed cleanly and uniquely into **15**, but at distinctively different rates.

In **15**, the anti conformation likely adopted in order to avoid electron−electron repulsion between the lone pair electrons of the ether and carbonyl oxygens greatly facilitates the addition of methyllithium from the α-face. The identity of **16** was easily recognized by NOE analysis. After conversion to ketone **17**, advantage was taken of the regioselectivity with which deprotonation could be achieved. Quite unexpectedly, however, the enolate of **17** proved to be quite unreactive. We were therefore forced instead to exploit the silyl enol ether, which condensed quite satisfactorily with aqueous formaldehyde in the presence of ytter-

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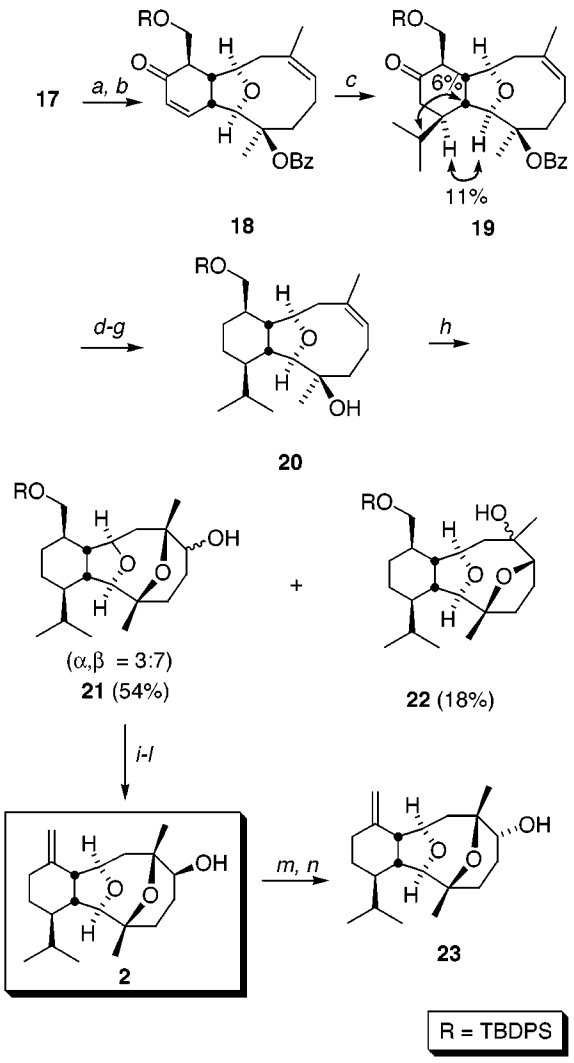
(22) The use of pyridinium camphorsulfonate has also been found to serve as well as an accelerant, but in contrast to $NaBF_4$ does induce some modest decomposition (~30%).

Scheme 3



[a] LHMDS, Me_3SiCl; 37% HCHO, $Yb(OTf)_3$ (65%). [b] TBDPSCl, imid (41%). [c] *i*-PrMgCl, CuBr•SMe_2, Et_3N, HMPA, THF; H_3O^+ (90%). [d] $NaBH_4$, $CeCl_3$, MeOH (95%). [e] $(Im)_2C{=}S$ (100%). [f] Bu_3SnH, AIBN, toluene, 100 °C. [g] Dibal-H, THF (72%). [h] $Hg(OCOCF_3)_2$, DMF; O_2, $NaBH_4$, DMF, 0 °C. [i] Ac_2O, py (91%). [j] TBAF, THF (89%). [k]  , Bu_3P; THF, py; H_2O_2. [l] Dibal, THF (91% for 2 steps). [m] TPAP, NMO, CH_2Cl_2 (90%). [n] Dibal-H, THF (100%).

bium triflate[23] (Scheme 3). After silylation of the primary hydroxyl,[24] the next phase of the effort involved 1,4-addition of the isopropyl group from the less-hindered β-face. As matters transpired, the specific stereochemical pathway followed in this instance could again be unequivocally defined by NOE techniques (see **19**). This advanced intermediate provided a target of opportunity for complete deoxygenation of the ketone carbonyl. With **20** in hand, the time had arrived to elaborate the second oxygen bridge.

Accordingly, this unsaturated carbinol was oxymercurated and subjected to oxidative demercuration with $NaBH_4$ and O_2 in DMF as solvent.[25] There was thus obtained predominantly the secondary carbinol **21** (54%, $\alpha/\beta = 3{:}7$) alongside the tertiary isomers **22** (18%).

Following construction of the targeted structural core in this manner, the *tert*-butyldiphenylsiloxy group was eliminated via selenium-based technology[26] to deliver (+)-**2** predominantly. Perruthenate oxidation[27] in tandem with stereodirected DIBAL-H reduction then gave (−)-**23** in 90% combined yield. While the $[\alpha]_D$ of the synthetic sample compares closely in magnitude with the natural coral metabolite, it is of opposite sign. More relevantly, their high-field ^{1}H NMR spectra are perceptively different. The structure proposed for **2** is firmly supported by ^{1}H,^{1}H−COSY, TOCSY, DEPT, HSQC, HMBC, and NOE difference measurements performed at the 600 MHz level. Equally striking is the very substantive difference in polarity exhibited by the two substances. The R_f value of **2** is more than double that of the natural sample. The ensuing paper provides convincing evidence for the revised structure of sclerophytins A and B,[28] stereoselective syntheses of which are in progress and will be reported in due course.

Acknowledgment. We thank Prof. K. Euler (University of Houston) for providing us with a sample of natural (−)-sclerophytin A, Prof. Larry Overman (UC Irvine) for a helpful exchange of information and spectra, and John Hofferberth for the molecular mechanics calculations. O.M. is grateful to CONICET, Republic of Argentina, for a postdoctoral fellowship. T.L. was the recipient of the Ciba-Geigy Jubilaeums-Stiftung.

Supporting Information Available: IR, NMR, and mass spectrometric data for the advanced intermediates in Scheme 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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