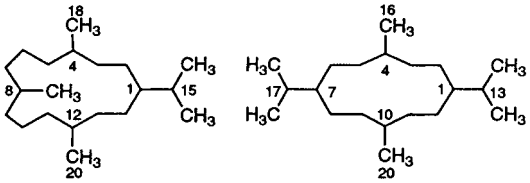
The First Cembrane−Pseudopterane Cycloisomerization

Abimael D. Rodríguez* and Jian-Gong Shi

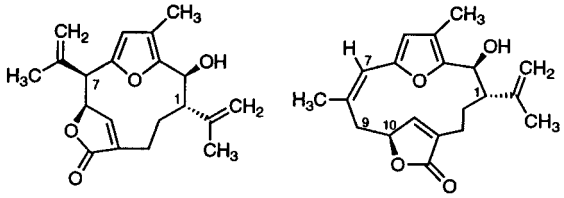
Department of Chemistry, University of Puerto Rico, P.O. Box 23346, Río Piedras, Puerto Rico 00931-3346, and Center for Molecular and Behavioral Neuroscience, Universidad Central del Caribe, Bayamón, Puerto Rico 00960-3001

Received October 14, 1997

Sesquiterpenoids and diterpenoids possessing a wide variety of well-known and rare carbon skeletons are the most common metabolites of gorgonians (order Gorgonacea) and soft corals (order Alcyonacea).[1] Thus far, cembrane diterpenoids account for the vast majority of compounds isolated from both orders of Alcyonaria.[1,2] Caribbean gorgonians of the genus *Pseudopterogorgia* are abundant and chemically rich marine invertebrates responsible for the production of several classes of metabolites that have attracted much interest for the synthetic and the natural products chemist for their structural complexity and their potential pharmacological value as cytotoxic or antiinflammatory agents.[3] One such family of *Pseudopterogorgia* metabolites is the pseudopterane diterpenoids discovered by the Fenical and Clardy groups in 1982.[4] To date, the pseudopteranes appear to be taxonomically restricted to several species of *Pseudopterogorgia* (Gorgonacea) and one species of *Gersemia* (Alcyonacea). In their original report, Fenical et al. noted that although in principle the pseudopterane carbon skeleton could be dissected symmetrically into two geranyl units, thus suggesting a biogenesis involving dimerization, they might instead arise from a ring contraction of a cembranoid precursor. Since 1987, several groups have reported that some gorgonian species actually contain both pseudopterane and cembrane diterpenes, a fact that supports the theory that metabolites belonging to these skeleton classes are intimately related biogenetically.[5] Interestingly, while many



elegant approaches to the synthesis of 2,5-bridged furanocyclic compounds of the cembrane and pseudopterane classes have been demonstrated,[6] no strategy whereby a pseudopterane is synthesized directly from a furanocembrane precursor has been reported. Recently, during an underwater expedition to the Eastern Caribbean Sea, we collected the sea plume *Pseudopterogorgia bipinnata* (Verrill), extracts of which were found to contain significant amounts of the known pseudopterane kallolide A (**1**)[7] and smaller quantities of the new furanocembranolide bipinnatin J (**2**). We now report the first cembrane−pseudopterane cycloisomerization reaction whereby bipinnatin J (**2**) was isomerized directly to kallolide A (**1**), thus definitively establishing their biogenetic relationship.



The present study was undertaken to test the feasibility of a fundamentally different approach to the preparation of the pseudopterane ring system using a novel cembrane−pseudopterane cycloisomerization reaction. Success would depend upon the ability of a 14-membered 2,5-furanocycle such as **2** to overcome the considerable ring strain associated with a two-carbon ring-contraction process leading to a pseudopterane. For such a strategy to work an indication was needed that the C9−C10 σ bond in **2**, which is flanked by two conjugated unsaturated systems, was indeed prone to bond cleavage. Detailed analysis of the HREIMS spectrum of **2** (see the Supporting Information) provided a clear indication as to the susceptibility of the C9−C10 σ bond to break under EIMS high energy conditions. In short, we envisioned, under appropriate reaction conditions, the C9−C10 σ bond in **2** migrating to C7 across the conjugated network of atoms with concomitant reorganization of the π system. The new bond should be formed on the same face of the π-framework (suprafacially), and of further interest was the possibility for retention of configuration at the migrating center. Since retention at the migrating group for such a suprafacial [1,3] allylic shift is allowed photochemically according to the Woodward−Hoffmann rules of orbital symmetry, we first attempted the photochemical conversion of **2** into kallolide A (**1**).[8,9] These predictions were in accord with experimental observation.

* To whom correspondence should be addressed. Tel.: (787)764-0000 Ext 4799. Fax. (787)751-0625. E-Mail: abrodrig@upracd.upr.clu.edu.

(1) Coll, J. C. *Chem. Rev.* **1992**, *92*, 613−631.

(2) Faulkner, D. J. *Nat. Prod. Rep*, **1996**, *13*, 75−125 and previous papers in this series.

(3) Rodríguez, A. D. *Tetrahedron* **1995**, *51*, 4571−4618.

(4) Bandurraga, M. M.; Fenical, W.; Donovan, S. F.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6463−6465.

(5) (a) Williams, D.; Andersen, R. J.; Van Duyne, G. D.; Clardy, J. *J. Org. Chem.* **1987**, *52*, 332−335. (b) Williams, D. E.; Andersen, R. J.; Kingston, J. F.; Fallis, A. G. *Can. J. Chem.* **1988**, *66*, 2928−2934. (c) Chan, W. R.; Tinto, W. F.; Laydoo, R. S.; Manchand, P. S.; Reynolds, W. F.; McLean, S. *J. Org. Chem.* **1991**, *56*, 1773−1776. (d) Rodríguez, A. D.; Soto, J. J. *J. Nat. Prod.* **1998**, *61*, in press.

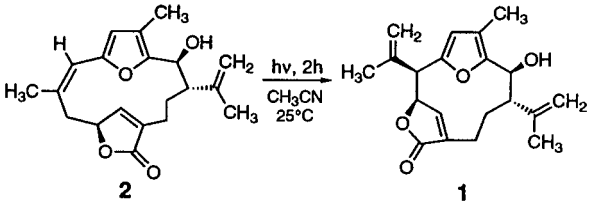
(6) For examples of synthetic approaches leading to pseudopteranes and furanocembranolides, see: (a) Kondo, A.; Ochi, T.; Iio, H.; Tokoroyama, T.; Siro, M. *Chem. Lett.* **1987**, 1491−1494. (b) Marshall, J. A.; Nelson, D. J. *Tetrahedron Lett.* **1988**, *29*, 741−744. (c) Paterson, I.; Gardner, M.; Banks, B. J. *Tetrahedron* **1989**, *45*, 5283−5292. (d) Paquette, L. A.; Rayner, C. M.; Doherty, A. M. *J. Am. Chem. Soc.* **1990**, *112*, 4078−4079. (e) Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450−3451. (f) Marshall, J. A.; Wang, X.−j. *J. Org. Chem.* **1991**, *56*, 6264−6266. Astley, M. P.; Pattenden, G. *Synlett.* **1991**, 335−336. (g) Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1992**, *57*, 3387−3396. (h) Paquette, L. A.; Doherty, A. M.; Rayner, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 3910−3926. (i) Rayner, C. M.; Astles, P. C.; Paquette, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 3926−3936. (j) Astley, M. P.; Pattenden, G. *Synthesis* **1992**, 101−105. (k) Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993**, *58*, 165−169. (l) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1993**, *58*, 3435−3443. (m) Marshall, J. A.; Yu, B.-c. *J. Org. Chem.* **1994**, *59*, 324−331. (n) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1994**, *59*, 1703−1708. (o) Marshall, J. A.; Wallace, E. M.; Coan, P. S. *J. Org. Chem.* **1995**, *60*, 796−797. (p) Marshall, J. A.; Bartley, G. S.; Wallace, E. M. *J. Org. Chem.* **1996**, *61*, 5729−5735. (q) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1997**, *62*, 4313−4320.

(7) Look, S. A.; Burch, M. T.; Fenical, W.; Qi-tai, Z.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 5741−5746.

(8) The suprafacial [1,3]-sigmatropic shift with retention at the migrating atom is also classified as a photochemically allowed $[_o2_s + _\pi2_s]$ or $[_o2_a + _\pi2_a]$ cycloaddition reaction; see: Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, Academic Press: New York, 1970.

(9) We also attempted the thermally induced cycloisomerization of **2** in the absence of solvent. After 1 h at 110−120 °C **2** remained unchanged. However, after 45 min at 150 °C complete decomposition took place.

S0022-3263(97)01884-7 CCC: $15.00
Published on Web 01/22/1998



2 1

Conventional chromatographic methods yielded pure samples of kallolide A (**1**) and bipinnatin J (**2**) from the $CHCl_3$ extract of *P. bipinnata*.[10] Kallolide A was identified unambiguously by direct comparison of its physical and chemical properties with those reported by Fenical et al. for material obtained from *Pseudopterogorgia kallos*.[7,11] The complete structural assignment of bipinnatin J (**2**), including relative stereochemistry, was accomplished by detailed analysis of spectroscopic data, mainly 2D NMR and HREI mass spectrometry.[11,12] The structure of **2** was subsequently confirmed by a single-crystal X-ray diffraction study (see Figure 1). Irradiation of **2** in CH_3CN (quartz) using a medium-pressure Hg lamp yielded **1** (40% conversion in 2 h, 50% of **2** recovered; the rest polymer) as the sole photoisomer.[13] This result suggested that the photochemical interconversion did not involve a diradical mechanism but was instead consistent with a [1,3]-sigmatropic rearrangement.[14] Moreover, the configuration at the migrating terminus remained unchanged during photoisomerization, and since no trace of other photoisomers was detected, the rearrangement was intrinsically stereospecific.[15,16]

The present study demonstrates the applicability of the photochemically induced [1,3]-allyl shift in our cycloisomerization approach to pseudopteranes and confirms our contention that a conjugated 2,5-furanocembrane can indeed undergo a facile ring-contraction to afford a 12-membered 2,5-furanocycle. This method of producing pseudopteranes should be amenable to the preparation of other members of this class. While we cannot completely rule out the possibility that the conversion of cembranes to pseudopteranes in nature is an enzyme-mediated process, our results suggest that their interconversion could be a sunlight-induced transformation.[17]

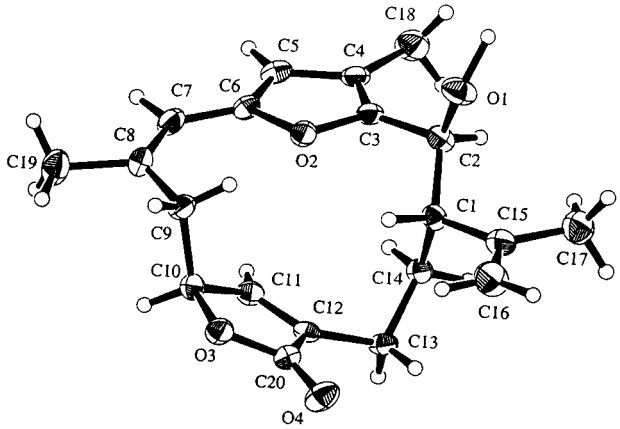


Figure 1. Computer-generated perspective drawing of the final X-ray model of bipinnatin J (**2**).

Acknowledgment. This report is Contribution No. 1 of the CMBN (Center for Molecular and Behavioral Neuroscience). The CMBN program is sponsored in part by the National Institute of Health (NIH) Grant No. RO1 GM52277. We thank Mr. Javier J. Soto for the collection of *P. bipinnata* and Mr. Juan A. Sánchez for its taxonomic identification. We are grateful to Professors R. Arce and S. D. Huang (University of Puerto Rico) for access to their photochemistry and X-ray diffraction facilities, respectively, and to Professor N. M. Carballeira for helpful discussions. The authors express their gratitude to the reviewers whose insightful comments improved this document. Support for this research at U.P.R. was kindly provided by the NSF−EPSCoR (Grant No. R118610677), NIH−MBRS (Grant No. S06RR08102-17), and NSF−MRCE (Grant No. R11-8802961) programs.

Supporting Information Available: Description of the X-ray diffraction determination, tables of intramolecular distances, torsion angles, positional parameters, and intramolecular bond angles for **2**, spectral data and interpretation of the HREI mass spectral data for **1** and **2** (19 pages).

JO971884G

(10) The dry animal (2.1 kg) was blended with MeOH−$CHCl_3$ (1:1) (5 × 1 L), and after filtration, the crude extract was evaporated under vacuum to yield a green residue (167.5 g). After the crude extract was partitioned between hexane and H_2O, the aqueous suspension was extracted with $CHCl_3$ (4 × 1 L). The resulting extract was concentrated in vacuo to yield 43.3 g of an oil that was chromatographed over silica gel (400 g) and separated into 30 fractions (I−XXX) on the basis of TLC analyses. Subsequent purification of fraction VIII (8.2 g) by column chromatography over silica gel (400 g) eluting with a gradient increasing EtOAc (0−100%) in hexane (100−0%) afforded 3.76 g of kallolide A (**1**) and 67 mg of bipinnatin J (**2**).

(11) Spectral data for kallolide A (**1**) and bipinnatin J (**2**) have been deposited as Supporting Information.

(12) Bipinnatin J (**2**): crystalline solid; mp 141−142 °C dec; $[\alpha]^{24}_D$ −125.4° (c = 1.65, $CHCl_3$); UV (MeOH) λ_{max} 210 (ϵ 19 800), 282 (ϵ 16 600) nm; IR (film) 3492, 1733, 1650, 1557, 1066 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (1H, br s, H-11), 6.09 (1H, br s, H-7), 6.02 (1H, s, H-5), 5.14 (1H, br s, H-16b), 5.03 (1H, br s, H-16a), 4.96 (1H, m, H-10), 4.49 (1H, br d, J = 10.8 Hz, H-2), 3.18 (1H, dd, J = 11.7, 12.0 Hz, H-9b), 2.71 (1H, dd, J = 4.5, 12.0 Hz, H-9a), 2.38 (1H, ddd, J = 3.0, 14.2, 14.2 Hz, H-13b), 2.35 (1H, dd, J = 10.8, 10.8 Hz, H-1), 2.07 (1H, m, H-13a), 2.03 (3H, s, Me-18), 1.98 (3H, br s, Me-19), 1.92 (1H, br s, OH, exchangeable), 1.78 (3H, br s, Me-17), 1.65 (1H, dddd, J = 3.3, 3.3, 10.8, 13.8 Hz, H-14b), 0.88 (1H, ddd, J = 3.3, 13.8, 13.8 Hz, H-14a); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2 (s, C-20), 152.2 (d, C-11), 151.0 (s, C-6), 149.3 (s, C-3), 142.2 (s, C-15), 132.6 (s, C-12), 128.9 (s, C-8), 121.0 (s, C-4), 118.4 (t, C-16), 117.3 (d, C-7), 113.8 (d, C-5), 78.6 (d, C-10), 65.0 (d, C-2), 51.1 (d, C-1), 39.7 (t, C-9), 30.1 (t, C-14), 25.7 (q, Me-19), 19.6 (t, C-13), 17.6 (q, Me-17), 9.4 (q, Me-18); EIMS m/z (rel intensity) 328 (16), 310 (29), 214 (12), 178 (52), 164 (70), 163 (100), 135 (38), 91 (34); HREIMS m/z [M^+] obsd 328.1677, calcd for $C_{20}H_{24}O_4$ 328.1675.

(13) The trace of polymer originates from concurrent photodegradation of **1**. After irradiation of pure kallolide A for 2 h under identical experimental conditions, clear signs of decomposition were detected by TLC and ^1H NMR studies. After 3−4 h, complete decomposition had occurred with no trace of **2** ever being detected. Therefore, we conclude that the photoisomerization of **2** to kallolide A takes place irreversibly.

(14) This is not the only mechanism that will explain our results. For example, irradiation may simply cause $Z \rightleftharpoons E$ interconversion of the conjugated double bond leading to a strained cyclophane which then proceeds thermally through either a [$\pi^2 + \sigma^2$] rearrangement or simply a photoinduced homolytic cleavage of the bisallylic σ bond followed by rapid recombination to form the valence isomer.

(15) Stereoequilibration is not observable at most of the centers that take part in this process, since there are no chiral centers on the migrating sidearm (atoms 7−9 in bipinnatin J) to test for specificity. The stereocenter at C10 is unchanged in this transformation. Thus, it would be inappropriate to claim stereospecificity at C10 without testing the derivative of the opposite chirality. Currently, the most one can claim is stereoselectivity for the process.

(16) For fundamental studies of photochemical [1,3]-allylic shift rearrangements see: Cookson, R. C.; Hudec, J.; Sharma, M. *J. Chem. Soc., Chem. Commun.* **1971**, 107 and 108.

(17) As light impinging on the surface of the earth and Pyrex have similar wavelength cut offs, we also irradiated **2** in a Pyrex vessel and again obtained **1** as the single major product. However, this time we detected the presence of two extremely minor products (<0.5% yield) by HPLC. Preliminary studies thus far suggest that these photoproducts might be isomers of **1** and **2** that belong to yet another skeletal class. Efforts toward elucidating the structures of these compounds are currently underway.