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Application of the Rodriguez–Pattenden Photo-Ring Contraction: Total Synthesis and Configurational Reassignment of 11-Gorgiacerol and 11-Epigorgiacerol

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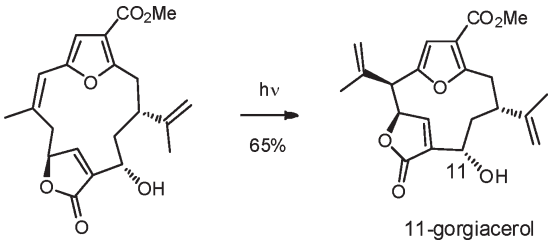
ABSTRACT

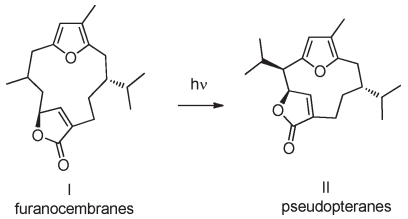


A stereospecific photochemical ring contraction was used as the key step in the first total synthesis of the marine pseudopteranyl diterpene 11-gorgiacerol and its 11-epimer. The synthesis allowed the correction of the configurations that had been misassigned in the literature. In addition, some novel pseudopteranyl derivatives have been made.

The furanocembranoids are a vast family of metabolites that have received wide attention in the synthetic, biosynthetic, and pharmacological communities.[1] Among the manifold structural modifications and rearrangements of the furanobutenolide-based cembranoids (**I**), the photoinduced ring contraction to the pseudopterane skeleton (**II**) (Scheme 1) is most remarkable.

This rearrangement has been postulated in the biosynthetic formation of **II**, but in vitro, it has been observed only by two groups so far: first by Rodriguez[2] and later by Pattenden,[3] who has also studied the stereochemistry of the reaction in detail. We now report the application of this Rodriguez–Pattenden ring contraction in the first total synthesis[4] of two metabolites reported as 11-gorgiacerol (= 11-pseudopteranol) (**1**)[5] and 11-epigorgiacerol (= 11-epipseudopteranol) (**2**)[56] (Figure 1). These pseudopteranoid diterpenes have been isolated from the gorgonian coral *Pseudopterogorgia acerosa* and have been characterized by NMR and mass spectrometry. In particular, the configurations at the carbinol center C-11 were assigned by $^1H-^1H$ NMR coupling constants only.

Scheme 1. Furanocembrane and Pseudopterane Skeletons



(1) For two excellent recent reviews, see: (a) Roethle, P. A.; Trauner, D. *Nat. Prod. Rep.* **2008**, *25*, 298–317. (b) Li, Y.; Pattenden, G. *Nat. Prod. Rep.* **2011**, *28*, 1269–1310.

(2) Rodriguez, A. D.; Shi, J.-G.; Huang, S. D. *J. Org. Chem.* **1998**, *63*, 4425–4432.

(3) (a) Yang, Z.; Li, Y.; Pattenden, G. *Tetrahedron* **2010**, *66*, 6546–6549. (b) Li, Y.; Pattenden, G. *Tetrahedron Lett.* **2011**, *52*, 3315–3319.

(4) For a profound recent review of photoreactions in total synthesis, see: Bach, T.; Hehn, J. P. *Angew. Chem.* **2011**, *123*, 1032–1077. *Angew. Chem., Int. Ed. Engl.* **2011**, *50*, 1000–1045.

(5) Tinto, W. F.; Laydoo, R. S.; Miller, S. L.; Reynolds, W. F.; McLean, S. *J. Nat. Prod.* **1995**, *58*, 1975–1977.

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Our synthesis of **1** and **2** has now demonstrated that these assignments were wrong and have to be permuted so that the former 11-gorgiacerol is now 11-epigorgiacerol and vice versa. Thus, Figure 1 shows the former and the corrected configurations.

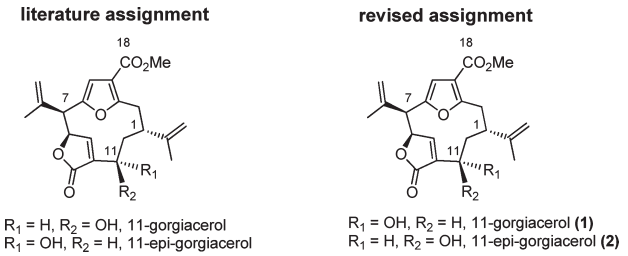
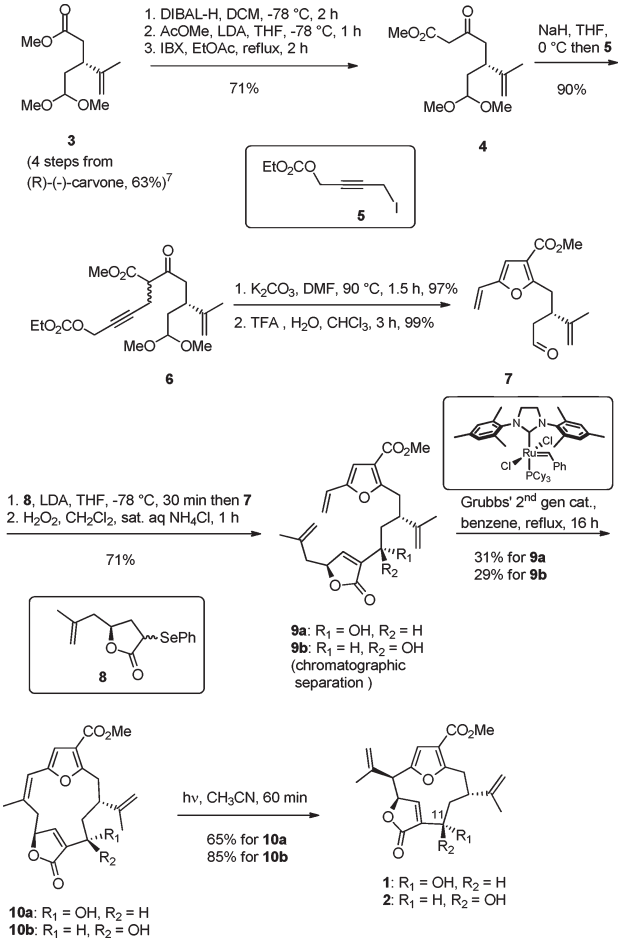


Figure 1. Original and corrected structures of 11-gorgiacerol and its 11-epimer.

The synthesis (Scheme 2) started with the known[7] ester acetal **3** (readily available in four steps from (*R*)-(−)-carvone). Reduction to the aldehyde, aldol addition of methyl acetate, and oxidation of the hydroxyl ester afforded keto-ester **4**. Deprotonation and alkylation with iodide **5** furnished keto acetylide **6**, which was cyclized[8] to the furan under basic conditions. Acid-catalyzed hydrolysis of the acetal led to aldehyde **7** which was subjected to an aldol addition with selenolactone **8**.[9] Oxidative elimination of the selenium gave butenolides **9a/b**,[10] readily separated by column chromatography. As both epimers were required for the envisaged structural assignment, no efforts were spent to improve the stereoselectivity of the aldol addition.

Ring-closing metathesis (RCM)[11] with Grubbs' second-generation catalyst gave (*Z*)-olefins **10a** and **10b** stereoselectively (Scheme 2).

Scheme 2. Total Syntheses of **1** and **2**



The synthesis was completed by a photoch emical ring contraction of **10a** and **10b** which furnished the desired pseudopteranes **1** and **2** in acceptable yields. Furan **2** was crystalline, which allowed the unambiguous assignment of its structure by single-crystal X-ray diffraction (Figure 2).

^{1}H and ^{13}C NMR data were in full agreement with the published data (see the Supporting Information).

The optical rotations of our samples differ from the published values but have the same sign (**1**: $[\alpha]^{20}_D = +83.0$ ($c = 0.33$; $CHCl_3$) vs +22 ($c = 0.1$, $CHCl_3$);[5] **2**: $[\alpha]^{20}_D = +130.0$ ($c = 0.25$; $CHCl_3$) vs +173.2 ($c = 0.12$, $CHCl_3$).[6]

An analogous sequence (Scheme 3) was applied to prepare 11-epigorgiacerol acetate **13** from **9a/b**. Crystalline acetate **12b** was subjected to a single crystal diffraction (Figure 3). To show that no epimerization occurred at the C-11 center during the photochemical ring contration, compound **2** was subjected to an acetylation reaction. The spectral data of the resulting product were in complete agreement with those of compound **13**.

On studying the photoreaction of compound **10b** in more detail, we found, in confirmation of Pattenden's earlier results,[3] that the labile (*E*)-isomer **14b** (Scheme 4) was produced first and was isolated after 20% conversion.

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(8) Wipf, P.; Rahman, L. T.; Rector, S. R. *J. Org. Chem.* **1998**, *63*, 7132–7133.

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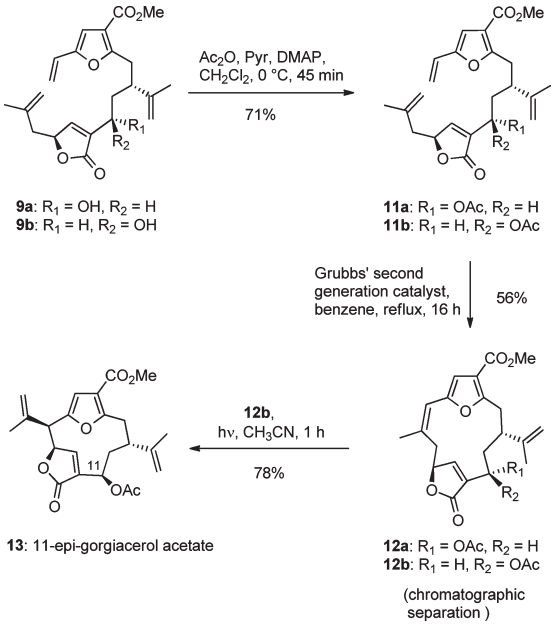
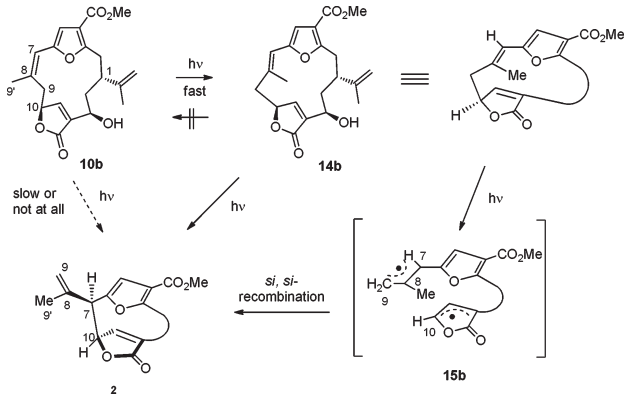
Scheme 3. Synthesis of 11-Epigorgiacerol Acetate **13**



Scheme 4. Mechanistic Considerations



In the ^{1}H NMR spectrum of **14b**, considerable line broadening was observed at room temperature because of restricted conformation mobility of the highly strained macrocyclic ring. On heating to 55 °C, the lines sharpened to give a resolved spectrum (see the Supporting Information). On prolonged irradiation, and without reisomerization to **10b**, the (*E*)-olefin **14b** underwent ring contraction to **2** with stereoselective generation of the new chiral center at C-7. Obviously, no direct isomerization of **10b** to **2** is involved. As pointed out by Pattenden,[1b,3] the conversion of **14b** into **2** may occur directly via a concerted [1,3]-sigmatropic shift or via a bis-allylic diradical such as **15b** in which the original configuration at C-10 (numbering as in Scheme 4) is lost. We do not know the conformation of **14b**. However the crystal structures of **2** and **12b** (Figures 2 and 3) show that the migrating σ-bond stands virtually perpendicular on the allylic plane. Hence, the conformational situation in such systems is well suited for a suprafacial 1,3-shift, whether concerted or stepwise.[12]

Aiming for novel pseudopterane derivatives (Scheme 5), acetate **13** was treated with K_2CO_3 to generate methyl ether **17** with complete retention of configuration.

As an S_N1 mechanism is highly unlikely under the conditions, this surprising result is interpreted in terms of an addition/elimination process via **16** (Nu=OMe), in which C-11 is attacked by the strongest nucleophile in the system (= OMe) from the less hindered ring face. By contrast, the reaction of **13** with methanol under acidic conditions furnished adduct **18**. Remarkably, only one of the isopropenyl groups was attacked, and the 11-OH was formed by acidic methanolysis of

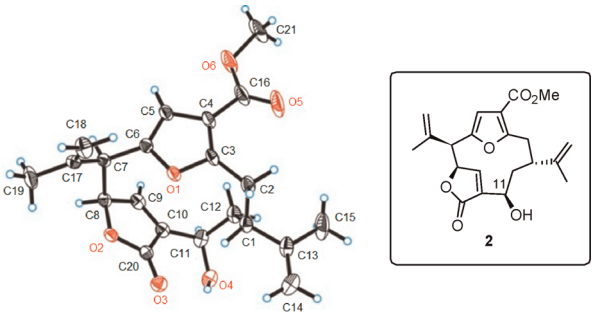


Figure 2. Crystal Structure of **2**.

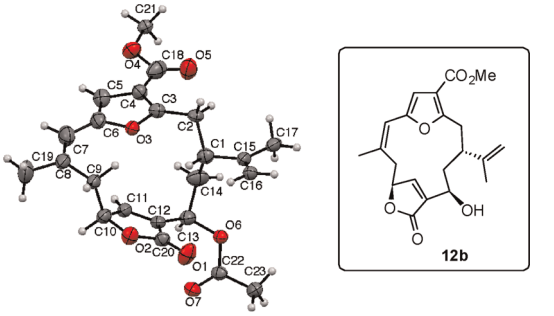


Figure 3. Crystal structure of **12b**.

the acetate. On attempting the dehydration of alcohol **1** with Burgess' reagent,[13] urethane **21** was obtained

(12) For similar considerations, see: Kimbrough, T. J.; Roethle, P. A.; Mayer, P.; Trauner, D. *Angew. Chem.* **2010**, *122*, 2675–2678. *Angew. Chem., Int. Ed.* **2010**, *49*, 2619–2621.

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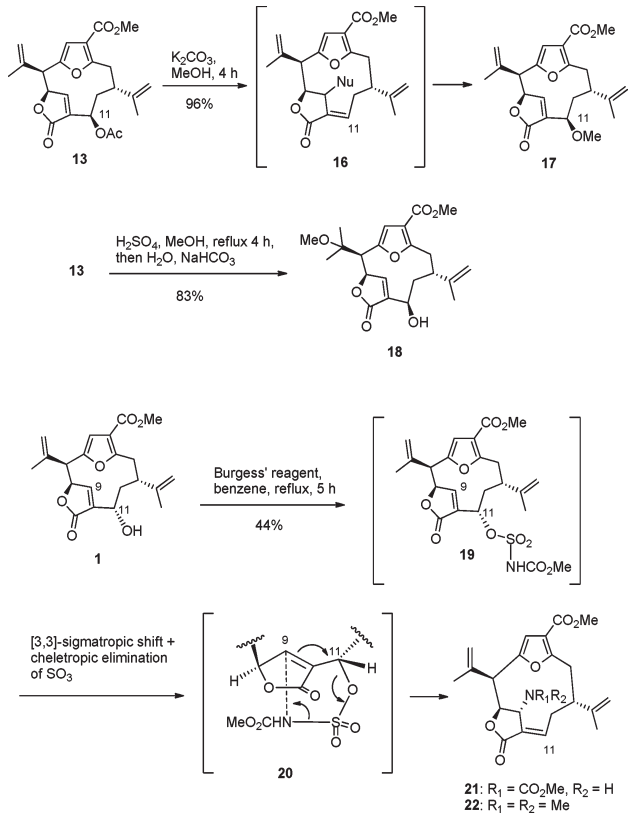
Scheme 5. Synthesis of Pseudopterane Derivatives



stereoselectively, which is a close analogue of deoxytobagolide (**22**).[14,15] We postulate that **21** is formed from primary adduct **19** via a [1,3]-sigmatropic shift with cheletropic elimination of SO_3. The stereochemistry of the rearrangement may be rationalized in terms of a six-membered transition state **20**, in which the nitrogen attacks C-9 from the less hindered side. This assumption is strengthened by the fact that **2** did not undergo rearrangement under the same conditions.

In conclusion, we have achieved (1) a concise synthesis of the pseudopteranyl alcohols **1** and **2** from (*R*)-(−)-carvone in 12 steps (plus two steps for the preparation of selenolactone **8** from (*S*)-tosyl glycidol) in 11% and 8% overall yield; (2) a reassignment of the configuration at C-11 and a confirmation of the absolute configuration of **1** and **2**; (3) a confirmation of the mechanism of the Rodriguez-Pattenden ring contraction; and (4) some substrate directed diastereoselective substitutions on the generic core which led to novel pseudopteranyl derivatives.

As for the biological properties of **1** and **2**, it has been shown that **2** has cytotoxic activity in the micromolar range, whereas **1** is inactive.[6] Thus, the behavior of our new pseudopterane derivatives is of interest and will be investigated in ongoing studies.

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Supporting Information Available. Experimental procedures and full characterization of all new compounds including copies of ^{1}H and ^{13}C NMR spectra and crystal structure analysis of **2** and **12b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

(15) The relative configuration of **21** has been safely assigned by appropriate $^{1}H-^{1}H$−NOE effects (see the Supporting Information).

The authors declare no competing financial interest.