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An expeditious entry to the hydrophenalene ring system of pseudopterosins

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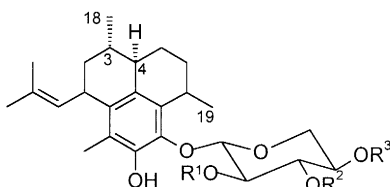
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Abstract

The preparation of the hexahydro-1*H*-phenalene core of natural pseudopterosins in five steps from readily available precursors is described. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: addition reactions; diastereoselection; hexahydro-1*H*-phenalene; pseudopterosins.

Pseudopterosins constitute a family of diterpene glycosides produced by the Caribbean sea whip *Pseudopterogorgia elisabethae*, isolated by Fenical et al. and showing remarkable anti-inflammatory activity.¹ A common structural feature of these compounds is the presence of a hexahydro-1*H*-phenalene ring system² showing a *cis* relative relationship³ between H-4 and Me-18 (Scheme 1).



Scheme 1.

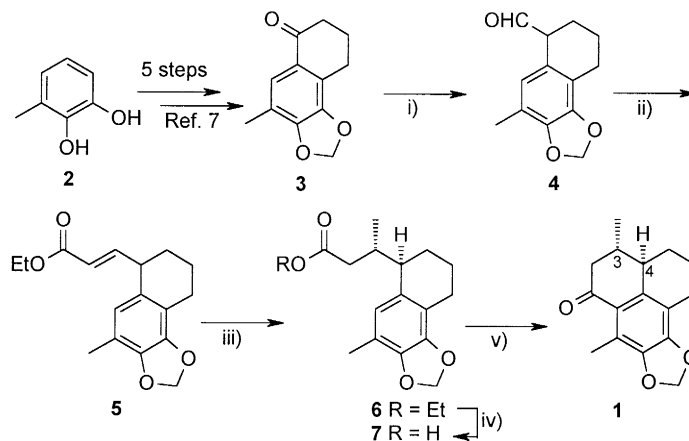
Due to the potential medical interest of these compounds, together with their limited availability from natural sources,⁴ different syntheses of pseudopterosins have been described.⁵ In this paper, we wish to account for a convenient entry to the hydrophenalene ring system of pseudopterosins⁶ **1** starting from the commercially available 3-methylcatechol **2**.

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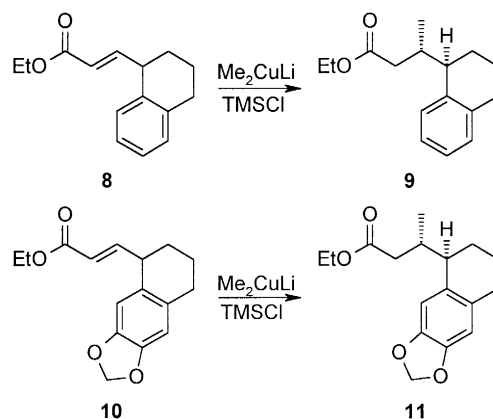
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The overall sequence is described in Scheme 2. Transformation of **2** into tetralone **3** was achieved in five steps using a previously reported procedure,⁷ by means of a Suzuki coupling–Friedel–Crafts acylation protocol. Reaction of **3** with $\text{Me}_2\text{S}=\text{CH}_2$ affords aldehyde **4**, which was transformed into the (*E*)- α,β -unsaturated ester **5** via a Horner–Emmons reaction. Treatment of **5** with Me_2CuLi at 0°C in the presence of TMSCl gave **6**. Hydrolysis of **6** followed by treatment with oxalyl chloride finally yields **1** (Scheme 3).⁸



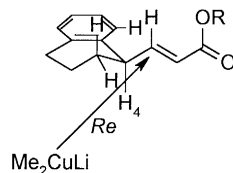
Scheme 2. *Reactions and conditions* (i) (a) NaH – DMSO , 70°C , 45 min; (b) $\text{Me}_2\text{S}^+=\text{CH}_2\text{I}^-$, -5°C , 10 min; (c) addition of **3**, -10°C , 30 min; (d) 18 h, rt (80%); (ii) (a) $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$, $\text{KO}^t\text{Bu}/\text{THF}$, 0°C to rt, 1 h; (b) addition of **4**, -78°C to rt, 2 h (90%); (iii) (a) $\text{CuBr}\cdot\text{SMe}_2$, 0°C , MeLi ; (b) addition of TMSCl ; (c) addition of **5**, 16 h, rt (90%); (iv) KOH/EtOH , 3 h, rt (90%); (v) ClCOCOCl , toluene, rt, 5 h (80%)



Scheme 3.

The configuration of **1** as $3S^*,4R^*$ has been established by ^1H NMR and molecular modelization. Thus, AM1 calculations carried out for $(3R^*,4R^*)$ -**1** (H-4 and Me-18 *trans*) indicate a minimum energy conformer with a pseudo-chair cyclohexanic ring and Me-18 in an axial disposition, for which a doublet of triplets is expected in the ^1H NMR spectrum for the H-4 signal (calculated dihedral angles: $\text{H4-H5}_{\text{ax}}=175^\circ$, $\text{H4-H5}_{\text{ec}}=57^\circ$, $\text{H4-H3}_{\text{ec}}=61^\circ$). On the other hand, for $(3S^*,4R^*)$ -**1** (H-4 and Me-18 *cis*), the minimum energy conformer showed a pseudo-chair cyclohexanic ring and Me-18 in an equatorial disposition, for which a triplet of doublets is expected in the ^1H NMR spectrum for the H-4 signal (calculated dihedral angles: $\text{H4-H5}_{\text{ax}}=173^\circ$, $\text{H4-H5}_{\text{ec}}=55^\circ$, $\text{H4-H3}_{\text{ax}}=174^\circ$), which is in agreement with the observed result (^1H NMR, 300 MHz, CDCl_3 , δ_{H4} 2.68 ppm, td, $^3J=12$ Hz, $^3J=6$ Hz).⁹

It is worth mentioning that the addition of Me_2CuLi to **5** in the presence of TMSCl affords compound **6** as a single diastereomer. This behaviour has also been observed in the reaction of Me_2CuLi /TMSCl with other related substrates, such as **8** and **10** (Scheme 3),^{10,11} and can be explained by an attack of the cuprate reagent from the *Re*-face of the starting materials in their minimum energy conformation, presumably due to severe interaction with the aromatic *ortho*-hydrogen in a *Si* approach (Scheme 4).¹²



Scheme 4.

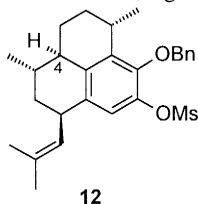
In conclusion, in this paper we have prepared the hexahydro-1*H*-phenalene core with the relative configuration of natural pseudopterosins at C3–C4 in five steps (49% overall yield) starting from readily available starting materials. Two points to be emphasized are the excellent acyclic stereocontrol exerted in the conjugate addition of Me_2CuLi to **5**, **8** and **10** with added TMSCl, and the spontaneous cyclization of the acid chloride of **7** to **1**.

Acknowledgements

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- The hexahydro-1*H*-phenalene ring system is also present in some members of the diterpene family of Helioporins, for instance, Helioporin-E. See: Tanaka, J. I.; Ogawa, N.; Liang, J.; Higa, T.; Gravalos, D. G. *Tetrahedron* **1993**, *49*, 811–822. See also: Geller, T.; Schmalz, H. G.; Bats, J. W. *Tetrahedron Lett.* **1998**, *39*, 1541–1544.
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- Substituents on C-19 will not be considered.
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- All compounds **4–7** gave satisfactory analytical and spectroscopic data.
- Although data for H-4 in the description of certain related natural products is given as multiplet or broad singlet, this proton has also been described as a triplet of doublets in certain cases, e.g. in compound **12**. See Ref. 5c.



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10. For a recent related example, in which the stereochemistry at carbon C-3 is determined in a highly diastereoselective Michael addition, see: Horstermann, D.; Schmalz, H. G.; Kociok-Köhn, G. *Tetrahedron* **1999**, *55*, 6905–6916.
11. A mixture of diastereomers and a lower overall yield were obtained when the reactions were carried out in the absence of TMSCl.
12. For compound **8**, a difference of 1.7 Kcal/mol (AM1) was found between the minimum energy conformer (Θ [H4–H18]=180°) and the conformer with (Θ [H4–H18]=0°).