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Syntheses and Stereochemical Revision of Pseudopterosin G–J Aglycon and Helioporin E

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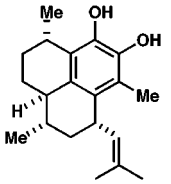
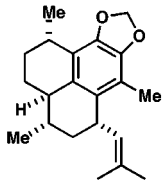
ABSTRACT



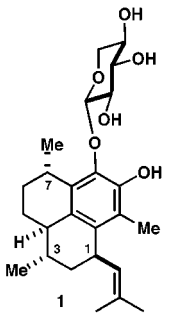
Pseudopterosin G-J Aglycone



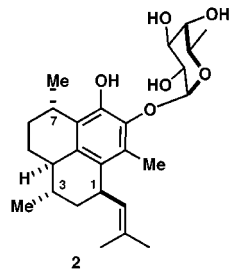
Helioporin E

Revised structures are proposed for pseudopterosin G–J aglycon and helioporin E.

We recently reported an especially simple and direct route for the synthesis of antiinflammatory pseudopterosins such as pseudopterosin A (**1**) and pseudopterosin E (**2**) from inexpensive (*S*)-(−)-limonene.[1] The synthetic strategy used involved an aromatic annulation process to form the benzenoid ring and a cationic cyclization to generate the third ring of the aglycon intermediate **3**.[2]



1



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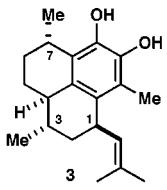

3

An interesting discovery made during this study was the finding that either the pseudopterosin A−F system or the

(1) Corey, E. J.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 12777.

(2) For other synthetic routes to the pseudopterosin family, see: (a) Broka, C. A.; Chan, S.; Peterson, B. *J. Org. Chem.* **1988**, *53*, 1584. (b) Corey, E. J.; Carpino, P. *J. Am. Chem. Soc.* **1989**, *111*, 5472. (c) Corey, E. J.; Carpino, P. *Tetrahedron Lett.* **1990**, *31*, 3857. (d) McCombie, S. W.; Cox, B.; Lin, S.-I.; Ganguly, A. K.; McPhail, A. T. *Tetrahedron Lett.* **1991**, *32*, 2083. (e) McCombie, S. W.; Ortiz, C.; Cox, B.; Ganguly, A. K. *Synlett* **1993**, 541. (f) Buszek, K. R. *Tetrahedron Lett.* **1995**, *36*, 9125. (g) Buszek, K. R.; Bixby, D. L. *Tetrahedron Lett.* **1995**, *36*, 9129. (h) Gill, S.; Kocienski, P.; Kohler, A.; Pontiroli, A.; Qun, L. *J. Chem. Soc., Chem. Commun.* **1996**, 1743. (i) Majdalani, A.; Schmalz, H.-G. *Tetrahedron Lett.* **1997**, *38*, 4545. (j) Majdalani, A.; Schmalz, H.-G. *Synlett* **1997**, 1303. (k) Kato, N.; Zhang, C.-S.; Matsui, T.; Iwabachi, H.; Mori, A.; Ballio, A.; Sassa, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2475.

(3) In these cases, the peak shapes are similar broad doublets with couplings of approximately 9 Hz.

(4) **3** arises from the deprotection of **6** (see ref 1).

(5) **15** arises via the deprotection of **7** (see Schemes 2 and 3 below).

(6) Roussis, V.; Wu, Z.; Fenical, W.; Strobel, S. A.; Van Duyne, G. D.; Clardy, J. *J. Org. Chem.* **1990**, *55*, 4916.

(7) Pseudopterosins G−J were originally assigned to be C(7) diastereomers of pseudopterosins A−F by NOE experiments. See ref 6.

(8) For isolation and original structural determination of the helioporins, see: Tanaka, J.-i.; Ogawa, N.; Liang, J.; Higa, T.; Gravalos, D. G. *Tetrahedron* **1993**, *49*, 811. For structural revision of helioporin C and D, see: (a) Geller, T.; Schmalz, H.-G.; Bats, J. W. *Tetrahedron Lett.* **1998**, *39*, 1537. (b) Hörstermann, D.; Schmalz, H.-G.; Kociok-Köhn, G. *Tetrahedron* **1999**, *55*, 6905.

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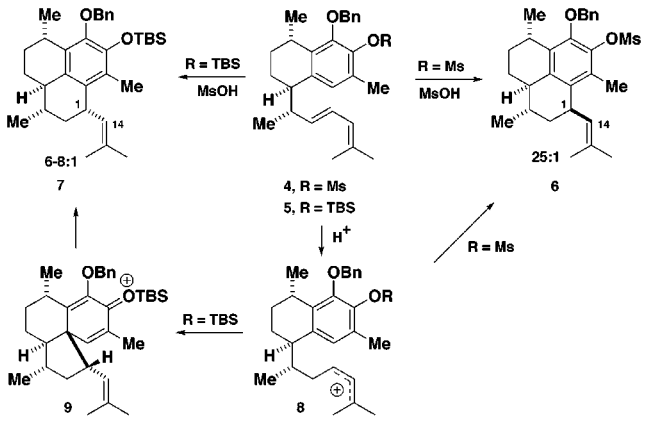
C(1)-diastereomeric analogues could be accessed depending on the intermediate used for the cationic closure of the third ring. As shown in Scheme 1, ring closure of mesylate **4**

Scheme 1



produced the pseudopterosin A−F system (**6**), whereas cyclization of the corresponding *tert*-butyldimethylsilyl ether **5** afforded selectively the C(1)-diastereomeric product **7**.

These results are readily understood in terms of two different reaction pathways. In the synthesis of **6**, the six-membered ring is likely formed by direct electrophilic attack by the intermediate allyl cation **8** on the benzenoid ring at the carbon *para* to benzyloxy. On the other hand, the transformation **5** → **7** probably occurs from **8** via the spiro intermediate **9**. The ^{1}H NMR spectra of **6** and **7** display a few small but characteristic differences with respect to the protons attached to C(1) and C(14). As expected, the pseudoaxial C(1) proton in **7** shows large couplings and resembles a broad doublet of doublets. In contrast, the pseudoequatorial C(1) proton in **6** shows small couplings and appears as a compressed multiplet. In addition, the proton attached to C(14) has a chemical shift of 4.97 ppm in **7**, whereas the corresponding C(14) proton in **6** appears at 5.11 ppm.[3] These differences are especially apparent from the ^{1}H NMR data for the fully deprotected cyclization products, aglycons **3**[4] and **15**[5] as shown in Figure 1.

In this paper we show that these ^{1}H NMR data, which clearly distinguish the known structures **3** and **15**, allow a reassignment of stereochemistry to the previously reported pseudopterosins G−J[6,7] and also helioporin E.[8] The aglycon corresponding to these previously reported structures for pseudopterosins G−J, which is pictured as **10** in Figure 2, differs from the pseudopterosin A−F aglycon **3** at the C(7) stereocenter. Similarly, the structure previously ascribed to helioporin E (formula **11** in Figure 2) also differs from **3** with regard to configuration at C(7).

(9) Shimshock, S. J.; Waltermire, R. E.; DeShong, P. *J. Am. Chem. Soc.* **1991**, *113*, 8791.

(10) A natural sample of pseudopterosin I was generously donated by Professor William Fenical. It was converted into its methylated aglycon by (1) treatment with methyl iodide and potassium carbonate in hot acetone to afford a mixture of methylated products (arising from acetyl migration in the sugar portion of the molecule) and (2) deglycosylation with HCl (aq) in methanol. See ref 6.

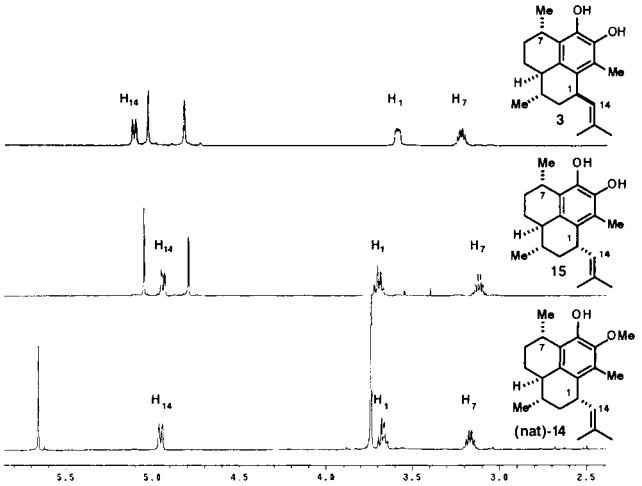


Figure 1. Spectral comparison of pseudopterosin A−F aglycon **3**, pseudopterosin G−J aglycon **15**, and monomethylated aglycon **14** derived from pseudopterosin I (^{1}H NMR, 500 MHz, $CDCl_3$).

Careful comparisons of the ^{1}H NMR data in Figure 1 for **3** and **15** with the data reported for pseudopterosins G−J[6] suggested that these pseudopterosins might correspond stereochemically to **15**.[7] This hypothesis is consistent with recent synthetic work by Schmalz and co-workers which showed that the stereochemistry of at least two members of the helioporins, a class of biologically active diterpenoids, were similarly misassigned at C(7).[8] These discoveries left the stereochemical configurations of both helioporin A and helioporin E ambiguous. Analysis of the ^{1}H NMR spectrum reported for helioporin E (**11**) suggested that it too might correspond stereochemically with **15**.

To test these proposals, cyclization product **7** was converted into its monomethyl ether **14** by the following sequence: (1) desilylation using Bu_4NF in THF, (2) careful preparative TLC purification to give phenol **12** in >25:1 purity at C(1), (3) alkylation of the C(10) oxygen using methyl iodide under phase-transfer conditions, and (4) treatment with lithium di-*tert*-butylbiphenylide (LDBB)[9] to effect debenzylation (i.e. **12** → **13** → **14**, Scheme 2).

When monomethyl ether **14** prepared in this way was compared with the corresponding methylated aglycon derived from pseudopterosin I,[10] the samples were found to be

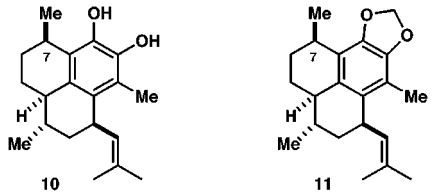
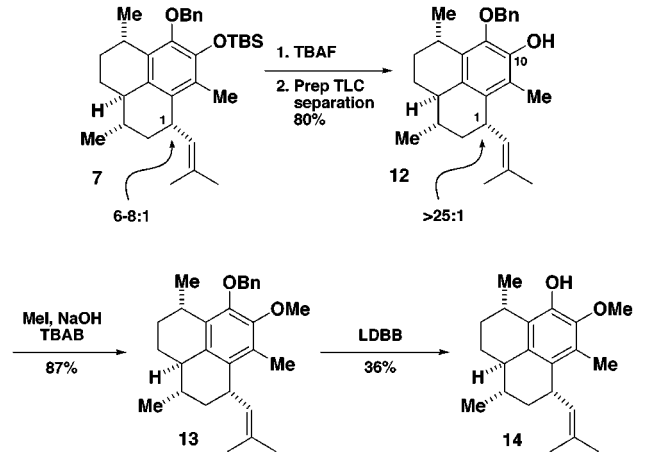


Figure 2. Originally reported structures for the pseudopterosin G−J aglycon **10** and helioporin E (**11**).

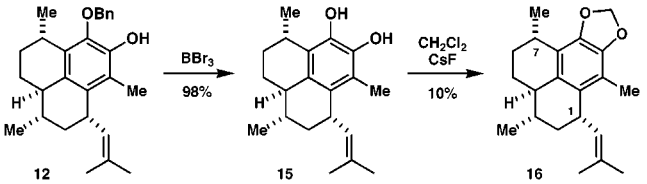
Scheme 2



identical by ^{1}H NMR, ^{13}C NMR, FTIR, and high-resolution mass spectroscopy.[11] Thus, the tricyclic core of pseudopterosins G−J must correspond stereochemically with cyclization product **7** and are not diastereomeric at C(1) and C(7) as reported (see Figure 2).[12] The ^{1}H NMR spectrum for the naturally derived version of monomethyl ether **14** is displayed in Figure 1 above. Its correspondence with synthetic aglycon **15** is evident.

The original stereochemical assignment of helioporin E was based primarily on spectral comparisons with pseudopterosins G−J,[13] which implies that helioporin E had been similarly misassigned. To prove this, phenol **12** was converted into the corresponding acetal **16** (Scheme 3). This was accomplished by boron tribromide-mediated debenzylation of **12** to give pseudopterosin G−J aglycone **15**, which was methylenated with methylene chloride and cesium fluoride in DMF at 110 °C for 45 min[14] to produce the desired acetal **16**, which was found to be identical to helioporin E by ^{1}H NMR, FTIR, and high-resolution mass spectroscopy.[15] Thus,

Scheme 3



(11) Synthetic methyl ether **14**: $[\alpha]_D^{25}$ +90 (*c* 0.05, $CHCl_3$). Methyl ether **14** derived from pseudopterosin I: $[\alpha]_D^{25}$ +98 (*c* 0.050, $CHCl_3$).

(12) Professor Fenical and co-workers independently discovered indirect evidence for this stereochemical reassignment, but lacked experimental proof (personal communication).

(13) Stereochemical assignments for pseudopterosins G−J were made by NOE. See ref 6.

(14) Clark, J. H.; Holland, H. L.; Miller, J. M. *Tetrahedron Lett.* **1976**, *38*, 3361.

(15) We are grateful to Professor Tatsuo Higa for copies of the ^{1}H NMR spectrum of helioporin E (**16**).

the revised structure of helioporin E (**16** as shown in Scheme 3) also differs at both C(1) and C(7) as compared with the reported structure (see Figure 2).[16]

Finally, to provide conclusive proof for the stereochemical reassignment for both pseudopterosin G−J aglycon **15** and helioporin E (**16**), the *p*-bromobenzoate **17** of synthetic intermediate phenol **12** was prepared, crystallized,[17] and subjected to analysis which unambiguously yielded the structure shown in Figure 3.[18]

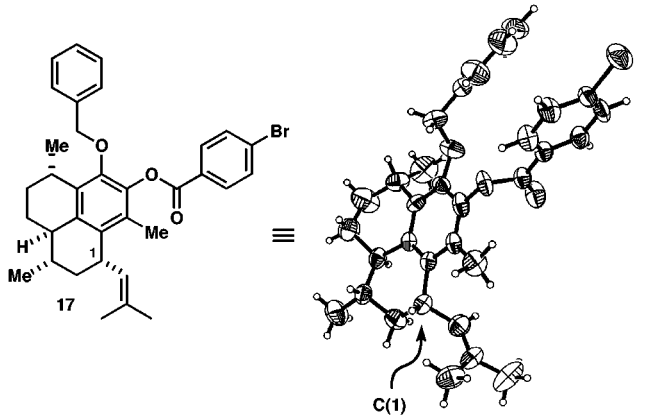


Figure 3. X-ray crystal structure of *p*-bromobenzoate **17**.

To summarize, by exploiting the versatile acid-catalyzed cyclization of dienes such as **4** and **5**, selective syntheses of both pseudopterosin G−J aglycon **15** and the potent cytotoxic agent helioporin E (**16**) were accomplished. These syntheses provided the first compelling evidence that these compounds are diastereomeric at C(1) relative to the pseudopterosins A−F, *not* at C(7) as originally reported. Thus, the stereochemical configurations of pseudopterosin G−J aglycon and helioporin E are best represented by **15** and **16**.

It is possible that the reported structure (**18**, Figure 4) for the related natural product pseudopteroxazole[19] may also require revision in line with **15** and **16**. Synthetic studies are ongoing in this laboratory to shed light on this matter.

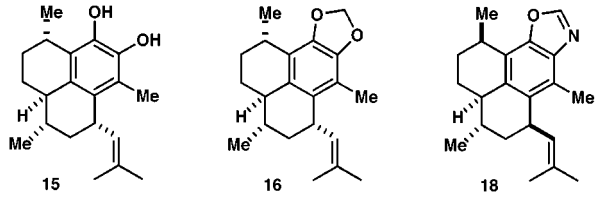


Figure 4. Revised structures for the pseudopterosin G−J aglycon **15** and helioporin E (**16**) and the reported structure for pseudopteroxazole **18**.

(16) A similar reassignment was hypothesized by Schmalz and coworkers. See ref 8b.

Acknowledgment. This research was assisted financially by a graduate fellowship from the Eli Lilly Corporation (S.E.L.) and postdoctoral fellowship from the National Institutes of Health (T.W.J.) as well as a grant from the National Science Foundation. Also, special thanks are extended to Eduardo J. Martinez for solving the crystal structure of **17** and to Professor Fenical for his help and advice.

Supporting Information Available: Experimental procedures and spectral characterization for compounds **7** and **12**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) *p*-Bromobenzoate **17** was prepared from phenol **12** by treatment with excess *p*-bromobenzoyl chloride and DMAP in CH_2Cl_2, followed by preparative TLC purification. Recrystallization from methanol afforded X-ray quality crystals, mp 140−144 °C.

(18) Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, U.K.

(19) Rodríguez, A. D.; Ramírez, C.; Rodríguez, I. I.; González, E. *Org. Lett.* **1999**, *1*, 527.