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# *iso*-PsE, a new pseudopterosin

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ABSTRACT

We describe the discovery of a new member of the pseudopterosin class of marine natural products. Its structure is isomeric with that of pseudopterosin E and has therefore been given the name *iso*-PsE.
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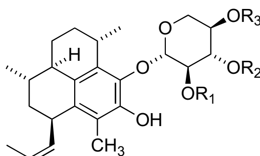
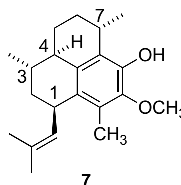
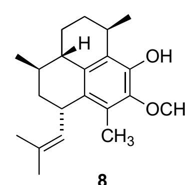
The pseudopterosins constitute a well-known class of more than twenty marine natural products. These interesting substances have been the focus of many investigations, some dealing with their isolation and characterization,[1] others with synthesis,[2] and others with their biological activity.[3] As illustrated in Figure 1, pseudopterosins A–D (**1**–**4**) differ simply by the degree of acylation of the D-xylose sugar unit, while pseudopterosins E (**5**) and K (**6**) differ in the location of the L-fucose sugar residue and in the absolute configuration of the stereogenic centers within the tricyclic diterpene core.




**1**, $R_1 = R_2 = R_3 = H$, PsA
**2**, $R_1 = Ac$, $R_2 = R_3 = R_4 = H$, PsB
**3**, $R_2 = Ac$, $R_1 = R_3 = R_4 = H$, PsC
**4**, $R_3 = Ac$, $R_1 = R_2 = R_4 = H$, PsD

In order to conduct a detailed structure–activity relationship study, we needed to develop a simple protocol whereby we could obtain substantial quantities of the tricyclic aglycon core. We began our search by using a well-established sequence wherein the phenolic hydroxyl group of raw material isolated from the feathers of *Pseudopterogorgia elisabethae* was converted to methyl ether (MeI, $K_2CO_3$, acetone, 60 °C, 24 h, 97%) and the sugar residue was removed (1 N HCl, MeOH, 50 °C, 4 h, 84%).[1b,4] The specific rotation of an HPLC-purified sample of the resulting material was in accord with that reported for the aglycon derived from pseudopterosin A methyl ether (**10**; PsA–OMe).[1b] We were surprised by this observation since the spectral data for the pseudopterosin that were used to begin the sequence matched those of pseudopterosin K (**6**; PsK).[1b] The problem, and therefore the source of our surprise, was that the aglycons of PsA and PsK (**7** and **8**, respectively) are enantiomers and ought to display specific rotations of equal magnitude but opposite sign. Therefore it appeared that we were dealing with a previously uncharacterized member of the pseudopterosin class of natural products, one possessing a PsA (**1**) core but with a sugar unit that is found in PsK (**6**).




**7** **8**

Given the fact that specific rotations do not always provide a reliable assessment of structure,[5] we felt that it was important to adopt a conservative and unambiguous approach to establish the structure of the tricyclic core. The idea was to determine whether the aglycon in question would be converted to PsA O-methyl ether (**10**), or to the diastereomeric structure **11** upon glycosylation with enantiomerically pure trichloroacetimidate **9**.[6] Isolation of **10** would confirm our suspicion that the tricyclic core was of the PsA, rather than the PsK variety.

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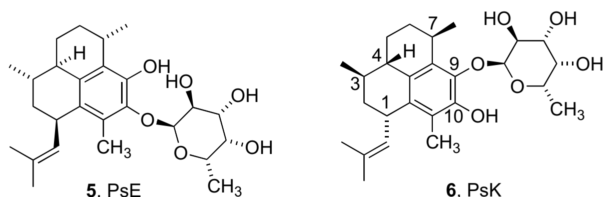
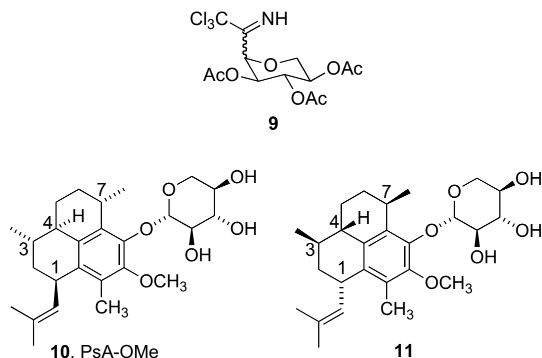


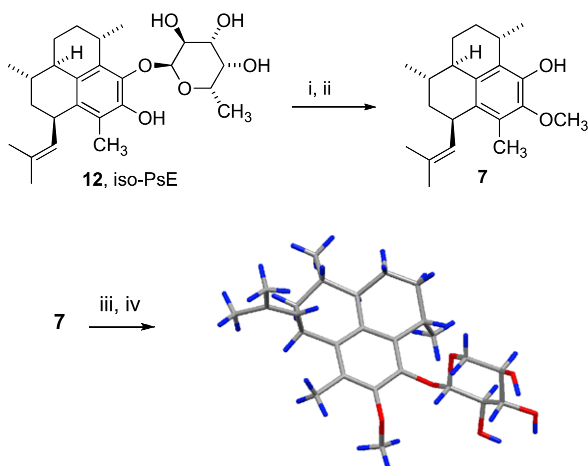

**Figure 1.** Structure of selected pseudopterosins.




In practice, 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl trichloroacetimidate (**9**) was coupled to the aglycon ($BF_3$ etherate, 4 Å molecular sieves, $CH_2Cl_2$, −78 °C; 91%), and the acetate units were removed ($K_2CO_3$, MeOH, room temperature; 95%) to afford an adduct that crystallized slowly upon standing; a single crystal X-ray analysis was performed (see Scheme 1).

Knowing that the configuration at each of the stereogenic centers in the sugar portion of the structure matches those found in D-xylose, the result of the single crystal X-ray analysis revealed the product to be PsA–OMe (**10**) rather than the diastereomer **11** (note Scheme 1). This discovery allows us to confidently formulate **12** as the structure for the new pseudopterosin.[7] Given its isomeric relationship to PsE (**6**), we suggest the name *iso*-PsE (**12**).[8]

Since *iso*-PsE is a newly characterized substance, we carried out a preliminary screening and comparison of its pharmalogical properties with other pseudopterosins. Like its relatives, *iso*-PsE (**12**) inhibits phorbol myristate acetate (PMA) induced inflammation of the inner pinnae of a mouse ear with an $ED_{50}$ of 27 μg/ear, compared with an $ED_{50}$ of 8 μg/ear for PsA (**1**) and 22 μg/ear for PsA–OMe (**10**). Thus, its activity is nearly the same as **10**. *iso*-PsE (**12**) also inhibits neutrophil infiltration at the application site. This is a key feature of the unique anti-inflammatory activities of the pseudopterosins in that they lack significant activity on eicosanoid biosynthesis but appear to act, in part, by blocking the release of pro-inflammatory mediators from neutrophils and macrophages.[3a] Recent reports described a role of neutrophil infiltration in wound-healing, while recent clinical reports, although debated, have emphasized an inflammatory role of neutrophil infiltration and degranulation during injury.[9]




X-ray derived structure corresponding to PsA-OMe (**10**)

**Scheme 1.** Transformations used to establish the structure of *iso*-PsE (**12**). For ease of visualization against the white background, the hydrogens in the X-ray derived structure for PsA–OMe (**10**) are shown in blue. Reagents and conditions: (i) MeI, $K_2CO_3$, acetone, 60 °C, 24 h (97%); (ii) 1 N HCl, MeOH, 50 °C, 4 h (84%); (iii) **9**, $BF_3$ etherate, 4 Å mol sieve, $CH_2Cl_2$, −78 °C (91%); (iv) $K_2CO_3$, MeOH, rt (95%).

In addition, at the cellular level *iso*-PsE (**12**), as well as PsA (**1**) and PsA–OMe (**10**), significantly decreases basal levels of phagocytosis in cultured tetrahymena cells.[10] In cultured human embryonic kidney cells (HEK-293) expressing several G-protein coupled receptors, isotope binding studies indicate that *iso*-PsE (**12**) displays a significant degree of selectivity toward adenosine $A_{2A}$ and $A_3$ receptors when tested at concentrations above 5 μM. At these concentrations *iso*-PsE (**12**), although markedly less potent than adenosine analogs,[11] followed binding kinetics similar to the adenosine standards. Studies are underway to examine effects of *iso*-PsE (**12**) in functional assays in cells expressing adenosine receptors.

## Acknowledgments

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7. As this manuscript was being prepared, a sample of *iso*-PsE (**12**) was crystallized. The resulting single crystal X-ray analysis left no doubt that the structural assignment given herein is correct.
8. *The spectral data for iso-PsE* (**12**) *are*: $^1$H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, d, *J* = 6.0), 1.05–1.09 (1H, m), 1.11 (3H, d, *J* = 7.3), 1.24 (3H, d, *J* = 6.7), 1.36–1.43 (1H, m), 1.50–1.57 (1H, m), 1.59–1.62 (1H, m), 1.63–1.69 (1H, m), 1.65 (3H, s), 1.74 (3H, s), 1.94–1.99 (1H, m), 1.96 (3H, s), 2.05–2.13 (2H, m), 3.39 (1H, m), 3.58 (1H, d, *J* = 9.2), 3.91 (1H, s), 4.02 (1H, br s, OH), 4.15 (2H, apparent s), 4.34 (1H, q, *J* = 6.5), 4.65 (1H, br s, OH), 5.06 (1H, s), 5.09 (1H, d, *J* = 9.2), 5.66 (1H, br

s, OH), 8.70 (1H, br s, OH); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 11.0 (C-20), 16.4 (C-6′), 17.8 (C-16), 21.2 (C-18), 24.3 (C-19), 25.9 (C-17), 27.3 (C-7), 28.3 (C-5), 30.2 (C-3), 30.5 (C-6), 35.7 (C-1), 39.6 (C-2), 43.0 (C-4), 67.8 (C-5′), 69.1 (C-2′), 70.7 (C-3′), 72.4 (C-4′), 103.7 (C-1′), 121.3 (C-11), 128.9 (C-15), 129.9 (C-13), 130.0 (C-14), 133.3 (C-8), 135.0 (C-12), 142.6 (C-9), 145.4 (C-10). HRMS (positive ion electrospray in $CH_3CN$) *m*/*z* found 469.2540, calcd 469.2560 for $C_{26}H_{38}O_6Na$.

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11. For example, the adenosine structural analog called NECA displays an $IC_{50}$ toward the $A_{2A}$ receptor of 36 nM, while IB-MECA displays an $IC_{50}$ toward the $A_3$ receptor of 1.2 nM. The $A_{2A}$ receptors have been shown to operate through a G-protein coupled receptor (GPCR) pathway and modulation of these receptors have shown positive effects in the acceleration of wound-healing.