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TETRAHEDRON: *ASYMMETRY*

Absolute stereochemistry of anisodorin 5

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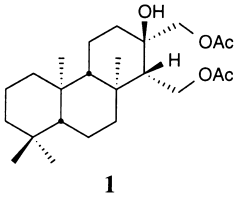
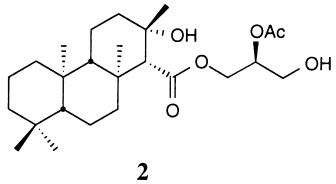
Abstract

The absolute stereochemistry of the natural diterpene anisodorin 5 **1**, previously isolated from the marine dorid nudibranch *Anisodoris fontaini*, has been established by synthesis of its enantiomer *ent*-anisodorin 5 **3**.

Recently, we reported the chemical characterization of the diterpene anisodorin 5 **1**, which was isolated, as a minor component of a mixture of isocopalane diterpenoid diacylglycerols, anisodorins (e.g. **2**), from the skin of the Patagonian dorid nudibranch *Anisodoris fontaini*.[1] The absolute stereochemistry of anisodorins was established by either synthesis or comparison of CD spectra with those of known isocopalane diterpenoid glyceryl esters. The absolute configuration of **1** was suggested to be the same as the other anisodorins, but the opposite stereochemistry, typical for metabolites from sponges belonging to the genus *Spongia*, could not be excluded. Therefore, differently from the other anisodorins, which are probably biosynthesized de novo, anisodorin 5 could derive from a dietary source, although we were not able to detect traces of **1** in the digestive gland of the mollusc.



1



2

In order to determine the absolute stereochemistry of **1**, we performed a partial synthesis of the *ent*-isocopalane diterpene **3**, that is reported here.

Synthesis of **3** was carried out starting from the *ent*-isocopalane acetyl derivative **4**, which was obtained from (−)-sclareol **5**, according to the literature procedure[2] (Scheme 1). The acetate **4** was oxidized by OsO_4 and $K_3Fe(CN)_6$ in *t*-BuOH, according to a procedure previously described,[3] to give compound **6**

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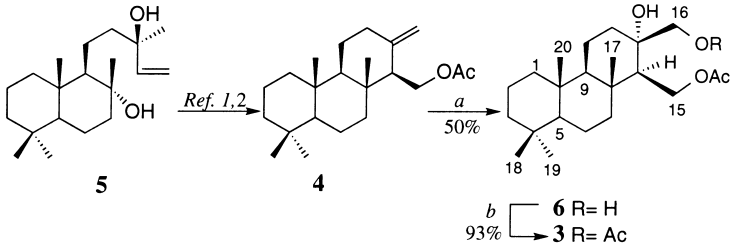
(50%),[4] which was acetylated by Ac_2O and pyridine into *ent*-anisodorin 5 **3** (93%). Compound **3** showed spectroscopic data[5] identical to those of natural **1**,[1] but opposite $[\alpha]_D$ and CD profiles,[6] thus confirming the proposed isocopalane configuration of anisodorin 5 **1**.



Scheme 1. Reagents and conditions: (a) OsO_4, $K_3Fe(CN)_6$, *t*-BuOH–H_2O, rt, 24 h; (b) Ac_2O, Py, rt, 12 h

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3. Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem*. **1990**, *55*, 766–768.
4. Compound **6**: mp 163–165°C (from petr. ether); $[\alpha]_D$ −1.4 (*c* 0.1, $CHCl_3$). IR: ν_{max} (liquid film) 3388, 1733 cm^{-1}. ^1H NMR: δ_H (400 MHz, $CDCl_3$) 0.80 (6H, s, H_3-18 and H_3-20), 0.83 (3H, s, H_3-19), 0.85 (3H, s, H_3-17), 2.06 (3H, s, OAc), 3.32 (1H, bs, OH), 3.44 (1H, dd, *J*=1.9 and 10.9 Hz, H-16a), 3.58 (1H, dd, *J*=8.1 and 10.9 Hz, H-16b), 4.12 (1H, dd, *J*=5.8 and 12.0 Hz, H-15a), 4.50 (1H, dd, *J*=3.3 and 12.0 Hz, 1H, H-15b). ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 39.9 (C-1), 18.1 (C-2 or C-6), 42.0 (C-3), 33.3 (C-4), 56.4 (C-5), 18.5 (C-6 or C-2), 41.2 (C-7), 38.4 (C-8), 60.2 (C-9), 37.5 (C-10), 18.7 (C-11), 37.2 (C-12), 74.2 (C-13), 60.1 (C-14), 61.8 (C-15), 64.3 (C-16), 17.1 (C-17), 21.4 (C-18), 33.3 (C-19), 16.2 (C-20), 171.8 (Ac), 21.4 (Ac). EIMS *m/z* 366 (M^+, 8), 348 (12), 335 (37), 306 (32), 293 (15), 275 (97), 257 (98), 219 (16), 205 (22), 191 (100). HRMS calcd for $C_{22}H_{38}O_4$ (M^+) *m/z* 366.2770, found 366.2762.
5. Compound **3**: mp 146–148°C (from petr. ether); $[\alpha]_D$ +4.5 (*c* 0.15, $CHCl_3$). CD $[\theta]_{213}$ (EtOH) −1,700. IR: ν_{max} (liquid film) 3498, 1748 cm^{-1}. ^1H NMR: δ_H (400 MHz, $CDCl_3$) 0.80 (s, 6H, CH_3-18 and CH_3-20), 0.86 (s, 3H, CH_3-19), 0.88 (s, 3H, CH_3-17), 2.06 (s, 3H, OAc-15), 2.10 (s, 3H, OAc-16), 3.06 (bs, 1H, OH), 4.01 (d, *J*=11.7 Hz, 1H, H-16a), 4.24 (d, *J*=11.7 Hz, 1H, H-16b), 4.19 (dd, *J*=6.0 and 11.9 Hz, 1H, H-15a), 4.50 (dd, *J*=3.5 and 11.9 Hz, 1H, H-15b). ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 39.9 (C-1), 18.1 (C-2), 42.0 (C-3), 33.3 (C-4), 56.4 (C-5), 18.5 (C-6), 41.2 (C-7), 38.4 (C-8), 60.3 (C-9), 37.5 (C-10), 18.8 (C-11), 38.1 (C-12), 73.1 (C-13), 59.8 (C-14), 61.6 (C-15), 67.3 (C-16), 17.2 (C-17), 21.4 (C-18), 33.3 (C-19), 16.2 (C-20), 171.4 (Ac-15), 21.0 (Ac-15), 171.0 (Ac-16), 21.4 (Ac-16). EIMS *m/z* 348 [(M^+−AcOH), 29], 335 (14), 275 (95), 257 (45), 219 (20), 205 (25), 191 (70), 137 (89), 123 (100), 69 (90). HRMS calcd for $C_{22}H_{36}O_3$ (M^+−AcOH)) *m/z* 348.2664, found 348.2655.
6. Anisodorin 5 **1**: $[\alpha]_D$ −3.2 (c 0.15, $CHCl_3$). CD $[\theta]_{215}$ (EtOH) +2,400.