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# Synthesis of Diastereoisomeric *ent*-Isocopalic Acid Glycerides

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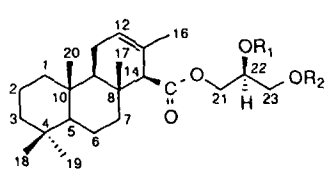
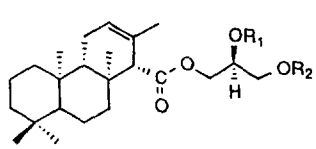
*Abstract*: A concise synthesis of two diastereoisomeric diterpenoid acid glycerides, **1a**, previously isolated from the skin of some dorid nudibranchs, and **3**, via 13*E*-labd-8(9),13-dienic acid **4**, is described. Copyright © 1996 Elsevier Science Ltd

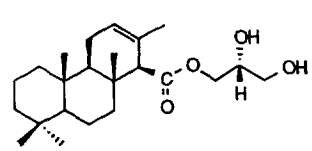
Nudibranchs are marine molluscs that have elaborated a series of defensive strategies [2] to compensate for the loss of the shell. These molluscs often contain in their mantles unusual chemicals that could play a defensive role against potential predators [3,4] and that also possess other biological functions. Many dorid nudibranchs belonging to the genera *Archidoris, Doris* and *Austrodoris* contain in their mantles diterpenoid acylglycerols[5-11] toxic to fish but also activators of protein kinase C and very active in the regenerative test with the fresh water hydrozoan *Hydra vulgaris*.[12] These molecules are most likely biosynthesized *de novo* by the molluscs.[6] Very surprisingly diastereoisomeric acylglycerols, esterified in position 1-*sn* by antipodal diterpenoid acids, have been isolated from geographically distinct populations of *Archidoris* nudibranchs.[8] *Archidoris tuberculata* (N. Spain) contains the same series (**1a-c**) of metabolites previously[6] isolated from *A. montereyensis*, whereas *Archidoris carvi* (S. Argentina) contains two acylglycerols (**2b-c**) characterized, at position 1-*sn*, by a diterpenoid acid enantiomer of that at position 1-*sn* of **1a-c**. The enantiomeric relationship between the diterpenoid acids of the two series of acylglycerols was suggested both by slight but diagnostic differences observed in the $^1$H-NMR spectra for the resonances assigned to $H_2$-21 and by opposite but identical CD profiles.[8]



**1a** $R_1 = R_2 = H$
**1b** $R_1 = H$; $R_2 = Ac$
**1c** $R_1 = Ac$; $R_2 = H$



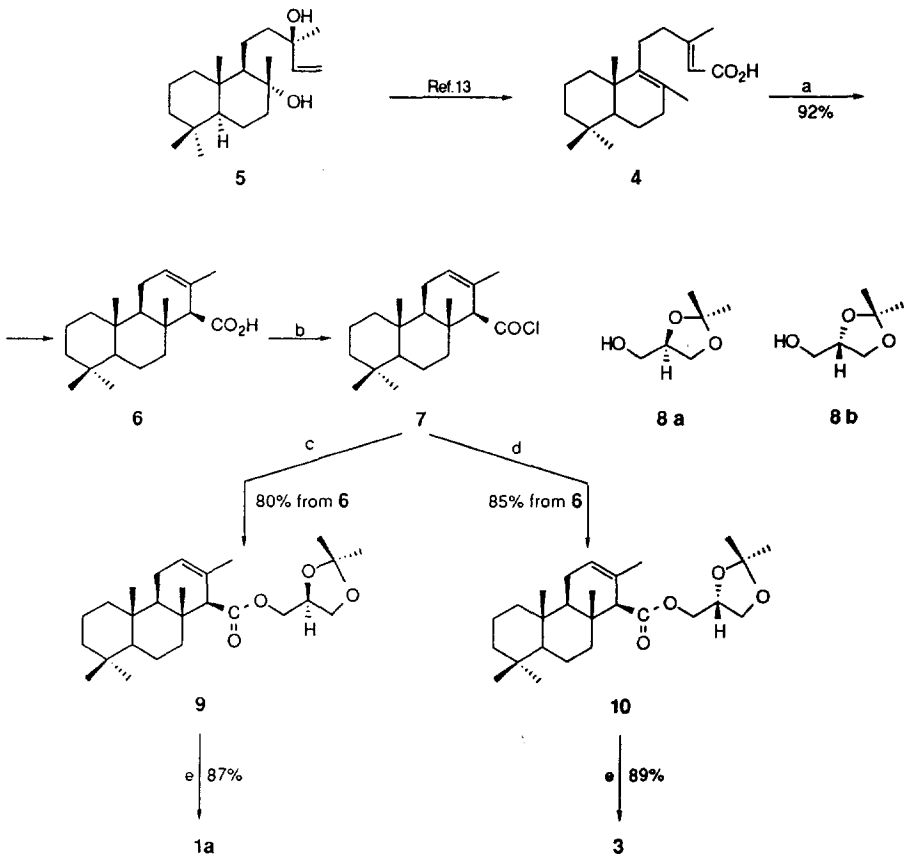
**2a** $R_1 = R_2 = H$
**2b** $R_1 = H$; $R_2 = Ac$
**2c** $R_1 = Ac$; $R_2 = H$



**3**

In order to confirm the suggested structures, the first synthesis of **1a** and that of its $C_{22}$ epimer **3**, enantiomer of **2a**, via 13*E*-labd-8(9),13-dienic acid **4**, has been performed. The last compound has previously been prepared in five steps [13] from sclareol **5**. Superacidic cyclization [13] of **4** (ratio **4** : $FSO_3H$ = 1:5 mmol, *i*-$PrNO_2$, -78° C, 45 min) afforded in a good yield (92%) the tricyclic *ent*-isocopalic acid **6** [14] {m.p. 177-178°C

(from petr.ether), $[\alpha]_D$ -9.1° (c 0.3, $CHCl_3$)}. The last compound **6** was transformed[15] [$(COCl)_2$ - $C_6H_6$, 25°C - 2h; 45°C - 30 min] into chloride **7**.[16] Compound **7** was immediately coupled with (-)-2,3-O-isopropylidene-*sn*-glycerol **8a** (NaH, $CH_2Cl_2$, 0°C, 20 min) and gave in good overall yield from **6** (80%) the acetonide **9** [17] {oil, $[\alpha]_D$ -35° (c 0.25, $CHCl_3$)}. Deprotection of **9** by 0.006 M solution of $H_2SO_4$ in $CH_3OH$ (r.t., 2h) afforded the crystalline glycerol ester **1a** {m.p.124-126° C (from $Et_2O$ - petr.ether), $[\alpha]_D$ -54.3° (c 0.3, $CHCl_3$)} {lit.[6]: m.p.125-126° C; $[\alpha]_D$ -12.5° (c 0.4, $CHCl_3$)}. The spectral data ($^1H$, $^{13}C$ NMR and IR) were identical in all aspects with those of the natural glycerol **1a**.[6]




Scheme: a. - $FSO_3H$ - *i*-$PrNO_2$, -78° C, 45 min; b. - $(COCl)_2$ - $C_6H_6$, 25° C (2 h); 45° C (30 min); c. - **8a**, NaH, $CH_2Cl_2$, 0° C, 20 min; d. - **8b**, NaH, $CH_2Cl_2$, 0° C, 15 min; e. - $H_2SO_4$ - MeOH, r. t.

The same synthetic approach led to glycerol **3**, which is the enantiomer of the natural glycerol **2a**.[8] The chloride **7** was coupled with (+)-1,2-O-isopropylidene-*sn*-glycerol **8b** (NaH, $CH_2Cl_2$, 0° C, 15 min) and afforded, after chromatographic purification on silica gel column (petr.ether - $Et_2O$ = 19:1), in good overall yield from **6** (85%) the acetonide **10** [18] [oil, $[\alpha]_D$ -24.0° (c 0.4, $CHCl_3$)]. Deprotection of the acetonide **10** in acid conditions (0.006 M $H_2SO_4$ - $CH_3OH$; r.t., 3.5h) afforded the glycerol **3** [19] [m.p. 135-136° C (from $Et_2O$ - petr.ether), $[\alpha]_D$ -51.8° (c 0.25, $CHCl_3$]. All spectral data ($^1H$, $^{13}C$ NMR and IR) were identical with those of the natural glycerol **2a** [8] with the exception of the CD spectra that display opposite profiles (**3**, negative

maximum at 213.2 nm; **2a**, positive maximum at 214.4 nm). In particular, the $^1$H NMR shape (fig.1) of the protons at C-21 are sufficiently diagnostic to distinguish between the two diastereoisomers **1a** and **3**.

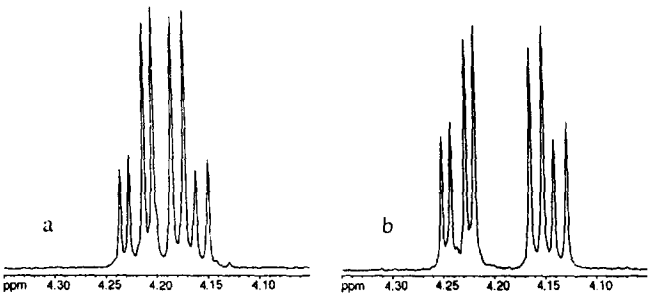



Fig. 1:
Partial $^1$H NMR spectrum ($CDCl_3$, 500 MHz) of **1a** (a) and **3** (b).

In conclusion, the synthesis of the natural 1-diterpenoid acyl-*sn*-glycerol **1a** and of its $C_{22}$ epimer, 3-diterpenoid acyl-*sn*-glycerol **3**, was carried out in four steps via 13*E*-labd-8(9),13-dienic acid **4** in overall yields 64% and 69%, respectively. The high output of this short synthesis opens an easily accessible way to deeply investigate the biological properties of acylglycerols esterified in position either 1-*sn* or 3-*sn* with diterpenoic acids. Very recently, the first synthesis of marine terpenoid glyceride esters has been reported [10] to confirm the structures of tanyolides A and B, two fish deterrent acylglycerols esterified in position 2-*sn* by monocyclofarnesoic acid.

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14. **6**: (a) IR (liquid film) $\nu_{max}$ 1715, 3500 $cm^{-1}$. (b) $^1H$ NMR (400 MHz, $CDCl_3$, δ): 0.82 (s, 3H, $CH_3$-18), 0.86 (s, 3H, $CH_3$-19), 0.91 (s, 3H, $CH_3$-20), 0.97 (s, 3H, $CH_3$-17), 1.67 (s, 3H, $CH_3$-16), 2.93 (br s, 1H, H-14), 5.55 (br s, 1H, H-12).
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16. The compound **7** was used in the next step without purification. IR (liquid film) $\nu_{max}$ 790, 1720, 1800, 2930, 3450 $cm^{-1}$.
17. **9**: (a) IR (liquid film) $\nu_{max}$ 860, 1050, 1160, 1210, 1730 $cm^{-1}$. (b)$^1H$ NMR (400 MHz, $CDCl_3$, δ): 0.81 (s, 3H, $CH_3$-18), 0.86 (s, 3H, $CH_3$-19), 0.90 (s, 3H, $CH_3$-20), 0.94 (s, 3H, $CH_3$-17), 1.37 (s, 3H, $CH_3$ acetonide), 1.43 (s, 3H, $CH_3$ acetonide), 1.60 (s, 3H, $CH_3$-16), 1.92-1.99 (m, 2H, $CH_2$-11), 2.96 (br s, 1H, H-14), 3.76 (dd, *J* = 6 and 8.5 Hz, 1H, H-23), 4.08 (dd, *J* = 6 and 8.5 Hz, 1H, H-23), 4.13 (dd, *J* = 5 and 6.5 Hz, 1H, H-21), 4.19 (m, 1H, H-22), 4.31 (dd, *J* = 5 and 11 Hz, 1H, H-21), 5.51 (br s, 1H, H-12).
18. **10**: (a) IR (liquid film) $\nu_{max}$ 850, 1060, 1170, 1220, 1735 $cm^{-1}$. (b) $^1H$ NMR (400 MHz, $CDCl_3$, δ): 0.81 (s, 3H, $CH_3$-18), 0.86 (s, 3H, $CH_3$-19), 0.90 (s, 3H, $CH_3$-20), 0.94 (s, 3H, $CH_3$-17), 1.36 (s, 3H, $CH_3$ acetonide), 1.43 (s, 3H, $CH_3$ acetonide), 1.59 (s, 3H, $CH_3$-16), 1.97-2.06 (m, 2H, $CH_2$-11), 2.94 (br s, 1H, H-14), 3.77 (dd, *J* = 6 and 8.5 Hz, 1H, H-23), 4.08 (dd, *J* = 6 and 8.5 Hz, 1H, H-23), 4.13 (dd, *J* = 6 and 10 Hz, 1H, H-21), 4.17 (m, 1H, H-22), 4.31 (dd, *J* = 6 and 12 Hz, 1H, H-21), 5.51 (br s, 1H, H-12).
19. **3**: (a) IR (liquid film) $\nu_{max}$ 1170, 1465, 1735, 2910, 3300 $cm^{-1}$. (b) CD, $[\Theta]_{213}$ (EtOH) = -6.292. (c)$^1H$ NMR (500 MHz, $CDCl_3$, δ): 0.81 (s, 3H, $CH_3$-18), 0.86 (s, 3H, $CH_3$-19), 0.91 (s, 3H, $CH_3$-20), 0.94 (s, 3H, $CH_3$-17), 1.60 (s, 3H, $CH_3$-16), 1.91-1.96 (m, 2H, $CH_2$-11), 2.16 (br s, 1H, OH), 2.51 (br s, 1H, OH), 2.96 (br s, 1H, H-14), 3.61 (dd, *J* = 5 and 11 Hz, 1H, H-23), 3.71 (d, *J* = 11 Hz, 1H, H-23), 3.94 (br s, 1H, H-22), 4.14 (dd, *J* = 7 and 12 Hz, 1H, H-21), 4.24 (dd, *J* = 7 and 12 Hz, 1H, H-21), 5.53 (br s, 1H, H-12). (d)$^{13}C$ NMR ($CDCl_3$, δ): 39.86 (C-1, t), 18.63* (C-2or C-6, t), 41.87 (C-3, t), 33.16 (C-4, s), 56.43 (C-5, d), 18.44* (C-6 or C-2, t), 41.87 (C-7, t), 37.41 (C-8, s), 54.24 (C-9, d), 36.61 (C-10, s), 22.63 (C-11, t), 124.44 (C-12, d), 128.44 (C-13, s), 62.56 (C-14, d), 173.53 (C-15, CO), 21.22 (C-16, q), 15.60 (C-17, q), 21.66 (C-18, q), 33.41 (C-19, q), 15.75 (C-20, q), 63.48 (C-21, t), 70.33 (C-22, d), 65.10 (C-23, t). (e) MS, *m/z* (relative intensity, %): 378 ($M^+$, 6), 363(3), 347(5), 286(43), 258(34), 243(28), 192(100), 177(98), 95(86).


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