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Regioselective Synthesis of Diterpenoid 1,2-Diacyl-*sn*-Glycerides

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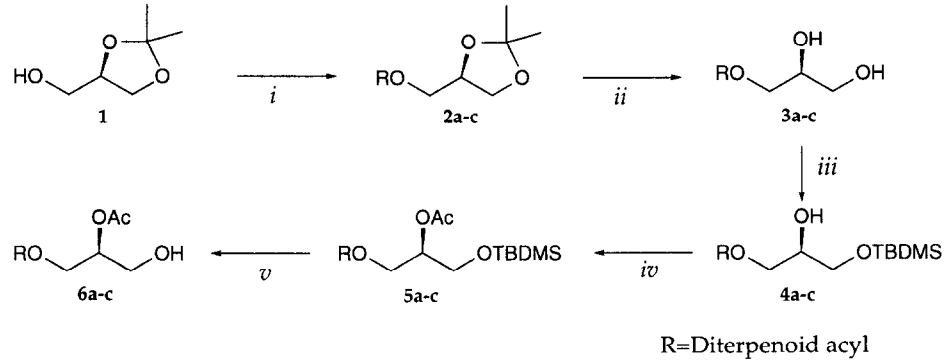
Abstract: The regioselective synthesis of optically active 1-diterpenoid acyl-2-acetyl-*sn*-glycerols is reported. The products are obtained by acylation of 2,3-isopropylidene-*sn*-glycerol. The key reaction is the deprotection of 1,2-diacyl-3-TBDMS-*sn*-glycerides by Lewis acid based treatment with $PdCl_2(CH_3CN)_2$ in acetone. © 1997 Elsevier Science Ltd.

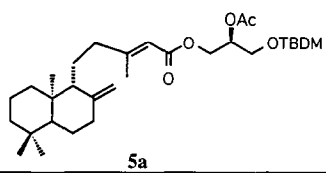
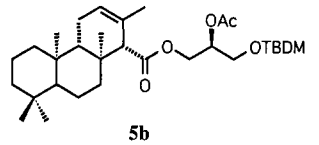
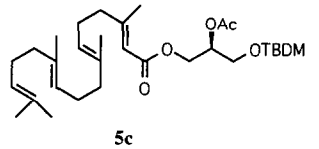
The 1,2-diacyl-O-*sn*-glycerols are key tools in many protein kinase C-mediated events including gene expression, cell proliferation and down-regulation of receptors.[3] Besides the common fatty acyl esters of glycerol, in the last years, many compounds of an unusual group of 1,2-diacylglycerides have been isolated from the skin of dorid nudibranchs.[4-8] Generally, such products show a terpenoid acid linked to the 1-position of glycerol further esterified at C-2 or C-3 with an acetyl group. Diterpenoid glyceryl esters are probably synthesized *de novo* [9] by the nudibranchs and involved in the defensive strategy of the molluscs.[4,7] Recent studies have demonstrated that the diterpenoid 1,2-diacyl-*sn*-glycerols are much more potent activators of PKC than the linear long chain analogs, such as 1,2-dioleoyl-*sn*-glycerol.[10] In spite of the interest for the pharmacological properties of such natural products, a few synthetic studies have been reported.[7,11] Here, we describe an easy and efficient way to prepare 1-diterpenoid acyl-2-acetyl-*sn*-glycerides starting from the 2,3-isopropylidene-*sn*-glycerol (**1**) (Scheme 1).



Scheme 1. Reagents: *i.* Diterpenoid acyl chloride (RCl), NaH, dry CH_2Cl_2, 0° C; *ii.* H_2SO_4, MeOH, 2h, r.t.; *iii.* 3 eq. TBDMSiCl, dry Pyridine, 12h, r.t.; *iv* Ac_2O, dry Pyridine, 2h, r.t.; 1 eq. $PdCl_2(CH_3CN)_2$, acetone, ca. 1h, r.t.

According to the procedure described by Ungur *et al.*,[11] the optically active monoacyl derivatives **2a-c** were obtained from the free diterpenoid acids.[12] The hydrolysis of the acetonide intermediates gave in good yields the corresponding diols **3a-c** that, after selective protection at C-1 by *t*-butyl-dimethylsilyl chloride (TBDMSCl), were acetylated in dry pyridine. The crucial step of the synthetic pathway is the deprotection of the primary alcoholic function. In fact, the removal of the protective group is often matched with the quick migration of the acetyl moiety *via* an intramolecular transesterification process. Thus, even if the reaction is carried out under mild conditions (data not reported), the final product is usually the thermodynamically more stable 1,3-diacylglyceride. Acidic removal of sylil protective group is well known.[13] Some times ago, it was reported that the *t*-butyldimethylsilyl ethers are susceptible to easy hydrolysis by treatment with catalytic amount of Pd (II).[14] Under these conditions, compounds **5a-c** gave the corresponding 1,2-diacylglycerides (**6a-c**) as minor components of mixtures containing 1,2- and 1,3-diacyl derivatives in a 1:8 ratio. The TLC analysis was able to monitor the progressive transformation, in the acidic medium, of 1,2-diacylglycerol to 1,3-diacyl isomers. All attempts to stop the reaction at the initial compounds (**6a-c**) have led to very low (ca. 10%) yields.

Table 1.Deprotection of 1,2-Diacyl-*sn*-glycerides **5a-c** by Equimolar Amount of $PdCl_2(CH_3CN)_2$ in Acetone.

	% Conversion[a]	1,2-diacyl	1,3-diacyl
 **5a**	100	78[b]	22[b]
 **5b**	95	80[b]	15[b]
 **5c**	100	83[c]	17[c]

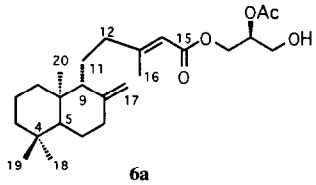
[a]Determined by SiO_2-TLC and ^{1}H-NMR spectrum of the reaction mixture; [b]Determined after purification on HPLC (Spherisorb 5 SW;*n*-hexane/ethyl acetate 8:2); [c]Determined on the basis of the ^{1}H-NMR spectrum of the reaction mixture.

The synthesis of the faster-formed products has been promoted by treating the silyl ether (**5a-c**) with equimolar amounts of Pd (II) at room temperature. The reaction is completed in 1h and the excellent yields of 1,2-diacylglycerol range between 78% and 83% (see Table 1).

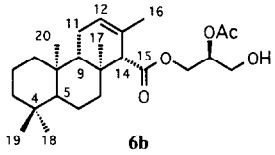
The glyceryl derivatives of copalic (**6a**)[15] and isocopalic (**6b**)[16] acids were obtained in good yields. The compound **6b** was identical in all respects to the natural product previously isolated from *Archidoris carvi*[6] and

Doris verrucosa .[8] The working-up of (*E,E,E*)-geranylgeranoic derivative (**6c**)[17] was more difficult than expected. The selective deprotection of the silyl intermediate **5c** afforded the required 1,2-diacylglycerol **6c** in very high yield (ca. 83%), but the chromatographic purification resulted in the 2,3 migration of the acetyl group which gave the 1,3-diacyl isomer as minor component (30%).

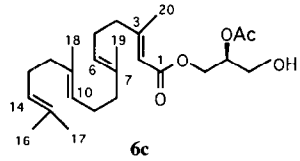
In summary, the natural glyceride **6b** and the compounds **6a** and **6c** were synthesised by a quick and stereospecific method based on the $PdCl_2(CH_3CN)_2$ deprotection of 1,2-diacyl-3-TBDMS-*sn*-glycerol precursors. The acidic removal of the silyl group affords selectively 1,2-diacyl-*sn*-glycerides in good yields.



6a



6b



6c

The reaction can be kinetically or thermodynamically controlled in order to obtain 1,2- or 1,3-diacyl derivatives, respectively. Although applied only to the synthesis of the glyceride derivatives of terpenoid acids **a-c**, the here reported route can be regarded as a general approach to the synthesis of bioactive glycerol esters.

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12. **a**. Copalic acid was obtained by the saponification of the corresponding methyl ester isolated from commercial "Copaiva Balsam" purchased from Lukas, W. Germany, as previously described in ref 8.

b. Isocopalic acid was synthesized by superacidic cyclization of the copalic acid, according to the procedure previously reported in ref. 11 for the *ent*-isocopalic acid.
c. (*E,E,E*)-Geranylgeranoic acid was obtained from (*E,E*)-farnesylacetone, as already reported by Vlad *et al.* in ref. 18.

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15. 1-Copaloyl-2acetyl-*sn*-glycerol (**6a**): 8.0 mg; $[\alpha]_D$ -18.8° ($CHCl_3$, 0.4), IR (liquid film) ν_{max} 3482,2945, 2842, 1745, 1722, 1653, 1223, 1146 cm^{-1}; UV (EtOH) λ_{max} 219 (5200), 205 (4705); EIMS, *m/z* (%): 420 (25), 405 (60), 305 (35) 288 (20), 117 (80), 82 (100); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.66 (1H, bs, H-14), 5.08 (1H, apparent quintet, *J*=5.0 Hz, H-2'), 4.84 (1H, bs, H-17a), 4.48 (1H, bs, H-17b), 4.30 (2H, dAB quartet, *J*=15.0 and 4.6 Hz, H_2-1'), 3.74 [2H, dd, *J*=6.2 and 5.4 Hz (simplified to d, *J*=5.4 Hz, after addition of D_2O), H_2-3'], 2.39 (1H, m, H-7a), 2.30 (1H, m, H-12a), 2.16 (3H, bs, H_3-16), 2.11 (3H, s, Ac), 1.97 (2H, m, H-7b and H-12b), 1.75 (2H, m, H-1a and H-6a), 1.65 (1H, m, H-11a), 1.55 (3H, m, H_2-2 and H-9), 1.50 (1H, m, H-11b), 1.40 (1H, m, H-3a), 1.32 (1H, m, H-6b), 1.17 (H, ddd, *J*= 13.2, 13.0 and 3.8 Hz, H-3b), 1.08 (1H, dd, *J*= 12.6 and 2.4 Hz, H-5), 1.00 (1H, ddd, *J*= 12.8, 12.7 and 2.8 Hz, H-1a), 0.87 (3H, s H_3-19), 0.80 (3H, s, H_3-18), 0.68 (3H, s, H_3-20); ^{13}C-NMR (125.77 MHz, $CDCl_3$): δ 170.6 (s, Ac), 166.7 (s, C-15), 163.0 (s, C-13), 148.3 (s, C-8), 114.3 (d, C-14), 106.3 (t, C-17), 72.5 (d, C-2'), 61.4 (t, C-1' or C-3'), 61.1 (t, C-3' or C-1'), 56.2 (d, C-9), 55.5 (d, C-5), 42.1 (t, C-3), 40.0 (t, C-12), 39.7 (s, C-10), 39.1 (t, C-1), 38.3 (t, C-7), 33.6 (s, C-4), 33.6 (q, C-19), 24.4 (t, C-6), 21.7 (q, C-18), 21.5 (t, C-11), 21.1 (q, Ac), 19.4 (t, C-2), 19.1 (q, C-16), 14.5 (q, C-20). Numbering is according to Ref. 8.
16. 1-Isocopaloyl-2acetyl-glycerol **6b**: 4.2 mg; {$[\alpha]_D$ +10.2° ($CHCl_3$, 0.17), $[\alpha]_D$ lit.[6] +66.9° ($CHCl_3$, 0.07). The optical activity of **6b** was measured many times giving the reported mean value. It is likely that the previously indicated $[\alpha]_D$[6] was affected by a systematic error due to the little amount of glyceride purified from the molluscs}; UV, IR, θ, MS and ^{1}H-and ^{13}C-NMR data are identical with those previously reported in ref. 6.
17. 1-Geranylgeranoyl-2acetyl-*sn*-glycerol (**6c**): 7.0 mg; $[\alpha]_D$ -5.7° ($CHCl_3$, 0.2), IR (liquid film) ν_{max} 3467, 2965, 2926, 2857, 1738, 1722, 1637, 1227, 1143 cm^{-1}; UV (EtOH) λ_{max} 203 (5714); EIMS, *m/z* (%): 420 (10), 286 (20), 243 (10), 117 (40), 69 (100), 43 (70); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.69 (1H, bs, H-2), 5.09 (4H, m, H-6, H-10, H-14 and H-2'), 4.30 (2H, dAB quartet, *J*= 12.1 and 4.8 Hz, H_2-1'), 3.73 (2H, m, H_2-3'), 2.18 (3H, bs, H_3-20), 2.17 (4H, m, H-4 and H-5), 2.11 (3H, s, Ac), 2.06 (4H, m, H_2-9 and H_2-13), 1.98 (4H, m, H_2-8 and H_2-12), 1.68 (3H, bs, H_3-16), 1.61 (3H, bs, H_3-17)[a], 1.60 (3H, s, H_3-18)[a] and 1.60 (3H, s H_3-19)[a]; ^{13}C-NMR (125.77 MHz, $CDCl_3$): δ 170.6 (s, Ac), 166.7 (s, C-1), 162.0 (s, C-3), 136.3 (s, C-7),[b] 135.1 (s, C-11),[b] 131.3 (s, C-15), 124.3 (d, C-14), 124.1 (d, C-10), 122.7 (d, C-6), 114.7 (d, C-2), 72.5 (d, C-2'), 61.3 (t, C-1'),[c] 61.1 (t, C-3'),[c] 41.1 (t, C-4), 39.7 (t, C-8 and C-12), 26.8 (t, C-13), 26.4 (t, C-9), 26.0 (t, C-5), 25.7 (q, C-16), 21.0 (q, Ac), 19.1 (q, C-20), 17.7 (s, C-17), 16.0 (q, C-18 and C-19). Values with the same letter are interchangeable. Numbering is according to Ref. 18.
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