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The absolute stereochemistry of a diterpene from *Ballota aucheri*

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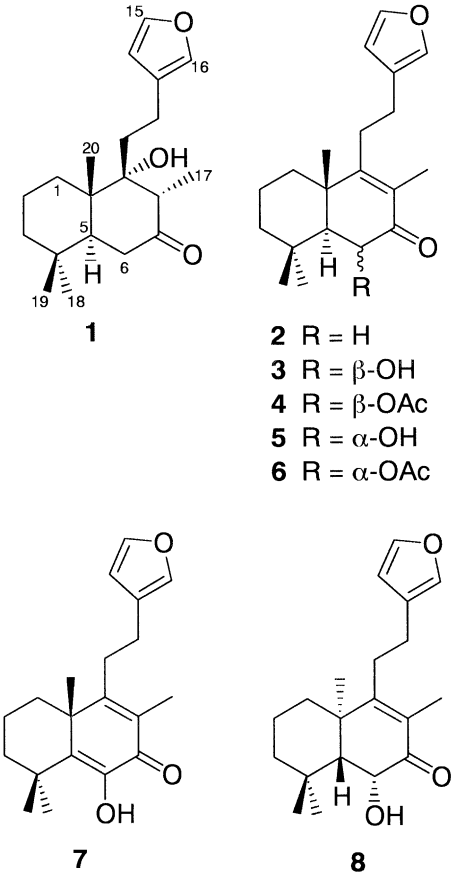
Abstract

The semi-synthetic transformation of hispanolone, isolated from *Ballota africana,* into 6β-hydroxy-15,16-epoxylabda-8,13(16),14-trien-7-one has established an *ent*-labdane absolute stereochemistry for a diterpene metabolite originally isolated from *B. aucheri*.

Keywords: *Ballota africana*; *Ballota aucheri*; Lamiaceae; Diterpene; Furanolabdane; Hispanolone; Hispanone; 6β-Hydroxy-15,16-epoxylabda-8,13(16),14-trien-7-one; 6α-Hydroxy-15,16-epoxylabda-8,13(16),14-trien-7-one; 6β-Acetoxy-15,16-epoxylabda-8,13(16),14-trien-7-one; 6α-Acetoxy-15,16-epoxylabda-8,13(16),14-trien-7-one

1. Introduction

The genus *Ballota* (Lamiaceae) consists of about 33 species growing mainly in the Mediterranean region and adjoining Asia Minor (Codd, 1985). Phytochemical investigations of about a third of these species have revealed that furanolabdane diterpenes are the predominant natural products (recently reviewed by Seidel et al., 1999). The indigenous southern African species, *Ballota africana*, is a good source of the furanolabdane, hispanolone (**1**), and we have demonstrated that this compound is a useful starting point for semi-synthetic transformations (Davies-Coleman and Rivett, 1993). Recently we have used the dehydrated analogue of **1**, hispanone (**2**), as a model compound to investigate the preparation of 6β,7α-hydroxylated labd-8-enes. Interestingly, one of the compounds prepared during this investigation, 6β-hydroxy-15,16-epoxylabda-8,13(16),14-trien-7-one (**3**), is a natural product originally isolated from *B. aucheri* by Rustaiyan et al. (1995). However, although the NMR data of synthetic **3** was compatible with those reported for the natural product, the sign of the optical rotation of **3** was opposite to that of the naturally occurring diterpene. In this paper we report the synthesis and spectroscopic data for **3**, its acetylated derivative **4** and their C-6 epimers (**5** and **6**).



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2. Results and discussion

The hispanolone used in this study was isolated from the aerial parts of local specimens of *B. africana* (0.8% dry weight) as described by Davies-Coleman and Rivett (1993). Treatment of **1** with catalytic iodine in refluxing benzene gave hispanone (**2**) as pale yellow needles in 87% yield. α′-Oxidation of the α,β-unsaturated ketone **2** was achieved via Vedejs' oxidation (Vedejs, 1974; Vedejs et al., 1978), in which the lithium dienolate of hispanone was treated with two molar equivalents of oxodiperoxymolybdenumpyridinehexamethylphosphoramide (MoOPH) to yield, after semi-preparative HPLC, 6β-hydroxy-15,16-epoxylabda-8,13(16),14-trien-7-one (**3**, 21%), 6α-hydroxy-15,16-epoxylabda-8,13(16),14-trien-7-one (**5**, 43%), 6-hydroxy-15,16-epoxylabda-5,8,13(16),14-tetraen-7-one (**7**, 5%) and unreacted hispanone (13%).

The structures of **3**, **5** and **7** were assigned from their respective spectroscopic data, and the stereochemistry at C-6 of **3** and **5** confirmed by the H-5–H-6 coupling constants ($J_{5,6}$ = 3.6 and 13.1 Hz, respectively) and 1D gradient selected NOESY experiments (Table 1). Although there was reasonable agreement (except concerning C-20, Table 2) between the NMR, IR and MS data obtained for 3 and those reported for the natural product isolated from *B. aucheri* (Rustaiyan et al., 1995), there was a discrepancy in their optical rotations. While Rustaiyan et al. (1995) reported an optical rotation of −34° for the natural product, we obtained optical rotations in the range +17° to +20° for our synthetically derived **3**. The optical rotation of the 6α-epimer (**5**) was +51°. From these data we conclude that the natural product from *B. aucheri* has an *ent*-labdane absolute stereochemistry (**8**) and not a labdane stereochemistry as originally proposed by Rustaiyan et al. (1995).

We also prepared the C-6 diastereomeric α′-acetoxy enones **4** and **6** (obtained pure in 30 and 57% yield respectively after semi-preparative HPLC) through manganese (III) acetate oxidation of **2** (Williams and Hunter, 1976; Dunlap et al., 1984). Although both **4** and **6** had previously been prepared from **1** via a different route by Garcia-Alvarez et al. (1981), only limited data for the equatorial acetate **6** has been reported (Garcia-Alvarez et al., 1981). Once again, the C-6 stereochemistries of the two products were assigned through analysis of 2D NOESY data and recourse to their H-5–H-6 coupling constants ($J_{5,6}$ = 3.3 and 13.4 Hz, respectively). With the acetate **4** in hand, we then treated **3** with acetic anhydride in anhydrous pyridine to yield an oil that was identical to 6β-acetoxy-15,16-epoxylabda-8,13(16),14-trien-7-one (**4**) by ^{1}H and ^{13}C NMR and gave an optical rotation ($[\alpha]_D = -53°$) which was consistent with that obtained for **4** derived from manganese (III) acetate acetoxylation of hispanone ($[\alpha]_D = -61°$).

Table 1
Selected NOE enhancements observed for compounds **3** and **5**

Irradiated ^{1}H	NOE correlated protons	
	3	**5**
H-5	H-6, H_3-18	H_3-18
H-6	H-5, H_3-18, OH	H_3-19, H_3-20, OH
H_3-18	H-5, H-6, H_3-19	H-5, H_3-19, OH
H_3-19	H_3-18, H-$_3$20	H_3-18, H_3-20, H-6
H_3-20	H_3-19	H_3-19
OH	H-6	H-6, H_3-18

3. Experimental

3.1. General

The ^{1}H and ^{13}C NMR spectra were recorded on a Brüker 400 MHz Avance NMR spectrometer using $CDCl_3$ as the solvent, referenced at δ 7.25/77.0 ppm. The HRFABMS data were acquired by Professor Louis Fourie of the University of Potchefstroom on a Micromass 70-70E spectrometer and the LREI mass spectra (70 eV) were obtained on a Finnegan-Matt GCQ mass spectrometer by Mr. Aubrey Sonemann of Rhodes University. The IR data for all compounds were obtained from thin films on NaCl discs using a Perkin-Elmer 2000 FTIR spectrometer. All rotations were

Table 2
^{13}C and ^{1}H NMR data for compound **3**[a]

Carbon	δ_C[b]	δ_H[c]
1	37.5 (*t*)	1.37 (1H, *td*, 12.6, 3.8) 1.90 (1H, *bd*, 12.2)
2	18.8 (*t*)	1.60 (1H, *m*) 1.81 (1H, *tt*, 13.6, 3.3)
3	43.4 (*t*)	1.23 (1H, *td*, 13.3, 3.8) 1.44 (1H, *bd*, 14.3)
4	34.2 (*s*)	
5	53.3 (*d*)	1.57 (1H, *d*, 3.6)
6	71.2 (*d*)	4.32 (1H, *dd*, 3.6, 2.6)
7	199.4 (*s*)	
8	128.5 (*s*)	
9	169.6 (*s*)	
10	41.1 (*s*)	
11	30.7 (*t*)	2.51 (2H, *m*)
12	24.4 (*t*)	2.57 (2H, *m*)
13	124.5 (*s*)	
14	110.6 (*d*)	6.31 (1H, *bs*)
15	143.1 (*d*)	7.37 (1H, *t*, 1.6)
16	138.7 (*d*)	7.27 (1H, *bs*)
17	11.7 (*q*)	1.86 (3H, *s*)
18	32.4 (*q*)	1.06 (3H, *s*)
19	24.0 (*q*)	1.31 (3H, *s*)
20[d]	22.2 (*q*)	1.38 (3H, *s*)
OH		2.25 (1H, *d*, 2.6)

[a] Values in ppm, spectra acquired in $CDCl_3$.
[b] 100 MHz; multiplicity by DEPT.
[c] 400 MHz; integrals, multiplicity and coupling constants (Hz) in parentheses.
[d] Lit. (Rustaiyan et al., 1995); δ_C 18.6 (*q*), δ_H 1.42 (*s*).

recorded on a Perkin-Elmer 141 polarimeter as $CHCl_3$ solns. Melting points were determined using a Reichert hot-stage microscope and are uncorrected. Reactions with exclusion of moisture were performed in flame-dried glassware under N_2. Immediately prior to their use in dry reactions, Et_2O, THF and C_6H_6 were distilled from sodium metal/benzophenone ketyl. Pyridine was distilled at reduced pressure from KOH and stored over 4 Å molecular sieves under nitrogen. General laboratory solvents were distilled from glass before use. The oxodiperoxymolybdenum·pyridine·hexamethyl - phosphoramide (MoOPH) used was prepared and stored as described by Vedejs et al. (1978). Reactions were monitored by analytical thin layer chromatography on DC-Plastikfolien Kieselgel 60 F_{254} plates visualised under UV light (254 nm) and developed by spraying with 10% H_2SO_4 in MeOH followed by heating. Open column chromatography was performed using Kieselgel 60 (70–230 mesh) silica gel and flash chromatography was performed using Kieselgel 60 (230–400 mesh) silica gel. Normal phase semi-preparative HPLC separations were performed on a Whatman Magnum 9 Partisil 10 column (9.5×500 mm) with an eluent flow rate of 4 mlmin^{-1} and a Waters R401 refractive index detector.

3.2. Dehydration of hispanolone (1)

Hispanolone (**1**, 1.00 g, 3.14 mmol) was dissolved in dry C_6H_6 (100 ml) and 0.1 M I_2 in dry C_6H_6 (1.60 ml, 0.16 mmol, 0.05 eq) added. The resulting pink soln was refluxed under anhydrous conditions (6 h) after which the benzene was removed in vacuo and the residue taken up in Et_2O (40 ml). The Et_2O soln was washed with 5% $Na_2S_2O_3$ (3×25 ml) and H_2O (25 ml), dried ($MgSO_4$) and concentrated to give a brown oil (1.07 g). The crude product was purified by column chromatography on silica gel in hexane–EtOAc (19:1) to give hispanone (**2**, 0.82 g, 2.73 mmol, 87%) as pale yellow needles and hispanolone (**1**, 91 mg, 0.29 mmol, 9%) as a colourless oil.

3.2.1. Hispanone (2)

Fine white needles (from MeOH); mp 60–61 °C, lit. 58–60 °C (Garcia-Alvarez et al., 1981); $[\alpha]_D^{24}$ + 41° (*c* 3.94, $CHCl_3$), lit. + 39.7° (Garcia-Alvarez et al., 1981); IR, ^{1}H NMR, ^{13}C NMR and EIMS consistent with literature values (Garcia-Alvarez et al., 1981); HRFABMS *m*/*z* 301.2167 (calc. for $C_{20}H_{29}O_2$ [(M + H)$^+$], 301.2168).

3.3. Vedejs' oxidation of hispanone (2)

Hispanone (**2**, 300 mg, 1.0 mmol) in THF (5.0 ml) was added dropwise via a cannula to LDA (2.0 M, 1.00 ml, 2.0 mmol, 2 eq) in THF (5.0 ml) at −78 °C. The resulting soln was stirred (−78 °C, 1 h) before MoOPH (870 mg, 2.0 mmol, 2 eq) was added in a single portion using a solids addition tube. The deep red reaction mixture was stirred at −78 °C for 12 h, warmed to 0 °C over 30 min and immediately quenched with satd. aq. Na_2SO_3 (5.0 ml). After stirring for a further 30 min at 0 °C, the mixture was warmed to RT, H_2O (5.0 ml) added and the aqueous and organic phases separated. The aqueous fraction was extracted with Et_2O (3×5 ml) and the combined organic phases washed with 0.5 M HCl (10 ml), 5% $NaHCO_3$ (5 ml) and H_2O (5 ml). Drying ($MgSO_4$), removal of solvent in vacuo and passage of the resulting brown oil (456 mg) through a column of silica in hexane–EtOAc (4:1) yielded a mixture of products as a pale yellow oil (264 mg). Semi-preparative normal phase HPLC of the mixture in 9:1 hexane–EtOAc yielded (in order of elution) 6-hydroxy-15,16-epoxylabda-5,8,13(16),14-tetraen-7-one (**7**, 16 mg, 0.05 mmol, 5%) as a colourless oil, 6α-hydroxy-15,16-epoxylabda-8,13(16),14-trien-7-one (**5**, 137 mg, 0.43 mmol, 43%) as a white crystalline solid, hispanone (**2**, 40 mg, 0.13 mg, 13%) as a yellow crystalline solid and 6β-hydroxy-15,16-epoxylabda-8,13(16),14-trien-7-one (**3**, 65 mg, 0.21 mmol, 21%) as a white crystalline solid.

3.3.1. 6-Hydroxy-15,16-epoxylabda-5,8,13(16),14-tetraen-7-one (7)

Pale yellow oil; $[\alpha]_D^{25}$ −41° (*c* 0.88, $CHCl_3$); IR ν_{max} 3367 (br), 2927, 1624, 1600, 1455, 1384, 1029, 872, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (1H, *br s*, H-15), 7.28 (1H, *br s*, H-16), 6.32 (1H, *br s*, H-14), 2.66 (1H, *m*, H-11a), 2.57 (2H, *m*, H_2-12), 2.53 (1H, *m*, H-11b), 2.05 (1H, *m*, H-1a), 1.98 (3H, *s*, H_3-17), 1.89 (1H, *m*, H-3a), 1.83 (1H, *m*, H-2a), 1.72 (1H, *m*, H-2b), 1.41 (1H, *m*, H-3b), 1.39 (3H, *s*, H_3-18), 1.38 (6H, *s*, H_3-19 and H_3-20) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.7 (*s*, C-7), 165.8 (*s*, C-9), 143.1 (*s*, C-6 and *d*, C-15), 140.5 (*s*, C-5), 138.7 (*d*, C-16), 127.4 (*s*, C-8), 124.4 (*s*, C-13), 110.5 (*d*, C-14), 43.9 (*s*, C-10), 37.3 (*t*, C-3), 35.7 (*s*, C-4), 31.5 (*t*, C-11), 29.4 (*t*, C-1), 28.1 (*q*, C-18), 28.0 (*q*, C-20), 27.6 (*q*, C-19), 23.8 (*t*, C-12), 17.2 (*t*, C-2), 11.6 (*q*, C-17) ppm; EIMS *m*/*z* (rel. int.) 314 [M$^+$] (76), 299 (69), 281 (72), 267 (14), 245 (19), 233 (23), 215 (100), 205 (58), 177 (39); HRFABMS *m*/*z* 315.1960 (calc. for $C_{20}H_{27}O_3$ [(M + H)$^+$], 315.1960).

3.3.2. 6α-Hydroxy-15,16-epoxylabda-8,13(16),14-trien-7-one (5)

White crystalline solid; mp 95–96 °C; $[\alpha]_D^{25}$ + 51° (*c* 4.29, $CHCl_3$); IR ν_{max} 3437 (br), 2924, 2855, 1660, 1464, 1345, 1315, 1118, 874, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (1H, *t*, *J* = 1.6 Hz, H-15), 7.26 (1H, *s*, H-16), 6.29 (1H, *d*, *J* = 0.8 Hz, H-14), 4.38 (1H, *dd*, *J* = 13.1, 2.0 Hz, H-6), 2.54 (2H, *m*, H_2-12), 2.52 (1H, *m*, H-11a), 2.44 (1H, *m*, H-11b), 1.95 (1H, *br d*, *J* = 12.4 Hz, H-1a), 1.85 (3H, *s*, H_3-17), 1.69 (1H, *d*, *J* = 13.1 Hz, H-5), 1.68 (1H, *m*, H-2a), 1.57 (1H, *m*, H-2b), 1.46 (1H, *br d*, *J* = 13.6 Hz, H-3a), 1.39 (1H, *m*, H-1b), 1.26 (1H, *m*, H-3b), 1.25 (3H, *s*, H_3-20), 1.17 (6H, *s*, H_3-18 and

H_3-19) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.7 (*s*, C-7), 168.9 (*s*, C-9), 143.1 (*d*, C-15), 138.7 (*d*, C-16), 127.4 (*s*, C-8), 124.3 (*s*, C-13), 110.5 (*d*, C-14), 73.3 (*d*, C-6), 56.7 (*d*, C-5), 42.8 (*t*, C-3), 42.5 (*s*, C-10), 36.7 (*t*, C-1), 35.8 (*q*, C-18), 34.0 (*s*, C-4), 30.6 (*t*, C-11), 24.0 (*t*, C-12), 22.0 (*q*, C-19), 19.4 (*q*, C-20), 18.6 (*t*, C-2), 11.6 (*q*, C-17) ppm; EIMS *m/z* (rel. int.) 316 [M^+] (5), 301 (100), 283 (45), 255 (16), 229 (11), 192 (10), 175 (12), 161 (29), 135 (12), 91 (17); HRFABMS *m/z* 317.2117 (calc. for $C_{20}H_{29}O_3$ [$(M+H)^+$], 317.2117).

3.3.3. 6β-Hydroxy-15,16-epoxylabda-8,13(16),14-trien-7-one (3)

White crystalline solid; mp 99–100 °C; $[\alpha]_D^{26}$ +17° (*c* 1.01, $CHCl_3$), lit. −34° (Rustaiyan et al., 1995); IR ν_{max} 3402 (br), 2930, 2856, 1651, 1604, 1470, 1385, 1026, 874, 782 cm^{-1}; ^1H and ^{13}C NMR see Table 2; EIMS *m/z* (rel. int.) 316 [M^+] (10), 314 (15), 301 (63), 283 (46), 255 (29), 203 (68), 192 (100), 175 (47), 161 (94), 151 (53); HRFABMS *m/z* 317.2117 (calc. for C_{20} $H_{29}O_3$ [$(M+H)^+$], 317.2117).

3.4. α′-Acetoxylation of hispanone (2)

Hispanone (**2**, 499 mg, 1.66 mmol) was dissolved in dry C_6H_6 (50 ml), dry $Mn(OAc)_3$ (2.50 g; dried over P_2O_5 at 70 °C and 0.5 mmHg for 6 h immediately prior to use) added and the resulting brown suspension heated under reflux with exclusion of moisture for 72 h. The heterogeneous reaction mixture was then cooled and the fine brown precipitate dissolved by vigorous stirring with 10% aqueous $Na_2S_2O_5$ (30 ml) for 30 min. Conc. HCl (3.0 ml) was added (to give a 0.9 M HCl soln in the aqueous phase) and the mixture stirred for a further 10 min. The organic and aqueous phases were then separated, the aqueous phase thoroughly washed with EtOAc (4×25 ml) and the combined organic phases washed with 5% $NaHCO_3$ (10 ml) and H_2O (10 ml). Drying with $MgSO_4$ and evaporation of the solvent gave a yellow oil (636 mg) that was purified by silica gel column chromatography (7:3 hexane/EtOAc) to yield a 2:1 mixture (by ^1H NMR spectroscopy) of 6α- and 6β-acetoxy-14,15-epoxylabda-8,13(16),14-trien-7-one (**6** and **4**) as a pale yellow oil (529 mg, 1.48 mmol, 89%). Normal phase semi-preparative HPLC of a portion (501 mg) of the diastereomeric mixture in hexane-EtOAc (9:1) afforded the pure acetoxy enones **6** (323 mg) and **4** (169 mg) as colourless oils.

3.4.1. 6α-Acetoxy-14,15-epoxylabda-8,13(16),14-trien-7-one (6)

Colourless oil; $[\alpha]_D^{25}$ +50° (*c* 1.00, $CHCl_3$), lit. +38° (Garcia-Alvarez et al., 1981); IR ν_{max} 2932, 2872, 1747, 1674, 1614, 1470, 1373, 1235, 1025, 874 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36 (1H, *t*, *J* = 1.6 Hz, H-15), 7.26 (1H, *br s*, H-16), 6.29 (1H, *d*, *J* = 0.8 Hz, H-14), 5.64 (1H, *d*, *J* = 13.4 Hz, H-6), 2.55 (2H, *m*, H_2-12), 2.49 (1H, *m*, H-11a), 2.44 (1H, *m*, H-11b), 2.19 (3H, *s*, 6-OAc), 2.04 (1H, *d*, *J* = 13.2 Hz, H-5), 1.99 (1H, *br d*, *J* = 11.6 Hz, H-1a), 1.76 (3H, *s*, H_3-17), 1.68 (1H, *tt*, *J* = 13.6, 3.2 Hz, H-2a), 1.60 (1H, *m*, H-2b), 1.45 (1H, *br d*, *J* = 13.3 Hz, H-3a), 1.42 (1H, *td*, *J* = 12.9, 3.7 Hz, H-1b), 1.29 (1H, *td*, *J* = 13.6, 4.1 Hz, H-3b), 1.28 (3H, *s*, H_3-20), 1.05 (3H, *s*, H_3-18), 1.01 (3H, *s*, H_3-19) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.6 (*s*, C-7), 170.4 (*s*, 6-OAc), 166.9 (*s*, C-9), 143.1 (*d*, C-15), 138.7 (*d*, C-16), 128.9 (*s*, C-8), 124.2 (*s*, C-13), 110.5 (*d*, C-14), 74.7 (*d*, C-6), 53.8 (*d*, C-5), 42.7 (*t*, C-3), 42.6 (*s*, C-10), 36.5 (*t*, C-1), 35.6 (*q*, C-18), 33.5 (*s*, C-4), 30.4 (*t*, C-11), 24.1 (*t*, C-12), 21.9 (*q*, C-19), 21.3 (*q*, 6-OAc), 19.9 (*q*, C-20), 18.5 (*t*, C-2), 11.6 (*q*, C-17) ppm; EIMS *m/z* (rel. int.) 358 [M^+] (4), 343 (25), 298 (62), 283 (84), 265 (45), 255 (100), 203 (57), 189 (78), 175 (41), 161 (91); HRFABMS *m/z* 359.2222 (calc. for $C_{22}H_{31}O_4$ [$(M+H)^+$], 359.2222).

3.4.2. 6β-Acetoxy-14,15-epoxylabda-8,13(16),14-trien-7-one (4)

Colourless oil; $[\alpha]_D^{26}$ −61° (*c* 1.04, $CHCl_3$); IR ν_{max} 2932, 2863, 1747, 1668, 1606, 1471, 1370, 1230, 1027, 874, 600 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37 (1H, *t*, *J* = 1.6 Hz, H-15), 7.27 (1H, *br s*, H-16), 6.31 (1H, *d*, *J* = 0.8 Hz, H-14), 5.79 (1H, *d*, *J* = 3.3 Hz, H-6), 2.58 (2H, *m*, H_2-12), 2.53 (1H, *m*, H-11a), 2.50 (1H, *m*, H-11b), 2.06 (3H, *s*, 6-OAc), 1.96 (1H, *br d*, *J* = 12.5 Hz, H-1a), 1.85 (3H, *s*, H_3-17), 1.77 (1H, *tt*, *J* = 13.8, 3.3 Hz, H-2a), 1.76 (1H, *d*, *J* = 3.3 Hz, H-5), 1.62 (1H, *dt*, *J* = 14.1, 3.5 Hz, H-2b), 1.46 (1H, *dd*, *J* = 13.2, 1.2 Hz, H-3a), 1.42 (3H, *s*, H_3-20), 1.37 (1H, *td*, *J* = 13.1, 3.8 Hz, H-1b), 1.24 (1H, *td*, *J* = 13.4, 3.8 Hz, H-3b), 1.05 (3H, *s*, H_3-18), 1.04 (3H, *s*, H_3-19) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.5 (*s*, C-7), 169.6 (*s*, 6-OAc), 168.5 (*s*, C-9), 143.1 (*d*, C-15), 138.7 (*d*, C-16), 129.3 (*s*, C-8), 124.4 (*s*, C-13), 110.5 (*d*, C-14), 70.2 (*d*, C-6), 53.0 (*d*, C-5), 43.6 (*t*, C-3), 41.1 (*s*, C-10), 37.6 (*t*, C-1), 33.8 (*s*, C-4), 32.5 (*q*, C-18), 30.7 (*t*, C-11), 24.3 (*t*, C-12), 23.0 (*q*, C-19), 21.8 (*q*, C-20), 21.4 (*q*, 6-OAc), 18.6 (*t*, C-2), 11.7 (*q*, C-17) ppm; EIMS *m/z* (rel. int.) 358 [M^+] (2), 298 (58), 283 (63), 265 (36), 255 (100), 234 (46), 203 (68), 192 (88), 161 (95), 81(21); HRFABMS *m/z* 359.2222 (calcd for $C_{22}H_{31}O_4$ [$(M+H)^+$], 359.2222).

3.5. Acetylation of 6β-hydroxy-14,15-epoxylabda-8,13(16),14-trien-7-one (3)

Compound **3** (15 mg) was dissolved in pyridine (0.5 ml) and Ac_2O (0.5 ml) and stirred at room temperature over-night before MeOH (1 ml) was added and the resulting soln. concentrated in vacuo to give a yellow oil (22 mg). The reaction product was passed through a small column of silica gel in hexane–EtOAc (7:3) to yield a colourless oil (16 mg, $[\alpha]_D^{27}$ −53°) that was identical to keto-ester **4** in all respects.

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