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# SESQUITERPENE LACTONES AND ALIPHATIC ESTER FROM *CHAMAEMELUM FUSCATUM*

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**Key Word Index**—*Chamaemelum fuscatum*; Compositeae; essential oil; aliphatic ester; sesquiterpene lactones; eudesmanolides.

**Abstract**—A new aliphatic ester, 2-methylene-3-oxobutyl methacrylate was isolated from the essential oil of *Chamaemelum fuscatum*. Four new eudesmanolides, 8-*O*-methacryloylfuscatin, 8-*O*-isobutyrylfuscatin, 3α-hydroxy-8α-methacryloyloxyreynosin and 3α-hydroxy-8α-isobutyryloxyreynosin were obtained from the chloroform extract of this plant.

## INTRODUCTION

Following our studies on the composition of *Chamaemelum fuscatum* (Brot.) Vasc., we have isolated from the essential oil, besides the compounds described in a previous paper [1], *trans*-pinocarveol (**1**) [2] and the new ester, 2-methylene-3-oxobutyl methacrylate (**2**). The structures of compounds **2** and **3** have now been confirmed by synthesis. From the chloroform extract, among previously described compounds [3], we have isolated armefolin (**9**) [4], and four new eudesmanolides **10a**, **11a**, **12a** and **13a**.

## RESULTS AND DISCUSSION

Compound **2** was isolated as a fragant oil from the essential oil. Its mass spectrum had a molecular ion at *m/z* 168 ($C_9H_{12}O_3$). The IR spectrum showed absorption bands of an unsaturated ester (1.725 $cm^{-1}$) and an α,β-unsaturated ketone (1.680 $cm^{-1}$), in accordance with the UV spectrum ($\lambda_{max}$218 nm).

The $^1$H NMR spectrum (Table 1) exhibited the presence of a methylene group conjugated with a carbonyl, a methyl ketone and an allylic methylene geminal to an ester group. These data allowed us to propose the structure 2-methylene-3-oxobutyl methacrylate for compound **2**. This was confirmed by oxidation of ester **4** followed by CuCl–MeOH–$Na_2SO_3$ [5] treatment which afforded compounds **2**, **5** and **6**.

The oxidation of **6** with an aqueous solution of palladium chloride [6], in the presence of CuCl and $O_2$ [7] afforded **3**, its transesterification product **7** as well as the diol **8**. The properties of the synthetic compound **3** were identical with those previously described for the natural product and this fact confirms the structure proposed for this compound.

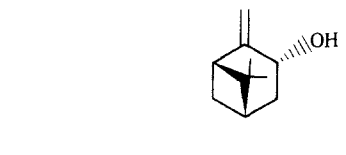
From the chloroform extract armefolin (**9**) and two crystalline products were isolated in addition to the previously described compounds [3].

The first product was a mixture (NMR) that showed in the IR spectrum absorption bands of γ-lactone (1.780 $cm^{-1}$), ester (1.720 $cm^{-1}$) and hydroxyl groups (3.420 $cm^{-1}$). The $^{13}$C NMR spectrum (Table 2) had peaks corresponding to four quaternary carbons (carbonylic, olefinic, oxygenated and angular), seven methynes (two of them olefinic and three bearing an oxygenated function), two methylenes (one olefinic) and two methyl groups. Also two sets of less intense signals were observed and assigned to methacrylate and to isobutyrate moieties.

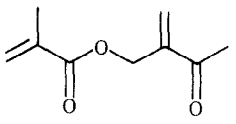
The $^1$H NMR spectrum (Table 3), in addition to the signals of the methacrylate and isobutyrate esters, displayed those of a *trans*-fused α-methylene-γ-lactone, two methyls (one of them angular and the other geminal with a hydroxyl group), an allylic hydrogen geminal with a hydroxy group, a singlet of two olefinic protons and the proton geminal to the equatorial ester group.

By treatment with acetic anhydride–pyridine a monoacetyl derivative was obtained, whose $^1$H NMR spectrum (Table 3) showed the hydrogen geminal to the acetate at δ5.29 and two different signals for the olefinic hydrogens at 5.59 and 5.39. The chromic oxidation of the natural products afforded the mixture of unsaturated ketones whose $^1$H NMR spectrum (Table 3) was very similar to that of arglanin [8] with the presence of the ester group and their geminal hydrogen as a major difference. Thus the chromic oxidation product must be a mixture of 8α-methacryloyloxy, and 8α-isobutyryloxyarglanin, and as a consequence the natural mixture must contain the methacryloyl and isobutyryl esters of 1,4-dihydroxy-*trans*-eudesma-2,11(13)-dien-6,7-olide, which we have called 8-*O*-methacryloyl, and 8-*O*-isobutyrylfuscatin, respectively. The equatorial disposition for the hydroxyl group at C-1 was deduced from the coupling constants of the corresponding geminal hydrogen in the natural alcohols and the acetylation products. The absolute configuration was deduced from the positive molecular rotation as that depicted in the structure figures. The mass spectrum did not show the molecular ion, but two peaks at *m/z* 335 $[M-Me]^+$ for **10a** and 333 $[M-Me]^+$ for **11a** were observed besides the characteristic fragmentations of the ester groups at *m/z* 247 $[M-Me-MacOH]^+$ for **10a** and $[M-Me\text{-}i BuOH]^+$ for **11a**.

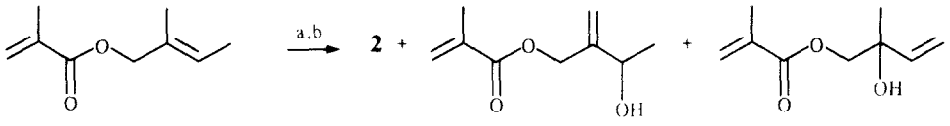
The other product also consisted of a mixture of a methacrylate and isobutyrate esters of the same alcohol. It showed absorption bands of γ-lactone, ester, hydroxyl



**1**

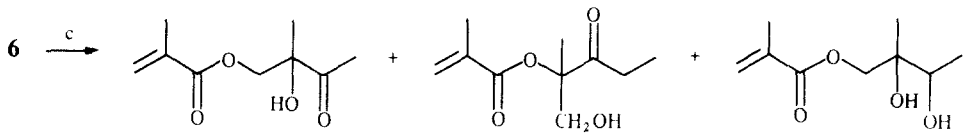


**2**



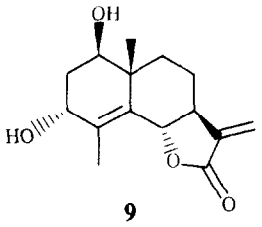
**4** **5** **6**

(a): $^1O_2$; (b): CuCl, MeOH, $Na_2SO_3$

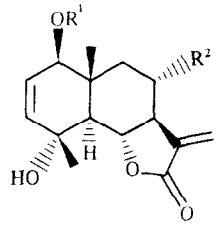


**3** **7** **8**

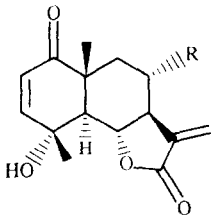
(c): $PdCl_2$, $H_2O$, CuCl, $O_2$



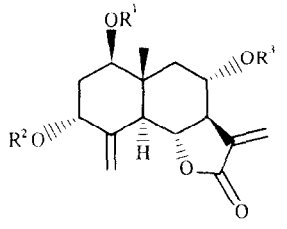
**9**



| | $R^1$ | $R^2$ |
|---|---|---|
| fuscatin | H | OH |
| **10a** | H | OMac |
| **10b** | Ac | OMac |
| **11a** | H | O*i*Bu |
| **11b** | Ac | O*i*Bu |



| | R |
|---|---|
| arglanin | H |
| **10c** | OMac |
| **11c** | OBi*u* |



| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **12a** | H | H | Mac |
| **12b** | Ac | Ac | Mac |
| **13a** | H | H | *i*Bu |
| **13b** | Ac | Ac | *i*Bu |

groups and double bonds in its IR spectrum. The $^{13}C$ NMR spectrum (Table 2) had peaks corresponding to four quaternary carbons (one of them of the lactone and two others of a double bond), six methynes (four bonded to oxygenated functions), four methylenes (two olefines) and a methyl group, besides those less intense peaks of the methacrylate and isobutyrate moieties.

The $^1H$ NMR spectrum (Table 3) showed signals of a 6,7-*trans*-eudesmanolide esterified at C-8, similar to those of mixture **10a** and **11a**. Other signals in this spectrum corresponding to a methyl, two hydrogen atoms geminal with hydroxyl groups ($\delta$3.95 and 4.37, shifted to 5.09 and 5.16, respectively, in the acetylation products), and two olefinic protons (5.21 and 5.04), allowed us to assign the structure of 8α-methacryloyloxy and 8α-isobutyryloxy-1β,3α-dihydroxy-4(15),11(13)dien-6,7-eudesmanolide, which we have named 3α-hydroxy-8α-methacryloyloxyreynosin (**12a**) and 3α-hydroxy-8α-isobutyryloxyreynosin (**13a**), respectively. The stereochemistries of C-1 and C-8 have been deduced from the

Table 1. $^1$H NMR spectra of compounds **2**, **7** and **8** (60 MHz; $CCl_4$; TMS as int. standard; *J* in Hz)

| H | 2 | 7 | 8 |
|---|---|---|---|
| 3 | 5.48 *br s* | 5.55 *br s* | 5.54 *br s* |
| | 6.03 *br s* | 6.05 *br s* | 6.07 *br s* |
| 4 | 1.92 *d* (1.6) | 1.91 *d* (1.6) | 1.96 *d* (1.6) |
| 1 | 4.72 *dd* (6.5; 2) | — | 4.04 *d* (12) |
| | | | 4.26 *d* (12) |
| 3 | — | 2.28 *s* | 3.58 *c* (7) |
| 4 | 2.28 *s* | 1.38 *s* | 1.17 *d* (7) |
| 5 | 5.83 *br s* | 4.18 *d* (12) | 1.18 *s* |
| | 6.03 *br s* | 4.40 *d* (12) | |

coupling constant values of hydrogen atoms H-1 and H-8 with those of the C-2 methylene. The absolute configurations were deduced from their positive molecular rotation.

The mass spectrum of this mixture does not show a molecular ion peak, the highest fragment peaks were observed at *m/z* 335 $[M-Me]^+$ for **13a** and 333 $[M-Me$ for **12a**$]^+$; other significant peaks were *m/z* 244 $[M-H_2O-MacOH]^+$ for **12a** and $[M-H_2O-i$BuOH$]^+$ for **13a** and *m/z* 226 $[M-2H_2O-MacOH]^+$ for **12a** and $[M-2H_2O-i$BuOH$]^+$ for **13a**.

## EXPERIMENTAL

The plant material was collected in April in Zarza de Granadilla (Cáceres, western Spain) and identified by Professor B. Casaseca Mena from the Department of Botany, Salamanca University, Spain, where a specimen is held (Herbarium no. 6679). Mps: uncorr. Optical rotations; $CHCl_3$; UV; EtOH; IR; KBr, discs, or film; $^1$H NMR spectra were recorded at 60 and 200 MHz; $^{13}$C NMR were recorded at 50.3 MHz. MS; 70 eV. Analytical TLC was performed on silica gel G (Merck 7731), prep. TLC on silica gel $PF_{234-236}$ (Merck 7748) and CC on silica gel 60 (Merck 7734); CD were measured in MeOH.

*Hexane extraction and separation of compounds.* The hexane extract of the air-dried material (4 kg) *Chamaemelum fuscatum* (Brot.) Vasc., was steam-distilled and yielded 9.12 g (0.26%) of essential oil. The oil was chromatographed over a silica gel column using hexane with gradually increasing proportions of $Et_2O$ as eluent. The first fraction (hexane) gave: (−)-**ar**-curcumene (530 mg); the second fraction (hexane–$Et_2O$ 19:1) gave 2-methyl-2*E*-butenyl methacrylate (547 mg), 2-methylallyl isobutyrate (105 mg), methyl-*trans*-5-(2-thienyl)pent-4-in-2-enoate (182 mg) and neryl isovalerate (646 mg). The third fraction (hexane–$Et_2O$, 9:1) gave methyl-*trans*-5-(2-thienyl)pent-4-in-2-enoate (35 mg), bisabolen 1,4-endoperoxide (50 mg), **2** (180 mg) and *trans*-pinocarveol (**1**, 100 mg). The fourth fraction (hexane–$Et_2O$, 4:1) gave 2-hydroxy-2-methyl-3-oxobutyl methacrylate (110 mg.) and 2-hydroxy-2-methyl-3-butenyl methacrylate (680 mg). *2-Methylene-3-oxobutyl methacrylate* (**2**). IR $\nu_{max}$ cm$^{-1}$; 3.070, 1.725, 1.680, 1.640, 940, 815. UV $\lambda_{max}$ = 218 (ε; 6.590)nm., $^1$H NMR; Table 1. MS, *m/z* (rel. int.): 168(2), 153(3), 127(22), 125(65), 99(18), 63(93), 43(100), 41(68). *Synthesis of* **2** *from* **4**. To a soln of **4** (300 mg) in *iso*-PrOH (30 ml), Rose Bengal (10 mg), was added, the mixture stirred for 12 hr and exposed to sunlight. When the *iso*-PrOH had been evapd, MeOH (2 ml) and CuCl (45 mg) in MeOH (1.15 ml) and pyridine (0.15 ml) were added at 0° with stirring. When the addition finished the mixture was maintained at room temp. for 24 hr and then an aqueous soln of 10% $Na_2SO_3$ was added until a negative test was obtained of oxidants. Evaporation of the solvent gave 108 mg of product, which by CC gave **2** (10 mg), **5** (30 mg) and **6** (35 mg).

Table 2. $^{13}$C NMR spectra of compounds **10a**–**13a** (150.3 MHz; $CDCl_3$; TMS as int. standard)

| C | 10a + 11a | | 12a + 13a | |
|---|---|---|---|---|
| 1 | 76.8 | | 73.3 | |
| 2 | 130.4 | | 37.5 | |
| 3 | 133.8 | | 73.6 | |
| 4 | 69.4 | | 144.3 | |
| 5 | 53.9 | | 46.7 | |
| 6 | 78.2 | | 76.5 | |
| 7 | 52.7 | | 52.5 | |
| 8 | 70.5 | | 72.9 | |
| 9 | 44.8 | | 42.2 | |
| 10 | 41.9 | | 42.8 | |
| 11 | 135.9 | | 136.7 | |
| 12 | 169.1 | | 169.7 | |
| 13 | 120.0 | | 119.5 | |
| 14 | 24.9 | | 11.9 | |
| 15 | 15.1 | | 113.4 | |
| Mac. | 166.4 | | 167.1 | |
| | 135.8 | | 136.0 | |
| | 126.6 | | 126.4 | |
| | 15.0 | | 14.5 | |
| *i*Bu. | | 176.1 | | 176.2 |
| | | 34.2 | | 34.1 |
| | | 18.2 | | 18.2 |
| | | 18.2 | | 18.9 |

Table 3. $^1$H NMR spectra of compounds **10a–13a**, **10b–13b** and

| H | **10a + 11a** | | **10b + 11b** | |
|---|---|---|---|---|
| 1 | 4.13 br s | | 5.29 *br s* | |
| 2 | 5.59 *s* | | 5.59 *m* | |
| 2′ | | | | |
| 3 | 5.59 *s* | | 5.39 *d* (10) | |
| 5 | 2.17 *d*; 2.14 *d* (11.6) | | — | |
| 6 | 4.17 *dd*; 4.14 *dd* (11.3, 11.3) | | 4.10 *dd* (11.1, 11.1) | |
| 7 | 2.95 *dddd* (11.3, 10.7, 3.0, 2.9) | | 2.95 *m* | |
| 8 | 5.19 *ddd* (10.7, 10.7, 4.1) | | 5.20 *ddd* (10.7, 10.7, 4.1) | |
| 9 | 2.49 *dd*; 2.47 *dd* (12.7, 4.1) | | — | |
| 9′ | 1.55–1.30 *m* | | — | |
| 13 | 6.18 *d* (3.0) | | 6.15 *d* (3.0) | |
| 13′ | 5.59 *d* (2.9) | | 5.58 *d* (2.9) | |
| 14 | 1.06 *s*; 1.04 *s* | | 1.09 *s*; 1.07 *s* | |
| 15 | 1.43 *s* | | 1.42 *s*; 1.41 *s* | |
| 15′ | | | | |
| Mac. | 6.14 *br s* | | 6.14 *br s* | |
| | 5.65 *t* (1.5) | | 5.62 *br s* | |
| | 1.96 *s* | | 2.03 *s* | |
| *i*Bu | | 2.60 *m* | | 2.58 *m* |
| | | 1.22 *d* (6.8) | | 1.20 *d* (6.6) |
| | | 1.19 *d* (6.8) | | 1.15 *d* (6.7) |
| OAc. | | | 2.07 s; 2.06 s | |

*Synthesis of* **3** *from* **6**. $PdCl_2$ (130 mg) and CuCl (360 mg) were added in a stream of $O_2$ with vigorous stirring to DMF (3 ml) and $H_2O$ (0.6 ml). Once the consumption of $O_2$ was finished 2-hydroxy-2-methyl-3-butenol (613 mg) was added and with a stream of $O_2$ stirring was continued for 72 hr. The mixture was poured into 3N HCl and the mixture extracted with $CH_2Cl_2$. The organic layer (500 mg) was chromatographed (silica gel) to afford **3** (22 mg), **7** (40 mg) and **8** (125 mg).

*1-Hydroxymethyl-1-methyl-2-oxopropyl methacrylate* (**7**). IR $\nu_{max}$cm$^{-1}$: 3.450, 1.725, 1.715, 1.650, 1.460, 1.170, 1.035, 950, 920, 820. $^1$H NMR, Table 1. *2,3-Dihydroxy-2-methylbutyl methacrylate* (**8**). IR $\nu_{max}$cm$^{-1}$: 3.460, 1.730, 1.655, 1.185, 1.030, 960, 830, $^1$H NMR, Table 1.

*Chloroform extraction and separation of compounds.* Air-dried plant material (14 kg) were extracted in a Soxhlet with $CHCl_3$ and the neutral fraction of the EtOH–$H_2O$ (2:3) soluble extract was chromatographed (silica gel), developing with $C_6H_6$, $C_6H_6$–$Et_2O$ and $C_6H_6$–AcOEt mixtures of increasing polarity to give among previously described compounds [3]: armefolin (180 mg) and the mixtures **10a + 11a** (200 mg) and **12a + 13a** (100 mg) which were chromatographed and crystallized several times, but no pure **10a**, **11a**, **12a** and **13a** were obtained.

8-*O*-metacryloylfuscatin (**10a**) and 8-*O*-isobutyrylfuscatin (**11a**):

| $\lambda$ | 589 | 578 | 546 | 436 | |
|---|---|---|---|---|---|
| $[\alpha]$ | +58.2 | +59.3 | +65.7 | +93.6 | (*c*, 1.4) |

IR $\nu_{max}$cm$^{-1}$: 3.420, 3.020, 1.780, 1.720, 1.655, 1.120, 980, 920, 820. MS *m/z* (rel. int.): 335 (7), 333 (21), 265 (3), 247 (8), 201 (10), 147 (8), 145 (7), 117 (16), 83 (57), 71 (40), 69 (100). $^1$H NMR, Table 3, $^{13}$C NMR, Table 2. Acetylation of **10a** and **11a**: Treatment of a mixture of **10a** and **11a** with $AC_2O$–pyridine in the usual way afforded a mixture of the acetates **10b** and **11b**. IR $\nu_{max}$cm$^{-1}$: 3.500, 3.020, 1.775, 1.745, 1.720, 1.200, 1.120, 980, 820. $^1$H NMR, Table 3.

**10c–11c** (200 MHz,$CDCl_3$, TMS as int. standard, $J$ in Hz)

| **10c + 11c** | | **12a + 13a** | | **13b** |
|---|---|---|---|---|
| | | 3.95 *dd* | | 5.09 *dd* |
| | | (11.0, 4.5) | | (12.0, 5.0) |
| 5.89 *d* | | 2.04 *ddd* | | 1.95–1.75 *m* |
| (10.4) | | (15.2, 4.5, 3.0) | | |
| | | 1.68 *ddd* | | 1.95–1.75 *m* |
| | | (15.2, 11.0, 3.0) | | |
| 6.60 *d* | | 4.37 *dd* | | 5.46 *t* |
| (10.4) | | (3.0, 3.0) | | (3.0) |
| 2.57 *d*; 2.55 *d* | | 2.82 *br d*; 2.80 *br d* | | 2.75 *d* |
| (11.4) | | (11.1) | | (11.2) |
| 4.23 *dd*; 4.21 *dd* | | 4.14 *dd*; 4.11 *dd* | | 4.05 *dd* |
| (11.4, 11.4) | | (11.1, 11.1) | | (11.2, 11.2) |
| 2.88 *dddd* | | 2.99 *dddd*; 2.93 *dddd* | | 2.90 *dddd* |
| (11.4, 10.8, 3.0, 2.9) | | (11.1, 11.1, 3.0, 2.6) | | (11.2, 10.8, 3.0, 2.9) |
| 5.25 *ddd*; 5.19 *ddd* | | 5.25 *ddd*; 5.21 *ddd* | | 5.16 *ddd* |
| (10.8, 10.8, 4.3) | | (11.1, 11.0, 4.4) | | (10.8, 10.8, 4.2) |
| 2.24 *dd*; 2.17 *dd* | | 2.54 *dd*; 2.46 *dd* | | 2.14 *dd* |
| (12.8, 4.3) | | (12.5, 4.4) | | (13.1, 4.7) |
| — | | 1.38 *m* | | 1.35–1.20 *m* |
| 6.19 *d* | | 6.14 *d* | | 6.12 *d* |
| (3.0) | | (3.0) | | (3.0) |
| 5.59 *d* | | 5.55 *d* | | 5.51 *d* |
| (2.9) | | (2.6) | | (2.9) |
| 1.27 *s*; 1.25 *s* | | 0.87 *s*; 0.85 *s* | | 0.94 *s* |
| 1.57 *d*; 1.56 *d* | | 5.21 *s* | | 5.34 *br s* |
| (1.6) | | | | |
| | | 5.04 *s* | | 5.15 *d* |
| | | | | (1.6) |
| 6.12 *br s* | | 6.14 *br s* | | |
| 5.64 *t* | | 5.66 *t* | | |
| (1.5) | | (1.6) | | |
| 1.96 *s* | | 1.99 *br s* | | |
| | 2.58 *m* | | 2.59 *m* | 2.57 *m* |
| | 1.19 *d* | | 1.21 *d* | 1.21 *d* |
| | (6.9) | | (7.0) | (7.0) |
| | 1.18 *d* | | 1.19 *d* | 1.18 *d* |
| | (6.9) | | (7.0) | (7.0) |
| | | | | 2.04 *s* |
| | | | | 2.02 *s* |

*Oxidation of* **10a** *and* **11a**. The mixture of **10a** and **11a** (20 mg) was dissolved in pyridine (0.1 ml) and $CH_2Cl_2$ (1 ml) and added to a soln of $CrO_3$ (30 mg) in pyridine (0.2 ml) and $CH_2Cl_2$ (0.5 ml). The mixture was stirred for 3 hr in an ice water bath under $N_2$. The oxidation product was chromatographed over silica gel. Elution with $CHCl_3$–MeOH (99:1) afforded 9 mg of the mixture of 8α-methacryloyloxy arglanin (**10c**) and 8α-isobutyryloxyarglanin (**11c**). IR $\nu_{max}cm^{-1}$; 3.340, 3.020, 1.775, 1.720, 1.660, 1.120, 975, 815. CD (MeOH): $\Delta\varepsilon_{212} = +12.0$, $\Delta\varepsilon_{235} = -6.5$, $\Delta\varepsilon_{250} = -3.2$, $\Delta\varepsilon_{330} = -1.6$. $^1$H NMR, Table 3.

3α-Hydroxy-8α-methacryloyloxy reynosin (**12a**) and 3α-hydroxy-8α-isobutyryloxyreynosin (**13a**):

| $\lambda$ | 589 | 578 | 546 | 436 | |
|---|---|---|---|---|---|
| [α] | +100.7 | +104.7 | +118.6 | +174.6 | (*c*, 0.7) |

IR $\nu_{max}cm^{-1}$; 3.440, 3.090, 1.770, 1.720, 1.640, 1.225, 970, 900, 815, MS *m/z* (rel. int.); 335 (7), 333 (5.5), 262 (11), 247 (7), 245 (6), 244 (24), 226 (7), 218 (30), 211 (8), 200 (15), 145 (22), 122 (29), 83 (74), 71 (60), 69 (100). $^1$H NMR, Table 3.

Acetylation of **12a** and **13a** gave the mixture of diacetates **12b** and **13b** which was chromatographed over silica gel–$AgNO_3$. Elution with $C_6H_6$–$Et_2O$ (19:1) afforded 20 mg of 3α-acetoxy-8α-isobutyryloxyreynosin (**13b**): IR $\nu_{max}cm^{-1}$: 3.090, 1.780, 1.740, 1.725, 1.240, 970, 910, 810. $^1$H NMR, Table 3; $^{13}$C NMR, Table 2.

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