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NORLACTARANE AND LACTARANE SESQUITERPENES FROM *LACTARIUS SCROBICULATUS**

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Key Word Index—*Lactarius* scrobiculatus; Basidiomycetes; lactarane and norlactarane sesquiterpenes; 4-*epi*-furandiol.

Abstract-Investigation of ***Lactarius scrobiculatus*** gave two new lactarane lactones, an 8-norlactarane sesquiterpene, which is the first representative of such a class of compounds, and 4-epi-furandiol. A possible biosynthetic mechanism for the formation of these sesquiterpenes is proposed.

INTRODUCTION

We continue to be interested in the chemistry of ***Lactarius scrobiculatus*** because of its peppery taste and the colour of its secreted milky juice which, for ***some*** reasons not yet understood, turns rapidly from white to yellow when it appears at the surface of the fruit-body. This colour change is probably an enzymatic reaction, but so far neither the colourless precursor(s) nor the yellow pigments have been isolated. In previous studies [1–4] *ca* 15 lactarane and secolactarane sesquiterpenes have been isolated by us from ***L. scrobiculatus.*** Later their true origin, whether they are native metabolites or chemical artifacts was questioned [5] as it has been shown that some furanoid lactaranes, at least, can also be formed from velutinal esters, e.g. 5, in the conditions of extraction and work-up of the extracts [6–8]. The present paper describes the isolation of four new sesquiterpenes, (**1–4a**) whose formation was not observed during the chemical degradation of velutinal [8]. Moreover, since their presence has not been detected until now in other ***Lactarius*** extracts, they seem to be formed by some enzyme catalysed reactions which take part in the special chemistry of ***L. scrobiculatus.***

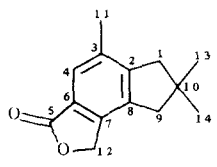
RESULTS AND DISCUSSION

During the separation of the main sesquiterpenes of *L. **scrobiculatus*** [4] ***we*** observed the presence of minor compounds with intermediate polarity between blennin C and monohydroxy furans. Further silica gel CC (see Experimental) allowed us to isolate, in addition to lactones 7-9, identical with our own authentic samples or literature data, compounds **1–4a** and other not yet identified compounds.

The less polar compound 1 is a crystalline solid, mp 93–96°, optically inactive, with molecular formula $C_{14}H_{16}O_2$ (MS, NMR counting of H and C atoms). IR bands were attributed to a y-lactone carbonyl stretching and to an aromatic nucleus. The latter was shown by the ^{13}C NMR spectrum to contain only one secondary carbon; moreover UV absorptions at 279 and 288 nm indicated a phthalide structure, in which the CH_2O group gives rise to a signal at δ 68.71 in the ^{13}C NMR spectrum and to a singlet at δ 5.16 in the ^1H NMR spectrum. The remaining carbon signals were attributed, with the aid of an off-resonance decoupled ^{13}C NMR spectrum, to three methyls, two methylenes and one tetrasubstituted carbon atom. The aromatic methyl (δ 2.31) was allylically coupled with the aromatic CH, while the two CH, groups and the remaining methyls give rise to three distinct singlets at 62.71, 2.74 and 1.20, respectively, in the ‘HNMR spectrum. These features are only compatible with a symmetric (mirror plane) structure where the geminal protons become enantiotopic. These restrictions, and obvious biogenetic considerations, made 1 the structure of choice. This was confirmed also by the appropriate NOE effects: enhancement of only Me-11 (1.3%) by irradiation of H-4; enhancement of only H-9 (1%) by irradiation of H- 12.

The chromatographic separation of compound 2 from 1 was very difficult because of their close polarity; compound 2 was finally obtained pure in a very tiny amount (1.5 mg from *ca.* 35 kg of mushrooms!). Compound 2, $C_{15}H_{16}O_4$ (MS, NMR data) contained an α,β-unsaturated y-lactone group (1760 cm $^{-1}$, δ 172.43), an unsaturated ketone function (1650 and 1615 cm-‘; δ 191.30) but no hydroxyl group. Besides the above signals, the ^{13}C NMR spectrum showed the presence of one tetrasubstituted and one trisubstituted double bond, two quaternary C-O and one tetra-alkyl substituted carbon atoms, one CH_2O group, two methylenes and three methyls. In the ^1H NMR spectrum of compound 2 the latter protons give rise to three isolated AB systems and three singlets, one of which is attributable to a methyl

*Part 25 in the series ‘Fungal Metabolites’. For Part 24 see De Bernardi, M., Garlaschelli, L., Vidari, G. and Vita-Finzi, P. (1989) *Rev. Latinoam.* Quim., (in press).



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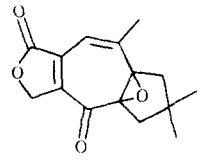

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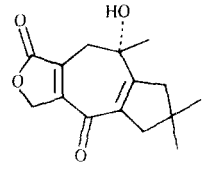

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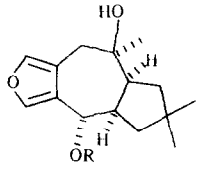
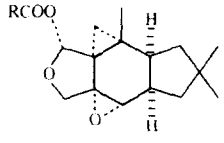


4a R = H
4h R = Ac



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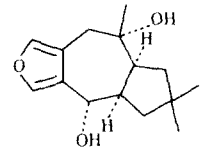

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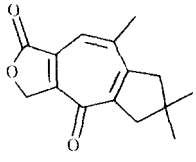

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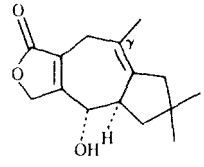

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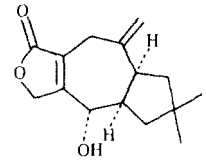

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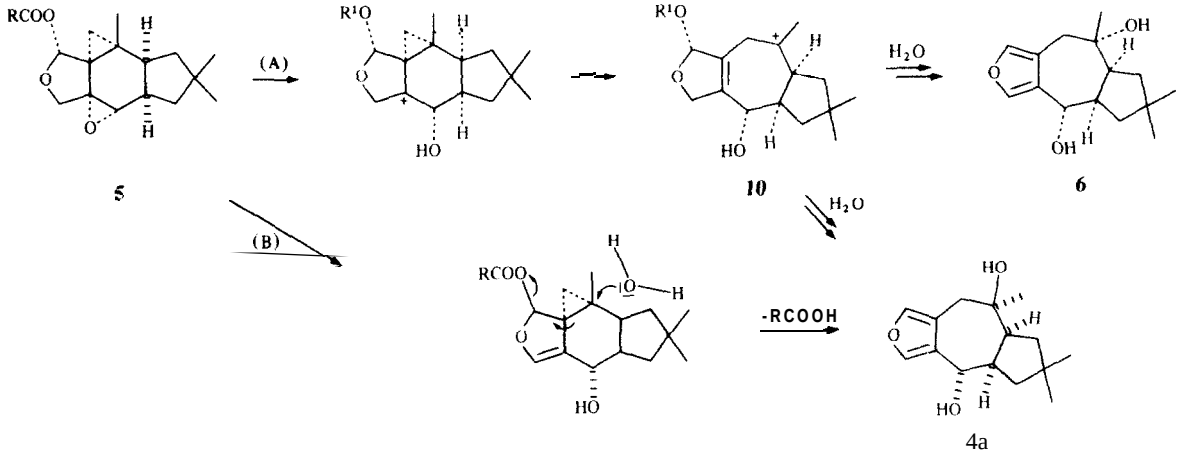
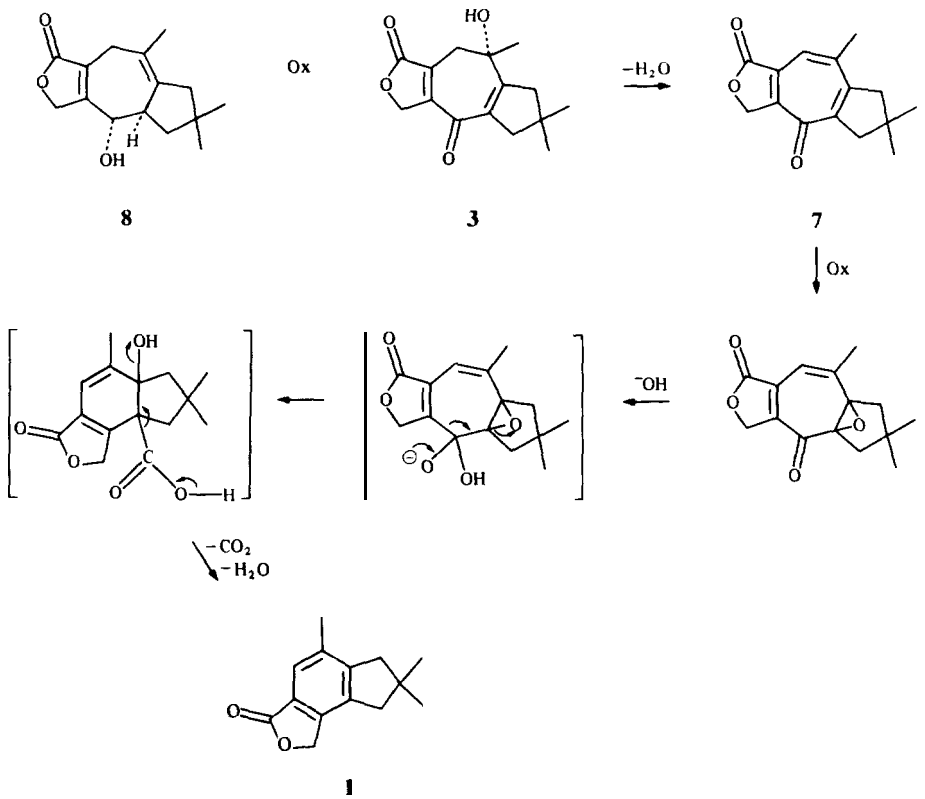
on a double bond (δ_H 2.25). Comparison of these data with those of lactarotropone (7) [9] clearly indicated that compound 2 is 2,9-epoxylactarotropone. The location of the lactone carbonyl at C-S instead than at C-13 was confirmed by NOEDS experiments. The selective irradiation of the olefinic proton (H-4) induced in fact a positive NOE on the C-12 protons (1.5%) but left C (13)H_2 unaffected.

The third lactone 3 is a very unstable compound which is rapidly decomposed by traces of acid (e.g. in $CDCl_3$ solution in the NMR tube), yielding lactarotropone (7) and minor unidentified products. Because of its instability and the small amount isolated, a ^{13}C NMR spectrum of compound 3 could not be recorded; however, counting of H atoms ('HNMR spectrum) combined with the M_r 262 (EIMS), suggested the formula $C_{15}H_{18}O_4$, which corresponds to lactarotropone 7 plus a molecule of H_2O. The presence of hydroxyl, unsaturated ketone and y-lactone functions was confirmed by the appropriate IR bands while the ^1H NMR spectrum showed three singlets (3H each), attributed to methyls on quaternary sp^3 carbon atoms, and four AB systems assigned to a γ-butenolide–CH_2O– group and to three allylic methylenes with no vicinal coupling. These data are consistent with structure 3 for this new lactarane sesquiterpene. This conclusion was corroborated by the results of the PDC oxidation [10] of alcohol 8: compound 3 was obtained as a minor product of the reaction, in mixture with ketone 7,



4a

Scheme 1



Scheme 2.

which is evidently formed by an easy aromatization of the initially formed dihydrotropone derivative. Chromium salts oxidation of the y-carbon atom of homoallylic alcohol 8 was anticipated in view of other precedents in the literature [11].

Compound 4a has molecular formula $C_{15}H_{22}O_3$ (EIMS, NMR data) and contains free alcoholic hydroxyl but no carbonyl functions (IR). The corresponding C-O signals in the off-resonance decoupled ^{13}C NMR spectrum indicated the presence of one tertiary and one secondary hydroxyl group, the latter being the only acetylable in the standard way, to give 4b [IR: 3460 cm^{-1} (OH); ^1H NMR: 6 6.07 (H-8), 2.10 (MeCOO)]. The third oxygen atom is contained in a 3,4-dialkyl substituted furan ring (positive Erlich test, IR bands at 1540 and 860 cm-'), the two furan protons H-5 and H-13 (lactarane numbering) being allylically coupled, respectively, with an isolated methylene group and the secondary protons H-5 and H-13 (lactarane numbering) being allylically coupled, respectively, with an isolated methylene group and the secondary CH-OH. To account for the entire structure of the compound, it was necessary to accomodate the presence of three methyl singlets (6 1.04, 1.16 and 1.23) on two quaternary sp^3 carbon atoms (^{13}C NMR spectrum) and two–CH–CH_2–groups, the two methine protons being coupled with each other. One of the CH signals is also coupled with the CHOH group showing a vicinal *trans* axial-axial coupling constant (J = 10.3 Hz). These data and obvious biogenetic considerations led to the structure 4a corresponding to the epimer at C-3 of furandiol 6. This conclusion, in particular the relative configuration of the molecule at the stereogenic centres, has been confirmed by the appropriate NOEDS effects in $CDCl_3$ solution. The selective irradiation of H-8 induced in fact a positive NOE on H-4 (0.5%), H-13 (2.9%), H-l (1.6%), H-10 (2%) and C (14)H_3 (0.3%). Moreover, irradiation of the methyl signal at δ 1.16 resulted in an enhancement of H-8 (5%), H-l (4.1%) and H-10 (4.3%), but left H-2 and H-9 unaffected, whereas the saturation of the methyl group at δ 1.04 affects the signals of H-l' and H-10 (3.1%) and those of H-2 and H-9 (4.2%). Finally, irradiation of the methyl singlet at δ 1.23 induced an enhancement of H-4 (3.7%), H-4' (3%), H-2 (4%). These results clearly indicated that H-8 is *trans* to H-2, H-9 and C (12)H_3 and allowed the assignment of the chemical shifts for H-l, H-l', H-10, H-10' and the geminal methyl groups.

The finding of 3-*epi*-furandiol 4a along with furandio16 in the same extract of *L. scrobiculatus* requires comment. Both of them, as well as other furanoid sesquiterpenes of lactarane and secolactarane type, can derive from velutinal (5) through rearrangements leading to carbon cation 10, which is then intercepted at C-3 by internal or external nucleophiles (Scheme 1, route A) [7, 8]. To account for the established stereochemistry of furans until now isolated, it has been assumed that nucleophilic attack always occurs from the a-side of the molecule, so that Me-12 ends up *trans* to the bridgehead protons H-2 and H-9 [7, 8]. The unexpected stereochemistry at C-3 of compound 4a may indicate that attack of H_2O is not stereospecific. Alternatively, to account for the formation of 3-*epi*-furandiol, another mechanism can be envisaged (Scheme

1, route B), which preserves the stereospecificity of velutinal transformations.

The aromatic compound **1** is the first example of norlactarane sesquiterpenes. Its biosynthesis, as well as that of lactones **2, 3, 7** can mechanistically be rationalized as depicted in Scheme 2, some of the reactions having been mimicked ***in vitro (vide supra)***. Expulsion of C-8 from the lactarane skeleton can likely occur through a benzylic rearrangement of a&epoxy-ketone 2, followed by a decarboxylative aromatization.

EXPERIMENTAL

Mps: uncorr. ^{1}H NMR: 300 MHz, in $CDCl_3$ soln unless otherwise indicated with TMS as int. standard. ^{13}C NMR in $CDCl_3$ (which also provided the lock signal), TMS as int. ref. Assignments of ^{13}C chemical shifts were made with the aid off-resonance and noise decoupled ^{13}C NMR spectra and, in the case ofcompound **4a**, determination of carbon multiplicities was made by DEPT pulse sequence. Compounds were visualized on GF_{254} silica gel plates under UV light or as coloured spots by spraying with a vanillin–H_2SO_4 soln and then heating at 120" for 10 min.

Isolation *of sesquiterpenes* **1**–**3**, **4a**, **7**–9, *from* L. scrobiculatus. Extraction of the mushrooms as well as isolation and chromatographic separations of the terpene fractions have already been described [4]. Fractions with intermediate polarity between furoscrobiculin B [4] and blennin C [12] were pooled into two groups A and B. MPLC of fraction A (0.3 g), on a silica gel column (Kieselgel 60 HR Merck, 50 g), with C_6H_6–Me_2CO (20: 1) as eluent, gave 68 mg of lactone 9 [13], 47.4 mg of a mixture of 9 and 4a and impure 4a (66.2 mg). The latter was rechromatographed on a silica gel column (Kieselgel 60, 0.040–0.063 mm, 18 g), with a hexane–Et_2O gradient system (TLC monitoring), to give pure 4a (14 mg). MPLC of fraction B (3.01 g) on a silica gel column (Kieselgel 60 HR, 150 g), with C_6H_6–Me_2CO (25: 1) as eluent, gave 8 groups of compounds (I–VIII). I (50mg): unknown; II (105 mg): unknown; III (70 mg): a mixture of **1, 2, 3,** 7; IV (110 mg): a mixture of 3 and 7; V (130 mg): lactone 7 [9]; VI (400 mg): mainly lactone 8; VII (1.3 g): a mixture of 8 and blennin C [12]; VIII (0.7 g): still a mixture of several compounds. Repetitive chromatographic separations of fractions III and IV on silica gel columns with hexane–EtOAc, hexane–Et_2O, C_6H_6–Et_2O and C_6H_6–EtOAc gradient mixtures, finally gave 1 (7 mg), 2 (1.4 mg). 3 (4.5 mg) and more 7 (25 mg).

8-*Norlactaranelactone* (1). Mp 93–96°. UV λ_{max}^{EtOH} nm (log E): 279 (3.22), 288 (3.19); IR ν_{max}^{KBr} cm^{-1}: 2950, 2920, 2860, 1760 (γ-lactone CO), 1620, 1450, 1380, 1360, 1325, 1295, 1220, 1110, 1042, 1015, 990, 770; ^{1}H NMR: δ 1.20 (6H, s, H_3-13 and H_3-14), 2.31 (3H, *s*, H_3-11), 2.71 (2H, *s*, H_2-9), 2.74 (2H, s, H_2-1), 5.16 (2H, s. H_2-12), 7.52 (1H, s, H-4); ^{13}C NMR (75.47 MHz): 19.21 (9, C-l 1), 29.20 (*q*, C-13 and C-14), 40.38 (*s*, C-IO), 45.18 and 46.82 (*t* and *t*, C-l and C-9). 68.71 (*t*, C-12), 124.19 (*d*, C-4), 124.38, 135.48, 136.60, 140.47 and 149.95 (5*s*, C-2, C-3, C-6, C-7 and C-8), 171.68 (s, C-5); EIMS (probe) 70 eV, m/z (rel. int.): 216 $[M]^+$ (26), 201 $[M-Me]^+$ (5), 187 (100), 173 (8), 159 (8), 157 (10), 145 (5), 141 (6), 128 (12), 115 (10), 105 (3), 91(8), 77 (8), 55 (8), 43 (5).

2,9-*Epoxylactarotropone* **(2).** Oil. IR ν_{max}^{film} cm^{-1}: 2950, 29 10, 2860, 1760 (γ-lactone CO), 1650, 1615, 1445, 1375, 1360, 1340 1325, 1295, 1225, 1182, 1165, 1130, 1090, 1037, 985, 952, 915, 850, 825, 790, 768, 734; 'HNMR (80 MHz): δ 1.12 (6H, *s*, H_3-14 and H_3-15; at 300 MHz this signal is split into two singlets at 1.12 and 1.13), 2.25 (3H, *br s*, H_3-12), 1.9–2.5 (4H, 2AB*q*, J_1 = 14 Hz and J_2 = 15 Hz, H_2-1 and H_2-10), centred at 5.05 (2H, AB*q*, J = 18 Hz, H_2-13), 6.55 (1H, *br* s. H-4); ^{13}C NMR (25.2 MHz): 24.71, 31.25 and 32.19 (*q*, *q* and *q*, C-12, C-14 and C-15), 32.2 (*s*, C-l 1), 40.96 and 45.42 (*t* and *t*, C-1 and C-10), 69.00 (*t*, C-13), 76.27 and 85.60 (s, and *s*, C-2 and C-9), 118.47 (d, C-4). 128.40 (s, C-3), 146.3 1 and 148.59 (s and *s*, C-6 and C-7). 172.43 (*s*, C-5), 191.30 (s, C-8); EIMS (probe) 70 eV, ***m/z*** (rel. int.): 260 $[M]^+$ (10), 245 $[M-Me]^+$ (5), 232 (45), 216 (30), 203 (8), 187 (80), 173 (9), 157 (8), 148 (9), 145 (8), 128 (9), 115 (8), 105 (6), 91 (15), 83 (100), 77 (11), 55 (16), 53 (8), 51 (8), 43 (52), 51 (14).

3,13-*Dihydroxy*-8-*oxo*-2(9),6-*lactaradien*-5-*oic* acid γ-*lactone* (3). Pasty solid; IR ν_{max}^{film} cm^{-1}: 3456 (OH), 2954, 2867, 1762 (γ-lactone CO), 1684 and 1611 (unsaturated ketone), 1449, 1419, 1366, 1346, 1300, 1218, 1163, 1126, 1072, 1037, 953, 915, 824, 778, 759; ^{1}H NMR (Me_2CO-d_6): 6 1.09 and 1.14 (3H each, *s* and *s*, H_3-14 and H_3-15), 1.34 (3H, s, H_3-12), 2.52 (2H, collapsing AB system further split by long range couplings, J, $_{1'}$ = 7.0 Hz, $H_{1-10} = J_{1-10'} = J_{1'-10} = J_{1'-10'}$ = 1.87 Hz, H-l and H-l'), 2.67 (1H, *dt*, $J_{10-10'}$ = 18.3 Hz, $J_{10-1} = J_{10-1'}$ = 1.87 Hz, H-IO), 2.78 (1H, *dt*, $J_{4-4'}$ = 16.75 Hz, $J_{4-13} \simeq J_{4'-13'}$ = 1.2 Hz, H-4). 3.01 (1H, *dt*, $J_{10-10'}$ = 18.3 Hz, $J_{10'-1} = J_{10'-1'}$ = 1.87 Hz, H-10'). 3.50 (1H, *dt*, $J_{4-4'}$ = 16.75 Hz, $J_{4'-13} \simeq J_{4'-13'}$ = 3.5 Hz, H-4'), 4.94 (2H, m, H_2-13). In $CDCl_3$ soln H-13 and H-13' give rise to two well separated sets of signals: 4.93 (1H, ***ddd, J***, $_{13-13'}$ = ***17.5*** Hz, $J_{13-4'}$ = 3.3 Hz, J_{13-4} = 1.5 Hz, H-13), 5.04 (1H, ***ddd,*** $J_{13-13'}$ = 17.5 Hz, $J_{13'-4'}$ = 3.5 Hz, $J_{13'-4}$ = 1.0 Hz, H-13'); EIMS (probe) 70eV. *m/z* (rel. int.): 262 $[M]^+$ (17), 247 [M -Me]+ (15), 245 (60), 244 $[M-H_2O]^+$ (30), 229 $[M-H_2O-Me]$ (84), 219 (21), 217 (18), 203 (19), 201 (24), 187 (21), 175 (18), 173 (22), 145 (17), 139 (27), 137 (21), 129 (16), 128 (18), 115 (20), 105 (15), 97 (16), 95 (16), 91 (22), 83 (31), 79 (19), 77 (27), 69 (48), 67 (19), 65 (17), 55 (43), 53 (24). 51 (21). 43 (100), 41 (40).

PDC oxidation *of deconjugated* ***anh****ydrolactarorufin* ***A (8).*** PDC (27.3 mg) was rapidly added to a stirred soln of the alcohol 8 (12 mg) in CH_2Cl_2 (2 ml) and stirring was continued for 24 hr at room temp. The mixture was then diluted with Et_2O, filtered through a Florisil pad and the chromium salts were washed with Et_2O. The solvent was removed under red. pres. and the products are isolated by CC on silica gel using C_6H_6–Me_2CO mixtures as eluent; yield: 7 (6.5 mg), 3 (3.3 mg).

3-epi-*Furandiol* (4a). Oil, $[\alpha]_D^{20}$ + 20" (CH_2Cl_2, *c* 0.2); IR ν_{max}^{film} cm^{-1}: 3350 (OH), 2950, 2920, 2860, 1540, 1460, 1450, 1375, 1365, 1265, 1120, 1105, 1050, 1030, 975, 945, 915, 890,860, 825, 790, 765, 740; ^{1}H NMR: δ 1.04 (3H, *s*, H_3-15), 1.16 (3H, *s*, H-14), 1.23 (3H, *s*, H_3-12), 1.64 (*dd*, 1H, $J_{10-10'}$ = 13.4 Hz, $J_{10'-9}$ = 7.3 Hz, H-10'), 1.64 (*dd*, 1H, $J_{1-1'}$ = 12.0 Hz, $J_{1'-2}$ = 7 Hz, H-1'), 1.72 (1H, *t*, $J_{1-1'} = J_{1-2}$ = 12.0 Hz, H-1), 1.80 (1H, *dd*, $J_{10-10'}$ = 13.4 Hz, J_{10-9} = 4.6 Hz, H-IO), 2.20–2.35 (2H, m, H-2 and H-9), 2.65 (1H, ***dd,*** $J_{4-4'}$ = 15.2 Hz, J_{4-5} = 1.3 Hz, H-4'), 2.88 (1H, ***dd,*** $J_{4-4'}$ = 15.2 Hz, J_{4-5} = 1.2 Hz, H-4), 4.78 (1H, *dd*, J_{8-9} = 10.3 Hz, J_{8-13} = 1.5 Hz, H-8), 7.20 (1H, *dt*, J_{4-5} = 1.2 Hz, $J_{4'-5}$ = 1.3 Hz, J_{5-13} = 1.7 Hz, H-5), 7.35 (1H, *t*, J_{8-13} = 1.5 Hz $\simeq J_{5-13}$ = 1.7 Hz, H-13): ^{13}C NMR (63 MHz): 30.53, 30.78, and 31.41 (C-15, C-14 and C-12), 35.77 (C-4), 36.41(C-11), 41.28 and 44.59 (C-l and C-10). 48.86 and 52.13 (C-2 and C-9), 68.26 (C-8) 72.67 (C-3), 118.91 (C-6), 129.8 (C-7). 139.25 and 140.56 (C-5 and C-13). EIMS (probe) 70 eV, ***m/z*** (rel. int.): 250 $[M]^+$ (5), 232 $[M-H_2O]^+$ (100), 217 $[M-H_2O-Me]^+$ (38), 214 (6), 203 (15), 199 (14), 189 (50), 177 (15), 176 (23), 175 (12), 161 (18), 147 (11), 137 (16), 136 (16) 135 (11), 133 (12), 123 (17), 119 (12), 109 (32), 107 (12), 105 (17), 95 (38), 91 (16), 81 (18), 79 (11), 77 (15), 69 (16). 55 (24), 53 (16). 43 (88), 41 (27).

8-*Acetyl*-3-epi-*furandiol* (**4b**). Obtained from compound 4a in the standard way. Oil. IR ν_{max}^{film} cm^{-1}: 3460 (OH), 2955, 2937, 2868, 1734 (acetate CO), 1458, 1371, 1236, 1105, 1050, 1025,914, 892, 863, 821,784; ^{1}H NMR (80 MHz): δ 1.00 (3H, s, H_3-15), 1.08 (3H, *s*, H_3-14), 1.20 (3H, *s*, H_3-12), 1.5–1.9 (4H, m, H-l, H-l', H-10 and H-10'), 2.10 (3H, s, MeCOO–), 2.2-2.5 (2H, m, H-2 and H-9).

centred at 2.75 (2H, *br*, ABq, $J_{4-4'}$ = 1 S Hz, H-4 and H-4'), 6.07 (1H, *br d*, J_{8-9} = 10 Hz, H-8), 7.07 (1H, *br s*, H-5), 7.18 (1H, *br s*, H-13).

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