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Reactions of guaianolide

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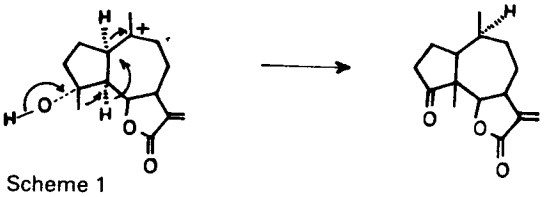
Abstract. Transformation of the guaianolide cynaropicrin to the pseudoguaianolide skeleton was attempted. Although the desired transformation could not be achieved, the attempt nevertheless led to the synthesis of C-1 and C-4 hydroxylated guaianolides which have been recently isolated from a natural source.

Keywords. Guaianolides; pseudoguaianolides; cynaropicrin; C-1 and C-4 hydroxylated guaianolides.

1. Introduction

The discovery of pseudoguaianolide skeleton was made in the laboratory of Prof W Herz in 1961 (Herz *et al* 1961, 1962) who also postulated that 4-hydroxy guaianolides are the biogenetic precursors of pseudoguaianolides as shown in scheme 1 (Herz 1973). This postulation was made taking into consideration the fact



Scheme 1

that most of the naturally occurring pseudoguaianolides have got a keto group at C-4.

2. Results and discussion

Availability of a large amount of guaianolide-cynaropicrin 1 from *Saussurea affinis* (Das *et al* 1983) prompted us to attempt this transformation in the laboratory. Although our efforts in this direction were not successful, it led to the synthesis of C-1 and C-4 hydroxylated guaianolides which have been recently isolated from natural sources (Bohlmann *et al* 1985; Ober *et al* 1985).

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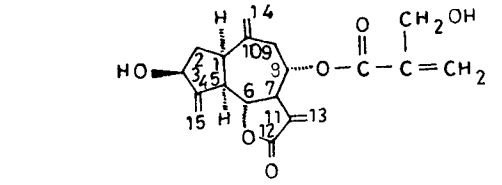
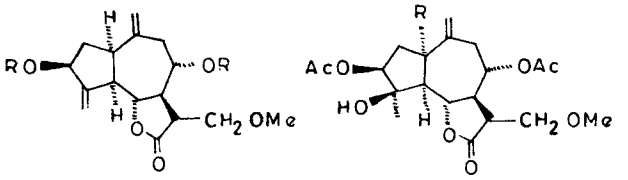
Alkaline hydrolysis of cynaropicrin 1 (Singhal *et al* 1982) with potassium carbonate in methanol furnished compound 2 in 80% yield which was acetylated to the diacetate 3. Reaction of the diacetate 3 with mercuric acetate in dioxane-water followed by sodium borohydride reduction (Brown and Geoghegan 1967) furnished a product whose mass spectrum recorded the molecular ion peak at *m/z* 396 suggesting that elements of water have been introduced in this reaction sequence. In the NMR spectrum, there was a broad singlet integrating to two protons at 5·16 ppm, overlapping signals of three protons between 4·2-4·8 ppm, four singlets at 3·35, 2·13, 2·06 and 1·38 ppm, each integrating to three protons and a two-proton multiplet at 3·6 ppm. The presence of a two-proton singlet at 5·16 ppm indicated that a hydroxyl group has been introduced at position C-4 which has resulted in the appearance of a methyl singlet at 1·38 ppm. H-15a, b usually appear as narrowly split multiplets near 5·3 ppm. Therefore structure 4 was assigned to this product.

When the ^{1}H NMR spectrum of compound 4 was recorded in presence of a drop of trichloroacetylisocyanate the C-15 methyl signal shifted to 1·84 ppm and the rest of the signals were not affected implying that the hydroxyl at C-4 is β-oriented. Had the hydroxyl been α-, H-3 would have moved downfield by at least 0.4 to 0.8 ppm.

In a bid to generate a carbonium ion at C-10, compound 4 was exposed to various mineral and Lewis acids but it invariably resulted in extensive decomposition and no homogeneous product could be isolated. It was, therefore, decided to introduce a hydroxyl group at C-1 which could act as a potential source for the generation of a carbonium ion at this centre leading to the desired transformation.



1



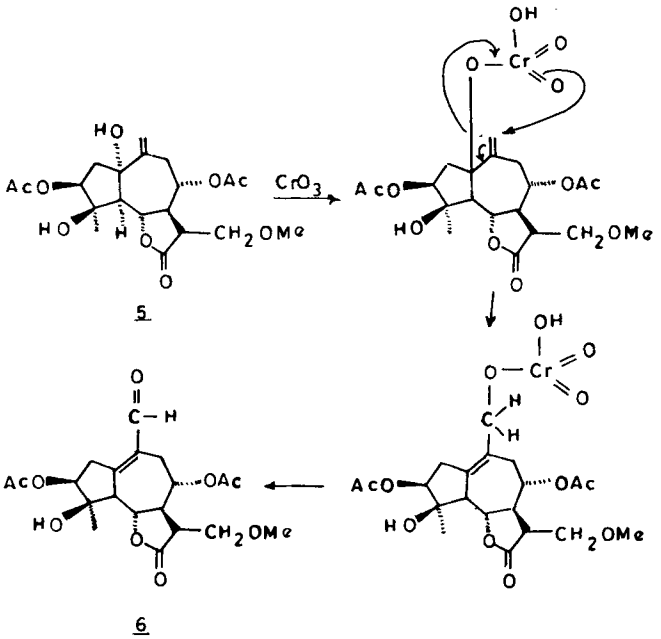
2 R = H
3 R = Ac

4 R = H
5 R = OH

Scheme 2

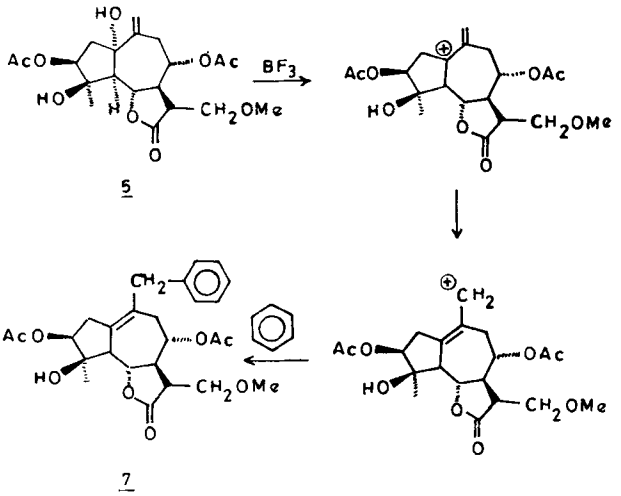
Selenium dioxide oxidation of compound 4 furnished a product in whose ^{1}H NMR spectrum H-14a, b appeared as sharp singlets at 5·30 and 5·25 ppm, H-3 as a doublet of doublets at 5·10 ppm with J = 11·3 and 6 Hz, H-8 as a doublet of triplets at 4·80 ppm with J = 10·5 and 4·2 Hz, H-6 as a doublet of doublets at 4·26 ppm with J = 10 & 9·7 Hz, and four sharp singlets at 3·37, 2·15, 2·10 and 1·47 ppm accounted for the methoxyl group, two acetate groups and the C-15 methyl group respectively. On the basis of the above data structure 5 was assigned to this compound which was in full accord with its mass spectral data.

Compound 5 was treated with chromium trioxide in dry benzene with the hope of generating a carbonium ion at C-1. The product obtained was identified as the aldehyde 6 on the basis of spectral data and scheme 2 rationalises its formation from 5 (Sundararaman and Herz 1977).



Scheme 3

Exposure of compound 5 to boron trifluoride etherate in dry benzene resulted in the formation of one major product which was identified as 7 on the basis of spectral evidence. In the ^{1}H NMR spectrum, there was a two-proton broad doublet at 7·10 ppm with J = 6·7 Hz and overlapping signals integrating to three protons appeared at 7·28 ppm. The rest of the spectrum was very much similar to that of

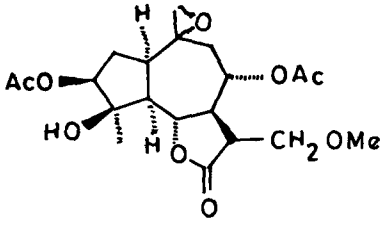


compound 5 except for the absence of signals due to the exomethylene group. On the basis of the above data structure 7 was assigned to this compound which was fully supported by its mass spectrum where the molecular ion peak appeared at *m/z* 472.

Formation of compound 7 can be rationalized as shown in scheme 3 which is a normal Friedel Crafts reaction but probably very rarely encountered with higher alcohols such as 5.

It was then decided to epoxidise the exomethylene group in compound 4 which on exposure to Lewis acids should generate a carbonium ion at C-10 as required in the biogenetic scheme (scheme 1).

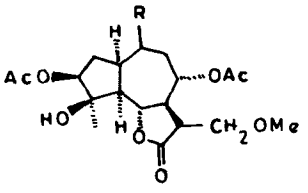
Epoxidation of compound 4 with MCPBA furnished a mixture of two epoxides in equal amounts which were separated by preparative TLC (1:1 EtOAc:Bz). The NMR spectra of both the epoxides were essentially identical and no attempt was made to assign their stereochemistry.



8 more polar epoxide

9 less polar epoxide

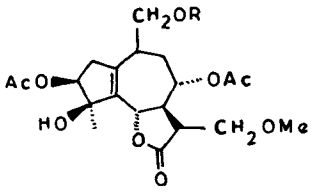
The reaction of the more polar epoxide 8 with various Lewis acids led to extensive decomposition and no pure product could be isolated. Exposure of the less polar epoxide 9 to boron trifluoride etherate furnished a mixture of two products which were separated by preparative TLC (1:1 EtOAc:Bz). The less polar product was identified as the aldehyde 10 on the basis of spectral evidences. In the ^1H NMR spectrum there was one proton doublet (J = 6Hz) at 9·5 ppm, the IR spectrum displayed absorption peaks at 1740 and 1715 cm^{-1} and the mass spectrum recorded the molecular ion peak at *m/z* 412 in full accord with the assigned structure. Sodium borohydride reduction of compound 10 gave the alcohol 11 which was acetylated to furnish the triacetate 12.



10 R = CHO

11 R = CH_2OH

12 R = CH_2OAc



13 R = H

14 R = Ac

The more polar product was identified as 13 which on acetylation furnished the triacetate 14.

3. Experimental

Melting points were determined on a Kofler block and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 237B grating infrared spectrophotometer as chloroform solution or potassium bromide pellet. All the NMR spectra were recorded on a Varian T-60 instrument, unless otherwise stated. TMS was used as the internal standard and deuterochloroform was used as solvent unless otherwise stated. Values are given in (δ) ppm (s = singlet, d = doublet, dd = double doublet, t = triplet, br = broad singlet, dbr = broad doublet, t br = broad triplet, q = quartet, m = multiplet). Low resolution mass spectra were recorded on an MS-30 instrument.

Thin layer chromatography (TLC) and preparative thin layer chromatography (preparative TLC) were performed on silica gel-G BDH, India) and plates were activated at 110°C for 1 h. All solvents were dried and distilled before use.

(i) *Alkaline hydrolysis of cynaropicrin 1*: A solution of 200 mg of cynaropicrin 1 in 20 ml of methanol and 4 ml of water was stirred at room temperature. To this solution 400 mg potassium carbonate were added and stirring was continued for 3 h. Finally the reaction mixture was acidified with acetic acid, diluted with water (300 ml), extracted with ethyl acetate (3 × 50 ml) and the extract dried over sodium sulphate. The dried extract was evaporated under reduced pressure and traces of acetic acid were removed by co-distillation with toluene. The residue thus obtained was purified by preparative TLC (1:1, EtOAc:Bz) to furnish 110 mg of 2, m.p. 155–156° (lit. m.p. 156–167°, Asakawa and Takemoto 1979). IR:3500, 1765 and 1640 cm^{-1}. NMR: 5·39 and 5·35 δ (t, J = 1 Hz, H-15), 5·09 δ (br, H-14a), 5.04 δ (br, H-14b), 4.55 δ (t br, J = 7 Hz, H-3), 4.15 δ (t, J = 10 Hz, H-6), 3·81 δ (dd, J = 10 and 2 Hz, H-13b), 3·70 δ (dd, J = 9, 5·5 and 4 Hz, H-8), 3·36 δ (dd, partly obscured, H-13a) and 3·36 δ (s, OMe); MS m/z 294 (M^+), 276 (M^+-18), 262 (M^+-32), 244 and 226.

(ii) *Acetylation of 2*: A solution of 100 mg of 2 in 1 ml of pyridine and 2 ml of acetic anhydride was kept overnight at room temperature. Usual work up and purification by preparative TLC (1:4, EtOAc:Bz) yielded 100 mg of the diacetate 3 as a gum. IR: 1775, 1730 (double strength), 1710, 1500, 1400, 1200, 1015 and 930 cm^{-1}; NMR: 5·52 δ (t br, J = 8 Hz, H-3), 5·44 δ (t, J = 1 Hz, H-15a), 5·29 δ (t, J = 1 Hz, H-15b), 5.10 δ (br, H-14a), 5·01 δ (br, H-14b), 4·94 δ (m, H-8), 4.08 δ (t, J = 10 Hz, H-6), 3·80 and 3·57 δ (dd, J = 10 and 3 Hz, H-13a, b), 3·38 δ (s, OMe) and 2·08 δ (s, OAc); MS: m/z 378 (M^+), 336 (M^+-42), 318 (M^+-60), 276 (M^+-60-42), 258 (M^+-60-60) and 231.

(iii) *Mercuric acetate-sodium borohydride reaction of 3*: To a solution of 100 mg of 3 in 10 ml of dioxane and 1 ml of water were added 506 mg mercuric acetate. The reaction mixture was stirred for 14 h at room temperature. It was then cooled to 0–5°C in an ice-bath, 200 mg of sodium borohydride were added and it was stirred

for another 10 min. The reaction mixture was then diluted with ice-cold water (300 ml), made acidic with acetic acid, extracted thoroughly with ethyl acetate (3 × 50 ml) and the extract dried over anhydrous sodium sulphate. The washed and dried extract was evaporated under reduced pressure, acetic acid removed by co-distillation with toluene, and the residue purified by preparative TLC (1:2, EtOAc:Bz, two and a half developments) to give 60 mg of 4, m.p. 154–156°C ($CHCl_3$-MeOH). IR: 3500, 1730, 1645, 1450, 1365, 1230, 1060, 980, 960 and 900 cm^{-1}; NMR: 5·16 δ (*br*, H-14a, b), 4·8 to 4·2 δ (H-3, H-6 and H-8), 3.6 δ(*m*, H-13a, b), 3·35 δ (OMe), 2·13 and 2·06 δ (OAc) and 1·38 δ (H-15). NMR spectrum, when recorded after adding 1 drop of trichloroacetylisocyanate, gave signals at 5·16 δ (H-14a, b), 4·85 to 4·25 δ (H-3, H-6 and H-8), 3·65 and 3·50 δ (H-13a b), 3·32 δ (OMe), 2.08 δ (OAc) and 1·84 δ (H-15); MS: *m/z* 396 (M^+), 355, 354, 336, 294, 293, 276, 258, 233 and 231.

(iv) *Selenium dioxide oxidation of 4* :A mixture of 50 mg of 4 and 50 mg of selenium dioxide in 4 ml dioxane was refluxed in an oil-bath, maintained at 120°C, for 10 min during which time TLC indicated disappearance of the starting material. The reaction mixture was poured into 200 ml of ice-cold water and extracted with ethyl acetate (3 × 50 ml). The dried extract was evaporated at reduced pressure and the residue purified by preparative TLC (1:1, EtOAc:Bz, one and a half developments) to give 35 mg of 5, m.p. 168–172°C ($CHCl_3$-EtOAc); IR: 3450, 1780, 1740, 1375, 1240, 1065 cm^{-1}; NMR (250 MHz):5·30 and 5·25 δ (H-14a, b), 5·10 δ (*dd*, *J* = 11·3 and 6 Hz, H-3), 4·8 δ (*dt*, *J* = 10·5 and 4·2 Hz, H-8), 4·26 δ(*dd*, *J* = 10 and 9·7 Hz, H-6), 3·82 and 3·55 δ (*dd*, *J* = 9·2 and 2·5 Hz, H-13a, b), 3·37 δ (OMe), 2·15 and 2·10 δ (OAc) and 1·47 δ (H-15); MS:*m/z* 352 (M^+-60), 334, 316, 292, 271, 256, 242, 231, 229 and 218.

(v) *Chromic anhydride oxidation of 5*: A solution of 50 mg of 5 in 6 ml dry benzene (dried over sodium wire) was stirred with 2 g of dry chromic anhydride for 6 h during which time TLC indicated disappearance of the starting material. The reaction mixture was poured into 200 ml ice-cold water and extracted with ethyl acetate (2 × 50 ml). The extract was washed with 5% aqueous sodium bicarbonate solution, then with water and finally dried over anhydrous sodium sulphate. Evaporation of the dried and washed extract under reduced pressure gave a crude substance which on purification by preparative TLC (1:12, MeOH:$CHCl_3$) yielded 20 mg of 6 as a gum; IR: 3450, 2850, 1740, 1675, 1240, 1185, 1050, 970 and 750 cm^{-1}; NMR (250 MHz): 9·92 δ (-CHO), 4·8 δ (overlapping signals of H-3 and H-8), 4.21 δ (*t*, *J* = 10·5 Hz, H-6), 3·85 δ (*dd*, *J* = 9 and 2·5 Hz, H-13a), 3·55 δ (*dd*, *J* = 9 and 2·8 Hz, H-13b), 3·39 δ (OMe), 2·2 and 2·12 δ (OAc) and 1·56 δ (H-15); MS:*m/z* 410 (M^+), 378, 349, 321, 308, 290, 289, 261, 247, 229 and 225.

(vi) *Reaction of 5 with boron trifluoride etherate*: A solution of 50 mg of 5 in 10 ml of dry benzene (dried over sodium wire) was cooled to 0°C in an ice-bath and 20 drops of freshly distilled boron trifluoride etherate were added to it with shaking. The reaction mixture was kept overnight at 0–5°C. It was diluted with 200 ml ethyl acetate, washed with 5% aqueous sodium bicarbonate solution followed by water, and finally dried over anhydrous sodium sulphate. The washed and dried extract was evaporated under reduced pressure and the residue was purified by preparative

TLC (9:1, $CHCl_3$:MeOH) to furnish 15 mg of 7 as a gum; IR: 3500, 1780, 1730, 1600, 1500, 1235, 1040 and 1025 cm^{-1}; NMR: (250 MHz): 7·28 δ (overlapping signals of three aromatic protons), 7·10 δ (*d br*, J = 6·7 Hz, for two aromatic protons), 4·78 δ (*dd*, J = 7·5 and 7 Hz, H-3), 4·67 δ (*dt*, J = 10 and 3·5 Hz, H-8), 4·2 δ (*t*, J = 10·2 Hz, H-6), 3·83 and 3·55 δ (*dd*, J = 9·2 and 9·3 Hz, H-13a, b), 3·36 δ (OMe), 2·15 and 2·00 δ (OAc) and 1·51 δ (H-15); MS:*m/z* 472 (M^+), 352, 334, 320, 290, 274, 262, 261, 249, 229, 205 and 185.

(vii) *Epoxidation of compound 4*: To a solution of 100 mg of compound 4 in 4 ml of chloroform were added 50 mg of *m*-chloroperbenzoic acid. The reaction mixture was kept at room temperature overnight. It was worked up by diluting with chloroform (150 ml) and the solution was washed thoroughly with 5% aqueous solutions of potassium iodide, sodium thiosulphate and sodium bicarbonate, followed by water. The chloroform solution was dried over anhydrous sodium sulphate and distilled. Purification of the residue by preparative TLC (1:1, EtOAc:Bz) furnished two compounds. The less polar compound 8, weighing 45 mg, was obtained as a gum. IR: 3500, 1770, 1730, 1440, 1230, 930 cm^{-1}; NMR:5·0–4·4 δ (H-3, H-6 and H-8), 3·5 δ (*m*, H-13a, b), 3·3 δ (OMe), 2·13 and 2·06 δ (OAc) and 1·3 δ (H-15); MS:*m/z* 412 (M^+), 371, 370, 352, 312, 311 and 299. The more polar compound, weighing 45 mg as a gum, was identified as 9. IR: 3445, 1765, 1730, 1440 and 1230 cm^{-1}; NMR: 5·0–4·4 δ (H-3, H-6 and H-8), 3·6 δ (*m*, H-13a, b), 3·34 δ (OMe), 2·06 and 2·00 δ (both *s*, OAc) and 1·34 δ (H-15); MS:*m/z* 412 (M^+), 371, 370, 352, 312, 311 and 293.

(viii) *Reaction of 9 with boron trifluoride etherate*: A solution of 40 mg of the epoxide 9 in 2 ml of dry ether and 0·5 ml of dry tetrahydrofuran was cooled to 0°C and 0·5 ml of boron trifluoride etherate was added to the solution dropwise. The reaction mixture was kept at room temperature overnight. It was diluted with chloroform (150 ml), washed first with 5% aqueous sodium bicarbonate solution and then with water. The washed and dried extract was evaporated under reduced pressure and the residue was purified by preparative TLC (1:1, EtOAc:Bz) to give two products. The less polar compound, weighing 15 mg was characterised as 10. IR: 3500, 3000, 1770, 1740, 1725, 1245 and 1150 cm^{-1}; NMR: 9·5 δ (*d*, J = 7 Hz, H-14), 5·2–4.6 δ (H-3, H-6 and H-8), 3·6 δ (*m*, H-13a, b), 3·4 δ (OMe), 2·2 and 2·14 δ (OAc) and 1·4 δ (*s*, H-15); MS:*m/z* 412 (M^+), 317, 352, 310, and 292. The polar compound, obtained as a gum (20 mg) was identified as 13. IR: 3500, 3000, 1775, 1740, 1670, 1240 and 1050 cm^{-1}; NMR: 5·0–4·5 δ (H-3, H-6 and H-8), 3·8–3·5 δ (H-13a, b and H-14), 3·3 δ (OMe), 2.00 δ (OAc) and 1·3 δ (H-15); MS:*m/z* 412 (M^+), 371, 370, 352, 310, 292 and 274.

(ix) *Reduction of 10 with sodium borohydride*: A solution of 15 mg of 10 in 2 ml of methanol was stirred at room temperature and 50 mg of sodium borohydride were added to it. After 1 h, the reaction mixture was acidified with acetic acid, diluted with water (300 ml) and extracted with chloroform (3 × 50 ml). The dried extract was evaporated under reduced pressure and traces of acetic acid were removed by co-distillation with toluene. The residue obtained was purified by preparative TLC (1:1, EtOAc:Bz) to give 10 mg of 11 as a gum. IR: 3000, 1770, 1740, 1450, 1250, 1150 and 100 cm^{-1}; NMR: 5·0–4·8 δ (H-3, H-6 and H-8), 4.1–3·5 δ (H-13a, b and

H-14), 3·4 δ (*s*, OMe), 2·10 and 2·03 (both *s*, OAc) and 1·3 δ (*s*, H-15); MS: *m/z* 414 (M^+), 373, 372, 354, 312, and 294.

(x) *Acetylation of 11*: 10 mg of compound 11 was kept overnight at room temperature with 0.25 ml pyridine and 0.50 ml acetic anhydride. The reaction was worked up as usual. Purification by preparative TLC (1:1, EtOAc:Bz) gave quantitative yield of compound 12 as a gum. IR: 3000, 1765, 1745, 1670, 1245 and 1150 cm^{-1}; NMR: 5·0–4·5 δ (H-3, H-6 and H-8), 4·4 δ (*m*, H-14), 3·6 δ (*m*, H-13a, b), 3·45 δ (OMe), 2·26 and 2·20 δ (OAc) and 1·4 δ (*s*, H-15), MS: *m/z* 456 (M^+), 414, 396, 354 and 336.

(xi) *Acetylation of 13*: 15 mg of compound 13 were acetylated with 0·25 ml pyridine and 0·50 ml acetic anhydride and worked up as usual. The residue was purified by preparative TLC (1:1, EtOAc:Bz) to furnish 13 mg of 14, m.p. 142–146°C ($CHCl_3$). IR: 3500, 3050, 1775, 1740, 1670, 1375 and 1050 cm^{-1}; NMR (250 MHz): 5·09 δ (*m*, H-8), 4·90 δ (*dd*, J = 8 and 2 Hz, H-3), 4·4–4·0 δ (overlapping signals of H-6 and H-14), 3·6 δ (*m*, H-13a, b), 3·38 δ (*s*, OMe), 2·10, 2·09 and 2·08 δ (all OAc) and 1·32 δ (*s*, H-15); MS: *m/z* 454 (M^+), 412, 354, 312 and 294.

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