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PARTIAL SYNTHESIS OF ISOEUCOMMIOL, A NEW CYCLOPENTENOID-TETROL†

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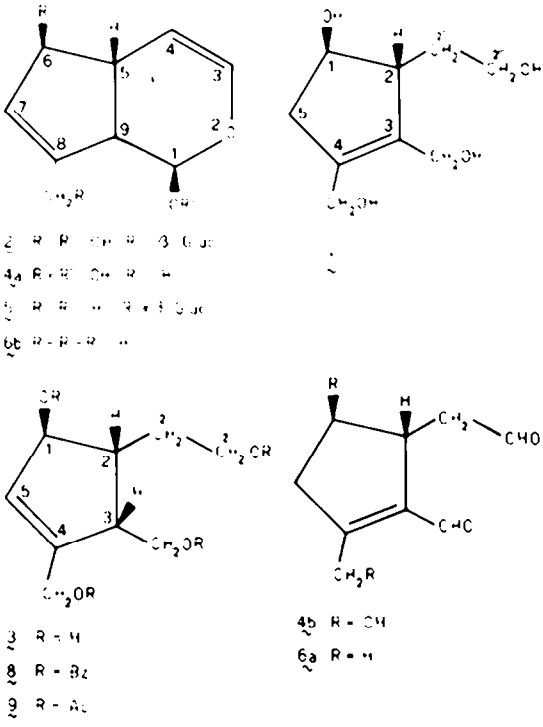
Abstract—Isoeucommiol 3, a cyclopentenoid-tetrol isomer of eucommiol 1, has been prepared by $NaBH_4$ reduction of the hemiacetal moiety of aucubigenin **4a**. The mechanism of this reduction has been investigated by using $NaBD_4$.

The isolation from *Eucommia ulmoides* (Eucommiaceae) of eucommiol **1**, a cyclopentenoid-tetrol (probably related in the plant with the aglycone of aucubin **2**) has been described.[1] In fact both **1** and **2**, (apart from the different double bond location in cyclopentane ring), show striking structural and stereochemical similarities but **1** may be found in the plant during the autumn only while **2** is present in very large amounts all the year round.

The isomeric cyclopentenoid-tetrol **3** (isoeucommiol), still more similar to aucubin, could not be found in the extracts.



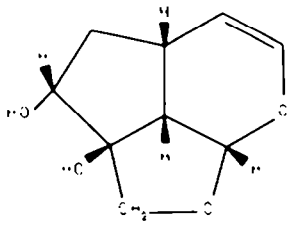
A direct partial synthesis of **1** and **3** from aucubigenin **4a** is the goal of our work. Compound **4a** is one of the more unstable iridoid aglycones and recently successfully isolated.[2] Although these aglycones, prepared by enzymatic hydrolysis of parent glucosides, have been found only in hemiacetalic form, a mild acid catalysis ought to favour the transformation of aucubigenin **4a** in its conjugated aldehydic form **4b**, whose cyclization is prohibited for sterical reasons. A fast reduction of **4b** could afford eucommiol **1** while isoeucommiol **3** could be obtained by reductive cleavage of dihydropiran ring of aucubigenin **4a**.

The possible existence of aucubigenin **4b** would be supported by the works of Grimshaw and Juneja[3] and Birch[4] on aucubin **2**, according to which the aglycone obtained by acid hydrolysis of 6,10-bisdeoxyaucubin **5** could exist in dialdehydic form **6a**, with an isolated and a conjugated carbonyl function respectively. These authors however did not isolate the aglycone, which was characterized only as bis-4-phenylsemicarbazone, and therefore we deemed necessary to check the real structure of free 6,10-bisdeoxyaucubigenin before of any experimental work on aucubigenin itself.

The acid hydrolysis of **5** afforded a stable enough aglycone whose spectroscopic (IR, UV, PMR) behaviour was in agreement with the dialdehydic structure **6a**. In particular the PMR spectrum ($CDCl_3$) of **6a** showed signals for two aldehyde groups one (δ 9.98, singlet) conjugated and slightly coupled, the other (δ 9.75, triplet, $J = 1.7$ Hz) coupled with an adjacent methylene group. The allylic methyl signal appears deshielded in **6a** (δ 2.13) with respect to **5** (δ 1.78, $CDCl_3$), being now the double bond conjugated with an aldehydic function.

As **6a** represents the only case of iridoid aglycone obtained in free dialdehydic form, we tried to verify if in non-acidic conditions it existed in the hemiacetalic form **6b**, this latter being the common stable form of all known iridoid aglycones. However the enzymatic hydrolysis of **5** in mild conditions afforded, although in small yields, only dialdehyde **6a**. Therefore the behaviour of 6,10-bisdeoxyaucubin **5** towards hydrolysis is border-line with respect to those of all iridoid glucosides, the conjugated dialdehydic form **6a** being preferred.

In order to prepare **1** we treated aucubigenin **4a** with diluted acids in mild conditions but instead of the expected dialdehyde **4b**, key-intermediate for the obtaining of **1**, we isolated in good yields (~33%) the cyclic acetal **7**, recently described in another paper.[2] This



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‡In alphabetical order.

confirmed that the acid-catalyzed transformation **6b** → **6a** does not represents a general feature of iridoid aglycones being favoured by the absence on the cyclopentane ring of hydroxyl groups which were proved to be responsible for the obtaining from iridoid aglycones of other transformation products (e.g. anhydroderivatives,[7] fulvoiridoids[8]).

On the contrary compound **3** was prepared by reducing aucubigenin **4a** with $NaBH_4$, which may be used in aqueous solution and does not reduce carbon–carbon double bonds. The reaction afforded as sole product **3**, appearing as colourless viscous oil. Its 90 MHz PMR spectrum (D_2O) compared with that of **2**,[6] shows the disappearance of glucosylic and dihydropyranic (H-1, H-3 and H-4) protons, while those on the cyclopentene ring maintain in both compounds identical shape and chemical shift. The presence at C-2 and C-3 of **3** of a β-oxyethyl and an oxymethyl group respectively, arising from the reductive cleavage of dihydropyran ring, is demonstrated by a detailed analysis of the PMR spectrum of the tetra-O-benzoylderivative **8**, obtained from **3** by benzoylation under mild conditions. The PMR spectrum of **8** (Fig. 1) compared with that of **3** (see Experimental), besides showing the expected paramagnetic shifts for one methine ($\Delta\delta$ = 1.36) and three methylene ($\Delta\delta \simeq 0.80$) groups with geminal OH functions, allows a more precise and complete analysis of the resonance patterns. In fact the second order complex multiplet (δ 2.3–1.7, H-2 and $\overset{\gamma}{C}H_2$) observed in **3**, is here simplified into a first order system: a pentuplet at δ 2.92 (J = 7.3 Hz) relative to H-2 and a quartet at δ 2.20 (J = 7.3 Hz) due to the $\overset{\gamma}{C}H_2$ protons, here magnetically equivalent. The methylene protons of the CH_2OH-3 (in **3** A_2 part of an A_2X system) are now magnetically not equivalent (AB part of an ABX system) giving rise to an eight-line system† between δ 4.90–4.30.

By irradiation of the pentuplet at δ 2.92‡ (H-2) the broad doublet§ at δ 5.96 (H-1) collapses to a broad singlet (the residual coupling constant $J_{1,5}$ is evidently very small) while the reverse irradiation transforms the pentuplet into a quartet ($J_{H\text{-}2,\overset{\gamma}{C}H_2} = J_{H\text{-}2,H\text{-}1} = 7.3$ Hz). The irradiation of the quartet at δ 2.20 ($\overset{\gamma}{C}H_2$) simplifies the triplet at δ 4.48 ($\overset{\gamma}{C}H_2OH$) into a singlet; conversely the irradiation of the triplet reduces the quartet into a doublet ($J_{H\text{-}2,\overset{\gamma}{C}H_2} = 7.3$ Hz). Finally the double irradiation at δ 3.34 (H-3) simplifies the eight-line system (CH_2OH-3) into a simple two spin AB system (J_{AB} = 12.0 Hz).

The ^{13}CMR spectra confirmed the structural features described above. The proton noise-decoupled spectrum of **3** (Table 1) consists of nine lines (two nearly superimposed). The lowest field line is assignable readily to the quaternary C-4 through the loss of nuclear Overhauser enhancement while the assignments for the remaining carbon nuclei were made with the aid of single frequency

†Two internal lines are hidden by the triplet at δ 4.48 (a seventh line is displayed in the decoupled spectrum) while in the PMR spectrum of the tetra-O-acetylderivative **9** in C_6D_6 all eight lines are clearly visible.

‡The same irradiation reduces the quartet at δ 2.20 into an ill defined triplet; analogous multiplicity assumes the pentuplet at δ 2.92 by reverse irradiation.

§The fine structure of triplet observed (300 Hz sweep width) for each line of the doublet is due to further coupling with allylic CH_2OH-4 at δ 5.04, disappearing by irradiation at this δ value.

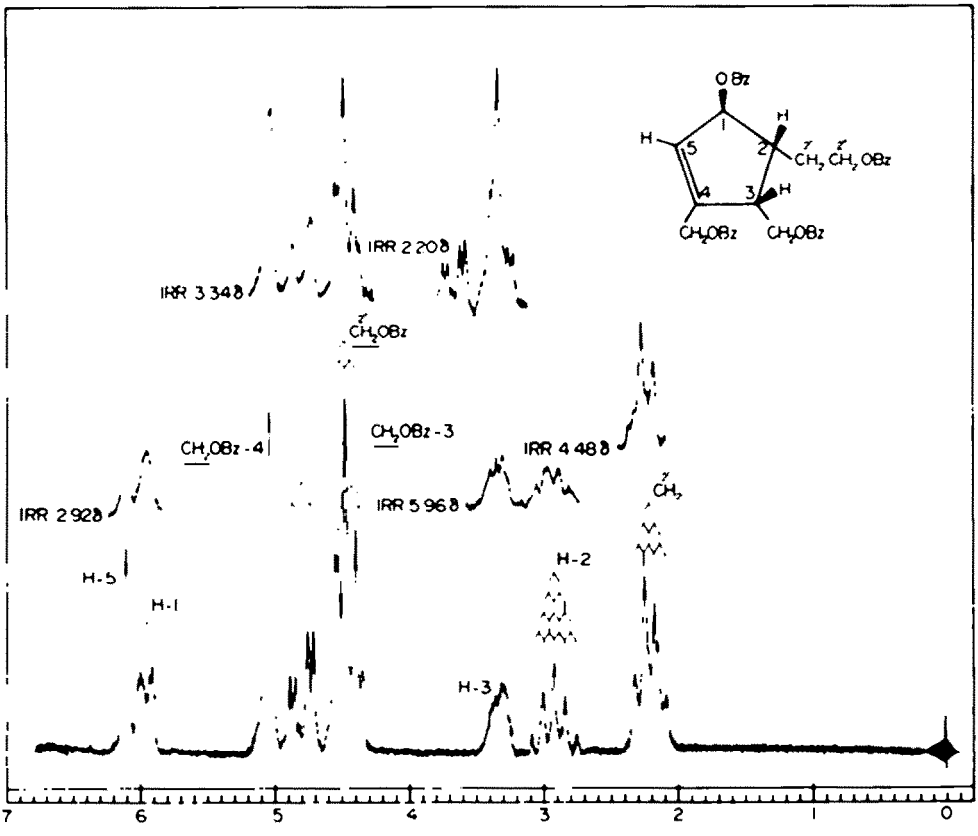


Fig. 1. Single and double ^{1}H resonance spectra at 90 MHz of tetra-O-benzoylisoeucommiol **8** in $CDCl_3$ solution.

Table 1. ^{13}C NMR chemical shifts assignments

Compound (solvent)	C-1	C-2	C-3	C-4	C-5	CH_2-3	CH_2-4	$\vec{C}$	$\overset{\leftarrow}{C}$
3(D_2O)	81.84 d	48.55† d	48.74† d	147.26 s	130.77 d	60.36‡ t	62.02 t	31.07 t	60.17‡ t

Multiplicity of the off-resonance spectrum: s, singlet; d, doublet; t, triplet.
†‡These assignments may be reversed.

off-resonance proton decoupling experiments, of known chemical shift rules[5] and of chemical shift (δ_C) comparison with eucommiol, eucommiol tetraacetate and aucubigenin triacetate.†

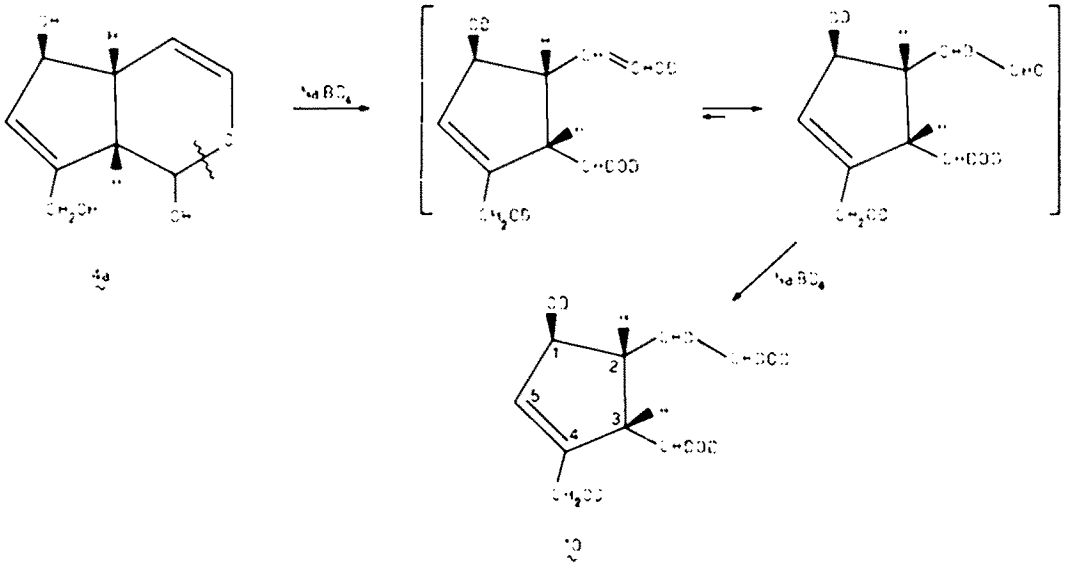
As regards the stereochemistry of **3**, the configuration of C-1 and C-2 centres must be identical to that of the corresponding centres C-6 and C-5 of aucubin **2**, because they are not involved in the reaction. Also the configuration at C-3 (C-9 of **2**) remains unchanged as demonstrated by the PMR analysis of deuteroiso-eucommiol **10** (see later). The cleavage of the dihydropyran ring causes on the contrary a strain release with notable conformational changes in the cyclopentene ring which assumes a preferential envelope conformation having the carbon atom (C-2) out of plane opposite to the double bond. This explains the anomalously high value (7.3 Hz) observed for $J_{H\text{-}1,H\text{-}2}$ (in cyclopentane derivatives the value of J_{trans} is normally small[6]) being now the dihedral angle $\Phi_{HC(1)\text{-}HC(2)}$ nearly 140° (Dreiding models). As $\Phi_{HC(2)\text{-}HC(3)}$ is very small (~ 15°), $J_{H\text{-}1,H\text{-}2}$ becomes accidentally identical to $J_{H\text{-}2,H\text{-}3}$.

In order to rationalize the mechanism of the $NaBH_4$ reduction of **4a** we repeated the reaction using sodium-borodeuteride. The PMR spectrum (D_2O) of deuteroiso-eucommiol **10** shows (Fig. 2) the following differences with that of **3**: (*a*) the four-line resonance pattern of **3** assigned to CH_2OH-3 (doublet at δ 3.71) and $\vec{C}H_2OH$ (triplet at δ 3.75) becomes in **10** a broad unresolved band centred at δ 3.69. The incorporation of two deuterium atoms in these functions is demonstrated by careful integration showing a ratio of this signal to allylic methylene protons at C-4 of 2:2 (in **3** the same ratio was 4:2); (*b*) the highly complex multiplet of **3** over the range δ 2.3–1.7 (3 protons) assigned to H-2 and $\vec{C}H_2$ protons, becomes in **10** a simpler pattern of lines (2 protons only) recognizable as a well defined quartet (H-2, δ 2.10, J = 7.3 Hz) and a slightly broadened‡ triplet ($\vec{C}H$, δ 1.90 J = 7.3 Hz). The following spin decoupling experiments confirmed the location of the three deuterium atoms on the CH_2OH-3, $\vec{C}H_2$ and $\vec{C}H_2OH$ functions. In fact by irradiation at δ 3.69 the broadened triplet at δ 1.90 simplifies into a broadened doublet due to the residual coupling of $\vec{C}H$ with H-2 ($J_{H\text{-}2,\vec{C}H} = J_{\vec{C}H,\overset{\leftarrow}{C}H} = 7.3$ Hz). The same irradiation transforms the H-3 signal at δ 2.86 (broad filled doublet) into a well defined doublet ($J_{H\text{-}2,H\text{-}3} = 7.3$ Hz). The simplification that the irradiation at δ 3.69 causes either on H-3 or on $\overset{\leftarrow}{C}H$ signals clearly demonstrates the presence in **10** of the $\vec{C}HDOH$ and CHDOH-3 functions. The quartet at δ 2.10 (H-2) is transformed, by distinct irradiations at δ 4.60 (H-1) and 2.86 (H-3) respectively, in two triplets with the same coupling constant (J = 7.3 Hz). The simple quartet multiplicity of H-2 originates therefore by its accidentally equal coupling (J = 7.3 Hz) with H-1, H-3 and $\vec{C}HD$.

The analysis of all hitherto-reported data suggest the mechanism shown in the Scheme.

The lack of deuteration at C-3, besides proving that the stereochemistry at C-3 remains unaffected, may be considered as a chemical support for the proposed mechanism.[9] This also excludes a dialdehyde form of **4a** as intermediate in formation of **3** and **10**, since exchange with

†Unpublished data.
‡The lines are broadened by additional coupling with the geminal deuterium atom.



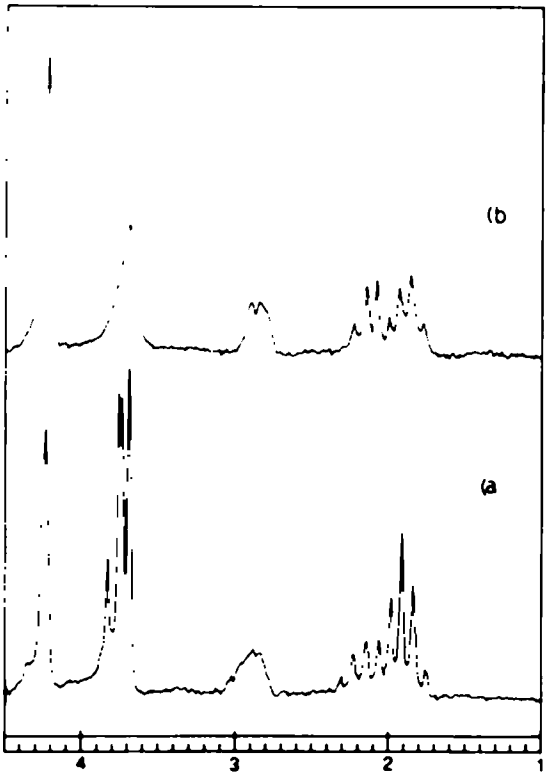


Fig. 2. Significant regions of PMR spectra (D_2O) of: *isoeucommiol 3, *trideuteroisoeucommiol **10**.

H-9 would be expected as well as C-3 racemisation, and is not observed.

Besides periodic controls on the possible presence of **3** in *Eucommia ulmoides*, research is in progress on the obtaining of similar cyclopentenoid derivatives from other iridoid aglycones.

EXPERIMENTAL

Silica gel (Merck, 140–230 mesh) used for column chromatography was washed several times with hot water then dried and activated at 120° for 12 h. Silica gel 60 F_{254} (Merck) and cellulose F (Merck) plates were used in TLC. Cellulose plates were eluted with BuOH–MeOH–H_2O (7:1:3). R_f values were determined on paper chromatograms (Schleicher and Schüll Nr 2043 b Mgl) eluted with BuOH–AcOH–H_2O (63:10:27). Visualization of spots was achieved by spraying either with 2N H_2SO_4 and heating for 2–3 min at 100° (silica gel plates) or with a 0.7% soln of vanillin in 2% methanolic HCl and heating for 2–3 min at 100° (cellulose plates and paper chromatograms). IR spectra were recorded on a Perkin Elmer 257 and UV spectra on a Perkin Elmer 137 spectrophotometers. Optical rotations were measured on a Galileo instrument. PMR spectra were registered with a Perkin Elmer R-32 (90 MHz) instrument, using TMS as internal reference for the spectra run in $CDCl_3$ while for those in D_2O the HDO signal (δ 4.70 from TMS) was taken as internal reference and the TMS signal as external reference. Spin decoupling experiments were performed with the spin decoupler accessory of the Perkin Elmer R-32 instrument using frequency sweep mode. Chemical shifts are expressed in δ (ppm downfield from TMS) and J are quoted in Hz. ^{13}CMR spectra, determined at 20 MHz using a Varian CFT-20 Fourier-Transform Spectrometer, were referred to the dioxane carbon signal and converted to δ_c values from TMS.

Acid hydrolysis of **5**: *dialdehyde* **6a**. **5** (100 mg) dissolved at 25° in 2N HCl (3 ml) appeared after 40 min completely transformed into a less polar compound (TLC in $CHCl_3$: MeOH = 95:5). The solution was extracted with EtOAc (3 × 30 ml) and collected extracts, neutralized with $NaHCO_3$ and evaporated *in vacuo*, gave a residue (25 mg) which, chromatographed on silica gel (3 g) in EtOAc: MeOH = 95:5, afforded amorphous pure **6a**. UV (MeOH), λ_{max} 250 nm (lg ϵ = 4.1); IR ($CHCl_3$): 2740 (C–H ald.), 1725 (C=O non conj.), 1665 (C=O conj.), 1635 (C=C conj.) cm^{-1}.

Enzymatic hydrolysis of **5**. **5** (100 mg) was dissolved in H_2O (3 ml) and treated at 37° with β-glucosidase (50 mg) (Fluka). After 12 h **5** appeared completely transformed into a compound showing the same chromatographic behaviour of **6a**. The solution was extracted with EtOAc (5 × 30 ml) and the organic layer evaporated *in vacuo*, afforded a residue (25 mg) which, chromatographed on silica gel in EtOAc: MeOH = 95:5, gave pure **6a** (15 mg).

$NaBH_4$ *reduction of* **4a**: *isoeucommiol* **3**. **4a** (100 mg), prepared by β-glucosidase hydrolysis of **2**,[2] was dissolved in H_2O (3 ml) and treated with an excess of $NaBH_4$ (~ 10 equiv). After 15 min the reaction was interrupted bubbling CO_2 until ~pH 7 and the solution adsorbed on decolorizing charcoal (1 g). The suspension, as a layer on a Gooch funnel, was washed with H_2O and then eluted with MeOH. The MeOH solution, containing **3** as main product (silica gel TLC in water-sat BuOH and cellulose TLC), was evaporated *in vacuo* affording a residue (80 mg) which, chromatographed on cellulose powder (8 g) in water-sat BuOH, gave pure **3** (55 mg) as colourless viscous oil. R_f = 0.52 (green-grey); IR (KBr), 1655 (C=C) cm^{-1}; PMR (D_2O): δ 5.80 (s, H-5), 4.60 (d, H-1), 4.24 (s, $\underline{CH_2}$OH-4), 3.75 (t, $\underline{CH_2}$OH, J = 6.6 Hz), 3.71 (d, $\underline{CH_2}$OH-3, J = 4.0 Hz, A_2 part of an $A_2 \times$ system), 2.85 (bs, H-3), 2.3–1.7 (cm, H-2 and $\underline{CH_2}$). $[\alpha]_D^{25}$ = − 123° (MeOH, c = 0.7%); (Found: C, 57.08; H, 8.74. Calc for $C_9H_{16}O_4$: C, 57.43; H, 8.59%).

Tetrabenzoate **8**. **3** (50 mg), dissolved in pyridine (0.5 ml), was treated with a solution of pyridine: benzoyl chloride = 2:1 (0.5 ml) for 1.5 h at room temp. After addition of H_2O (1 ml), the solution was allowed to stand for 30 min and then extracted with benzene. The organic layer, successively washed with 2N H_2SO_4, sat aq $NaHCO_3$, and H_2O, appeared to contain only **8** (TLC in benzene: Et_2O = 8:2). The residue (150 mg) obtained after evaporation *in vacuo*, chromatographed on silica gel (15 g) in benzene: Et_2O = 8:2, afforded pure **8** (125 mg) as colourless viscous oil. (Found: C, 73.13; H, 5.44. Calc. for $C_{37}H_{32}O_8$: C, 73.50; H, 5.33%).

Tetraacetate **9**. **3** (50 mg) was treated with pyridine (0.3 ml) and Ac_2O (0.6 ml) for 2h at room temp. After addition of MeOH (1 ml) the solution was allowed to stand for 20 min, then evaporated to give a residue (60 mg) which on TLC ($CHCl_3$: Et_2O = 7:3) appeared to be constituted only by **9**. This residue, chromatographed on silica gel (6 g) in $CHCl_3$: Et_2O = 8:2, gave pure **9** (50 mg) as colourless viscous oil. IR ($CHCl_3$): 1735 (C=O), 1655 (C=C) cm^{-1}. PMR ($CDCl_3$): δ 5.82 (bs, H-5), 5.50 (bd, H-1), 4.70 (bs, $\underline{CH_2}$OAc-4), 4.60–3.85 (o, $\underline{CH_2}$OAc-3), 4.14 (t, $\underline{CH_2}$OAc, J = 6.6 Hz), 2.94 (bs, H-3), 2.7–2.3 (m, H-2), 2.1–1.7 (m, $\underline{CH_2}$).

Deuteroisoeucommiol **10**. **4a** (80 mg) was dissolved in D_2O (3 ml) and treated with an excess of $NaBD_4$. The resulting mixture, worked up as described for **3**, gave pure **10** (45 mg) as colourless viscous oil. (Found: C, 56.27; H, 10.16. Calc. for $C_9H_{13}D_3O_4$: C, 56.53; H, 10.00%).

REFERENCES

[1]A. Bianco, C. Iavarone and C. Trogolo, *Tetrahedron* **30**, 4117 (1974).
[2]A. Bianco, M. Guiso, C. Iavarone, P. Passacantilli and C. Trogolo, *Ibid.* in press.
[3]J. Grimshaw and H. R. Juneja, *Chem. and Ind.* 656 (1960).
[4]A. J. Birch and G. Subba Rao, In *Advances in Organic Chemistry* (Edited by E. C. Taylor), Vol. 8, p. 39. Wiley-Interscience, New York (1972).
[5]A. Bianco, M. Guiso, C. Iavarone, R. Marini-Bettolo and C. Trogolo, *Gazz. Chim. Ital.* **106**, 733 (1976).
[6]A. Bianco, M. Guiso, C. Iavarone and C. Trogolo, *Ibid.* **106**, 725 (1976).
[7]G. C. Levy and G. L. Nelson, *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*, Wiley-Interscience, New York (1972).
[8a]G. Wolczunowicz, F. G. Cocu and Th. Posternak, *Helv. Chim. Acta* **53**, 2275 (1970); [8b]F. G. Cocu, G. Wolczunowicz, L. Bors and Th. Posternak, *Ibid.* **53**, 739 (1970).
[9]H. O. House, *Modern Synthetic Reactions*, 2nd Edn, p. 55, Benjamin, New York (1972).