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IRIDOID GLUCOSIDES AS SOURCES OF CYCLOPENTANOID 1,5-DIALDEHYDES: CONVERSION OF AUCUBIGENIN TO EUCOMMIAL AND EUCOMMIOL

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Key Word Index—*Eucommia ulmoides*; Eucommiaceae; aucubin; aucubigenin; iridoid aglycones; eucommial; eucommiol; ^{1}H NMR and ^{13}C NMR.

Abstract—Aucubigenin, which exists only in the closed hemiacetal form, has been transformed into a stable conjugated 1,5-dialdehyde form, 'eucommial', by a base-catalysed $\Delta^7 \rightarrow \Delta^8$ double-bond shift. Further reduction of eucommial leads to eucommiol, which co-occurs with aucubin in the autumn in *Eucommia ulmoides* and *Aucuba japonica*. The successful transformation of aucubin to eucommiol seems to support an *in vivo* relationship between these compounds.

INTRODUCTION

In recent years we isolated from *Eucommia ulmoides*, besides aucubin (**1**) and other iridoid glucosides, cyclopentenetetrol (**2**) [1] (eucommiol) and two of its glucosides, eucommioside I (**3**) (2″-*O*-*β*-glucopyranosyleucommiol) [2] and, more recently, eucommioside III, the structure of which is now under investigation. A third glucoside, eucommioside II (**4**) (1-*O*-*β*-glucopyranosyleucommiol) was isolated, in addition to **1** and **2**, from *Aucuba japonica* (Cornaceae) [3].

Compounds **2**, **3** and **4** are all present in these plants only in the autumn, whereas **1** is present in the plants all the year round and is the most abundant iridoid. These facts and the structural analogy between **2** and the dialdehyde form of aucubigenin (**5**) (the aglycone of **1**) seem to indicate that there is a relationship between these compounds *in vivo*. We have now verified the possibility of converting **1** into **2**, via **5**, by inducing a double-bond shift ($\Delta^7 \rightarrow \Delta^8$) in the aglycone and reducing the conjugated dialdehyde **6**.

RESULTS

This attempt was made easier by the application of our recent method, which provides **5** quantitatively (yield > 95%), by continuous extraction with refluxing ethyl acetate of the aqueous mixture obtained upon enzymatic hydrolysis of **1** with *β*-glucosidase [4].

The equilibrium of aucubigenin (**5**) is completely shifted towards the hemiacetal form (the resonance signal of the formyl proton is absent in its ^{1}H NMR spectrum in D_2O), as found in all iridoid aglycones. The only exception to this rule is represented by the aglycone of 6,10-bisdeoxyaucubin (**7**) which, upon hydrolysis under either acidic [5, 6] or enzymatic [7] conditions, leads to the conjugated dialdehyde form **8** of the aglycone.

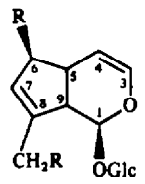
Previous attempts to obtain the double-bond shift on **5** by mild acid catalysis were unsuccessful because instead of the expected dialdehyde **6**, 1,10-anhydro-3,4-dihydro-4-decarbomethoxy-3α-hydroxygardenogenin (**9**) [8, 9] was isolated.

The target has now been reached by treating **5** with anhydrous sodium carbonate in ethyl acetate or acetone solution at 70° for 24–48 hr. Compound **6** (named eucommial because of its analogy with **2**) was obtained in good yields (70–80%) and exhibits interesting spectral features. The ^{1}H NMR spectrum in CD_3COCD_3 (see Experimental) fits perfectly with the assigned dialdehyde structure, showing a singlet at δ10.23 for the conjugated formyl group at C-3†, and a narrow triplet (J = 1.9 Hz) at δ9.74 for the formyl group of the side chain at C-2. By contrast, the ^{1}H NMR spectrum in D_2O shows the contemporaneous presence at equilibrium of dialdehyde **6** and its monohydrate form **10**, whereas only the unconjugated CHO group is involved in the hydration. An approximate 2:3 ratio can be inferred from the integral 2.5:1 ratio between the signals at δ9.90 (conjugated CHO) and δ9.60 (unconjugated CHO). This integral difference is balanced by the appearance of a triplet (J = 5.5 Hz) at δ5.10, partly masked by the HDO signal, which can be clearly assigned to the methine proton of the hydrated formyl group. The other protons give a mixture of overlapping signals from both forms.

In agreement with the ^{1}H NMR spectrum, the ^{13}C NMR spectra (PND and SFORD) of **6** in CD_3COCD_3 (see Experimental) show two aldehyde carbons at δ189.81 (conjugated) and 202.24 (unconjugated), respectively, and two conjugated olefinic carbons at δ163.29 (α C-3) and 139.00 (*β* C-4), whereas the spectra of the same compound in D_2O are characterized by the presence of signals of both anhydrous and hydrated forms at equilibrium.

The selective hydration of the unconjugated carbonyl group of eucommial (**6**) is consistent with the known

†By analogy with previous papers [1–3], cyclopentenpoliols and derivatives were numbered according to IUPAC rules.



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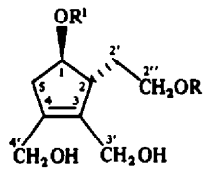
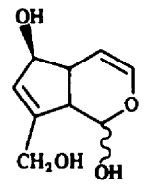
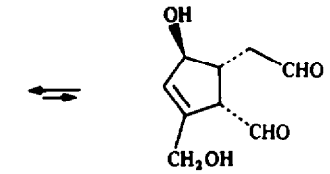
7 R = H



2 R = R¹ = H
3 R = Glc; R¹ = H
4 R = H; R¹ = Glc



β >> α



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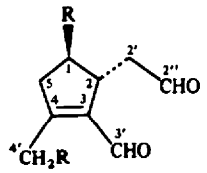
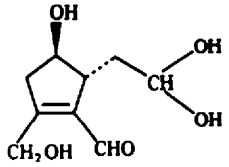


6 R = OH
8 R = H
11 R = OAc



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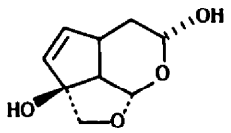

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differences in reactivity of conjugated and unconjugated aldehyde groups in water [10].

Acetylation of eucommial (**6**) gave the diacetate **11**, the structure of which is consistent with its ^{1}H NMR and ^{13}C NMR spectra (see Experimental). As expected, sodium borohydride reduction of **6** in aqueous solution gave, in quantitative yields, a cyclopententetrol whose ^{1}H NMR and ^{13}C NMR data were coincident with those of natural **2**. The ready transformation of **1** to **2** supports the initial hypothesis that the co-occurrence of these compounds in plants is of biogenetic significance. On the other hand, the fact that the chiral synthons **6** and **2** are easily obtained in good yields is of great interest for the synthesis of natural cyclopentanoid compounds, which we are currently carrying out [11].

EXPERIMENTAL

General techniques have been described earlier [4]. ^{1}H NMR were run at 300 or 90 MHz; chemical shifts as δ, coupling constants in Hz, HDO as internal standard at 4.70 ppm for D_2O solns and TMS as internal standard for $CDCl_3$ and CD_3COCD_3 solns. ^{13}C NMR spectra were run at 20 MHz; chemical shifts as ppm from TMS, dioxane as internal standard (67.4 ppm from TMS) for D_2O solns, TMS as internal standard for $CDCl_3$ and CD_3COCD_3 solns.

General procedure for the preparation of eucommial (**6**). Dry Na_2CO_3 (5 g) was added to an EtOAc or Me_2CO soln (300 ml) of aucubigenin (**5**) (500 mg) [4]. The soln was stirred at 70° until **5** was completely transformed (*ca* 24–48 hr), and the reaction was checked by TLC (EtOAc–MeOH, 9:1). After cooling, the salts were filtered and washed with EtOAc. The combined solns were dried (Na_2SO_4) and evaporated *in vacuo*. For analytical purposes, the amorphous residue (400 mg) was chromatographed on 'washed' silica gel with EtOAc–Me_2CO (4:1) and afforded pure **6** (300 mg). ^{1}H NMR of **6** (300 MHz, CD_3COCD_3): δ 10.23 (1H, *s*, H-3'), 9.74 (1H, *t*, $J_{H\text{-}2'',2H\text{-}2'}$ = 1.9 Hz, H-2''), 4.65 (2H, *br s*, 2H-4'), 4.06 (1H, *sext*, $J_{1,5}$ = 6.0, $J_{1,2}$ = 2.0 Hz, H-1), 3.01 (1H, *dd*, $J_{5\alpha,5\beta}$ = 18.0, $J_{1,5}$ = 6.0 Hz, H-5), 2.98–2.90 (1H, *complex m*, H-2, overlapped by signals of H-5 to lower field), 2.64 (1H, *oct*, J_{AB} = 18.0, $J_{H\text{-}2,B}$ = 6.0, $J_{H\text{-}2'',B}$ = 1.9 Hz, H_B-2'), 2.54 (1H, *br d*, $J_{5\alpha,5\beta}$ = 18.0 Hz, H-5), 2.41 (1H, *oct*, J_{AB} = 18.0, $J_{H\text{-}2,A}$ = 9.0, $J_{H\text{-}2'',A}$ = 1.9 Hz, H_A-2'). ^{1}H NMR of **6** + **10** (90 MHz, D_2O): δ 9.90 (1H, *s*, H-3'), 9.60 (1H, *t*, H-2''), 5.10 (1H, *t*, CH(OH)$_2$ at 2''), 1.70 (2H, *m*, $CH_2CH(OH)_2$). ^{13}C NMR of **6** (CD_3COCD_3): δ 202.24 (*d*, C-2''), 189.81 (*d*, C-3'), 163.29 (*s*, C-3), 139.00 (*s*, C-4), 74.98 (*d*, C-1), 59.91 (*t*, C-4'), 49.25 (*d*, C-2), 45.94 (*t*, C-5), 44.30 (*t*, C-2'). ^{13}C NMR of **6** + **10** (D_2O): 206.97 (*d*, C-2''), 192.22 (*d*, C-3'), 90.64 (*d*, C-2''), 38.88 (*t*, C-2').

Bis-O-acetyleucommial (**11**). Compound **6** (100 mg) was dissolved in dry C_5H_5N (2.5 ml) and Ac_2O (5 ml) and after standing at room temp. for 1 hr, MeOH (5 ml) was added at 0°. After

30 min, the soln was evaporated *in vacuo*, affording a residue which was chromatographed on silica gel ($CHCl_3$–Et_2O, 7:3) to give **11** as an oil (90 mg). ^{1}H NMR (90 MHz, $CDCl_3$): δ 10.03 (1H, *s*, H-3'), 9.68 (1H, *t*, H-2''), 5.10 (2H, *br s*, 2H-4'), 4.98 (1H, *sext*, H-1), 3.43 (1H, *m*, H-2), 3.22 (1H, *dd*, H-5), 2.80 (2H, *m*, 2H-2'), 2.60 (1H, *br d*, H-5), 2.10 and 2.02 (*s*, AcO). ^{13}C NMR ($CDCl_3$): δ 200.21 (*d*, C-2''), 187.23 (*d*, C-3'), 170.67 (*s*, AcO), 154.82 (*s*, C-3), 139.82 (*s*, C-4), 76.25 (*d*, C-1), 59.38 (*t*, C-4'), 46.28 (*d*, C-2), 44.60 (*t*, C-5), 41.73 (*t*, C-2'), 20.99 (*q*, AcO), 20.64 (*q*, AcO).

Eucommiol (**2**) *by reduction of* **6** *with* $NaBH_4$. Compound **6** (300 mg) was dissolved in H_2O (5 ml) and treated with an excess of $NaBH_4$ (*ca* 10 equiv.). After 15 min, the reaction was interrupted by neutralization to pH 7 by bubbling CO_2. The soln was adsorbed on decolourizing charcoal (5 g). The suspension, as a layer on a Gooch funnel, was washed with H_2O to remove the salts, and then eluted with MeOH. The MeOH soln was evaporated *in vacuo* and left a residue (250 mg) which was chromatographed on cellulose powder with *n*-BuOH saturated with H_2O, to give pure **2** (200 mg). ^{1}H NMR and ^{13}C NMR data were in agreement with those reported [2, 12]. ^{1}H NMR (90 MHz, D_2O) [2]: δ 4.24 (5H, *br s*, H-1, 2H-3', 2H-4'), 3.71 (2H, *t*, J = 7.0 Hz, 2H-2''), 2.90 (1H, *br dd*, J_{AB} = 18.0 Hz, H_B-5), 2.72 (1H, *m*, H-2), 2.32 (1H, *br d*, J_{AB} = 18.0 Hz, H_A-5), 2.1–1.2 (2H, *complex m*, 2H-2'). ^{13}C NMR (D_2O) [12]: δ 138.96 (*s*, C-4), 137.11 (*s*, C-3), 75.30 (*d*, C-1), 60.84 (*t*, C-2''), 57.91 (*t*, C-4'), 56.17 (*t*, C-3'), 52.93 (*d*, C-2), 42.19 (*t*, C-5), 33.11 (*t*, C-2').

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