ORGANOMERCURY CHEMISTRY OF IRIDOID GLUCOSIDES - Part 3[1,2]

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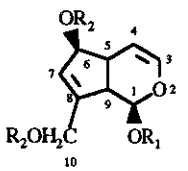
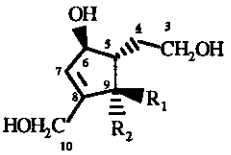
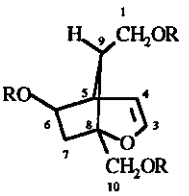
Abstract - The hydroxymercuration (OM) reaction of nonconjugated diene system of aucubin (**1**) with at least 2 equivalents of Hg(II) salts involved not only the enol ether Δ^3 double bond, but also the less reactive Δ^7 cyclopentene double bond; the unique intermediate was observed to be the organobismercurial derivative (**10**). Surprisingly, the reductive demercuration (DM) of **10** with $NaBH_4$ gave a mixture of three products isoeucommiol (**3**), 6-hydroxy-8,9-dihydroxymethyl-2-oxabicyclo[3.2.1]oct-3-ene (**5**), and 7,8-dihydro-8-α-hydroxyisoeucommiol (**6**). The way these different compounds may be formed from common intermediate (**10**) is discussed. The aptitude to reversion showed by the OM reaction of the cyclopentene double bond of **1** was confirmed by the analogous tendency observed in the OM/DM of **3**; this latter reaction afforded a good yield of the reaction product 6-hydroxy-8,9-dihydroxymethyl-2-oxabicyclo[3.2.1]octane (**12**) only when the DM of organomercurial intermediate (**13**) was carried out in basic conditions. Lastly, when the DM of monomercurial intermediate (**2**) was performed with Zn/CH_3COOH, this led to the conservation of the hidden 1,5-dialdehydic system of **1** and the formation of aucubigenin (**16**), i.e. to the achievement of a nonenzymatic hydrolysis of **1**.

We recently reported[3] the first application of the hydroxymercuration-demercuration reaction

(OM/DM) to the nonconjugated diene system of aucubin (1), the most common iridoid glucoside.







1 R_1 = D-Gluc, R_2 = H

16 $R_1 = R_2$ = H

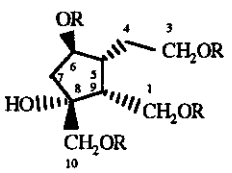
17 $R_1 = R_2$ = Ac

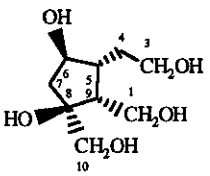
3 R_1 = H, R_2 = CH_2OH

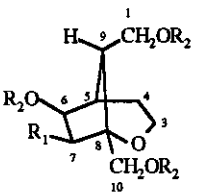
4 R_1 = CH_2OH, R_2 = H

5 R = H

7 R = Ac







6 R = H

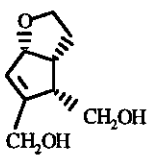
8 R = Ac

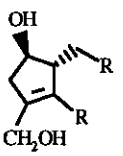
9

12 $R_1 = R_2$ = H

13 R_1 = HgOAc, R_2 = H

14 R_1 = H, R_2 = Ac





15

18 R = CHO

19 R = CH_2OH

We had previously observed that an equimolar amount of $Hg(OAc)_2$ (in water as solvent and nucleophile) added chemoselectively to the enol ether double bond of **1**; the reduction ($NaBH_4$) of the organomonomercurial intermediate (**2**) in appropriate conditions led to the selective formation[3]

of epimeric cyclopentenetetrols (3) (isoeucommiol)[4] or (4) (9-epiisoeucommiol),[5] both chiral starting material for syntheses of bioactive cyclopentanoid compounds.[6a,b]

Here we describe the results obtained carrying out the OM/DM of 1 with 2 equivalents (or more) of $Hg(OAc)_2$. We aimed to test the actual reactivity of trisubstituted Δ^7 double bond which in the previous work[3] had proved far less reactive than the enol ether Δ^3 double bond (in previous works we had described the substantial "unreactivity" of the analogous trisubstituted double bond of 3 in OM/DM conditions[3,6b]).

The OM reaction of 1 with a slight $Hg(OAc)_2$ excess (2.2 equivalents) in H_2O led to a fast and complete transformation of 1 into the probable organomercurial intermediate (10) (tlc, Rf=0). Successive reduction of the latter with $NaBH_4$ (DM) gave a mixture of three products (5) (12%), (3) (25%) and (6) (35%); the structures of these products were demonstrated by a detailed analysis of their ^1H and ^{13}C nmr data (see Experimental), which was supported by spin decoupling and COSY 45° experiments, also extended to the acetyl derivatives of 5 (7) and 6 (8).

As regards 3 a further evidence of its structure was provided by the observation of identical chromatographic and spectroscopic data (^1H and ^{13}C nmr), compared with those[7] of an authentic sample of isoeucommiol. Conversely, 6 proved to be the epimer at C-8 (α-OH, β-CH_2OH) of known cyclopentanepentol (9) previously obtained by $LiAlH_4$ reduction of β-epoxyisoeucommiol.[6b] In fact, compared to the corresponding values observed in 9 (C-8, 83.02 ppm; C-10, 66.71 ppm; C-7, 44.25 ppm; C-9, 52.25 ppm), the ^{13}C nmr spectrum of 6 in D_2O (more diagnostic than ^1H nmr) demonstrated significative differences for resonance values of C-8 (81.95 ppm), C-10 (69.31 ppm), C-7 (45.10 ppm) and C-9 (47.64 ppm). Since the same mixture of final products was also obtained with more electrophilic Hg(II) salts such as $HgSO_4$, $Hg(NO_3)_2$ or $Hg(O_2CCF_3)_2$, in these conditions the OM/DM course of 1 proved practically independent from the particular Hg(II) salt employed.

Given the simultaneous formation by OM/DM of 1 - together with the expected cyclopentanepentol (6) - of compounds as different as 3 and 5, we were obliged to ascertain the real composition of the OM mixture; that is, we were forced to determine the existence of one or more organomercurial intermediates.

Since the organomercurial intermediate could not be isolated by chromatographic resolution of the OM mixture to achieve direct spectroscopic evidence of its structure, we decided to perform certain OM experiments directly in a nmr tube; this was done by adding $Hg(OAc)_2$ in different molar ratios

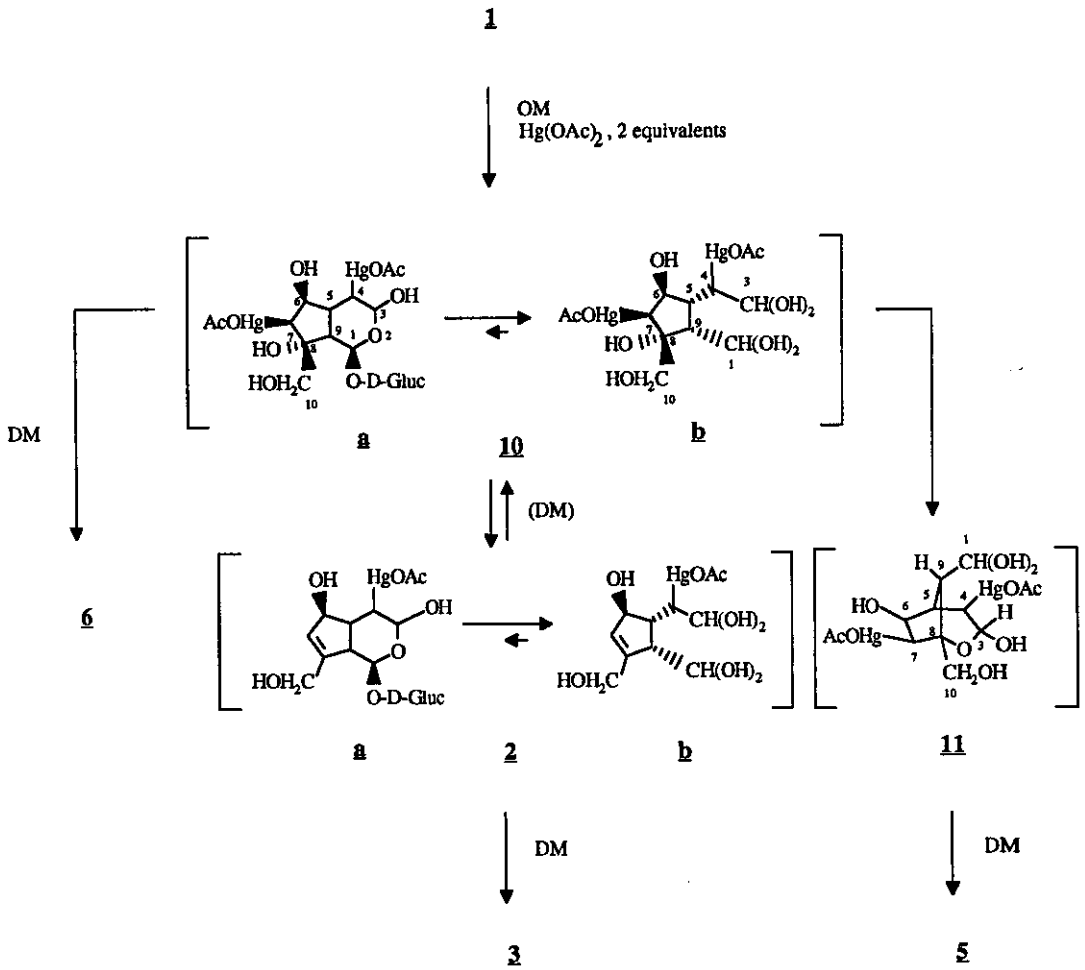
to a solution of **1** in D_2O and monitoring the reaction at different times, as was done in analogous successful nmr tests performed during previous research on the methoxymercuration-demercuration reaction of **1**.[1]

A first experiment performed with $Hg(OAc)_2$ and **1** in equimolar ratio confirmed the already ascertained[3] chemoselective reaction of the enol ether double bond of **1**.

In fact, a set of ^1H nmr spectra (see Experimental) recorded at different times showed a rapid OM reaction of **1**; this is because as early as the first control 10 min after the start of the experiment, no signals were observed from the olefinic protons of enol ether system of **1** (δ 6.18, H-3; δ 4.98, H-4), while signals from olefinic H-7 and allylic 2H-10 protons were still detectable. These spectral data confirmed the chemoselectivity of the OM reaction of **1** (previously inferred from reaction products[3]); although this reaction initially led to the predictable formation of the hemiacetalic monomercurial intermediate (**2a**), this was however shortly almost completely transformed into the corresponding opened dialdehyde, existing partly in its hydrated form (**2b**). In fact a careful examination of the first ^1H nmr spectrum showed the existence of free D-glucose in the OM mixture, inferrable from the presence of characteristic doublets at δ 5.10 ($J_{1',2'}$= 3.6 Hz) and δ 4.52 ($J_{1',2'}$= 7.8 Hz); these were respectively attributable to anomeric H-1' protons of α- and β-D-glucopyranose forms (corresponding nmr data from literature[8] were δ 5.09, $J_{1',2'}$= 3.6 Hz and δ 4.51, $J_{1',2'}$= 7.8 Hz respectively; the H-1' of β-D-glucose moiety of **1** resonates[9] at δ 4.80, $J_{1',2'}$= 7.5 Hz). In successive spectra[10] registered at 22°C, the mutarotation reached equilibrium with a final integral ratio of 4:6 for the above mentioned doublets; this ratio was in perfect agreement with the value reported in literature and deduced from nmr data.[11] As previously mentioned the dialdehydic system of **2b** was partly hydrated[12] as indicated by the integral value of free formyl protons signals; this was counterbalanced by a doublet at δ 4.90 (J = 3.4 Hz) temptatively assigned by spin decoupling to the hydrated formyl proton H-1 (the acetalic H-1 proton of **1** resonates[15] at δ 5.16, $J_{1,9}$ = 5.0 Hz). The ^{13}C nmr spectra too showed mutarotational equilibrium exhibiting signals from α- and β-anomeric carbons in agreement with literature data.[8]

In a successive nmr experiment carried out analogously on **1** with an excess of $Hg(OAc)_2$ (2,2 equivalents or more) in D_2O solution, all the olefinic signals (H-3, H-4 and H-7) disappeared as early as the first nmr control (5 min); this indicated that the Δ^7 double bond had also reacted and **1** had been completely transformed into an organobismercurial intermediate. Here too, the analysis of a set of ^1H nmr spectra of the OM mixture registered at different times demonstrated that the

initially predictable hemiacetal structure (10a) was rapidly and totally equilibrated into the corresponding opened dialdehydic system, which exists mainly in the hydrated form (10b).



Since the spectroscopic features were identical to those expected for the 2a ⇌ 2b equilibrium (presence of signals of free D-glucose and successive achievement of a perfect mutarotational equilibrium between its α- and β-anomeric forms), this equilibration was evident as early as the first control. A significant difference with the situation depicted for monomercurial intermediate (2) was that in 10 signals from free formylic protons were lower; this indicates a rapid and more thorough

transformation of the opened dialdehydic system into its bis hydrated form (**10b**).

Some significant features of the ^{1}H nmr spectrum of this OM mixture were the doublet at δ 5.57 (J = 3.1 Hz) of hydrated H-3 formyl proton together with that of hydrated H-1 formyl proton at δ 5.08 (J = 2.7 Hz) (C-3 and C-1 counterparts resonated at 89.89 and 94.32 ppm respectively). Other noteworthy signals were the doublet centered at δ 3.23 ($J_{6,7}$ = 7.1 Hz; partly covered by D-glucose signals), assigned by spin decoupling and COSY 45° experiments to the H-7 proton geminal with mercury moiety (counterpart C-7 resonance at 60.19 ppm). Another interesting characteristic was the diamagnetic shift undergone by the doublet (δ 4.20, $J_{6,7}$ = 7.1 Hz) of H-6 hydroxymethine proton (counterpart C-6 resonance at 80.06 ppm), that was previously allylic (δ 4.60) in **1**. As expected, the effect of the irradiation at δ 4.20 was to simplify the doublet at δ 3.23 (H-7) to a sharp singlet. The broad multiplet at δ 2.66, identified by spin decoupling, was attributed to the proton (H-4) linked to mercuriated C-4 carbon (39.47 ppm).[16] The resonances of the remaining protons and carbons of **10** were as follows: H-5 (δ 2.92, d, J = 5.3 Hz), H-9 (δ 2.49, br s), C-5 (44.19 ppm), C-9 (47.14 ppm), quaternary C-8 (88.00 ppm). The COSY 45° experiment performed directly on the OM mixture enabled us to visualize the highly diagnostic cross peaks relative to coupling correlations H-6/H-7, H-3/H-4, H-4/H-5, H-1/H-9 and H-5/H-9. The successive DM ($NaBH_4$) of this OM mixture naturally led to the expected set of compounds (**3**), (**5**) and (**6**).

At this point it was clear that the formation of compounds as different as **3**, **5** and **6** occurred from the common organomercurial intermediate (**10**) during the reductive DM stage; the latter once again proved to be the crucial point of solvomercuration-demercuration reactions.[1,3]

After the reductive cleavage with $NaBH_4$ of both C-Hg linkages at C-4 and C-7 and the contemporary reduction to corresponding diol of its hemiacetal (1,5-dialdehydic) system, the expected product of ''normal'' DM of **10** was cyclopentanepentol (**6**). The α configuration of OH-8 indicates that the Hg(II) salt attack occurs preferably from the less hindered convex (β) side of aucubin (**1**).

On the contrary, the only explanation for the formation of **3** was the regeneration of the monomercurial adduct (**2**) by partial reversion[17] of bismercurial intermediate (**10**) favored by DM conditions. We have already described[3] the easy formation of isoeucommiol (**3**) by direct reduction ($NaBH_4$) of **2**. As regards the formation of **5** from **10**, a feasible pathway may consist of the initial reaction of α OH-8 of bismercurial intermediate (**10b**) to the formyl group of the syn(α)upper side chain at C-5 (internal acetalization), which gives the hemiacetal bismercurial intermediate (**11**). The reason for the final formation of **5** from **11** could arise from the different behaviour,

under DM conditions, of two β-hydroxymercuriated systems of **11**. The C-Hg linkage at C-7 is easily reduced by $NaBH_4$ because of syn relationship between mercury moiety at C-7 with adjacent OH-6 (the elimination of hydroxymercury moiety is thus not favored); on the contrary, the mercury unit at C-4 becomes involved into a dehydroxymercuration reaction[17] with formation of the enol ether double bond.

These results demonstrate the formation of the organobismercurial intermediate (**10**) and the reversibility[17] of the hydroxymercuration reaction at Δ^7 cyclopentene double bond to regenerate the monomercurial intermediate (**2**); these events may also account for the previous unsuccessful attempts[3,6b] to transform isoeucommiol (**3**) by OM/DM directly into the cyclopentanepentols (**6**) or (**9**), which are key-intermediates in a synthesis[6b] of a methyl jasmonate precursor.

We decided to carry out a thorough study of the whole OM/DM reaction in water with a slight $Hg(OAc)_2$ excess in order to better ascertain the actual reactivity of trisubstituted cyclopentene double bond of **3**. An accurate tlc control showed that in the OM stage, **3** was indeed completely transformed into the probable organomercurial intermediate (Rf=0); however, the DM step ($NaBH_4$) led to recovery of almost pure **3** .

In actual fact, **3** proved to be contaminated by traces of a less polar compound (tlc), evidently neglected in previous experiments.[3,6b] After chromatographic separation, the impurity was attributed (by ^1H and ^{13}C nmr analysis) the structure (**12**); this was derived from **3** by intramolecular OM reaction of the β-hydroxyethyl side chain at C-5[20] on the olefinic carbon C-8, followed by DM of the mercurial intermediate (**13**). The structure assigned to the reaction product (**12**) was further confirmed by the formation of its tri-O-acetyl derivative (**14**). The hypotheses regarding the structure and key role of intermediate (**13**) were once again supported by a direct experiment of OM of **3** with $Hg(OAc)_2$ (1.2 equivalents) in D_2O solution in a nmr tube. When the ^1H and ^{13}C nmr spectra of this OM mixture were analyzed, we in fact observed the rapid formation of a single mercurial intermediate from **3** through an internal alkoxymercuration reaction leading to the monomercuriated 2-oxabicyclo[3.2.1]octane derivative (**13**). The olefinic H-7 and allylic 2H-10 protons signals of **3** were seen to disappear completely as early as the first ^1H nmr control (10 min after the start). Since the new doublet at δ 3.38 ($J_{6,7}$ = 7.1 Hz) collapsed into a singlet by irradiation of hydroxymethine H-6 proton doublet (δ 4.31, $J_{6,7}$ = 7.1 Hz; counterpart C-6 resonance at 77.48 ppm), this new doublet was assigned to the H-7 proton geminal with Hg moiety (the C-7 counterpart resonated at 60.89 ppm). The octet centered at δ 3.61 was assigned to the oxymethylene 2H-3 protons (C-3 and C-4

counterparts appeared at 68.89 and 24.95 ppm respectively). The remaining proton assignments were supported by spin decoupling and, above all, by COSY 45° experiments registered directly on the OM mixture. The comparison of COSY 45° spectra of organomercurial intermediates (**10**) and (**13**) clearly showed the common cross peaks relative to correlation H-6/H-7 (the site of mercury attack in both adducts proved to be carbon C-7). As expected, the successive demercuration ($NaBH_4$) of **13** to **12** led to the disappearance of the H-7 proton doublet at δ 3.38; this was replaced by a double doublet and a slightly splitted doublet relative to the non equivalent protons 2H-7, which were respectively centered at δ 2.36 ($J_{7,7'}$= 15.7 Hz, $J_{6,7}$ = 7.3 Hz) and δ 1.59 ($J_{7,7'}$= 15.7 Hz). These results confirmed that the apparent lack of reactivity of **3** at the end of the whole OM/DM procedure consisted of the balance of two opposing reactions: an initial OM step with formation of the organomercurial intermediate (**13**), followed by a successive rapid and almost complete dehydroxymercuration reaction of **13** (caused by DM conditions) to the original isoeucommiol (**3**) which consequently appeared to remain unreacted.

Because of the already mentioned tendency to reversibility of hydroxy- and alkoxymercuration reactions,[17] we decided to repeat the OM/DM reaction of **3** and carry out the DM step ($NaBH_4$) after alkalinization of the OM mixture.

In these conditions, the selective formation of **12** was observed to be highly enhanced, and a non-optimized experiment enabled us to obtain this compound in 65% yield.[22] Here too, the internal alkoxymercuration reaction was preferred to the hydration of the trisubstituted double bond.

Sodium borohydride is considered the reagent of choice for reductive cleavage of C-Hg linkage in the DM step; however, in the case of aucubin (**1**), it unfortunately causes the simultaneous reduction of 1,5-dialdehydic system (at iridoidic C-1 and C-3 carbons) to the corresponding 1,5-diol system. If it had proved possible to discover a chemoselective reducing agent capable of cleaving the C-Hg linkage while leaving the aldehydic functions unchanged, this might well have represented a new nonenzymatic way of obtaining iridoid aglycones from parent glucosides. Such features were found in the Zn/CH_3COOH system which enabled us to obtain aucubigenin (**16**) through the selective reduction of aucubin monomercurial intermediate (**2**). The aglycone was extracted from the DM mixture with EtOAc (50%); after careful tlc and nmr comparison, this was recognized either as tri-O-acetyl aucubigenin (**17**)[23] or as isoeucommiol (**3**)[6] (by reduction of **16** with $NaBH_4$).

On the contrary, when **16** was extracted from the DM mixture with boiling EtOAc (78°C) in a liquid-liquid extractor[15], the final extracts were found to contain mainly eucommial (**18**) (formed

by the shift of double bond of **16** to a more stable tetrasubstituted and conjugated position); this compound had already obtained from **1** in different conditions[13] and represented the immediate precursor of eucommiol (**19**), a natural cyclopentenetetrol.[24a-c]

EXPERIMENTAL

^{1}H Nmr spectra were recorded on an XL-300 W.B. Varian spectrometer using TMS as internal standard for spectra in $CDCl_3$ and the HDO signal (δ 4.70 at probe temperature of 21°C) for spectra in D_2O. Chemical shifts are reported in parts per million and are given in δ units. ^{13}C Nmr were recorded on the same spectrometer, operating at 75.4 MHz. Chemical shifts of spectra run in D_2O solution were referenced to dioxane (67.4 ppm), and those in $CDCl_3$ to TMS (0 ppm). We used the following symbols to report the multiplicity and shape of signals: br d (broad doublet), br m (broad multiplet), br s (broad signal), cm (complex multiplet), d (doublet), dd (double doublet), dt (double triplet), m (multiplet), o (octet), pq (pseudoquartet), q (quartet), qp (quintuplet), s (singlet), t (triplet), td (triplet of doublets). ^{13}C Nmr assignments marked with * or ** may be interchangeable. Aucubin (**1**) was isolated from Aucuba japonica as previously described[25] (about 100 g of **1** were obtained from 5 Kg of fresh plant and recrystallized from EtOH as colorless crystals). The progress of the reactions and chromatographic separations were monitored by tlc on silica gel plates (Merck kieselgel 60 F_{254} 0.25mm). Compounds were visualized by spraying with 2N H_2SO_4 and heating on a hot plate until spots developed. Column chromatographies were performed on silica gel (Merck kieselgel, 70-230 mesh). The yields were not optimized. Purity of each compound was checked by silica gel plates.

Preparation of 3, 5, 6 by OM/DM of 1 - To a solution of **1** (1.0 g, 2.9 mmol) in H_2O (20 ml), $Hg(OAc)_2$ (1.85 g, 5.8 mmol) was added. The solution was stirred at room temperature until the complete disappearance of **1** on tlc (15 min) and the formation of the organomercurial intermediate (Rf=0, tlc in $CHCl_3$/MeOH 7:3). A $NaBH_4$ excess (270 mg, 7.1 mmol) was then added under stirring with instantaneous precipitation of Hg(0). After 15 min mercury was removed by filtration and CO_2 was bubbled through the solution until pH 7-8. Decolorizing charcoal was added under stirring until a tlc control showed the complete adsorption of the organic compounds. The suspension was placed on a silica gel layer stratified in a Gooch funnel and charcoal was washed with distd H_2O (2-3 l) until the complete elution of inorganic salts. Successive elution of organic fraction with MeOH (0.5 l) gave, after evaporation of solvent under reduced pressure, an oily residue which consisted of a mixture of

three compounds with Rf 0.58, 0.35 and 0.22 respectively (tlc in $CHCl_3$/MeOH 8:2). When the crude residue (450 mg) was subjected to a silica gel column chromatography ($CHCl_3$/MeOH 9:1) monitored by tlc, it gave - in sequence - pure **5** (64 mg, 12%), **3** (135 mg, 25%) and **6** (208 mg, 35%) as colorless oils.

Compound (5) - **^{1}H nmr** (D_2O, δ): 1.68 (1H, d, $J_{7,7'}$= 15.8 Hz, H-7), 2.21 (1H, br s, H-9), 2.26 (1H, br d, H-5), 2.38 (1H, dd, $J_{7,7'}$= 15.8 Hz, $J_{6,7'}$= 6.8 Hz, H-7'), 3.60 (2H, o, overlapped to 2H-10, 2H-1), 3.62 (2H, dd, $J_{10,10'}$= 12.0 Hz, 2H-10), 4.19 (1H, d, $J_{6,7'}$= 6.8 Hz, H-6), 4.78 (1H, td, $J_{3,4}$ = 5.9 Hz, $J_{4,5}$ = 1.7 Hz, H-4), 6.08 (1H, d, $J_{3,4}$ = 5.9 Hz, H-3); **^{13}C nmr** (D_2O, ppm): 41.56 (C-9, d), 43.60 (C-5, d), 47.19 (C-7, t), 58.91 (C-1, t), 65.96 (C-10, t), 75.41 (C-6, d), 86.39 (C-8, s), 101.37 (C-4, d), 142.71 (C-3, d). Anal. Calcd for $C_9H_{14}O_4$: C 58.05, H 7.58. Found: C 58.01, H 7.50.

Compound (3) - *For ^{1}H nmr and ^{13}C nmr spectra (D_2O), see ref. 7.*

Compound (6) - **^{1}H nmr** (D_2O, δ): 1.46 (1H, m, H-4), 1.60 (1H, m, overlapped to H-7, H-4'), 1.64 (1H, dd, $J_{7,7'}$= 14.4 Hz, $J_{6,7}$ = 5.4 Hz, H-7), 1.88 (1H, cm, H-5), 1.99 (1H, dd, $J_{7,7'}$= 14.4 Hz, $J_{6,7'}$= 7.0 Hz, H-7'), 2.15 (1H, q, J = 6.6 Hz, H-9), 3.40 (2H, dd, $J_{10,10'}$= 11.7 Hz, 2H-10), 3.53 (2H, td, J_1 = 6.6 Hz, J_2 = 1.2 Hz, 2H-3), 3.60 (2H, d, $J_{1,9}$ = 6.6 Hz, 2H-1), 4.03 (1H, q, $J_{6,7}$ = 5.4 Hz, H-6) ; **^{13}C nmr** (D_2O, ppm): 31.26 (C-4, t), 45.10 (C-7, t), 46.04 (C-5, d), 47.64 (C-9, d), 59.22 (C-1, t), 61.57 (C-3, t), 69.31 (C-10, t), 75.80 (C-6, d), 81.95 (C-8, s). Anal. Calcd for $C_9H_{18}O_5$: C 52.41, H 8.80. Found: C 52.27, H 8.73.

General procedure for preparation of acetyl derivatives (7) and (8) - To a solution of **5** or **6** (1 mmol) in anhydrous pyridine (2 ml), $(CH_3CO)_2O$ (4 ml, 42 mmol) was added and the reaction mixture was stirred for 4-5 h at room temperature. After cooling in an ice-bath, MeOH (10 ml) was added and after 30 min volatile fraction was removed under reduced pressure. The residue, diluted with EtOAc (20 ml), was washed with 1N HCl (3 x 5 ml), then with saturated solution of $NaHCO_3$ (3 x 5 ml), and finally with water. The final EtOAc solution was dried over Na_2SO_4 and evaporated under reduced pressure to give an oily residue. Chromatographic purification of this residue on a silica gel column eluted with benzene/Et_2O 75:25 gave pure acetyl derivatives (**7**) (295 mg, 95%) or (**8**) (350 mg, 93%) as colorless oils.

Compound (7) - **^{1}H nmr** ($CDCl_3$, δ): 1.97 (1H, d, J = 16.1 Hz, H-7), 2.02 (3H, OAc), 2.06 (3H, OAc), 2.11 (3H, OAc), 2.42 (1H, br m, H-9), 2.46 (1H, br d, H-5), 2.63 (1H, dd, $J_{7,7'}$= 16.1 Hz, $J_{6,7'}$= 7.1 Hz, H-7'), 4.22 (2H, dd, $J_{1,1'}$= 6.1 Hz, $J_{1,9}$ = 3.6 Hz, 2H-1), 4.28 (2H, dd, $J_{10,10'}$= 11.7 Hz, 2H-10), 4.83 (1H, td, $J_{3,4}$ = 5.8 Hz, $J_{4,5}$ = 1.6 Hz, H-4), 5.08 (1H, d, $J_{6,7'}$= 7.1 Hz, H-6), 6.21 (1H, d,

$J_{3,4}$ = 5.8 Hz, H-3); ^{13}C **nmr** ($CDCl_3$, ppm): 20.78, 20.92, 21.19 (CH_3 of OAc, s), 38.43 (C-9, d), 40.76 (C-5, d), 45.03 (C-7, t), 60.95 (C-1, t), 66.74 (C-10, t), 76.63 (C-6, d), 83.99 (C-8, s), 98.98 (C-4, d), 143.20 (C-3, d), 170.34, 170.60, 170.87 (CO of OAc). Anal. Calcd for $C_{15}H_{20}O_7$: C 57.68, H 6.45. Found: C 57.59, H 6.49.

Compound (8) - ^{1}**H nmr** ($CDCl_3$, δ): 1.65-1.90 (2H, m, overlapped, 2H-4), 1.93 (1H, dd, $J_{7,7'}$= 15.1 Hz, $J_{6,7}$ = 3.5 Hz, H-7), 2.03, 2.06, 2.09, 2.13 (OAc), 2.25-2.35 (1H, cm, overlapped to H-7', H-5), 2.32 (1H, dd, overlapped to H-5, $J_{7,7'}$= 15.1 Hz, $J_{6,7'}$= 6.8 Hz, H-7'), 2.41 (H, q, J = 6.4 Hz, H-9), 4.12 (2H, dd, $J_{10,10'}$= 11.4 Hz, 2H-10), 4.13 (2H, t, J = 6.6 Hz, 2H-3), 4.30 (2H, o, J = 11.5 Hz, 2H-1), 5.09 (1H, qp, $J_{6,7}$ = 3.5 Hz, H-6); ^{13}**C nmr** ($CDCl_3$, ppm): 20.82, 20,91, 21,05, 21,19 (CH_3 of OAc, s), 27.26 (C-4, t), 43.47 (C-7, t), 43.77*(C-5, d), 45.01*(C-9, d), 60.93 (C-1, t), 62.80 (C-10, t), 70.65 (C-3, t), 77.61 (C-6, d), 79.39 (C-8, s), 170.40, 170.91, 170.96, 171.25 (CO of OAc). Anal. Calcd for $C_{17}H_{26}O_9$: C 54.54, H 7.00. Found: C 54.61, H 6.92.

OM of 3 and DM in "non-basic conditions" - To a solution of **3** (0.5 g, 2.6 mmol) in H_2O (10 ml), $Hg(OAc)_2$ (0.85 g, 2.7 mmol) was added and the resulting clear solution was stirred until complete formation of organomercurial intermediate (Rf=0, tlc in $CHCl_3$/MeOH 7:3). Solid $NaBH_4$ (120 mg, 3.2 mmol) was added under stirring, with instantaneous precipitation of Hg(0). After 10 min mercury was removed by filtration on paper and CO_2 was bubbled through the aqueous solution until pH 7-8. Small amounts of decolorizing charcoal were subsequently added until a tlc control showed the complete absorption of organic material. The suspension was then placed on a silica gel layer stratified in a Gooch funnel, and subsequently charcoal was washed with distd water (2 l) to remove inorganic salts. Successive elution of organic fraction with MeOH (250 ml) gave, after evaporation of solvent, a crude residue (330 mg) containing **3** (Rf=0.35, $CHCl_3$/MeOH 8:2) as almost unique product, accompanied by traces of a less polar compound (**12**) (Rf=0.43). Chromatographic purification of this residue on a silica gel column with $CHCl_3$/MeOH 8:2 gave pure **12** (20 mg, 4%) and **3** (290 mg, 58%) as colorless oils.

Compound (12) - ^{1}**H nmr** (D_2O, δ): 1.20 (1H, dt, $J_{4,4'}$= 13.8 Hz, H-4), 1.59 (1H, d, $J_{7,7'}$= 15.7 Hz, H-7), 1.77 (1H, cm, H-4'), 1.98 (1H, pq, H-9), 2.21 (1H, br s, H-5), 2.36 (1H, dd, $J_{7,7'}$= 15.7 Hz, $J_{6,7'}$= 7.3 Hz, H-7'), 3.46 (2H, dd, $J_{10,10'}$= 11.9 Hz, 2H-10), 3.48 (1H, td, overlapped to 2H-10, H-3), 3.68 (1H, dd, $J_{3,3'}$= 12.8 Hz, $J_{3',4'}$= 7.3 Hz, H-3'), 3.75 (2H, dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 2H-1), 4.20 (1H, dd, $J_{6,7'}$= 7.3 Hz, $J_{6,7}$ = 2.4 Hz, H-6); ^{13}**C nmr** (D_2O, ppm): 23.60 (C-4, t), 42.88 (C-7, t), 44.50* (C-5, d), 45.65* (C-9, d), 58.31 (C-1, t), 61.64 (C-10, t), 66.36 (C-3, t), 73.50 (C-6, d),

85.32 (C-8, s). Anal. Calcd for $C_9H_{16}O_4$: C 57.43, H 8.57. Found: C 57.36, H 8.55.

Compound (3) - For ^1H and ^{13}C nmr spectra, see ref. 7.

Preparation of acetyl derivative (14) - See general procedure given for preparation of **7** and **8**.

Compound (14) - **^1H nmr** ($CDCl_3$, δ): 1.37 (1H, dt, $J_{4,4'}$= 13.2 Hz, $J_{3',4}$= 6.3 Hz, $J_{3,4}$= 4.5 Hz, H-4), 1.80-1.95 (1H, m, overlapped to H-7, H-4'), 1.85 (1H, d, $J_{7,7'}$= 16.2 Hz, H-7), 2.06, 2.07, 2.08 (OAc), 2.22 (1H, pq, H-9), 2.44 (1H, br s, H-5), 2.57 (1H, dd, $J_{7,7'}$= 16.2 Hz, $J_{6,7'}$= 7.2 Hz, H-7'), 3.63 (1H, td, $J_{3,3'}$= 12.3 Hz, $J_{3,4}$= 4.5 Hz, H-3), 3.89 (1H, dd, $J_{3,3'}$= 12.3 Hz, $J_{3',4}$= 6.3 Hz, H-3'), 4.11 (2H, dd, $J_{10,10'}$= 11.7 Hz, 2H-10), 4.39 (2H, d, J = 7.0 Hz, 2H-1), 5.06 (1H, dd, $J_{6,7'}$= 7.2 Hz, $J_{6,7}$ = 2.4 Hz, H-6); **^{13}C nmr** ($CDCl_3$, ppm): 20.87, 20.95, 21.04 (CH_3 of OAc, s), 23.39 (C-4, t), 40.58 (C-7, t), 42.18*(C-5, d), 42.81*(C-9, d), 60.58** (C-10, t), 60.73**(C-1, t), 67.38 (C-3, t), 75.73 (C-6, d), 81.74 (C-8, s), 170.72, 170.78, 170.96 (CO of OAc). Anal. Calcd for $C_{15}H_{22}O_7$: C 57.32, H 7.05. Found: C 57.29, H 7.1.

Preparation of 12 "via" OM of 3 and DM in "basic" conditions - To a solution of **3** (500 mg, 2.6 mmol) in H_2O (10 ml), $Hg(OAc)_2$ (0.85 g, 2.7 mmol) was added and the stirring was continued until complete formation of organomercurial intermediate (Rf=0, tlc in $CHCl_3$/MeOH 7:3). The OM mixture was made alkaline (pH 10-11) by addition of 5N NaOH solution with formation of a bright yellow suspension. Solid $NaBH_4$ (130 mg, 3.4 mmol) was added and stirring was continued until complete reduction of organomercurial intermediate. After removal of Hg(0) by filtration, CO_2 was bubbled through the solution until pH 7-8. Decolorizing charcoal was added until the organic material had been totally adsorbed and the suspension was then stratified on a silica gel layer in a Gooch funnel. Charcoal was washed with distd water (2-3 l) to remove inorganic salts, and subsequently eluted with MeOH (250 ml). The methanolic solution was evaporated under reduced pressure to give a residue (380 mg), which was chromatographed on a silica gel column ($CHCl_3$/MeOH 9:1) to give pure **12** (315 mg, 65%) and **3** (35 mg, 7%) as colorless oils.

Preparation of aucubigenin (16) by OM/DM of 1 - To a solution of **1** (1 g, 2.9 mmol) in H_2O (20 ml), $Hg(OAc)_2$ (0.95 g, 3 mmol) was added and the resulting clear solution was stirred until complete disappearance of **1** and formation of monomercurial intermediate (Rf=0, tlc in $CHCl_3$/MeOH 7:3). The OM solution was acidified with AcOH (0.5 ml), then Zn powder (390 mg, 6 mmol) was added and the reaction mixture was stirred until the complete reduction and formation of a new compound, less polar than **1** (tlc, EtOAc/MeOH 9:1). After filtration, the aqueous solution was extracted with EtOAc (4 x 20 ml). The combined organic layers were dried with anhydrous

Na_2SO_4, before being filtered and evaporated under reduced pressure at 20°C. The crude residue (310 mg), chromatographed on silica gel, afforded pure **16** (264 mg, 50%) as colorless oil.

Compound (16) - For ^1H nmr and ^{13}C nmr spectra, see ref. 15.

Preparation of acetyl derivative (17) - See general procedure given for preparation of acetyl derivatives (**7**) and (**8**).

Compound (17) - For ^1H nmr spectrum, see ref. 23.

Formation of eucommial (18) by OM/DM of 1 - The above procedure for preparation of **16** from **1** was followed until the complete reduction of organomercurial intermediate with Zn/AcOH. The aqueous suspension was filtered and extracted in a continuous liquid-liquid extractor with boiling EtOAc for several hours. Organic phase was dried (Na_2SO_4) and evaporated to dryness. The oily residue, which contained eucommial (**18**) as almost unique product was chromatographed on silica gel with EtOAc/Me_2CO 4:1 to give pure **18** (325 mg, 62%) as colorless oil.

Compound (18) - For ^1H nmr and ^{13}C nmr spectra, see ref. 13.

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