Organomercury Chemistry of Iridoid Glucosides. Part 2.† Chemoselective Methoxymercuriation-Demercuriation of Aucubin: a New Approach to Optically Active Cyclopentenols [1]

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Methoxymercuriation of aucubin (**1**) occurred chemoselectively at the enol ether Δ^3 double bond with formation, after the demercuriation of the organomercurial intermediate (**6**), of the chiral cyclopentenoid *O*-methyl ethers (**5**), (**12**), and (**13**). The mechanism proposed for the demercuriation of (**6**) was supported by selective formation of the three products on adjusting the pH of the reduction medium. The structural features of (**5**), (**12**), and (**13**) make them useful precursors for syntheses of bioactive cyclopentanoid compounds.

In continuation of our program of syntheses of cyclopentanoid compounds starting from iridoid glucosides,[2] we recently reported[2i] the first application of a hydroxymercuriation–demercuriation reaction (OM/DM) to aucubin (**1**), the most abundant iridoid glucoside. This entailed chemoselective addition of a mercury salt and water as nucleophile to the enol ether double bond of (**1**) and successive reduction ($NaBH_4$) of the organomercurial intermediate (**4**) so obtained.

The choice of appropriate demercuriation conditions led to the selective formation of epimeric cyclopentene tetrols (**8**)[3] (isoeucommiol) and (**9**) (3-*epi*-isoeucommiol) both easily transformed into the corresponding cyclization products 6,7-dihydroxymethyl-*cis*-2-oxabicyclo[3.3.0]oct-7-enes (**10**)[2a,b] and (**11**).

Here we describe some results obtained in the corresponding methoxymercuriation–demercuriation reaction of (**1**) (MM/DM) carried out in MeOH as nucleophile and solvent. As with the earlier reactions, this one proved chemoselective towards the enol ether double bond of (**1**) but afforded, besides the expected 3,4-dihydro-3-methoxyaucubin (**5**), the isomeric cyclopentenoid methyl vinyl ethers (**12**) and (**13**), both having side chains at C-2 and C-3 differentiated in terms of oxidation level and protection.

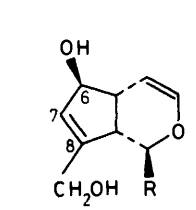
These structural features make the compounds particularly useful as a chiral starting material for syntheses of cyclopentenoids.

Our target was to obtain the above compounds selectively, and the successful result represented indirect support of the mechanism we proposed for demercuriation of the unique organomercurial intermediate (**6**).

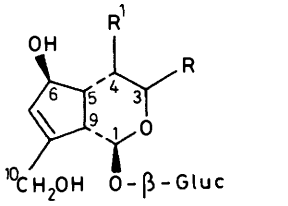
Results and Discussion

Our first attempt at a MM/DM reaction of (**1**) was carried out along the lines of classical MM/DM reactions,[4] *i.e.* by treating (**1**) with $Hg(OAc)_2$ in MeOH as nucleophile and solvent. On the basis of literature data relative to MM/DM reactions of enol ether systems[5] the exclusive formation of 3,4-dihydro-3-methoxyaucubin (**5**) was expected through $NaBH_4$ reduction of the organomercurial intermediate (**6**).

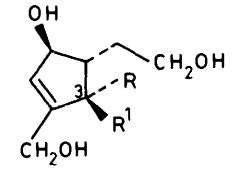
To our surprise the reaction afforded three products (initially in variable ratio) which were separated by careful chromatography and identified by detailed NMR analysis (^1H and ^{13}C).



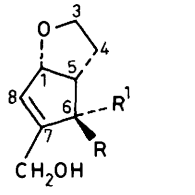
(**1**) R = O-β-Gluc
(**2**) R = H
(**3**) R = OH



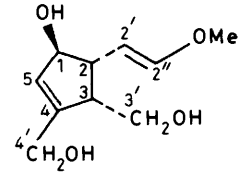
(**4**) R = OH, R^1 = HgOAc
(**5**) R = αOCH$_3$, R^1 = H
(**6**) R = αOCH$_3$, R^1 = βHgOAc
(**7**) R = αOCD$_3$, R^1 = βHgOAc



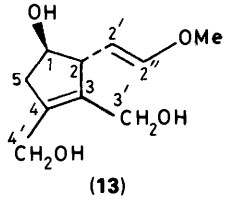
(**8**) R^1 = H, R = CH_2OH
(**9**) R = H, R^1 = CH_2OH



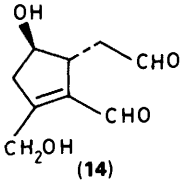
(**10**) R^1 = H, R = CH_2OH
(**11**) R = H, R^1 = CH_2OH



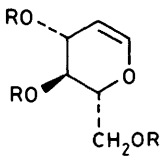
(**12**)



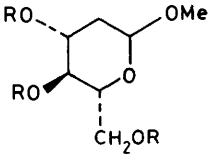
(**13**)



(**14**)



(**15**) R = H
(**16**) R = Ac



(**17**) R = H
(**18**) R = Ac

The most polar compound [R_F value slightly greater than that of (**1**)] proved to be the expected methyl acetal (**5**) as a mixture of epimers at C-3 in 9:1 ratio (inferred by the pair of 7-H signals in ^1H NMR spectrum).

The stereochemistry at the C-3 centre was established

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through a careful analysis of ^1H NMR data corroborated by selective spin decoupling experiments. The identical value (*ca.* 40–45°) of the dihedral angle $\Phi_{1,9}$ in (**1**) ($J_{1,9}$ 5.0 Hz)[6] and (**5**) ($J_{1,9}$ 5.4 Hz) indicates that in the latter compound the *O*-β-D-glucose entity at C-1 has the same axial β orientation as in (**1**).[7] The stereochemical nature of C-1 of (**5**) strongly limits the possible conformations of the tetrahydropyran ring. An analysis of a Dreiding model indicates that α attack of methanol on (**1**) is favoured by the lack of dipole–dipole repulsions[8] between the incoming 3-methoxy group and the β-oriented *O*-D-glucose entity at C-1. The consequent α equatorial orientation of the 3-OMe group is confirmed by the coupling constants $J_{3,4}$ and $J_{3,4'}$ (3.7 and 9.1 Hz respectively) which are in good agreement with the dihedral angles of *ca.* 50° and 160° respectively observed in the model between 3-βH/4-βH and *trans* -diaxial 3-βH/4-αH[9] (a β orientation of 3-OMe would cause almost identical values for both coupling constants).

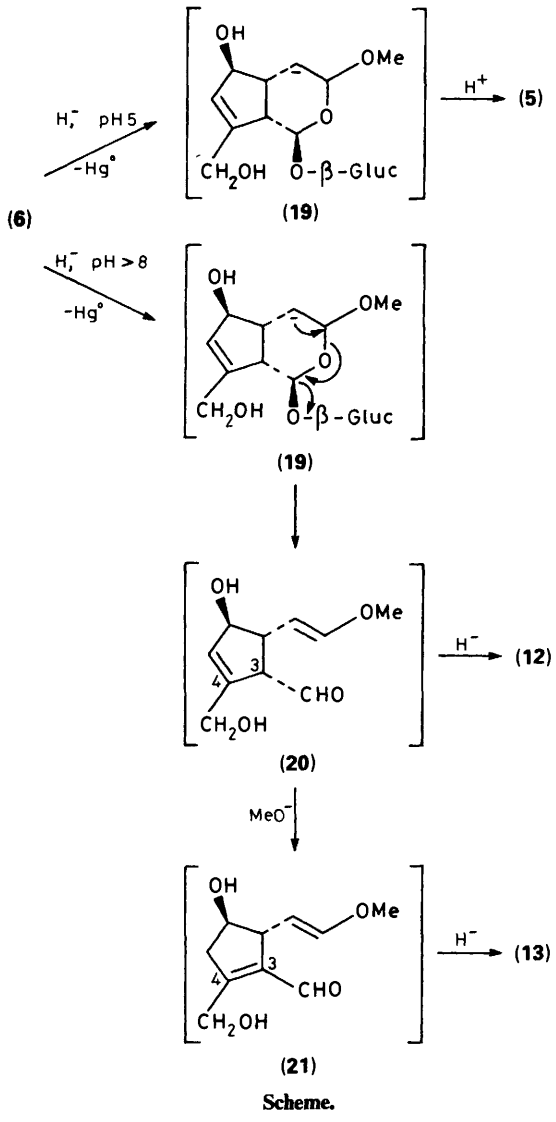
Far less predictable were, however, the isomeric structures (**12**) and (**13**) assigned to the other compounds. In fact, as common features they exhibit the loss of the glucose entities and the formation of a *trans* methyl vinyl ether function at C-2 [$J_{2',2''}$ 12.6 Hz in (**12**) and 11.9 Hz in (**13**)],* while differing only in the position of the cyclopentene double bond [Δ^4 in (**12**) and Δ^3 in (**13**)]. A noteworthy result was that (**12**) proved rather unstable and slowly transformed into the stable cyclic enol ether (**2**) (the reaction was accelerated by mild acid catalysis).

We successfully proved that (**6**) was the sole and common organomercurial intermediate of (**5**), (**12**), and (**13**) performing an MM experiment on (**1**) directly in a NMR 5 mm tube with $Hg(OAc)_2$ (1 mol equiv.) and CD_3OD. A series of ^1H and ^{13}C NMR spectra of the reaction mixture, registered at different times showed, as expected, the formation of an organomercurial intermediate (**7**) (the adduct, stable for several days in CD_3OD solution, contained, as impurity, a small amount of its diastereoisomer). In fact, signals from the enol ether system of (**1**) disappeared and good agreement was observed between the aglycone resonances of (**5**) and the corresponding ones of (**7**); these showed the expected downfield shift for 4-H and C-4 signals. The stereochemistry of the C-3 and C-4 centres of (**7**) [or (**6**)] is well supported both by the α equatorial position demonstrated for 3-OMe in (**5**) (see above) and by the '*trans* addition' observed in the methoxymercuriation of a similar vinyl ether system.[10]

The formation of (**5**), (**12**), and (**13**) from the sole intermediate (**6**) evidently took place in the reductive DM stage which proved once again—as in the corresponding OM/DM reaction of (**1**)[2i]—the critical point of the whole reaction.

Bearing in mind the conditions which promoted, respectively, the selective formation of (**8**) and (**9**) from (**4**)[2i] and the double-bond shift in the transformation aucubigenin (**3**)→eucommial (**14**),[2e] we hypothesized a mechanism (see Scheme)—absolutely new for this type of reaction—which could reasonably explain the formation of (**5**), (**12**), and (**13**) from the anion (**19**) initially formed during the reduction (H^-) of organomercurial intermediate (**6**). We therefore applied the appropriate experimental conditions which led to the selective formation of (**5**), (**12**) and (**13**).

In fact, carrying out a reductive demercuriation of (**6**) under mild acidic conditions ($NaBH_4$ in 5M phosphate buffer at pH 5), simple protonation of anion (**19**) took place and (**5**) was selectively obtained in practically quantitative yield [80% + 5% of (**12**)].



Scheme.

Alternatively, the demercuriation of (**6**) with $NaBH_4$ in an aqueous, basic medium (NaOH) afforded as the sole product methyl vinyl ether (**12**) (60%) through initial formation from (**19**) of the intermediate aldehyde (**20**) and its successive reduction to (**12**). In contrast, carrying out the demercuriation of (**6**) under anhydrous basic conditions (see Experimental section) resulted in the formly group reduction being preceded by a shift of the Δ^4 double bond of (**20**) towards the more stable conjugated Δ^3 position of (**21**). Thus (**13**), obtained in good yield (52%) under these conditions, was contaminated by smaller amounts of (**12**) (13%).

The mechanism we propose is unique for OM/DM[2i] or MM/DM reactions but the peculiar reactivity of (**1**) towards MM/DM seems to be connected with the nature of the iridoidic enol ether function which owes its origin to a 1,5-dialdehyde system [in (**1**) the C-1 adjacent to the oxygen is an acetal carbon]. In fact, the MM/DM reactions of D-glucal (**15**) and its tri-*O*-acetylderivative (**16**), containing a simple enol ether system, show normal reactivity and regioselectivity[4b,10] and afford as the sole products the corresponding *O*-methyl acetals (**17**) and (**18**); the DM stage was carried out under strongly basic systems.

The good selectivity found in preparing the chiral cyclopentenoids (**5**), (**12**), and (**13**) makes them valuable synthetic

* The $J_{2',2''}$ value for the '*cis*' isomer of (**12**) was 6.3 Hz (unpublished data).

intermediates. In fact, the chemoselective protection of the Δ^3 double bond of (**5**) allows selective functionalization of the Δ^7 double bond, while in (**12**) and (**13**) the functionality of the important side chains at C-2 and C-3 is suitably differentiated and allows their selective elaboration towards cyclopentanoid compounds of biological interest.

Experimental

General Procedures.—General techniques have been described earlier.[2d] Aucubin was isolated from *Aucuba japonica* as previously described.[2g] Compound (**1**) (49 g) obtained from 2.5 kg of fresh plant was recrystallized from EtOH as colourless crystals. For ^{1}H NMR spectra recorded in D_2O the HDO signal (δ 4.70) was taken as internal standard with a probe temperature in the range 20.8–21 °C.

Methoxymercuriation (MM) of Compound (**1**) *to give the Organomercurial* (**6**).—To a stirred solution of mercuric acetate (0.35 g) in anhydrous MeOH (35 ml), crystalline compound (**1**) (0.35 g, 1.0 mmol) was added. After 20 min, TLC ($CHCl_3$–MeOH, 7:3) showed the complete disappearance of (**1**) and the presence of a product of R_F0 [the organomercurial (**6**)].

A sample of the [$^2H_3$]organomercurial intermediate (**7**) was prepared with CD_3OD in a like manner and immediately subjected to NMR spectroscopy. Compound (**7**): δ_H(300 MHz, solvent CD_3OD, probe temperature 38.7 °C to shift the signal of HDO impurity) of aglycone moiety*: 5.74 (1 H, br s, 7-H), 4.92 (1 H, d, $J_{1,9}$ 6.4 Hz, 1-H), 4.90 (1 H, d, $J_{3\beta,4\alpha}$ 9.4 Hz, 3-H), 4.66 (6-H, overlapped by 1′-H doublet), 4.19 (2 H, dd, J_{AB} 15.2 Hz, 10-CH_2), 2.71 (1 H, dd, $J_{3,4}$ 9.4 Hz, $J_{4,5}$ 5.6 Hz, 4-H), 2.63* (1 H, dd, 9-H), 2.58* (1 H, m, 5-H), 2.15 (3 H, s, HgOAc); δ_H of D-glucose entity: 4.66 (1 H, d, $J_{1',2'}$, 7.9 Hz, 1′-H), 3.74 (centre, 2 H, $J_{6'A,6'B}$ 12.0 Hz, 6′-CH_2), 3.38 (1 H, t, *J* 9.1 Hz, 3′-H), 3.26 (1 H, c m, 5′-H overlapped by other signals), 3.24 (1 H, t, *J* 9.1 Hz, 4′-H), and 3.21 (1 H, dd, $J_{2',3'}$ 9.3 Hz, 2′-H); δ_C(solvent CD_3OD, internal reference dioxane signal) of the aglycone entity: 147.06 (C-8), 130.11 (C-7), 99.93 (C-1, C-3), 79.55 (C-6), 61.50 (C-10), 53.31 (C-4), 50.14 (C-9), 43.95 (C-5); δ_C of D-glucose entity: 102.65 (C-1′), 78.41 (C-3′), 77.99 (C-5′), 74.98 (C-2′), 71.62 (C-4′), and 62.78 (C-6′).

Demercuriation (DM) of Compound (**6**): *'Non-selective' Formation of* (**5**), (**12**), *and* (**13**).—To the basified (2M NaOH) methanolic solution of (**6**), an excess of $NaBH_4$ was added and stirring maintained until all the Hg° had coagulated (30 min). A TLC ($CHCl_3$–MeOH, 7:3) showed the formation of product (**5**) with a R_F value slightly higher than (**1**) and of less-polar compounds (R_F *ca.* 0.9), which in a different eluant ($CHCl_3$–MeOH, 95:5) appeared as two products [(**12**) and (**13**)] with very close R_F values. The solution was filtered free from Hg° (Schleicher-Schüll paper, blauband 589/3) after which CO_2 was carefully bubbled through it until it reached pH 8; it was concentrated under reduced pressure and diluted with water. Decolourizing charcoal was added and the suspension poured onto a silica gel layer stratified in a Gooch funnel. The inorganic salts were totally eluted with water and, successively, the organic fraction with MeOH. Evaporation under reduced pressure of the MeOH afforded a residue (280 mg) which was purified by column chromatography. Initial elution with $CHCl_3$–MeOH (95:5) afforded, in order of elution, (**13**) (10 mg), a mixture of (**12**) and (**13**) (15 mg), and (**12**) (18 mg). Then, by increasing the polarity of the mobile phase ($CHCl_3$–MeOH, 7:3) (**7**) (150 mg) was eluted. All the compounds, obtained as oils, were further purified before recording of their spectra and satisfactory analytical data (+/− 0.3% for C, H and O) were obtained for compounds (**5**), (**12**), and (**13**). Compound (**5**): δ_H(300 MHz, solvent D_2O) of aglycone entity 5.66 (1 H, br s, 7-H), 5.01 (1 H, d, $J_{1,9}$ 5.4 Hz, 1-H), 4.77 (1 H, dd, $J_{3\beta,4\beta}$ 3.7 Hz, $J_{3\beta,4\alpha}$ 9.1 Hz, 3-H), 4.64 (6-H, partly covered by 1′-H signals), 4.12 (2 H, dd, J_{AB} 15.4 Hz, 10-CH_2), 3.38 (3 H, s, 3-OMe), 2.81 (1 H, pseudo t, $J_{5,9}$ 8.5 Hz, 9-H), 2.40 (1 H, br sfs, 5-H), 2.01–1.81 (2 H, cm, $J_{4\alpha,4\beta}$ 14.4 Hz, 4-CH_2); δ_H of D-glucose entity: 4.65 (1 H, d, $J_{1',2'}$ 7.9 Hz, 1′-H), 3.79 and 3.59 (2 H, dd, $J_{6'A,6'B}$ 12.4 Hz, $J_{5',6'A}$ 1.6 Hz, $J_{5',6'B}$ 5.4 Hz, 6′-CH_2), 3.40 (1 H, t, *J* 9.3 Hz, 3′-H), 3.34 (1 H, 5′-H covered by OMe, 3′-H and 4′-H signals), 3.25 (1 H, t, *J* 9.3 Hz, 4′-H), 3.22 (1 H, dd, $J_{2',3'}$ 9.3 Hz, 2′-H); δ_C(solvent D_2O, internal reference dioxane signal) of aglycone entity*: 147.06 (s, C-8), 130.11 (d, C-7), 98.95* (d, C-1), 98.24* (d, C-3), 80.35 (d, C-6), 60.35 (t, C-10), 56.55 (q, OMe), 47.90 (d, C-9), 43.96 (d, C-5), 29.57 (t, C-4); δ_C of D-glucose entity: 99.68 (d, C-1′), 76.99 (d, C-3′), 76.53 (d, C-5′), 73.75 (d, C-2′), 70.42 (d, C-4′), and 61.45 (t, C-6′).

Compound (**12**): δ_H(300 MHz, solvent D_2O) 6.35 (1 H, d, $J_{2',2''}$ 12.6 Hz, 2″-H), 5.66 (1 H, br s, 5-H), 4.93 (1 H, dd, $J_{2,2'}$ 9.3 Hz, 2′-H), 4.50 (1 H, m, 1-H), 4.09 (2 H, dd, J_{AB} 15.0 Hz, 4′-CH_2), 3.58 (2 H, d, 3′-CH_2), 3.49 (3 H, s, OMe), 2.67 (1 H, br s, 3-H), and 2.55 (1 H, m, 2-H); δ_C(solvent D_2O) 149.32 (d, C-2′), 147.01 (s, C-4), 130.33 (d, C-5), 102.97 (d, C-2″), 81.71 (d, C-1), 60.52 (t, C-4′), 60.16 (t, C-3′), 57.06 (q, OMe), 51.37 (d, C-2), and 50.96 (d, C-3).

Compound (**13**): δ_H(300 MHz, solvent D_2O) 6.36 (1 H, d, $J_{2',2''}$ 11.9 Hz, 2″-H), 4.62 (1 H, dd, $J_{2,2'}$ 9.6 Hz, 2′-H), 4.12 (2 H, br s, 4′-CH_2), 4.10 (1 H, d, J_{AB} 12.6 Hz, 3′-H_A), 4.01 (1 H, m, *J* 3.9 Hz, 1-H), 3.93 (1 H, d, J_{AB} 12.6 Hz, 3′-H_B), 3.46 (3 H, s, OMe), 3.05 (1 H, s, $J_{2,2'}$ 9.6 Hz, 2-H), 2.73 (1 H, dd, $J_{A,B}$ 17.0 Hz, $J_{5A,1}$ 6.6 Hz, 5-H_A), 2.22 (1 H, dd, J_{AB} 17.0 Hz, $J_{5B,1}$ 3.9 Hz, 5-H_B); δ_C(solvent D_2O) 148.97 (d, C-2′), 138.42 (s, C-3), 137.50 (s, C-4), 104.09 (d, C-2″), 77.65 (d, C-1), 61.31 (t, C-4′), 56.99 (t, C-3′), 55.97 (d, C-2), 54.79 (q, OMe), and 41.41 (t, C-5).

Selective Demercuriation (DM) of Compound (**6**) *to* 3,4-*Dihydro-3α-methoxyaucubin* (**5**).—To a cooled solution of $NaBH_4$ (1.5 g) in KH_2PO_4 buffer (5M) at pH 5.0 (15 ml), a methanolic solution of (**6**) was slowly added. After 20 min TLC ($CHCl_3$–MeOH 7:3), showed the complete disappearance of (**6**) and the formation of almost pure (**5**). The reaction mixture, filtered free from Hg° was worked up as before. The residue (345 mg) obtained by evaporation of Gooch funnel MeOH eluate was chromatographed on silica gel ($CHCl_3$–MeOH, 7:3) to afford (**12**) (10 mg) and pure (**5**) (302 mg, 80%).

Selective Demercuriation (DM) of Compound (**6**) *to* (**12**).—A methanolic solution of compound (**6**) was slowly added to a cooled (0–5 °C) solution of $NaBH_4$ (1.7 g) in 2M NaOH (5 ml). After 20 min TLC ($CHCl_3$–MeOH, 85:15) showed the complete disappearance of (**6**) and the formation of a product with a higher R_F value. The reaction mixture was filtered free from Hg° and then CO_2 was bubbled through it until it reached pH 8, it was then concentrated under reduced pressure. The aqueous solution was transferred to a liquid-liquid extractor and extracted with EtOAc (2 × 100 ml) and the combined extracts were dried and evaporated. The residue (150 mg) chromatographed on silica gel ($CHCl_3$–MeOH, 93:7) gave pure compound (**12**) (120 mg, 60%).

Selective Demercuriation (DM) of Compound (**6**) *to* (**13**).—A methanolic solution of compound (**6**) was basified (pH >8) with a 4M methoxide solution in anhydrous MeOH. To this solution was slowly added a solution of $NaBH_4$ (250 mg) in

* The assignments marked with an asterisk may be reversed.

4M methoxide solution (10 ml). After 20 min TLC ($CHCl_3$–MeOH, 95:5) showed the absence of (**6**) and the formation of two products with very close R_F values [the lowest identical with that of (**12**)]. The reaction mixture was worked up as described for (**12**) and the residue (158 mg) from the EtOAc extracts, chromatographed on silica gel ($CHCl_3$–MeOH, 95:5) to give compounds (**13**) (104 mg, 52%) and (**12**) (27 mg, 13%).

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