The conformation of some estrane acetals

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The X-ray crystal structures of a number of 6-ketoestra-1,3,5(10)-trien-17-ones and 6-ketoestra-1,3,5(10)-triene-17-one 17-*O,O*-acetals have been determined and the effect of the acetal group on the conformation of rings B and D are discussed.

Keywords: estranes, acetals, 6-keto, X-ray crystallography

In our synthesis of C-7 substituted estrane derivatives[1] as diagnostic agents for the early detection of minimal breast cancer,[2] estra-1,3,5(10)-trien-6,17-diones, protected at C-17 as acetals, are key intermediates. The nature of the protection at C17 was deemed to influence the conformation of not only the D ring but also the reactive B-ring. In order to evaluate this influence, X ray crystal structural analyses of compounds **1**–**5** were carried out.

All compounds show one independent molecule per asymmetric unit, except for **2**, which shows two independent molecules, named here as A and A', differing in the conformation of ring D (see below). Estranes **1**–**5** exhibit a nearly planar A ring. The B ring of all 6-ketoestrane derivatives **1**, **3**–**5** is in the envelope conformation, whereas the B ring of **2** has a half chair conformation. The carbonyl group C(6)=O(2) in all 6-ketoestrane derivatives **1**, **3**–**5** is nearly in the plane defined by the A ring with torsion angles C(4)–C(5)–C(6)–O(2) ranging from –0.1(4)° for **5** to 2.6(2)° for **3**. Torsion angles in ring B are influenced by the acetalisation of the carbonyl group C(17)=O in ring D. In particular the torsion angle C(6)–C(7)–C(8)–C(9) is affected with –51.8(3)° for the diketone **1** being smaller than for the acetalised products (ranging from –57.6(2)° for **3** to –60.4(4)° for **4**). Less affected are the torsion angles that include one or more carbons of ring A such as the torsion angle C(7)–C(8)–C(9)–C(10) with a value of 56.0(3)° for diketone **1** and values for the acetals ranging from 57.8(2)° for **3** to 59.2(4)° for both **4** and **5**. Importantly, this means that the angle that the carbonyl function at C6 forms with the mean plane of ring B is influenced by the acetalisation at the C17 keto group. This can also be noted in the difference in the torsion angle O(2)–C(6)–C(7)–C(8) with –157.0(3)° for **1** and a range of –150.4(4)° for **5** and –153.1(2)° for **3**. It must be noted, however, that an X-ray crystal structure of the 17-keto derivative of **5** has been published recently,[3] where it could be shown that the B-ring conformation can also be influenced by other than purely geometric parameters such as the described hydrogen bonding between the 9-hydroxy function and the 17-keto group.[3]

The torsion angles C(7)–C(8)–C(14)–C(13) and C(7)–C(8)–C(9)–C(11), which include the bridge head atoms C8, C9, C13 and C14 for fused ring systems B, C and D, are totally conserved, with a difference of torsion angle between the acetals **3**–**5** and the diketone **1** of 0.3(3)° and 1.6(3)°, respectively. This signifies conformational rigidity of the molecules in this region of their framework.

The C ring of all compounds exists in a chair conformation. The torsion angles within ring C among the compounds are more conserved. Compounds **1**, and **3**–**5** do not differ much in torsion angle C(11)–C(9)–C(11)–C(12), with the maximum difference of 2.7° between **4** and **5** stemming from the substitution at C9 in **5,** and in torsion angle C(11)–C(12)–C(13)–C(14), with the maximum difference of 2.8° between compounds **3** and **5** on the one hand and **4** on the other resulting from an interaction between the acetal function and the angular methyl group [C(17)] connected to C(13). This difference between compounds **3**, **5** and **4** can also be found in the torsion angle C(11)–C(12)–C(13)–C(17).

Naturally, the largest difference in conformation of the compounds, influenced by the acetalisation and the type of acetalisation lies in ring D. While the ring D of the diketone **1** takes up an envelope conformation (envelope 96.6% with the flap at C14, half-chair 3.4%), ring D of all the acetals resides in a conformation that is between half-chair and envelope (for **2A**, envelope 47.8%, half-chair 52.2%; for **2A×**, envelope 40.6%, half-chair 59.4%, for **3**, envelope 64.9% with the flap at C17, half-chair 35.1%; for **4**, envelope 48.3%, half-chair 51.7%; for **5**, envelope 55.5% with the flap at C13, half-chair 44.5%). Clearly, the type of acetal formed from the 17-keto functionality has an influence on the D ring conformation (*e.g.*, **3** [1,3-dioxolane] *vs* **2A**, **2A×**, **4** and **5** [1,3-dioxane]), where the more rigid dioxybenzo group favours a D ring with a higher envelope content than the more flexible dioxane function. Interestingly, the 9-hydroxy function group not also influences the conformation of ring B, but it affects the conformation of ring D to some degree (**5** *vs* **2A**, **2A×** and **4**) through the steroidal framework.

From the studies above it can be seen that acetalisation of the 17-keto function in ring D can change the conformation of ring B in 6-ketoestrane derivatives. The change has an effect on the torsion angles defined by the 6-keto group with the neighbouring atoms of ring B. It must be kept in mind that the above results apply to the conformational differences of the ketosteroids in the crystal. In solution, conformational differences are harder to discern for these steroids. Thus, the differences in shift value for the readily identifiable β-proton at C7 are within Δδ 0.1 ppm and differences in coupling constant $^3J_{H\beta(C7)H(C8)}$ are within 0.3 Hz. It must be noted, however, that the difference in dihedral angle $\Phi_{H\beta(C7)H(C8)}$ of the compounds in the crystal is also small. Thus, the difference in dihedral angle $\Phi_{H\beta(C7)H(C8)}$ in **3** as compared to **4**, calculated from the X-ray crystal structure, is only 0.6°.

Experimental

Starting materials estrone (estra-1,3,5(10)-trien-17-one) (**6**) (Wako Pure Chemical Industries, Ltd) were used as purchased. 3-*O*-Methylestra-1,3,5(10)-trien-17-one (KOH, MeI, DMSO),[5] 3-*O*-methylestra-1,3,5(10)-trien-17-one 17,17-dimethyldioxane (**2**) (neopentyl glycol, *p*-toluenesulfonic acid, benzene)[2] and 17,17-benzodioxy-3-*O*-methylestra-1,3,5(10)-trien-3-ol-17-one (catecol, *p*-TsOH)[6] were synthesised by known procedures. 3-*O*-Methylestra-1,3,5(10)-trien-6,17-dione (**1**)[7] was prepared by deacetalisation of **4** (*p*-toluenesulfonic acid, acetone). Melting points were measured on a Yanaco microscopic hotstage and are uncorrected. Infrared

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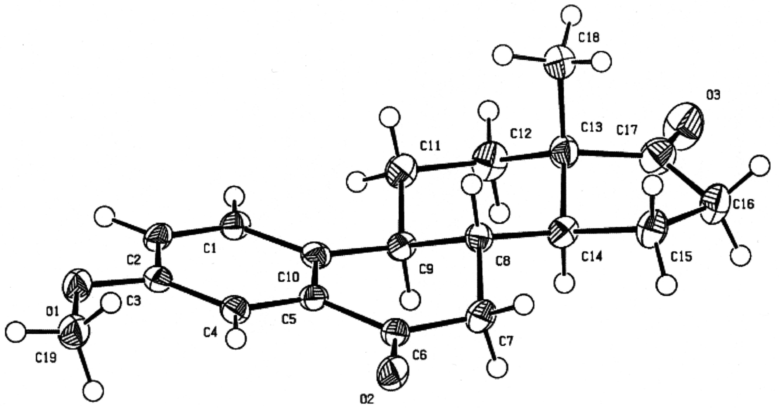


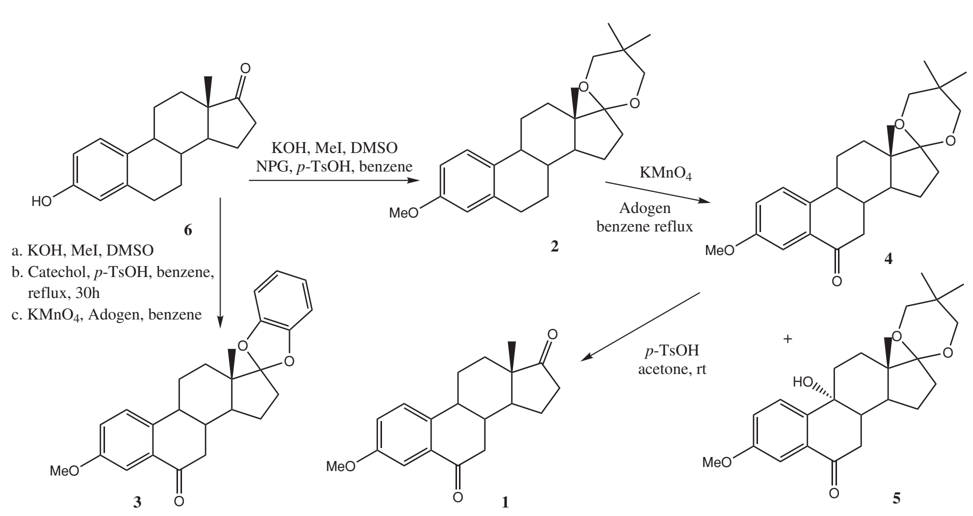
Fig. 1 X ray crystal structure of compound **1**. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

spectra were measured with a JASCO IR-700 and Nippon Denshi JIR-AQ2OM machines. ^{1}H and ^{13}C NMR spectra were recorded with a JEOL EX-270 spectrometer. The chemical shifts are relative to TMS (solvent CDCl$_3$, unless otherwise noted). Mass spectra were measured with a JMS-01-SG-2 spectrometer [electron impact mode (EI), 70 eV or fast atom bombardment (FAB)]. Column chromatography was carried out on Wakogel 300.

17,17-Benzodioxy-3-O-methylestra-1,3,5(10)-trien-3-ol-6,17-dione (**3**): A mixture of 17,17-benzodioxy-3-*O*-methylestra-1,3,5(10)-trien-3-ol-17-one (1.1 g, 2.92 mmol), KMnO$_4$ (1.88g, 11.8 mmol), Adogen 464 (530 mg) and NaHCO$_3$ (245 mg, 2.92 mmol) in benzene (32 ml) and water (32 ml) was heated under reflux for 6 h. Then, the upper organic layer was carefully pipetted off; benzene (50 ml) was added to the aqueous layer (50 ml). Thereafter, the organic layer was pipetted off once more and this process was repeated one more time. The combined organic layer was dried over anhydrous MgSO$_4$, concentrated *in vacuo* and the residue was submitted to column chromatography on silica gel (ether/hexane/chloroform 1:1:1) to give **3** (455 mg, 40%) as colourless crystals, (Found: M$^+$, 390.1833. C$_{25}$H$_{26}$O$_4$ requires M$^+$, 390.1831);ν_{max} (KBr)/cm^{-1} 3074, 3002, 2976, 2946, 1678, 1608, 1481, 1307, 1279, 1261, 1231, 1147, 1083, 547; δ_H 0.99 (3H, s, CH$_3$), 1.43–2.55 (12H, m), 2.81 (1H, dd, *J* 16.7 and 2.7 Hz), 3.85 (3H, s, OCH$_3$), 6.73–6.77 (4H, m), 7.10 (1H, dd, *J* 8.4 and 2.7 Hz), 7.31 (1H, d, *J* 8.4 Hz), 7.56 (1H, d, *J* 2.7 Hz); MS (EI, 70 eV) *m/z* (%) 390 (99) [M$^+$], 376 (39), 281 (10), 267 (24), 147 (100).

3-Methoxyestra-1,3,5(10)-trien-6,17-dione 17,17-dimethyldioxane (**4**) *and 9-hydroxy-3-methoxy-6-oxoestra-1,3,5(10)-triene-17,17-dioxane* (**5**): A solution of 3-methoxy-estra-1,3,5(10)-triene-17,17-dioxane (**2**) (5.38 g, 14.6 mmol), KMnO$_4$ (9.64 g, 61.0 mmol), Adogen 464 (1.17 g) and NaHCO$_3$ (438 mg) in benzene (56 ml) and water (56 ml) was stirred at reflux temperature. Thereafter, the cooled reaction mixture was extracted with benzene (5 × 20 ml). The organic layer was washed with water and dried over MgSO$_4$, filtered and evaporated to dryness. The residue was separated by column chromatography on silica gel (eluant: ether/chloroform/*n*-hexane 1:1:2). The resulting solid was crystallised from *n*-hexane to provide pure 3-methoxyestra-1,3,5(10)-trien-6,17-dione 17,17-dimethyldioxane[2] (**4**) (1.23 g, 22%). Further elution with the same solvent gave 9-hydroxy-3-methoxy-6-oxoestra-1,3,5(10)-triene-17,17-dioxane (**5**) (340 mg, 5.6%). (M$^+$ Found: 400.2250 C$_{24}$H$_{32}$O$_5$ requires 400.2250); ν_{max} (KBr) cm^{-1} 3536, 2958, 2864, 1671, 1604, 1318, 1287, 1236, 1101, 1026, 564; δ_H 0.73 (3H, s, CH$_3$), 0.85 (3H, s, CH$_3$), 1.16 (3H, s, CH$_3$), 2.80 (1H, m), 3.51-3.36 (4H, m), 3.84 (3H, s, OCH$_3$), 7.11 (1H, dd, ^{3}J = 8.5 Hz, ^{4}J = 2.9 Hz), 7.51 (1H, d, ^{3}J = 8.5Hz) 7.54 (1H, d, ^{4}J = 2.9 Hz); ^{13}C NMR (CDCl$_3$, 67.8 MHz and DEPT 90, DEPT 135 at 150.8 MHz) δ_C 13.0 (CH$_3$), 22.0 (CH$_3$-acetal), 22.5 (CH$_3$-acetal), 22.6 (–), 25.4 (–), 26.9 (–), 30.3 (C$_{quat}$), 32.0 (–), 37.6 (–), 41.3, 41.6, (C8 and C14), 46.9 (C13), 55.6 (OMe), 69.6 (C9), 70.6 (OCH$_2$-Acetal), 72.6 (OCH$_2$-Acetal), 108.1 (C17), 110.1 (C2), 121.4 (C4), 125.8 (C1), 132.9 (C10), 140.2 (C5), 159.4 (C3), 198.3 (C6); MS (EI, 70 eV) m/z (%) 400 (13.3) [M$^+$].

X-Ray crystal data and structure determination (*a*) *3-O-methyl-estra-1,3,5(10)-trien-3-ol-6,17-dione* (**1**) (Fig. 1). C$_{19}$H$_{22}$O$_3$, M_r 298.38, monoclinic, space group P2$_1$ (No. 4), Z = 2, D_{calc} = 1.26 g/cm^3, a = 8.330(5) Å, b = 6.962(4) Å, c = 13.550(8) Å, β = 93.81(5)°, V = 784.0(8) Å^3, Z = 2, D_{calc} = 1.26 g/cm^3, μ(MoKα) 0.84 cm^{-1}; F(000) = 320, λ = 0.71075 Å. Data were collected using a crystal of 0.25 × 0.2 × 0.1 mm^3 on a Rigaku RAXIS-RAPID diffractometer. A total number of 30948 reflections were collected for 3.0° < θ < 30.6° and $-10 \le h \le 10$, $-9 \le k \le 9$, $-17 \le l \le 17$. There were 1932 independent reflections and 1459 reflections with I > 2σ(I) were used in the refinement. The structure was solved by direct methods and refined using CRYSTALS. ψ Scan absorption correction was applied with T_{min} = 0.447 and T_{max} = 0.992. CrystalStructure 3.6.0[8] was used for the preparation of the material for publication.The final *R* indices



Scheme 1 Preparation of compounds of which X-ray crystal structures were carried out.

were [$I > 2\sigma(I)$] R_1 0.036 and (all data), $R_1 = 0.048$, $wR_2 = 0.077$. The goodness-of-fit on F^2 was 1.019 and the largest difference peak and hole was 0.30 and -0.25 eÅ^3.

The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 273305).

(*b*) *3-O-methylestra-1,3,5(10)-trien-3-ol-17-one dimethyldioxane* (**2**) (Fig. 2), $C_{24}H_{34}O_3$, M_r 370.53, monoclinic, space group P2$_1$ (No. 4), $a = 16.557(2)$ Å, $b = 7.2811(8)$ Å, $c = 18.067(2)$ Å, $\beta = 108.081(6)°$, $V = 2070.5(4)$ Å^3, $Z = 4$, $D_{calc} = 1.19$ g/cm^3, μ(MoKα) 0.76 cm^{-1}, F(000) = 808, $\lambda = 0.71075$ Å. Data were collected using a crystal of 0.4 × 0.2 × 0.1 mm^3 on a Rigaku RAXIS-RAPID diffractometer. A total number of 50732 reflections were collected for $3.7° < \theta < 30.0°$ and $-23 \le h \le 23$, $-10 \le k \le 9$, $-25 \le l \le 25$. There were 6475 independent reflections and 4865 reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and refined using CRYSTALS. Multi-scan absorption correction was applied with $T_{min} = 0.794$ and $T_{max} = 0.992$. CrystalStructure 3.6.0[8] was used for the preparation of the material for publication. The final R indices were [$I > 2\sigma(I)$] $R_1 = 0.070$ and (all data), $R_1 = 0.088$, $wR_2 = 0.202$. The goodness-of-fit on F^2 was 0.974 and the largest difference peak and hole was 0.62 and -0.47 e Å^{-3}.

The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 273306).

(*c*) *17,17-benzodioxy-3-O-methylestra-1,3,5(10)-trien-3-ol-6,17-dione* (**3**) (Fig. 3), $C_{25}H_{26}O_4$, M_r 390.48, orthorhombic, space group P2$_1$2$_1$2$_1$ (No. 19), $a = 30.134(6)$ Å, $b = 6.688(1)$ Å, $c = 9.547(2)$ Å, $V = 1923.9(7)$ Å^3 , $Z = 4$, $D_{calc} = 1.35$ g/cm^3, μ(MoKα) 0.90 cm^{-1}, F(000) = 832, $\lambda = 0.71070$ Å. Data were collected using a crystal of 0.15 × 0.04 × 0.02 mm^3 on a Rigaku RAXIS-RAPID diffractometer. A total number of 15390 reflections were collected for $3.0° < \theta < 27.5°$ and $-39 \le h \le 38$, $-8 \le k \le 8$, $-12 \le l \le 10$. There were 4391 independent reflections and 2588 reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and refined using CRYSTALS. Multi-scan absorption correction was applied with $T_{min} = 0.866$ and $T_{max} = 0.998$. CrystalStructure 3.6.0[8] was used for the preparation of the material for publication. The final R indices were [$I > 2\sigma(I)$] $R_1 = 0.064$ and (all data), $R_1 = 0.046$, $wR_2 = 0.116$. The goodness-of-fit on F^2 was 0.966 and the largest difference peak and hole was 0.28 and –0.34 e Å^{-3}.

The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 273307).

(d) *3-O-methylestra-1,3,5(10)-trien-3-ol-6,17-dione dimethyldioxane* (**4**) (Fig. 4), $C_{24}H_{32}O_4$, M_r 384.51, triclinic, space group P1 (No. 1), $a = 7.728(4)$ Å, $b = 7.873(4)$ Å, $c = 9.103(5)$ Å, $\alpha = 81.42(4)°$, $\beta = 75.01(5)°$, $\gamma = 81.73(5)°$, $V = 525.8(5)$ Å^3, $Z = 1$, $D_{calc} = 1.21$ g/cm^3, μ(MoKα) 0.81 cm^{-1}, F(000) = 208, $\lambda = 0.71075$ Å. Data were collected using a crystal of 0.25 × 0.2 × 0.2 mm^3 on a Rigaku RAXIS-RAPID diffractometer. A total number of 20810 reflections were collected for $3.1° < \theta < 30.6°$ and $-10 \le h \le 10$, $-10 \le k \le 10$, $-11 \le l \le 11$. There were 2385 independent reflections and 1987 reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and refined using CRYSTALS. Multi-scan absorption correction was applied with $T_{min} = 0.536$ and $T_{max} = 0.984$. CrystalStructure 3.6.0[8] was used for the preparation of the material for publication. The final R indices were [$I > 2\sigma(I)$] $R_1 = 0.058$ and (all data), $R_1 = 0.065$, $wR_2 = 0.161$. The goodness-to-fit on F^2 was 1.004 and the largest difference peak and hole was 0.34 and –0.34 e Å^{-3}.

The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 273308).

(e) *3-O-methylestra-1,3,5(10)-trien-3,9-diol-6,17-dione dimethyldioxane* (**5**) (Fig. 5), $C_{24}H_{32}O_5$, M_r 399.51, triclinic, space group P1 (No. 1), $a = 7.35(1)$ Å, $b = 8.11(1)$ Å, $c = 9.07(2)$ Å, $\alpha = 79.45(6)°$, $\beta = 75.61(7)°$, $\gamma = 79.99(6)°$, V = 510.1(15) Å^3, $Z = 1$, $D_{calc} = 1.304$ g/cm^3, μ(MoKα) 0.90 cm^{-1}, F(000) = 215, $\lambda = 0.71075$ Å. Data were collected using a crystal of 0.4 × 0.25 × 0.2 mm^3 on a Rigaku RAXIS-RAPID diffractometer. A total number of 19792 reflections were collected for $3.2° < \theta < 27.6°$ and $-8 \le h \le 9$, $-10 \le k \le 10$,

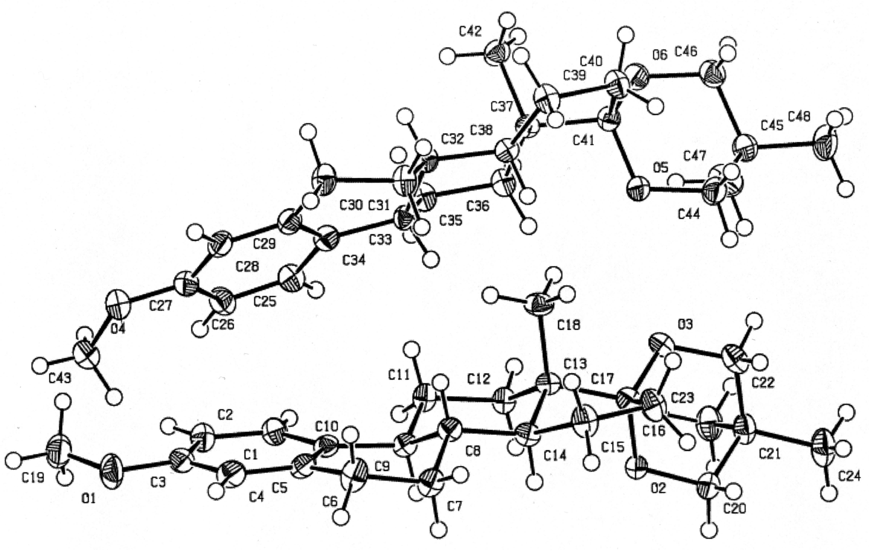


Fig. 2 X ray crystal structure of compound **2**. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

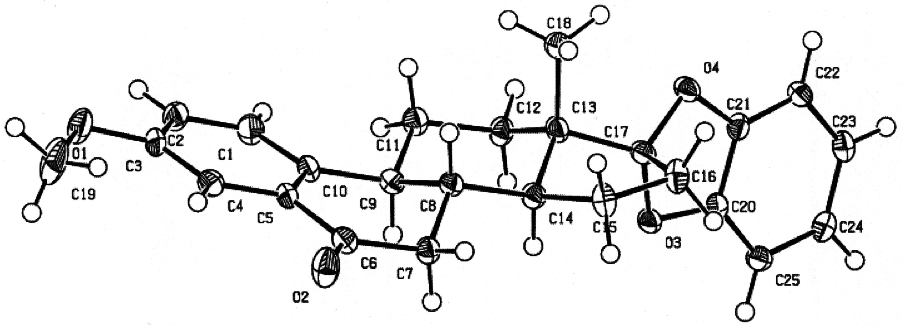


Fig. 3 X ray crystal structure of compound **3**. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

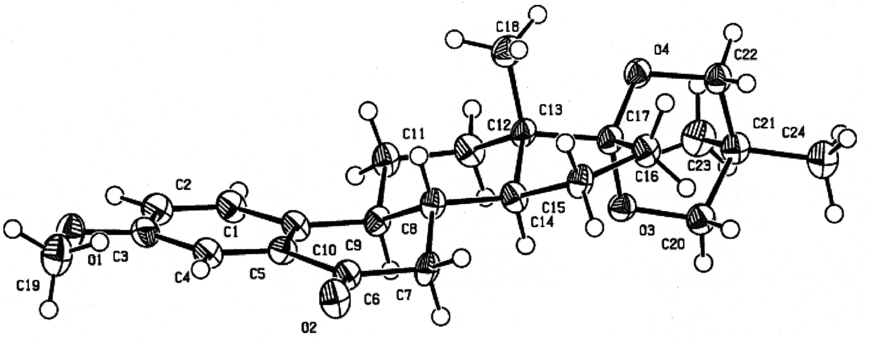


Fig. 4 X ray crystal structure of compound **4**. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

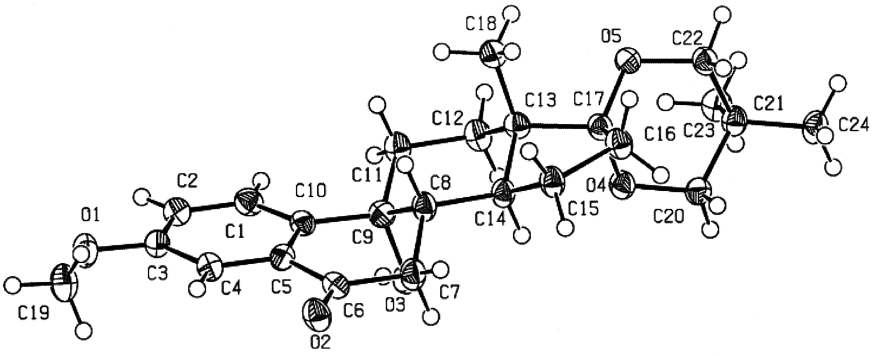


Fig. 5 X ray crystal structure of compound **5**. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

$-11 \le l \le 11$. There were 3742 independent reflections and 1762 reflections with $I > 2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and refined using CRYSTALS. Multi-scan absorption correction was applied with $T_{\min} = 0.964$ and $T_{\max} = 0.982$. CrystalStructure 3.6.0[8] was used for the preparation of the material for publication. The final R indices were $[I > 2\sigma(I)]$ $R_1 = 0.063$ and (all data), $R_1 = 0.073$, $wR_2 = 0.186$. The goodness-to-fit on F^2 was 1.093 and the largest difference peak and hole was 0.49 and -0.40 e Å^{-3}.

The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 273309).

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