2,4-Dioxaadamantane

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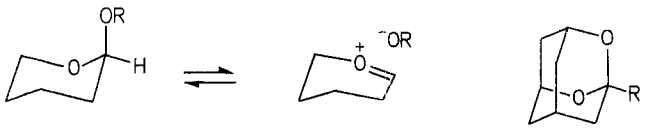
2,4-Dioxatricyclo[3.3.1.1^{3,7}]decane, a unique acetal with both oxygens axial on tetrahydropyran rings, is formed spontaneously when all-*cis* 3,5-dihydroxy-1-cyclohexaneacetaldehyde is generated in acid.

Crystal-structure correlations within a series of tetrahydropyranyl acetals **1**[1] provide important information about the anomeric effect.[2] In the axial structure shown the C—O bond lengths at the acetal centre are notably sensitive to the nature of the substituent R: the more electron-withdrawing is R, the longer is the exocyclic C—O bond x and the shorter is the endocyclic bond n.[2,3]

We have attempted to relate this pattern of bond lengths to the initial stages of the reaction coordinate for C—OR bond breaking (**1** → **2**) of a parent alkyl tetrahydropyranyl acetal **1**. In such a compound anomeric and *exo*-anomeric[2] effects should be in balance, but our correlations show that when the electronegativities of the two acetal oxygens are equal, as judged by the estimated pK_a of the two derived alcohols, the C—O bond lengths are not (in fact, bond length $n > x$).[3] To define a standard acetal bond length in this situation, we therefore prepared the dioxaadamantane (**3**, R = H), in which the two C—O bonds at the acetal centre are identical by symmetry.

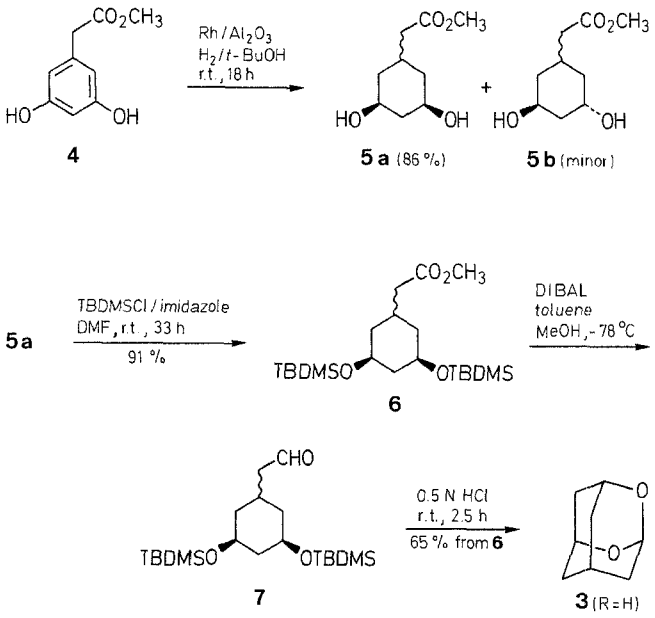


1 **2** **3**

The only previous preparation of a 2,4-dioxaadamantane (**3**, R = CH_3) involved as the key step Raney-nickel reduction of the ethylene glycol acetal of (3,5-dihydroxyphenyl)acetone;[4] but the corresponding aldehyde proved too reactive even for chromatography on silica gel. The problem was solved by finding conditions for the selective hydrogenation of the aromatic ring of methyl 3,5-dihydroxyphenylacetate **4**, using 5%

rhodium on alumina as catalyst. Thin layer chromatography showed rapid formation of a stable intermediate (not identified), which was slowly converted to the cyclohexanediols **5**, though only in the presence of large amounts of catalyst.

Of the fully hydrogenated products only one **(5b)** was readily separable into its diastereomers. Further purification of the mixture of diastereoisomers of **5a**, however was not necessary, because only the all-*cis* isomer can eventually cyclise to the dioxaadamantane; this isomer turned out to be the major product. Diisobutylaluminium hydride (DIBAL) reduction of the ester group of **5a** required protection of the hydroxyl groups, but when these were deprotected in acid the dihydroxycyclohexaneacetaldehyde **7** produced cyclised spontaneously to dioxaadamantane **3** (R = H). This, as expected, is a high-melting solid (**3**, R = CH_3, is reported as an oil, but we note that the introduction of a 1-methyl substituent into adamantane is sufficient to lower its mp by 163 °C). Dioxaadamantane **3** (R = H) could be purified by sublimation, but all attempts to grow crystals suitable for X-ray examination failed. (At least this meant that we did not have to face the problem of disorder expected for such a symmetrical molecule.[6])



Methyl 3,5-Dihydroxy-1-cyclohexaneacetate (5):
Methyl 3,5-dihydroxybenzeneacetate[7] (**4**; 1.00 g, 5.49 mmol) and 5% Rh/Al_2O_3 catalyst (1.00 g), in dry *t*-BuOH (20 mL), are stirred under H_2 for 18 h. The mixture is filtered through Celite, the catalyst washed with MeOAc (40 mL) and the washings evaporated to dryness *in vacuo*. Remaining *t*-BuOH is removed by azeotropic distillation with heptane (2 × 40 mL). Purification by flash chromatography on silica gel (100 g) eluting with MeOH/Et_2O (1:20) then MeOH/Et_2O (1:14) and rechromatography of the mixed fractions give the diol ester **5a** as a mixture of two diastereomers, (not separated); yield: 0.890 g (86%).

HRMS (DEI): calc. for $C_9H_{14}O_3$: m/z = 170.0943 (M-18); found 170.0947.

IR ($CHCl_3$): ν = 3370 (OH), 1720 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$): δ = 0.70–2.65 (complex m, 11 H); 3.75 (s, 3 H), which is superimposed on 3.35–4.40 (m, 2 H).

Less polar minor isomer **(5b)**:

^{1}H-NMR ($CDCl_3$) δ = 0.80–2.75 (complex m, 11 H); 3.70 (s, 3 H); 4.07 (br m, 1 H); 4.26 (br t, 1 H).

Methyl 3,5-Bis(*tert*-butyldimethylsiloxy)-1-cyclohexaneacetate (6):
The diol ester mixture of diastereomers **5a** (0.839 g, 4.46 mmol), *tert*-butyldimethylsilyl chloride (TBDMSCl; 1.617 g, 10.7 mmol), imidazole (1.517 g, 22.3 mmol) and dry DMF (5 mL) are stirred under N_2 for 33 h.[8] Sat. aq. Na_2CO_3 solution (60 mL) is then added, and the mixture extracted with hexane (5 × 25 mL). The combined organic phase is washed with water (40 mL), dried ($MgSO_4$) and evaporated to dryness *in vacuo*. Purification by chromatography on Fluorosil (20 g) eluting with Et_2O/hexane (1:5) gives the diprotected ester **6** as an oil; yield: 1.689 g (91%).

HRMS (DEI): calc. for $C_{20}H_{41}O_4Si_2$: m/z = 401.2543; found 401.256 (M-15).

IR (film): ν = 2950, 2870, 1740 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$): δ = 0.20 (s, 12 H); 1.00 (s, 18 H); 0.80–2.10 complex m, 9 H); 2.10–2.50 (m, 2 H); 3.70 (s, 3 H), which is superimposed on 3.40–3.85 (m, 1 H); 3.85–4.25 (m, 1 H).

3,5-Bis(*t*-butyldimethylsiloxy)cyclohexaneacetaldehyde (7):
DIBAL (4.85 mL of a 1.0 M solution in toluene, 4.85 mmol) is added dropwise to a stirred solution of diprotected ester **6** (1.689 g, 4.06 mmol) and MeOH (0.2 mL) in dry toluene (10 mL) at −78 °C. Sat. aq. Rochelle salt solution (50 mL) and water (2 mL) are added; the mixture vigorously stirred for 2 h at room temperature, diluted with Et_2O (30 mL) and the aqueous phase further extracted with Et_2O (2 × 50 mL). The combined organic phase is dried ($MgSO_4$), and the solvents removed *in vacuo* to give virtually (^{1}H-NMR) pure aldehyde **7**; this is used immediately in the final step.

HRMS (DEI): calc. for $C_{19}H_{39}O_3Si_2$: m/z = 371.2437; found 371.2435 (M-15).

IR (film): ν = 2950, 2860, 1725 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$): δ = 0.00 (s, 12 H); 0.80 (s, 18 H); 0.7–2.15 (complex m, 9 H); 2.15–2.45 (m, 2 H); 3.30–3.75 (m, 1 H); 3.75–4.20 (m, 11 H); 9.65 (apparent d, 1 H, J = 2 Hz).

2,4-Dioxatricyclo[3.3.1.1^{3,7}]decane (2,4-Dioxaadamantane; 3, R = H):
The virtually pure aldehyde **1** produced above is dissolved in 0.5 N HCl (14 mL) and allowed to stand for 2.5 h at room temperature. The mixture is extracted with pentane (3 × 40 mL), dried ($MgSO_4$) and evaporated to dryness *in vacuo* (water pump). Purification by flash chromatography on silica gel (400 g) eluting with Et_2O/pentane (2:3) gives **3** (R = H) as a volatile white solid; yield: 0.367 g (65% from ester **6**).

A sample sublimed for analysis and recrystallised from pentane softened at 204 °C (sealed tube) and melted at 210–212 °C.

$C_8H_{12}O_2$	calc.	C 68.5	H 8.65
(140.2)	found	68.7	8.60

MS (DEI): m/z = 140 (M^+, 100%), 84 (53%), 79 (84%).

IR (CCl_4): ν = 3020, 2900 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.4–2.7 (m, 9 H); 4.19 (m, 2 H, H-1, H-5); 5.11 (m, 1 H, H-3).

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(1) Briggs, A.J., Glenn, R., Jones, P.G., Kirby, A.J., Ramaswamy, P. *J. Am. Chem. Soc.* **1984**, *106*, 6200.
(2) Kirby, A.J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer Verlag, Heidelberg, 1983.
(3) Jones, P.G., Kirby, A.J. *J. Chem. Soc. Chem. Commun.* **1979**, 288.
(4) Stetter, H., Hess, R. *Monatsh. Chem.* **1967**, *98*, 754.
(5) Prelog, V., Seiwerth, R. *Ber. Dtsch. Chem. Ges.* **1941**, *74*, 1769. Schleyer, P. von R., Nicholas, R.D. *Tetrahedron Lett.* **1961**, 305.
(6) See for example: Ermer, O. *Angew. Chem.* **1983**, *95*, 251. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 251.
(7) Theilacker, W., Schmid, W. *Liebigs Ann. Chem.* **1950**, *570*, 15.
(8) Method based on: Corey, E.J., Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.