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NMR Spectra and Stereochemistry of 6- and 7-Substituted Cyclopenta[*d*][1,3]dioxanes

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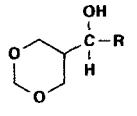
The reaction between 6- and 7-ketocyclopenta[*d*][1,3]dioxane and methyl-phenylmagnesium bromide gave in each case only one isomer of the 6-hydroxy-6-methyl-phenyl- and 7-hydroxy-7-methyl-phenylcyclopenta[*d*][1,3]dioxanes. The configurations of these derivatives were determined from a detailed analysis of the ^{1}H NMR spectra. All the compounds were found to adopt the *O*-inside *cis*-fused conformations.

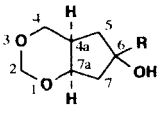
KEY WORDS ^{1}H NMR ^{13}C NMR Cyclopenta[*d*][1,3]dioxanes

INTRODUCTION

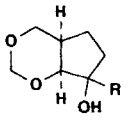
1,3-Dioxanes with C-5 substituents carrying alkyl, aryl and hydroxy groups (**A**, **B**) have been shown[1] to exhibit analgesic activity. Accordingly, the related cyclopenta[*d*][1,3]dioxanes **1**–**4** were chosen for study.



A R = alkyl
B R = aryl



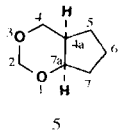
1 R = Me
2 R = Ph



3 R = Me
4 R = Ph

RESULTS AND DISCUSSION

The reaction between 6-ketocyclopenta[*d*][1,3]dioxane and methylmagnesium iodide/phenylmagnesium bromide proceeded stereoselectively to give single isomers of 6-hydroxy-6-methyl- and 6-hydroxy-6-phenylcyclopenta[*d*][1,3]dioxane (**1** and **2**), respectively. Similar reactions on the corresponding 7-keto derivative also gave single isomers **3** and **4**. The assignments of the *cis*-ring fusion in all compounds is based on the stereochemistry of the *cis*-fused 4,4a,5,7a-tetrahydro-2*H*-cyclopenta[*d*][1,3]dioxin[2] used as the starting material to prepare the ketones. The stereospecificity of the Grignard reactions must be largely due to preferred nucleophilic attack at the east hindered side of the carbonyl group in the favoured *O*-inside *cis*-fused conformation of the 6- and 7-ketocyclopenta[*d*][1,3]dioxanes (see stereochemistry of **5** in Fig. 1).



5

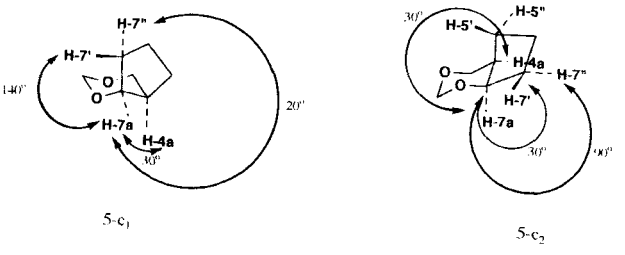


Figure 1. Dihedral angles (estimated from unconstrained Dreiding models) in the *O*-outside *cis* conformer **5-c$_1$** and *O*-inside *cis* conformer **5-c$_2$** of cyclopenta[*d*][1,3]dioxane (**5**) (5″ and 7″ refer to C—H bonds *cis* to the angular C—H-4a and C—H-7a bonds).

Stereochemistry of *cis*-(H-4a, H-7a)-cyclopenta[*d*][1,3]dioxane (5)

cis-(H-4a, H-7a)-Cyclopenta[*d*][1,3]-dioxane (**5**) can exist in solution as an equilibrium between the two *cis*-fused conformers, **5-c$_1$** and **5-c$_2$** (Fig. 1). The *cis* conformation **5-c$_1$** is destabilized by two *gauche* butane-type interactions involving H-2ax, H-4ax and the C-7 methylene group. These are greater than in the carbocyclic analogue as a result of the shorter C—O bond length (1.43 Å) compared with the C—C bond (1.54 Å) and by the puckering of the 1,3-dioxane ring in the O—C—O region.[3,4] The alternative *cis* conformation **5-c$_2$** suffers from less severe non-bonded interactions between the C-5 methylene group and the two axial oxygen lone pairs.[3] This latter conformation might then be expected to predominate. Such an expectation is in

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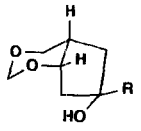
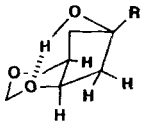
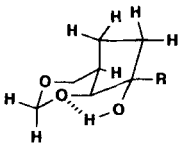
line with the conformational equilibria positions in *cis*-perhydrobenz[*d*][1,3]oxazines and benz[*e*][1,3]oxazines.[5] Since **1**, **2**, **3** and **4** all showed stable intramolecular hydrogen bonding in the IR spectra (recorded at concentrations of 0.0001 M), the stereochemistry can be assigned as shown in structures **1-c$_2$**–**4-c$_2$**.



1-c$_1$ R = Me
2-c$_1$ R = Ph



1-c$_2$ R = Me
2-c$_2$ R = Ph



3-c$_2$ R = Me
4-c$_2$ R = Ph

NMR spectra and stereochemistry of cyclopenta[*d*][1,3]dioxanes (1–4)

The ^{1}H NMR spectrum of **1** showed the expected AB quartet (J = −6.4 Hz) for the C-2 methylene protons with an additional small coupling between H-2eq and presumably H-4eq.[6,7] H-7a absorbed as a broadened triplet and decoupling experiments gave J(4a, 7a) = 3.3 Hz and J(7a, 7″) = 3.5 Hz. (For the definition of 7′, 7″, etc., see Fig. 1). The small J(4a, 7a) value is consistent with both *cis*-fused conformations, but a distinction between these is possible on the basis of the J(4ax, 4a) and J(4eq, 4a) values. Thus, in **1-c$_1$** the dihedral angles between H-4a and the C-4 methylene bonds are *ca* 60° and 180°, corresponding to vicinal coupling constants of *ca.* 3 and 11 Hz, whereas in **1-c$_2$** two small vicinal coupling constants (*ca.* 3Hz) are expected (two dihedral angles of *ca.* 60°). Examination of the ^{1}H NMR spectrum of **1**, however, showed non-first-order signals for the C-4 methylene protons. In addition, the splitting patterns for the C-5 and C-7 methylene protons approximated to two overlapping ABX systems with clear evidence of long-range coupling (J = 1.1 Hz) between the low-field C-5 methylene proton signal (H-5′, δ 2.17) and the low-field C-7 methylene proton signal (H-7′, δ 1.94). Decoupling of the C-4 methylene protons and H-7a identified the H-4a (δ 1.88) and the C-7 methylene proton signals (δ 1.94, 1.68), respectively. In the expected *O*-inside *cis* conformation **1-c$_2$** there is a *ca.* 90° dihedral angle between H-7a and H-7′, corresponding to a vicinal coupling constant of *ca.* 0 Hz. Since the low-field signal (δ 1.94) of the two C-7 methylene proton signals shows a zero coupling constant to H-7a, this can be assigned to H-7′.

An alternative explanation of the difference in J(7a, 7′) and J(7a, 7″) assumes a conformation of **1-c$_2$** such that the C-7 methylene protons are bisected by the C-7a—H bond. The differences in couplings could then arise from the effects of the neighbouring oxygen atom.[8] The achievement of this geometry, however, requires an increase in the ring fusion strain between the six- and five-membered rings. The more distorted conformer shown in Fig. 1 for the analogue **5-c$_2$** is accordingly preferred, but the influence of the adjacent C—O bond on the magnitude of the observed vicinal coupling constants means that the conformations drawn are only approximations.

Individual assignments to the C-5 methylene proton signals were made difficult because of the spectral simplicity and their similar chemical shifts. Since H-5′ is directed towards the two ring oxygen atoms, it is expected to be more deshielded than H-5″, and it is this lower field absorbing proton which is long-range coupled (long-range COSY experiment) to H-7′. Such *cis*-orientated protons are more readily linked by a near planar zig-zag pathway than the *trans*-orientated protons H-7′ and H-5″. In addition, irradiation of the 6-methyl group protons (in differential nuclear Overhauser experiments) gave effects with both H-7″ and H-5″, confirming their assignments. Decoupling of the H-7a signals gave a seven-spin system which was subjected to computer simulation and gave the ^{1}H NMR spectral parameters shown in Table 1. The magnitude of the vicinal coupling constants between H-4a and the C-4 methylene protons of 1.7 and 3.0 Hz thus obtained demonstrates clearly the preference for the *O*-inside *cis* conformation **1-c$_2$**.

The single isomer obtained for *cis*-(H-4a, H-7a)-6-hydroxy-6-phenylcyclopenta[*d*][1,3]dioxane was shown to adopt the *O*-inside *cis* conformation **2-c$_2$** by the magnitude of the apparent vicinal couplings between H-7a and the C-7 methylene protons [J(7a, 7″) = 3.3 Hz, J(7a, 7′) = 0 Hz; see Table 1 for accurate coupling constants]. In addition, the C-6 configuration was demonstrated by the intramolecular hydrogen bonding (IR spectrum), as described for **1**.

The ^{1}H NMR spectrum of **2** in the δ 2.00–2.50 region was more complex than that of **1** but still showed a clear AB part of an ABX type system for the C-7 methylene protons. The C-5 methylene protons gave rise to a non-first-order set of signals. Irradiation of the H-7a broadened triplet at δ 4.32 gave rise to a seven-spin system (ignoring the C-2 methylene proton signals) amenable to computer simulation, and enabled the coupling constants shown in Table 1 to be determined. The C-5 methylene proton assignments were reversed relative to **1** owing to the change in nature of the C-6 substituent. The ^{1}H NMR spectral simulations were found to be very sensitive to long-range couplings, in particular J(4ax, 5″) = 1.0 Hz and J(5′, 7′) = 1.5 Hz. Long-range COSY experiments were undertaken to assist in the analysis. These showed couplings between H-2eq and H-4eq, between H-2eq and H-7a and between H-5′ and H-7′ (compare with the spectrum of **1**).

The C-4 methylene proton resonances were reproduced on an expanded scale, and the Gaussian and exponential window functions (line sharpening) were altered in an attempt to observe some of the fine long-range couplings. The absorbances were recorded both before and after decoupling of H-2eq and H-7a. Changes in signal shapes confirmed the presence of coupling between the C-4 methylene protons and H-7a and H-2eq. A similar experiment showed that irradiation of H-2eq changed the absorption of H-7a from a broadened triplet to a new triplet of doublets with J(7a,

Table 1. ^{1}H NMR data[a] for derivatives of cyclopenta[*d*][1,3]dioxane

	Chemical shifts (δ, ppm)												
Compound	2eq	2ax	4eq	4ax	4a	5′	5″	6′	6″	7′	7″	7a	Other
1	4.97	4.54	3.84	3.83	1.88	2.17	1.99	—	—	1.94	1.68	4.08	1.35, CH_3 3.47, OH
2	5.10	4.66	3.99	3.97	2.17	2.54	2.57	—	—	2.29	2.16	4.32	7.19–7.50, aromatic-H
3	5.07	4.65	3.89	3.86	1.97	2.05	1.80	2.01	1.78	—	—	3.53	1.22, CH_3 2.89, OH
4	5.13	4.66	3.84	3.75	1.87	2.26	1.96	2.26	2.44	—	—	3.70	7.25–7.52, aromatic-H 3.31, OH

	Coupling constants (J, Hz)									
	J(2eq, 2ax)	*J*(4eq, 4ax)	*J*(4eq, 4a)	*J*(4ax, 4a)	*J*(4a, 7a)	*J*(5′, 5″)	*J*(5′, 4a)	*J*(5″, 4a)	*J*(5′, 7′)	Other
1	−6.4	−11.0	1.7	3.0	3.3	−13.1	9.9	9.7	1.1	*J*(7′, 7″) −14.7 *J*(7′, 7a) 0 *J*(7″, 7a) 3.5
2	−6.4	−11.0	1.7	3.0	3.3	−14.6	9.8	10.0	1.5	*J*(4ax, 5″) 1.0 *J*(7′, 7″) −14.7 *J*(7′, 7a) 0.8 *J*(7″, 7a) 3.3
3	−6.2	−11.0	2.8	0.5	2.4	—	—	—	—	
4	−6.2	−11.5	<1.5	2.6	3.1	—	—	—	—	

[a] C-2 methylene parameters extracted from the spectra; all other data obtained by decoupling and simulation procedures.

7′) = 0.8 Hz, *J*(7a, 7″) = 3.3 Hz, *J*(7a, 4a) = 3.3 Hz, showing removal of a long-range coupling between H-2eq and H-7a. The simulation experiments utilizing the determined long-range couplings enabled vicinal couplings of 1.7 and 3.0 Hz to be evaluated for *J*(4a, 4eq) and *J*(4a, 4ax), respectively. These confirm the *O*-inside *cis*-fused conformation **2-c$_2$**.

The ^{13}C NMR assignments for **1** and **2** are shown in Table 2. C-4a and C-7a resonances were readily distinguished on the basis of electronegativity effects. The C-5 and C-7 resonances were assigned from 2D ^{13}C–^{1}H correlations.

The ^{1}H NMR spectra of the 7,7-disubstituted derivatives **3** and **4** were much more complex than those of **1** and **2** due largely to the coupled system extending from C-4 to C-6 unbroken by substituents. Assignments were made as for **1** and **2** by decoupling experiments, ^{1}H–^{1}H and ^{13}C–^{1}H 2D correlations. The ^{1}H NMR parameters obtained from these measurements (Table 1) are all in accord with the *O*-inside *cis*-fused conformers **3-c$_2$** and **4-c$_2$**. The orientation of the Me group in **3** was shown to be *cis* to the angular CH bonds from the strong NOE between the 7-Me and H-7a, and NOEs between the Me group protons and protons absorbing at δ 1.78 and 1.97 permitted the assignment of these latter to H-6″ and H-4a, respectively. A strong NOE between H-7a and H-2ax confirmed the *O*-inside *cis*-fused conformer **3-c$_2$**. In addition, ^{1}H–^{1}H long range COSY experiments identified couplings between H-2eq and H-4eq, between H-2eq and H-7a and between H-4ax and H-7a. In contrast, a similar long-range COSY experiment on **4** showed couplings between the following: an aromatic ring proton and H-7a, H-2eq and H-4eq; H-5″ and H-7a; H-5″ and H-4eq; H-2ax and H-7a, H-2ax and the C-4 methylene protons; and H-6″ and H-7a; and H-6″ and H-4a. Line sharpening of the H-2eq signals of **3**, both before and after decoupling of H-7a, clearly showed long-range couplings of *J*(2eq, 7a) = 0.7 Hz and *J*(2eq, 4eq) = 0.6 Hz. Similar non-planar zig-zag long-range couplings in 1,3-dioxanes have been observed previously.[9]

EXPERIMENTAL

Elemental analyses were carried out by ICI Pharmaceuticals Division (Macclesfield, Cheshire, UK). Melting points were determined on a hot-stage microscope. IR spectra were recorded on Perkin-Elmer Model 683 and 577 grating instruments for 0.0001 M solutions in carbon tetrachloride using 1.0 cm matched

Table 2. ^{13}C NMR chemical shifts of derivatives of cyclopenta[*d*][1,3]dioxane

	Chemical shifts (δ, ppm)							
Compound	C-2	C-4	C-4a	C-5	C-6	C-7	C-7a	Others
1	92.7	67.3	39.3	43.3	79.5	48.8	79.9	28.6, CH_3
2	92.8	67.3	39.9	45.9	82.9	50.9	80.1	Aromatics: C-1′ 146.9, C-2′ 126.5, C-3′ 128.1, C-4′ 124.7
3	92.2	67.7	35.8	23.8	38.2	79.9	82.8	24.5, CH_3
4	92.2	67.4	35.1	24.9	37.4	83.7	83.7	Aromatics: C-1′ 143.5, C-2′ 127.6, C-3′ 128.2, C-4′ 126.1

silica cells. ^1H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ solution in 5 mm tubes, on a JEOL GSX-270 (^1H, ^{13}C) Fourier transform spectrometer at 270.16 (^1H) and 67.97 (^{13}C) MHz, using the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measurement parameters were as follows: sweep width 3 (^1H) and 18 (^{13}C) kHz, pulse width 3 μs (^1H) and 4.2 μs (^{13}C) (*ca.* 40° and 45° flip angle), acquisition time 5.459 or 0.901 s, number of scans 16 to 320 (^1H) and 1–20K (^{13}C), computer memory 32K. Long-range COSYs were adapted from the standard COSY by altering the fixed pulse interval to a much higher value, i.e. 300 ms. Line sharpening was obtained using a combination of exponential/Gaussian window functions applied to the FID before Fourier transformation; typical combination: exp broadening factor (BF) −0.5 Hz; Gaussian GF 0.25 Hz. Standard NOESY spectra were run with t_m 350 ms. ^1H NMR parameters were obtained by an NMR spin simulation/interaction program V2.10 (JEOL NMR COMIC program).

cis-(H-4a, H-7a)-6-Hydroxycyclopenta[*d*][1,3]dioxane

cis-(H-4a, H-7a)-4,4a,5,7a-Tetrahydro-2*H*-cyclopenta[*d*][1,3]dioxin (12.6 g, 0.1 M)[5] was added to a mixture of mercury (II) acetate (35 g, 0.11 M) in water (100 ml) and tetrahydrofuran (100 ml). After 0.5 h of stirring, the reaction mixture was cooled and sodium hydroxide solution (3 M, 100 ml) added, immediately followed by a solution of sodium tetrahydroborate (2 g) in sodium hydroxide solution (3 M, 100 ml) and stirring continued for a further 15 min. The reaction mixture was then left at room temperature for 1 h, allowing solids to settle out. After decanting the supernatant solution from the deposits, an aqueous solution of saturated sodium chloride (600 ml) was added and the resultant solution extracted with ethyl acetate (3 × 200 ml), dried (Na_2SO_4), concentrated and the residue distilled *in vacuo* to give an isomeric mixture of *cis*-(H-4, H-7a)-6-hydroxycyclopenta[*d*][1,3]dioxanes (9.5 g, 66%) as a colourless oil, b.p. 99–101 °C at 0.8 mmHg (found, C 58.0, H 8.1; $C_7H_{12}O_3$ requires C 58.3, H 8.4%.) The mixture of isomers was used in the next stage without separation.

cis-(H-4a, H-7a)-6-Ketocyclopenta[*d*][1,3]dioxane

Chromium trioxide (80 g) dissolved in water (80 ml) was added gradually, with stirring, to pyridine (800 ml) cooled in an ice–water bath. To the resultant solution was added a solution of the isomeric mixture of *cis*-(H-4a, H-7a)-6-hydroxycyclopenta[*d*][1,3]dioxanes (16 g, 0.11 M) in pyridine (50 ml) and the reaction mixture was left at room temperature for 72 h. The mixture was then poured into water (200 ml), filtered through a Celite pad, extracted with chloroform (4 × 250 ml) and the extracts dried (Na_2SO_4). Removal of the solvent *in vacuo* yielded *cis*-(H-4a, H-7a)-6-ketocyclopenta[*d*][1,3]dioxane as a yellow oil which crystallized on standing. This was recrystallized from light petroleum (b.p. 40–60 °C) to give colourless plates (11 g, 70%), m.p. 44 °C (found, C 58.8, H 7.1; $C_7H_{10}O_3$ requires C 59.1, H 7.1%.)

cis-(H-4a,H-7a)-7-Hydroxycyclopenta[*d*][1,3]dioxane

Borane-tetrahydrofuran complex (0.15 M, 150 ml) was added slowly, with stirring, to a solution of *cis*-(H-4a, H-7a)-4,4a,5,7a-tetrahydro-2*H*-cyclopenta[*d*][1,3]dioxin (12.6 g, 0.1 M) in dry tetrahydrofuran (300 ml) cooled to −10 °C in an ice–salt mixture, under an atmosphere of nitrogen. After a further 1 h stirring, aqueous sodium hydroxide solution (2.5 M, 200 ml) was added cautiously at −10 °C with continuous stirring. This caused much frothing at first but by keeping the temperature below 0 °C, the frothing gradually stopped. The reaction mixture was then recooled to −5 °C and 30% hydrogen peroxide (20 ml) was added dropwise. After a further 0.5 h of stirring, saturated sodium chloride solution (100 ml) was added and the tetrahydrofuran layer separated. The aqueous layer was extracted with ethyl acetate (3 × 150 ml) and the combined organic layers dried (Na_2SO_4), concentrated and the residue distilled *in vacuo* to yield *cis*-(H-4a, H-7a)-7-hydroxycyclopenta[*d*][1,3]dioxane (11 g, 76%) as a colourless oil, b.p. 75–77 °C at 0.1 mmHg (found, C 58.4, H 8.7; $C_7H_{12}O_3$ requires C 58.3, H 8.4%); δ_H 4.93, 4.63 (J − 6.2 Hz, H_2-2), 3.95 (J − 11, 1.7 Hz, H-4eq), 3.94 (J − 11, 3.0 Hz, H-4ax), 3.89 (J 3.3 Hz, H-7a); δ_C 92.3 (C-2), 67.2 (C-4), 36.7 (C-4a), 24.5 (C-5), 32.8 (C-6), 76.9 (C-7), 83.5 (C-7a).

cis-(H-4a,H-7a)-7-Ketocyclopenta[*d*][1,3]dioxane

Chromic acid (79 ml, 0.21 M) [prepared by dissolving chromium trioxide (26.72 g) in a mixture of concentrated sulphuric acid (23 ml) and water (77 ml)] was added to a stirred solution of *cis*-(H-4a, H-7a)-7-hydroxycyclopenta[*d*][1,3]dioxane (10.1 g, 0.07 M) in diethyl ether (800 ml) over a period of 20 min. After stirring for a further 5 h, the reaction mixture was neutralized with saturated sodium carbonate solution and extracted with diethyl ether (3 × 150 ml). The extract was dried (Na_2SO_4), concentrated and the residue distilled *in vacuo* to give *cis*-(H-4a, H-7a)-7-ketocyclopenta[*d*][1,3]dioxane (8 g, 80%) as a colourless oil, b.p. 88–90 °C at 0.12 mmHg (found C 58.8, H 7.1; $C_7H_{10}O_3$ requires C 59.1, H 7.1%).

6- Or 7-hydroxy-6- or -7-alkyl-arylcyclopenta[*d*][1,3]dioxanes

To a stirred ethereal solution of aryl-alkylmagnesium halide [prepared by addition of either bromobenzene (0.03 M) or methyl iodide (0.03 M) in dry diethyl ether (25 ml) to magnesium turnings (0.72 g) in the presence of a trace of iodine] was added a solution of the appropriate ketone (0.015 M) in dry diethyl ether (50 ml) and, after completion of the addition, the mixture was boiled under reflux for 3 h. After cooling, saturated ammonium chloride solution (50 ml) was added and the resultant solution extracted with diethyl ether (3 × 100 ml). The ether extracts were combined, dried (Na_2SO_4), concentrated and the residue either distilled *in vacuo* or recrystallized. The following compounds were obtained: *rel*-(4a*R*, 6*R*, 7a*R*)-6-hydroxy-6-phenylcyclopenta[*d*][1,3]dioxane (**2**) as a viscous oil, which was triturated with diethyl ether (4 × 50 ml) and then recrystallized from

light petroleum (b.p. 40–60 °C)–diethyl ether (2:1) as white needles (2.7 g, 82%), m.p. 96–97 °C (found, C 71.2, H 7.2; $C_{13}H_{16}O_3$ requires C 70.9, H 7.3%), ν_{max} 3549 cm^{-1}; *rel*-(4a*R*,6*R*,7a*R*)-6-hydroxy-6-methylcyclopenta[*d*][1,3]dioxane (**1**) (1.6 g, 66%) as a colourless oil, b.p. 83–84 °C at 0.6 mmHg (found, C 60.5, H 8.8; $C_8H_{14}O_3$ requires C 60.7, H 8.9%), ν_{max} 3559 cm^{-1}; *rel*-(4a*R*,7*R*,7a*R*)-7-hydroxy-7-phenylcyclopenta[*d*][1,3]dioxane (**4**) (3 g, 89%) as colourless needles from light petroleum (b.p. 40–60 °C)–diethyl ether (2:1), m.p. 105 °C (found, C 70.7, H 7.1; $C_{13}H_{16}O_3$ requires C 70.9, H 7.3%), ν_{max} 3571 cm^{-1}; and *rel*-(4a*R*,7*R*,7a*R*)-7-hydroxy-7-methylcyclopenta[*d*][1,3]dioxane (**3**) as a colourless oil which crystallized on standing, the crystals being collected and recrystallized from diethyl ether as colourless plates (2 g, 83%), m.p. 65 °C (found, C 60.8, H 9.1; $C_8H_{14}O_3$ requires C 60.7, H 8.9%), ν_{max} 3579 cm^{-1}. In each of these Grignard reactions the formation of only a single isomer could be detected.

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