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CONFIGURATIONAL ASSIGNMENT AND ^{1}H-NMR SPECTRAL PARAMETERS OF THE ISOMERIC 1,4-DIACETOXY-2,3-DIMETHYLCYCLOPENTANES

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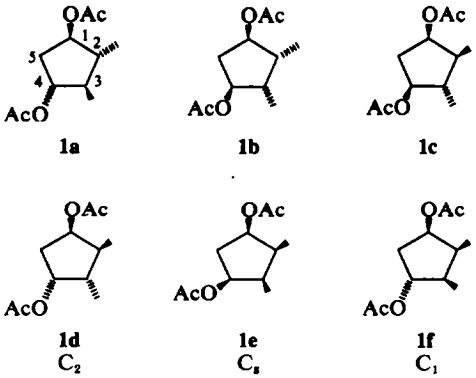
Abstract—All six 1,4-diacetoxy-2,3-dimethyl-cyclopentanes have been prepared starting from 2, 3-dimethyl-4-hydroxy-2-cyclopentenone. ^{1}H-NMR spectral parameters, allowing configurational assignment, are discussed.

^{1}H-NMR spectral parameters of 1,4-diacetoxy-2,3-dimethyl-cyclopentanes (**1**) are of interest for the configurational assignment of synthetic prostaglandines. The six isomeric compounds **1** were synthesised; they have the following point groups: two C_2, two C_s and two C_1 forms (Scheme 1). According to the ^{1}H-NMR spectral parameters each isomer can be classified in a proper point group, thereby allowing a partial but unequivocal configurational assignment. As will be demonstrated the study of the ^{1}H-NMR data and further chemical transformations allow the configurational determination of each isomer.

Syntheses. The synthesis and transformation of the title compounds are outlined in Scheme 2. The starting material **2**[1] was reduced with lithium in liquid ammonia with tetrahydrofuran as the co-solvent and ethanol as the proton source.[2] The diols obtained are acetylated and separated by preparative GC. The isomers featuring *trans* Me groups make up 64% of the reaction mixture. This is in qualitative agreement with the greater stability of *trans*-2,3-dimethyl-cyclopentanone over the *cis* isomer.[3]



1a **1b** **1c**

1d C_2 **1e** C_s **1f** C_1

SCHEME 1

The ketone **2** was, on the other hand, transformed[4] in the trimethylsilylether **3**, which was hydrogenated on a Raney nickel catalyst. The stereochemical outcome depends critically on the activity of the catalyst and on the solvent. A freshly prepared W_7 catalyst[5] at pH = 8 should be used. The highest stereoselectivity is obtained in 1,4-dioxane as solvent (only three isomers are formed; **1e** 92%, **1c** 5% and **1f** 3%) while in methanol five isomers (Scheme 2) are found. In the absence of the trimethylsilyl protecting group[6] an extensive hydrogenolysis[7] of the allylic hydroxyl group in **2** occurs.

NMR *parameters and chemical transformations.* Table 1 gives the NMR parameters of **1a–f** obtained at 300 MHz in carbon tetrachloride and benzene solution (TMS internal standard, room temp). It follows immediately that **1e** and **1b** are C_s, **1d** and **1a** are C_2, and **1c** and **1f** are C_1 forms. As all the possible isomers are available, there cannot be a misassignment due to accidental isochronism of diastereotopic groups.[8]

The proper configuration within each pair of C_2, C_s and C_1 forms still remains to be specified.

Inversion of one acetoxy group in either of the C_2 pair isomers can only give rise to one C_1 form. Experimentally, **1a** was transformed through the half-tosylate to **1c**, whose configuration is thereby known and, indirectly, also **1f** is identified.

Reaction of both C_s isomers with *p*-nitrobenzaldehyde yielded isomeric 3 - (*p* - nitro) - phenyl - 6, 7 - dimethyl - 2, 4 - dioxabicyclo [3.2.1] octanes (**4**). Between the Me resonances and the benzylic H-3 atom NOE experiments[9] were performed. For the acetal derived from **1b** no intensity increase was found, while for a bicyclic derivative of **1e**, the in-

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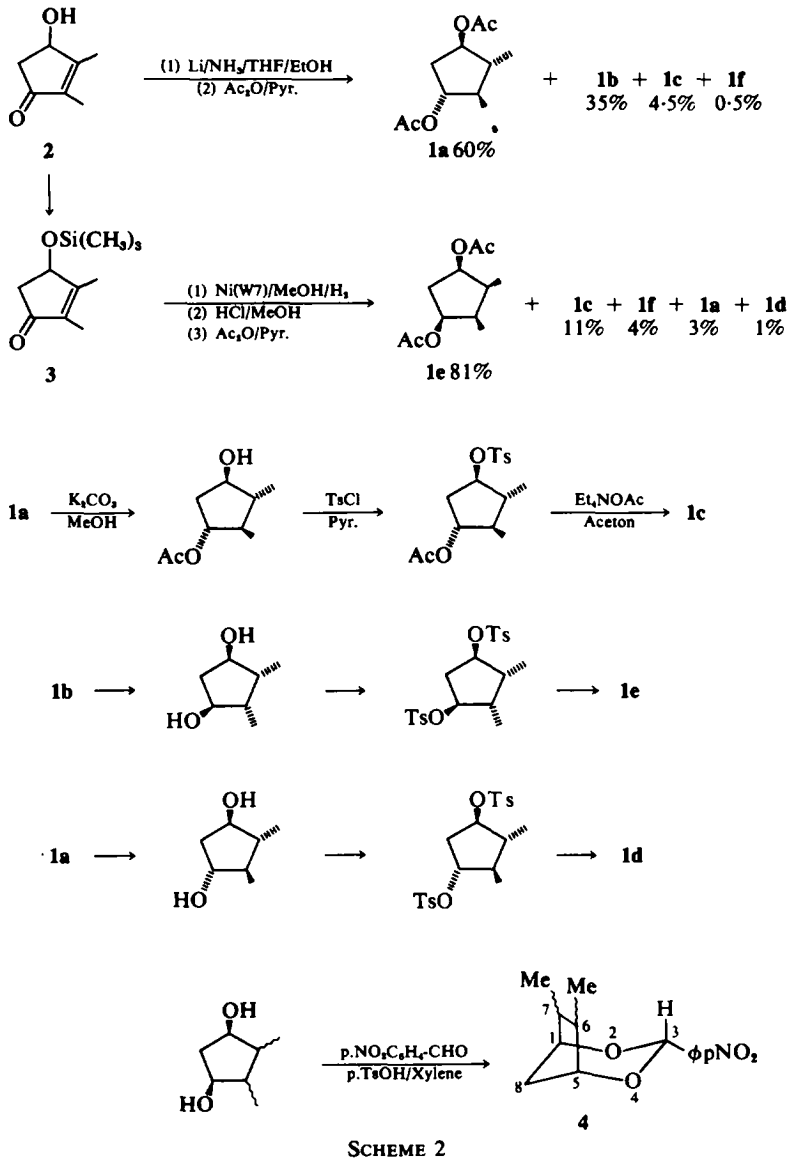

SCHEME 2

tensity of H-3 was enhanced for 19%. The all-*cis* configuration of **1e** is thereby unequivocally determined. Furthermore the di-tosylate derived from **1b** was subjected to an SN_2 reaction with tetraethylammonium acetate; the substitution was accompanied by extensive elimination (*ca* 60%); this probably reflects the strain in the prospective isomer **1e**. In comparison, the same experiment performed on the di-tosylate of **1a** yielded **1d** accompanied only with 20% elimination products.

The two C_2 isomers can be discriminated easily by the magnitude of their ^{1}H-NMR parameters. The sum of coupling constants in the H-1 and H-4 resonance is larger for **1a** than for **1d**. In cyclopentanes, a *cis* relation of two vicinal substituents (OH and some other group) results in a smaller sum of coupling constants than a *trans* relation.[10-13] We therefore assign to isomer **1d** the configuration with the vicinal acetoxy and Me group in a *cis* relation. This assignment is corroborated by the almost identical coupling parameters of **1a** and of a similarly substituted cyclopentane, reported in the previous paper,[2] where the 1,3-*cis*-relation of the OH and the alkyl group was established by chemical evidence.

Summarising, the configurational assignment of 1, 4 - diacetoxy - 2, 3 - dimethyl - cyclopentanes can be made on the strength of ^{1}H–NMR parameters. A 1,3-*cis* relation of the acetoxygroups results in an enormous shift difference of the H-5 atoms, but not a *trans* relation.[14] A 1,2-*cis* relation of the acetoxy

Table 1

	Ia		Id		Ib		Ie		Ic		If	
	CCl_4	C_6H_6	CCl_4	C_6D_6	CCl_4	C_6D_6	CCl_4	C_6D_6	CCl_4	C_6D_6	CCl_4	C_6D_6
δH-5[a]	1·97	2·06	2·05	1·96	1·50	1·68	1·67	1·73	1·53	1·68	2·13	2·10
δH-5'[a]					2·66	2·60	2·57	2·40	2·51	2·36	2·02	1·99
δH-1	4·67	4·79	5·20	5·27					5·03	5·02	5·16	5·24
δH-4					4·68	4·77	4·96	4·93	4·57	4·63	4·79	4·92
δH-2	1·49	1·37	1·82	1·60					1·52	1·03	2·38	2·16
δH-3					2·17	2·16	2·19	1·84	1·79	1·84	2·04	1·91
δMe-2	1·07	0·89	0·92	0·80	0·94	0·69	0·90	0·84	0·96 or/and	0·88	0·87 or/and	0·73
δMe-4									1·03	0·91	1·00	0·87
δAc-1	1·98	1·68	1·96	1·65	1·99	1·65	1·99	1·65	1·99 or/and	1·66	1·96 or/and	1·62
δAc-4									2·00	1·67	1·98	1·65
J5,5'[b]	—	—	—	—	−15·7	−15·8	−15·1	−15·1	−15·7	−15·7	−15·5	−15·4
J1,5					4·0	3·8	5·8	5·7	1·8	1·8	4·7	4·8
J4,5	7·1	7·0	4·5	4·6					5·0	4·9	7·6	7·6
J1,5'					7·7	7·7	8·2	8·2	6·2	6·2	7·6	7·5
J4,5'									8·8	8·9	4·1	3·8
J1,2	7·6	7·8	5·0	5·0	4·5	4·5	6·6	6·5	4·9	4·8	6·1	6·1
J4,3									7·8	7·8	3·7	4·3
J2,3	10·4	10·3	11·8	11·7	6·7	6·7	6·0	6·3	11·8	11·5	6·7	7·2
$J_{2\,Me\text{-}2}$	6·7	6·6	6·9	6·9	7·3	7·5	7·4	7·2	6·8	6·8	7·3 or/and	7·3
$J_{3,Me\text{-}3}$									6·7	6·8	7·4	7·4
$J_{2,Me\text{-}3}$	−0·2	−0·2	−0·5	−0·4	−0·4	−0·5	−0·4	−0·2				
$J_{3,Me\text{-}2}$												
J2,5	—	—	—	—	0·8	0·7	—	—	—	—	—	—
J3,5												

[a] H-5: *cis* with Ac-1; H-5': *trans* with Ac-1 (Scheme 1).
[b] coupling constants are given in Hz.

and the Me group gives a smaller sum of coupling constants of the H-1 and H-4 atoms than a *trans* relation. When the alkyl groups are in *trans* relation, the vicinal coupling constant $J_{2,3}$ is large (> 10 Hz), for *cis* alkyl groups the coupling is small (~ 7 Hz).[15]

EXPERIMENTAL

2, 3 - Dimethyl - 4 - trimethylsiloxy - 2 - cyclopentenone (3). A mixture of 2[2] (8·4 g; 0·066 mol) and commercial hexamethyldisilazane (21·3 g; 0·132 mol) was heated for 2 h at 80°. Destillation of the mixture under reduced pressure afforded 3 as a light yellow liquid (b.p.: 110–115°/16 mm), yield 12·2 g (93%). The purity was checked by GC (SE. 30/160°) and by TLC (R_f = 0·63 with EtOAc as eluent). UV spectrum (MeOH): 228 nm (ε ~ 11,500). IR spectrum: peaks at 1715, 1665, 1440, 1385, 1350, 1325, 1295, 1250, 1200, 1160, 1090, 1065, 1020, 930, 890, 840 and 755 cm^{-1}. MS spectrum (peaks with a relative intensity more than 10%): *m/e* at 198 (M^+; 51%), 184 (15%), 183 (100%), 170 (10%), 155 (44%), 109 (57%), 75 (78%) and 73 (79%). ^{1}H-NMR spectrum δ 60 MHz/CCl_4): 2-CH_3, δ = 1·63; 3-CH_3, δ = 1·92; –OSi $(CH_3)_3$, δ = 0·15; 4-CH, δ = 4·53; 5-CH_AH_B/δ = 2·06 (m = 4) and 5-$CH_A\underline{H}_B$/δ = 2·51 (m = 4); ABX-system (J_{AB} = − 17·5 Hz; J_{AX}(*trans*) = 2·7 Hz; J_{BX}(*cis*) = 5·8 Hz). Both Me groups and the H-4 atom are broadened by long range couplings.

Catalytic hydrogenation of the trimethylsiloxy cyclopentenone (3). To a solution of 3 (9·1 g; 0·046 mol) in dry MeOH (225 ml) was added about 10 g of freshly prepared Raney-Ni catalyst, modification W_7[5], and the pH of the soln was adjusted to 8–8·5 with NaOH. The reduction was carried out in a Parr-apparatus (starting pressure: 40 lbs in^{-2} H_2) and was completed after 30 min. The catalyst was filtered off and the filtrate was acidified with dil HCl. The MeOH was removed under reduced pressure and the remaining aqueous soln was submitted to continuous extraction with ether for 24 h. The extract was then washed with a sat NaCl aq, dried over $MgSO_4$ and evaporated. The mixture of isomeric 2, 3-dimethyl-1, 4-cyclopentanediols was obtained as a viscous oil which needed no further purification, yield 5·74 g (96%). Preparative GC after formation of the di-acetates[2] yielded **1e** (81%), **1c** (11%), **1f** (4%), **1a** (3%) and **1d** (1%).

With 1,4-dioxane as solvent a mixture **1e** (92%), **1c** (5%) and **1f** (3%) was obtained.

Formation of **1d** *from* **1a**. To a soln of **1a** (1·5 g; 7 mmol) in dry MeOH (60 ml) was added powdered, anhyd K_2CO_3[16] (1·93 g; 14 mmol) and the mixture was stirred for 24 h. It was then neutralised with dil HCl, the MeOH was removed under reduced pressure and the remaining aqueous soln was extracted several times with ether, followed by continuous extraction for 24 h. The combined ether layers were worked up the usual way.

The diol[2] (yield 85%) was converted to the di-tosylate with *p*-toluenesulfochloride in dry pyridine as described in ref 2. The di-tosylate, a yellow oil which crystallised on cooling (m.p. = 82°, R_f = 0·67 in EtOAc yield 70%), was refluxed for 18 h in dry acetone with tetraethylammonium acetate. The acetone was then removed *in vacuo*, the

residue was poured in water and extracted with ether. After working up the usual way[2] the residue was purified by preparative GC. The product **1d** was identical (GC retention time and ^{1}H-NMR spectrum) with **1d** obtained by reduction of **3**.

Formation of **1e** *from* **1b**. In the same way as **1d** from **1a**. The product **1e** obtained is identical (GC retention time and ^{1}H-NMR spectrum) with **1e** obtained by reduction of **3**.

Formation of **1c** *from* **1a**. A soln of **1a** (1·5 g; 7 mmol) in dry MeOH (60 ml) was treated with one equivalent of anhyd K_2CO_3 and stirred at room temp. The reaction was followed by TLC (the hydroxy-acetate has $R_f = 0·51$ with EtOCa as eluent) and was stopped by adding one equivalent of diluted HCl. After working up in the usual way the hydroxy-acetate was isolated by column chromatography (silicagel; eluent: EtOAc). The yield is 70%. IR spectrum: peaks at 1740, 1460, 1380, 1250, 1100, 1030 and 985 cm^{-1}. MS spectrum (peaks with a relative intensity more than 10%): *m/e* at 112 (14%), 83 (10%), 69 (31%), 56 (12%), 55 (16%), 43 (100%), 41 (22%). Formation of the tosylate and reaction with tetraethylammonium acetate was performed as described for product **1d**. The product **1c** is identical (GC retention time and ^{1}H-NMR spectrum) with **1c** obtained by direct reduction of **2**.

3 - *p* - *Nitrophenyl* - 6,7 - *dimethyl* - 2,4 - *dioxabicyclo* - [3.2.1] - *octane* (**4b** *from* **1b**). Satisfying yields were obtained only when the 1,3-diol was reacted with 2–3 equivs of *p*-nitrobenzaldehyde. The acetal formed could however hardly be separated from the remaining aldehyde (both showed almost identical mobilities on TLC). The excess of *p*-nitrobenzaldehyde was therefore reduced to *p*-nitrobenzylalcohol with sodiumborohydride, allowing easy isolation of the acetal by column chromatography.

A mixture of diol (**1b**; 0·75 g; 5·7 mmol), *p*-nitrobenzaldehyde[17] (2·58 g; 17·1 mmol) and a catalytic amount of *p*-toluene sulphonic acid in dry *m*-xylene (110 ml) was heated and the azeotrope *m*-xylene/water was destilled slowly until the volume was reduced to about 40 ml. The soln was cooled, neutralised with $NaHCO_3$, filtered and the remaining *m*-xylene removed under reduced pressure. The solid residue was taken up in a mixture of MeOH (50 ml) and a 1 M dipotassium hydrogen phosphate soln (50 ml), and cooled in an ice-water bath. Sodiumborohydride (1·28 g; 3·4 mmol) was added and the mixture was stirred for 15 min. The MeOH was then evaporated and the remaining aqueous soln, diluted with 50 ml water, was extracted several times with ether. The combined ether layers were washed with water, dried over $MgSO_4$ and evaporated. The *p*-nitrobenzylidene acetal of **1b** was isolated by column chromatography on silicagel with isooctane/ether 70:30 as eluent ($R_f = 0·28$) and recrystallised from *n*-pentane/ether (**4b** m.p. = 109°). The yield was 0·90 g (60%).

A similar acetal of the diol **1e** was prepared by the same procedure (TLC: $R_f = 0·30$ with isooctane/ether 70:30 as eluent; m.p. = 100°). UV spectrum (MeOH): **4b** and **4e** 261 nm ($\epsilon \sim 9{,}500$). IR spectrum (almost the same for both acetals): **4b** peaks at 1615, 1535, 1460, 1390, 1350, 1220, 1150, 1110, 1090, 1055, 1040, 1015, 980, 935, 900, 870, 855, 835, 760, 745 and 705 cm^{-1}. MS spectrum (peaks with a relative intensity more than 10%): **4b** *m/e* at 263 ($M^{+\cdot}$; 35%), 262 (19%), 179 (21%), 163 (15%), 150 (17%), 107 (17%), 100 (17%), 97 (16%), 95 (70%), 83 (27%), 81 (17%), 79 (10%), 77 (13%), 70 (16%), 69 (100%), 68 (17%), 67 (16%), 56 (19%), 55 (74%), 51 (10%), 43 (15%), and 41 (45%). **4e** *m/e* at 263 ($M^{+\cdot}$; 38%), 262 (25%), 248 (11%), 219 (19%), 179 (50%), 178 (17%), 164 (16%), 163 (57%), 153 (10%), 152 (17%), 151 (16%), 150 (72%), 130 (11%), 112 (23%), 107 (30%), 106 (14%), 105 (24%), 104 (41%), 100 (45%), 97 (53%), 96 (53%), 95 (100%), 94 (22%), 93 (14%), 92 (15%), 89 (13%), 84 (42%), 83 (93%), 81 (80%), 79 (38%), 78 (19%), 77 (66%), 76 (39%), 75 (13%), 70 (87%), 69 (87%), 68 (78%), 67 (58%), 66 (10%), 65 (15%), 63 (17%), 58 (12%), 57 (41%), 56 (76%), 55 (91%), 54 (16%), 53 (49%), 51 (72%), 50 (25%), 43 (79%), 42 (46%) and 41 (77%).

NMR spectral analysis. The NMR spectrometer was a 300 Mhz apparatus. The spectra of the symmetric isomers are first order as far as shift differences are concerned. However, the isochronous nuclei are magnetic non equivalent in the spin coupling sense,[8] resulting in spectra which are, in principle, of a more complex type e.g. AA'MM'PP'X_3X_3' for the C_2 isomers. Some of the coupling constants are small, and we factorized into two independent AA'MM' and PP'X_3X_3' systems. With the parameters thus obtained a spectrum was simulated using the simex II/16 program. Long range couplings smaller than 0·2 Hz were not considered. Blanks in Table 1 therefore do not imply a coupling constant of zero Hz. Similar considerations apply to the C_s forms. As for the asymmetric isomers, the spectrum of **1c** is essentially first order, the smallest $\Delta\nu/J$ ratio being 7. In **1f**, the H-5 H atoms are rather tightly coupled ($\Delta\nu \sim 0·11$ ppm). Here a subspectral second order analysis ABXY with $J_{XY} \sim 0$ was applied for H-5, H-1 and H-4.

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