The Preparation of 5-Methylene-4-caranone from 5-Hydroxymethylene-4-caranone

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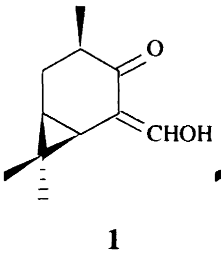
A simple and convenient synthesis of 5-methylene-4-caronones from 5-hydroxymethylene-4-caranone is presented. The configurations of 5-hydroxymethylene-*cis*/*trans*-4-caranone and 5-methylene-*cis*/*trans*-4-caranone are confirmed by their 1D and 2D ^{1}H and ^{13}C NMR spectra.

α-Methylene ketones are reactive compounds which can be prepared by several methods originally used as an approach to ketosteroids.[1] Bessière-Chrétien and Grison[2] have used the method of Manson and Wood[1] to obtain a group of methylenebicyclo[3.1.1]heptanones by reaction of the corresponding hydroxymethylenebicyclo[3.1.1]heptanones with an aqueous solution of formaldehyde in the presence of potassium carbonate. Otorowska and Piatkowski[3] reported that the reduction of 5-hydroxymethylene-*cis*-4-caranone (**1**) by $LiAlH_4$ yielded a mixture of eight compounds, containing only 1.8 % of 5-methylene-*cis*-4-caranone (**2**). They were not able to separate **2** from the reaction mixture and all their attempts to prepare **2** by many other known methods[3] also failed. Bondavalli *et al.*[4] had earlier investigated the same reduction, using both $LiAlH_4$ and $NaBH_4$, but none of their products was **2**. In connection with investigations concerning the aminomethylation of *cis*-4-caranone (**3a**)[5] it was observed that 5-methylene-4-caranone (**2**) could be easily prepared from the amino ketone by thermal decomposition of the hydrochloride, but surprisingly the elimination of the homogeneous amino ketone produced two mass spectroscopically equivalent products. Because 5-hydroxymethylene-4-caranone is easily available[6] it seemed worthwhile to apply the method of Manson and Wood to the preparation of 5-methylene-4-caranone.

Results and discussion

The synthesis of 5-hydroxymethylene-4-caranone. 5-Hydroxymethylene-4-caranone (2-hydroxymethylene-4,7,7-trimethylbicyclo[4.1.0]heptan-3-one) was prepared from *cis*-4-caranone (**3a**) according to the method reported by Bondavalli *et al.*[6] The product was a mixture of two components **A** and **B**, 63:37, respectively. Previous reports[3,6] from two different groups stated that the product mixture consisted of the two components **4a** and **4b**. This interpretation has possibly been influenced by the discussion of the NMR spectral data for 3-formylcamphor by Garbisch.[7] He has studied the direction of enolization of a number of cyclic β-keto aldehydes by NMR spectroscopy and his results showed that the direction is strongly dependent upon the



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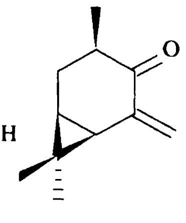

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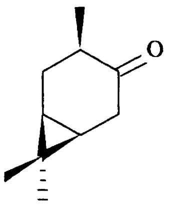
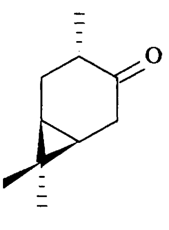
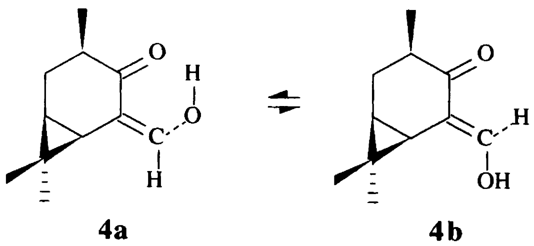


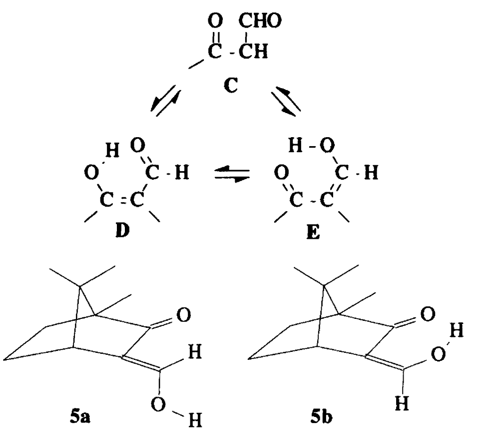
3a



3b



4a **4b**



Scheme 1.

structure of the cyclic β-keto aldehyde.[7,8] The equilibria between β-keto aldehyde **C** and aldo enol **D** and between **C** and the hydroxymethylene ketone **E** are expected to be slow with regard to spectral averaging, and the equilibrium between **D** and **E** to be fast (Scheme 1). Consequently, the recorded spectrum should show unenolized **C** and a weighted average of enols **D** and **E**. The NMR spectrum of 3-formylcamphor (**5**) showed a signal at 10.15 ppm assigned to the hydroxy proton and a doublet at 9.68 and 9.62 ppm assigned to the *exo*- and *endo*-non-enolized aldehyde proton (6%). The resonances at 7.33 ppm and 6.71 ppm were assigned to the vinyl proton of **5a** and **5b**, respectively.

A mixture of **A** and **B** was separated by flash chromatography (eluent hexane–diethyl ether 5:1) and the components were identified by analysis of their 1D and 2D spectra. There was no evidence for the presence of an aldehyde group, but ^{1}H NMR spectra showed broad singlets at 14.48 and 14.43 ppm, typical of a hydroxy proton subject to strong intramolecular hydrogen bonding in an enol.[9] On careful interpretation of the NMR spectra **A** and **B** were confirmed to be 5-hydroxymethylene-*cis*-4-caranone (**4a**) and 5-hydroxymethylene-*trans*-4-caranone (**6**), respectively (Fig. 1).

The ^{1}H NMR spectrum of **4a** exhibits a one-proton multiplet centred on 2.46 ppm. This methine proton at C-3 gives vicinal couplings to adjacent protons at C-2 of 12.3 Hz (H-2a) and 6.0 Hz (H-2e), and at C-10 of 6.7 Hz. The resonance of the cyclopropane ring proton H-1 of **4a** is centred on 1.13 ppm. This multiplet shows couplings with protons on C-2 and C-6. The chemical shift of H-2a (1.15 ppm) is so close to H-1 that they form an AB system. Therefore it was not possible reliably to solve the coupling constants directly from the splitting patterns and the Lequor-modelling program[10] was used to simulate spectra on the basis of the measured chemical shifts and coupling constants. The couplings of 9.4 and 6.8 Hz between H-1 and H-2e and H-1 and H-2a, respectively, indicate a very small dihedral angle between H-1 and H-2e and a larger angle between H-1 and H-2a, which is consistent with the Dreiding model of the proposed structure **4a**. The H,H-COSY spectrum showed that H-6 is coupled to H-2e and a four-bond W-path coupling of 0.4 Hz was observed between them.

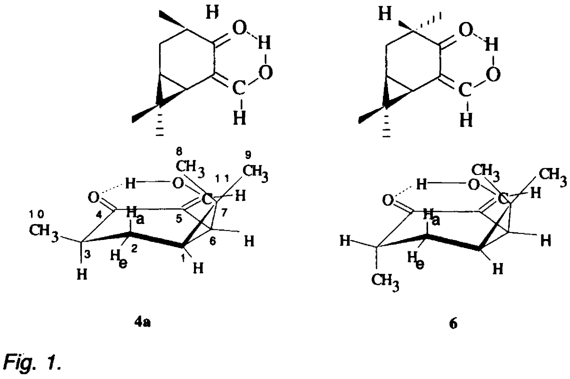


Fig. 1.

Determination of the corresponding coupling constants for **6** indicated that the dihedral angles between H-3 and H-2a and H-3 and H-2e are about 55 and 65°, respectively. the splitting patterns of the protons H-2 and H-1 were solved according to the first-order splitting rules. All the splitting patterns of **4a** and **6** were simulated with the Lequor-modelling program and the simulated spectra fitted very well with the recorded ones. ^{1}H Chemical shifts and the determined spin–spin coupling constants of **4a** and **6** are presented in Table 1.

Comparing some ^{1}H chemical shifts of **4a** and **6** with the shifts of *cis*-(**3a**) and *trans*-4-caranone (**3b**)[11,12] (Table 1) shows that the difference in proton chemical shifts of the methyl groups (H-8, -9 and -10) between **4a** and *cis*-4-caranone (**3a**) and between **6** and *trans*-4-caranone (**3b**) is parallel and about the same size.

The ^{13}C spectral data for **4a** and **6** provide further evidence for the assigned configurations. The major difference in the ^{13}C spectra of **4a** and **6** is observed in the chemical shifts of C-10,-2,-3, and -1. The other shifts are located in pairs very close to each other. DEPT(90°) and two-dimensional experiments verified that one of the carbon atoms of the double bond is quaternary and that the other is coupled to one proton.

Consequently, unlike 3-formylcamphor, 5-hydroxymethylene-4-caranone does not form, in equilibrium, a β-keto aldehyde or an aldo enol form **D**, and **4a** and **6** are the products of hydroxymethylation of *cis*-4-caranone. The formation of 5-hydroxymethylene-*trans*-4-caranone (**6**) can be explained by the fact that *cis*-4-caranone (**3a**) under basic conditions is capable of epimerization to *trans*-4-caranone (**3b**).[11]

The synthesis of 5-methylene-4-caranone. 5-Hydroxymethylene-4-caranone (2-methylene-4,7,7-trimethylbicyclo[4.1.0]heptan-3-one) (*cis*:*trans* 63:37) was converted into the corresponding methylene ketone by the procedure of Manson and Wood.[1] The solvents used were triethylamine, pyridine and diethyl ether. Triethylamine was first chosen as the solvent. The reaction was followed by thin

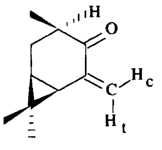
Table 1. ^1H Chemical shifts and some spin–spin coupling constants[a] of **4a**, **6**, **3a** and **3b**. Target nuclei are shown in parentheses.

Proton[b]	**4a**			**6**			**3a**	**3b**
	δ_H[c]		J_{HH}/Hz	δ_H[c]		J_{HH}/Hz	δ_H	
1	1.13	m	9.0 (6), 6.8 (2a), 9.4 (2e)	1.02	td	9.2 (6), 6.1 (2a), 9.2 (2e)		
2a	1.15	m	14.8 (2e), 12.3 (3)	1.63	ddd	14.8 (2e), 4.9 (3)		
2e	2.16	m	6.0 (3)	1.87	ddd	2.6 (3)		
3	2.46	m	6.7 (10)	2.26	ddq	7.2 (10)		
6	1.30	d		1.35	d			
8	0.84	s		0.85	s		0.86	0.95
9	1.09	s		1.12	s		1.05	1.08
10	1.05	d		1.25	d		0.92	1.18
11	8.29	s		7.72	s			
OH	14.48	br s		14.43	br s			

[a]The signs of the coupling constants were not determined. [b]For protons at C-2, a = axial and e = equatorial. [c]m = multiplet, s = singlet, d = doublet, t = triplet, q = quartet and br = broad.

layer (TLC) and gas (GC) chromatography. After 15 min TLC and GC indicated the formation of two main products and some minor ones, and that all of the starting material had reacted. Isolation of the products from triethylamine was difficult and the yield was very poor. The reaction was repeated with pyridine as the solvent. After standing overnight 5-hydroxymethylene-4-caranone was unchanged, but the addition of an equal amount of triethylamine to the reaction mixture completed the reaction within 10 min. Even if all the 5-hydroxymethylene-4-caranone was consumed and the isolation of products from the reaction mixture by petroleum ether extraction was done carefully, the yield was still poor. Acidification of the residual triethylamine solvent and extraction of it with dichloromethane revealed that 5-hydroxymethylene-4-caranone had reacted with triethylamine to form a salt, which was not detected by TLC or GC. In accordance with the procedure of Bessière-Chrétien and Grison,[2] diethyl ether was also chosen as the solvent. The reaction was complete within 2 h. GC–MS analysis of the crude product indicated that 5 % of the starting compound was left, a mixture of two isomers **I** and **II** (52:48, respectively), was formed and that the product contained a further 4 % impurities. According to mass spectra those two isomers were the same compounds obtained from β-elimination of 5-*N*,*N*-dimethylaminomethyl-4-caranone.[5] At the end of the reaction, sufficient water was added to dissolve the K_2CO_3. The aqueous K_2CO_3 solution was neutralized with dilute HCl and extracted with diethyl ether. According to GC analysis the extract did not contain any of the starting material or products. The isomers obtained from the original organic phase were spearated by flash chromatography (hexane–diethyl ether 6:1 and dichloromethane) and identified by analysis of their 1D and 2D NMR spectra.

Compound **II** exhibits a one-proton multiplet centred on 2.35 ppm. According to the 2D proton spectrum this proton is vicinally coupled to adjacent protons which give signals at 2.03, 1.82 and 1.21 ppm, integrating in the ratio 1:1:3, respectively. The protons resonating at 2.03 and 1.82 ppm are geminally coupled (J_{gem} = 15.0 Hz) and the signal at 1.21 ppm is a doublet (J = 7.2 Hz). The coupling constants of the proton at 2.35 ppm to the proton at 1.83 ppm (J = 5.0 Hz) and to the proton at 2.03 ppm (J = 2.5 Hz) indicate dihedral angles similar to those which H-3 of **6** forms with H-2a and -2e, respectively. Geminal protons at 2.03 and 1.82 ppm are further coupled to the proton at 1.09 ppm (J = 9.2 and 5.3 Hz, respectively) which in turn is coupled to the proton at 1.77 ppm (J = 8.4 Hz). One-proton multiplets at 6.09 and 5.29 ppm indicate unsaturated methylene protons, which are coupled to the proton at 1.77 ppm. In addition there are two methyl proton singlets at 1.12 and 0.83 ppm. The presented proton resonances and spin–spin coupling constants imply a structure very closely related to **6**. The Lequor-modelling program using the proton chemical shifts and the determined spin–spin coupling constants simulated splitting patterns identical with the recorded ones. The relative position of the exocyclic methylene protons was determined by means of the rule of additive shielding increment for olefins and on the basis of the determined coupling constants to H-6. ^{13}C Chemical shifts and a CH-COSY spectrum verified the structure as 5-methylene-*trans*-4-caranone (**7**).



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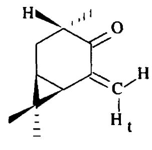

7

The analysis of 1D and 2D ^1H and ^{13}C spectra showed that compound **I** was 5-methylene-*cis*-4-caranone (**2**). H-3 at 2.46 ppm shows vicinal couplings to adjacent protons on C-2 of 13.2 Hz (H-2a) and 6.5 Hz (H-2e), which imply a *trans* diaxial and axial–equatorial orientation, respectively, between the coupled protons. These as well as the other

Table 2. ^{13}C Chemical shifts in δ of **2**, **4a**, **6** and **7**.

Compd.	Carbon										
	1	2	3	4	5	6	7	8	9	10	11
2	22.69	28.21	42.28	204.63	142.57	28.58	22.76	16.39	27.89	14.10	121.09
4a	21.30	27.69	38.66	202.86	107.83	20.78	22.23	16.20	27.44	13.87	173.91
6	18.18	25.41	37.06	196.74	106.50	20.71	22.91	15.87	27.71	18.35	182.83
7	19.54	26.00	41.94	205.79	140.63	28.73	23.01	16.38	28.14	17.27	123.25

Table 3. ^{1}H Chemical shifts and some spin–spin coupling constants[a] of **2** and **7**. Target nuclei are shown in parentheses.

Proton	**2**			**7**		
	δ_H		J_{HH}/Hz	δ_H		J_{HH}/Hz
1	1.25	m	8.5 (6), 5.6 (2a), 9.3 (2e)	1.09	td	8.4 (6), 5.3 (2a), 9.2 (2e)
2a	1.32	m	14.4 (2e), 13.2 (3)	1.82	dt	15.0 (2e), 5.0 (3)
2e	2.31	m	6.5 (3)	2.03	ddd	2.5 (3)
3	2.31	m	6.5 (10)	2.35	ddq	7.2 (10)
6	1.72	td	1.6 (11*c*), 1.4 (11*t*)	1.77	td	1.6 (11*c*), 1.4 (11*t*)
8	0.79	s		0.83	s	
9	1.10	s		1.12	s	
10	1.00	d		1.21	dd	
11*c*	6.00	dd	2.0 (11*t*)	6.09	m	2.0 (11*t*)
11*t*	5.21	dd		5.29	m	

^{1}H chemical shifts and spin–spin coupling constants of **2** are very similar to the corresponding values of **4a**. The proton chemical shifts and spin–spin coupling constants of **2** and **7** are presented in Table 3 and the carbon chemical shifts in Table 2.

In summary, this study establishes a simple and convenient method of preparing 5-methylene-4-caranones from 5-hydroxymethylene-4-caranones in diethyl ether by use of an excess formaldehyde and K_2CO_3.

Experimental

Equipment. GC analyses of the mixtures were performed on a Perkin Elmer 8420 gas chromatograph equipped with a fused silica capillary column, OV-1 (length 25 m, diameters i.d./o.d. 0.32 mm/0.44 mm, phase-layer 0.15 μm) or NB-351 (25 m, i.d./o.d. 0.32 mm/0.44 mm, phase-layer 0.20 μm). ^{1}H and ^{13}C NMR spectra were recorded on a JEOL GX-400 spectrometer, using $CDCl_3$ as the solvent and reference. Mass spectra were obtained using a Kratos MS80RF Autoconsole, 70 eV. flash chromatography was carried out on silica gel 60 columns (0.040–0.063 mm, diameter 1.5 cm, height 25 cm) and TLC on pre-coated glass supported plates (Merck silica gel 60 F_{254}, 0.25 mm layer).

Hydroxymethylation of cis*-4-caranone.* 5-Hydroxymethylene-4-caranone was prepared from *cis*-4-caranone[11] (15.0 g, 0.100 mol), ethyl formate (11.3 g, 0.152 mol) and metallic sodium (2.4 g, 0.100 mol) in anhydrous diethyl ether. The starting compounds were mixed together and 2 ml of absolute ethanol were added to start the reaction. The mixture was stirred for 20 h at room temperature. Water (60 ml) was added and the two layers were separated. The aqueous layer was acidified to pH ca. 5 with 6 M HCl and then extracted with diethyl ether. The combined ethereal phases were washed with water, dried over $MgSO_4$, and the solvent was removed. Yield 16.5 g. 5-Hydroxymethylene-4-caranone distilled at 110–112 °C/12 Torr (lit.[6] 63–65 °C/0.2 Torr) and was a mixture of two forms **A** and **B** (63:37, respectively). The two enol forms were separated by flash chromatography (hexane–diethyl ether 5:1). Form **A** was 5-hydroxymethylene-*cis*-4-caranone (**4a**): MS [*m*/*z* (relative intensity %)]: $M^{+\cdot}$ 180 (57), 165 (100), 151 (6), 147 (6), 137 (9), 123 (35), 121 (15), 119 (9), 109 (25), 107 (8), 105 (7), 95 (26), 93 (14), 91 (24), 81 (14), 79 (15), 77 (19), 69 (7), 67 (15), 65 (10), 55 (23), 53 (17), 51 (7), 43 (41), 41 (39). Form **B** was 5-hydroxymethylene-*trans*-4-caranone (**6**): MS [*m*/*z* (relative intensity %)]: $M^{+\cdot}$ 180 (52), 165 (100), 151 (8), 147 (5), 137 (10), 123 (34), 121 (17), 119 (10), 109 (28), 107 (9), 105 (8), 95 (26), 93 (16), 91 (29), 81 (14), 79 (15), 77 (20), 69 (8), 67 (16), 65 (12), 55 (24), 53 (20), 51 (7), 43 (53), 41 (46).

5-Methylene-4-caranone. 5-Hydroxymethylene-4-caranone (7.4 g, 41 mmol, *cis*:*trans* 63:37) was added to a stirred suspension of diethyl ether (140 ml) and K_2CO_3 (26.0 g, 0.236 mol). 37 % aqueous formaldehyde (27 ml) was added dropwise to the reaction mixture. A change in colour and a slight rise in temperature were observed. The reaction was maintained at room temperature for 2 h. Sufficient water was added to dissolve K_2CO_3. The organic layer was separated, and washed with water, dried over $MgSO_4$, and the solvent was removed. Yield 6.6 g. Distillation under reduced pressure resulted largely in the dimerization of 5-methylene-4-caranone and decomposition to 4-caranone. Purification for the structure elucidation was therefore done by flash chromatography (hexane–diethyl ether 6:1 and dichloromethane). 5-Methylene-*cis*-4-caranone (**2**): MS [*m*/*z* (relative intensity, %)]: $M^{+\cdot}$ 164 (63), 149 (39), 136 (8), 135 (5), 122 (21), 121 (70), 108 (13), 107 (30), 105 (16), 94 (14), 93 (100), 79 (76), 77 (51), 67 (12), 65 (13), 55 (17), 53 (17), 51 (8), 41 (17), 39 (16).[5] 5-Methylene-*trans*-4-caranone (**7**): MS [*m*/*z* (relative intensity, %)]: $M^{+\cdot}$ 164 (60), 149 (39), 136 (10), 135 (5), 122 (23), 121 (72), 108 (13), 107 (33), 105 (18), 94 (16), 93 (100), 79 (82), 77 (55), 67 (16), 65 (16), 55 (22), 53 (19), 51 (9), 41 (19), 39 (22).

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