Short Communication

Synthesis and Structural Elucidation of 3(10)-Caren-4-ols

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Rücker and Frey[1] recently reported the isomerization of (+)-3α,4α-epoxycarane (**1**) with aluminium isopropoxide (AIP) in 96 % yield to a product mixture containing predominantly *trans*-3(10)-caren-4-ol (**2**) (77 %), some *trans*-4-caren-3-ol (**3**) (16%) and *trans*-2-caren-4-ol (**4**) (0.5 %) (Scheme 1).

We had earlier used AIP for the isomerization of 3α,4α-epoxycarane (**1**), but applied only catalytic amounts of AIP[2,3] and obtained the three carenols **2**, **3** and **4** in the approximate ratio 13:67:20, respectively.[4]

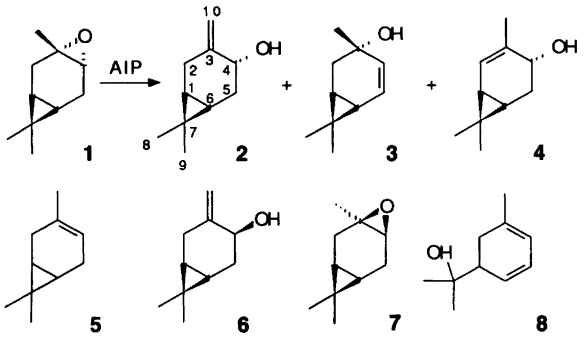
Most of the papers which mention 3(10)-caren-4-ols concern the *trans*-isomer **2**. The principal starting material was 3α,4α-epoxycarane (**1**) and the isomerizations effected by Al_2O_3,[5] propyllithium,[6] TiO_2-ZrO_2[7] and Li_3PO_4[4] produced, besides other compounds, *trans*-3(10)-caren-4-ol. The photocatalytic oxidation of 3-carene (**5**) with Rose Bengal as a sensitizer also gave the *trans*-isomer in addition to other products.[8] Reports about *cis*-isomer **6** are few. The formation of **6** in the reaction of 4-chloro-3(10)-carene with acetic anhydride and tetraethylammonium acetate followed by hydrolysis was based on mechanistic assumptions.[9] The isomerizations of 3β,4β-epoxycarane (**7**) by Al_2O_3,[10] propyllithium,[6] acetic anhydride[11] or potassium *tert*-butoxide[12] in pyridine gave **6** by stereospecific *cis*-opening of the oxirane ring.

Spectral data (^1H and ^{13}C NMR,[1,4] MS[1,4] and IR[6]) for **2** have been reported but structural evidence for **6** is based only on IR[6,9] data and insufficient ^1H NMR[10,12] values.

This communication reports for the first time the formation of both isomers of 3(10)-caren-4-ol (**2** and **6**) in the product from the isomerization of 3α,4α-epoxycarane and presents a detailed interpretation of the high resolution ^1H and ^{13}C NMR spectra of the isomers **2** and **6**.

Results and discussion

Synthesis. Treatment of **1** with AIP in toluene under reflux conditions as used by Rücker and Frey,[1] gave a product composition, different from that reported by these authors: *p*- and *m*-cymene (38 %), *trans*-3(10)-caren-4-ol (**2**) (39 %), *cis*-3(10)-caren-4-ol (**6**) (12 %), *trans*-2-caren-4-ol (**4**) (5 %) and *m*-mentha-4,6-dien-8-ol (**8**) (3 %) (Scheme 1).



Scheme 1.

The optimum reaction temperature for the isomerization was 90–95 °C, when the yield of *p*- and *m*-cymene was lowest (19 %) and the amounts of **2** and **6** were approximately 35 and 23 %, respectively. Monitoring the isomerization by GLC showed that **2** formed faster than **6**.

The formation of **6** in the isomerization was unexpected. The acid- or base-induced isomerizations of 3α,4α-epoxycarane or 3β,4β-epoxycarane to the corresponding allylic alcohols have occurred with retention of configuration of the original C–O bond.[4–7,10–12] To study the action of AIP in toluene on *trans*-3(10)-caren-4-ol, **2** was isolated from the above reaction mixture and purified through the 3,5-dinitrobenzoate derivative. **2** was then heated at 95 °C with AIP in anhydrous toluene under an atmosphere of N_2. After 12 h 37 % of **2** had been transformed into **6**.

In conclusion, the primary product in the isomerization of 3α,4α-epoxycarane with AIP is *trans*-3(10)-caren-4-ol **2**, which under the reaction conditions is in part transformed into **6**.

Structural analysis. ^1H and ^{13}C chemical shifts of the *trans*-isomer **2** given in the Tables 1 and 2 are very similar to those reported earlier.[1,4] Also the two-dimensional experiments are in agreement with the structure of **2**. The vicinal H–C–C–H couplings[13] and geminal H–C–H couplings adjacent to π bonds[14] are stereochemically dependent and allow the determination of the conformation of the mole-

Table 1. ^{1}H chemical shifts and some spin–spin coupling constants[a] of **2** and **6**. The target nuclei are shown in parentheses.

	2		**6**	
Proton[b]	δ_H/ppm	J_{HH}/Hz	δ_H/ppm	J_{HH}/Hz
1	0.78	9.1(6), 8.0(2a), 0.9(2e)	0.58	8.9(6), 7.1(2a), 1.7(2e)
2e	2.22	16.4(2a), 0.3(4), 0.9(10b), 0.6(10a)	2.52	16.0(2a)
2a	2.71	2.6(10b), 2.6(10a)	2.62	1.2(4), 2.4(10a), 2.4(10b)
4	4.04	3.6(5a), 3.4(5e), 0.6(10a)	4.04	11.8(5a), 6.3(5e)
5a	1.51	15.2(5e), 3.8(6)	1.18	13.4(5e), 4.3(6)
5e	2.19	9.2(6), 0.6(10a)	2.31	9.7(6)
6	0.66		0.75	
8	0.85		0.90	
9	0.98		0.93	
10b	4.71	1.9(10a)	4.73	
10a	4.78		4.84	
OH	1.80		1.89	

[a]The signs of the coupling constants were not determined. [b]For protons at C-2 and C-5, a = axial and e = equatorial. The relative position of the protons in the exocyclic methylene group (at C-10) was not determined.

Table 2. ^{13}C chemical shifts in δ/ppm of *trans*-3(10)-caren-4-ol (**2**) and *cis*-3(10)-caren-4-ol (**6**).

Carbon	1	2	3	4	5	6	7	8	9	10
2	20.52	24.65	149.32	70.89	28.84	15.47	18.03	14.20	28.60	109.04
6	20.54	30.11	151.03	70.76	30.91	19.69	18.70	14.60	28.63	104.29

cule with reasonable certainty when sufficient coupling constants are known.

The ^{1}H NMR spectrum of **2** exhibits a one-proton triplet centered at δ 4.04. This methine proton at C-4 gives vicinal couplings to adjacent protons at C-5 of 3.6 Hz (H-5a) and 3.4 Hz (H-5e). The coupling constants indicate dihedral angles of about 60° between H-4 and the protons at C-5. There is also quite a large difference between the vicinal couplings from the cyclopropane ring methine protons (H-1 and H-6) to the adjacent methylene protons (at C-2 and C-5). The couplings of 8.0 and 0.9 Hz between H-1 and H-2a and H-1 and H-2e, respectively, are in agreement with the dihedral angles of 35 and nearly 90°. The corresponding couplings of H-6 are 9.2 Hz (H-5e) and 3.8 Hz (H-5a), indicate dihedral angles of about 0 and 110°.

These coupling constants fit the conformation of **2** depicted in Fig. 1. The conformation is further supported by the geminal coupling constant between the protons at C-2. The coupling of 16.4 Hz is typical for a H–C–H system, where the π-orbital and the C–H bond are at an angle of about 60–70°. The observed four-bond couplings are also in good agreement with the proposed structure. For example there is a W-path coupling of 0.3 Hz between H-2e and H-4.

All the signals in the ^{1}H and ^{13}C NMR spectra of **6** were well resolved, and the structure recorded in Fig. 1 is in accordance with the results obtained from two-dimensional experiments. The few ^{1}H chemical shifts reported earlier[10,12] for **6** are in agreement with those presented in Table 1.

Comparing the ^{1}H NMR spectra of **2** and **6** (Table 1), the major difference is the coupling constants between the protons at C-4 and C-5. The methine proton at C-4 in **6** gives a rather complicated multiplet. Besides the allylic couplings to the exocyclic double bond protons at C-10 (which could not be determined), H-4 is coupled to H-5a and H-5e with coupling constants of 11.8 and 6.3 Hz, respectively. These couplings imply a *trans* di-axial and axial–

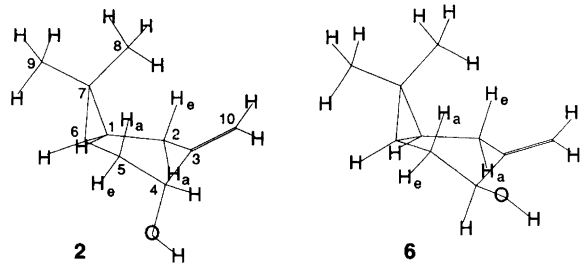


Fig. 1. Computer-generated conformations* of **2** and **6** based on minimum-energy calculations. The conformations are in good agreement with those deduced from the ^{1}H NMR measurements.

*ALCHEMY, molecular-modeling program developed and distributed by Tripos Associated, Inc., St. Louis, USA.

equatorial pathway between the coupled protons, respectively. The coupling constant between H-5a and H-6 is only 4.3 Hz, which is in agreement with an approximately 120° dihedral angle. These coupling constants are possible for a structure in which the OH-group is equatorial and H-4 axial. The H,H-COSY spectrum also shows quite large allylic couplings betweeen the exocyclic double-bond protons and the proton at C-4. This establishes the axial position of H-4 allowing a large π-contribution to the couplings.[15] The remaining H,H-coupling constants of **6** given in Table 1 are very similar to those of **2**, indicating roughly the same conformation for both isomers (Fig. 1).

The ^{13}C spectral data for **2** and **6** (Table 2) provide further evidence for the assigned conformations. The main difference in the ^{13}C spectra of the two compounds is observed in the chemical shifts of C-2, C-6 and C-10. The first two are shielded by 5.5 and 4.2 ppm, respectively, in **2** due to the 1,3-interaction from the axial hydroxy group. All the other chemical shifts in Table show only minor differences for the two isomers supporting the conformations shown in Fig. 1.

Experimental

Equipment. A Perkin-Elmer 8420 gas chromatograph was used with a methyl silicone capillary column, OV-1 (length 25 m, diameters i.d./o.d. 0.32 mm/0.44 mm, phase-layer 0.15 μm). ^1H and ^{13}C NMR spectra were recorded on Jeol GX-400 (for **2**) and Bruker AM-200 (for **2** and **6**) spectrometers, using $CDCl_3$ as the solvent. Mass spectra were obtained using a Kratos MS80RF Autoconsole, 70 eV. Flash chromatography was carried out on a silica gel 60 column (0.040–0.063 mm, diameter 1.5 cm, height 25 cm) with hexane–diethyl ether (1:1) as the eluent.

Reagents. 3α,4α-Epoxycarane[16] (100 %, GLC) b.p. 70–72 °C/8 mmHg, n_D^{20} 1.4672. Toluene was dried by distillation over Na. Aluminium isopropoxide (Fluka) was distilled, b.p. 95–100 °C/0.01–0.02 mmHg.

Isomerization of 3α,4α-epoxycarane **1**. 3α,4α-Epoxycarane (20.0 g, 0.132 mol), aluminium isopropoxide (26.8 g, 0.132 mol) and dry toluene (180 ml) were heated under reflux under an atmosphere of N_2. Gentle reflux was continued until thin layer chromatography indicated that all the epoxide had been consumed (approximately 12 h). After being cooled the reaction mixture was poured into a mixture of petroleum ether (600 ml) and diethyl ether (200 ml) and the mixture was washed twice with 10 % acetic acid. The precipitated $Al(OH)_3$ was filtered off and the filtrate was further washed with water, 5 % $NaHCO_3$ and saturated NaCl solution. After the solution had been dried (Na_2SO_4) the solvent was evaporated. The product (17.2 g, 86 %) contained (based on capillary GLC) 38 % *p*- and *m*-cymene, 39 % *trans*-3(10)-caren-4-ol (**2**), 12 % *cis*-3(10)-caren-4-ol (**6**), 5 % *trans*-2-caren-4-ol (**4**), 3 % *m*-mentha-4,6-dien-8-ol (**8**) and 3 % unidentified products. The mixture was fractionated by vacuum distillation. The mixture of alcohols **2** and **6** was distilled at b.p. 100 °C/10 mmHg and the stereoisomers were separated by flash chromatography.

trans-3(10)-Caren-4-ol (**2**): MS [70 eV; *m/z* (% rel. int.)]: 152 (6, *M*), 137 (20, $M-CH_3$), 134 (41), 119 (38), 109 (56), 95 (50), 92 (100), 91 (95), 83 (67), 81 (45), 79 (36), 77 (26), 70 (34), 69 (38), 67 (39), 55 (80), 43 (32), 41 (66), 39 (34). Lit.[1,4]

cis-3(10)-Caren-4-ol (**6**): MS [70 eV; *m/z* (% rel. int.)]: 152 (1, *M*), 137 (14, $M-CH_3$), 134 (14), 119 (33), 109 (44), 95 (44), 92 (100), 91 (85), 83 (50), 81 (43), 79 (42), 77 (22), 70 (30), 69 (37), 67 (36), 65 (38), 59 (40), 55 (71), 43 (33), 41 (61), 39 (31).

p- and *m*-cymene, *m*-mentha-4,6-dien-8-ol (**8**) and *trans*-2-caren-4-ol (**4**) were identified by comparison of GC retention times and mass spectra with those of authentic samples.

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