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Synthesis of syn- and anti-Epoxides of α-Campholenic and Fencholenic Derivatives

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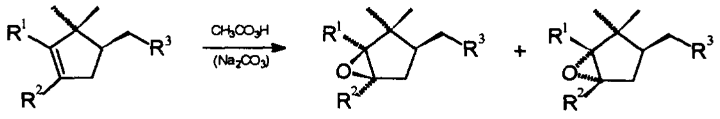
Abstract: syn-Epoxides of α-campholenic and fencholenic derivatives were synthesized by special epoxidation with peracetic acid besides the anti-isomers. This method is used to synthesize the syn-epoxide of Brahmanol® which gives a more intensive sandalwood odour compared to the anti-isomer. © 1999 Elsevier Science Ltd. All rights reserved.

We have been concerned with variations at the electronegative centre of the 5-membered ring of α-campholenic **1a-e** (R^1: $-CH_3$; R^2: -H) and fencholenic **1 f-i** (R^1: -H; R^2: $-CH_3$) derivatives to get novel Brahmanol®-type fragrances. The epoxidation of **1** achieves the anti-epoxides as the synthetically preferred products which can be used as building blocks [1,2,3].

There are some inconsistent statements about syn- and anti-epoxides of campholenic compounds [4]. syn-Epoxides of fencholenic derivatives are unkown. Recently Fehr [5] reported on diastereomeric epoxides of cyclohexyl derivatives by using various epoxidation reagents.

On investigation of other side-chain derivatives we found that the syn-epoxides can also be formed as side products with maximum percentage ratio of 8 % to the anti-products, if the side-chain has a carbonyl carbon on the β-position (**1a, b, f**) (table) [6].

The percentage ratio of the syn-epoxides to the anti-isomers could be increased with peracetic acid using drastic epoxidation conditions. The isolation of the isomers was achieved by normal column chromatography (petrol ether (85-100 °C) - ethyl acetate) [6].



1 2 3

Sandalwood odour was found for the Brahmanol® derivatives **2d, 3d**. It is more intensive with a light green note indication in the case of the syn-epoxide **2d**.

syn-Epoxide **2i** can be selectively formed from the anti-isomer **3i** by acid ring opening to the diol followed by forming the tosylate and finally ring closure yielding **2i** [7].

On acidic conditions α-campholenic epoxides undergo the Nametkin rearrangement to give only β-campholenic derivatives [2].

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table: ^{1}H NMR and ^{13}C NMR data of geminal methyl groups of syn- and anti-epoxides **2** and **3**

				product ratio [%] syn **2** : anti **3**		^{1}H NMR (400 MHz) δ in ppm				^{13}C NMR (100 MHz) δ in ppm			
				CH_2Cl_2, RT	toluene, 110 °C	CH_3 (cis)[a]		CH_3 (trans)[a]		CH_3 (cis)[a]		CH_3 (trans)[a]	
	R^1	R^2	R^{3,b}	**2** : **3**	**2** : **3**	**2**	**3**	**2**	**3**	**2**	**3**	**2**	**3**
a	CH_3	H	a'	8 : 92	21 : 79	0.93	0.75	1.00	0.99	17.83	18.50	26.52	20.18
b	CH_3	H	b'	7 : 93	19 : 81	1.00	0.75	0.99	0.99	18.58	19.27	27.48	21.05
c	CH_3	H	c'	0 : 100	9 : 91	1.00	0.77	0.98	1.00	19.02	18.00	27.86	20.10
d	CH_3	H	d'	0 : 100	12 : 88	1.00	0.72	0.95	0.96	18.89	19.18	28.18	21.47
e	CH_3	H	e'	0 : 100	11 : 89[c]		0.75		1.00		17.60		19.52
f	H	CH_3	a'	8 : 92	21 : 79	1.01	0.76	0.99	1.05	20.60	19.39	26.55	22.78
g	H	CH_3	d'	0 : 100	8 : 92[c]		0.74		1.04		19.02		22.55
h	H	CH_3	e'	0 : 100	11 : 89[c]		0.73		1.02		19.12		23.06
i	H	CH_3	f'	3 : 97	20 : 80	1.06	0.68	0.97	0.96	20.59	19.15	26.97	22.93

overall yield min. 90 %, reaction time at RT max. 24 h, at 100 °C max. 5 h.

[a] **cis and trans of the geminal methyl group to the side-chain.**

[b] a' $-COCH_3$; b' $-COOCH_2CH_3$; c' $-CH_2OCOCH_3$; d' $-CH_2CH(CH_3)CH_2OH$; e' $-CH(-OCH_2CH_2O-)$; f' $-CH_2OCH_3$.

[c] **syn-epoxides were not separated - determined by GC-MS.**

The configurations of the syn- and anti-epoxides were characterized by NMR-NOE difference spectroscopy and X-ray studies. The epoxides can now be easily discriminated by chemical shift of the geminal methyl groups. syn-Epoxides indicate significant smaller differences in the ^{1}H NMR data and higher differences in the ^{13}C NMR data than the anti-epoxides (table). These results are probably caused by different distances (molecular modelling) and ring conformations.

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