

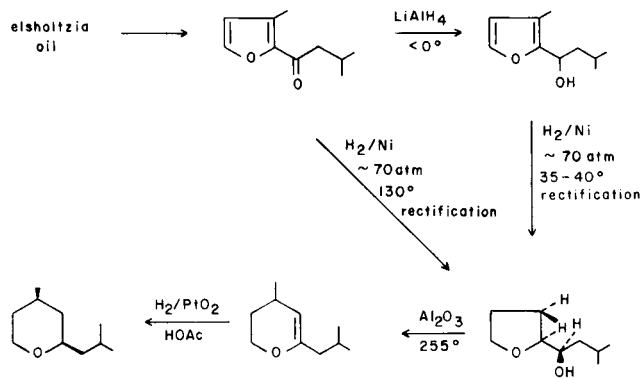
Chu-tsin Liu*, Chi-hsien Chang and Tsu-liang Chou

Shanghai Institute of Organic Chemistry,
Academia Sinica, Shanghai 200032, China
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A new synthesis of *cis*-dihydro-rose oxide from elsholtzia oil is presented. The stereochemistry of catalytic hydrogenation of elsholtziol is discussed, and configurations of the diastereoisomers of the resulting tetrahydroelsholtziol have been deduced with the aid of gas chromatography, infrared spectroscopic analysis and conformational analysis. Stereochemical study of catalytic dehydration of tetrahydroelsholtziols indicates that the dehydration-rearrangement reactions follow a *trans*-elimination process.

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cis-Dihydro-rose oxide is a fragrant material relevant to rose oil. It has been synthesized before by two groups of workers [1] [2]. The present synthesis starts from elsholtzione (**1**), the main constituent (60%) of a natural product, elsholtzia oil. The synthetic sequence is as follows.



Elsholtzione (**1**) was isolated from the essential oil either *via* the semicarbazone [3,4] or through the rectification of the main fraction of the oil. Elsholtziol (**2**) was prepared by reduction of **1** with lithium aluminium hydride [5] and proved to be a quite labile compound at room temperature [6]. The key intermediate, *cis*-*erythro*-tetrahydroelsholtziol (**3a**), was obtained by hydrogenation of **2** over Raney nickel under pressure, followed by rectification of the resulting mixture of hydrogenation products. Compound **3a** could also be obtained directly from **1** by catalytic hydrogenation over nickel, but higher temperature was required and repeated rectification was necessary to isolate **3a** in pure form. Compound **3a** was dehydrated on active alumina in the vapor phase with rearrangement to form 2-isobutyl-4-methyl-5,6-dihydro-4*H*-pyran (**4a**). The end product, *cis*-dihydro-rose oxide (**5a**), was obtained by hydrogenation of **4a** over Adam's catalyst in acetic acid.

All the compounds mentioned above were identified by spectrometric methods along with elementary analysis and gas chromatography. The key spectral data are listed in Table 1.

Table 1

Key Spectral Data of Related Compounds

Compound	IR (cm ⁻¹)	NMR δ	MS m/e (%)
1	1674, 1385, 1368	7.39 (d, 1H), 6.39 (d, 1H)	166 (M ⁺ , 21), 109 (100)
2	3350	7.28 (d, 1H), 6.19 (d, 1H)	168 (M ⁺ , 6), 111 (100)
3a	3460	1.89 (s, 1H, OH) 2.12 (m, 2H, one OH), no 7.28 and 6.19	172 (M ⁺ , 0.4) 85 (100)
4a	1670, 1295 [a], 1080 [a]	4.36 (d, 1H, O-C=CH)	154 (M ⁺ , 43), 41 (100)
5a	1450-1436, [b] 1373-1361, [b] 1171-1159, [b] 1091-1079, [b]	no 4.36	156 (M ⁺ , 0.8), 99 (100)

[a] Characteristic for 2-alkyl-5,6-dihydro-4*H*-pyran [7]. [b] Corresponds to the literature value of *cis*-dihydro-rose oxide [8] [2].

As might be expected, four diastereoisomers of tetrahydroelsholtziol (**3**) were formed by catalytic hydrogenation of elsholtziol (**2**) and elsholtzione (**1**). The gas chromatograms of the hydrogenation products from **2** and **1** are similar and show four peaks A, B, C and D, coming out in the order shown in Figures 1 and 2, respectively. By repeated rectification, pure A, B and D were obtained. The results of elementary analysis, thin layer chromatography [9], and spectroscopic analysis all tend to the conclusion that they are diastereoisomers of **3**. GC-MS analysis revealed that compound C was also a diastereoisomer of **3**, although it has not been isolated in pure form as yet. The configurations assigned to A, B and D are supported by infrared spectroscopy of their dilute solutions as well as conformational analysis. The principal product D proved to be the *cis*-*erythro*-isomer **3a**, which we needed for the subsequent synthetic steps.

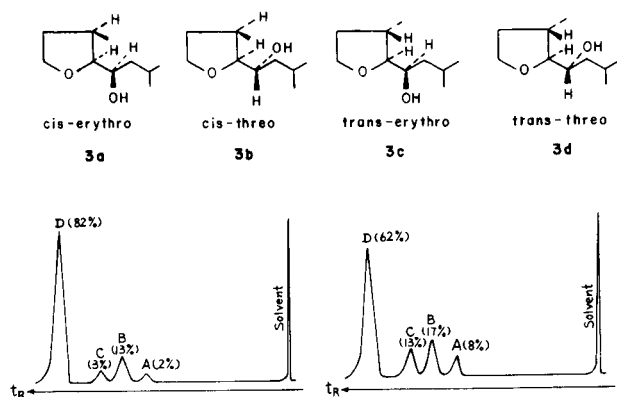


Figure 1. Chromatogram of hydrogenation product of **2**, hydrogenation at 35-40° and 71.5 atmospheres.

Figure 2. Chromatogram of hydrogenation product of **1**, hydrogenation at 130° and 71.5 atmospheres.

It has been shown that in sufficiently dilute solutions two bands of free and intramolecularly-bonded OH groups could be observed for both *erythro* and *threo* diastereoisomers of compounds of the type R-CHX-CHOH-R'. When the difference of frequency of these two bands is denoted by $\Delta\nu$ ($\Delta\nu = \nu_{OH_f} - \nu_{OH_b}$), and the intensity ratio of the bonded and free absorption is denoted by ϵ_b/ϵ_f , then, as a general rule, $\Delta\nu$ *threo* is greater than $\Delta\nu$ *erythro* and the intensity of the bonded absorption band is greater in the *threo* series [10]. As shown in Table 2, the ir data of dilute solutions of A, B and D suggest that D should be an *erythro* isomer and A, B *threo* isomers. Thus, C would also be an *erythro* isomer.

Table 2

IR Spectral Data of Dilute Solutions of A, B and D

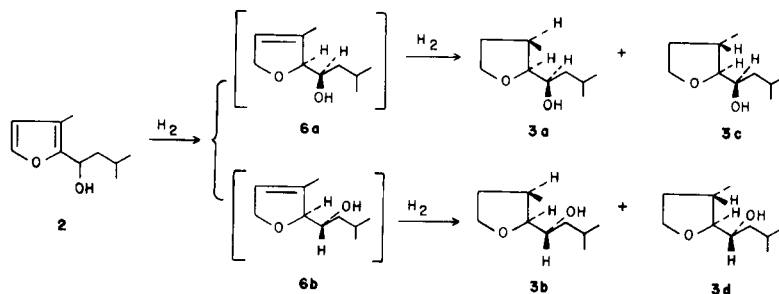
Diastereo-isomer	ν_{OH} (cm ⁻¹)	ν_{OH} (cm ⁻¹)	$\Delta\nu$ (cm ⁻¹)	ϵ_b/ϵ_f
A	3676	3569	107	≥ 1
B	3667	3587	80	≥ 1
D	3620	3587	37	~ 1

On the other hand, it is well known that catalytic hydrogenation takes place by *cis*-addition of hydrogen. The fact that hydrogenation of elsholtziol (**2**) led to four diastereoisomers instead of two indicates that saturation of the furan nucleus in **2** is a stepwise hydrogenation process. Otherwise, only two *cis*-isomers would be obtained. The proposed mechanism and stereochemistry of the hydrogenation is shown in Scheme 1. Thus, **2** presumably absorbs one mole of hydrogen first to yield intermediates **6a** and **6b**, which absorb a second mole of hydrogen to yield products **3a**, **3c**, and **3b**, **3d**, respectively. As hydrogenation usually takes place by *cis*-addition of hydrogen atoms to the less hindered side of the unsaturated center, the predominant intermediate is **6a** (*erythro*). Because of the existence of the bulky side chain at position 2 of **6a**, the proportion of **3a** (*cis-erythro*) is much higher than that of **3c**. Similarly, the proportion of **3b** is much higher than that of **3d**. Therefore, *cis*-isomers **3a** and **3b** are the main products, in which the quantity of **3a** is much greater. Compounds **3c** and **3d** would be the secondary products, in which the amount of **3c** is greater. By comparison with the results of chromatographic analysis, we are able to conclude that D, C, B and A should correspond to **3a**, **3c**, **3b** and **3d** respectively, and fortunately the principal product D proved to be the *cis-erythro* tetrahydroelsholtziol **3a** that we wanted.

cis-erythro-Tetrahydroelsholtziol (**3a**) proved to form only one main dehydration product **4a**, the structure of which was in consistency with its spectral data. *cis-threo*-Tetrahydroelsholtziol (**3b**) was dehydrated in the same manner, but it formed two main dehydration products. Furthermore, higher dehydration temperature was required. The dehydration product having the same gc retention time (t_R) and ms data as those of **3a**, is believed to be **4a**. The other having the same M^+ and base peak as those of **4a** but with different t_R , is presumed to be the isomer **4b**. All these can be explained with the stability of conformers and *anti*-elimination mechanism of dehydration.

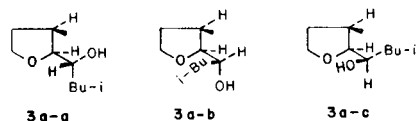
Compound **3a** has three probable conformers **3a-a**, **3a-b** and **3a-c**. Conformer **3a-a**, in which the *i*-Bu group is *anti* to the C₂-C₃ bond, is the most stable conformer of **3a**

Scheme 1

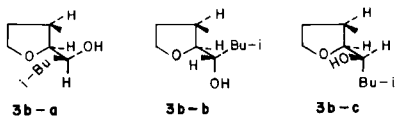
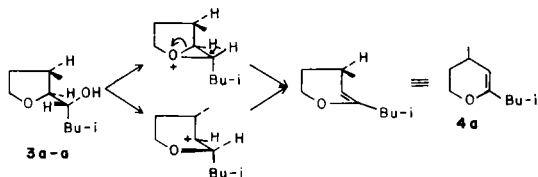


and happens to have the OH group *anti* to the C₂-O bond, so that dehydration can be anchimerically assisted *via* an epoxonium intermediate or by the C₂-O bond as shown in Scheme 2. Formation of **4b** from **3a** is possible, but would have to occur from a high energy conformer **3a-b** (anchimerically assisted by C₂-C₃ bond). As to another high energy conformer **3a-c**, dehydration cannot be anchimerically assisted (which is far more difficult). So, **3a** formed only one main dehydration product **4a**.

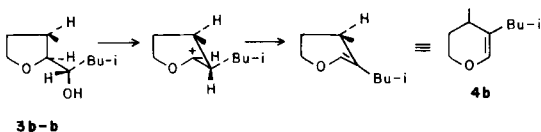
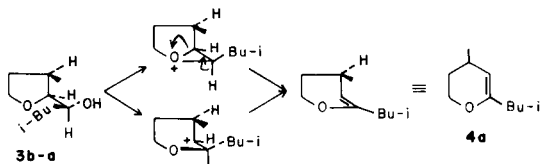
In contrast, for the most stable conformer of **3b** (**3b-c**), dehydration cannot be anchimerically assisted. Dehydration, if assisted, must take place through the higher energy, less populated conformers **3b-a** and **3b-b** as shown in Scheme 3. Thus, two main dehydration products **4a** and probably **4b** were formed. This also implies that **3b** is less easily dehydrated than **4a**.



Scheme 2



Scheme 3



EXPERIMENTAL

Rectification was carried out with a Perkin-Elmer Model 251 auto annular still. The ir spectra were recorded on a Specord 75 IR spectrophotometer. The nmr spectra were determined on a Varian XL-200 spectrometer using TMS as internal standard. Mass spectra were obtained on a Finnigan 4021 mass spectrometer. The gc analysis was carried out on a Model 102-G gas chromatograph using a glass column (3.5 m × 3 mm) filled with 5% OV-225 on Chromosorb W (60-80 mesh) and nitrogen as carrier gas.

Elsholtzine (**1**).

Elsholtzia oil (containing 60% of **1**) was distilled under reduced pressure. The main fraction (bp, 54.5-56.5°, containing 80% of **1**) was used as the raw material for the following steps.

Method a.

Semicarbazide hydrochloride (120 g) and sodium acetate (150 g) were dissolved in 400 ml of water with gentle heating. To the solution was poured the main fraction mentioned above (150 ml, 144 g) and then sufficient ethanol (*ca.* 700 ml) was added with stirring to dissolve the oily layer. After adding some crystalline seeds of the semicarbazone of **1** (**1a**), the solution was allowed to stand for 3-4 days until the crystallization was complete. The crystals were filtered, washed with 50% ethanol and dried. The crude **1a** (130 g, mp 166-168°) was obtained and recrystallized from 7 times its weight of methanol to give pure **1a** (106 g, mp 169-170° [lit {3} mp 170-171°]). The mother liquor was concentrated. After two recrystallizations of the resulting crystals, additional pure **1a** (12 g) was obtained. The total yield of **1a** was 76%.

Compound **1a** (89.2 g, 0.4 mole) and oxalic acid (100.8 g, 0.8 mole) were placed in a 1-litre three necked flask and 400 ml of water was added. After refluxing for half an hour, the solid disappeared and then steam distillation was carried out. The distillate was extracted with ether and the yellow ethereal layer was dried over anhydrous sodium sulfate. After removal of ether, the residue was distilled under reduced pressure to give **1** (61 g, 92%), bp, 48°. The yield of **1** calculated by the amount of the main fraction used was about 70%, ir: ν 1674, 1385, 1368 cm⁻¹ [5]; ¹H nmr: δ 7.39 (d, 1H, CH=CH-O, J = 2 Hz), 6.39 (d, 1H, CH=CH-O, J = 2 Hz), 2.72 (d, 2H, CH₂-CH, J = 7 Hz), 2.40 (s, 3H, C=C-CH₃), 2.27 (m, 1H, CH(CH₃)₂), 0.98 (d, 6H, CH(CH₃)₂, J = 7 Hz); ms: m/e (%) 166 (M⁺, 21), 109 (100).

Anal. Calcd. for C₁₀H₁₄O₂: C, 72.26; H, 8.49. Found: C, 72.10; 72.27; H, 8.70, 8.62.

Method B.

The main fraction (15 ml) of elsholtzia oil was rectified under reduced pressure to give **1** (10.6 ml, 88%), bp, 48-49°.

Elsholtziol (**2**).

Lithium aluminium hydride (2.4 g) was placed in a 1-litre three necked flask containing 400 ml of absolute ether (dried over sodium wire). Under cooling with dry ice and stirring, 32 g of **1** was added dropwise, keeping the temperature below 0°. After stirring for 5-6 hours below 0°, about 100 ml of water was added to decompose the unreacted lithium aluminium hydride and then about 100 ml of 10% sulfuric acid was added to dissolve the resulting aluminium hydroxide. The ethereal layer was separated, washed to neutral with water, and dried over anhydrous sodium sulfate. After removal of ether, the residue was distilled under reduced pressure [11] to yield **2** (27.5 g, 85%), bp, 62-63°. In order to obtain an analytical sample, half its volume of petroleum ether (30-60°) was added to **2** and the solution was chilled in a refrigerator (-10°). The resulting crystals were collected by filtration, washed with cooled petroleum ether and dried in the air to give **2** as white needles (24.8 g, 90%), mp 33-34.5°; ir: ν 3350 cm⁻¹ [5]; ¹H nmr: δ 7.28 (d, 1H, CH=CH-O, J = 2 Hz), 6.19 (d, 1H, CH=CH-O, J = 2 Hz), 4.77 (t, 1H, CH₂-CH-OH, J = 8 Hz), 2.03 (s, 3H, C=C-CH₃), 1.89 (s, 1H, OH), 1.76 (m, 2H, CH-CH₂-CH), 1.55 (m, 1H, CH(CH₃)₂), 0.91 (d, 3H, CH<CH₃, J = 4 Hz), 0.89 (d, 3H, CH<CH₃, J = 4 Hz); ms: m/e (%) 168 (M⁺, 6), 111 (100).

Anal. Calcd. for C₁₀H₁₆O₂: C, 71.39; H, 9.59. Found: C, 71.24, 71.35; H, 9.65, 9.62.

cis-erythro-Tetrahydroelsholtziol (**3a**).

A solution of **2** (6.5 ml, 6.2 g) in 13 ml of absolute alcohol was hydrogenated in the presence of W-4 Raney nickel (5 g) at 71.5 atmospheres and 35-40° until the uptake of hydrogen ceased (*ca.* 2.5 hours). The mixture was cooled to room temperature and the catalyst was separated by filtration. After removal of alcohol the residue was analyzed by gas chromatography.

graphy. The overall content of four diastereoisomers of **3** was close to 100% and the ratio of **3a**, **3b**, **3c** and **3d** were 82, 13, 3 and 2%, respectively. The residue was rectified under reduced pressure to give 3.0 g of

3a (>98% in purity), bp₁ 54.5-55°. The fraction of pure **3a** (~100% in purity) was taken as analytical sample, d_4^{20} 0.9881; n_D^{20} 1.4543; ir: ν 3440 cm^{-1} ; ^1H nmr: 3.90 (q, 1H), 3.73 (m, 2H), 3.48 (q, 1H), 2.36 (m, 1H, C₄-H), 2.12 (m, 2H, OH and C₄-H), 1.83 (m, 1H, C₃-H), 1.58 (m, 1H, CH₂CH(CH₃)₂), 1.42 (m, 2H, CHCH₂CHOH), 1.00 (d, 3H, CHCH₃, J = 7 Hz), 0.92 (d, 3H, CH< $\begin{smallmatrix} \text{CH}_3 \\ \text{CH}_3 \end{smallmatrix}$, J = 6 Hz), 0.89 (d, 3H, CH< $\begin{smallmatrix} \text{CH}_3 \\ \text{CH}_3 \end{smallmatrix}$, J = 6 Hz); ms: m/e (%) 172 (M⁺, 0.4), 171 (M-1, 1.4), 85 (100).

Anal. Calcd. for C₁₀H₂₀O₂: C, 69.72; H, 11.70. Found: C, 69.52, 69.70; H, 11.64, 11.52.

(H₆,J.

2-Isobutyl-4-methyl-5,6-dihydro-4H-pyran (**4a**).

Catalytic dehydration of **3a** was carried out in a column filled with active alumina (10 g, 10-14 mesh) [12] under nitrogen (3 bubbles per minute) at 255°. After pretreatment with anhydrous pyridine (30 ml), a mixture of **3a** (13.7 ml, 13.1 g) and pyridine (3.5 ml) was added with a rate of 6-9 drops per minute. The eluted condensate separated into two layers. The upper organic layer was separated and dehydrated again to give 13.2 ml of a new organic layer. The combined aqueous layer was extracted with ether. The ether layer and the organic layer was combined, washed to neutral with water and dried over anhydrous sodium sulfate. After removal of ether, the residue (10.7 ml, 9.3 g, containing 86% of **4a**) was rectified under reduced pressure to give 7.5 ml (6.5 g) of **4a** (~99% in purity), yield 56%; bp₁₂ 66-69°; ir: ν 1670, 1295, 1080 cm^{-1} ; ^1H nmr: δ 4.36 (d, 1H, O-C=CH, J = 3 Hz), 3.95 (m, 2H, OCH₂CH₂), 2.26 (m, 2H, OCH₂CH₂), 1.82 (m, 3H, CHCH₃ and C=C-CH₃), 1.44 (m, 1H, CH(CH₃)₂), 0.98 (d, 3H, CHCH₃, J = 7 Hz), 0.88 (d, 6H, CH(CH₃)₂, J = 7 Hz); ms: m/e (%) 154 (M⁺, 43), 41 (100).

cis-Dihydro-rose Oxide (**5a**).

A solution of 3.7 ml (3.1 g) of **4a** (95% in purity) in 3.7 ml of acetic acid was hydrogenated over Adam's catalyst (200 mg) with magnetic stirring at atmospheric pressure until the uptake of hydrogen ceased (ca. 5 hours). Ether was added to the mixture. The catalyst was separated by filtration and the filtrate was washed to neutral with water. The ether layer was separated and dried over anhydrous sodium sulfate. After removal of ether 3.6 ml of residue was obtained, in which the content of **5a** was about 95%. From 3 portions of the same **4a** (8.7 ml), 8.5 ml of residue was obtained. The residue (8.2 ml) was rectified under reduced pressure to give 3.1 ml [13] of **5a** (>99% in purity), bp_{14.5} 66° (lit [8] bp₁₀ 60-62°). The fraction of pure **5a** (100% in purity) was taken as analytical sample, d_4^{20} 0.8416 (lit [8] d_4^{20} 0.8400); n_D^{20} 1.4283 (lit n_D^{20} 1.43140 [8], 1.4305 [2]); ir: ν 1450-1436 (vs), 1373-1361 (vs), 1340 (s), 1300 (m), 1261-1253 (s), 1171-1159 (vs), 1131 (m), 1091-1079 (vs), 1019 (s), 983 (s), 967 (s), 900 (mw), 891 (m), 871 (w), 836 (w), 807 (ms), 779 (m) cm^{-1} ; ^1H nmr: δ 4.01 (m, 1H, O-CH), 3.38 (m, 2H, OCH₂CH₂), 1.88 (m, 1H), 1.58 (m, 4H), 1.22 (m, 3H), 1.03 (d, 3H, CHCH₃, J = 2 Hz), 1.00 (d, 3H, CH< $\begin{smallmatrix} \text{CH}_3 \\ \text{CH}_3 \end{smallmatrix}$, J = 4 Hz), 0.98 (d, 3H, CH< $\begin{smallmatrix} \text{CH}_3 \\ \text{CH}_3 \end{smallmatrix}$, J = 4 Hz); ms: m/e (%) 156 (M⁺, 0.8), 99 (100).

Anal. Calcd. for C₁₀H₂₀O: C, 76.86; H, 12.90. Found: C, 76.61, 76.66; H, 12.73, 13.09.

The analytical sample of **5a** was analyzed by gas chromatography with SE-30 and DEGS capillary column. Only one peak appeared in both cases.

Catalytic Hydrogenation of **1** as Well as the Separation and Identification of Diastereoisomers of **3**.

The hydrogenation procedure of **1** was similar to that of **2**, only higher temperature was needed. By repeated rectification pure **3a**, **3b** and **3d** were obtained. The physical constants and elementary analysis data are listed in Table 3. The spectral data are listed in Table 4. The infrared spectral data of dilute solutions are listed in Table 2.

Table 3

	bp ₁ (°C)	d ₄ ²⁰	n _D ²⁰	t _R	R _f [9]	Analyses %	
						Calcd./	(Found)
						C	H
3d (A)	50	0.9703	1.4448	9'14"	0.35	69.72 (69.49)	11.70 (11.34)
3b (B)	51-52	0.9744	1.4466	10'36"	0.35	69.72 (69.74)	11.70 (11.77)
3c (C)				11'48"		69.51 (69.51)	11.89 (11.89)
3a (D)	54.5-55	0.9881	1.4543	15'	0.35	69.72 (69.52)	11.70 (11.64)
						69.70 (69.70)	11.52 (11.52)

Table 4

	IR (cm^{-1})	^1H NMR, δ	MS, m/e (%)
3a	3460	3.90 (q, 1H), 3.73 (m, 2H), 3.48 (q, 1H)	172 (M ⁺ , 0.4), 171 (1.4), 85 (100)
3b	3467	3.97 (q, 1H), 3.74 (m, 2H), 3.55 (q, 1H)	173 (7), 172 (M ⁺ , 0.5), 85 (100)
3d	3466	3.85 (m, 2H), 3.52 (m, 1H), 3.24 (q, 1H)	173 (M+1, 68), 155 (100), 85 (87)

The mixture of **3a** and **3c** was analyzed by gc/ms. The mass spectral data were m/e (%) **3a**: 172 (M⁺, 0.03), 85 (100); **3c**: 172 (M⁺, 0.07), 85 (100).

Catalytic Dehydration of **3b**.

The experimental procedure was similar to that of **3a**, only the dehydration temperature was raised to 267°. After removal of ether, the residue was analyzed by gas chromatography. The chromatogram showed two main peaks of smaller retention times, corresponding to 60% of the total. The first peak corresponds to that of **4a**. The residue was rectified under reduced pressure. The fraction containing these two components in the highest content (>90%) was taken for gc/ms analysis. The mass spectral data were m/e (%) peak 1 (**4a**): 154 (M⁺, 24), 41 (100); peak 2 (probably **4b**): 154 (M⁺, 20), 41 (100).

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- [9] Thin layer alumina plate supplied by the workshop of Shanghai Institute of Materia Medica was used for tlc analysis with 15% of ethyl acetate-petroleum ether as developing solvent and 3% alcoholic solution of vanillin as spray reagent.
- [10] H. B. Kagan, "Stereochemistry Fundamentals and Methods", Vol 1, "Determination of Configurations by Spectrometric Methods", Georg Thieme Publishers, Stuttgart, 1977, p 41.
- [11] The distillation of **2** should be carried out at higher vacuum and lower bath temperature as quickly as possible due to its poor thermal stability.
- [12] It is a product of Shanghai Molecular Sieve Factory.
- [13] The lower yield of **5a** in distillation was attributed to its higher volatility.