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The Synthesis and the Absolute Configurations of Lilac Alcohols, New Naturally Occurring Odorous Ingredients of Lilac Flower

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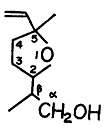
The conversion of racemic linalyl acetate to racemic lilac alcohols has been completed in 5 steps and four diastereoisomers of β,5-dimethyl-5-vinyl-2-tetrahydrofuranethanol were obtained. *d*-Lilac alcohols were also synthesized from *d*-linalyl acetate and confirmed to be identical with natural ones. The absolute configurations of lilac alcohol-a, -b, -c, and -d were respectively shown to be (βS, 2*S*, 5*S*), (βR, 2*S*, 5*S*), (βR, 2*R*, 5*S*), and (βS, 2*R*, 5*S*) by the chemical and physical evidences.

In previous papers,[1,2] it has been reported that four new terpene alcohols with exquisite floral fragrance have been isolated from the flower of lilac, *Syringa vulgaris* L. They have been named lilac alcohol-a, -b, -c, and -d according to decreasing order of the relative abundance and the diastereomers of β,5-dimethyl-5-vinyl-2-tetrahydrofuranethanol (I) were assigned as the structures of lilac alcohol-a and -b. It was soon confirmed by spectroscopic evidence that lilac alcohol-c and -d are also diastereomers of (I). (*cf.* Table 1).



I

TABLE 1. CHARACTERIZATION OF LILAC ALCOHOLS

Lilac alcohol	a	b	c	d
Relative abundance	9.7	3.5	2.5	1
R_t[a] (min)	17.8	13.4	20.8	14.8
$[\alpha]_D^{21}$(natural)	+12.2	−6.6	−1.4	+4.3
$[\alpha]_D^{25}$(from *d*-II)	+ 6.7	−1.4	−0.5	+1.4
$[\alpha]_D^{25}$(from *l*-II)	−11.6	+3.0	+2.5	−2.9

a) Gas chromatographic analyses were carried out at 120 °C with a 3mm × 3m column packed with 20% DEGS on Chromosorb W using JEOL GC-750.

Therefore, the lilac flower oil contains interestingly all diastereomers expected from the structure (I), but their extremely low yield from natural flower oil (-c and -d) made it difficult to investigate their stereochemical relationships. In this paper we wish to report the synthesis of lilac alcohols from linalyl acetate and their absolute configurations.[3]

Synthesis of Lilac Alcohols and the Absolute Configurations at C-2 and C-5. Four diastereomers of β,5-dimethyl-5-vinyl-2-tetrahydrofuranethanol (I) were obtained from racemic linalyl acetate in the following manner (Chart 1).

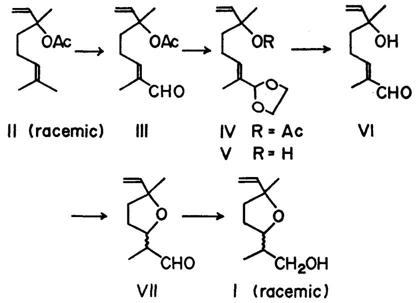


Chart 1.

Racemic linalyl acetate (II) was treated with selenium dioxide to afford α,β-unsaturated aldehyde (III) in 40% yield. Treatment of (III) with ethylene glycol in the presence of *p*-toluenesulfonic acid in benzene gave ethylene acetal (IV) which was hydrolysed with a 5% solution of sodium hydroxide to afford V. When the elution chromatography of V was carried out through a silica gel column, the ethylene acetal group underwent easy hydrolysis to afford VI (77% overall yield from III).[4] The direct hydrolysis of III afforded VI in only 6% yield along with VII. The intramolecular Michael addition of the tertiary alcohol to the α,β-

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1) S. Wakayama, S. Namba, and M. Ohno, *Nippon Kagaku Zasshi*, **92**, 256 (1971).

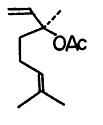
2) S. Wakayama, S. Namba, and M. Ohno, This Bulletin, **43**, 3319 (1970).

3) S. Wakayama, S. Namba, K. Hosoi, and M. Ohno, *ibid.*, **44**, 875 (1971).

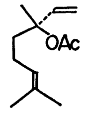
4) During the course of our synthetic work on lilac alcohols from linalyl acetate, Naegeli and Weber published the use of the aldehyde III as an intermediate to davanone synthesis.
P. Naegeli and G. Weber, *Tetrahedron Lett.*, **1970**, 959.

unsaturated aldehyde was effected with triethylamine to give a tetrahydrofuran derivative VII in 43% yield. Reduction of VII with $LiAlH_4$ afforded a mixture of four diastereomers of racemic lilac alcohol in 75% yield. From the mixture, each diastereomer was cleanly separated and purified by vapor phase chromatography. The relative concentration of the synthetic lilac alcohol-a, -b, -c, and -d was 2.0, 3.0, 2.5, and 1.0, respectively. The identity of the synthetic lilac alcohols with natural ones was confirmed by IR, NMR, and R_t (vpc) except for the optical activity.

In order to establish the absolute configuration of natural lilac alcohols, *d*-linalyl acetate[5] (*d*-II, $[\alpha]_D^{25}$ +2.9) and *l*-linalyl acetate (*l*-II, $[\alpha]_D^{25}$ −5.0) were separately converted into the corresponding lilac alcohols in the manner described above for the racemic case. Although these starting materials were not optically pure, they proved to be pure enough for the diagnostic purpose of the absolute configuration.



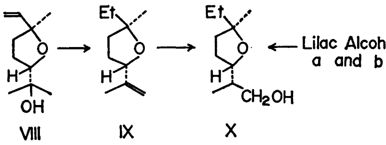
d-II



l-II

Thus, the physical properties of *d*-lilac alcohol-a, -b, -c, and -d derived from *d*-II were found to be consistent with the data obtained from the natural alcohols, as shown in Table 1.

Stereochemistry of the Tetrahydrofuran Ring. In a previous paper[2] lilac alcohol-a and -b and racemic *trans*-linalool oxide[6–8] (VIII) were converted into the same derivative (X).



Therefore, the stereochemistry of lilac alcohol-a and -b was clearly shown to be *trans* as for the tetrahydrofuran ring, and also concluding that the stereochemistry of lilac alcohol-c and -d must be *cis* as for the tetrahydrofuran ring.

Furthermore, since the absolute configuration of *d*-linalool[9] is known, it follows from the above results that the absolute configurations at C-2 and C-5 of lilac alcohol-a, -b, -c, and -d are (2*S*, 5*S*), (2*S*, 5*S*), (2*R*, 5*S*), and (2*R*, 5*S*), respectively.

Configurations at C-2 and C-β. The NMR spectra of lilac alcohols are very similar to one another except for the signal of the carbinol methylene shown in Fig. 1.

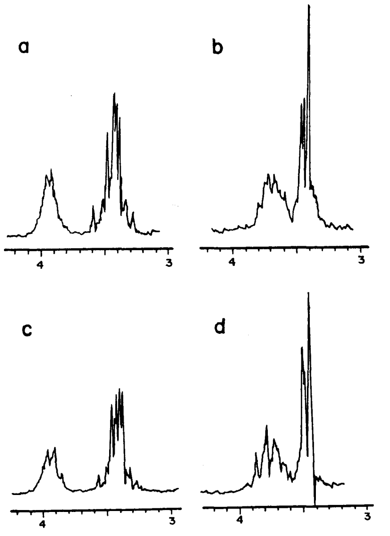
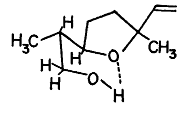


Fig. 1. The signal patterns of $-CH_2OH$ group.

Lilac alcohol-a and -c show common patterns (ABX type) regarding the methylene signal of the CH_2OH group, while lilac alcohol-b and -d show another common signal for the same group. This fact suggests that the former pair and the latter pair have respectively the same configurations at C-2 and C-β, and it was considered that such configurational problem might be solved by the study of intramolecular hydrogen bonding between the hydroxyl group and the ether oxygen, as seen in the formula of *threo* isomer, for example.



threo Isomer

Therefore, we determined the relative extent of hydrogen bonding[10,12,13] in the diastereomeric lilac alcohol-a, -b, -c, and -d by (1) measuring the hydroxyl absorption of their IR spectra in high dilution and (2) observing the dilution shift of the hydroxyl proton in the NMR spectrum of each isomer. In addition, we examined in detail the coupling constants (half-height width), $J_{2,\beta}$, since the magnitude of the vicinal proton coupling constant $J_{2,\beta}$ is a measure of the relative population of the various conformations.[10] Consideration of non-bonded interactions and intramolecular hydrogen bonding between the hydroxyl group and the ether oxygen in the rotational isomers of *threo* lilac alcohols[11] suggests that conformer A would be more stable than B or C (Chart 2). Similar consideration suggests that conformer E and F of the *erythro* isomer would be more stable than D.

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[5] *d*-Linalyl acetate was synthesized from *d*-linalool (coriabder oil). The oil and *l*-linalyl acetate were supplied by Takasago Perfumery Co., Ltd., Japan.

[6] This compound is a mixture of equal amount of (2*R*, 5*R*)- and (2*S*, 5*S*)-configuration.

[7] D. Felix, A. Melera, J. Seibe, and E. Sz. Kovatz, *Helv. Chim. Acta*, **46**, 1513 (1963); *ibid.*, **47**, 918 (1964).

[8] E. Klein, H. Farnow, and W. Rojahn, *Ann. Chem.*, **675**, 73 (1964).

[9] R. H. Cornforth, J. W. Cornforth, and V. Prelog, *ibid.*, **634**, 197 (1960).

[10] K. D. Carlson, D. Weisleder, and M. E. Daxenbichler, *J. Amer. Chem. Soc.*, **92**, 6232 (1970), and references contained therein.

[11] In the case of lilac alcohol, the ether oxygen and the hydroxy methylene group, and the ring methylene and methyl group are taken as the like groups, respectively.

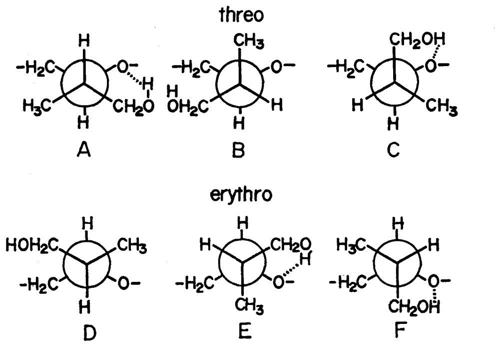

Chart 2. Staggered rotational isomers of the diastereoisomeric lilac alcohols*
(*Only one enantiomer is shown in each case.)

Infrared Study: Hydroxyl bands in the 3600 cm^{-1} region in the IR spectra of lilac alcohols were examined in carbon tetrachloride (0.005—0.025 M). At concentrations lower than 0.025 M, each alcohol shows two OH bands independent of concentration, which are assigned to free (3634—3640 cm^{-1}) and intramolecularly bonded (3520—3525 cm^{-1}) hydroxyl groups, showing that intermolecular hydrogen bonding is negligible in these concentrations. Table 2 shows that lilac alcohol-b and -d exhibit a longer frequency shift, $\Delta\nu$, than lilac alcohol-a and -c, and the former isomers have most significantly a clearly larger ratio of the integrated band intensity of bonded and free hydroxyl bands than that of the latter isomers. Therefore, lilac alcohol-b and -d should have a much more populous hydrogen bonded conformation than lilac alcohol-a and -c. From this evidence, it was assumed that lilac alcohol-b and -d have the *threo* configuration and -a and -c have the *erythro* configuration. In the latter case, conformers E and F may be composed to the similar order as acyclic analog, 3-methoxypropanol[12] $CH_3OCH_2CH_2CH_2OH$, and in the former case conformer A may be most stable owing to not only the nonbonded interaction but also the intramolecular hydrogen bonding.

TABLE 2. INFRARED DATA FOR LILAC ALCOHOLS

Lilac alcohol	ν OH (free, cm^{-1})	ν OH (bonded, cm^{-1})	$\Delta\nu$ (cm^{-1})	Ratio of integrated band intensity (bonded/free)
a	3638	3525	113	5
b	3640	3520	120	12
c	3634	3522	112	4
d	3640	3520	120	14

NMR Studies: NMR spectra (100 MHz) of the alcohols were obtained in carbon tetrachloride. In Fig. 2, the chemical shift of each hydroxyl proton (tetramethylsilane as an internal standard) is plotted as a function of concentration of lilac alcohols. The smaller limiting slope of the lilac alcohol-b and -d compared with lilac alcohol-a and -c is consistent with stronger bonding[13,14] as confirmed by our IR studies. The -b and -d isomers have the larger limiting chemical shift for the hydroxyl proton. Thus, it was tentatively proposed to assign the *erythro* configuration to lilac alcohol-a and -c, and the *threo* configuration to lilac alcohol-b and -d.

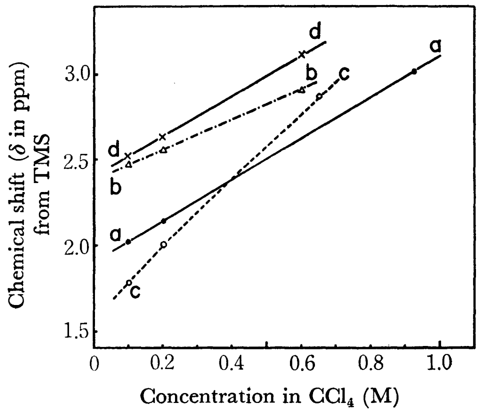

Fig. 2. Hydroxy proton chemical shift dependence on concentration of Lilac alcohols in CCl_4.

If this conclusion is reasonable, *threo* isomers should have a larger vicinal coupling constant ($J_{2,\beta}$) than *erythro* isomers, because the coupling of the hydrogen at C-2 of *threo* and *erythro* isomers to the neighboring methylene group in the ring is considered to be the same order, but the coupling to the hydrogen at C-β should be stronger in *threo* configuration (anti conformation). In the *erythro* configuration, the contribution of conformer E and F seems to be larger than D to decrease the proton dihedral angle ($\phi_{2,\beta}$) of the averaged conformers (*gauche* conformation) or causing a smaller coupling constant than that of conformer A. The magnitudes of the vicinal coupling constants, $J_{2,\beta}$, are obtained as half-height width (Table 3), clearly showing as expected that lilac alcohol-b and -d have the larger coupling constants than those of lilac alcohol-a and -c.

TABLE 3. HALF-HEIGHT WIDTH OF THE VICINAL COUPLING CONSTANTS ($J_{2,\beta}$)

Lilac alcohol	Half-height width of $>$CH-O- (Hz)
a	13
b	22
c	15
d	22

All of the spectroscopic evidences obtained above consistently support the view that lilac alcohol-a and -c have *erythro* configuration and lilac alcohol-b and -d have *threo* configuration.

Both chemical and physical evidences indicate that the absolute configurations of lilac alcohol-a, -b, -c, and -d are (βS, 2S, 5S), (βR, 2S, 5S), (βR, 2R, 5S), and (βS, 2R, 5S), respectively.

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12) A. B. Foster, A. H. Haines, and N. Stacey, *Tetrahedron*, **16**, 177 (1961).

13) R. J. Ouellette, K. Liptak, and G. E. Booth, *J. Org. Chem.*, **32**, 2394 (1967).

14) C. J. Cheer and C. R. Johnson, *J. Amer. Chem. Soc.*, **90**, 178 (1968).

Experimental

General Methods. The IR spectra were measured with a Hitachi EPI S-2 IR spectrophotometer and hydroxyl absorption bands in the 3600 cm^{-1} region in the IR spectra of lilac alcohols were examined in carbon tetrachloride (0.005—0.025 M), using Perkin-Elmer Model 125 infrared grating spectrophotometer. A 5.0 cm sodium chloride cell was used for the carbon tetrachloride solutions and the temperature of the measurements was about 25 °C. Spectrograde carbon tetrachloride was used directly after passing a molecular sieve column.

The NMR spectra were recorded on a Varian Associates HA-100 instrument and chemical shifts (δ) are given relative to internal tetramethylsilane standard.

The optical rotations were mersured on a Carl Zeiss photoelectric polarimeter in chloroform.

2,6-Dimethyl-6-acetoxy-2,7-octadienal (III): Linalyl acetate (II, 39.2 g, 0.2 mol) and selenium dioxide (22.2 g, 0.2 mol) were dissolved in 100 ml of 90% dioxane and the solution was heated at 80 °C for 5 hr. After removal of selenium deposited by filtration, the solvent was removed under a reduced pressure. The residue was treated with 100 ml of a mixed solvent of ether and petroleum ether (1: 1). The organic layer was separated by decantation. The solvent was removed and the residue was subjected to vacuum distillation (bp 113—115 °C/1.3 mmHg), affording 16 g (38% yield) of 2,6-dimethyl-6-acetoxy-2,7-octadienal (III).

Vpc: R_t 15.5 min (PEG 20 M, 180 °C, 3 mm × 2 m, He 30 ml/min)

IR: $\nu_{\max}$ 2720, 1735, 1685, 1640, 1365, 1245, 1170, 1105, 1020, 930 cm^{-1}.

NMR: 1.57 (*t*-Me, s), 1.73 (CH_3–C=C, d J=0.7 Hz), 1.98 (CH_3COO, s), 5.12, 5.16, 5.96 (–HC=CH_2), 6.49 (–HC=C–), 9.38 δ (CHO).

Found: C, 68.53; H, 8.58%. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63%.

6-Hydroxy-2,6-dimethyl-2,7-octadienal (VI): 2,6-Dimethyl-6-acetoxy-2,7-octadienal (III, 6.3 g, 0.03 mol), ethylene glycol (2.1 g, 0.033 mol), and *p*-toluenesulfonic acid (0.05 g) were dissolved in 100 ml of dry benzene, and the solution was refluxed for about 3 hr until 0.9 ml of water was removed, using a moisture collector. The solvent was removed under a reduced pressure and the residue was treated with 40 ml of 5% sodium hydroxide solution in aqueous methanol (75%) for 1 hr at room temperature. After removal of methanol, the residue was extracted with ether, and the ethereal solution was dried over anhydrous sodium sulfate. The solvent was removed and the residue was subjected to silica gel chromatography, using chloroform as an eluent. 6-Hydroxy-2,6-dimethyl-2,7-octadienal (VI) (3.9 g, 77% yield) was obtained, showing that the ethylene acetal group was hydrolysed during the chromatography.

Vpc: R_t, 12.1 min (PEG 20 M, 180 °C, 3 mm × 2 m, He 30 ml/min)

IR: $\nu_{\max}$ 3420 (OH), 2720 (CHO), 1680 (CHO), 1640 (C=C) cm^{-1}.

NMR: ($CDCl_3$) 1.32 (*t*-Me, s); 1.73 (CH_3–C=C); 5.01, 5.25, 5.93 (–CH=CH_2); 6.50 (–C=C–H), 9.31 δ (CHO).

Found: C, 71.21; H, 9.63%. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59%.

2-(1-Formylethyl)-5-methyl-5-vinyltetrahydrofuran (VII): The hydroxyaldehyde (VI, 1.0 g) dissolved in 10 ml of methanol was treated with a catalytic amount of triethylamine under nitrogen atmosphere at 50 °C for 5 hr.

After removal of the solvent, the residue was subjected to silica gel chromatography. The fractions eluted with a mixed eluent of petroleum ether and ether (20: 1) afforded 0.23 g of VII and 0.7 g of the starting hydroxyaldehyde (VI) was recovered from the fractions eluted with methylene chloride–ether (10: 1). The recovered material was subjected to the same procedure for the intramolecular Michael reaction, giving 0.20 g of VII. The total yield was 43%.

Vpc: R_t 2.65 and 2.90 min (2: 1).

IR: $\nu_{\max}$ 2720, 1720 (CHO), 1640 (C=C), 1040 (–O–) cm^{-1}.

NMR: ($CDCl_3$) 1.26 (*t*-Me, s); 4.07, 5.00, 5.76 (–CH=CH_2); 9.70 δ (CHO).

The analytical sample was purified by vacuum distillation, bp 99—101 °C/23 mmHg.

Found: C, 71.53; H, 9.48%. Calcd for $C_{10}H_{16}O_2$: C, 71.53; H, 9.59%.

Lilac Alcohols (I): The cyclic aldehyde (VII, 1.17 g) was dissolved in 20 ml of dry ether and 0.4 g of lithium aluminum hydride was added in small portions. After stirring at room temperature for 30 min followed by decomposition of the excess lithium aluminum hydride with water, the reaction mixture was acidified with 1M sulfuric acid and extracted with a mixed solvent of methylene chloride and ether. The organic layer was dried over sodium sulfate. After removal of the solvent, the residue was subjected to chromatography on alumina. Elution with ether gave 0.88 g (75%) of lilac alcohols, which were shown to be a mixture of four diastereomers and separated by vapor phase chromatography to afford each alcohol in pure state. The relative concentration of the synthetic lilac alcohol-a, -b, -c, and -d was 2.0, 3.0, 2.5, and 1.0, respectively. The identity of the synthetic lilac alcohols with natural ones was confirmed by IR, NMR and R_t (vpc).

Vpc: R_t; 12.3 (b), 13.75 (d), 15.8 (a), 19.1 (c) min. (PEG 20 M, 120 °C, 3 mm × 2 m, He 30 ml/min)

IR: $\nu_{\max}$ 3420 (OH), 1640 (C=C), 1100, 1025 (–O–) cm^{-1}.

NMR: see Fig. 1 and Table 4.

TABLE 4. NMR SPECTRAL DATA (δ in ppm in $CDCl_3$)[a]

Lilac alcohol		a	b	c	d
s-CH_3		0.94 d J=6.0	0.80 d J=6.0	0.93 d J=6.0	0.78 d J=6.0
t-CH_3		1.31 s	1.30 s	1.27 s	1.28 s
$-CH_2-CH_2-\underset{H\ \ CH_3}{\overset{}{-C-}}$		1.82 m	1.80 m	1.80 m	1.80 m
$>\underset{H}{C}-CH_2OH$		3.66	3.62	3.59	3.60
$>C\genfrac{}{}{0pt}{}{O-}{H}$		4.12 m	3.80 m	4.10 m	3.78 m
$H_3>C=C\genfrac{}{}{0pt}{}{H_1}{H_2}$	H_1[a]	4.99	5.01	5.01	5.01
	H_2	5.17	5.19	5.19	5.19
	H_3	5.87	5.89	5.89	5.89

a) The signals of alcohols appear at 2.96—2.60 δ, depending on the concentration, and typical signals of vinyl group are observed with $J_{1,2}$=1.6Hz, $J_{1,3}$=8.0Hz and $J_{2,3}$=18 Hz.

The analytical sample was prepared by vacuum distillation, bp 110—112 °C/18 mmHg.

Found: C, 70.50; H, 10.69%. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66%.

d-Lilac alcohols were synthesized from *d*-linalyl acetate with $[\alpha]_D^{25}$ +2.9 (*c* 3.2) according to the same manner as described above and cleanly separated by vpc. The optical rotation was measured in chloroform, showing +6.7 (*c* 2.7), −1.4 (*c* 2.9), −0.5 (*c* 1.6), and +1.4 (*c* 2.8) for *d*-lilac alcohol-a, -b, -c, and -d, respectively.

l-Lilac alcohols were synthesized from *l*-linalyl acetate with $[\alpha]_D^{25}$ −5.0 (*c* 0.8) according to the same manner as described above, and cleanly separated by vpc. The optical rotations were measured in chloroform, showing −11.6 (*c* 1.1), +3.0 (*c* 1.0), +2.5 (*c* 0.8), and −2.9 (*c* 1.0) for *l*-lilac alcohol-a, -b, -c, and -d, respectively. The optical rotations of natural lilac alcohols listed in Table 1 were measured in chloroform, showing +12.2 (*c* 4.1), −6.6 (*c* 3.6), −1.4 (*c* 1.8), and +4.3 (*c* 1.7) for the alcohol-a, -b, -c, and -d, respectively.