A New Synthesis of 4-(4-Methyl-4-hydroxyamyl)-Δ^3-cyclohexenecarboxaldehyde

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A new synthetic route of 4-(4-methyl-4-hydroxyamyl)-Δ^3-cyclohexenecarboxaldehyde (Lyral) from myrcene (**1**) was investigated. It involves subjecting **1** first to the diene synthesis with acrolein (**2**) followed by hydration of the morpholine enamine of the adduct in 50% sulfuric acid at 0–5° and the subsequent hydrolysis in diluted sulfuric acid at 15–20°.

The present method is superior in simplicity as well as productivity for the preparation of Lyral to any other methods hitherto reported.

On a étudié une nouvelle méthode synthétique pour l'obtention du (méthyl-4 hydroxy-4 amyl)-4 cyclohexène-Δ^3 carboxaldéhyde (Lyral) à partir du myrcène (**1**). Cette méthode implique tout d'abord la réaction de **1** avec l'acroléine (**2**) suivie par l'hydratation de la morpholine énamine du composé d'addition dans l'acide sulfurique 50% à 0–5° puis par une hydrolyse dans l'acide sulfurique dilué à 15–20°.

La méthode que l'on présente, est supérieure à cause de la simplicité ainsi que du rendement obtenu pour la préparation du Lyral, à toutes les méthodes connues jusqu'à cette date.

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4-(4-Methyl-4-hydroxyamyl)-Δ^3-cyclohexenecarboxaldehyde and its structural isomer (Lyral) have been prepared from myrcene (**1**) by two routes of low yield: (*a*) Diels–Alder condensation of 2-hydroxy-2-methyl-6-methylene-Δ^7-octene (myrcenol) prepared by acetoxylation of **1** and subsequent saponification with acrolein (**2**) (1) and (*b*) that of 2-hydroxy-2-methyl-6-methylene-$\Delta^{3,7}$-octadiene and 3-hydroxy-2,6-dimethylene-Δ^7-octene prepared by the reduction of photooxidized myrcene with **2** and subsequent selective hydrogenation (2). The former gives 15% of the theoretical yield of Lyral from **1** and the latter 20%.

The present paper describes a new, successful synthesis giving as much as 65% of the theoretical yield of hydroxyaldehydes, 4-(4-methyl-4-hydroxyamyl)-Δ^3-cyclohexene-carboxaldehyde (**5**) and 5-(4-methyl-4-hydroxyamyl)-Δ^4-cyclohexene-carboxaldehyde (**6**) by the procedure shown in Scheme 1. **1** was reacted with **2** according to the method described in the literature (**3**). The reaction time, temperature, and yield of cycloadduct, Myrac aldehydes (**3** and **4**, the ratio **3**:**4** of 80:20) are given in Table 1. The morpholine enamines of **3** and **4** were obtained quantitatively by condensation of the aldehydes with morpholine in the molar ratio 1:1.4 in toluene using phosphoric acid as catalyst. The enamine purified by distillation was used in the hydration and hydrolysis (Table 2) (4, 5). The desired hydroxyaldehydes, **5** and **6**, were obtained in the mixture at a good yield (71%) but the estimation of isomers by g.l.c. was found to be very difficult. The dimethyl acetals were prepared and gave an isomer ratio **5**:**6** of 70:30. Comparison of the isomer ratios between the Myrac aldehydes and the Lyral dimethylacetals obtained suggests that **5** is more easily cyclized to a mixture of isomers of 1,1-dimethyl-7-methylal-octaline than **6** (6, 7).

Protection of the aldehyde group in the Myrac aldehydes by conversion into the dimethyl acetal, diacetate, or sodium hydrogen sulfite-adduct instead of enamine, resulted in only a small amount of the hydroxyaldehydes. Without protecting the aldehyde group, however, hardly any hydration took place.

Experimental

Materials

Myrcene (**1**) consisting of a mixture of 76% myrcene, 12% dipentene, 2% β-pinene, and 10% of other terpene hydrocarbons was purchased from the LDRT Co., Ltd.; b.p. 163–178°; d_{20}^{20} 0.8104; n_D^{20} 1.4740. Myrac aldehydes, **3** and **4**, and Lyrals, **5** and **6**, were purchased from the IFF Co., Ltd. Myrac aldehydes: b.p. 136–138°/4 Torr; d_{25}^{25} 0.9326; n_D^{25} 1.4896. Lyrals: b.p. 126–130°/1 Torr; d_{25}^{25} 0.9956; n_D^{25} 1.4893. Acrolein (**2**) and morpholine were of chemically pure grade reagent and used without further purification.

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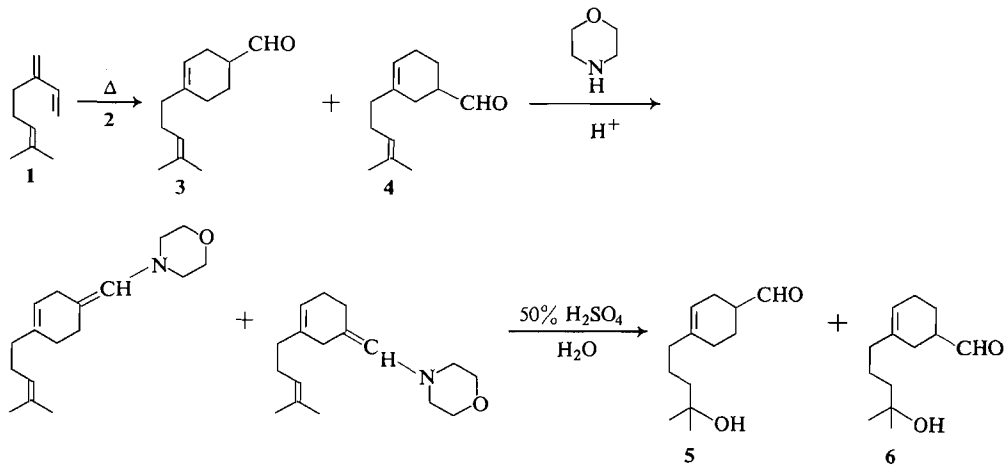

SCHEME 1

TABLE 1. Diels-Alder reaction of myrcene (**1**) with acrolein (**2**)[a]

Run	Hydroquinone (g)	Reaction Temperature (deg)	Reaction Time (h)	Myrac aldehydes yield In g	Myrac aldehydes yield In %	Ratio of isomer (%)[b] **3**	Ratio of isomer (%)[b] **4**
1	3.5	110–120	4.5	510	95.0	81	19
2	3.5	110–120	4.5	506	94.3	80	20
3	3.3	130–140	2.0	516	96.1	78	22
4	3.3	150–160	1.0	504	94.0	77	23

[a]1 (2.8 mol, 500 g) was reacted with 2 (3.59 mol, 201 g in Run 1 and 2.98 mol, 167 g in Runs 2–4).
[b]Based on the Myrac aldehyde dimethyl acetals (3′ + 4′) estimated by g.l.c.

TABLE 2. Hydration of morpholine enamines and other derivatives

Run	Derivative	Amount In g	Amount In mol	$[H_2SO_4]$ Wt. %	$[H_2SO_4]$ g	Reaction Temperature (dec.)	Reaction Time (min)[a]	Yield of Lyral In g	Yield of Lyral In %
1	Enamine	100	0.38	40	300	−2 to 10	65	31	40
2	Enamine	100	0.38	50	300	−2 to 10	45	54	70
3	Enamine	100	0.38	60	300	−2 to 10	10	31	40
4	Enamine	100	0.38	40	300	10 to 20	65	50	65
5	Enamine	100	0.38	50	300	10 to 20	20	46	60
6	Enamine	100	0.38	60	300	−15 to −5	5	53	69
7	Enamine	100	0.38	50	300	0 to 5	50	55	71
8	Enamine	100	0.38	50	600	0 to 5	50	53	69
9	Enamine	350	1.33	50	1050	0 to 5	65	260	67.5
10	Enamine	350	1.33	50	1050	−2 to 10	50	270	70
11	Myrac aldehydes	73	0.38	50	300	0 to 5	50	0	0
12	Myrac aldehydes	73	0.38	50	300	−2 to 10	50	0	0
13	Dimethyl acetal	90	0.38	50	300	0 to 5	50	2	2.6
14	Diacetate	112	0.38	50	300	0 to 5	60	3	3.8
15	Sodium hydrogen sulfite adduct	112	0.38	50	300	0 to 5	60	3	3.8

[a]Values indicate the time at which a maximum peak of Lyral was observed on the analysis of hydrated products by g.l.c.

Spectral Data

Infrared spectra were obtained with a Nihon Bunko IR-spectrometer, Model IR-S. Nuclear magnetic resonance spectra were determined in carbon tetrachloride with tetramethylsilane as internal standard on a JEOL 4H-100 spectrometer. Mass spectra were measured by means of a Hitachi RMU-6E mass spectrometer under the following conditions: ionization energy 70 eV; ionization current 80 μA; ionization potential 1800 V. The pressure of ion source and ionization chamber was kept at 10^{-4} to 10^{-5} Torr. A column (2 m × 3 mm) containing Carbowax 20 M (10 wt. %) on Celite 545 SK (100–120 mesh) was used for g.l.c.; the column temperature was fixed at 180° and helium was used as a carrier gas.

Cyclic Adduct of Myrcene (1) with Acrolein (2)

Compounds **1** (500 g, 2.8 mol), **2** (167 g, 2.98 mol), and hydroquinone (3.3 g) were placed into a 1-l stainless steel autoclave, the temperature of which was elevated to 110° in 30 min under stirring, kept at 110–120° for 4.5 h, and then lowered. The resulting product was distilled *in vacuo* with a packed column type rectifier to give the following fractions: (*i*) b.p. 30–135°/4 Torr, 94 g; (*ii*) b.p. 136–138°/4 Torr, 506 g; (*iii*) residue, 27 g. Fraction *i* was found to be a mixture of other terpene hydrocarbons except **1**. Fraction *ii* was identified as Myrac aldehydes by comparing the n.m.r., i.r., and mass spectra with those of authentic samples (IFF Co., Ltd.): aldehyde content 99.8% (hydroxylamine method); d_{25}^{25} 0.9323; n_D^{25} 1.4893 (Run 2, Table 1). The Myrac aldehydes are difficult to separate by g.l.c. Therefore, they were converted into dimethylacetal derivatives (**3′** and **4′**) with methanol containing 1% *p*-toluenesulfonic acid; **3′** and **4′** were separated from the mixture by repeated preparative g.l.c. The obtained ratio (**3′**:**4′** of 80:20) was found to agree with that of Canet and Mousseron (3). The analytical conditions and retention times of the isomers were as follows: gas chromatograph, Kotaki GU-21 with a thermal conductivity type detector; column, stainless steel (2 m × 3 mm); packing material, support, Celite 545 SK (60–80 mesh) and liquid phase, Carbowax 20 M (10 wt. %); column temperature, 180°; helium pressure, 14 p.s.i.; flow rate, 40 ml/min; chart speed, 0.5 cm/min; retention times, **3′**, 5 min 40 s, **4′**, 6 min 25 s.

Spectral data were as follows; n.m.r. spectra (δ, p.p.m.): **3′**, 1.72 and 1.82 (singlets, —HC=C(CH_3)$_2$), 1.9–2.8 (superimposed, —CH_2—, =CH—CH_2—, —CH—, 3.58 (singlet, (OCH_3)$_2$), 4.40 (doublet, —CH(OCH_3)$_2$), 5.54 (broad singlet, —CH=C(CH_3)$_2$), 5.58 (broad singlet, —CH=CH—); **4′**, 1.74 (singlet, 1.84 (singlet, —CH=C(CH_3)$_2$), 1.9–2.8 (superimposed, —CH_2—, =CH—CH_2—, —CH—), 3.60 (singlet, (OCH_3)$_2$), 4.08 (doublet, —CH(OCH_3)$_2$), 5.52 (broad singlet, —CH=C(CH_3)$_2$), 5.90 (broad singlet, —CH=CH—). Both the i.r. and mass spectra of **3′** were almost superimposable on those of **4′**. Infrared spectra (neat, cm^{-1}): 2830 (CH(OCH_3)$_2$), 1200–1040 (C—O—C—O—C), 828 (—C=CH—). Mass spectra (*m/e*): 206 M^+; 191 (M − 15, CH_3); 174 (M − CH_3OH), 137 (M − 67, (CH_3)$_2$—C=CH—CH_2—); 123 (M − 83), 105 (M − 69–32), 75 (base peak, CH_3O=C^+H—OCH_3); 41 (CH_3—C=CH_2).

Synthesis of Morpholine Enamines of Myrac Aldehydes

Morpholine (329 g, 3.80 mol) was added to the solution of Myrac aldehydes (450 g, 2.33 mol) in toluene (1600 ml) containing 85% phosphoric acid (4.5 g) at room temperature. After refluxing the mixture at 112–148° for 8 h, the theoretical amount of water was stripped off. The residue obtained by removal of toluene and morpholine from the resultant solution was submitted to distillation *in vacuo*: (*i*) b.p. 70–130°/0.05 Torr, 8 g; (*ii*) b.p. 130–139°/0.05 Torr (morpholine enamine), 426 g; (*iii*) residue, 16 g. Characteristic properties of the morpholine enamine were as follows: b.p. 130–139°/0.05 Torr, d_{25}^{25} 0.9339; n_D^{25} 1.5165; n.m.r. (δ, p.p.m.): 1.62 (6 H, doublet, —CH_3), 1.28–2.8 (10 H, multiplet, —CH_2—), 2.53 (4 H, multiplet, —N—CH_2—), 3.60 (4 H, triplet, —CH_2—CH_2—O—CH_2—CH_2—), 5.05 (1 H, broad singlet, isopropylidene olefine), 5.32 (1 H, broad singlet, cyclohexene olefine), 5.38 (1 H, broad singlet, =CN—N—); i.r. (cm^{-1}): 1665 (=CH—N—), 1120 (C—N); mass spectrum (*m/e*); 261 (M^+), 246 (M − 15), 204 (M − 57), 192 (M − 69, (CH_3)$_2$—C=CH—CH_2—), 178 (M − 83), 105 (192–87), 100 (—CH_2—N(—CH_2—CH_2—)$_2$O), 91, 86 (—N(—CH_2—CH_2—)$_2$O), 79, 69, 41 (base peak, CH_3—C=CH_2).

Hydration of Morpholine Enamine and Other Derivatives

Rectified morpholine enamine (100 g, 0.38 mol) was added immediately to 50% sulfuric acid (300 g) with vigorous stirring at 0–5° (4, 5). Further stirring was continued for 50 min at the same temperature. The reaction mixture was poured into 1 kg of ice water. The mixture was stirred at 15–20° for 5 h and an oily product separated and was extracted with benzene. The benzene solution was washed with an aqueous solution of 5% sodium carbonate until the wash solution was substantially alkaline. After removal of the benzene, the remaining oil was distilled *in vacuo*: (*i*) b.p. 102–105°/1 Torr, 12 g; (*ii*) b.p. 105–126°/1 Torr, 4 g; (*iii*) b.p. 126–130°/1 Torr, 55 g (Lyral, theoretical yield 71%), d_{25}^{25} 0.9958, n_D^{25} 1.4895; (*iv*) b.p. 130–138°/1 Torr, 1.1 g; (*v*) residue, 5.3 g (Run 7, Table 2). Fraction (*i*) with the following properties was estimated by g.l.c. to be a mixture of 1,1-dimethyl-7-methylaloctaline and 1,1-dimethyl-6-methylaloctaline (6), accompanied by a small amount of Myrac aldehydes; d_{25}^{25} 0.9877, n_D^{25} 1.5031, aldehyde content (hydroxylamine method) 100%. The spectral data of the mixture of dimethyl octaline isomers separable by preparative gas chromatography were as follows: n.m.r. (δ, p.p.m.): 1.00 (6 H, singlet, (CH_3)$_2$), 1.5 (complex, —CH_2—), 1.7–2.6 (complex, =CH—CH_2— and —CH—), 5.4 (broad singlet, =CH—), and 9.66 (singlet, aldehyde proton); i.r. (cm^{-1}): 2820, 2720 (ν CH of CHO), 1730 (ν C=O), 1390, 1370 (CH_3—C—CH_3), 1205, 1180 (CH_3—C—CH_3), and 805 (δ, CH=CH—); mass spectrum (*m/e*): 192 (M^+), 177 (M − 15), 163 (M − 29), 159 (M − 15 − 18), 149 (177 − 28), 136, 107 (149 − 42), 105, 93, 91, and 41 (base peak). Fraction (*iii*) was identified to be Lyral and structural isomer by comparing the n.m.r., i.r., and mass spectra with those of an authentic

sample, Lyral of the IFF Co., Ltd. The fraction gave 99.5% aldehyde estimated by oximation, corresponding to 65.3% theoretical yield based on the **1** used, the fragrance of which was very pleasant like that of a fine lilac-lily. The spectral data found: n.m.r. (δ, p.p.m.): 1.12 (6 H, singlet, $-CH_3$), 1.36 (broad singlet, $-CH_2$), 1.7–2.5 (complex, $=C(-CH_2-)-$ and $-CH-$), 3.2 (1 H, singlet, —OH), 5.4 ($=CH-$), and 0 (1 H, CHO); i.r. (neat, cm^{-1}): 3480 (associated —OH), 2860, 2740 (ν CH of CHO), 1730 (ν C=O), 1385, 1370 ($CH_3-C(-CH_3)-$), 1210, 1160 ($CH_3-C(-CH_3)-$), 1130 (ν $-C(-OH)-$), 910 (δ CH of CHO), and 805 (δ $-C=C-H$); mass spectrum (*m/e*): 210 (M^+), 192 (M − 18), 136 (192 − (CH_2=CH—CHO)), 59 (base peak, $(CH_3)_2$—C—OH) and 29 (CHO).

Direct hydration of unprotected Myrac aldehydes gave very low yields. Therefore a modification of the conversion of aldehydes into the dimethyl acetal, diacetate, and sodium hydrogen sulfite adduct by the usual method (8), was attempted. However, the hydration of these derivatives resulted in only a small percent of Lyral (Table 2). Hence we suggest the use of morpholine enamine.

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