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Stereostructure of Rengyol and Isorengyol, Phenylethanoids of Forsythia suspensa

Katsuya Endo, Kazuhiko Seya and Hiroshi Hikino*
Pharmaceutical Institute, Tohoku University, Aoba-yama, Sendai 980, Japan

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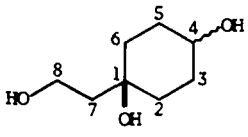
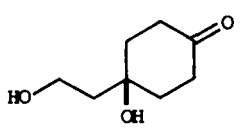
Abstract — Determination of the stereostructure of rengyol (**1**), a novel nonaromatic phenylethanoid natural product isolated from Forsythia suspensa, by synthetic means has been described. The Reformatsky reaction of 4-acetoxycyclohexanone with ethyl bromoacetate afforded two isomeric acetoxy esters (**5**, **6**) and the one (**5**) which has an equatorial acetoxyl group yielded on LAH reduction a triol identified as rengyol (**1**). The isomer (**7**), obtained similarly from the other isomeric acetoxy ester (**6**), has also been isolated from the natural source and is named isorengyol. Further, dehydration of the esters (**5**, **6**) and subsequent pyrolytic deacetoxylation afforded a 1,3-cyclohexadiene derivative (**12**), which on photosensitized cis-dioxygenation, followed by reduction, yielded rengyol (**1**) establishing its stereostructure to have 1,4-cis-cyclohexanediol system. These results supported the previous conclusion based on the ^{1}H and ^{13}C NMR spectral data.

The crude drug "rengyo", the fruits of Forsythia suspensa Vahl (Oleaceae), has been used in Oriental medicine for antiinflammatory, diuretic, drainage and antidotal purposes. The crude drug has also been known to exhibit antibacterial activity, and the glycosides, forsythoside A, C, D and E have been isolated from this crude drug as the antibacterial principles.[1,2] Furthermore, the same drug material has been revealed to contain three new novel natural alcohols, rengyol, rengyoxide and rengyolone, whose structures have been suggested as **1**, **2** and **3**, respectively.[3] This unusual nonaromatic C_6-C_2 carbon skeleton may be derived from the phenylpropanoids since the drug is rich in lignan derivatives.[4]

Previous assignment of the stereostructure **1** for rengyol was mainly based on the analysis of ^{1}H and ^{13}C NMR spectra by assuming that the cyclohexane ring has a chair conformation, and that the hydroxyethyl group with the highest conformational energy prefers an equatorial orientation.[3,5] However, the conformational flexibility for such a simple cyclohexane system deserves any conclusions especially when the intramolecular hydrogen bondings are possible. Therefore it was felt necessary to establish the stereochemistry of rengyol (**1**) by a more reliable method. Experiments to obtain the isomeric alcohol (**7**) for the spectral comparison by the chromic oxide oxidation-sodium borohydride reduction reaction, or by direct S_N2 type inversion such as the Mitsunobu reaction[6] and solvolysis of mesylate were not successful due to the formation of only the undesired products.



1 :—OH
7 :···OH



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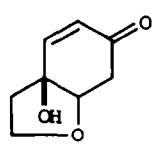

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Hence, the present study was designed to perform complete stereostructure determination of **1** for rengyol by a sequence of chemical transformations as follows (Chart 1). The Reformatsky reaction of 4-acetoxycyclohexanone (**4**) with ethyl bromoacetate in refluxing dry benzene afforded two isomeric acetates (**5**, **6**) in a ratio of three to two in 71% yield. The acetoxyl groups of **5** and **6** were assigned equatorial and axial, respectively, on the basis of the chemical shifts and the half-height widths of the respective carbinyl methine hydrogen signals in the ^{1}H NMR spectra of these acetates (**5**: δ 4.66, W_H 17 Hz; **6**: δ 4.95, W_H 9 Hz). The assignment was supported by the chemical shift of C-4 carbon in the ^{13}C NMR spectrum of **6** appearing at a higher field than that for **5** (Table I).[5] A triol, obtained by LAH reduction of **5**, and the natural rengyol were found identical in their spectral data and physical properties. Similarly, the isomeric triol (**7**), obtained from **6** by the analogous transformations, was also found in the F. suspensa extract and then named as isorengyol.

It thus becomes certain that the secondary hydroxyl group of rengyol (**1**) adopts an equatorial orientation, and hence, it is deduced to be cis with respect to the tertiary hydroxyl group, so the configuration of the corresponding hydroxyl groups in isorengyol (**7**) is trans.

As it was expected that the photosensitized cis-dioxygenation of a 1,3-cyclohexadiene derivative should afford a 1,4-cis-diol stereospecifically when the O-O bond of the endoperoxide is cleaved by a reductive manner, the following experiments were conducted to further provide a creditable proof for the stereostructure of rengyol (**1**).

Treatment of a mixture of **5** and **6** with hydrobromic acid in acetic acid afforded the two isomeric bromoesters (**8**, **9**) (2:3) in 76% yield (Chart 2). The ^{1}H NMR signal due to the carbinyl

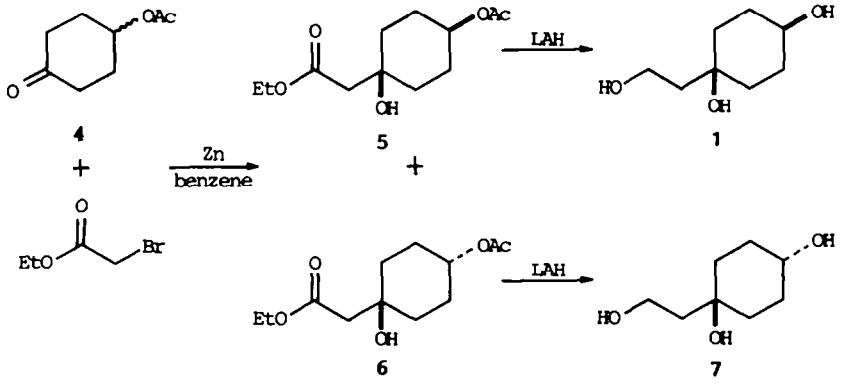

Chart 1.

Table I. Carbon-13 NMR chemical shifts of rengyol and its related substances.

Carbon			1	2	3	4	5	6	7	8
Rengyol	natural	**1**	69.92	36.05	31.59	69.75	31.59	36.05	45.09	58.71
	synthetic		69.98	36.11	31.70	69.75	31.70	36.11	45.09	58.83
	calcd.*		69.9	38.6	28.6	69.3	28.6	38.6		
Isorengyol	synthetic	**7**	71.22	34.35	30.94	67.40	30.94	34.35	42.93	58.93
	calcd.*		70.5	34.6	25.6	65.3	25.6	34.6		
ester (4-equatorial)		**5**	68.46	34.87	26.60	72.16	26.60	34.87	45.56	172.43
ester (4-axial)		**6**	69.22	32.29	25.77	69.63	25.77	32.29	45.56	172.61
bromoester (4-equatorial)		**8**	66.64	38.75	28.00	71.45	28.00	38.75	50.26	169.14
bromoester (4-axial)		**9**	68.10	35.46	27.07	68.10	27.07	35.46	50.90	169.20

* Calculated values for 1-alkyl-1,4-cyclohexanediol.[5]

methine hydrogen at δ 4.67 (W_H 25 Hz) in **8** is associated with an axial hydrogen, whereas that at δ 5.00 (W_H 12 Hz) in **9** is attributed to an equatorial hydrogen.[5] The assignment is also supported by the chemical shift of C-4 carbon in the ^{13}C NMR spectrum of **9**, appearing at a higher field than that in **8** (Table I).

Treatment of a mixture of **8** and **9** with DBU in benzene at the refluxing temperature for one hour afforded only the exo-olefin (**10**), whereas on prolongation of the reaction time for five hours caused isomerisation to the endo-olefin (**11**) (exo:endo=1:5). On the other hand, treatment with thionyl chloride in pyridine under ice-cooled condition, **8** and **9** were easily converted to a mixtured of the isomeric olefins (**10**, **11**) in 98% yield (exo:endo=3:1).

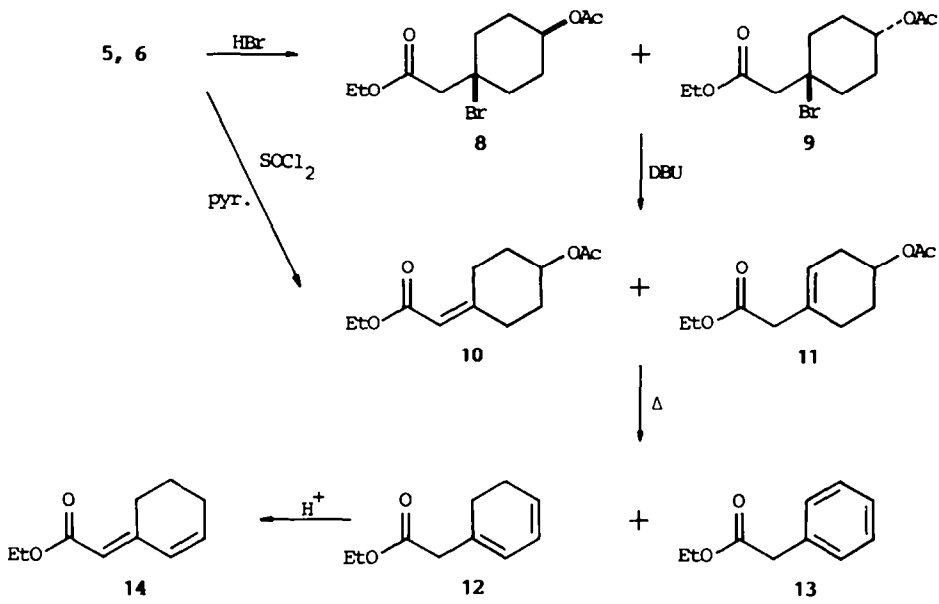

Chart 2.

The pyrolytic deacetoxylation of a mixture of **10** and **11** (3:1) at 295° in the absence of solvent and under nitrogen atomosphere, afforded a mixture of a cyclohexadiene derivative (**12**) and an aromatic ester (**13**) in a three to two ratio, in addition to a trace of heteroannular diene (**14**). While at 240°, only isomerization of **10** to **11** was observed.

The mechanism of these pyrolytic reactions may be rationalized as follows (Chart 3). Isomerization of **10** to **11** probably proceeds via the ground state allowed 1,5-sigmatropic hydrogen shift with the participation of the ester carbonyl group. The simple 1,3-sigmatropic hydrogen shift requires an antarafacial mode under the ground state, according to the Woodward-Hoffmann theory, and it therefore is in the practical sense forbidden. It is regarded that the pyrolytic deacetoxylation of **11** also proceeds via six-electron systems with the involvement of the ester carbonyl group, allowing for the ground state reaction. The diene (**12**) is majoured probably due to the difference in the acidity of the two hydrogens at C-3 and C-5 in **11**. Further, the 1,4-diene (**12a**) will suffer an aromatization by the thermally allowed retro Diels-Alder type reaction, while the 1,3-diene (**12**) is devoid of such aromatization because it requires an antarafacial mode for the ground state reaction. Consequently, end products of the pyrolytic reaction are mainly the 1,3-diene (**12**) and the aromatic ester (**13**). Formation of a trace of the heteroannular diene (**14**), possibly formed by the prototropy of **12**, is indicated by the olefinic hydrogen signal at δ 6.3 in the ^1H NMR spectrum of the reaction mixture.[7]

Photosensitized oxygenation of the 1,3-diene (**12**) with rose bengal in methanol for one hour afforded an endoperoxide (**15**) in 89% yield (Chart 4). The chemical shifts of two olefinic hydrogen signals at δ 6.66 (dd, J=10 and 1 Hz) and δ 6.69 (d, J=10 Hz), in the ^1H NMR spectrum of

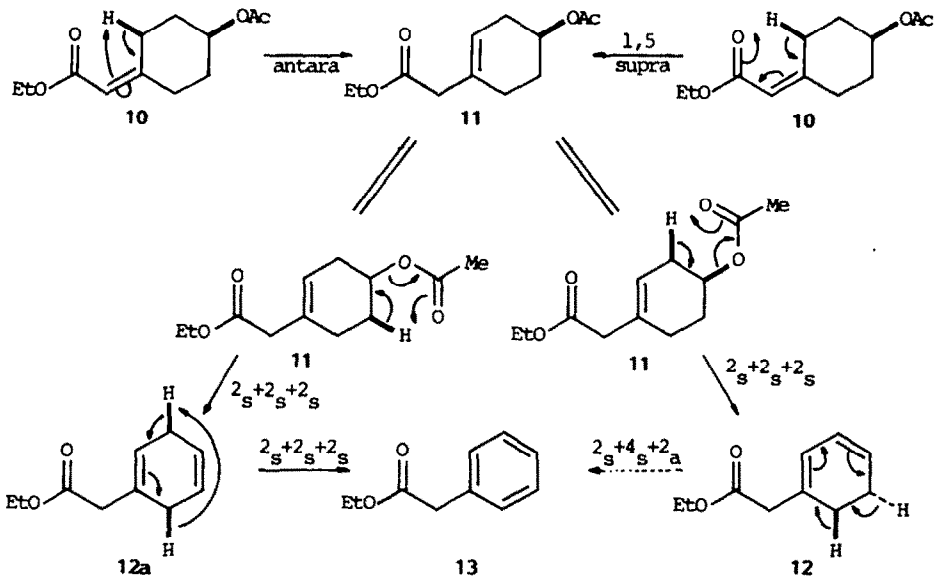

Chart 3. Mechanistic presentation of the thermal reactions of **10** and **11**.

15, exhibited a large deshielding effect due to an 1,2-dioxane ring system which is consistent with the expected endoperoxide structure for **15**.[8]

LAH reduction of **15** led to a 1,4-cis-cyclohexanediol (**16**) in 96% yield. In the ^{1}H NMR spectrum of **16**, the chemical shifts of two olefinic hydrogens restored at the normal region, i.e. δ 5.65 and 5.70, respectively, in consequence with the opening of the O–O linkage. Then the catalystic hydrogenation of **16** with 5% Pd-C yielded a 1,4-cis diol which was found to be identical with the natural rengyol (**1**). In parallel to the above transformation, catalytic hydrogenation of **15** with 5% Pd-C gave a 1,4-cis-dihydroxyester (**17**), which in turn was affected by LAH reduction to afford a triol which was also identified as **1**.

In conclusion, the stereostructure of rengyol and isorengyol has been established unambiguously as the β-hydroxyethyl-1,4-cis-cyclohexanediol (**1**) and β-hydroxyethyl-1,4-trans-cyclohexanediol (**7**), respectively, by the chemical transformations.[9]

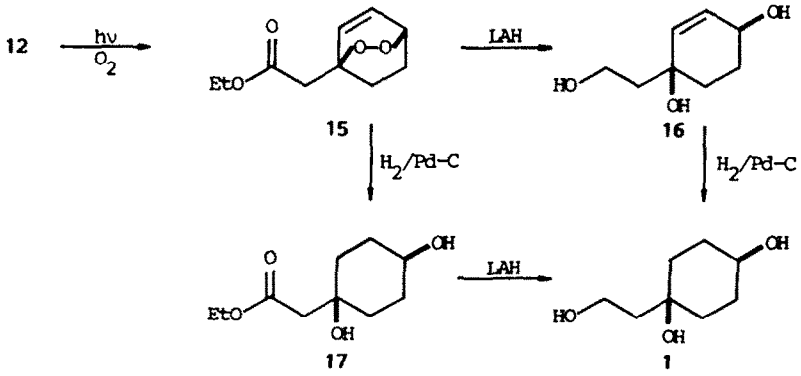

Chart 4.

Experimental

Melting points were taken on a hot-stage microscope and are uncorrected. IR spectra were obtained with a Shimadzu IR-27G spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM FX-100 spectrometer with TMS as an internal standard. Mass spectra (MS) were taken with a Hitachi-M52 or JEOL JMS-01SG-2 (high-resolution MS) spectrometer. Column chromatography was performed on silica gel (Merck Kieselgel 60) and TLC on Merck Kieselgel 60 F_{254}.

Photosensitized oxygenation was conducted by irradiating a sample solution in a Pyrex reactor, cooled by ice-water, with a 100 watt high-pressure halogen lamp (USHIO, ICV 100-200GS). O_2 gas was bubbled in the reaction mixture.

Monoacetylation followed by oxidation of 1,4-cyclohexanediol——Pyridine (8 ml, 0.1 mole) and Ac_2O (14 ml, 0.15 mole) were added to a solution of 1,4-cyclohexanediol (5.91 g, 50 mmole) in CH_2Cl_2 (60 ml) under stirring at room temperature. After 8 h, the excess reagent was quenched with ice-water. Concentration of the reaction mixture gave a residue which was chromatographed over a silica gel column (150 g). Elution with hexane-AcOEt (1:2) gave a monoacetate (3.85 g, 49 %) and a diacetate (4.97 g, 50 %).

Monoacetate as colorless powder; ^1H NMR ($CDCl_3$) δ: 2.04 (3H s, acetyl), 3.80 (1H m, -CHOH), 4.83 (1H m, -CHOAc).

Diacetate as colorless prisms from CH_2Cl_2, mp 34.5-35.0°; IR (liquid film) cm^{-1}: 1720 (ester); ^1H NMR ($CDCl_3$) δ: 2.05 (6H s, acetyl), 4.87 (2H m, -CHOAc); MS m/z : 201 (M^++1), 140 (M^+-AcOH), 80 (M^+-2AcOH, base peak).

To a solution of the monoacetate (4.35 g, 27.5 mmole) in acetone (20 ml), Jones' reagent (10 ml) was added slowly at room temperature. After 2.5 h of stirring, the reaction mixture was dissolved in water. The solution was extracted with AcOEt. The extract was washed with brine and then dried over $MgSO_4$. Removal of the solvent afforded the ketone (**4**) (3.73 g, 87 %) as a colorless oil; ^1H NMR ($CDCl_3$) δ: 1.8-2.3 (4H m, 2x-CH_2CHOAc), 2.10 (3H s, acetyl), 2.3-2.7 (4H m, 2x-CH_2CO), 5.19 (1H m, -CHOAc); MS m/z: 114 (M^+-CH_2CO), 96 (M^+-AcOH, base peak), 68.

Reformatsky reaction of the ketone (**4**) with ethyl bromoacetate——A mixture of activated Zn powder (2.5 g), **4** (1.24 g, 7.94 mmole) and ethyl bromoacetate (1.06 ml, 9.53 mmole) in anhydrous benzene (20 ml) was heated at the refluxing temperature for 30 min. After 1 h of stirring, AcOH (3 ml) was added to the reaction mixture and then the suspension was diluted with water and extracted with AcOEt. The extract was washed with brine and then dried over $MgSO_4$. Removal of the solvent gave a residue which was chromatographed over a silica gel column (50 g). Elution with hexane-ether (3:2) gave the esters (**5**) (0.86 g, 41 %) and (**6**) (0.58 g, 29 %).

5 as a colorless oil; ^1H NMR ($CDCl_3$) δ: 1.28 (3H t, J=7 Hz, -OCH_2CH_3), 2.03 (3H s, -$OCOCH_3$), 2.44 (2H s, -CH_2CO), 3.51 (1H s, -OH), 4.16 (2H q, J=7 Hz, -OCH_2CH_3), 4.66 (1H m, -CHOAc); ^{13}C NMR ($CDCl_3$) δ:14.1 (-OCH_2CH_3), 21.3 (-$OCOCH_3$), 26.6 (C-3,5), 34.9 (C-2,6), 45.6 (C-7), 60.6 (-OCH_2CH_3), 68.5 (C-1), 72.2 (C-4), 170.5 (-$OCOCH_3$), 172.4 (C-8). Anal. ($C_{12}H_{20}O_5$) C, H.

6 as a colorless oil; ^1H NMR ($CDCl_3$) δ: 1.28 (3H t, J=7 Hz, -OCH_2CH_3), 2.04 (3H s, -$OCOCH_3$), 2.50 (2H s, -CH_2CO), 3.55 (1H s, -OH), 4.17 (2H q, J=7 Hz, -OCH_2CH_3), 4.95 (1H m, -CHOAc); ^{13}C NMR ($CDCl_3$) δ:14.2 (-OCH_2CH_3), 21.4 (-$OCOCH_3$), 25.8 (C-3,5), 32.3 (C-2,6), 45.6 (C-7), 60.6 (-OCH_2CH_3), 69.2 (C-1), 69.6 (C-4), 170.4 (-$OCOCH_3$), 172.6 (C-8). Anal. ($C_{12}H_{20}O_5$) C, H.

LAH reduction of the ester (**5**)——A solution of **5** (122 mg, 0.5 mmole) in ether (10 ml) was added dropwise to a cooled solution of LAH (38 mg, 1.0 mmole) in ether (5 ml) during 20 min. After 30 min of stirring at room temperature, the suspension was heated at the reflux temperature for 2 h. The excess LAH was decomposed by adding 25 % aq. NH_4OH (1 ml) under ice-cooling. The precipitate was filtered off with celite. Removal of the solvent gave a residue which was chromatographed over a silica gel column (30 g). Elution with 10 % MeOH-$CHCl_3$ gave the alcohol (**1**) (74 mg, 93 %) as colorless prisms from CH_2Cl_2-MeOH-AcOEt, mp 123-124°; ^1H NMR (CD_3OD) δ: 1.67 (2H t, J=7 Hz, -CH_2CH_2OH), 3.51 (1H m, -CHOH), 3.72 (2H t, J=7 Hz, -CH_2CH_2OH); ^{13}C NMR (pyridine-

d_5) δ: 31.7 (C-3,5), 36.1 (C-2,6), 45.1 (C-7), 58.8 (C-8), 69.7 (C-4), 70.0 (C-1). These data were identical with those of natural rengyol.

LAH reduction of the ester (6)——A solution of **6** (122 mg, 0.5 mmole) in ether (10 ml) was reduced with LAH (38 mg, 1.0 mmole) in ether (5 ml), followed by the working up as above, to give a residue which was chromatographed over a silica gel column (30 g). Elution with 10 % MeOH-$CHCl_3$ gave the alcohol (**7**) (76 mg, 95 %) as colorless prisms from CH_2Cl_2-MeOH-AcOEt, mp 107-108°; ^{1}H NMR (CD_3OD) δ: 1.75 (2H t, J=7 Hz, -CH_2-CH_2OH), 3.60 (1H m, -CHOH), 3.74 (2H t, J=7 Hz, -CH_2-CH_2OH); ^{13}C NMR (pyridine-d_5) δ: 30.9 (C-3,5), 34.3 (C-2,6), 42.9 (C-7), 58.6 (C-8), 67.4 (C-4), 71.2 (C-1); MS m/z: 142 (M^+-H_2O), 115 (M^+-C_2H_4OH), 103, 98.
Treatment of **7** with Ac_2O in pyridine yielded the diacetate as a colorless oil; ^{1}H NMR ($CDCl_3$) δ: 1.83 (2H t, J=7 Hz, -CH_2-CH_2OAc), 2.06 (6H s, acetyl), 4.29 (2H t, J=7 Hz, -CH_2-CH_2OAc), 4.95 (1H m, -CHOAc).

Isolation and characterization of isorengyol (7)——A crude rengyol fraction was applied on a HPLC with LS-410 (Toyo Soda Co.) and eluted with water to afford rengyol (**1**) (T_R 10.8 min., 124 mg) and isorengyol (**7**) (T_R 6.2 min., 1.2 mg).
Isorengyol (**7**) as colorless powder; IR (nujor) cm^{-1}: 3500 (alcohol); ^{1}H NMR ($CDCl_3$) δ: 1.75 (2H t, J=7 Hz, -CH_2-CH_2OH), 3.60 (1H m, -CHOH), 3.73 (2H t, J=7 Hz, -CH_2-CH_2OH); MS m/z: 142 (M^+-H_2O), 115 (M^+-C_2H_4OH), 103, 98. Anal. ($C_8H_{16}O_3$) C, H. All of these data are in accord with those of synthetic **7**.

Bromination of the esters (5) and (6)——To a mixture of **5** and **6** (3:2), 30 % HBr-AcOH (2 ml) in Ac_2O (1 ml) was added at room temperature. After 2.5 h of stirring at 80°, the excess reagent was quenched with ice-water and the mixture was extracted with CH_2Cl_2. The extract was washed successively with 5 % aq. $NaHCO_3$ and brine, and then dried over $MgSO_4$. Removal of the solvent gave a residue which was chromatographed over a silica gel column (20 g). Elution with hexane-ether (3:1) gave the bromides (**8**) (93 mg, 30 %) and (**9**) (140 mg, 46 %).
8 as a colorless oil; IR (liquid film) cm^{-1}: 1740 (ester); ^{1}H NMR ($CDCl_3$) δ: 1.18 (3H t, J=7 Hz, -OCH_2-CH_3), 2.05 (3H s, -$OCOCH_3$), 2.97 (2H s, -CH_2CO), 4.16 (2H q, J=7 Hz, -OCH_2CH_3), 4.67 (1H m, -CHOAc); ^{13}C NMR ($CDCl_3$) δ:14.2 (-OCH_2CH_3), 21.3 (-$OCOCH_3$), 28.0 (C-3,5), 38.7 (C-2,6), 50.3 (C-7), 60.7 (-OCH_2CH_3), 66.6 (C-1), 71.5 (C-4), 169.1 (C-8), 170.4 (-$OCOCH_3$); MS m/z: 167 (M^+-Br-AcOH), 121, 93.
9 as a colorless oil; IR (liquid film) cm^{-1}: 1735 (ester); ^{1}H NMR ($CDCl_3$) δ: 1.19 (3H t, J=7 Hz, -OCH_2-CH_3), 2.04 (3H s, -$OCOCH_3$), 2.98 (2H s, -CH_2CO), 4.17 (2H q, J=7 Hz, -OCH_2CH_3), 5.00 (1H m, -CHOAc); ^{13}C NMR ($CDCl_3$) δ:14.3 (-OCH_2CH_3), 21.4 (-$OCOCH_3$), 27.1 (C-3,5), 35.5 (C-2,6), 50.9 (C-7), 60.6 (-OCH_2CH_3), 68.1 (C-1,4), 169.2 (C-8), 170.2 (-$OCOCH_3$); MS m/z : 219, 217 (M^+-$C_4H_8O_2$), 167 (M^+-AcOH-Br), 139, 121, 93.

Dehydrobrominations of the bromides (8, 9)——DBU (0.35 ml, 2.54 mmole) was added to a solution of the mixture (2:3) of **8** and **9** (0.78 g, 2.54 mmole) in anhydrous benzene (5 ml) at room temperature. The suspension was refluxed under stirring for 1 h and the reaction mixture was neutralized by addition of dil. H_2SO_4, and extracted with AcOEt. Removal of the solvent gave a residue which was chromatographed over a silica gel column (40 g). Elution with haxane-AcOEt (5:1) gave the olefin (**10**) (0.57 g, 100 %). A prolonged refluxing of the reaction mixture for 5 h afforded the mixture of **10** and **11** (ca. 1:5, 100 %).

Dehydration of the esters (5, 6)——Pyridine (1.09 ml) was added to a solution of a mixture of **3** and **4** (1.83 g, 7.49 mmole) in CH_2Cl_2 (20 ml) and then treated with a 25 % solution of $SOCl_2$ in CH_2Cl_2 (5.35 ml) at 0°. After 1.5 h of stirring under ice-cooling, the reaction mixture was concentrated *in vacuo* and diluted with water. The suspension was extracted with CH_2Cl_2. The extract was washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue which was chromatographed over a silica gel column (20 g). Elution with hexane-AcOEt (3:1) afforded the

olefins (**10**) and (**11**) (3:1, 1.66 g, 98 %).

10 as a colorless oil; ^{1}H NMR ($CDCl_3$) δ: 1.26 (3H t, J=7 Hz, $-OCH_2\underline{CH_3}$), 2.05 (3H s, $-OCO\underline{CH_3}$), 4.13 (2H q, J= 7 Hz, $-OCH_2\underline{CH_3}$), 4.96 (1H m, -CHOAc), 5.65 (1H br s, =CHCO); ^{13}C NMR ($CDCl_3$) δ: 14.3 ($-OCH_2\underline{CH_3}$), 21.3 ($-OCO\underline{CH_3}$), 25.5 (C-5), 31.5 (C-3), 32.2 (C-6), 33.8 (C-2), 59.6 ($-O\underline{CH_2}CH_3$), 70.6 (C-4), 114.3 (C-7), 159.9 (C-1), 166.4 (C-8), 170.4 ($-O\underline{CO}CH_3$); MS m/z: 181, 166 (M^+-AcOH, base peak), 138 (M^+-CH_2CO_2Et-1), 120, 93. High-resolution MS for $C_{12}H_{18}O_4$: Calcd. m/z: 226.1224; Found: 226.1220.

11 as a colorless oil; ^{1}H NMR ($CDCl_3$) δ: 1.26 (3H t, J=7 Hz, $-OCH_2\underline{CH_3}$), 2.16 (3H s, $-OCO\underline{CH_3}$), 2.95 (2H br s, $-\underline{CH_2}CO$), 4.12 (2H q, J=7 Hz, $-OCH_2\underline{CH_3}$), 4.98 (1H m, -CHOAc), 5.40 (1H m, -C=CH); ^{13}C NMR ($CDCl_3$) δ: 14.3 ($-OCH_2\underline{CH_3}$), 21.4 ($-OCO\underline{CH_3}$), 26.2 (C-5), 27.4 (C-6), 30.8 (C-3), 42.9 (C-7), 60.6 ($-O\underline{CH_2}CH_3$), 69.2 (C-4), 122.2 (C-2), 131.1 (C-1), 170.7 ($-O\underline{CO}CH_3$), 171.5 (C-8); MS m/z: 166 (M^+-AcOH), 152 (M^+-CO_2Et), 138 (M^+-CH_2CO_2Et-1), 120, 93, 92, 91 (base peak), 88. High-resolution MS for $C_{12}H_{18}O_4$: Calcd. m/z: 226.1224; Found: 226.1184.

Pyrolytic deacetoxylation of the acetate (**10**) and (**11**)——A mixture of **10** and **11** (3:1, 1.20 g, 5.31 mmole) was heated, without solvent, at 295° under N_2 atomosphere for 4 h. The reaction mixture was subjected to silica gel (50 g) chromatography. Elution with hexane-ether (1:5) gave a mixture of the diene (**12**) and the aromatic ester (**13**) (10:7, 202 mg) and recovered **10** and **11** (ca. 5:1, 655 mg).

12 as a colorless oil; IR (liquid film) cm^{-1}: 1735 (ester); ^{1}H NMR ($CDCl_3$) δ: 1.26 (3H t, J=7 Hz, $-OCH_2\underline{CH_3}$), 3.02 (2H s, $-\underline{CH_2}CO$), 4.10 (2H q, J=7 Hz, $-OCH_2\underline{CH_3}$), 5.3-5.8 (3H m, olefinic); MS m/z: 166 (M^+), 94, 91, 89 (base peak). High-resolution MS for $C_{10}H_{14}O_2$: Calcd. m/z: 166.0993; Found: 166.0988.

13 as a colorless oil; ^{1}H NMR ($CDCl_3$) δ: 1.23 (3H t, J=7 Hz, $-OCH_2\underline{CH_3}$), 3.58 (2H s, $-\underline{CH_2}CO$), 4.12 (2H q, J=7 Hz, $-OCH_2\underline{CH_3}$), 7.26 (5H br, aromatic); MS m/z: 164 (M^+), 91 (base peak).

Photooxygenation of the diene (**12**)——The mixture of **12** and **13** (170 mg) and rose bengal (30 mg) in MeOH (150 ml) was irradiated for 1 h with O_2 bubbling at 0° in a Pyrex flask under a high-pressure halogen lamp. The solution was concentrated in vacuo to give a residue which was chromatographed over a silica gel column (20 g). Elution with hexane-AcOEt (4:1) gave the endoperoxide (**15**) (102 mg, 89 %) and recovered **13** (69 mg).

15 as a colorless oil; ^{1}H NMR ($CDCl_3$) δ: 1.28 (3H t, J=8 Hz, $-OCH_2\underline{CH_3}$), 2.66 (2H dd, J=15, 8 Hz, $-\underline{CH_2}CO$), 4.16 (2H q, J=8 Hz, $-OCH_2\underline{CH_3}$), 4.64 (1H m, -CHO), 6.66 (1H dd, J=10, 1 Hz, -CH=CHCO), 6.69 (1H d, J=10 Hz, -CH=CHCO); MS m/z: 180, 166 (M^+-O_2), 110, 91 (base peak). High-resolution MS for $C_{10}H_{14}O_4$: Calcd. m/z: 198.0892; Found: 198.0919.

Reduction of the endoperoxide (**15**) to 2,3-dehydrorengyol (**16**)——A solution of **15** (19.8 mg, 0.1 mmole) in ether (0.75 ml) was added dropwise to a cooled solution of LAH (17.1 mg, 0.45 mmole) in ether (0.25 ml) during 5 min. After 10 min of stirring at room temperature, the reaction mixture was refluxed for 3 h and then the excess LAH was decomposed by adding 25 % aq. NH_4OH (0.1 ml). The precipitate was filtered off with celite. The filtrate was evaporated to give a residue which was chromatographed over a silica gel column (10 g). Elution with 10 % MeOH in $CHCl_3$ gave 2,3-dehydrorengyol **16** (15.2 mg, 96 %) as a colorless oil; ^{1}H NMR (CD_3OD) δ: 3.68 (2H t, J=7 Hz, $-CH_2\underline{CH_2}OH$), 4.03 (1H m, -CHOH), 5.65 (1H d, J=10 Hz, -CH=CHCH<), 5.70 (1H dd, J=10, 2 Hz, -CH=CHCH<); ^{13}C NMR (pyridine-d_5) δ: 29.7 (C-5), 34.3 (C-6), 44.9 (C-7), 58.7 (C-8), 66.3 (C-4), 69.3 (C-1), 133.5 (C-2), 134.5 (C-3); MS m/z: 140 (M^+-H_2O), 112 (M^+-C_2H_6O). Anal. ($C_8H_{14}O_3$) C, H.

Hydrogenation of 2,3-dehydrorengyol (**16**) to rengyol (**1**)——A solution of **16** (7.8 mg, 0.049 mmole) in MeOH (1 ml) was reduced under H_2 atomosphere with 5 % Pd-C (10 mg) at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentration to afford a residue which was subjected to column chromatography on silica gel (10 g). Elution with 10 % MeOH in $CHCl_3$ gave **1** (7.4 mg, 94 %) as colorless prisms from CH_2Cl_2-MeOH-AcOEt, mp 121-123°; ^{1}H NMR (CD_3OD) δ: 1.67 (2H t, J=7 Hz, $-\underline{CH_2}CH_2OH$), 3.50 (1H m, -CHOH), 3.74 (2H t, J=7 Hz, $-CH_2\underline{CH_2}OH$). These data

were identical with those of natural rengyol.

Hydrogenation of the endoperoxide (15)——A solution of **15** (30 mg, 0.15 mmole) and 5 % Pd-C (30 mg) in EtOH (2 ml) was stirred under H_2 atmosphere at room temperature for 1 h. The catalyst was filtered off and the filtrate was concentrated to afford a residue which was chromatographed on silica gel (15 g). Elution with 10 % MeOH in $CHCl_3$ gave the ester **17** (11 mg) as a colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H t, J=7 Hz, $-OCH_2\underline{CH_3}$), 2.42 (2H s, $-\underline{CH_2}CO$), 3.57 (1H m, $-\underline{CH}OH$), 4.15 (2H q, J=7 Hz, $-OCH_2\underline{CH_3}$).

LAH reduction of the ester (17) to rengyol (1)——A solution of **17** (4.3 mg, 0.021 mmole) in ether (0.5 ml) was added slowly to a solution of LAH (1.0 mg, 0.026 mmole) in ether (0.5 ml) during 5 min. After 1 h of stirring at room temperature, the excess LAH was decomposed by adding moist ether. The precipitate was filtered off with celite. The solvent was evaporated to give a residue which was chromatographed over a silica gel column (10 g). Elution with 10 % MeOH in $CHCl_3$ gave **1** (2.8 mg) as colorless prisms from CH_2Cl_2-MeOH-AcOEt; ^{1}H NMR (CD_3OD) δ: 1.67 (2H t, J=7 Hz, $-\underline{CH_2}CH_2OH$), 3.55 (1H m, $-\underline{CH}OH$), 3.73 (2H t, J=7 Hz, $-CH_2\underline{CH_2}OH$). These data were identical with those of natural rengyol.

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