Stereoselective Synthesis of Nerol

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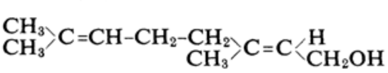
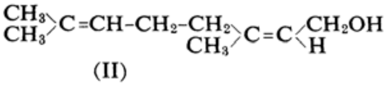
It is well known that geraniol and nerol are the most fundamental acyclic monoterpenoid alcohols and that both are geometric isomers. Their geometric configurations were mainly elucidated by the following chemical and physical evidence. Zeitschel[1] showed in 1906 that when fifty grams each of geraniol, linalool and nerol were cyclized to α-terpineol with dilute sulfuric acid, the yields of the reaction were 0.35 g., 1.75 g. and 2.5 g. respectively. Judging from the ease of cyclization, he assumed that the isohexenyl group and the hydroxymethyl group in geraniol (I) were trans to each other and that these groups in nerol were cis, based upon the ease of the cyclization.



$(CH_3)_2C=CH-CH_2-CH_2(CH_3)C=C(H)(CH_2OH)$

(I)

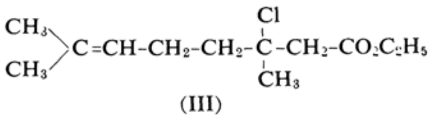


$(CH_3)_2C=CH-CH_2-CH_2(CH_3)C=C(CH_2OH)(H)$

(II)

Recently Jeffery[2] has established by X-ray crystallographic study that geranyl amine hydrochloride derived from geraniol has a structure which agrees with the chemically-assigned configuration. Thus, geraniol, in which relatively bulky groups are trans, may be thermodynamically more stable than nerol, and this may be correlated to the fact that the melting point of geranyl derivatives is higher than that of neryl compounds.[3,4]

Two synthetic methods of nerol have been reported in the literature. One[5] is the isomerization of geraniol to nerol; this reaction involves the addition of hydrogen iodide to geraniol and the subsequent elimination of the acid with alcoholic sodium hydroxide to give nerol. In the other,[6] nerol is obtained by the lithium aluminum hydride reduction of *cis*-geranic acid, which has been prepared by the elimination of hydrogen chloride with pyridine from the chloroester III. Both routes to form the double bond concerned are base-catalyzed eliminations; it seems probable that a major product would be a more thermodynamically stable isomer in these reactions. In the syntheses of nerol, thus, an ambiguity still remains.



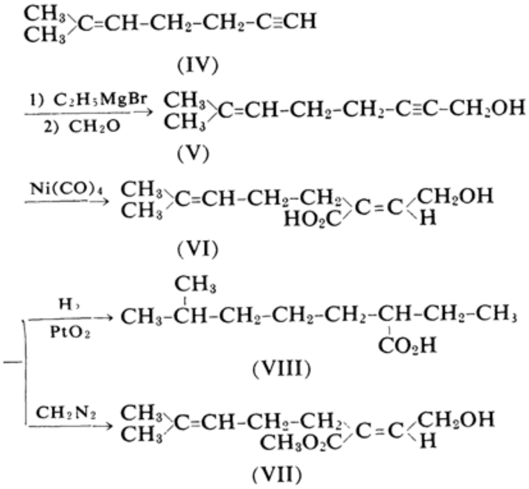
$(CH_3)_2C=CH-CH_2-CH_2-C(Cl)(CH_3)-CH_2-CO_2C_2H_5$

(III)

In this paper we wish to report the stereoselective synthesis of nerol allophanate, starting with an acetylenic compound.

Results and Discussion

The starting material, 6-methyl-5-hepten-1-yne (IV), was prepared from γ-butyrolactone and acetylene according to Eschenmoser's procedure[7] and was converted into 7-methyl-6-octen-2-yn-1-ol (V) by the reaction of its Grignard compound with paraformaldehyde. The acetylenic alcohol V was reacted with nickel carbonyl in a solvent mixture of alcohol, acetic acid and water at 70°C to give unsaturated hydroxylic acid VI, which did not lactonize on being heated to 120°C for 5 hr. The catalytic hydrogenation of this acid VI over platinum oxide afforded 2-ethyl-6-methylheptanoic acid (VIII), with hydrogenolysis of



$(CH_3)_2C=CH-CH_2-CH_2-C\equiv CH$ (IV)

$\xrightarrow[2)\ CH_2O]{1)\ C_2H_5MgBr} (CH_3)_2C=CH-CH_2-CH_2-C\equiv C-CH_2OH$ (V)

$\xrightarrow{Ni(CO)_4} (CH_3)_2C=CH-CH_2-CH_2(HO_2C)C=C(CH_2OH)(H)$ (VI)

$\xrightarrow[PtO_2]{H_2} CH_3-CH(CH_3)-CH_2-CH_2-CH_2-CH(CO_2H)-CH_2-CH_3$ (VIII)

$\xrightarrow{CH_2N_2} (CH_3)_2C=CH-CH_2-CH_2(CH_3O_2C)C=C(CH_2OH)(H)$ (VII)

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[1] O. Zeitschel, *Ber.*, **39**, 1782 (1906).

[2] G. A. Jefferey, *Proc. Roy. Soc.*, **A183**, 388 (1945).

[3] H. von Soden and O. Zeitschel, *Ber.*, 36, 266 (1903); A. Blumann and O. Zeitschel, ibid., **44**, 2593 (1911).

[4] D. Barnard, L. Bateman, A. J Harding, H. P. Koch, N. Sheppard and G. B. B. M. Sutherland, *J. Chem. Soc.*, **1950**, 915.

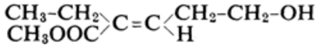
[5] A. Verley, *Bull. soc. chim. France*, **25**, (4) 68 (1919).

[6] A. Mondon and G. Teege, *Chem. Ber.*, **91**, 1020 (1958).

[7] G. Gamboni, H. Schinz and A. Eschenmoser, *Helv. Chim. Acta*, 37, 964 (1954).

the allylic hydroxyl group, which was characterized as its anilide (m. p. 66∼67°C[8]). If the carboxylation of the acetylenic alcohol V with nickel carbonyl occurred in the β-position of the hydroxyl group, the hydrogenation of this reaction product should give 2, 7-dimethyloctanoic acid, which is an isomer of VIII. However, it is reported that its anilide melted at 93°C.[8] Since it has been established[9,10] that this carboxylation of the acetylenic compound, developed by Jones,[9] results in the formation of α, β-unsaturated carboxylic acid, in which the carboxyl function and the hydrogen atom introduced are on the same side of the double bond, these evidences confirm the correctness of the above formulation.

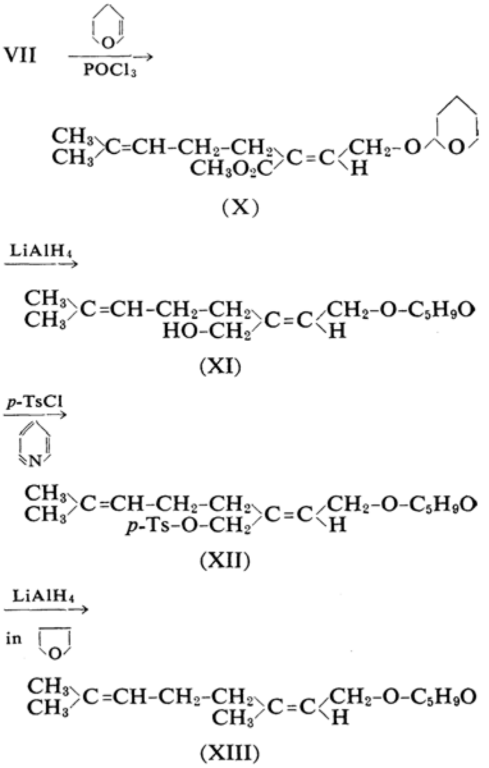
The esterification of the unsaturated hydroxylic acid VI smoothly proceeded using diazomethane to give an unsaturated ester VII. During the subsequent reduction of the ester function to the methyl group it is necessary to protect the hydroxyl function in a form unaffected by reducing agents. In our previous investigation,[10] 4-methoxycarbonyl-3-hexen-1-ol (IX) was converted into triphenylmethyl ether of IX in order to prevent the elimination of the hydroxyl function during hydrolysis and decarboxylation. It was found, however, that in this case the triphenylmethoxy group in the trityl ether of VII was replaced by a hydrogen atom during the course of the reduction of the ester function to the methyl group. Recently we reported[11] that the reaction of dihydropyran with catechol furnished protection to the hydroxyl group in catechol to give the di-(tetrahydropyranyl)ether of catechol, which was stable in basic media and which was readily hydrolyzed with dilute mineral acid. This procedure has also been employed in the study of aliphatic unsaturated hydroxylic compounds.[12]



$$\begin{matrix} CH_3\text{-}CH_2 \\ CH_3OOC \end{matrix}\!\!>C=C<\!\!\begin{matrix} CH_2\text{-}CH_2\text{-}OH \\ H \end{matrix}$$

(IX)

The ester VII was treated with dihydropyran and a catalytic amount of phosphorous oxychloride to afford tetrahydropyranyl ether X. The ester function of the tetrahydropyranyl derivative X was transformed into the hydroxymethyl group with lithium aluminum hydride in a cold ethereal solution. The reaction of the resulting alcohol XI with p-toluenesulfonyl chloride in pyridine gave a sulfonate XII, which was further reduced with lithium aluminum hydride in tetrahydrofuran under reflux. In some reactions of allylic derivatives, allylic rearrangement may occasionally occur. However, it has proved by a study using ^{14}C as a tracer[13] that allylic rearrangement does not occur when the p-toluenesulfoxyl group in an allylic situation is replaced with nucleophilic reagents. This procedure has ordinarily been employed in the transformation of the hydroxymethyl group to the methyl group.[14]



The reduction product was purified by alumina chromatography, and the pure tetrahydropyranyl ether XIII was eluted with petroleum ether. It has been reported that the hydrolysis of tetrahydropyranyl ether has been carried out by the action of warm dilute mineral acid, a boiling aqueous oxalic acid solution, 2, 4-dinitrophenylhydrazine in 2 N hydrochloric acid or p-toluenesulfonic acid in aqueous alcohol.[15] In this case it was experimentally found that the last of these reagents

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[8] H. Suzuki, *J. Pharm. Soc. Japan* (*Nippon Yakugaku Zasshi*), **56**, 860 (1936).

[9] E. R. H. Jones, T. Y. Shen and M. G. Whiting, *J. Chem. Soc.*, **1951**, 48.

[10] Y. Yukawa and T. Hanafusa, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zassi*), **76**, 572 (1955).

[11] T. Hanafusa and Y. Yukawa, *Chem. Ind.*, **1961**, 23.

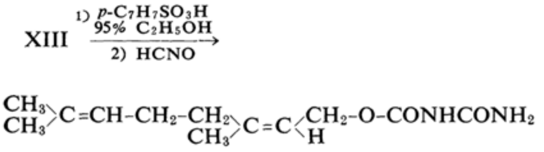
[12] G. F. Woods and E. L. Anderson, *J. Am. Chem. Soc.*, **69**, 2246 (1947); H. B. Henbest, E. R. H. Jones and I. M. S. Walls, *J. Chem. Soc.*, **1950**, 3648; S. S. Nigam and B. C. L. Weedon, ibid., **1956**, 4050.

[13] R. F. Nystrom and J. C. Leak, *J. Am. Chem. Soc.*, **75**, 3039 (1953).

[14] W. G. Brown, "Organic Reactions," Vol. VI, 471 (1951).

[15] Houben-Weyl, "Methoden der Organischen Chemie," 4 Aufl.. VI, (1), (1954), p. 423.

was the most satisfactory. The tetrahydropyranyl ether XIII was treated with a small amount of *p*-toluenesulfonic acid in 95% ethyl alcohol at 55°C for one-and-a-half hours to give an oil, into which cyanic acid was then introduced at room temperature. The allophanate XIV was obtained as colorless needles after one recrystallization each from benzene and from petroleum ether. It was much more soluble in benzene or petroleum ether than in geranyl allophanate and melted at 84~86°C. The melting point was not raised by further recrystallization and was not depressed upon admixture with geranyl allophanate (m. p. 110°C).



$$\text{XIII} \xrightarrow[\text{2) HCNO}]{\text{1) } p\text{-}C_7H_7SO_3H \;\; 95\%\ C_2H_5OH} \frac{CH_3}{CH_3}\!\!>\!C{=}CH{-}CH_2{-}\overset{CH_2}{\underset{CH_3}{}}\!\!>\!C{=}C\!<\!\!\frac{CH_2{-}O{-}CONHCONH_2}{H}$$

(XIV)

Other investigators[3,4,16,17] have also recorded that the crystalline derivatives of nerol are much more soluble in ordinary solvents than that of geraniol, that the melting points of neryl derivatives are lower than that of geranyl derivatives, and that they did not depress upon admixture with geranyl compounds. It is evident that the allophanate XIV is neryl allophanate since its behavior agrees with these results.

As has been described above, Mondon[6] has reported obtaing *cis*-geranic acid by the reaction of chloroester III with pyridine and by the hydrolysis of the resulting ester. Its *S*-benzylthiourea adduct recrystallized from dioxane melted at 133°C, while the adduct of *trans*-geranic acid, prepared by the oxidation of geraniol, melted at 141~143°C after recrystallization from dilute alcohol. However, it was found that these two adducts were the same compound. The adduct of *cis*-acid melted at 141~143°C when it was recrystallized from dilute alcohol, and the reduction product of *cis*-acid purified by Mondon's procedure was geraniol, which was characterized as its allophanate (m. p. 107~110°C). These results agree with the generality that the base-catalyzed elimination of hydrogen halide from a halogeno compound gives a more thermodynamically stable isomer at a higher rate.[18]

Experimental

7-Methyl-6-octen-2-yn-1-ol (V).—6-Methyl-5-octen-1-yne (IV) (16 g.), prepared according to Eschenmoser's procedure, was added to an ethereal solution of ethylmagnesium bromide prepared from ethyl bromide (22 g.) and magnesium (5 g.) in ether (150 ml.). The reaction mixture was heated under reflux for 2 hr., after which paraformaldehyde (22 g.) was stirred in efficiently at −5°C over a 1 hr. period. After being stirred for 2 hr. at 0°C, the mixture was decomposed with a saturated aqueous ammonium chloride solution. The ether extracts were washed with water and dried over anhydrous magnesium sulfate. This compound (12 g.) was obtained as an oil (b. p. 93~95°C/3 mmHg, n_D^{23} 1.4761). Its phenyl urethane did not solidify.

3-Carboxy-7-methyl-2, 6-octadien-1-ol (VI).—A solution of nickel carbonyl (7.5 ml.) in absolute ethyl alcohol (15 ml.) was added dropwise at 65~70°C with stirring under an inert atmosphere into a solution of the acetylenic alcohol (V) in ethyl alcohol (32 ml.) acetic acid (6.5 ml.), and water (3 ml.). After being heated under reflux for 2 hr., the mixture was treated with 5% sulfuric acid (35 ml.) and ether (100 ml.) at 0~5°C. The water layer was repeatedly extracted with ether. The combined ether was extracted with saturated aqueous sodium hydrogen carbonate until the pH value in an alkaline solution did not change (twelve times). The alkaline layer was acidified with dilute hydrochloric acid. Continuous ether extraction from the acidic solution afforded, after removal of the solvent, this acid VI (6.9 g.) (b. p. 145~147°C).

Found: C, 65.19; H, 8.75. Calcd. for $C_{10}H_{16}O_3$: C, 65.38; H, 8.43%.

The compound was redistilled unchanged under reduced pressure and did not change on being heated at 120°C for 5 hr.

2-Ethyl-6-methylheptanoic Acid (VIII).—The acid VI was hydrogenated in ethyl acetate over platinum oxide under atmospheric pressure. 3.5 equivalents of hydrogen were absorbed over a 6 hr. period. The product was then extracted with a 10% aqueous sodium carbonate solution. After acidification with 2 N hydrochloric acid, the saturated acid VIII was extracted with ether in a 63% yield. This compound was distilled at 105°C/20 mmHg and showed no band in the region of 3000~4000 cm^{-1}.

Found: C, 69.14; H, 11.70. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70%.

The anilide of this acid melted at 66~67°C; this agrees with Suzuki's finding.[8]

3-Methoxycarbonyl-7-methyl-2, 6-octadien-1-ol (VII).—A solution of diazomethane prepared from *N*-nitrosomethylurea (15 g.) in ether (30 ml.) was introduced into a solution of the unsaturated acid (VI) (6.9 g.) in an ice-salt bath. After it had been left standing overnight, the reaction mixture was shaken with 2 N hydrochloric acid, with a saturated aqueous sodium hydrogen carbonate solution, and with water successively. The ester VII (5 g.) was distilled at 128~129°C/3 mmHg; n_D^{28} 1.4737.

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[16] Y. R. Naves and A. V. Grampoloff, *Helv. Chim. Acta*, **25**, 1500 (1942).

[17] Y. R. Naves, ibid., **29**, 557 (1946).

[18] D. J. Gram, "Steric Effects in Organic Chemistry," Ed. by M. S. Newman, John Wiley & Sons, Inc., New York (1956), p. 339.

Found: C, 66.77; H, 9.59. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15%.

3-Methoxycarbonyl-7-methyl-2,6-octadienyl Tetrahydropyranyl Ether (X). — A few drops of phosphorous oxychloride were added to a mixture of the ester VII (5 g.) and dihydropyran in an ice bath. After it had stood at room temperature for 3 hr., the reaction mixture was added to a 20% aqueous sodium carbonate solution. Ether extraction gave, after removal of the solvent, the ether X (4 g.) (b. p. 120~121°C/0.1 mmHg).

Found: C, 68.20; H, 9.37. Calcd. for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28%.

3-Hydroxymethyl-7-methyl-2, 6-octadienyl Tetrahydropyranyl Ether (XI).—A solution of the above ether X (4 g.) in absolute ether (50 ml.) was stirred, at −10°C, into a solution of lithium aluminum hydride (0.6 g.) in absolute ether (30 ml.). The reaction mixture was heated under reflux for a short time. After ethyl acetate (1 ml.) had been added to the mixture in an ice-salt bath, 2 N hydrochloric acid (30 ml.) was introduced. An ethereal layer was washed with water and dried over anhydrous magnesium sulfate. This compound XI (2.8 g.) was distilled at 130~137°C/0.3 mmHg.

Found: C, 70.25; H, 10.30. Calcd. for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30%.

The Sulfonate of XI (XII).—A solution of XI (2.8 g.) in dry pryridine (30 ml.) was stirred, at −1~−3°C, into a solution of *p*-toluenesulfonyl chloride (4.5 g.) in the solvent. After having been stirred for 3 hr. at room temperature, the mixture was poured into cold dilute hydrochloric acid. Chloroform extraction afforded this compound XII as an viscous oil after evaporation of the solvent under reduced pressure. The sulfonate was easily soluble in chloroform or tetrahydrofuran, only but with difficult in ether, and it was not further purified.

Neryl Tetrahydropyranyl Ether (XIII).—A solution of the above sulfonate XII in tetrahydrofuran (50 ml.) was stirred into a solution of lithium aluminum hydride (1 g.) in tetrahydrofuran (50 ml.) in an ice-salt bath. The reaction mixture was heated under reflux for 10 hr. After having been cooled, the mixture was decomposed with ethyl acetate (4 ml.), water (10 ml.) and 2 N hydrochloric acid (50 ml.) successively. The water layer was extracted with ether. The combined ether solution was then washed with a 20% sodium carbonate solution and an aqueous saturated sodium chloride solution. After removal of the solvent, the residue was purified by alumina column chromatography. Elution with light petroleum (600 ml.) gave neryl tetrahydropyanyl ether XIII (0.4 g.) (b. p, 150°C (bath temp.)/0.3 mmHg). The infrared spectrum of this compound resembled that of the geranyl derivative.

The Allophanate of Nerol (XIV).—A solution of the neryl tetrahydropyranyl ether (XIII) (0.4 g.) and *p*-toluenesulfonic acid (0.05 g.) in 95% ethyl alcohol (8 ml.) was heated to 52~58°C for one and a half hours. The mixture was then extracted with light petroleum after having been added to water. An organic layer was washed with a 10% aqueous sodium carbonate solution and water, and then dried over magnesium sulfate. After removal of the solvent, the cyanic acid generated from the thermal decomposition of cyanuric acid (0.5 g.) was introduced into the residue in an ice bath. The solids thus produced were washed with light petroleum and recrystallized once from benzene and once from light petroleum. The allophanate XIV (0.1 g.) was obtained as needles, which melted at 84~86°C by themselves and which melted at 84~88°C on admixture with the allophanate of geraniol. The melting point was not raised by further recrystallization.

Found: C, 59.03; H, 8.39; N, 11.72. Calcd. for $C_{12}H_{20}O_3N_2$: C, 59.98; H, 8.46; N, 11.66%.

Reduction of the Triphenylmethyl Ether of VII. —A mixture of VII (4 g.), triphenylmethyl chloride (7 g.) and pyridine (3 g.) in benzene (70 ml.) was heated under reflux for 4 hr. After removal of the solvent under reduced pressure, the residue was extracted 4 times with light petroleum (100 ml.). The trityl ether (5.4 g.) was obtained as a viscous oil after having been purified by alumina column chromatography.

A solution of the substance (5 g.) in absolute ether (30 ml.) was ordinarily reduced with lithium aluminum hydride in an ice bath. The reaction products were chromatographed on alumina. 3-Hydroxymethyl-7-methyl-2, 6-octadienyl triphenylmethyl ether (1.8 g.) was eluted, using 30% benzene-light petroleum as a syrup, a syrup which was decomposed on distillation, even under highly reduced pressure.

Found: C, 84.30; H, 7.92. Calcd. for $C_{29}H_{32}O_2$: C, 84.42; H, 7.82%.

The reduction procedure of this compound was analogous to that described in the reduction of XI through its sulfonate XII with lithium aluminum hydride. The products were chromatographed on alumina. An olefin was eluted with light petroleum and seemed to be 2, 6-dimethyl-2, 6-octadiene judging from its boiling point (100~110°C (bath temp.)/20 mmHg), its analytical datum and its infrared spectrum.

Found: C, 87.49; H, 11.63. Calcd. for $C_{10}H_{18}$: C, 86.88; H, 13.12%.

The other product was eluted with 50% benzene-light petroleum as plates; the m. p. was 150~155°C, which was not depressed when the product was admixed with triphenylmethyl alcohol.

Geranyl Tetrahydropyranyl Ether.—This compound (3.5 g.) (b. p. 122~124°C/5 mmHg) was prepared from geraniol (3 g.) and dihydropyrane (3 g.) in a manner similar to that described in the synthesis of X.

Found: C, 76.05; H, 10.70. Calcd. for $C_{15}H_{26}O_2$: C, 75.63; H, 10.92%.

Hydrolysis of Geranyl Tetrahydropyranyl Ether.—1) A mixture of the ether (1 g.) and oxalic acid (0.5 g.) in water (5 ml.) was heated while being stirred at 100°C for 1.5 hr. Steam distillation gave the starting material (0.6 g.) unchanged; this was confirmed by its infrared spectrum.

2) A mixture of the ether (1 g.) in 2 N sulfuric acid (10 ml.) was slowly distilled with steam to give an alcohol, but its allophanate melted at 70~80°C.

3) The ether was shaken with excess 2, 4-dinitrophenylhydrazine in 2 N hydrochloric acid for 7 hr. The ether was recovered unchanged.

The Reduction of *cis*-Geranic Acid.—*cis*-Geranic acid was prepared from III following Mondon's procedure. Its *S*-benzylthiuronium salt melted at 133°C on recrystallization from dioxane and at 141∼143°C on recrystallization from dilute alcohol. The purified acid through the *S*-benzylthiuronium salt was reduced with lithium aluminum hydride by Mondon's procedure. The reduction product (b. p. 86∼87°C/4 mmHg) was converted into its allophanate, which melted at 107∼110°C after having been recrystallized from benzene. The melting point was not depressed when the product was admixed with geranyl allophanate.

Summary

Nerol, acyclic monoterpene alcohol, has been stereoselectively synthesized using as an intermediate the unsaturated hydroxylic acid VI, in which the carboxyl and the hydroxymethyl groups are evidently in the cis-relation.

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