Syntheses and ^{13}C NMR Spectra of *trans,cis*- and *trans,trans*-Nepetalinic Acids and Photocitral A

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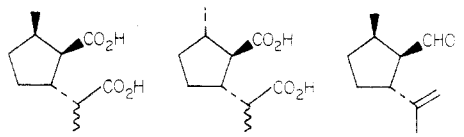
New syntheses of (±)-*trans,cis*- and (±)-*trans,trans*-nepetalinic acids (**1** and **2**) and (±)-photocitral A (**3**) using ethyl (±)-5-methyl-1-cyclopentenecarboxylate (**5**) as a common starting material are described. Michael addition of ethyl sodio-C-methylmalonate to **5** gave a 47:53 mixture of *trans,cis*- and *trans,trans*-α,2-bis(ethoxycarbonyl)-α,3-dimethylcyclopentaneacetates **6a** and **6b** in 54% yield. Hydrolysis of **6** followed by decarboxylative pyrolysis gave a mixture of **1** and **2** (86% yield from **6**). These acids, without separation, were converted to the corresponding mixture of methyl esters (**8a,b** and **9a,b**). Michael addition of (1-methylvinyl)magnesium bromide to **5** in the presence of CuI afforded a mixture of four diastereomers of ethyl 2-(1-methylvinyl)-5-methylcyclopentanecarboxylate (**17a-d**) in 75% yield. Hydrolysis of **17a-d** with 3 N NaOH gave the free acid **20**, a 21:9 (^1H NMR) mixture of the acids **20a** and **20c**, in 83% yield. Reduction of **17a-d** with $LiAlH_4$ gave a mixture of the corresponding alcohols (**18a-d**). On the contrary, reduction of the free acid **20** with $LiAlH_4$ afforded a 76:24 (GLC) mixture of the alcohols **18a** and **18c** in 85% yield. Oxidation of this product with pyridinium chlorochromate gave a 24:76 mixture of photocitral A and its trans,trans isomer **21a** (49% yield from **17a-d**). The relative stereochemistry of a series of 1,2,3-trisubstituted cyclopentanes, which were obtained in the present work, was elucidated by consideration of the steric effects of substituents observed in ^1H and ^{13}C NMR spectra.

C-α epimeric mixture of *trans,cis*-nepetalinic acid (**1**)[1] and C-α epimeric mixture of *trans,trans*-nepetalinic acid (**2**)[2] have been known as the oxidation products derived from natural cyclopentanoids such as nepetalactone and myodesertin, respectively. On the other hand, photocitral



1 **2** **3**

A (**3**), a major photocyclization product of citral,[3,4] has been used as a key intermediate for the synthesis of furopelargone A.[5] As a part of our interest in cyclopentanoid syntheses by means of Michael additions,[6,7] we now describe new syntheses of (±)-**1**, (±)-**2**, and (±)-**3** by the introduction of a C_3 unit at the C-2 position of ethyl (±)-5-methyl-1-cyclopentenecarboxylate (**5**). The relative stereochemistry of a series of 1,2,3-trisubstituted cyclopentanes, obtained in the present work, was elucidated both by ^1H NMR and by ^{13}C NMR,[7,8,9] focusing our attention on side-chain carbons as well as ring carbons. Tables I and II summarize ^{13}C NMR spectral data of these cyclopentane derivatives. IR and ^1H NMR spectral data as well as analytical data have been listed in Table III.

The starting ester **5**[10] was prepared by the dehydrochlorination of the chloro ester **4c** (pyridine, 64%), which was in turn obtained from ethyl 2-methyl-5-oxocyclopentanecarboxylate (**4a**)[11] following the sequence of reactions shown in Scheme I. Michael addition of ethyl C-methylmalonate to the unsaturated ester **5** in the presence of NaOEt gave a 47:53 mixture of *trans,cis*- and *trans,trans*-α,2-bis(ethoxycarbonyl)-α,3-dimethylcyclopentaneacetates **6a** and **6b**, in 54% yield.[12] The ^{13}C signal of C-7 (methyl group) of **6a** (15.8 ppm) was observed at higher field than that of **6b** (18.5 ppm) owing to the proximity of the C-7 methyl group and the adjacent ethoxycarbonyl group which are in a cis configuration.[8] It should be noted here that signals of the ring carbons of **6a** appeared at higher field than those of **6b**. The ^1H signal of methyl (C-7) protons of **6a** (δ 0.94) similarly appeared at higher field when compared with that of **6b** (δ 1.03).[13]

The hydrolysis of the triester **6** with 3 N NaOH (H_2O–EtOH, 1:1) followed by pyrolysis (190 °C) gave a mixture of nepetalinic acids **1** and **2** (86% yield from **6**). These acids, without separation, were converted into the corresponding methyl esters (**8** and **9**, 44:56 by GLC), which were then separated by preparative GLC. The ^{13}C NMR spectra indicated that each ester consisted of a mixture of two epimers[14] due to the C-α carbon of the side chain, since paired signals were observed in the ratio of 1:1 and 5:3, respectively. The structural assignment of **8a** was made based on the fact that its ^{13}C NMR chemical shift bears a close parallel to that of the free acid (**10**),[15] as

(1) McElvain, S. M.; Eisenbraum, E. J. *J. Am. Chem. Soc.* **1955**, *72*, 1599.
(2) Grant, H. G.; Sutherland, M. D. *Aust. J. Chem.* **1973**, *26*, 2183.
(3) (a) Cookson, R. C.; Hudec, J.; Knight, S. A.; Whitear, B. *Tetrahedron Lett.* **1962**, 79. (b) Cookson, R. C.; Hudec, J.; Knight, S. A.; Whitear, B. *Tetrahedron* **1963**, *19*, 1995.
(4) (a) Barany, F.; Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1948. (b) Wolff, S.; Agosta, W. C. *J. Org. Chem.* **1978**, *43*, 3627. (c) Wolff, S.; Barany, F.; Agosta, W. C. *Ibid.* **1980**, *102*, 2378.
(5) Büchi, G.; Wüest, H. *J. Am. Chem. Soc.* **1965**, *87*, 1589.
(6) Takeda, A.; Shinhama, K.; Tsuboi, S. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1831.
(7) Takeda, A.; Shinhama, K.; Tsuboi, S. *J. Org. Chem.* **1980**, *45*, 3125.
(8) Christl, M.; Reich, H. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 3463.
(9) Kagan, H. B. "Stereochemistry"; Georg Thieme Verlag: Stuttgart, 1977; Vol. 1, pp 93–94. The results available so far concerning simply substituted cyclopentane derivatives suggest that the steric effect observable in ^{13}C NMR chemical shift may be of great help in establishing the relative stereochemistry of appropriate compounds, although a systematic study on diastereomers of 1,2,3-trisubstituted cyclopentanes has not been reported (see also ref 7 and 8).
(10) We previously reported the alternative preparation of **5** by the dehydrochlorination–decarbonylation of ethyl 1-chloro-5-methyl-2-oxocyclohexanecarboxylate (ref 6).
(11) Preparation from (±)-pulegone: Marx, J. N.; Norman, L. R. *J. Org. Chem.* **1975**, *40*, 1602.
(12) Trans addition of malonate anion is preferential: Cook, A. H.; Linstead, R. P. *J. Chem. Soc.* **1934**, 956.
(13) Inoue, K.; Ide, I.; Sakai, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2361.
(14) Further attempts to separate these C-α epimers (**8a,b** and **9a,b**) were not successful.
(15) Murai, F.; Tagawa, M. *Planta Med.* **1979**, *37*, 234.

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Table I. ^{13}C NMR Spectral Data ($CDCl_3$, ppm) of Cyclopentaneacetates[a,b]

compd	C-1 (d)	C-2 (d)	C-3	C-4[e] (t)	C-5[e] (t)	C-6 (q)	C-α	C-7 (q)	C-8 (s)	C-9 (s)	ester CH_2 (t)	ester CH_3 (q)
6a	47.0	50.8	39.1 (d)	34.0	27.9	18.6	56.6 (s)	15.8	172.0	176.9	60.1	14.5
											61.3	14.0
6b	47.4	54.4	41.6 (d)	34.6	28.2	18.9	56.6 (s)	18.5	172.0	176.9	60.4	14.0
											61.2	13.4
8a[f]	43.7	52.0	37.7 (d)	33.9	29.4	15.5	44.8 (d)	16.2	175.3	176.0		51.4
8b[g]	44.2				29.8		45.0 (d)					
9a[h,i]	43.7	56.0	40.6 (d)	33.5	28.8	15.2	46.5 (d)	19.3	176.4	175.9		51.4
9b[h,j]	43.5	56.4	40.4 (d)	33.3		14.7	46.4 (d)	19.9				51.6
10[c]	(43.6)	(51.4)	(37.7)	(34.0)	(29.3)	(15.3)	(44.5)	(16.1)	(181.5)	(182.3)		
12	45.8[d]	46.8[d]	32.6 (t)	25.9	29.3	18.6	53.6 (s)		171.6	176.6	60.3	13.9
											61.1	14.2
15a[k,l]	46.3	47.3	31.2 (t)	25.1	30.5	15.4	43.4 (d)		176.8	175.9		51.5
15b[k,m]		47.7	31.0 (t)		30.2	14.9						51.7

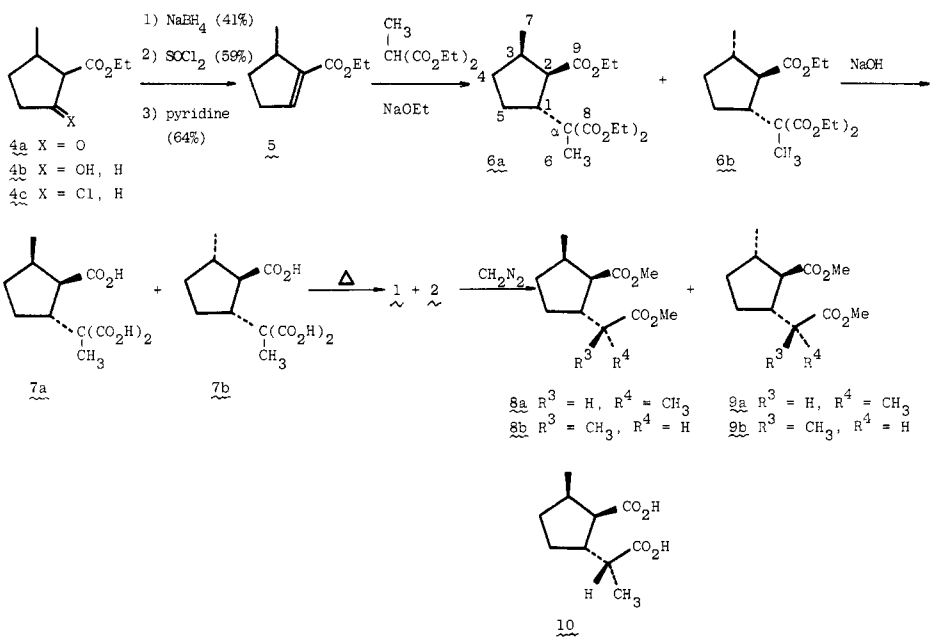
[a] Superscripts e, h, and k: assignments may be interchangeable. [b] Relative intensity, f:g = 1.1; i:j = 5.3; l:m = 2.1. [c] Chemical shifts reported in the literature (see ref 15). [d] Assigned by single-frequency off-resonance decoupling.

Table II. Product Ratios and ^{13}C NMR Spectral Data ($CDCl_3$, ppm) of Photocitral A and Related Compounds

compd	product ratio,[a] %	C-1 (d)	C-2 (d)	C-3[b] (t)	C-4[b] (t)	C-5 (d)	C-6 (s)	C-7 (s)	C-8 (q)	C-9 (t)	C-10 (q)	ester CH_2 (t)	ester CH_3 (q)
16a	59	51.6	48.4	30.5	24.6	31.7[c]	176.5	146.6	20.3	110.2		60.3	14.3
16b	41	51.0	47.3	28.4	23.8	28.8[c]	162.9	145.3	23.2	110.5		59.9	14.3
17a	18	56.8	51.8	33.7	29.9	39.8	175.8	146.7	20.1	110.0	19.5	60.2	14.4
17b	11	55.5	49.8	33.8	29.8	37.0	174.7	145.4	22.9	110.8	21.3	59.8	14.3
17c[d]	25[e]	52.1	48.5	34.2	30.6	36.9	174.5	147.1	20.9	109.3	17.0	59.4	14.4
17d[e]	46[e]	53.6	50.8	31.1	26.9	38.2	173.1	144.8	23.3	109.8	16.5	60.0	14.4
18a	22	52.1[f]	52.9[f]	33.5	29.7	36.6	65.5[c]	149.2	20.0	110.6	19.1		
18b	10	48.4[f]	51.4[f]	35.2	29.4	36.5	64.2[c]	149.0	27.3	110.6	21.8		
18c[d]	27[g]	48.3[f]	49.3[f]	30.1	23.8	33.7	64.1[c]	148.9	19.2	110.4	15.5		
18d[g]	30[g]	47.8[f]	50.3[f]	30.8	25.8	37.4	60.4[c]	148.0	24.3	110.0	16.5		
21a	76	63.7	49.1	33.5	30.3	36.2	203.8	145.8	20.4	110.4	19.5		
21b[d]		60.4	49.0	34.2	30.4	34.5	205.2	143.8	23.1	111.6	20.9		
3	24	58.5	45.8	34.6	30.4	37.1	204.0	146.2	20.5[h]	109.6	16.4[h]		

[a] Based on GLC analysis. [b] Assignments may be interchangeable. [c] Triplet. Assignments may be interchangeable with C-3. [d] Sample recorded was derived from photocitral A. [e] Sample recorded was a 25:46 (signal intensity in ^{13}C NMR) mixture of **17c** and **17d**. [f] Assignments may be interchangeable. [g] Sample recorded was a 27:30 (signal intensity in ^{13}C NMR) mixture of **18c** and **18d**. [h] Assigned by single-frequency off-resonance decoupling.

Scheme I



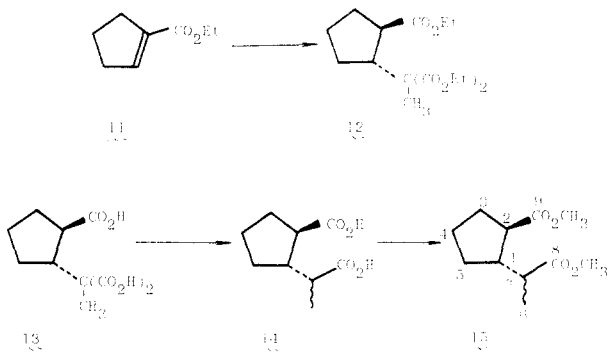
shown in Table I. Relative stereochemistry of the side chains of **8** as well as **9** was determined by consideration of their ^1H NMR and ^{13}C NMR spectra as was done in the case of **6a** and **6b**.

Table III. IR and ^{1}H NMR Spectral Data and Elemental Analyses of Cyclopentanoids

compd	IR, cm^{-1}	^{1}H NMR[a] ($CDCl_3$) δ	anal. found (calcd) % C	% H
6a	1735	0.94 (d, 3, 7), 1.23 (t, 6, 7), 1.27 (t, 3, 7), 1.38 (s, 3), 1.5-3.2 (m, 7), 4.15 (q, 6, 7)	61.94 (62.18)	8.48 (8.59)
6b	1735	1.03 (d, 3, 6), 1.23 (t, 6, 7), 1.25 (t, 3, 7), 1.39 (s, 3), 1.3-3.3 (m, 7), 4.12 (q, 2, 7), 4.15 (q, 4, 7)	62.04 (62.18)	8.52 (8.59)
8a,b	1735	0.90 (d, 3, 7), 1.12 (d, 1.5, 7), 1.13 (d, 1.5, 7), 1.4-3.0 (m, 8), 3.62, 3.65, 3.66, 3.67 (s, 6)	63.34 (63.14)	9.05 (8.83)
9a,b	1735	1.03 (d, 3, 6), 1.12 (d, 3, 7), 1.4-3.0 (m, 8), 3.65 (s, 3), 3.68 (s, 3)	63.11 (63.14)	8.72 (8.83)
12	1730	1.25[b] (t, 9, 7), 1.35 (s, 3), 1.5-3.2 (m, 7), 4.0 (q, 7, 2), 4.05 (q, 7, 4)	61.42 (61.13)	8.38 (8.34)
16a	1735 1643	1.22 (t, 3, 7), 1.71 (br s, 3), 1.0-3.0 (m, 8), 4.11 (q, 2, 7), 4.72 (m, 2)	72.56 (72.49)	9.77 (9.95)
16b	1732 1643	1.18 (t, 3, 7), 1.77 (br s, 3), 1.1-3.1 (m, 8), 4.03 (q, 2, 7), 4.72 (m, 2)	72.31 (72.49)	9.76 (9.95)
17a	1730 1643	1.05 (d, 3, 6), 1.23 (t, 3, 7), 1.70 (br s, 3) 1.4-3.1 (m, 7), 4.13 (q, 2, 7), 4.72 (m, 2)	73.29 (73.43)	10.52 (10.27)
17b	1730 1640	1.05 (d, 3, 6), 1.20 (t, 3, 7), 1.75 (br s, 3), 1.4-3.1 (m, 7), 4.04 (q, 2, 7), 4.72 (m, 2)	73.40 (73.43)	9.98 (10.27)
17c[c]	1730 1643	0.93 (d, 3, 7(, 1.25 (t, 3, 7), 1.70 (br s, 3) 1.4-3.05 (m, 7), 4.13 (q, 2, 7), 4.75 (m, 2)	73.22 (73.43)	9.94 (10.27)
17d[d]	1730 1643	1.01 (d, 3, 7), 1.25 (t, 3, 7), 1.76 (br s, 3), 1.4-3.1 (m, 7), 4.13 (q, 2, 7), 4.75 (m, 2)	73.62 (73.43)	10.37 (10.27)
18a	3370 1641	1.04 (d, 3, 6), 1.52 (br s, 1),[e] 1.73 (br s, 3), 1.0-2.5 (m, 7), 3.64 (d, 2, 5), 4.77 (m, 2)	77.72 (77.87)	11.57 (11.76)
18b	3370 1641	1.06 (d, 3, 7), 1.50 (br s, 1),[e] 1.83 (br s, 3), 1.0-2.7 (m, 7), 3.63 (d, 2, 6), 4.75 (m, 2)	77.95 (77.87)	11.89 (11.76)
18c[c]	3410 1642	0.94 (d, 3, 7), 1.50 (br s, 1),[e] 1.73 (br s, 3), 1.0-2.7 (m, 7), 3.63 (d, 2, 6), 4.75 (m, 2)	[f]	
18d[g]	3400 1642	1.05 (d, 3, 6), 1.55 (br s, 1),[e] 1.87 (br s, 3), 1.0-2.8 (m, 7), 3.56 (d, 6), 4.87 (m, 2)	78.03 (77.87)	11.52 (11.76)
21a	1725 1643	1.06 (d, 3, 6), 1.72 (br s, 3), 0.9-3.0 (m, 7), 4.74 (m, 2), 9.53 (d, 1, 4)	78.76 (78.90)	10.54 (10.59)
21b	1720 1642	1.03 (d, 3, 6), 1.72 (br s, 3), 0.9-3.0 (m, 7), 4.74 (m, 2), 9.38 (d, 1, 4)	[h]	
3	1720 1642	1.06 (d, 3, 7), 1.68 (br s, 3), 0.9-3.1 (m, 7), 4.63 (m, 2), 9.64 (d, 1, 4)	[h]	

[a] Multiplicity, signal intensity (H), and coupling constant (hertz) indicated by values in parentheses. [b] CCl_4. [c] Compound recorded was derived from photocitral A. [d] Contains the minor component **17c**. [e] Signal due to OH. [f] Known compound (ref 3b). [g] Contains the minor component **18c**. [h] Known compound (ref 3 and 5).

Scheme II



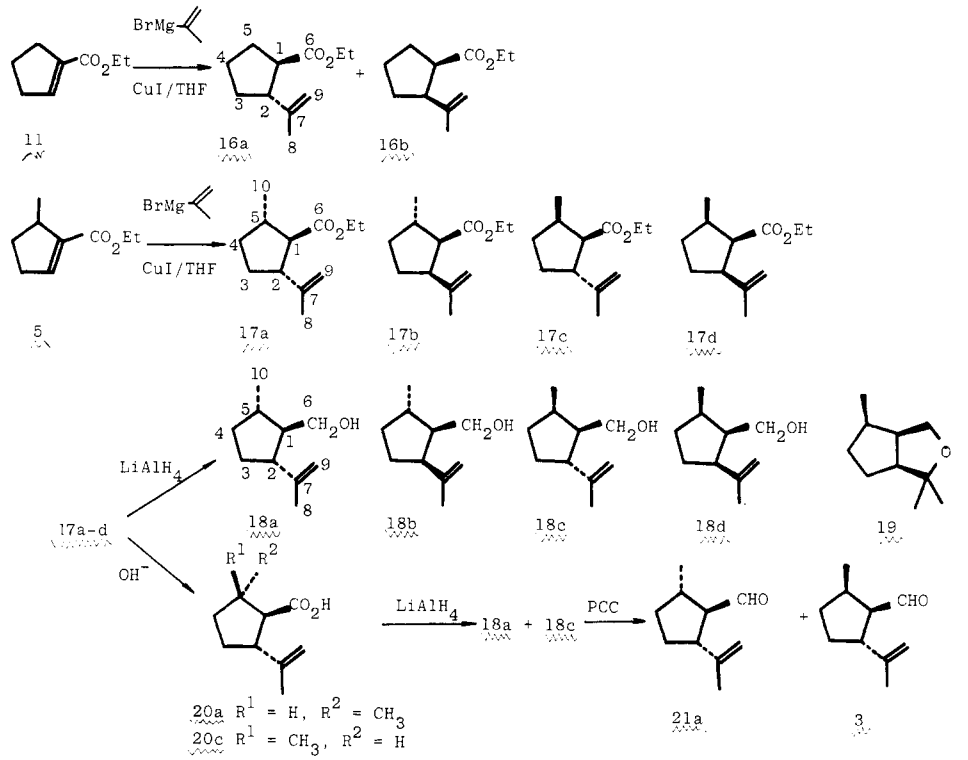
Nornepetalinic acid[16] (C-α epimeric mixture of *trans*-2-carboxy-α-methylcyclopentaneacetic acid, **14**) as well as its methyl ester (**15**) were synthesized in a similar way starting from ethyl 1-cyclopentenecarboxylate (**11**)[17] in order to ensure the assignment of the methyl (C-6 and C-7) groups in compounds **6**, **8**, and **9**.[12] The reaction sequence is shown in Scheme II. It is reasonable to assume the ^{13}C shift values (14.9 and 15.4 ppm) of **15** are representative of the C-6 methyl groups in these compounds.[12]

A new approach toward the synthesis of **3** began with the CuI-catalyzed Michael addition of (1-methylvinyl)-magnesium bromide[18] to ester **5** in THF, which gave 18:11:25:46 mixture of four diastereomers of ethyl 2-(1-methylvinyl)-5-methylcyclopentanecarboxylate (**17a–d**)[19a] in 75% yield (Scheme III). The product ratios and the ^{13}C NMR spectral data for **17a–d** are summarized in Table II. The relative stereochemistry of four isomers is elucidated on the basis of the steric effect observed in their ^{13}C NMR spectra. Signals for the C-10 (cis methyl group) of **17c** (17.0 ppm) and **17d** (16.5 ppm) appeared at higher field as compared with those of the trans isomers [**17a** (19.5 ppm), and **17b** (21.3 ppm)]. A similar effect was observed for C-7 of the 1-methylvinyl group. Moreover, the signals of ring carbons C-1, C-2, and C-5 of **17a** were observed at lowest field among the four isomers reflecting its stereochemistry.[8,9] Compound **17c** was alternatively prepared by the esterification ($EtOH–H_2SO_4$) of *trans*-2-(1-methylvinyl)-*cis*-5-methylcyclopentanecarboxylic acid (**20c**), which was obtained by the oxidation (CrO_3) of photocitral A (Scheme IV).

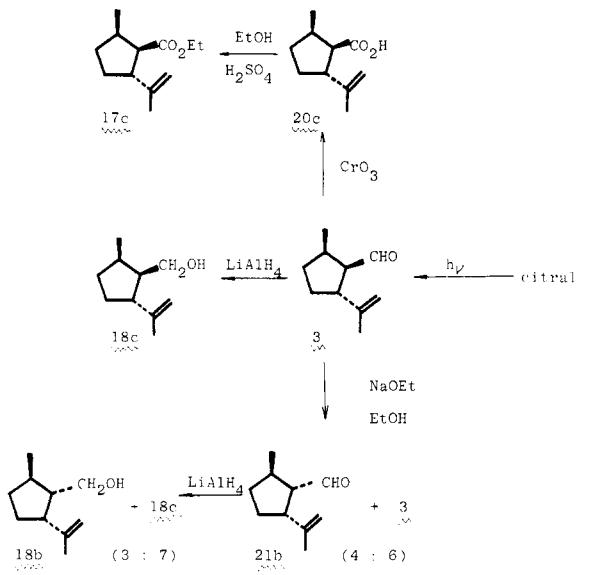
The reaction of (1-methylvinyl)magnesium bromide with the unsaturated ester **11** gave a 59:41 mixture of trans and cis isomers of ethyl 2-(1-methylvinyl)cyclopentanecarboxylate (**16a,b**). The fact that the C-8 methyl signals

(16) Tanaka, T. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1890.
(17) Büchi, G.; Hochstrasser, U.; Pawlak, W. *J. Org. Chem.* **1973**, *38*, 4348.
(18) House, H. O.; Latham, R. A.; Slater, C. C. *J. Org. Chem.* **1966**, *31*, 3667.
(19) (a) Acids **17a–d** and their methyl esters are described by: Wolinsky, J.; Hull, P.; White, E. M. *Tetrahedron* **1976**, *32*, 1335. (b) Alcohols **18a–d** and their acetates are described by: Wolinsky, J.; Gibson, T.; Chan, D.; Wolf, H. *Tetrahedron* **1965**, *21*, 1247.

Scheme III



Scheme IV



of these isomers (**16a** and **16b**) appeared at a field no less than 20 ppm (20.3 and 23.2 ppm) also supports the assignment of C-8 and C-10 (methyl group) of **17** by means of ^{13}C NMR.

Reduction of the diastereomeric mixture of **17a–d** with $LiAlH_4$ gave a mixture of the corresponding alcohols (**18a–d**)[19b] in 68% yield. Hexahydro-1,1,4-trimethyl-1*H*-cyclopenta[*c*]furan (**19**)[20] was isolated as a minor product (8% yield). Compound **19** is considered to be produced by the cyclization of the cis,cis isomer (**18d**) in the course of the reduction, since this compound is gradually transformed to **19** when allowed to stand at room temperature.[21] The product ratio and ^{13}C NMR spectral data of **18a–d** also are given in Table II. The ^{13}C NMR signals of the C-10 cis methyl group of **18c** (15.5 ppm) and **18d** (16.5 ppm) appeared at higher field as compared with that of trans isomers [**18a** (19.1 ppm) and **18b** (21.8 ppm)]. However, it was difficult to determine the relative stereochemistry of the 1-methylvinyl group of **18** by means of ^{13}C NMR, since the differences of observed chemical shifts at C-7 of these diastereomers were very small (within 1.2 ppm). The stereochemistry of **18b** and **18c** was examined independently by chemical conversion as shown in Scheme IV, which unambiguously correlated the stereochemistry of photocitral A (**3**) with those of **17c** and **18c**.[3b] Treatment of **3** with ethanolic NaOH caused a partial epimerization at C-1 to give a 4:6 mixture of epiphotocitral A (**21b**) and **3**,[3b,5] which was further converted to a 3:7 mixture of **18b** and **18c**,[3b] thereby correlating the stereochemistry of photocitral A with that of **18b**. Furthermore, compound **18a** showed ^{13}C NMR signals at the lowest field among the four isomers and was assigned as the trans,trans isomer.

The hydrolysis of the diastereomeric mixture **17a–d** with 3 N ethanolic NaOH gave the free acid **20**, as a 21:9 (^1H NMR) mixture of acids **20a** and **20c**, in 83% yield.[22] This fact suggests that the epimerization at C-1 has occurred during the course of the alkaline hydrolysis so that the more thermodynamically stable trans configuration predominates. Reduction of the above acid with $LiAlH_4$ gave a 76:24 mixture of the diastereomeric alcohols **18a** and **18c** in 81% yield. Oxidation of this product with pyridinium chlorochromate (PCC) afforded photocitral A (18% yield) in addition to the trans,trans isomer **21a** (55% yield).

Experimental Section

General Procedures. Melting points were determined on a Yamato Model MP-21 melting point apparatus and are uncorrected. The evaporative bulb-to-bulb distillations were done with a Büchi Kugelrohr oven at the pressure and oven temperature

(20) Yamada, Y.; Sanjoh, H.; Iguchi, K. *Chem. Lett.* **1978**, *1405*.
(21) Forty-one percent (by GLC) conversion in 30 days.
(22) The exclusive formation of acids **20a** and **20c** is parallel to the formation of *trans*-pulegenic acid on hydrolysis of ethyl pulegenate. See: Wolinsky, J.; Chan, D. *J. Org. Chem.* **1968**, *30*, 41.

indicated. Elemental analyses were carried out by Mr. Eiichiro Amano of our laboratory. IR spectra were taken with a Hitachi Model EPI-S2 spectrometer. ^1H NMR spectra (60 MHz) were recorded with a Hitachi Model R-24 spectrometer. Both ^1H NMR spectra (100 MHz) and ^{13}C NMR spectra (25 MHz) were measured in $CDCl_3$ with a JEOL JNM FX-100 spectrometer with FT facilities, using Me_4Si as an internal standard. Analytical determinations by GLC were performed on a Hitachi Model K-53 gas chromatograph (N_2, 42 mL/min), using the following columns: A, 10% polyneopentyl glycol succinate on Chromosorb W, 3 mm o.d. × 1 m; B, 10% Apiezone Grease L on Chromosorb W, 3 mm o.d. × 2 m. Preparative isolations by GLC were done with a Yanagimoto Model G-80 gas chromatograph at the same conditions as those employed in the analytical determination.

Materials. The unsaturated ester **11** was prepared from ethyl 1-chloro-2-oxocyclohexanecarboxylate by Büchi's procedure.[17] (±)-Photocitral A was obtained in 15% yield[3b,5] by the photocyclization of citral, using a 180-W mercury arc lamp (Taika Kogyo Co. Ltd.). Epimerization of (±)-photocitral A with ethanolic NaOEt afforded a 4:6 mixture of (±)-epiphotocitral A and (±)-photocitral A.[5]

Ethyl 2-Hydroxy-5-methylcyclopentanecarboxylate (4b).[23] To a stirred suspension of 0.4 g (0.01 mol) of NaOH in 50 mL of ethanol was added 2.02 g (0.053 mol) of $NaBH_4$ with caution. A solution of 9.1 g (0.054 mol) of the keto ester **4a**[11,24] in 50 mL of ethanol was added dropwise to this mixture. After being stirred for 1 h at room temperature, the resulting mixture was filtered and the filtrate was concentrated under vacuum. The residual oil was acidified with 10% HCl, extracted with ether, dried over $MgSO_4$, and filtered. After the ether was removed, the residue was distilled under reduced pressure to give 3.82 g (41% yield) of the hydroxy ester **4b**: bp 84–90 °C (4 mm); IR (neat) 3500 and 1725 cm^{-1}; ^1H NMR (CCl_4) δ 1.08 (d, 3 H, J = 6 Hz, CH_3), 1.28 (t, 3 H, J = 7 Hz, ester CH_3), 1.45–2.4 (m, 6 H, ring protons), 3.02 (m, 1 H, CHOH), 4.13 (q, 1 H, J = 7 Hz, ester CH_2), 4.15 (q, 1 H, J = 7 Hz, ester CH_2), 4.1–4.5 (br s, 1 H, OH).

Ethyl 2-Chloro-5-methylcyclopentanecarboxylate (4c). To a stirred solution of 1.64 g (13.8 mmol) of $SOCl_2$ in 50 mL of CH_2Cl_2 was added dropwise a solution of 846 mg (4.92 mmol) of the hydroxy ester **4b** in 50 mL of pyridine at room temperature. After being stirred under reflux for 30 min, the mixture was diluted with 10 mL of water. The organic layer was extracted with benzene, washed with 10% HCl and then with water, and dried over $MgSO_4$. Evaporation of the solvent followed by distillation gave 552 mg (59% yield) of the chloro ester **4c**: bp 120–123 °C (0.2 mm); IR (neat) 1740 cm^{-1}; ^1H NMR (CCl_4) δ 1.05 (d, 3 H, J = 6 Hz, CH_3), 1.26 (t, 3 H, J = 7 Hz, ester CH_3), 1.3–3.1 (m, 6 H, ring protons), 4.11 (q, 2 H, J = 7 Hz, ester CH_2), 4.3–4.6 (m, 1 H, CHCl). Anal. Calcd for $C_9H_{15}O_2Cl$: C, 56.69; H, 7.92. Found: C, 56.76; H, 7.95.

Ethyl 5-Methyl-1-cyclopentenecarboxylate (5). A solution of 456 mg (2.39 mmol) of the chloro ester **4c** in 2 mL of pyridine was heated under reflux for 14 h. The resulting mixture was acidified with 10% HCl and the organic layer was extracted with ether, washed with water, and dried over $MgSO_4$. The distillation [bp 76–78 °C (10 mm)] of the residue after evaporation of the solvent gave 215 mg (64% yield) of the ester **5**. Spectral data of this product were identical with those reported.[6]

Ethyl *trans,cis*- and *trans,trans*-α,2-Bis(ethoxycarbonyl)-α,3-dimethylcyclopentaneacetates (6a and 6b). Ethyl *C*-methylmalonate (1.46 g, 8.44 mmol) was added dropwise to a solution of sodium (194 mg, 0.00844 mol) in 11 mL of ethanol. To the mixture was added slowly 1.0 g (6.50 mmol) of the unsaturated ester **5** at room temperature. After the mixture was stirred under gentle reflux for 42 h, the solvent was evaporated under vacuum. The residue was acidified with 10% HCl and the organic layer was extracted with ether and dried over $MgSO_4$, and the solvent was removed on the rotary evaporator. Distillation [bp 120–125 °C (1 mm)] of the residual oil gave 1.92 g (54% yield) of the triester **6**. GLC analysis (column A, oven temperature 200 °C) of this product showed two peaks with retention times (component, integrated percentage) of 9.1 (**6b**, 53%) and 10.1 min (**6a**, 47%). Pure samples of **6a** and **6b** were obtained by preparative GLC.

Ethyl *trans*-α,2-Bis(ethoxycarbonyl)-α-methylcyclopentaneacetate (12). The reaction of the unsaturated ester **11** with ethyl sodio-*C*-methylmalonate was carried out in the manner similar to the preparation of **6** and gave **12** in a 89% yield: bp 90–95 °C (0.07 mm).

Hydrolysis of the Triester 6. Acids 7a and 7b. A suspension of 1.60 g (4.88 mmol) of the distilled ester (**6a** and **6b**) in 14 mL of 3 N ethanolic NaOH (H_2O–EtOH, 1:1) was heated under reflux for 3 h. After the mixture was acidified with 10% HCl, the organic layer was extracted with ether and dried over $MgSO_4$. Evaporation of the solvent left 1.12 g of the mixture of acids **7a** and **7b** as white crystals, yield 94%. One recrystallization of the crude product from hexane–acetone (1:1) gave an analytical sample of the diastereomeric mixture of **7a** and **7b**: mp 179–179.5 °C dec; IR (KBr) 3550–2350 and 1705 cm^{-1}; ^1H NMR (CD_3COCD_3) δ 0.99 (d, 1.5 H, J = 7 Hz, cis 3-CH_3), 1.16 (d, 1.5 H, J = 6 Hz, trans 3-CH_3), 1.41 (s, 3 H, α-CH_3), 1.2–3.2 (m, 7 H, ring protons), 7.8–9.0 (br s, 3 H, 3 CO_2H). Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 53.86; H, 6.32.

C-α Epimeric *trans,cis*- and *trans,trans*-Nepetalinic Acids (1 and 2). The mixture of **7a** and **7b** (1.02 g, 4.18 mmol) obtained in the foregoing experiment was heated on an oil bath at 190 °C for 30 min until evolution of CO_2 ceased. After the mixture cooled to room temperature, the product was recrystallized from hexane–acetone (1:1) to give 758 mg (92% yield) of the mixture of **1** and **2**: mp 69–69.5 °C; IR (KBr) 3500–2850 and 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93–1.30 (m, 6 H, 2 CH_3), 1.3–3.0 (m, 8 H, ring and C-α protons), 11.05 (br s, 1 H, CO_2H).

C-α Epimeric Methyl *trans,cis*- and *trans,trans*-2-(Methoxycarbonyl)-α,3-dimethylcyclopentaneacetates (8a,b and 9a,b). The epimeric mixture of **1** and **2** (880 mg, 40 mmol) was treated with an excess of CH_2N_2 in the usual manner to give 925 mg of the mixture of methyl esters **8a,b** and **9a,b**. GLC analysis (column A, oven temperature 160 °C) of this product showed two peaks at retention times (component, integrated percentages) of 9.6 (**9a** and **9b**, 56%) and 11.2 min (**8a** and **8b**, 44%). These fractions[14] were separated by preparative GLC.

***trans*-α,2-Dicarboxy-α-methylcyclopentaneacetic Acid (13).** The hydrolysis of **12** with 3 N ethanolic NaOH (H_2O–EtOH, 1:1) gave **13** in 85% yield: mp 143–145 °C dec (hexane–acetone 1:1); IR (KBr) 3500–2500 and 1700 cm^{-1}; ^1H NMR (CD_3COCD_3) δ 1.40 (s, 3 H, CH_3), 1.6–3.2 (m, 7 H, ring protons), 9.9 (br s, 3 H, 3 CO_2H). Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.10; H, 6.22.

Nornepetalinic acid (14)[16] was obtained in 89% yield by the pyrolysis of **13** at 150–175 °C. Compound **14**: mp 126–128 °C (hexane–acetone, 2:1); IR (KBr) 3500–2500 and 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (d, 3 H, J = 7 Hz, CH_3), 1.3–2.7 (m, 9 H, ring and C-α protons), 11.71 (br s, 1 H, CO_2H).

Methyl *trans*-2-(methoxycarbonyl)-α-methylcyclopentaneacetate (15) was obtained in 94% yield by the treatment of **14** with CH_2N_2 in ether. Compound **15**: IR (neat) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (d, 3 H, J = 7 Hz, CH_3), 1.5–2.6 (m, 9 H, ring protons), 3.66 (s, 3 H, ester CH_3), 3.67 (s, 3 H, ester CH_3). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.92; H, 8.51.

Ethyl 2-(1-Methylvinyl)-5-methylcyclopentanecarboxylate (17a–d). To a stirred mixture of magnesium turnings (214 mg, 8.93 mmol) and a trace of iodine in 10 mL of THF was added with caution 1.25 g (10.4 mmol) of 2-bromopropene[25] at room temperature. The stirring was continued until the magnesium turnings completely dissolved. After the mixture cooled to −15 °C, 170 mg (0.89 mmol) of CuI was added, and the mixture was stirred for 30 min at −15 °C. The ester **5** (1.0 g, 6.49 mmol) was added dropwise to the resulting solution and the stirring was continued for an additional 1 h at −15 °C. The mixture was poured into aqueous NH_4Cl and the organic layer was extracted with ether and dried over $MgSO_4$. The solent was removed under vacuum and the residue was distilled to give 954 mg (75%) of the dia-

(23) Sakan, T.; Fujio, A.; Murai, F.; Butsugan, Y.; Terashima, Y. *Nippon Kagaku Zasshi* **1960**, *81*, 1447.

(24) (±)-Pulegone used in this study was prepared from (±)-3-methylcyclohexanone by the procedure described by Black et al.: Black, C.; Buchanan, G. L.; Jarvie, A. W. *J. Chem. Soc.* **1956**, 2971.

(25) Hatch, L. F.; Harwell, K. E. *J. Am. Chem. Soc.* **1953**, *75*, 6004.

stereomeric mixture of **17a–d**: bp 45–50 °C (1 mm). GLC analysis (column B, oven temperature 180 °C) of this product showed three peaks at the retention times (component, integrated percentage) of 11.6 (**17a**, 18%), 12.9 (**17b**, 11%), and 14.2 min [**17c** (25%) and **17d** (46%)].[26] These fractions were separated by preparative GLC.

Ethyl *trans*- and *cis*-2-(1-Methylvinyl)cyclopentanecarboxylates (16a and 16b). The reaction of ester **11** (1.0 g, 7.1 mmol) with (1-methylvinyl)magnesium bromide [2-bromopropene (1.42 g, 11.8 mmol), magnesium (0.26 g, 10.7 mmol)] in the presence of CuI (0.1 g, 0.5 mmol) similarly gave 554 mg (68% yield) of the diastereomeric mixture of esters **16a** and **16b**: bp 70–77 °C (3 mm). GLC analysis (column B, oven temperature 160 °C) of this product showed two peaks at the retention times (component, integrated percentage) of 13.9 (**16a**, 59%) and 15.4 min (**16b**, 41%). These isomers were separated by preparative GLC.

***Hydrolysis of* 17a–d. 2-(1-Methylvinyl)-5-methylcyclopentanecarboxylic Acid (20).** A suspension of 517 mg (2.6 mmol) of **17a–d** in 10 mL of 1.5 N ethanolic NaOH (H_2O–EtOH, 1:1) was stirred under reflux for 22 h. After being acidified with 10% HCl, the organic layer was extracted with ether and dried over $MgSO_4$. After the evaporation of the solvent, the residual oil was distilled under diminished pressure to give 437 mg of a 21:9 (^1H NMR) mixture of acids **20a** and **20c**: yield 83%, bp 97–101 °C (0.08 mm); IR (neat) 3700–2100, 1710, and 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (d, 0.9 H, J = 7 Hz, cis 5-CH_3), 1.18 (d, 2.1 H, J = 7 Hz, trans 5-CH_3), 1.2-3.3 (m, 7 H, ring protons), 1.75 (br s, 3 H, CH_3), 4.78 (m, 2 H, $=CH_2$), 9.10 (br s, 1 H, CO_2H). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.57; H, 9.63.

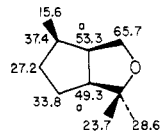
***trans*-2-(1-Methylvinyl)-*cis*-5-methylcyclopentanecarboxylic Acid (20c). Oxidation of (±)-Photocitral A.**[3b,5] To a solution of 5.5 g (36.2 mmol) of photocitral A in 220 mL of acetone was added a suspension of 7.15 g (71.5 mmol) of CrO_3 in 44 mL of 3.6 N H_2SO_4 at 0 °C. After the solution was stirred for 2 h at 0 °C and for an additional 12 h at room temperature, the solvent was evaporated under vacuum. The organic layer was extracted with CH_2Cl_2, washed with water, and dried over $MgSO_4$. After the solvent was removed under vacuum, the residue was distilled under diminished pressure to give 3.60 g of the acid **20c**: yield 59%; bp 95–105 °C (0.08 mm); IR (neat) 3600–2400, and 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (d, 3 H, J = 7 Hz, CH_3), 1.73 (s, 3 H, CH_3), 1.10–3.15 (m, 7 H, ring protons), 4.75 (m, 2 H, $=CH_2$), 11.40 (br s, 1 H, CO_2H). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.04; H, 9.74.

Ethyl *trans*-2-(1-Methylvinyl)-*cis*-5-methylcyclopentanecarboxylate (17c). Esterification of Acid 20c. A solution of 3.0 g (0.0178 mol) of **20c** in 50 mL of ethanol and 2.2 mL of H_2SO_4 was heated under reflux for 12 h. After the solvent was evaporated under vacuum, the residue was diluted with 20 mL of water. The organic layer was extracted with ether, and dried over $MgSO_4$. Evaporation of the solvent followed by distillation [bp 80–88 °C (3 mm)] gave 3.44 g (82% yield) of **17c**. GLC analysis (column B, oven temperature 180 °C) of this product showed one peak with a retention time of 14.2 min.

2-(1-Methylvinyl)-5-methylcyclopentanemethanol (18a–d). To a suspension of 200 mg (5.3 mmol) of $LiAlH_4$ in 8 mL of ether was added dropwise a solution of 676 mg (3.4 mmol) of **17a–d** in 3 mL of ether at 0 °C. After being stirred for 5 h at room temperature, the resulting mixture was poured into water and acidified with 10% HCl. The organic layer was extracted with ether and dried over $MgSO_4$. Evaporation of the solvent under vacuum left 402 mg of clean oil. GLC analysis (column B, oven temperature 180 °C) of this product showed four peaks at the retention times (component, integrated percentage) of 8.4 (**19**, 11%), 9.6 (**18a**, 22%), 11.6 (**18b**, 10%), and 13.3 min [**18c** (27%) and **18d** (30%)].[27] The yields of **18a–d** and **19** by preparative GLC were 68% and 8%, respectively.

Hexahydro-1,1,4-trimethyl-1*H*-cyclopenta[*c*]furan (19). A 27:30 mixture of the alcohols **18c** and **18d**, which was obtained in the preceding experiment, was allowed to stand in a capped sample tube at room temperature for 30 days. GLC analysis (column B, oven temperature 180 °C) of this sample showed two peaks at the retention times (component, integrated percentage) of 8.4 (**19**, 21%) and 13.3 min (27:17 mixture of **18c** and **18d** by ^1H NMR, 79%). These fractions were separated by preparative GLC. Compound **19**:[20] IR (neat) 1063 and 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (d, 3 H, J = 7 Hz, CH_3), 1.18 (s, 3 H, CH_3), 1.21 (s, 3 H, CH_3), 1.3–2.4 (m, 6 H, ring protons), 2.75 (m, 1 H, 3a-H), 3.69 (d, 1 H, J = 6.2 Hz, 3-H), 3.70 (d, 1 H, J = 7.6 Hz, 3-H).

The ^{13}C NMR spectrum ($CDCl_3$, ppm) of **19** is summarized in the following formula (a, assigned by the partially reluxed FT (PRFT) NMR technique):



Reduction of Acid 20. The reduction of 123 mg (0.7 mmol) of acid **20** with 30 mg (0.8 mmol) of $LiAlH_4$ in 3 mL of ether gave 87 mg of a 76:24 (GLC, column B, oven temperature 180 °C) mixture of alcohols **18a** and **18c**, yield 81%. These components were separated by preparative GLC.

Reduction of (±)-Photocitral A.[3b,5] The reduction of 80 mg (0.53 mmol) of photocitral A with 27 mg (0.71 mmol) of $LiAlH_4$ in 2 mL of ether gave 70 mg of **18c**, yield 86%.

Reduction of a 4:6 Mixture[5] of (±)-Epiphotocitral A and (±)-Photocitral A. The reduction of a 4:6 mixture of epiphotocitral A and photocitral A (95 mg, 0.62 mmol), which was prepared by the epimerization of photocitral A, with 30 mg (0.8 mmol) of $LiAlH_4$ in 3 mL of ether gave 78 mg of a 3:7 mixture (GLC, column B, oven temperature 180 °C) of **18b** and **18c**, yield 82%. These diastereomers were separated by preparative GLC.

Oxidation of a 76:24 Mixture of 18a and 18c. (±)-Photocitral A and Trans,Trans Isomer (21a). To a suspension of 200 mg (0.9 mmol) of pyridinium chlorochromate in 2 mL of CH_2Cl_2 was added a solution of 72 mg (0.5 mmol) of the mixture of alcohols **18a** and **18c** in 2 mL of CH_2Cl_2. After the mixture was stirred for 1.5 h at room temperature, the oily layer was extracted with ether and the solvent was evaporated under vacuum. Purification of the residual oil with short-column chromatograph (silica gel, hexane) gave 55 mg of a mixture of **3** and **21a**, yield 73%. GLC analysis (column B, oven temperature 180 °C) of this product showed two peaks with retention times (component, integrated percentage) of 7.2 (**21a**, 76%) and 8.4 min (**3**, 24%), which were separated by preparative GLC.

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Registry No. 1 (isomer 1), 78962-88-6; 1 (isomer 2), 78962-89-7; 2 (isomer 1), 50429-16-8; 2 (isomer 2), 78962-90-0; 3, 43219-98-3; 4a, 58073-90-8; 4b, 78891-07-3; 4c, 78891-08-4; 5, 78891-09-5; 6a, 78891-10-8; 6b, 78962-91-1; 7a, 78891-11-9; 7b, 78962-92-2; 8a, 78962-93-3; 8b, 78962-94-4; 9a, 78962-95-5; 9b, 78962-96-6; 11, 10267-94-4; 12, 78891-12-0; 13, 78891-13-1; 14 (isomer 1), 78962-97-7; 14 (isomer 2), 78962-98-8; 15 (isomer 1, 78891-14-2; 15 (isomer 2), 78962-99-9; 16a, 78891-15-3; 16b, 78891-16-4; 17a, 78891-17-5; 17b, 78963-00-5; 17c, 78963-01-6; 17d, 78963-02-7; 18a, 78963-03-8; 18b, 78963-04-9; 18c, 78963-05-0; 18d, 78963-06-1; 19, 70051-06-8; 20a, 78963-07-2; 20c, 78963-08-3; 21a, 78963-09-4; 21b, 78963-10-7; ethyl *C*-methylmalonate, 609-08-5; 2-bromopropene, 557-93-7.

(26) Attempts to separate **17c** and **17d** by preparative GLC were not successful. Therefore, the ratio indicated was based on the signal intensity in ^{13}C NMR spectrum.

(27) Attempts to separate **18c** and **18d** by preparative GLC were not successful. Therefore, the ratio indicated was based on the signal intensity in ^{13}C NMR spectrum.