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Stereochemical Studies of Monoterpene Compounds. XIII.[1] The Conformational Analysis of the Acetyl Group of 4-Methyl-10-nor-8-oxomenthols by Circular Dichroism

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The conformational analysis of the acetyl group of a stereoisomeric pair of 4-methyl-10-nor-8-oxomenthols was made by means of the temperature-dependent circular dichroism. (1R:3S:4R)-(+)-4-Methyl-10-nor-8-oxoneomenthol (**1**) exhibited a double-humped Cotton effect at a low temperature. This phenomenon seems to indicate the existence of a conformational equilibrium among **1b**, **1c**, and **1d**, but not **1a**. On the other hand (1R:3R:4R)-(−)-4-methyl-10-nor-8-oxomenthol (**3**) exhibited an inversion in the sign of the Cotton effect when the solvent and the temperature were changed. This phenomenon was interpreted in terms of the conformational equilibrium among **3a**, **3b**, and **3c**. These phenomena were interpreted in terms of the competition of the steric factor and the intramolecular hydrogen bonding.

The temperature-dependent circular dichroism (CD) has been found useful for investigating the rotational conformation of the 17-acetyl group of 20-ketosteroids.[2-4] We have previously studied[5] the rotational conformation of the acetyl group of an epimeric pair of 10-nor-8-oxomenthols. In order now to investigate the influence of the C-4 methyl group on the conformation of the acetyl group, the conformational analysis of (1R: 3S: 4R)-(+)-4-methyl-10-nor-8-oxoneomenthol (**1**), (1R: 3R: 4R)-(−)-4-methyl-10-nor-8-oxomenthol

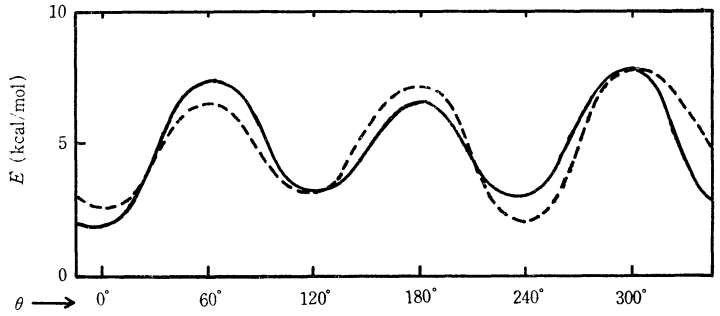
1) Paper XII of this series: T. Hitata and T. Suga, This Bulletin, under the contribution (71173).

2) G. Snatzke and E. Schwinum, *Tetrahedron*, **22**, 761 (1966).

3) K. M. Wellman and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 60 (1965).

4) G. Snatzke, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Heyden and Son Ltd., London (1967), p. 335.

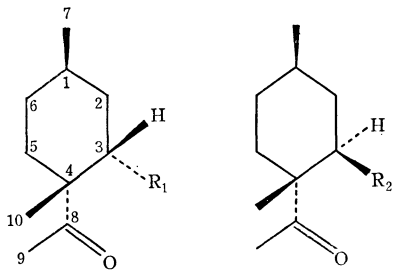
5) T. Suga, T. Shishibori, and T. Matsuura, This Bulletin, **41**, 1175 (1968).



Compd.	The sign of Cotton effect predicted											
1	±	+	+	+	+	+	−	−	−	−	−	−
3	+	+	+	+	+	±	−	−	−	−	−	+

Fig. 1. Conformational energy calculated for the rotational conformation of the acetyl group of the compounds **1** and **3** as a function of θ: - - - for **1** and —— for **3**, and the sign of the Cotton effect for each conformation.

(**3**), and their acetates, (**2**) and (**4**), was undertaken by means of the solvent- and temperature-dependent circular dichroisms.



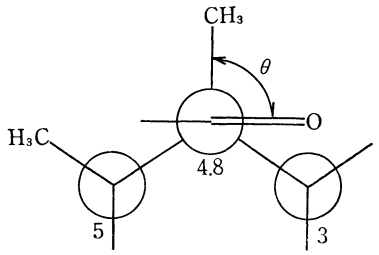
1: R_1=OH
2: R_1=OAc

3: R_2=OH
4: R_2=OAc

Results and Discussion

4-Methyl-10-nor-8-oxomenthols (**1**) and (**3**) were prepared from (1R : 3S : 4S)-(+)-4-methylneoisopulegol and (1R : 3R : 4S)-(−)-4-methylisopulegol respectively by ozonization. The configuration of the isopulegol derivatives was assigned according to Brewster's benzoate rule.[6] Thus, the configuration of the-4-methyl-10-nor-8-oxomenthols was determined to be as is shown by **1** and **3**.

Throughout the following discussion of the conformational analysis, the conformation of the C-4 acetyl group has been assumed to be equatorial for the following reasons: (a) the compounds, **1** and **3**, with equatorial acetyl group are energetically more stable by 0.5 and 2.0 kcal/mol respectively than the axial isomers on the basis of the $-\Delta G°$ value,[7] although the stabilization energy of the hydrogen bonding is not involved in this value. (b) The nuclear magnetic resonance spectra indicated the C-3 proton of compounds **1** and **3** in carbon tetrachloride to be equatorial and axial respectively. (c) The C-4 acetyl group of the acetates, **2** and **4**, was proved to be equatorial



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by studying the nuclear mangnetic resonance spectrum.

As is shown in Fig. 1, the conformational energy of the acetyl group of compounds **1** and **3** around the C(4)—C(8) bond was estimated by using the energy functions given for our previous calculation of 10-nor-8-oxomenthols,[5] where θ corresponds to a dihedral angle of the Newman projection (5). The sign of the Cotton effect shown was predicted by an examination of the model[8] for each conformer, according to the octant rule.[9] The conformers with θ=120, 240, or 360° may be preferred to both compounds, **1** and **3**. This is supported by the speculation[10,11] that the carbonyl group would eclipse the C–C bond in its equilibrium position. In the calculation of the energy, the energy function of the intramolecular hydrogen bonding between the hydroxyl and the carbonyl groups has not been considered. However, the energy of hydrogen bonding should affect the preference of the rotational conformation of the acetyl group. The **1b** and **3b** conformers may be stabilized by hydrogen bonding. However, if intramolecular hydrogen bonding is obstructed by such a factor as polar solvents, the electrostatic interaction between the hydroxyl lone-pair electrons and the carbonyl π and/or lone-pair electrons may destabilize the bonded conformers, (**1b**) and (**3b**). This would, then, cause the occurence

6) J. H. Brewster, *Tetrahedron*, **13**, 106 (1961); J. H. Brewster, *J. Amer. Chem. Soc.*, **81**, 5475, 5483, 5493 (1959).

7) N. L. Allinger and E. L. Eliel, "Topics in Stereochemistry, Vol. 1," Interscience Publishers, New York (1968), p. 199.

8) Examined by "Dreiding Stereomodels," W. Buchi Manufacture of Glass Apparatus Flwail, Switzerland.

9) W. Moffit, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961).

10) D. M. Piatak and E. Caspi, *Tetrahedron*, **24**, 2899 (1968).

11) A. A. Bother-By, C. Naar-Colin, and H. Günsther, *J. Amer. Chem. Soc.*, **84**, 2748 (1962).

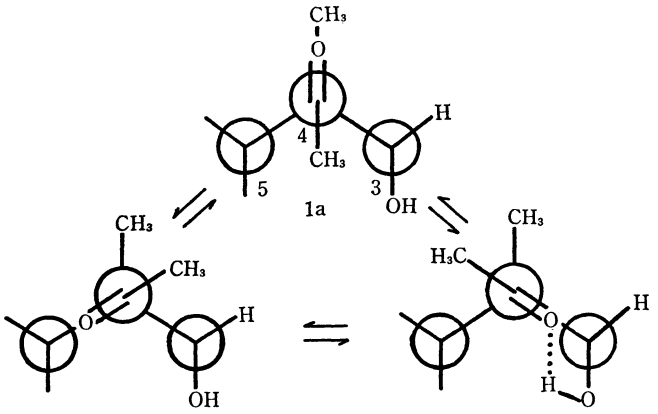


Chart 1. Possible preferred conformation of the acetyl group of (1R:3S:4R)-(+)-4-methyl-10-nor-8-oxoneomenthol (**1**) as viewed from C-8 to C-4.

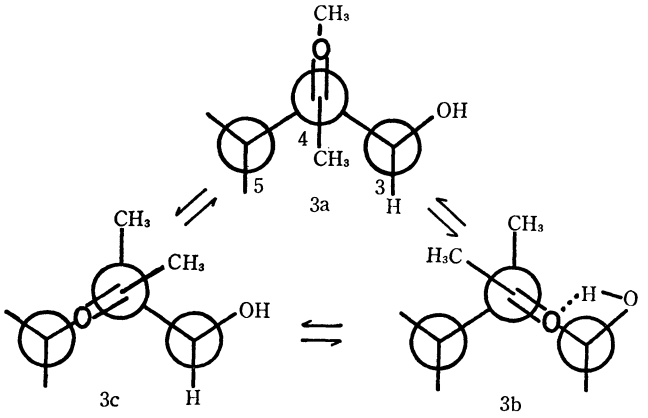
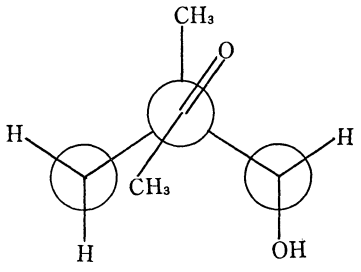


Chart 2. Possible preferred conformation of the acetyl group of (1R:3R:4R)-(−)-4-methyl-10-nor-8-oxomenthol (**3**) as viewed from C-8 to C-4.



of unstable conformers, (**1a**) and (**1c**), and (**3a**) and (**3c**). According to the octant rule,[9] the **1b**, **3a**, and **3b** conformers should exhibit a positive Cotton effect, while the (**1c**) and (**3c**) conformers should exhibit a negative one. On the other hand, the **1a** conformer may not show any Cotton effect at all.

(1R : 3S : 4R)-(+)-4-Methyl-10-nor-8-oxoneomenthol (1). The CD curves of the compound (**1**) showed a positive Cotton effect regardless of the solvent polarity (Fig. 2), although the maximum position and the molecular ellipticity exhibited a remarkable difference when the solvent was changed from a nonpolar to a polar one. The weak positive Cotton effect in the polar solvents may be attributable to the **1d** conformer rather than to **1a**, while the strong one in the nonpolar

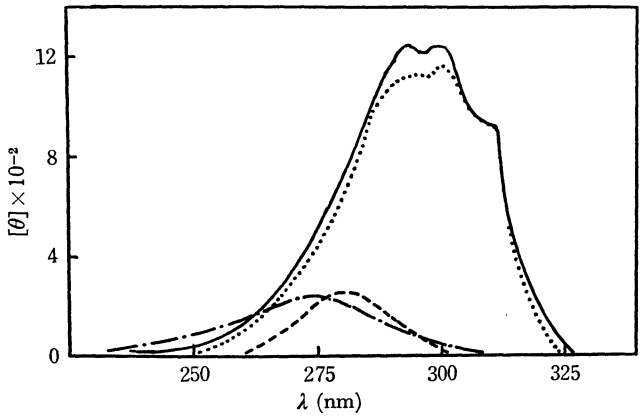


Fig. 2. CD curves of (1R:3S:4R)-(+)-4-methyl-10-nor-8-oxo-neomenthol (**1**) in selected solvents at +25°C: ····· in CCl_4, —— in isooctane, —·— in MeOH, and - - - in DMSO.

media may be attributable to the bonded conformer (**1b**). The attribution of this weak positive Cotton effect to the **1d** conformer in place of the **1a** conformer may here be justified by the apperance of the positively-rotating conformer (**1d**) as a result of the interaction between the hydroxyl and the methyl groups in the **1a** conformer. The intramolecularly-hydrogen-bonded conformer (**1b**) is preferred in the nonpolar solvents, whereas the nonbonded conformer (**1d**) is preferred in the polar ones. This was supported by the infrared spectrum in the carbon tetrachloride solution, which exhibited a free hydroxyl band at 3623 cm^{-1} (ε=28), along with two peaks, at 3580 (ε=32) and 3535 cm^{-1} (ε=20), due to the interacted hydroxyl group[12] between the π-electrons of the carbonyl and the hydroxyl groups and between the lone-pair electrons of the hydroxyl groups and the carbonyl oxygen respectively.

The variable-temperature CD curves of the compound (**1**) in EPA (Fig. 3) showed a double-humped Cotton effect at −192°C. The positions of the re-

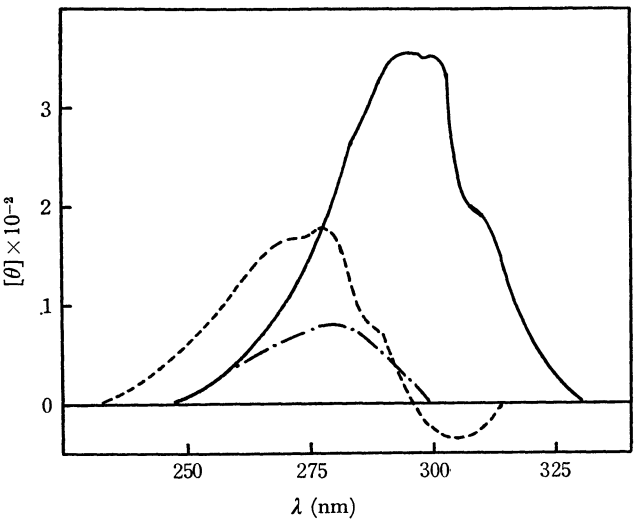


Fig. 3. CD curves of (1R:3S:4R)-(+)-4-methyl-10-nor-8-oxo-neomenthol (**1**) in EPA: —— at +25°C, —·— at −74°C, and ····· at −192°C.

12) T. Shishibori, *J. Sci. Hiroshima Univ., Ser. A-II*, **32**, 125 (1968).

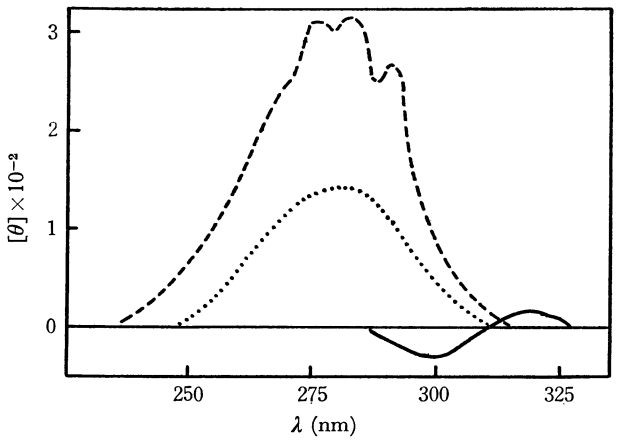


Fig. 4. CD curves of (1R:3S:4R)-(+)-4-methyl-10-nor-8-oxomenthyl acetate (**2**) in EPA: —— at +25°C, ····· at −127°C, and - - - at −190°C.

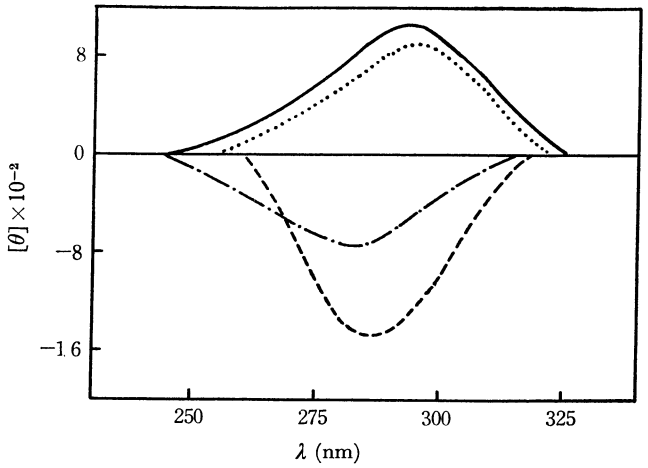
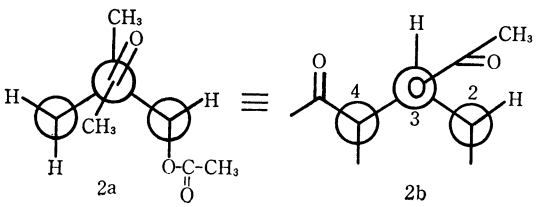


Fig. 5. CD curves of (1R:3R:4R)-(−)-4-methyl-10-nor-8-oxomenthol (**3**) in selected solvents at +25°C: ····· in CCl_4, —— in isooctane, —·— in MeOH, and - - - in DMSO.

spective extremes differ by nearly 25 nm. The positive maximum observed at the same position as in the case of other polar solvents at room temperature was attributed to the **1d** conformer, whereas the negative one was attributed the **1a** conformer. The strong positive maximum at 25°C contrasted with that at −192°C, showing the similarity to the position in the case of nonpolar solvents at 25°C, but the rotational strength was slightly weakened. This positive Cotton effect curve implied a preference for the **1b** conformer at 25°C in EPA. A similar phenomenon was also observed in the variable-temperature CD curves in the MI solvent. Consequently, these results, together with the conformational energy in Fig. 1, seem to indicate the existence of a conformational equilibrium among **1b**, **1c**, and **1d**. The positively-rotating hydrogen-bonded conformer (**1b**) is preferred at room temperature, whereas the nonbonded conformers (**1c**) and (**1d**) are preferred at low temperatures. On the other hand, the acetate (**2**) in EPA exhibited only the positive Cotton effect at −190°C (Fig. 4), in contrast with the parent compound (**1**) under the same conditions. The replacement of the hydroxyl group with the acetoxy one made the positively-rotating conformation (**2a**) preferred at low temperatures because of the increase in the electrostatic interaction between the acetoxy and the carbonyl groups. At low temperatures, the frozen staggerd conformation[3] (**2b**) may be considered to prescribe the orientation of the lone-pair electrons of this group. Accordingly, the **2a** conformation with about θ=0—30° would be preferred because of the strengthened interaction due to the orientation of the electrons.

(1R : 3R : 4R)-(−)-4-Methyl-10-nor-8-oxomenthol (3). The CD curves of the oxomenthol (**3**) exhibited a



positive Cotton effect in isooctane and carbon tetrachloride, and a negative one in methanol and dimethyl sulfoxide (Fig. 5). Such an inversion of the sign of the Cotton effect upon the change of the solvent can be ascribed to the conformational alteration of the acetyl group among **3a**, **3b**, and **3c**. For the compound **3**, the **3a** conformer with θ=0° may be expected because of the absence of the steric interaction between the methyl (of the acetyl group) and the hydroxyl groups; this is in contrast with the **1a** conformer to be expected for the compound **1**. In a nonpolar medium at a room temperature, the positively-rotating conformer (**3b**) with θ=120° is implied to be dominant because of the stabilizing intramolecular hydrogen bonding. This is further supported by the infrared spectrum, which exhibited a weak free hydroxyl band at 3620cm^{-1} (ε=21), along with two peaks at 3575 (ε=35) and 3530 cm^{-1} (ε=20) due to the intramolecularly-interacting hydroxyl group between π-electrons of the carbonyl and the hydroxyl groups and between lone-pair electrons of the hydroxyl group and the carbonyl oxygen respectively. In polar solvents at room temperature, the negatively-rotating conformer (**3c**) with θ=240° is interpreted as preferred becasue of the losses of the stabilization energy due to hydrogen bonding and, consequently, because of the destabilizing electrostatic repulsion between the carbonyl and the hydroxyl groups. This idea is supported by the solvent- and temperature-dependent CD curves of the acetate (**4**), which inherently possesses no ability of intramolecular hydrogen bonding but which does possess the ability to have an electrostatic repulsion between the carbonyl and the acetoxy groups. The CD curves of the acetate exhibited only a negative Cotton effect in both nonpolar and polar solvents. The rotational strength of the Cotton effect increased exceedingly in proportion as the temperature was lowered from −74 to −190°C in EPA. Accordingly, the acetate (**4**) exists predominantly in a negatively-rotating and energetically-favorable conformation, with θ=about 240°.

The CD curves of the compound (**3**) in EPA at low temperatures (at −74 and −180°C) exhibited a

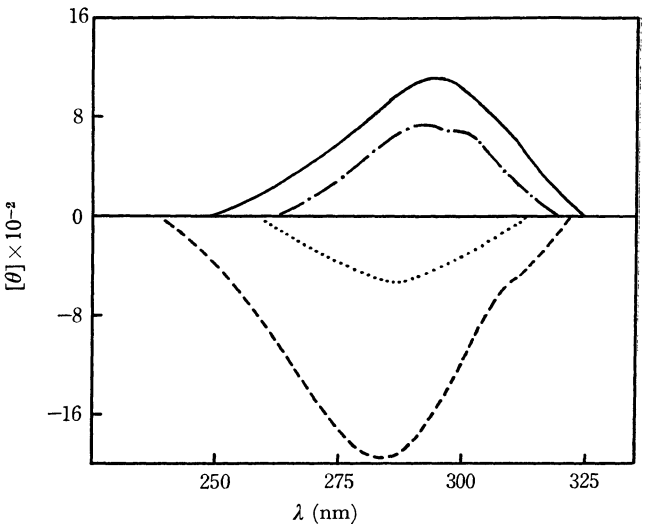


Fig. 6. CD curves of (1R:3S:4R)-(−)-4-methyl-10-nor-8-oxomenthol (**3**) in MI: —— at +25°C, −·− at −74°C, ····· at −127°C, and − − − at −186°C.

strong negative Cotton effect, in contrast with the curve at 25°C, whereas the curves in MI showed a positive Cotton effect at 25 and −74°C and a negative one at lower temperatures, as is shown in Fig. 6. This inversion in the sign of the Cotton effect with the change in the temperature is very similar to the phenomenon observed upon changing the solvent. The inversion of the sign was interpreted as an indication of the increase in the nonbonded conformer at the sacrifice of the bonded conformer with a lowering of the temperature. Thus, at lower temperatures in both polar and nonpolar media, the **3c** conformer, with $\theta=240°$, should be preferred. Our interpretation of such phenomena of the compound (**3**) can be understood after due consideration of the explanation given of the CD curve of 2-oxo-1-*p*-menthanol,[13] which exhibits such an inversion of the sign from a positive Cotton effect to a negative one at lower temperatures. The decrease in the rotational strength for the positive CD curves of the compound (**3**) in decalin at both higher and lower temperatures suggested also that the hydrogen-bonded conformer (**3b**) would be diminished with an increase in the population of the nonbonded conformers by being kept out of room temperature.

Thus, it was concluded that the presence of the C-4 methyl group remarkably alters the conformational preference of the acetyl side-chain of 4-methyl-10-nor-8-oxomenthols in comparison with that of 10-nor-8-oxomenthols.[5] The presence of the C-4 methyl group decreases the population of the conformer when $\theta=180°$, whereas the absence of this group increases the conformer when $\theta=150$—$210°$. These results were very consistent with a prediction judging from the calculated energy function.

Experimental

Measurements. The CD curves were measured on a Japan Spectroscopic Co., Ltd., automatically-recording spectropolarimeter, Model ORD/UV-5, equipped with a circular dichroism attachment. The low- and high-temperature CD curves were obtained by the use of the same spectrometer, using low- and high-temperature CD cells designed and constructed by the present authors. The EPA solvent was composed of ether-isopentane-ethanol in the ratio of 5:5:2 by volume. The MI solvent was composed of methylcyclohexane-isopentane in the ratio of 1:3 by volume.

The IR spectra in the hydroxyl-stretching region were measured with a Perkin-Elmer Model 621 Grating Infrared spectrometer at 25°C. A sodium chloride absorption cell (10 mm long) was used; the concentration of the solution was 0.005 mol/*l*.

(1R: 3S: 4S)-(+)-4-Methylneoisopulegol and (1R: 3R: 4S)-(−)-4-Methylisopulegol. (−)-Methylisopulegone (bp 69—70°C/8 mmHg; n_D^{25} 1.4682; d_4^{25} 0.9231; $[\alpha]_D^{25}-139.18°$ (neat); the semicarbazone derivative, mp 201—202°C) was synthesized by the methylation of (+)-pulegone (81—82°C/5 mmHg; n_D^{25} 1.4843; d_4^{25} 0.9303; $[\alpha]_D^{25}+23°$ (neat)) following the method in the literature,[14] and then it was reduced with lithium alminum hydride in dry ether to two isomeric alcohols. The configuration of the alcohols was identified as (1R: 3S: 4S)-(+)-4-methyl-neoisopulegol, 62.0—63.0°C/3 mmHg; n_D^{25} 1.4735; d_4^{25} 0.9204; $[\alpha]_D^{25}+54.32°$ (neat); the 3,5-dinitrobenzoate derivative, mp 142—143°C, $[\alpha]_D^{25}+59.24°$ (*c* 0.00211, $CHCl_3$), and (1R: 3R: 4S)-(−)-4-methylisopulegol, 63.0—64.5°C/3 mmHg; n_D^{25} 1.4776; d_4^{25} 0.9192; $[\alpha]_D^{25}-1.67°$ (neat); the 3,5-dinitrobenzoate derivative, mp 107°C, $[\alpha]_D^{25}-29.66°$ (*c* 0.00236, $CHCl_3$), by applying Brewster's benzoate rule.

(1R: 3S: 4R)-(+)-4-Methyl-10-nor-8-oxoneomenthol (1). The ozonization of (1R: 3S: 4S)-(+)-4-methyl-neoisopulegol gave (1R: 3S: 4R)-(+)-4-methyl-10-nor-8-oxoneomenthol (**1**): mp 69.5°C; $[\alpha]_D^{25}+57.46°$ (*c* 0.1514, MeOH); NMR ($CDCl_3$), >CH–C<u>H</u>$_3$ 0.92 ppm (doublet, $J=6.0$ Hz, 3H), –C–CH_3 1.15 (singlet, 3H), O=C–CH_3 2.15 (singlet, 3H), >C<u>H</u>–OH 4.0 (broad singlet, 1H), >CH–O<u>H</u> 2.79 (broad singlet, 1H); ν_{max}^{Nujol} 3503 cm^{-1} (OH), 1690 (C=O), 1352 (–$COCH_3$); λ_{max}^{MeOH} 282 nm ($\varepsilon=30.32$), $\lambda_{max}^{isooctane}$ 288 (32.94); mass spectrum, *m/e* 170 (M^+); CD (max) in decalin (*c* 0.154): $[\theta]_{295}^{+150°}$ +549, $[\theta]_{292}^{+74°}$ +922, $[\theta]_{301}^{+25°}$ +922, $[\theta]_{293}^{+25°}$ +1093, $[\theta]_{300}^{+25°}$ +1111, $[\theta]_{293}^{-74°}$ +634, $[\theta]_{301}^{-74°}$ +617, $[\theta]_{324}^{-74°}$ −137, MI (*c* 0.15): $[\theta]_{293}^{+25°}$ +1350, $[\theta]_{301}^{+25°}$ +1350, $[\theta]_{295}^{-74°}$ +901, $[\theta]_{300}^{-74°}$ +801, $[\theta]_{270}^{-192°}$ +313, $[\theta]_{297}^{-192°}$ −128.

The acetate (2): The acetylation of (**1**) with acetic anhydride in the presence of pyridine afforded the acetate (**2**): mp 60.5°C; $[\alpha]_D^{25}+66.96°$ (*c* 0.134, MeOH); NMR (CCl_4) >CH–C<u>H</u>$_3$ 0.89 ppm (doublet, $J=5.5$ Hz, 3H), –$\underset{|}{C}$–CH_3 1.09 (singlet, 3H), O=$\underset{|}{C}$–CH_3 1.92 and 1.96 (each singlet, 6H), >CH–O– 5.09 (singlet, 1H); ν_{max}^{Nujol} 1730, 1374 cm^{-1} (acetate), 1708 (C=O), 1350 (methyl ketone); λ_{max}^{MeOH} 280 nm ($\varepsilon=31.55$), $\lambda_{max}^{isooctane}$ 281 (31.29); CD (max) in CCl_4 (*c* 0.4362): $[\theta]_{292}^{+25°}$ −92, in MeOH (*c* 0.4544): $[\theta]_{282}^{+25°}$ −20, $[\theta]_{315}^{+25°}$ +22, in isooctane (*c* 0.4018): $[\theta]_{300}^{+25°}$ −48.

(1R: 3R: 4R)-(−)-4-Methyl-10-nor-8-oxomenthol (3). The ozonization of (1R: 3R: 4S)-(−)-4-methylisopulegol gave (1R: 3R: 4R)-(−)-4-methyl-10-nor-8-oxomenthol (**3**): bp 83.0°C/0.5 mmHg; $[\alpha]_D^{25}-30.77°$ (*c* 0.156, MeOH); n_D^{25} 1.4682; NMR ($CDCl_3$) >CH–C<u>H</u>$_3$ 0.94 ppm (doublet, $J=5.5$ Hz, 3H), –$\underset{|}{C}$–CH_3 1.16 (singlet, 3H), O=$\underset{|}{C}$–CH_3 2.16 (singlet, 3H), >C<u>H</u>–OH 3.98 (double doublet, $J_{vic}=3.0$ and 11.0 Hz, 1H), –CH–O<u>H</u> 2.90 (singlet, 1H); $\nu_{max}^{liq.}$ 3490 cm^{-1} (OH), 1690 (C=O), 1350 (–$COCH_3$); λ_{max}^{MeOH} 284 nm ($\varepsilon=27.35$), $\lambda_{max}^{isooctane}$ 287 (25.54); mass spectrum, *m/e* 170 (M^+);

13) K. M. Wellman, W. S. Briggs, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 73 (1965).

12) M. V. Kulkarni, E. V. Kulkarni, E. J. Eisenbraun, and M. M. Marsh, *J. Org. Chem.*, **33**, 1661 (1967).

CD (max) in EPA (c 0.143): $[\theta]^{+25°}_{280}$ −667, $[\theta]^{-74°}_{260}$ −1687, $[\theta]^{-186°}_{280}$ −1820, $[\theta]^{-186°}_{287}$ −2040, in decalin (c 0.164): $[\theta]^{+155°}_{295}$ +726, $[\theta]^{+25°}_{293}$ +1026, $[\theta]^{-74°}_{292}$ +644, $[\theta]^{-74°}_{300}$ +596.

The Acetate (4). The acetylation of (**3**) in the same manner as above gave the acetate (**4**): mp 35°C; $[\alpha]^{25}_{D}$ −27.54° (c 0.138, MeOH); NMR (CCl_4), >CH–C$\underline{H}_3$ 0.96 ppm (doublet, J=5.5 Hz, 3H), –$\overset{|}{\underset{|}{C}}$–$CH_3$ 1.13 (singlet, 3H), O=$\overset{|}{C}$–CH_3 1.90 and 2.03 (each singlet, 6H), >CH–O– 5.08 (double doublet, J_{vic}=3.0 and 11.0 Hz, 1H); ν^{Nujol}_{max} 1730, 1375 cm^{-1} (acetate), 1698 (C=O), 1367 (methyl ketone); λ^{MeOH}_{max} 285 nm (ε=33.27), $\lambda^{isooctane}_{max}$ 285 (29.71); CD (max) in CCl_4 (c 0.13): $[\theta]^{+25°}_{290}$ −585, in isooctane (c 0.132): $[\theta]^{+25°}_{290}$ −606, in dioxane (c 0.133): $[\theta]^{+25°}_{292}$ −333, in EPA (c 0.114): $[\theta]^{+25°}_{290}$ −67, $[\theta]^{-74°}_{290}$ −87, $[\theta]^{-190°}_{292}$ −1996, $[\theta]^{-190°}_{302}$ −1641, $[\theta]^{-190°}_{312}$ −710.

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