Stereochemical Studies of Monoterpene Compounds. IX.[1] Pinacol-Type Rearrangements of α-Pineneglycol Tosylate[2]

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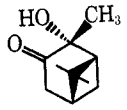
Treatment of (−)-*cis*-α-pineneglycol monotosylate (**4**) with methanolic potassium hydroxide yielded (+)-2α-acetyl-5,5-dimethylbicyclo[2.1.1]hexane (**5**), (+)-3β-methylnopinone (**6**), (−)-pinocamphone (**7**), and (−)-*cis*-α-pineneglycol (**2**). The formation of ketone **5** is a unique example of the ring contraction of a bicyclo[3.1.1]-heptane skeleton to the highly strained bicyclo[2.1.1]hexane system by a pinacol-type rearrangement. The reaction mechanism is discussed from a stereochemical viewpoint. A preferred conformation for **4**, **5**, and **6** (**4a**, **5a**, and **6a**, respectively) is also proposed.

We have previously discussed[4,5] the stereochemistry of (+)-2-hydroxypinocamphone (**1**) and its reduction products **2** and **3**. In order to obtain more chemical evidence for establishing the stereochemistry of **1**, α-pineneglycol monotosylate (**4**) derived from **2** was treated with methanolic potassium hydroxide. We wish to discuss the stereochemical and mechanistic implications of the reaction as well as the stereochemistry of the monotosylate **4** and the reaction products **5** and **6**.

Results and Discussion

Treatment of (−)-*cis*-α-pineneglycol monotosylate (**4**) with potassium hydroxide in methanol yielded an oily reaction mixture, which was composed of (+)-2α-acetyl-5,5-dimethylbicyclo[2.1.1]hexane (**5**) (50% yield), (−)-*cis*-α-pineneglycol (**2**) (26%), (+)-3β-methylnopinone (**6**) (8.5%), and (−)-pinocamphone



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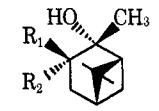
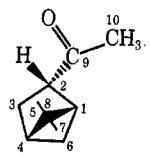


2, $R_1 = H; R_2 = OH$
3, $R_1 = OH; R_2 = H$
4, $R_1 = H; R_2 = OTs$



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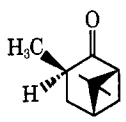

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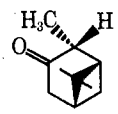

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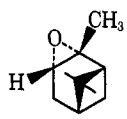
(**7**) (5.6%). These compounds were identified by a combination of spectroscopic and chemical methods.[6] The structure of ketone **5** was further confirmed by its conversion to 5,5-dimethylbicyclo[2.1.1]hexan-2-one (**9**) *via* 5,5-dimethylbicyclo[2.1.1]hexane-2α-carboxylic acid (**8**).

8, $R_1 = COOH; R_2 = H$
9, $R_1, R_2 = O$



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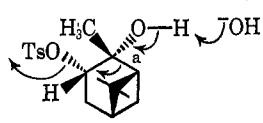
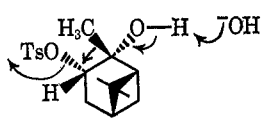
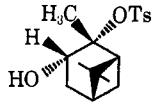
Reaction Mechanism.—Treatment of *cis*-α-pineneglycol (**2**) and 2α,3α-epoxypinane (**11**) with methanolic potassium hydroxide resulted in recovery of starting material. Accordingly, neither **2** nor **11** is an intermediate in the formation of ketones **5**, **6**, and **7** from the tosylate **4**. Glycol **2** is clearly the hydrolyzed product of **4**. Thus, the formation of **5**, **6**, and **7** is best explained by pinacol-type rearrangements as shown below. The driving force for the rearrangements is the base-catalyzed elimination of the tosyloxy group of **4**; concerted migration of bond a then gives ketone **5** (eq 1). On the other hand, migration of the C-2 methyl group instead of bond a forms ketone **6** (eq 2). The formation of **7** from **4** is difficult to explain because it seems quite improbable that the hydroxyl group would ionize to the extent of 5.6% in the presence of a leaving group as good as the tosyloxy group. The admixture of the isomeric monotosylate **12** in **4**, in amounts small enough



4 → **5** (1)



4 → **6** (2)



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to escape detection by nmr analysis is a possible explanation. This isomer would be expected to give **7** readily by the elimination of the tosyloxy group, followed by concerted migration of the C-3 proton.

Stereochemistry of the Reaction and the Reaction Products.—If the reactive conformation of *cis*-α-

(1) Paper VIII of this series: T. Hirata, T. Suga, and T. Matsuura, *Bull. Chem. Soc. Jap.*, **43**, 2588 (1970).

(2) A part of this paper has been reported in the form of a communication in *Tetrahedron Lett.*, 5553 (1968).

(3) To whom all inquiries regarding this paper should be addressed.

(4) T. Suga, T. Shishibori, T. Hirata, and T. Matsuura, *Bull. Chem. Soc. Jap.*, **41**, 1180 (1968).

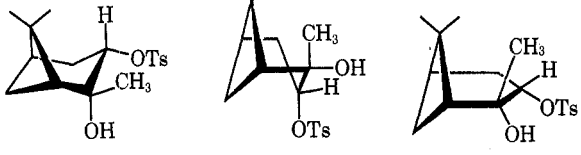
(5) R. G. Carlson, J. K. Pierce, T. Suga, T. Hirata, T. Shishibori, and T. Matsuura, *Tetrahedron Lett.*, 5941 (1968).

(6) The ir spectra of **5** and **9**, and of the 2,4-dinitrophenylhydrazone of **9**, were generously donated by J. Meinwald,[7] ketone **6** was obtained from E. Klein,[8] and pinocamphone (**7**) was prepared in our laboratory.[4]

(7) J. Meinwald and P. G. Gassman, *J. Amer. Chem. Soc.*, **82**, 5445 (1960).

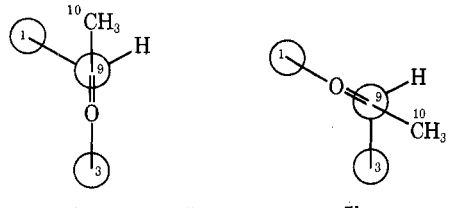
(8) E. Klein and W. Rojahn, *Chem. Ber.*, **100**, 1902 (1967).

pineneglycol monotosylate (4) is assumed to be **4a**, the ring-contracted ketone **5** would be expected to form readily, because the migrating moiety would be anti-coplanar to the leaving group. If the tosylate **4** is in conformation **4b**, ketone **6** would be expected to be formed as the main product, because the anti-coplanar migrating group is the methyl group. On the other hand, if the reactive conformation is **4c**, ketones **5** and **6** would be expected to be formed in equal amounts, because both migrating moieties are in equal surroundings with respect to the leaving group. Ketones **5** and **6** were produced in the ratio of 50 to 8.5. Hence it is proposed that the preferred reactive conformation of *cis*-α-pineneglycol monotosylate (4) is **4a**. Accordingly, both C-2 and C-3 hydroxyl groups of the starting glycol **2** are trans to the *gem*-dimethyl group.

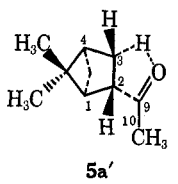


4a **4b** **4c**

We now wish to deal with the conformation of the acetyl group of ketone **5**. Ketone **5** can exist in either of the preferred conformations **5a** and **5b**. According to the octant rule,[9] the Cotton effect should be positive for **5a** and negative for **5b**. The optical rotatory dispersion (ORD) and circular dichroism (CD) curves of ketone **5** showed a positive Cotton effect both in methanol and in isooctane at room temperature. Variable-temperature CD curves in an EPA solvent[10] and in decalin indicated that the positively rotating conformer **5a** is more favored at low temperature and that the amount of the negatively rotating conformer **5b** increases slightly at high temperature, as shown in Figure 1. In addition, the $C_{3\alpha}$ proton is shifted to lower field (δ 2.84 ppm) by the anisotropy of the carbonyl group (*cf.* **5a'**) in the nmr spectrum, because a weak intramolecular interaction as shown in **5a'** may exist in conformer **5a** but not in **5b**. These facts indicate the preferred conformation of ketone **5** to be **5a**.



5a **5b**



5a'

The configuration of the C-3 carbon of dextrorotatory 3β-methylnopinone (6) has been assigned[8] as R. The nmr spectrum of the C-3 methyl group showed a small upfield shift ($\Delta\delta_{CDCl_3-C_6H_6}$ = +0.03 ppm) by benzene, and the conformation of the C-3 methyl group of **6** should be equatorial.[11] The preferred conformation of (+)-**6** is therefore **6a**.

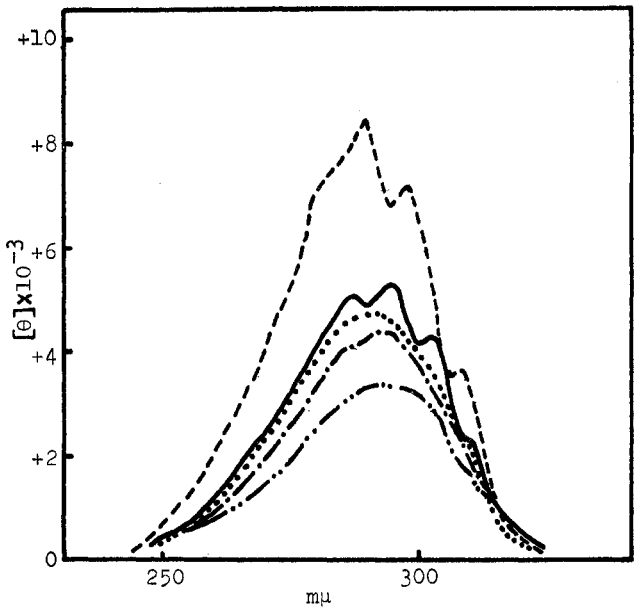
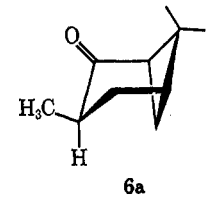


Figure 1.—CD curves of ketone **5** in an EPA solvent at −192° (------), and +19° (· · · · ·) and in decalin at −74° (———), +21° (— · —), and +133° (— · · —).



6a

Experimental Section[12]

***cis*-α-Pineneglycol Monotosylate** (4).—A mixture of 2.2 g of (−)-*cis*-α-pineneglycol (2) {$[\alpha]^{25}D$ −0.89° (*c* 7.91, chloroform), derived from (+)-2-hydroxypinocamphone[4]}, 2.7 g of *p*-toluenesulfonyl chloride, and 20 ml of pyridine was left to stand at room temperature for 3 days. The whole reaction mixture was poured into ice water to yield 3.4 g of a crude crystalline mass, which was recrystallized from a mixture of *n*-hexane and ethyl acetate and furnished 3.0 g of *cis*-α-pineneglycol monotosylate (4): mp 76–77°; $[\alpha]^{25}D$ −4.4° (*c* 2.6, MeOH); ir (KBr disk) 3536 (OH), 1593 cm^{-1} (C=C).

Anal. Calcd for $C_{17}H_{24}O_4S$: C, 62.94; H, 7.46. Found: C, 62.95; H, 7.75.

Rearrangement of *cis*-α-Pineneglycol Monotosylate (4).—To a solution of 7.0 g of potassium hydroxide in 20 ml of methanol was added 6.2 g of **4**. The solution was heated to 65° for 3 hr and then kept at room temperature overnight. The reaction mixture was diluted with 500 ml of water and extracted with ether. Removal of the solvent from the ether layer yielded 2.5 g of an oily product which was chromatographed on a silica gel column with a mixture of ethyl acetate and *n*-hexane to separate four fractions: fraction 1, 0.29 g; fraction 2, 0.85 g; fraction 3, 0.32 g; fraction 4, 0.55 g.

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

(10) EPA solvent is composed of ether–isopentane–ethanol in the ratio of 5:5:2 by volume.

(11) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965, p 163.

(12) The ORD and CD spectra were measured at 25° with a Japan Spectroscopic Co., Ltd., Model ORD/UV-5 spectropolarimeter, equipped with a circular dichroism attachment. The nmr spectra were recorded with a Varian Associates HA-100, high-resolution spectrometer using tetramethylsilane as an internal standard. Microanalysis was done at the Microanalytical Center in the Faculty of Pharmacy of Kyoto University. The mass spectral analysis was performed on a Hitachi mass spectrometer, Model RMU-D, ionizing at the order of 70 eV.

Fraction 2 was proved to be 2α-acetyl-5,5-dimethylbicyclo[2.1.1]hexane (**5**), which was identified by comparing its infrared spectrum with that of an authentic sample[6] and by its conversion to **8** and **9** as described below. Fraction 4 was identified as (−)-*cis*-α-pineneglycol (**2**), mp 55–56°. Fraction 1 was further subjected to preparative gas chromatography. This resulted in separation of 0.11 g of (+)-3β-methylnopinone (**6**) and 0.04 g of ketone **5**. Fraction 3 consisted of **5** and two components, which were further subjected to preparative gas chromatography. This resulted in isolation of (−)-pinocamphone (**7**), $[\alpha]^{25}D$ −15.2° (*c* 0.42, MeOH).

The physical properties of **5** are given as follows: $[\alpha]^{25}D$ +16.0° (*c* 0.86, MeOH); ir (liquid film) 1357 ($-COCH_3$), 1710 (C=O), 1369 and 1386 cm^{-1} (gem-CH_3); uv (MeOH) 280 mμ (ε 35.2); ORD $[\phi]_{400}^{methanol}$ +1650, $[\phi]_{304}$ +1870, $[\phi]_{263}$ −2390, $[\phi]_{230}$ −1730°; ORD $[\phi]_{400}^{isooctane}$ +204, $[\phi]_{316}$ +1970, $[\phi]_{311}$ +1840, $[\phi]_{307}$ +1940, $[\phi]_{268}$ −2450, $[\phi]_{225}$ −1700°; CD $[\theta]_{320}^{methanol}$ 0, $[\theta]_{286}$ +2310, $[\theta]_{235}$ 0°; CD $[\theta]_{325}^{isooctane}$ 0, $[\theta]_{294}$ +2610, $[\theta]_{230}$ 0°; nmr (CCl_4) δ 0.81 (s, C_8 3 H), 1.27 (s, C_7 3 H), 2.09 (s, OAc), and 2.84 (m, $C_{3\alpha}$ H); mass spectrum (70 eV) *m/e* (rel intensity) 152 (8, M^+), 137 (10), 109 (84), 67 (60), 43 (100).

The 2,4-dinitrophenylhydrazone of **5** showed the following properties: mp 113.0–113.5° (from MeOH); uv (MeOH) 364 mμ (ε 9500), 264 (4200), and 228 (6850).

Anal. Calcd for $C_{16}H_{20}O_4N_4$: H, 6.07; C, 57.82; N, 16.86. Found: H, 6.15; C, 58.09; N, 16.86.

The physical properties of **6** are $[\alpha]^{25}D$ +59.7° (*c* 0.64, MeOH); ir (liquid film) 1710 (C=O), 1376 and 1391 cm^{-1} (gem-CH_3); ORD $[\phi]_{400}^{methanol}$ +380, $[\phi]_{301}$ +3550, $[\phi]_{265}$ −3380, $[\phi]_{230}$ −1080°; ORD $[\phi]_{400}^{isooctane}$ +157, $[\phi]_{304}$ +1490, $[\phi]_{268}$ −1530, $[\phi]_{230}$ −315°; CD $[\theta]_{317}^{methano}$ 0, $[\theta]_{285}$ +2740, $[\theta]_{240}$ 0°; CD $[\theta]_{322}^{isooctane}$ 0, $[\theta]_{290}$ +1240, $[\theta]_{238}$ 0°. The nmr signals of the methyl protons appeared at δ 1.35 (s, C_8 3 H), 0.73 (s, C_9 3 H), and 1.17 (d, J = 7.0 Hz, C_{10} 3 H) in 10% deuteriochloroform solution, and δ 1.00 (s, C_8 3 H), 0.57 (s, C_9 3 H) and 1.14 (d, J = 7.0 Hz, C_{10} 3 H) in 10% benzene solution.

5,5-Dimethylbicyclo[2.1.1]hexane-2α-carboxylic Acid (8).—To a sodium hypobromite solution prepared from 1.20 g of sodium hydroxide, 0.5 ml of bromine, and 20 ml of water was added 0.30 g of **5**. The reaction mixture was stirred at room temperature for 3 hr. The usual work-up yielded 0.11 g of acid **8**: mp 54–55° (lit.[7] mp 55.0–55.5°); ir (KBr disk) 1693 cm^{-1} (C=O).

5,5-Dimethylbicyclo[2.1.1]hexan-2-one (9).—Following the literature method,[7] the permanganate oxidation of 0.34 g of the acid **8** afforded 0.12 g of **9**: ir (liquid film) 1750 cm^{-1} (C=O); 2,4-dinitrophenylhydrazone, mp and mmp 155.5–156.0° (lit.[7] mp 155.5–156.0°).

Registry No.—**2**, 27040-84-2; **4**, 22339-18-0; **5**, 22339-19-1; **5** 2,4-DNP, 27040-87-5; **6**, 27040-88-6; **7**, 22339-21-5; **8**, 27040-90-0; **9**, 22339-20-4.

Acknowledgment.—The authors wish to express their gratitude to Professor J. Meinwald of Cornell University for a gift of the 2,4-dinitrophenylhydrazone of ketone **9** and the ir spectra of **5** and **9**, to Dr. E. Klein of Dragoco Co. for a gift of ketone **6** and its 2,4-dinitrophenylhydrazone, and to Dr. E. von Rudollof of the National Research Council of Canada for measuring the nmr spectra on a Varian Associates, HA-100, spectrometer.

The Synthesis of the (3*S*)-Methylcyclopentane-1,2-dicarboxylic Acids (Nepetic Acids Related to the Nepetalactones)[1a]

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The synthesis of the (3*S*)-methylcyclopentane-1,2-dicarboxylic acids [(+)-**3a**, (−)-**3c**, (+)-**3e**, and (+)-**3g**] related to the nepetalactones (**1a** and **1b**) is described. This synthesis starts with (−)-(3*S*)-methylcyclohexanone (**4**) and employs a Favorskii-type rearrangement of γ-bromo β-oxo esters. Also studied was the resolution of intermediates in this synthesis through use of optically active derivatives. This latter technique provides predominately the trans 3*R* or 3*S* nepetic acids and was studied mainly in the more abundant 3*R* series.

Our synthesis of the four (3*R*)-methylcyclopentane-1,2-dicarboxylic acids[2] and their racemic counterparts could not immediately be extended to the 3*S* series since (−)-(3*S*)-methylcyclohexanone (**4**) was not available. These 3*S* acids[3a] [(+)-*t*-3-methyl-*r*-1,*c*-2-cyclopentanedicarboxylic acid (**3a**), (−)-*c*-3-methyl-*r*-1,*t*-2-cyclopentanedicarboxylic acid (**3c**), and (+)-*t*-3-methyl-*r*-1,*t*-2-cyclopentanedicarboxylic acid (**3g**)], except for (+)-*c*-3-methyl-*r*-1,*c*-2-cyclopentanedicarboxylic acid (**3e**), are known as nepetic acids. Their chemical correlation [except (+)-**3e**] with the nepetalactones (**1a** and **1b**)[3a] has been accomplished as shown in Scheme I, and consequently their absolute configurations and stereochemistry are known.[3b-e] It should be noted that the reference position for cis and trans designations of the nepetic acids and the corresponding diols is the carboxyl group or the hydroxymethyl group at the ultimate position from the methyl group.[3a] The rapid expansion of the methylcyclopentane monoterpenoids to many new structural types and their role in biosynthesis place an increased emphasis on the importance of these acids in structure elucidation as well as their absolute configuration and stereochemical assignments.[2,4]

Although the resolution[5a,b] of (±)-**4** to (−)-**4** and its use in the synthesis shown in Scheme II became the suc-

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(1) (a) E. J. Eisenbraun, G. H. Adolphen, K. S. Schorno, and R. N. Morris, presented at the 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 22–27, 1970; (b) Research Associate, 1967–1969; (c) Graduate Research Assistant, 1965–1967; (d) National Science Foundation Graduate Trainee, 1969–1970.

(2) E. J. Eisenbraun, P. G. Hanel, K. S. Schorno, F. Dilgen, and J. Osiecki, *J. Org. Chem.*, **32**, 3010 (1967).

(3) (a) We thank Dr. K. L. Loening for kindly advising us about the systematic nomenclature for this paper and supplying the names for **1a** and **1b** as (4a*S*,7*S*,7a*R*)-5,6,7,7a-tetrahydro-4,7-dimethylcyclopenta[*c*]pyran-1(4a*H*)-one and (4a*S*,7*S*,7a*S*)-5,6,7,7a-tetrahydro-4,7-dimethylcyclopenta-[*c*]pyran-1(4a*H*)-one, respectively; *cf.* "International Union of Pure and Applied Chemistry," *J. Org. Chem.*, **35**, 2849 (1970); (b) E. J. Eisenbraun and S. M. McElvain, *J. Amer. Chem. Soc.*, **77**, 3383 (1955); (c) S. M. McElvain and E. J. Eisenbraun, *ibid.*, **77**, 1599 (1955); (d) R. B. Bates, E. J. Eisenbraun, and S. M. McElvain, *ibid.*, **80**, 3413 (1958); (e) *ibid.*, **80**, 3420 (1958).

(4) (a) W. I. Taylor and A. R. Battersby, Ed., "Cyclopentanoid Terpene Derivatives," Marcel Dekker, New York, N. Y., 1969; (b) A. G. Horodysky, G. R. Waller, and E. J. Eisenbraun, *J. Biol. Chem.*, **244**, 3110 (1969).

(5) (a) R. Adams and J. D. Garber, *J. Amer. Chem. Soc.*, **71**, 522 (1949); (b) G. Adolphen, E. J. Eisenbraun, G. W. Keen, and P. W. K. Flanagan, *Org. Prep. Proced.*, **2**, 93 (1970); (c) A. W. Ingersoll, *Org. React.*, **2**, 376 (1944).