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.

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

E. J. EISENBRAUN,* G. H. ADOLPHEN,[1b] K. S. SCHORNO,[1c] AND R. N. MORRIS[1d]

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74074

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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-

* To whom correspondence should be addressed.

(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.

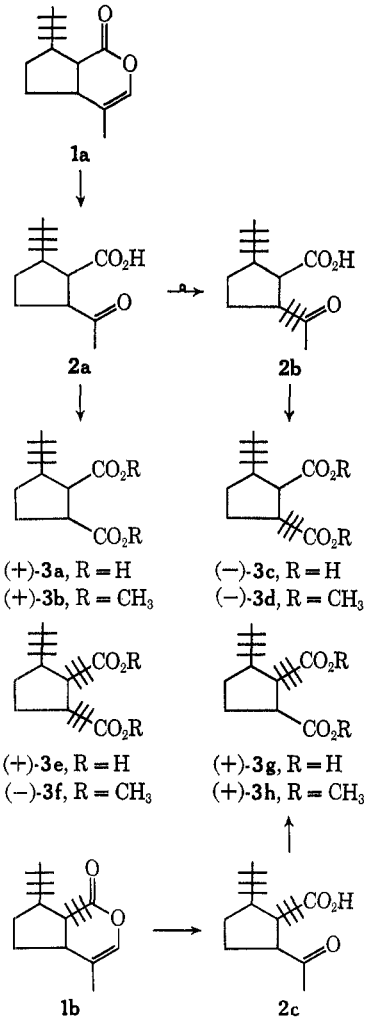
(2) E. J. Eisenbraun, P. G. Hanel, K. S. Schorno, F. Dilgen, and J. Osiecki, *J. Org. Chem.*, **32**, 3010 (1967).

(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).

Scheme I

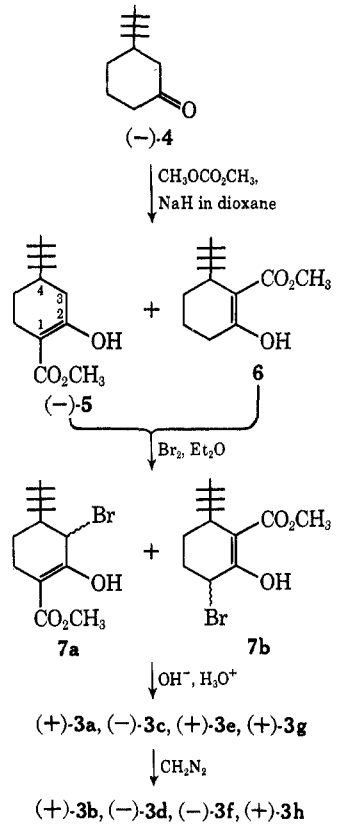


cessful route to the optically active acids and esters (**3a–h**), we first attempted their synthesis by converting[6] (±)-**5** to the optically active menthyl β-oxo esters shown in Scheme III. Two of the latter were crystalline [(+)-**9a** and (−)-**9a**] and hence permitted resolution. These crystalline, optically active β-oxo esters were used in subsequent steps to prepare resolved nepetic acids. For example, bromination of (−)-**9a** gave the menthyl γ-bromo β-oxo ester (+)-**10** which on successive treatment with alkali and then acid yielded the 3*R trans*-nepetic acids[6b] (+)-**3c** and (−)-**3g**. In a like manner, the less abundant enantiomer, (+)-**9a**, carried through the same sequence, gave the 3*S trans*-nepetic acids[6c] (−)-**3c** and (+)-**3g**. The other menthyl β-oxo esters, (+)-**9b** and (−)-**9b**, remaining in mother liquors from the resolutions failed to crystallize and therefore were not studied except to confirm that the isomer (+)-**9b** is not crystalline, since an independent preparation from (+)-**5** and (+)-**8**[6a,c] gave an oil.

That effective resolution of the C-4 centers of (+)-**9a** and (−)-**9a** had been achieved was established by ob-

(6) (a) The exchange of alkoxyl groups is easily accomplished by heating the β-oxo ester in the presence of an excess of the appropriate alcohol; after exchange is complete, the surplus alcohol is removed under partial vacuum. (b) The product from the use of (−)-menthol leads to the (3*R*)-methylcyclopentane-1,2-dicarboxylic acid series (*trans*-carboxyl groups) related to (+)-pulegone. (c) The use of (+)-menthol provides the nepetic acids (*trans*-carboxyl groups) of the 3*S* series derived from the nepetalactones. (d) These studies were carried out on the more abundant compounds derived from (+)-(3*R*)-methylcyclohexanone.

Scheme II



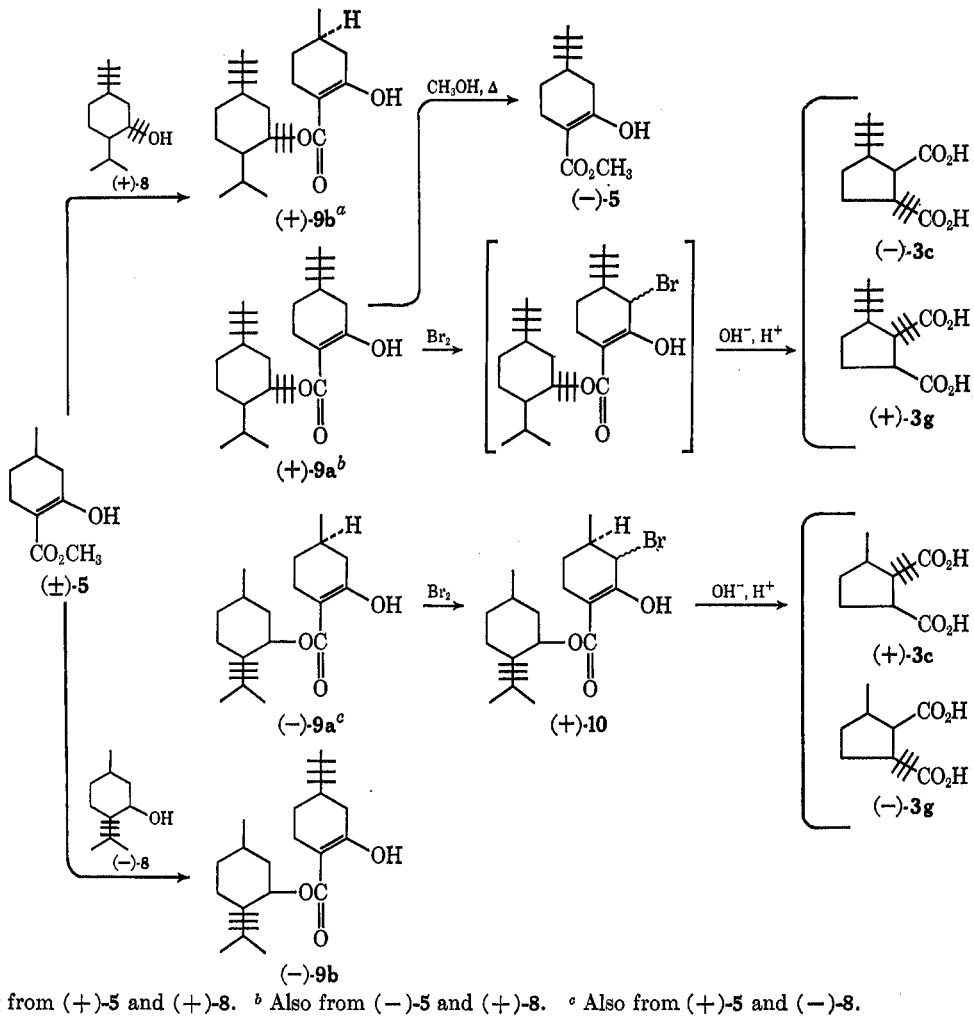
taining the same crystalline menthyl β-oxo ester, (+)-**9a**, from the reaction of (±)-**5** and (+)-**8** as from (−)-**5** and (+)-**8**, and, similarly, (−)-**9a** resulted from either (+)-**5** and (−)-**8** or (±)-**5** and (−)-**8**. A further test of the completeness of the resolution and the reversibility of the ester exchange in the formation of the menthyl β-oxo esters was to heat the menthyl β-oxo ester (+)-**9a** in the presence of a large excess of methanol and recover pure and resolved (−)-**5** from the reaction mixture.

The 3*S* nepetic acids (−)-**3c** and (+)-**3g** having *trans*-carboxyl groups and prepared from (+)-**9a** were shown to be identical with the corresponding nepetic acids derived from **1a** and **b** by comparing optical rotation data,[7] melting points including melting points of appropriate mixtures of pure nepetic acids, and retention times of gas chromatography peaks of their dimethyl esters.

The nepetic acids (+)-**3c** and (−)-**3g** obtained from the menthyl β-oxo ester (−)-**9a** were shown to be identical with the 3*R trans*-nepetic acids previously prepared[2] from (+)-**5**. Thus the reactions shown in Scheme III may be used to prepare nepetic acids of the 3*R* or 3*S* absolute configuration. However, it should be noted that the menthyl β-oxo esters do not provide significant yields of the nepetic acids having *cis*-carboxyl groups unless these esters are reconverted to the methyl β-oxo esters [*e.g.*, (+)-**9a** to (−)-**5** in Scheme III] before bromination and Favorskii-type rearrangement. Unfortunately, the preparation of (+)-**9a** and (−)-**5** at this stage was dependent upon the prior preparation of (+)-menthol (**8**) by resolution.[5c] When it became clear that synthesis of all the 3*S* nepetic acids *via* (+)-**9a**

(7) We thank Dr. P. M. Scopes, Chemistry Department, Westfield College, Hampstead, London, NW 3, England, for these determinations.

SCHEME III



[a] Also resulting from (+)-5 and (+)-8. [b] Also from (−)-5 and (+)-8. [c] Also from (+)-5 and (−)-8.

was impractical, we turned to the direct resolution of (±)-**4** to optically pure (−)-**4**, which was accomplished through recrystallization of the amine bisulfite salts obtained from reaction with SO_2 and (+)-α-methylphenethylamine.[5a,b] Once (−)-**4** became available, the reactions in Scheme II provided the four nepetic acids (+)-**3a**, (−)-**3c**, (+)-**3e**, and (+)-**3g** as expected.[2]

This work, particularly the preparation of the unknown and thermodynamically unstable (+)-*cis,cis*-nepetic acid (**3e**), completes our synthesis of all possible isomeric forms of these acids.[2]

Application of the reactions of Scheme II to pure (±)-**5** yielded essentially the same mixture of racemic nepetic acids as obtained from a mixture of (±)-**5** and (±)-**6**. The purity of the methyl β-oxo esters [*e.g.*, (±)-**5** or (±)-**6**] or the composition of a mixture of them was determined by cleavage with alkaline hydrogen peroxide and conversion to (±)-**11** or (±)-**12** or a mixture of these as shown in Scheme IV. These esters were distinguished by glc studies and were identified by comparison with known standards. This method was also used to show that the ratio of (±)-**5** to (±)-**6** in the crude β-oxo ester mixture from a typical preparation was 85:15.

An explanation of the inability to obtain *cis* acids from (+)-**9a** or (−)-**9a** is desirable. The change of alkyl group (methyl to menthyl) causes a dramatic change in product ratio of nepetic acids in the reactions of Schemes II and III. Whereas the Favorskii-type rearrangement of the methyl γ-bromo β-oxo esters of Scheme II provides a high percentage of the *cis* acids (+)-**3a** and (+)-**3e**, under the same conditions the products from (+)-**9a** or (−)-**9a** (Scheme III) are mainly *trans* acids **3c** and **3g** with *none* of the *cis,cis* acids **3e** and only *about 2%* of the *cis,trans* acids **3a** being observed. These differences may possibly be due to a steric effect of alkyl groups (menthyl *vs.* methyl) imposing an important hindrance to the hydrolysis of the ester function as compared to the epimerization of the carbon–hydrogen bond at the position α to the carbalkoxyl groups of the intermediate half-esters **14** and **15** of Scheme V. This premise would account for the dramatic change in ratio of nepetic acids produced by these competing reactions.

To test this steric concept, Favorskii-type rearrangements of brominated β-oxo esters (Scheme V) as well as hydrolysis of half-esters and diesters were carried out under a variety of conditions. Of these conditions, minimal exposure of (+)-**5**[6d] to dilute aqueous alkali at room temperature and then acidification provided the highest yield of the thermodynamically less stable cis products, implying that **14** and **15** are formed first and that **16** and **17** are formed by epimerization. The ratios of these products were determined by glc studies of the respective dimethyl esters obtained by reaction with diazomethane.

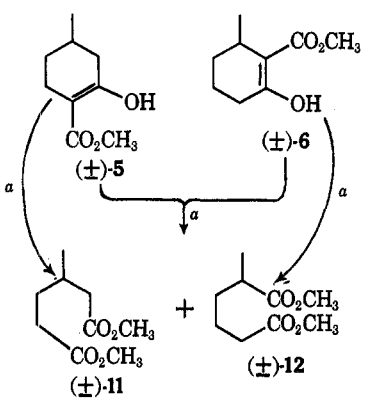
TABLE I

GLC RATIO OF FAVORSKII-TYPE REARRANGEMENT PRODUCTS[a]

β-Oxo ester	Base:solvent ratio[b]	Time at room temp	%[c] t,c 3d	t,t 3h	c,t 3g	c,c 3f
(±)-5	Na_2CO_3:CH_3OH:H_2O = 1:1:5	1 hr	8[d,e]	0	35[d,e]	57[d,e]
			7[d]	0	43[d]	50[d]
(+)-5	NaOH:CH_3OH:H_2O = 2:15:10	4 hr	23	17	20	40
(+)-5	$NaOCH_3$:CH_3OH = 1:4	20 min	73	22	5	0
(+)-5	KOH:CH_3OH = 1:10	3 min	53	22	14	11
(+)-5	KOH:H_2O = 1:5	3 min	18	15	25	42
7a	KOH:CH_3OH:H_2O = 1:6:12	1 hr	10	6	32	52
7a and 7b	KOH:CH_3OH:H_2O = 1:1:5	2 hr	12	8	29	51
(−)-9a	NaOH:CH_3OH:H_2O = 2:15:10	4 hr	64	36	0	0
(−)-9a	NaOH:CH_3OH:H_2O = 2:25:5	3 min	47 (21)[f]	9 (20)[f]	20 (19)[f]	24 (18)[f]
9c[g]	NaOH:CH_3OH:H_2O = 2:25:5	4 hr	34	25	5	36
9d[h]	NaOH:CH_3OH:H_2O = 2:25:5	4 hr	39	27	14	20
9e[i]	NaOH:CH_3OH:H_2O = 2:25:5	4 hr	73	27	0	0
(+)-10	NaOH:CH_3OH:H_2O = 2:10:15	4 hr	72	28	Trace	Trace
(+)-10	NaOH:CH_3OH:H_2O = 2:10:15	1 hr	66	34	Trace	Trace

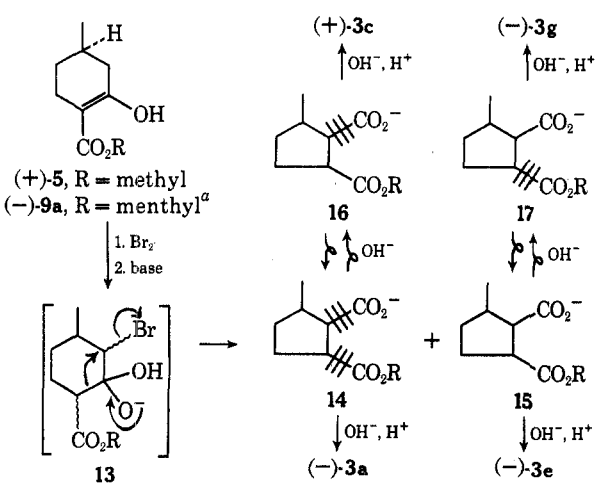
[a] The β-oxo esters except for (+)-10 were brominated and then subjected to base-catalyzed reaction. [b] g:ml:ml. [c] In order of elution (l to r) from LAC 886 column at 210°. [d] Glc curves of racemic dimethyl nepetates from this reaction were compared with those of corresponding esters in the 3S series. [e] Esters obtained by ether extraction of alkaline reaction product. [f] These diols (*cf.* Scheme VI) were analyzed by glc (*cf.* Experimental Section). [g] 2-Methyl-1-butyloxyl group exchanged for methoxyl group of (+)-5. [h] Ethoxyl group exchanged for the methoxyl group of (+)-5. [i] $C_{10}H_{17}O$ group (bornyloxyl) exchanged for the methoxyl group of (+)-5.

SCHEME IV



[a] OH^-, H_2O_2; H_3O^+:CH_2N_2.

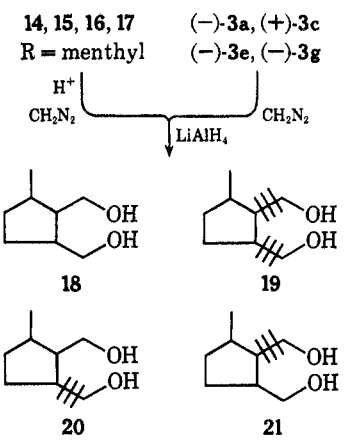
SCHEME V



[a] Prepared from (+)-5 and (−)-8.

To establish the composition of the menthyl half-ester products (Scheme V), they were converted to the diols **18**, **19**, **20**, and **21** with $LiAlH_4$ as shown in Scheme VI, and the resulting mixture was analyzed by glc through comparison with standards prepared from pure nepetic acids. In the case of mixtures of the menthyl half-esters **14**, **15**, **16**, and **17**, the conversion to and the analysis of the diols showed that the ratio of cis:trans products strongly favored cis if the Favorskii-type reaction was terminated promptly, since products measured as diols then showed the ratio 47:9:20:24 (**21**:**20**:**19**:**18**) as compared to the considerably altered ratio 64:36:0:0 (**3d**:**3h**:**3b**:**3f**) obtained on prolonged hydrolysis. These and other glc data related to the stereochemistry of diols and esters are consolidated in Table I.

SCHEME VI



It should be pointed out that the Favorskii-type rearrangement of (±)-**5** in aqueous methanolic sodium carbonate gives in low yield a neutral fraction which has been shown to contain dimethyl nepetates (Table I) in the ratio 8:0:35:57 (**3d**:**3h**:**3b**:**3f**) This ratio is particularly remarkable since the isomer (±)-**3f**, the least stable one, is present in greatest abundance. This is comparable to the ratio 7:0:43:50 found for the remaining products following the usual isolation procedure (*cf* Table I).

At this time we prefer the semibenzilic intermediate (**13** of Scheme V) to the cyclopropanone intermediate

as an explanation for the observed Favorskii-type rearrangements.[8]

The behavior of the dimethyl nepetates during acid hydrolysis is of interest. The esters having trans functional groups [(+)-**3d** and (−)-**3h** of the 3*R* series] retain this stereochemistry during hydrolysis to the corresponding *trans* acids. However, the (3*R*)-*cis,cis*-dimethyl ester (+)-**3f** is partially epimerized and yields some of each of the other 3*R* nepetic acids (about 10%), whereas the (3*R*)-*cis,trans* ester (−)-**3b** is hydrolyzed to *cis,trans* acid (−)-**3a** and in low yield (1–2%) to the *trans,cis* acid (+)-**3c**.

Experimental Section[9]

(−)-(3*S*)-Methylcyclohexanone (4).—(+)-α-Methylphenethylamine was used to resolve (±)-**4** to (−)-**4**: bp 70–71° (20 mm); $[\alpha]^{23}D$ −11.8° (neat) [lit.[3c] +11.3° (enantiomer) (neat)].[5b] Optical rotatory dispersion data[7] are reported elsewhere.[5b]

(−)-Methyl (4*S*)-Methyl-2-oxocyclohexanecarboxylate (5).—A 7.4-g sample of (−)-**4** was converted as described[2] to 8.0 g (76%) of a mixture of (−)-**5** and **6**, bp 65° (0.7 mm). This mixture was cooled to −20° and, after solidification, was recrystallized twice from cold petroleum ether, bp 60–70°, to give 4.5 g of pure colorless (−)-**5**: mp 41–42°; $[\alpha]^{23}D$ −105° (*c* 4.4, $CHCl_3$) [lit.[2] $[\alpha]^{28}D$ +101.5° (enantiomer) (*c* 0.5, $CHCl_3$)]; the ir spectra (KBr) of (−)-**5** and (+)-**5** were identical.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.32; H, 8.24.

Oxidation of (+)-5 and a Mixture of (±)-5 and (±)-6.—A 1.7-g sample of (+)-**5** prepared as described[2] was added to a stirred solution of 1 g of NaOH in 8 ml of H_2O and 4 ml of 30% H_2O_2. Heat was evolved and the stirred reaction mixture foamed. After 30 min, an additional 4 ml of 30% H_2O_2 was added and the mixture was heated with stirring. The reaction mixture was cooled, acidified, and extracted with ether. The ether extracts were washed with acidified ferrous sulfate solution and water and then dried ($MgSO_4$) and concentrated to give a colorless solid which on crystallization from benzene gave 3-methyladipic acid: mp 86–87°; $[\alpha]^{25}D$ +7.24° (*c* 1.3, H_2O) [lit.[3c] mp 85–89°, $[\alpha]^{26}D$ +9.6° (*c* 4.25, $CHCl_3$)]. The melting point of a mixture with authentic (+)-3-methyladipic acid showed no depression. Esterification with CH_2N_2 and gas chromatography on a 0.25 in. × 10 ft column of LAC 886 on acid-washed, DCMS-treated Chromosorb G showed one peak with the same retention time as authentic dimethyl 3-methyladipate.

In a similar manner, a mixture of (±)-**5** and (±)-**6** was oxidized. Gas chromatography analysis of the methyl esters gave two peaks having 5 and 5.7 min retention times, respectively, in the ratio of 15:85, the last peak being due to the dimethyl ester of 3-methyladipic acid. These peaks were identified by successive enrichments with authentic (±)-**11** and (±)-**12**.

(±)-Methyl 6-Methyl-2-oxocyclohexanecarboxylate (6).—A mixture of (±)-**5** and (±)-**6** was refrigerated and crystals of (±)-**5** were cropped by filtration until the residual mixture contained about two-thirds (±)-**5**. Fractional distillation through a 6-in. Vigreux column gave pure (±)-**6** as a last cut: bp 72° (0.7 mm); ir (neat) 834, 1028, 1079, 1155, 1225, 1258, 1285, 1357, 1440, 1615, 1650, 1715, 1745, and 2945 cm^{-1}.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.69; H, 8.33.

Favorskii-Type Rearrangement of 7a and 7b.—To a stirred mixture of 7.5 g of the oxo esters (−)-**5** and **6** in 25 ml of CCl_4 was added 7.05 g of Br_2 in 10 ml of CCl_4 during 30 min. Ether was added and the mixture was washed with bicarbonate solution and water. After drying ($MgSO_4$), the solution was concentrated *in vacuo* and the residue, dissolved in 10 ml of methanol, was added during 15 min to a stirred and cooled (tap water) mixture of 10 g of KOH in 50 ml of water. After the mixture was stirred for 2 hr, it was extracted with ether (three 25-ml portions) to remove neutral material and then acidified with 20% HCl. To avoid prolonged extraction with ether, the acidified solution was stirred with diazomethane, which rapidly extracts and esterifies the nepetic acids.[10] The mixture was analyzed on the 0.25 in. × 10 ft LAC 886 column at 190° and showed the ratio 12:8:29:51 (**3d**:**3h**:**3b**:**3f**).

Separation, Purification, and Properties of Dimethyl (3*S*)-Methylcyclopentane-1,2-dicarboxylates (3b, 3d, 3f, and 3h).—The crude alkaline reaction product from the Favorskii-type rearrangement of **7a** (Scheme II) was acidified and the aqueous solution was then treated with an ether solution of diazomethane.[10] The ether layer was dried ($MgSO_4$) and concentrated to give a crude mixture of dimethyl nepetates **3b, 3d, 3f, and 3h.** These esters were separated by preparative gas chromatography on a $^3/_8$ in. × 45 ft LAC 886 (30% on acid-washed Chromosorb W) column at 210°. A 5.4-g sample of the mixed esters was injected in 0.2-ml portions. The elution order was **3d, 3h, 3b,** and **3f,** and the retention times were 55, 65, 70, and 75 min, respectively.

These esters were evaporatively distilled: bp 110° (0.8 mm); $[\alpha]^{25}D$, for **3b**, +47.2° (*c* 2.2, $CHCl_3$); **3d**, −37.1° (*c* 1.4, $CHCl_3$); **3f**, −27.5° (*c* 1.1, $CHCl_3$); and **3h**, +44.8° (*c* 0.8, $CHCl_3$) [lit.,[2] for (−)-**3b**, −54° (*c* 2.0, $CHCl_3$); (+)-**3d**, +36° (*c* 2.5, $CHCl_3$); (+)-**3f**, +32° (*c* 0.6, $CHCl_3$); and (−)-**3h**, −52° (*c* 2.5, $CHCl_3$)]; **3f**, ir (neat) 1720 s and 1790 w cm^{-1} (ester C=O); the other bands in the spectra of (−)-**3f** and (+)-**3f** were identical.

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98, H, 8.05. Found for **3b**: C, 59.72; H, 7.89. Found for **3f**: C, 59.78; H, 8.12. Found for **3h**: C, 59.75; H, 7.84.

The infrared spectra (cm^{-1}) of **3b, 3d, 3f,** and **3h** were determined as neat liquids (Table II).

(+)-*t*-(3*S*)-Methyl-*r*-1,*c*-2-cyclopentanedicarboxylic Acid (3a).—A 0.402-g sample of (+)-**3b** was saponified by heating 1 hr with 20 ml of barium hydroxide solution saturated at room temperature. The precipitate of the barium salt of the acid which formed was filtered out and washed with distilled water. The salt was treated with dilute hydrochloric acid, and the total mixture was evaporated to dryness under reduced pressure. Ether extraction afforded 0.197 g of **3a**: mp 130–130.5°; $[\alpha]^{24}D$ +62° (*c* 1.15, $CHCl_3$), +59° (*c* 1.7, CH_3OH) (lit.[3c] mp 125–126°, $[\alpha]^{25}D$ +69°). The melting point of a mixture of synthetic and natural **3a** showed no depression.

(−)-*c*-(3*S*)-Methyl-*r*-1,*t*-2-cyclopentanedicarboxylic Acid (3c).—A 0.103-g sample of (−)-**3d** was saponified as described for (+)-**3b** to give 0.064 g of **3c**: mp 119–120°; $[\alpha]^{24}D$ −39.1° (*c* 1.2, $CHCl_3$) [lit.[3c] mp 117–118°, $[\alpha]^{23}D$ −35.4°]. The melting point of a mixture of synthetic and natural **3c** showed no depression.

(+)-*c*-(3*S*)-Methyl-*r*-1,*c*-2-cyclopentanedicarboxylic Acid (3e).—Saponification of 0.345 g of (−)-**3f** yielded 0.068 g of **3e**: mp 140–141°; $[\alpha]^{24}D$ +7.2° (*c* 2.6, $CHCl_3$) and −38.2° (*c* 2.1, CH_3OH) [lit.[2] mp 140–141°, $[\alpha]D$ −4.07° (enantiomer) (*c* 1.0, $CHCl_3$) and +37° (enantiomer) (*c* 0.54, CH_3OH) for 3*R* series].

Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: 55.94; H, 6.86.

(+)-*t*-(3*S*)-Methyl-*r*-1,*t*-2-cyclopentanedicarboxylic Acid (3g).—Saponification of 0.073 g of (+)-**3h** yielded 0.042 g of **3g**: mp 113–115°; $[\alpha]^{24}D$ +82.6° (*c* 0.9, $CHCl_3$) [lit.[3c] mp 114–115°, $[\alpha]^{21}D$ +85.8° (*c* 5.54, $CHCl_3$)].

Preparation of (+)-9a, (−)-9a, and (+)-9b.—A 17-g sample of (±)-**5** and 20 g of (+)-menthol[5c] (**8**) were dissolved in 40 ml of toluene, and the mixture was heated at reflux for 10 hr.[11] The toluene and excess (+)-**8** were removed *in vacuo*. The product crystallized after 2 days. Recrystallization from hexane gave 9.5 g (65%) of (+)-**9a** as colorless crystals: mp 126–129°; $[\alpha]^{25}D$ +50° (*c* 1.0, $CHCl_3$); ir (KBr) 651, 684, 762, 775, 787, 832, 843, 866, 916, 962, 993, 1015, 1040, 1048, 1110, 1178, 1223, 1260, 1290, 1318, 1373, 1450, 1725, 2890, and 2950 cm^{-1}.

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.69; H, 10.38.

In a similar manner, a 10-g sample of (+)-**5** and 15 g of (−)-**8** gave 14.1 g (81%) of colorless crystals of (−)-**9a**: mp 128–130°;

(8) E. W. Warnhoff, C. M. Wong, and W. T. Tai, *J. Amer. Chem. Soc.*, **90**, 514 (1968).

(9) Infrared spectra were recorded with a Beckman IR-5A spectrophotometer; C and H analyses were obtained from Galbraith Laboratories, Knoxville, Tenn.; a Varian Associates Model A-60A nuclear magnetic resonance spectrometer was used for nmr spectra; optical rotations were determined using an O. C. Rudolph Model 80 polarimeter. The melting points are corrected and were taken in the stirred bath of a Hoover–Thomas apparatus.

(10) E. J. Eisenbraun, R. N. Morris, and G. Adolphen, *J. Chem. Educ.*, **47**, 710 (1970).

(11) A. R. Bader, L. O. Cummings, and H. A. Vogel, *J. Amer. Chem. Soc.*, **73**, 4195 (1951).

Table II
Infrared Bands of Methyl 3S Nepetates

3b	925		1048		1205	1287	1365		1435	1735	
3d	908	1025	1050	1175	1210	1275	1335	1375	1440	1740	1795 w
3f	915	1020	1050		1205	1285	1340	1395	1435	1735	1790 w
3h	920	1027		1175	1200		1333	1380	1440	1735	

$[\alpha]^{25}D$ −49.5° (*c* 2.5, $CHCl_3$); ir (KBr) was identical with that of (+)-**9a**.

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.67; H, 10.43.

A 10-g sample of (±)-**5** and 15 g of (−)-**8** were treated as described in the preparation of (+)-**9a**. The crude product (16.7 g) was allowed to crystallize for several days and after filtration was recrystallized twice from hexane to give 7.2 g (84%) of (−)-**9a**: mp 128–130°; $[\alpha]D$ −49.5° (*c* 2.6, $CHCl_3$); ir (KBr) identical with the spectrum described above for (+)-**9a**.

A 1.7-g sample of (+)-**5** was treated with 2.0 g of (+)-**8** as previously described to give 2.4 g (80%) of (+)-**9b** as a colorless oil: $[\alpha]^{23}D$ +104° (*c* 3.9, $CHCl_3$); ir (neat) 827, 959, 983, 1046, 1088, 1163, 1223, 1280, 1365, 1400, 1455, 1625, 1660, 1750, and 2950 cm^{-1}.

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.37; H, 10.18.

Conversion of (+)-9a to (−)-5 and (−)-9a to (+)-5.—A mixture of 17 g of (+)-**9a** and 90 ml of anhydrous methanol was introduced into a stainless steel autoclave and heated for 13 hr at 110–120°. After cooling, the mixture was distilled to give 7.7 g (78%) of colorless (−)-**5**: bp 63–67° (0.1 mm); mp 42–43°; $[\alpha]^{25}D$ −104° (*c* 2.2, $CHCl_3$).

In a similar manner, (−)-**9a** was converted to (+)-**5** in 73% yield.

(+)-2-Methyl-1-butyl (4*R*)-Methyl-2-oxocyclohexanecarboxylate (9c).—This β-oxo ester was prepared through the exchange of alkoxyl groups by heating (+)-**5** in the presence of excess (+)-2-methyl-1-butanol. The excess alcohol was distilled off to give 70% yield of liquid **9c**: bp 108° (0.3 mm); $\alpha^{24}D$ +79° (neat); ir (neat) 827, 1042, 1088, 1163, 1222, 1280, 1330, 1360, 1405, 1460, 1625, 1660, 1725, and 2950 cm^{-1}.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.72; H, 9.87.

(+)-1-Methyl 3-Bromo-(4*R*)-methyl-2-oxocyclohexanecarboxylate (10).—A 1.5-g sample of (−)-**9a** was dissolved in 10 ml of anhydrous ether, 0.80 g of Br_2 was added dropwise, and the mixture was stirred for 1 hr at room temperature. The ether was removed and the solid residue was recrystallized from hexane to give 1.6 g (90%) of (+)-**10** as colorless crystals: mp 98–99°; $[\alpha]^{23}D$ +11.4° (*c* 2.2, $CHCl_3$); ir (KBr) 708, 847, 873, 912, 953, 996, 1042, 1088, 1125, 1154, 1197, 1240, 1335, 1375, 1425, 1462, 1730, and 2945 cm^{-1}.

Anal. Calcd for $C_{13}H_{29}BrO_3$: C, 57.91; H, 7.83. Found: C, 58.20; H, 7.68.

Favorskii-Type Rearrangement of (+)-10.—A 0.005-mol sample of (+)-**10** was rearranged by dissolving it in 15 ml of methanol, adding the solution dropwise to 10 ml of 20% NaOH, and stirring for 4 hr at 25°. The resulting mixture of nepetic acids was converted to methyl esters with diazomethane[10] and analyzed (Table I), and the individual esters were separated by preparative glc on a LAC column at 190°. After hydrolysis, the individual acids were shown to be (+)-**3c**, mp 118–119°, and (−)-**3g**, mp 113–115°. These acids showed no depression in melting point on admixture with those previously obtained.[2]

(3*R*)-Diols (18, 19, 20, and 21).—A 1-g sample of (+)-**3c** was esterified with diazomethane, and the resulting solution of methyl esters was dried ($MgSO_4$) and added dropwise to a stirred suspension of 1 g of $LiAlH_4$ in 20 ml of refluxing ether. After 1 hr, water was added, the suspension was filtered, and the filtrate was concentrated to give 0.73 g (100%) of **21**. The diols **18**, **19**, and **20** were prepared in a like manner from the appropriate 3*R* nepetic acid and evaporatively distilled: bp 140° (0.8 mm); $[\alpha]^{24}D$, for **18**, −9.4° (*c* 0.7, $CHCl_3$); **19**, −31.7° (*c* 2.9, $CHCl_3$); **20**, +23.9° (*c* 1.3, $CHCl_3$); **21**, −73.8° (*c* 1.4, $CHCl_3$). The ir spectra (cm^{-1}, neat) were determined (Table III).

Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found for **18**: C, 66.84; H, 11.34. Found for **19**: C, 66.34; H, 11.32. Found for **20**: C, 66.87; H, 11.30. Found for **21**: C, 66.85; H, 11.24.

The gas chromatography curves of these diols on a 0.25 in. × 13 ft column of acid-washed, DMCS-treated Chromosorb G coated with 5% silicone rubber heated to 160° showed 17.6, 19.2, 20.4, and 22.0 min retention times for **21**, **19**, **20**, and **18**, respectively.

Table III
Infrared Bands of Diols from 3*R* Nepetic Acids

18	953	1033	1074	1375	1450		2940	3300
19		1032	1065	1375	1455	2875	2945	3275
20		1035	1072	1380	1455		2930	3290
21	953	1025	1058	1375	1455	2880	2945	3295

The Conversion of (−)-9a to the Diols 18, 19, 20, and 21.—A 2.94-g sample of (−)-**9a** was brominated to (+)-**10** as previously described, the latter was dissolved in 10 ml of methanol, and the solution was added to a vigorously stirred mixture of 2 g of NaOH dissolved in 5 ml of water and 25 ml of methanol at 0°. After 3 min, the reaction was quenched by acidifying to pH 5 with 20% hydrochloric acid. The mixture was extracted with three portions of ether, dried ($MgSO_4$), and concentrated. A 1.0-g sample of the crude mixture was reduced with $LiAlH_4$ to a mixture of **18**, **19**, **20**, and **21**, as described for the preparation of **21**. The mixture of diols was analyzed by glc as described, which showed the ratio 47:9:20:24 (**21**:**20**:**19**:**18**); *cf.* Table I.

Favorskii-Type Rearrangement of (±)-5 in Aqueous Methanolic Sodium Carbonate.—A 1.7-g sample of (±)-**5** was treated with 0.8 g of bromine in ether solution. The bromo derivative was stirred for 1 hr at room temperature with a solution of 5.7 g of Na_2CO_3 in 50 ml of H_2O and 10 ml of methanol. The reaction mixture was extracted with ether to remove neutral products. Analysis of this neutral fraction on the LAC 886 glc column at 190° showed the ratio 8:0:35:57 (**3d**:**3h**:**3b**:**3f**);[12] *cf.* Table I. The dimethyl esters obtained from the alkaline layer showed the corresponding ratio 0:7:50:43.

Acid Hydrolysis of Dimethyl Nepetates.—About 100 mg of each of the dimethyl esters of (−)-**3b**, (+)-**3d**, (−)-**3f**, and (−)-**3h** were heated at reflux in 20 ml of 10% sulfuric acid for 9 hr. The reaction mixture was cooled, made basic with 30% NaOH, and extracted with ether to remove neutral material. Sulfuric acid was added and the acidic solution was extracted 8–10 times with ether. The ether extracts were dried ($MgSO_4$) and treated with CH_2N_2. Glc analyses of each run were made and these showed no change in isomer composition for the *trans* acids (−)-**3g** and (+)-**3c**, respectively. The *cis,cis*-dimethyl ester (+)-**3f** was accompanied by about 10% of the dimethyl esters (−)-**3b**, (+)-**3d**, and (−)-**3h**, whereas the *cis,trans*-dimethyl ester (−)-**3b** was accompanied by 1–2% of the (+)-*trans,cis*-dimethyl ester **3d**.

Registry No.—(+)-**3a**, 13368-64-4; (+)-**3b**, 27040-65-9; (−)-**3c**, 13350-94-2; (−)-**3d**, 27040-67-1; (+)-**3e**, 27040-68-2; (−)-**3f**, 27040-69-3; (+)-**3g**, 13368-63-3; (+)-**3h**, 27040-71-7; (−)-**5**, 27040-72-8; (+)-**5**, 27040-83-1; (±)-**6**, 27040-73-9; (+)-**9a**, 27040-74-0; (−)-**9a**, 27040-75-1; (+)-**9b**, 27040-76-2; (+)-**9c**, 27040-77-3; (+)-**10**, 27040-78-4; (−)-**18**, 27040-79-5; (−)-**19**, 27040-80-8; (+)-**20**, 27040-81-9; (−)-**21**, 27040-82-0.

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(12) Dimethyl esters (−)-**3b**, (+)-**3d**, (+)-**3f**, and (−)-**3h** were used to obtain these comparisons.