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Elucidation of the Racemization Mechanism of the α-Hydroxy Ketone Moiety (C_9-Position) of Optically Active Anthracyclinone Derivatives[1)]

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In order to discriminate the possible racemization mechanisms shown in Chart 1 (for (*S*)-(−)-**1a**) for the α-hydroxy ketone moiety (C_9-position of the optically active anthracyclinones ((*S*)-(+)-**1a**—**c**), some plausible intermediates ((±)-**2** and -**3**) and their equivalent ((*R*)-(−)-**12**) were first synthesized. Thus, the tertiary alcohol ((*R*)-(−)-**12**) was prepared from the 1′(*S*),2(*R*)-diol ((−)-**10**) according to the reaction scheme shown in Chart 2. The isomeric seven-membered α-hydroxy ketones ((±)-**2** and -**3**) were elaborated from the 1,4-dihydronaphthalene (**13**), following the synthetic scheme shown in Charts 3 and 4 based on Dieckmann condensation, dihydroxylation, regioselective enol acetate formation, and oxidation as key steps.

By subjecting the plausible intermediates ((±)-**2** and -**3**, **5**, and (*R*)-(−)-**12**) to the racemization conditions, the facile loss of optical integrity observed for (*S*)-(+)-**1a**—**c** was found to proceed through the ring-expanded seven-membered α-hydroxy ketones ((±)-**2** and -**3** for (*S*)-(+)-**1a**), which might be produced by equilibrium C (Chart 1).

Keywords——optically active anthracyclinone; racemization; six-membered α-hydroxy ketone; seven-membered α-hydroxy ketone; rearrangement; non-concerted process; Dieckmann condensation; dihydroxylation; regioselective enol acetate formation; oxidation

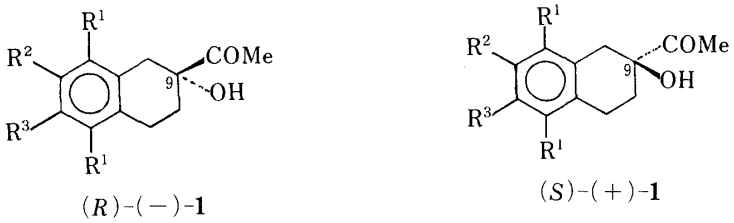
In connection with our synthetic studies on optically pure 4-demethoxyanthracyclinones whose glycosides, 4-demethoxyanthracyclines, have been reported to exhibit better therapeutic indices than natural anthracyclines,[3-7)] we recently explored two novel resolution methods for the racemic key intermediates ((±)-**1a**—**c**) by employing stereoselective reduction with fermenting baker's yeast (for (±)-**1a**, **b**)[3,6)] and formation of the diastereomeric acetals with readily available C_2-symmetric *vicinal*-diol (for (±)-**1c**).[7)] The practical and economic value of these methods is clearly enhanced by the successful racemization of the undesired enantiomers ((*S*)-(+)-**1a**—**c**) by heating them under strongly acidic conditions.[3,6,7)]

Since the racemized asymmetric carbons [C_9-position (anthracycline numbering)] are present in α,α-disubstituted-α-hydroxy ketone systems and carry no hydrogen atom, we were interested in the facile loss of optical integrity. By subjecting various plausible intermediates to the conditions employed for racemizing (*S*)-(+)-**1a**, we have now found that the racemization of (*S*)-(+)-**1a**—**c** could proceed through the novel ring-expanded seven-membered α-hydroxy ketones ((±)-**2** and/or -**3** for (*S*)-(+)-**1a**).

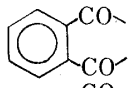
This report deals with our analysis of the racemization mechanism of (*S*)-(+)-**1a** by synthesizing various plausible intermediates of the racemization, and treating these intermediates under the conditions used for racemization.

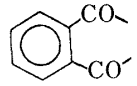
Results and Discussion

Three possible equilibria (A—C) shown in Chart 1 can be considered to account for the racemization of (*S*)-(+)-**1a**. Thus, protonation of the hydroxy group of (*S*)-(+)-**1a** followed



a : R^1=Me, R^2=R^3=H

b : R^1=Me, R^2, R^3= 

c : R^1=H, R^2, R^3= 

by elimination of water would produce the acetyl carbonium ion (**4**) and/or the enone (**5**) (equilibrium A)). Formation of the carbonium ion (**8**) carrying the hydrated acetyl group at the α-position might be possible by successive protonation of the ketonic oxygen, intramolecular nucleophilic attack by the hydroxy group, and acid-catalyzed opening of the epoxides (**6** and/or **7**) (equilibrium B)). Protonation of the ketonic oxygen might give rise to migration of the carbon–carbon bond (C_8–C_9 or C_9–C_{10}) (see **9**) partly by way of a non-concerted process (the transient formation of charge-separated species), affording the ring-expanded seven-membered α-hydroxy ketones ((±)-**2** and/or -**3**) (equilibrium C)).[8] These equilibria should lie far to the left since extensively racemized (*S*)-(+)-**1a** can be obtained in more than 70% recovery yield after the racemization.[3,6,7]

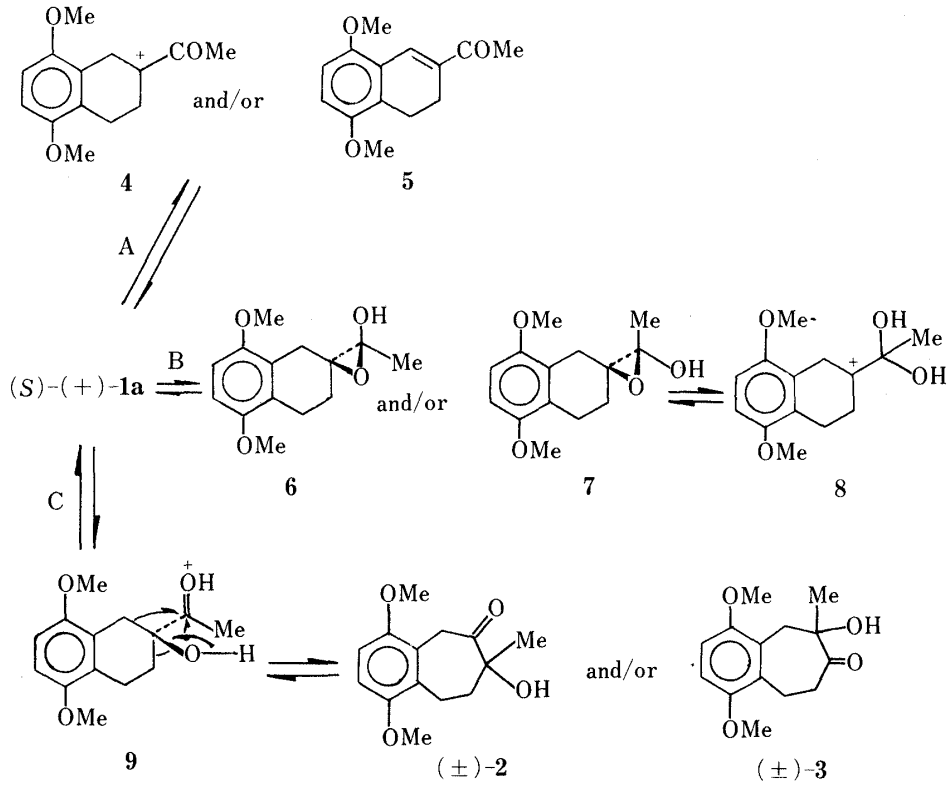
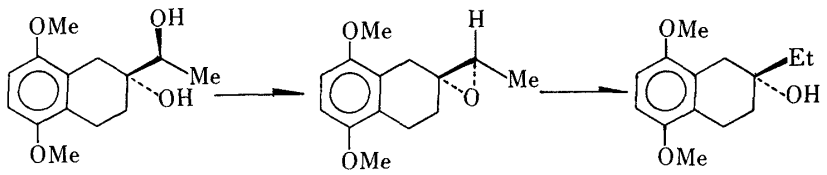


Chart 1

In order to discriminate these possibilities, the optical and/or chemical properties of the racemic seven-membered α-hydroxy ketones ((±)-**2** and -**3**), the enone (**5**), and the (*R*)-(−)-tertiary alcohol ((*R*)-(−)-**12**) were studied. The tertiary alcohol ((*R*)-(−)-**12**) was chosen as a reaction substrate because it was anticipated that, when (*R*)-(−)-**12** racemizes under acidic conditions, it could afford the carbonium ion, which might be similar to **8** and should be more stable than **4**. Since **5** had been synthesized in connection with the asymmetric synthesis of optically pure anthracyclinones,[5] syntheses of (±)-**2**, (±)-**3**, and (*R*)-(−)-**12** were first examined.

As shown in Chart 2, (*R*)-(−)-**12** was readily accessible from the (1′*S*,2*R*)-(−)-diol ((−)-**10**) obtained by the microbial reduction of (±)-**1a**[3,6] followed by fractional recrystallization. Thus, monotosylation of optically pure (−)-**10**, $[\alpha]_D^{20}$ −49.9° (ethanol), followed by treatment with sodium hydroxide, gave the (+)-epoxide ((+)-**11**), $[\alpha]_D^{20}$ +34.5° (chloroform). Reduction of (+)-**11** with lithium aluminum hydride afforded (−)-**12**, $[\alpha]_D^{20}$ −24.5° (chloroform). Since monotosylation of (−)-**10** should occur highly regioselectively on the secondary alcohol and the epoxide formation should proceed in an S_N2 fashion under alkaline conditions, (+)-**11** and (−)-**12** could be assigned as (2*R*,2′*R*,3′*R*) and (*R*) configurations, respectively.



(−)-**10** (+)-**11** (*R*)-(−)-**12**

Chart 2

Two isomeric seven-membered α-hydroxy ketones ((±)-**2** and -**3**) were synthesized regioselectively, starting with the readily available olefin (**13**)[9] as shown in Charts 3 and 4.

Epoxidation of **13** followed by acid-catalyzed epoxide opening, oxidative cleavage of the glycol, and reduction gave the diol (**14**). This was converted to the diester (**15**) by sequential mesylation, substitution with potassium cyanide, alkaline hydrolysis, and esterification. The diester (**15**) was subjected to the Dieckmann condensation,[10] affording the β-keto ester (**16**), which on acidic treatment gave the seven-membered symmetrical ketone (**17**). Transformation of **17** to (±)-**2** was achieved by successive Grignard addition, dehydration, dihydroxylation, and oxidation by way of the alcohol (**18**), the olefin (**19**), and the diol ((±)-**20**). Although dehydration of **18** accompanied formation of the *exo*-methylene olefin, the whole olefinic mixture was directly subjected to the next dihydroxylation and (±)-**20** was separated from the undesired diol derived from the *exo*-methylene compound.

Preparation of (±)-**3** was carried out according to the reaction scheme shown in Chart 4. Thus, methylation of **16**, followed by simultaneous hydrolysis and decarboxylation gave the β-methyl ketone ((±)-**22**) by way of the β-keto ester ((±)-**21**). Sequential regioselective enol acetate formation and dihydroxylation of the enol acetate (**26**) readily gave (±)-**3**. The same seven-membered ketone ((±)-**3**) was also elaborated by reduction of (±)-**22** followed by dehydration of the alcohol ((±)-**23**), dihydroxylation of the olefin (**24**), and oxidation of the diol ((±)-**25**). As was the case in the dehydration of **18**, the alcohol ((±)-**23**) gave a mixture of **24** and the isomeric olefin. However, this was immediately dihydroxylated without separation and the desired (±)-**25** was separated from the isomeric diol.

The two isomeric seven-membered α-hydroxy ketones ((±)-**2** and -**3**) were identified on the basis of their spectral data and elemental analyses.

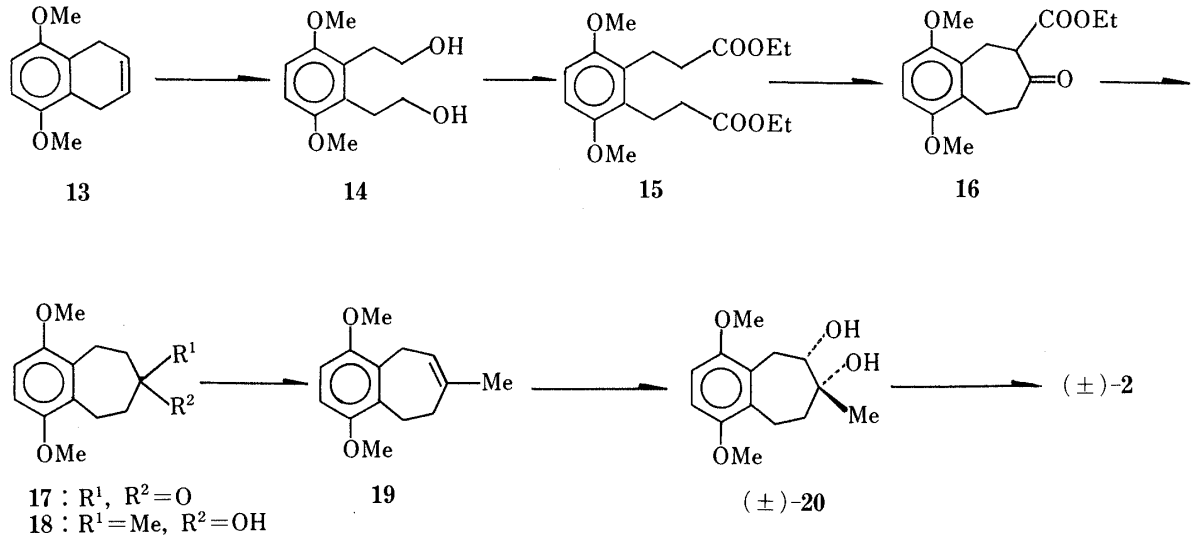


Chart 3

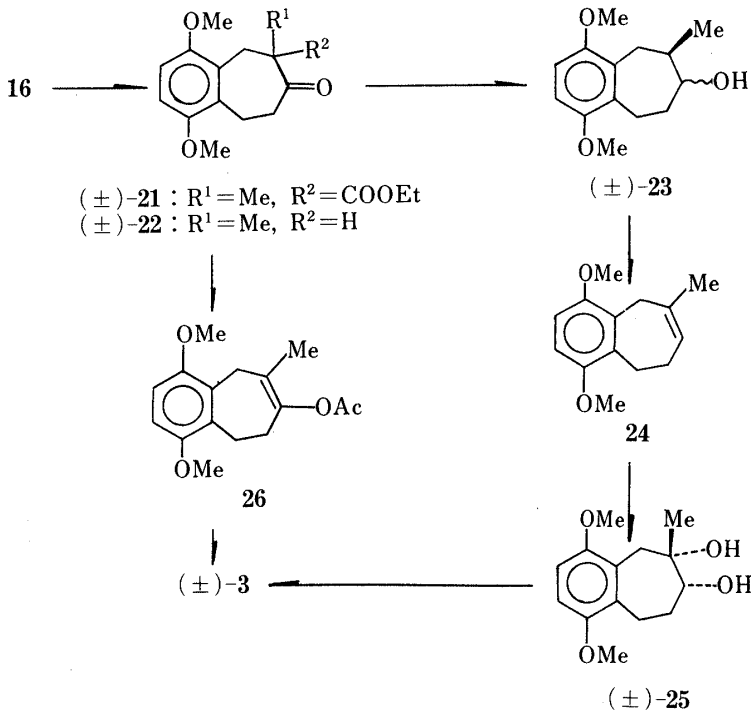


Chart 4

With the desired reaction substrates ((±)-**2**, (±)-**3**, **5**, and (*R*)-(−)-**12**) in hand, studies on the optical and/or chemical properties of these compounds under the same conditions as those employed for the racemization of (*S*)-(+)-**1a**—**c** were begun. These results are summarized in Table I, along with those previously obtained for the racemization of (*S*)-(+)-**1a**—**c** (Table I, runs 1—4).[3,6,7]

It was found that (*R*)-(−)-**12** completely decomposed when treated under conditions which induced 88% racemization of (*S*)-(+)-**1a** (condition A) (Table I, runs 1 and 5). Under milder conditions which racemized 41% of (*S*)-(+)-**1a** (condition C), (*R*)-(−)-**12** could be obtained in 28% recovery yield with 2% racemization (Table I, runs 4 and 6). Survival of the enone (**5**) could not be observed at all even under condition C. These results clearly show that

TABLE I. Results for the Reactions under Acidic Conditions

Run	Reaction substrate		Reaction conditions[a]	Reaction product			
	Structure	Optical purity (%)		Structure	Chemical yield (%)[b]	Optical purity (%)[c]	Racemization (%)[c]
1[d]	(*S*)-(+)-**1a**	65	A	(*S*)-(+)-**1a**	(74)	8	87
2[d]	(*S*)-(+)-**1b**	22	A	(*S*)-(+)-**1c**[e]	(70)	8	64
3[f]	(*S*)-(+)-**1c**	58	B	(*S*)-(+)-**1c**	(77)	22	62
4[d]	(*S*)-(+)-**1a**	71	C	(*S*)-(+)-**1a**	(89)	42	41
5	(*R*)-(−)-**12**	100	A	—[g]	—	—	—
6	(*R*)-(−)-**12**	100	C	(*R*)-(−)-**12**	(28)	98	2
7	**5**	—	C	—[g]	—	—	—
8	(±)-**2**	—	A	(±)-**1a**	7	—	—
9	(±)-**2**	—	C	(±)-**1a**	10	—	—
10	(±)-**3**	—	A	(±)-**1a**	66	—	—
11	(±)-**3**	—	C	(±)-**1a**	79	—	—

a) A: A mixture of the reaction substrate and TsOH–H_2O (70 eq) in aqueous acetic acid (acetic acid–H_2O, 7:4) was heated at 110 °C for 20 h under an argon atmosphere. B: Trifluoromethanesulfonic acid (70 eq) was used in place of TsOH–H_2O under condition A. C: TsOH–H_2O (10 eq) was used under condition A.
b) Figures in parentheses show recovery yields of starting material.
c) See footnotes *c*) and *d*) of Table I cited in ref. 3.
d) Reported in refs. 3 and 6.
e) Racemization of (*S*)-(+)-**1b** was accompanied by exhaustive demethylation. See refs. 3 and 6.
f) Reported in ref. 7.
g) TLC analysis of the reaction mixture showed complete decomposition of the starting material.

the equilibria A and B in Chart 1 are incompatible with the observed optical instability of (*S*)-(+)-**1a**.

Treatments of (±)-**2** and -**3** under condition A were found to afford (±)-**1a** in 7 and 66% yields, respectively (Table I, runs 1, 8, and 10). Higher yields of (±)-**1a** could be achieved by subjecting (±)-**2** and -**3** to condition C (Table I, runs 4, 9, and 11). While reaction products other than (±)-**1a** were found to be complex mixtures, the absence of the starting ketones ((±)-**2** and -**3**) in the reaction mixtures could be confirmed by chromatographic and spectral analyses.

Since transient formation of a charge-separated species between (*S*)-(+)-**1a** and **2** or **3** due to the intervention of a non-concerted process is anticipated to be feasible, the equilibrium C should be the origin of the facile racemization of (*S*)-(+)-**1a** under acidic conditions. Although the higher chemical yield of (±)-**1a** from (±)-**3** than from (±)-**2** might be explained by the difference of stability between the arylmethyl and the 2-arylethyl anion, the reason why the thermal equilibrium lies so far in favor of (±)-**1a** is quite obscure; one possibility is the intrinsic conformational strain of 6,7,8,9-tetrahydro-5*H*-benzocycloheptene-6- and -7-one systems.

While mechanistic studies have only been carried out on the AB ring system of anthracyclinones ((*S*)-(+)-**1a**), the same mechanistic explanation might hold for the acid-catalyzed racemization of optically active tetracyclic anthracyclinone intermediates ((*S*)-(+)-**1b**, **c**).[3,6,7] Racemization of (*S*)-(+)-**1b**, **c** has been found to be less efficient than that of (*S*)-(+)-**1a**. This might be due to the increased instability of charge-separated species brought about by the dihydroxyanthraquinone system.

Since the practical and economic usefulness of the previously developed optical resolution of (±)-**1a**—**c** can clearly be enhanced by racemization of the undesired enantiomers ((*S*)-(+)-**1a**—**c**), the racemization reaction, whose mechanism has been unambiguous-

ly elucidated as described above, could well be valuable for the industrial preparation of optically pure anthracyclinones.

Experimental[11]

(*R*)-(−)-2-Ethyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((*R*)-(−)-12)——a) (+)-5,8-Dimethoxy-3′(*R*)-methyl-3,4-dihydro-spiro[naphthalene-2(*R*)(1*H*),2′(*R*)-oxirane] ((+)-**11**): Tosyl chloride (225 mg, 1.18 mmol) was added to a solution of (−)-**10**[3,6] (mp 154—155 °C, $[\alpha]_D^{20}$ −49.9° (*c*=0.86, EtOH)) (250 mg, 0.99 mmol) in pyridine (2.5 ml), and the whole was kept standing at room temperature for 2.5 h. After being cooled in an ice bath, the mixture was diluted with H_2O and CH_2Cl_2, and the lower organic layer was separated. The aqueous phase was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed successively with 5% HCl, $NaHCO_3$, and H_2O. Filtration and concentration of the filtrate *in vacuo* gave a residue which was dissolved in iso-PrOH (7.5 ml). Powdered NaOH (250 mg, 6.3 mmol) was added to the alcoholic solution, and the mixture was stirred at room temperature for 1 h. After cooling in an ice bath, the reaction mixture was diluted with H_2O and CH_2Cl_2, and the organic layer was separated. The organic extracts were combined, and washed with H_2O. Filtration and concentration of the filtrate *in vacuo*, followed by purification by column chromatography (SiO_2, C_6H_6) gave (+)-**11** (156 mg, 67%). Recrystallization from C_6H_{12} gave pure (+)-**11**, mp 100—103 °C, $[\alpha]_D^{20}$ +34.5° (*c*=1.27, $CHCl_3$). NMR ($CDCl_3$) δ: 1.35 (3H, d, *J*=6 Hz, $CHC\underline{H}_3$), 1.85 (2H, t, *J*=6 Hz, $ArCH_2C\underline{H}_2$), 2.73 (2H, s, $ArC\underline{H}_2$), 2.96 (2H, t, *J*=6 Hz, $ArC\underline{H}_2CH_2$), 3.01 (1H, q, *J*=6 Hz, $C\underline{H}CH_3$), 3.73 and 3.76 (each 3H, two s, $OC\underline{H}_3\times2$), 6.58 (2H, s, aromatic protons). This sample was immediately used for the next reduction.

b) (*R*)-(−)-**12**: Lithium aluminum hydride (20 mg, 0.53 mmol) was added to a solution of (+)-**11** (120 mg, 0.51 mmol) in THF (6 ml), and the mixture was stirred at room temperature for 3 h. H_2O (0.5 ml) was gradually added to the reaction mixture to quench the reduction. After being further diluted with 5% HCl (1 ml), the aqueous mixture was extracted with Et_2O. The ethereal extracts were combined, and washed successively with 5% HCl, satd. $NaHCO_3$, and satd. NaCl. Filtration and concentration of the filtrate *in vacuo*, followed by purification by PTLC (SiO_2, C_6H_6–EtOAc, 10:1), gave (*R*)-(−)-**12** (101 mg, 83%), bp 200 °C (3 mmHg) (bath temp.), $[\alpha]_D^{20}$ −24.5° (*c*=1.31, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3430, 1605, 1480, 1255, 1085. NMR ($CDCl_3$) δ: 0.85—1.15 (3H, m, $CH_2C\underline{H}_3$), 1.48 (1H, s, O<u>H</u>), 1.4—2.0 (4H, m, $C\underline{H}_2CH_3$ and $ArCH_2C\underline{H}_2$), 2.6—2.9 (4H, m, $ArC\underline{H}_2\times2$), 3.76 and 3.77 (each 3H, two s, $OC\underline{H}_3\times2$), 6.54 (2H, s, aromatic protons). MS *m/e*: 236 (M^+).

2,3-Bis(2-hydroxyethyl)-1,4-dimethoxybenzene (14)——a) 2,3-Epoxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene: *N*-Bromosuccinimide (20.6 g, 0.12 mol) was added over 15 min to a solution of **13**[9] (mp 49—50 °C) (20 g, 0.11 mol) in a mixture of DMSO (150 ml) and H_2O (20 ml) at 10—15 °C, and the whole mixture was stirred at the same temperature for 1 h. Potassium hydroxide (86% pure) (7.5 g, 0.12 mol) was added to the aqueous mixture at 15—20 °C over 5 min, and the stirring was continued for 1 h. After being diluted with satd. NaCl, the mixture was extracted with CH_2Cl_2, and the combined extracts were washed with satd. NaCl. Filtration and concentration of the filtrate *in vacuo* gave a residue which was triturated with Et_2O (100 ml). The ethereal suspension was cooled at −20 °C, and the crystals were collected and washed with cold Et_2O. The product weighed 19.3 g (89%), mp 128—131 °C. Recrystallization from iso-Pr_2O gave a pure sample, mp 132—133 °C (lit.,[12] mp 132—133 °C). IR ν_{max}^{KBr} cm^{-1}: 1476, 1247, 1092, 1077, 810, 778. NMR ($CDCl_3$) δ: 2.64—2.96 (2H, m, C<u>H</u>×2), 3.32—3.64 (4H, m, $C\underline{H}_2\times2$). 3.76 (6H, s, $OC\underline{H}_3\times2$), 6.56 (2H, s, aromatic protons).

b) **14**: A 10% H_2SO_4 solution (15 ml) was added to a solution of the epoxide (15 g, 73 mmol) in a mixture of THF (113 ml) and H_2O (113 ml), and the mixture was heated at reflux for 30 min. The mixture was cooled to 10 °C, then $NaIO_4$ (16.4 g, 77 mmol) was added to the acidic solution at 10—15 °C over 15 min. The whole was stirred at the same temperature for 1 h, then neutralized (pH 7.5—8.0) with satd. $NaHCO_3$ (40 ml). An aqueous solution (17.2 ml) of sodium borohydride (4.3 g, 0.11 mol) was added over 1 h to the neutralized solution, and stirring was continued at 15—20 °C for 30 min. After successive addition of Me_2CO (30 ml) and satd. NaCl (500 ml), the mixture was extracted with EtOAc. The ethyl acetate extracts were combined, and washed successively with aq. $NaHSO_3$, H_2O, 5% HCl, satd. $NaHCO_3$, and satd. NaCl. Filtration and concentration of the filtrate *in vacuo* gave a residue, which was triturated with Et_2O (70 ml) at −20 °C to give crude **14** (14.1 g, 86%), mp 166—170 °C. Recrystallization from C_6H_6–Et_2O gave an analytical sample, mp 173—175 °C. IR ν_{max}^{KBr} cm^{-1}: 3245, 1478, 1464, 1250, 1209, 1100, 1039, 1018. NMR (Me_2CO-d_6) δ: 2.91 (4H, t, *J*=7 Hz, $C\underline{H}_2CH_2OH\times2$), 3.42 (2H, s, O<u>H</u>×2), 3.60 (4H, t, *J*=7 Hz, $CH_2O\underline{H}\times2$), 3.73 (6H, s, $OC\underline{H}_3\times2$), 6.67 (2H, s, aromatic protons). *Anal.* Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.58; H, 7.99.

2,3-Bis(2-ethoxycarbonylethyl)-1,4-dimethoxybenzene (15)——a) 2,3-Bis(2-mesyloxyethyl)-1,4-dimethoxybenzene: Mesyl chloride (8.2 ml, 0.11 mol) was gradually added to a cooled (−30 °C) solution of **14** (10 g, 44 mmol) in pyridine (75 ml) with stirring. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 1 h, poured into H_2O, and then extracted with CH_2Cl_2. The combined organic extracts were washed successively with 5% HCl, satd. $NaHCO_3$, and satd. NaCl. Filtration and concentration of the filtrate *in vacuo* afforded a residue which was triturated with Et_2O (80 ml) at −20 °C to give the crude bis-mesylate (16.4 g, 97%),

mp 99—102 °C. Recrystallization from EtOH gave an analytical sample as colorless crystals, mp 103—104 °C. IR ν_{max}^{KBr} cm^{-1}: 1480, 1358, 1346, 1168, 1106, 972, 940. NMR ($CDCl_3$) δ: 2.88 (6H, s, $CH_3SO_2 \times 2$), 3.12 (4H, t, J= 7 Hz, $CH_2CH_2O \times 2$), 3.75 (6H, s, $OCH_3 \times 2$), 4.31 (4H, t, J=7 Hz, $CH_2O \times 2$), 6.66 (2H, s, aromatic protons). *Anal.* Calcd for $C_{14}H_{22}O_8S_2$: C, 43.97; H, 5.80. Found: C, 44.08; H, 5.76.

b) 2,3-Bis(2-cyanoethyl)-1,4-dimethoxybenzene: A mixture of the bis-mesylate (15 g, 0.039 mol) and sodium cyanide (6.2 g, 95 mmol) in DMSO (120 ml) was heated at 90 °C for 5 h with stirring. After being cooled, the mixture was poured into H_2O, and extracted with CH_2Cl_2. The combined organic extracts were washed successively with 5% NaOH, H_2O, 5% HCl, and satd. NaCl. Filtration and concentration of the filtrate *in vacuo* gave a residue which was triturated with Et_2O (40 ml) at −20 °C to afford the crude product (7.95 g, 83%), mp 127—130 °C. Recrystallization from EtOH gave an analytical sample, mp 132—133.5 °C. IR ν_{max}^{KBr} cm^{-1}: 2250, 1477, 1466, 1254, 1210, 1079. NMR ($CDCl_3$) δ: 2.57 (4H, t, J=7 Hz, $CH_2CH_2CN \times 2$), 3.02 (4H, t, J=7 Hz, $CH_2CN \times 2$), 3.76 (6H, s, $OCH_3 \times 2$), 6.68 (2H, s, aromatic protons). *Anal.* Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.95; H, 6.68; N, 11.59.

c) 2,3-Bis(2-carboxyethyl)-1,4-dimethoxybenzene: A mixture of the bis-cyanide (6.0 g, 25 mmol) and 50% KOH (10 ml) in MeOH (20 ml) was heated at reflux for 5 h with stirring. The mixture was concentrated *in vacuo*, diluted with H_2O (100 ml), then washed with CH_2Cl_2. The aqueous solution was cooled in an ice bath, and acidified with conc. HCl. The crude dicarboxylic acid separated as crystals, which were collected and washed with cold H_2O. The wet dicarboxylic acid was immediately subjected to the next esterification.

On the other hand, the crude dicarboxylic acid, mp 138—140 °C, similarly obtained by alkaline hydrolysis, was dried *in vacuo*, and recrystallized from C_6H_6, giving an analytical sample as colorless crystals, mp 139—140 °C. IR ν_{max}^{KBr} cm^{-1}: 2650, 1705, 1682, 1480, 1246, 1082. NMR (Me_2CO-d_6) δ: 2.3—2.6 (4H, m, $CH_2CH_2COOH \times 2$), 2.8—3.1 (4H, m, $CH_2COOH \times 2$), 3.76 (6H, s, $OCH_3 \times 2$), 6.53 (2H, s, aromatic protons). *Anal.* Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.37; H, 6.35.

d) **15**: The wet dicarboxylic acid obtained in c) was dissolved in C_6H_6 (9 ml) and the mixture was heated at reflux using a Dean–Stark apparatus to remove H_2O present in the starting acid. After EtOH (9 ml) and conc. H_2SO_4 (2 drops) had been added to the dried benzene solution, the mixture was further heated at reflux for 10 h with removal of H_2O by the Dean–Stark apparatus. After cooling, the mixture was diluted with H_2O and extracted with Et_2O. The ethereal extracts were combined, and washed successively with H_2O, satd. $NaHCO_3$, and satd. NaCl. Filtration and concentration *in vacuo* afforded crude **15** (7.06 g, 85% from the bis-cyanide). This was further purified by bulb-to-bulb distillation, giving pure **15**, bp 250 °C (3 mmHg) (bath temp.). IR ν_{max}^{film} cm^{-1}: 1731, 1480, 1437, 1253, 1085. NMR ($CDCl_3$) δ: 1.25 (6H, t, J=7 Hz, $CH_2CH_3 \times 2$), 2.3—2.6 (4H, m, $CH_2CH_2CO \times 2$), 2.8—3.1 (4H, m, $CH_2CO \times 2$), 3.76 (6H, s, $OCH_3 \times 2$), 4.14 (4H, q, J=7 Hz, $CH_2CH_3 \times 2$), 6.66 (2H, s, aromatic protons). MS *m/e*: 338 (M^+).

1,4-Dimethoxy-6-ethoxycarbonyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-7-one (16)——A mixture of sodium hydride (50% oil dispersion) (180 mg, 3.8 mmol) and EtOH (1 drop) in benzene (20 ml) was stirred under reflux. The diester (**15**) (500 mg, 1.5 mmol) was added to the stirred benzene suspension under reflux over 18 h. After cooling, the mixture was diluted successively with EtOH and H_2O, then extracted with EtOAc. The organic extracts were combined and washed with satd. NaCl. Filtration and concentration of the filtrate *in vacuo*, followed by purification by column chromatography (SiO_2, C_6H_6), afforded pure **16** as a solid (328 mg, 76%). Recrystallization from EtOH gave an analytical sample, mp 98—99.5 °C. IR ν_{max}^{KBr} cm^{-1}: 1733, 1694, 1483, 1259, 1074. NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz, CH_2CH_3), 2.2—3.6 (7H, m, $CH_2CHCOCH_2CH_2$), 3.75 (6H, s, $OCH_3 \times 2$), 4.14 (2H, q, J=7 Hz, CH_2CH_3), 6.66 (2H, s, aromatic protons). *Anal.* Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.49; H, 6.89.

1,4-Dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-7-one (17)——A mixture of **16** (200 mg, 0.68 mmol), conc. HCl (1.5 ml), and H_2O (1.5 ml) in MeOH (3 ml) was heated at reflux for 3 h. After being cooled, the mixture was diluted with H_2O and extracted with EtOAc. The combined organic extracts were washed with satd. $NaHCO_3$ and satd. NaCl. Filtration and concentration of the filtrate *in vacuo*, followed by purification by PTLC (SiO_2, C_6H_6) gave **17** (127 mg, 84%), mp 120—124 °C. An analytical sample was prepared by recrystallization from MeOH, mp 124—125.5 °C. IR ν_{max}^{KBr} cm^{-1}: 1693, 1480, 1253, 1169. NMR ($CDCl_3$) δ: 2.4—2.6 (4H, m, $ArCH_2 \times 2$), 2.9—3.1 (4H, m, CH_2COCH_2), 3.78 (6H, s, $OCH_3 \times 2$), 6.66 (2H, s, aromatic protons). *Anal.* Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.77; H, 7.39.

1,4-Dimethoxy-7-methyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-7-ol (18)——An ethereal solution of methylmagnesium bromide [prepared from magnesium turnings (220 mg, 9.0 mmol) and methyl iodide (1.29 g, 9.1 mmol) in Et_2O (20 ml)] was added to a solution of **17** (1.0 g, 4.5 mmol) in THF (40 ml) at room temperature, and the mixture was stirred at the same temperature for 15 h. After cooling, the mixture was poured into satd. NH_4Cl, and extracted with EtOAc. The combined organic extracts were washed successively with 5% HCl, satd. $NaHCO_3$, and satd. NaCl, then filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, C_6H_6–EtOAc, 10 : 1), giving pure **18** as a solid (730 mg, 68%), mp 98—100 °C. Recrystallization from iso-Pr_2O gave an analytical sample, mp 100—101 °C. IR ν_{max}^{KBr} cm^{-1}: 3540, 1483, 1263, 1232. NMR ($CDCl_3$) δ: 1.21 (3H, s, CH_3), 1.4—1.9 (4H, m, $ArCH_2 \times 2$), 1.60 (1H, s, OH), 2.6—3.2 (4H, m, $ArCH_2CH_2 \times 2$), 3.73 (6H, s, $OCH_3 \times 2$), 6.59 (2H, s, aromatic protons). *Anal.* Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.21; H, 8.72.

(±)-1,4-Dimethoxy-7(*R)-methyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6(*S**),7(*R**)-diol ((±)-20)**——a) 1,4-

Dimethoxy-7-methyl-8,9-dihydro-5*H*-benzocycloheptene (**19**): A mixture of **18** (500 mg, 2.1 mmol) and tosyl chloride (445 mg, 2.3 mmol) in pyridine (10 ml) was stirred at 110 °C for 5 h. After being cooled, the mixture was poured into satd. NaCl, and extracted with Et_2O. The combined ethereal extracts were washed successively with 5% HCl, satd. $NaHCO_3$, and H_2O, then filtered and concentrated *in vacuo*. The residue was subjected to column chromatography (SiO_2, petr. ether–Et_2O, 50 : 1) to give crude **19**, contaminated with 1,4-dimethoxy-7-methylene-6,7,8,9-tetrahydro-5*H*-benzocycloheptene, as an oil (360 mg, 78%). NMR ($CDCl_3$) δ: 4.56 (br s, $C\underline{H}_2=C$ of the 7-methylene isomer), 5.15—5.65 (m, $CH_2C\underline{H}=C$ of **19**). The intensity ratio of these signals was estimated to be 2 : 5. Therefore, the ratio of **19** to the 7-methylene isomer was determined as *ca.* 5 : 1. This was directly used for the next dihydroxylation.

b) (±)-**20**: Osmium tetraoxide (524 mg, 2.1 mmol) was added to a solution of the crude olefin mixture (300 mg, 1.4 mmol) in a mixture of pyridine (7.9 ml) and C_6H_6 (7.9 ml), and the whole was stirred at room temperature for 15 h. A solution of $NaHSO_3$ (943 mg, 9.1 mmol) in a mixture of pyridine (10.5 ml) and H_2O (15.7 ml) was added to the reaction mixture, and the stirring was continued for an additional 1 h at room temperature. The reaction mixture was diluted with H_2O, and extracted with EtOAc. The combined organic extracts were washed successively with satd. $CuSO_4$ and H_2O. Filtration and concentration of the filtrate *in vacuo* gave a residue which was purified by PTLC (SiO_2, petr. ether–Et_2O, 1 : 10), giving pure (±)-**20** (241 mg, 54% from **18**), mp 89—93 °C. Recrystallization from iso-Pr_2O gave an analytical sample, mp 93—94 °C. IR ν_{max}^{KBr} cm^{-1}: 3350, 1480, 1250, 1078. NMR ($CDCl_3$) δ: 1.28 (3H, s, $C\underline{H}_3$), 1.3—2.0 (2H, m, $ArCH_2C\underline{H}_2$), 1.92 (1H, s, O$\underline{H}$), 2.42 (s, 1H, O$\underline{H}$), 2.5—3.6 (5H, m, $C\underline{H}_2CH_2C(OH)C\underline{H}C\underline{H}_2$), 3.71 and 3.73 (each 3H, two s, $OC\underline{H}_3\times2$), 6.62 (2H, s, aromatic protons). *Anal.* Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.62; H, 8.11.

(±)-7-Hydroxy-1,4-dimethoxy-7-methyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-one ((±)-2)——A DMSO solution (3.0 ml) of sulfur trioxide–pyridine complex (950 mg, 5.9 mmol) was added to a mixture of (±)-**20** (150 mg, 0.59 mmol) and Et_3N (2.5 ml, 18 mmol) in DMSO (1.5 ml), and the mixture was stirred at room temperature for 2 h, then diluted with H_2O, and extracted with Et_2O. The ethereal extracts were combined, washed with H_2O, filtered, then concentrated *in vacuo* to give a residue. This was purified by PTLC (SiO_2, petr. ether–Et_2O, 2 : 1), giving pure (±)-**2** (119 mg, 80%), mp 107—109 °C. An analytical sample was obtained by recrystallization from C_6H_{14}, mp 110—111 °C. IR ν_{max}^{KBr} cm^{-1}: 3430, 1705, 1484, 1258, 1086. NMR ($CDCl_3$) δ: 1.51 (3H, s, $C\underline{H}_3$), 1.6—1.8 (1H, m, one of $C\underline{H}_2C(OH)$), 2.0—2.3 (1H, m, one of $C\underline{H}_2C(OH)$), 2.5—2.8 (1H, m, one of $C\underline{H}_2CH_2C(OH)$), 3.0—3.4 (1H, m, one of $C\underline{H}_2CH_2C(OH)$), 3.72 and 3.77 (each 3H, two s, $OC\underline{H}_3\times2$), 3.7—3.8 (1H, br s, O$\underline{H}$), 3.77 (1H, d, J=13 Hz, one of $C\underline{H}_2CO$), 4.11 (1H, d, J=13 Hz, one of $C\underline{H}_2CO$), 6.65 (2H, s, aromatic protons). *Anal.* Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.02; H, 7.38.

(±)-1,4-Dimethoxy-6-methyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-7-one ((±)-22)——a) (±)-6-Ethoxycarbonyl-1,4-dimethoxy-6-methyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-7-one ((±)-**21**): The β-keto ester (**16**) (1.5 g, 5.1 mmol) was gradually added to a stirred suspension of sodium hydride (50% oil dispersion) (270 mg, 5.6 mmol) in DMF (30 ml) below 15 °C over 30 min. The stirring was continued at room temperature for 1 h, then methyl iodide (1.5 g, 11 mmol) was added to the reaction mixture at 20 °C over 5 min. After being stirred at room temperature overnight, the mixture was poured into H_2O, and extracted with petr. ether. The organic extracts were combined, and washed successively with 5% HCl, satd. NaCl, and H_2O. Filtration and concentration of the filtrate *in vacuo*, followed by purification by column chromatography (SiO_2, petr. ether), gave pure (±)-**21** (1.48 g, 94%). MS *m/e*: 306 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1735, 1695, 1485, 1260, 1075. This sample was immediately subjected to simultaneous hydrolysis and decarboxylation as described below.

b) (±)-**22**: A mixture of AcOH (2 ml) and conc. HCl (1 ml) was added to (±)-**21** (200 mg, 0.65 mmol) prepared in a), and the mixture was stirred at 100 °C for 5 h. After cooling, the mixture was poured into H_2O, and extracted with Et_2O. The ethereal extracts were combined, washed with satd. $NaHCO_3$ and satd. NaCl, filtered, and concentrated *in vacuo*. The residue was purified by PTLC (SiO_2, C_6H_6) to give pure (±)-**22** as a colorless solid (110 mg, 68% from **16**), mp 83—86 °C. Recrystallization from MeOH gave an analytical sample, mp 86—87 °C. IR ν_{max}^{KBr} cm^{-1}: 1694, 1479, 1251, 1073. NMR ($CDCl_3$) δ: 1.09 (3H, d, J=6 Hz, $C\underline{H}_3$), 2.2—2.3 (7H, m, $C\underline{H}_2C\underline{H}_2COC\underline{H}C\underline{H}_2$), 3.78 (6H, s, $OC\underline{H}_3\times2$), 6.67 (2H, s, aromatic protons). *Anal.* Calcd for $C_{14}H_8O_3$: C, 71.77; H, 7.74. Found: C, 71.88; H, 7.92.

7-Acetoxy-1,4-dimethoxy-6-methyl-8,9-dihydro-5*H*-benzocycloheptene (26)——A mixture of (±)-**22** (500 mg, 2.1 mmol) and TsOH–H_2O (406 mg, 2.1 mmol) in acetic anhydride (25 ml) was heated at 140 °C for 7 h. After cooling, the reaction mixture was diluted with ice and satd. $NaHCO_3$, then extracted with CH_2Cl_2. The combined organic extracts were washed successively with cold satd. $NaHCO_3$ and ice-H_2O. Filtration and concentration of the filtrate *in vacuo*, followed by purification by column chromatography (SiO_2, C_6H_6), gave **26** (318 mg, 54%), mp 103—106 °C. Recrystallization from C_6H_{12} gave an analytical sample, mp 107—109 °C. IR ν_{max}^{KBr} cm^{-1}: 1743, 1483, 1259, 1077. NMR ($CDCl_3$) δ: 1.58—1.74 (3H, m, $C\underline{H}_3$), 2.05 (3H, s, $C\underline{H}_3CO$), 2.18—2.42 (2H, m, $CH_2C\underline{H}_2C=$), 2.94—3.14 (2H, m, $C\underline{H}_2CH_2C=$), 3.38—3.54 (2H, m, $C\underline{H}_2C(CH_3)=$), 3.73 (6H, $OC\underline{H}_3\times2$), 6.62 (2H, s, aromatic protons). *Anal.* Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.92; H, 7.42.

(±)-1,4-Dimethoxy-6(*S)-methyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-6(*S**),7(*R**)-diol ((±)-25)**——a) (±)-1,4-Dimethoxy-6(*S**)-methyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-7(*R**)-ol and Its (±)-7(*S**)-Isomer ((±)-**23**): Sodium borohydride (49 mg, 1.3 mmol) was added to a methanolic solution (16 ml) of (±)-**22** (600 mg,

2.6 mmol) at room temperature over 5 min, and the mixture was stirred at the same temperature for 30 min. After being diluted with H_2O, the mixture was extracted with Et_2O. The ethereal extracts were combined, and washed successively with H_2O, 5% HCl, satd. $NaHCO_3$, and satd. NaCl. Filtration and concentration of the filtrate *in vacuo* gave a residue, which was purified by PTLC (SiO_2, petr. ether–Et_2O, 1 : 1) to afford a mixture of the two diastereomeric alcohols ((±)-**23**) (509 mg, 84%), mp 117—124 °C. IR ν_{max}^{KBr} cm^{-1}: 3370. NMR ($CDCl_3$) δ: 0.81 (3H, d, J=7 Hz, $CHC\underline{H}_3$ for one diastereomer of (±)-**23**), 1.02 (3H, d, J=7 Hz, $CHC\underline{H}_3$ for the other diastereomer of (±)-**23**). The intensity ratio of the two doublets showed that this sample consists of the two diastereomeric alcohols in a ratio of 3 : 2. This mixture was directly subjected to the next dehydration.

b) 1,4-Dimethoxy-6-methyl-8,9-dihydro-5*H*-benzocycloheptene (**24**): Tosyl chloride (807 mg, 4.2 mmol) was added to a solution of a mixture of the diastereomeric alcohols ((±)-**23**) (500 mg, 2.1 mmol) in pyridine (10 ml). The mixture was stirred at room temperature for 15 h, then poured into ice-H_2O. The aqueous mixture was extracted with EtOAc, and the combined organic extracts were washed successively with 5% HCl, satd. $NaHCO_3$, and satd. NaCl. The residue obtained by successive filtration and concentration of the filtrate *in vacuo* was dissolved in pyridine (10 ml), and the pyridine solution was heated at reflux for 5 h. After being cooled, the reaction mixture was poured into ice-H_2O, and extracted with Et_2O. The ethereal extracts were combined, and washed successively with 5% HCl, satd. $NaHCO_3$, and satd. NaCl. Filtration and concentration of the filtrate *in vacuo*, followed by successive purification PTLC (SiO_2, petr. ether–Et_2O, 20 : 1) and bulb-to-bulb distillation, gave a mixture of **24** and its isomeric olefin as an oil (337 mg, 73%), bp 230 °C (5 mmHg) (bath temp.). The NMR spectrum of this sample exhibited signals of the methyl groups of **24** and its isomer at 1.77 (br s) and 0.97 (d, J=6 Hz) (the integration ratio 2 : 1), respectively. Therefore, the formation ratio of **24** and its isomeric olefin could be calculated as 2 : 1.

c) (±)-**25**: A part of the olefinic mixture (300 mg, 1.4 mmol) obtained in b) was treated in the same manner as described for **19**, giving pure (±)-**25** (208 mg, 60% (37% from (±)-**22**)), mp 94—95 °C, after extractive isolation and purification by column chromatography (SiO_2, petr. ether–Et_2O, 1 : 10). An analytical sample was obtained by recrystallization from iso-Pr_2O, mp 96—97 °C. IR ν_{max}^{KBr} cm^{-1}: 3380, 1480, 1252, 1055. NMR ($CDCl_3$) δ: 1.13 (3H, s, $C\underline{H}_3$), 1.5—1.9 (2H, m, $ArCH_2C\underline{H}_2$), 1.93 (1H, s, $O\underline{H}$), 2.35—2.67 (1H, s, $O\underline{H}$), 2.7—3.45 (5H, m, $C\underline{H}_2CH_2C\underline{H}(OH)C\underline{H}_2$), 3.72 and 3.74 (each 6H, two s, $OC\underline{H}_3\times2$), 6.62 (2H, s, aromatic protons). *Anal.* Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.61; H, 8.17.

(±)-6-Hydroxy-1,4-dimethoxy-6-methyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-7-one ((±)-3)——a) Preparation of (±)-**3** from **26**: Treatments of **26** (100 mg, 0.36 mmol) with osmium tetraoxide in pyridine in a similar manner as described for **19** gave pure (±)-**3** (57 mg, 63%), mp 54—56 °C, after extractive isolation with Et_2O, followed by purification with PTLC (SiO_2, petr. ether–Et_2O, 2 : 1). The spectral (IR and NMR) and chromatographic (TLC) properties of this sample were identical with those of (±)-**3** obtained in b).

b) Preparation of (±)-**3** from (±)-**25**: Oxidation of (±)-**25** (150 mg, 0.59 mmol) with a combination of sulfur trioxide·pyridine complex–Et_3N–DMSO in the same manner as described for (±)-**20** gave pure (±)-**3** as a colorless solid (95 mg, 64%), mp 54—56 °C, after purification by PTLC (SiO_2, petr. ether–Et_2O, 2 : 1). Recrystallization from C_6H_{12} gave an analytical sample as colorless crystals, mp 56—57 °C. IR ν_{max}^{KBr} cm^{-1}: 3470, 1695, 1482, 1252, 1078. NMR ($CDCl_3$) δ: 1.11 (3H, s, $C\underline{H}_3$), 2.18—2.85 (4H, m, $ArC\underline{H}_2\times2$), 3.45—3.69 (2H, m, $ArCH_2C\underline{H}_2CO$), 3.69 (1H, s, $O\underline{H}$), 3.79 and 3.81 (each 6H, two s, $OC\underline{H}_3\times2$), 6.78 (2H, s, aromatic protons). *Anal.* Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.15; H, 7.33.

Treatment of (*R*)-(−)-2-Ethyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((*R*)-(−)-12) under the Conditions for Racemization (Table I, Runs 5, 6)——A solution of (*R*)-(−)-**12** ($[\alpha]_D^{20}$ −24.5° (c=1.31, $CHCl_3$)) (200 mg, 0.85 mmol) and TsOH–H_2O (1.6 g, 8.5 mmol, 10 eq to (*R*)-(−)-**12**)) in a mixture of AcOH (2.5 ml) and H_2O (1.4 ml) was heated at 110 °C for 20 h. After being cooled, the mixture was diluted with H_2O, and extracted with CH_2Cl_2. The combined organic extracts were washed successively with H_2O, satd. $NaHCO_3$, and H_2O. Filtration and concentration of the filtrate *in vacuo*, followed by purification by PTLC (SiO_2, C_6H_6–EtOAc, 10 : 1), gave (*R*)-(−)-**12** as an oil (56 mg, 28% recovery), bp 200 °C (3 mmHg) (bath temp.), $[\alpha]_D^{20}$ −23.9° (c=1.03, $CHCl_3$), 98% ee, 2% racemization. The recovered alcohol was identified by spectral (IR and NMR) comparisons with an authentic sample.

When (*R*)-(−)-**12** (100 mg, 0.42 mmol) was treated with TsOH–H_2O (5.6 g, 30 mmol, 70 eq to (*R*)-(−)-**12**) in a mixture of AcOH (4.9 ml) and H_2O (2.8 ml) at 110 °C for 20 h, a complex mixture of reaction products was obtained after extractive isolation followed by concentration *in vacuo*, due to complete decomposition of (*R*)-(−)-**12**.

Treatment of 2-Acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (5) under the Conditions for Racemization (Table I, Run 5)——A solution of **5**[5] (50 mg, 0.22 mmol) and TsOH–H_2O (2.9 g, 15 mmol, 70 eq to **5**) in a mixture of AcOH (2.5 ml) and H_2O (1.4 ml) was heated at 110 °C for 20 h. After cooling, the mixture was diluted with H_2O, and extracted with CH_2Cl_2. The combined organic extracts were washed successively with H_2O, satd. $NaHCO_3$, and H_2O. Filtration and concentration *in vacuo* gave a complex mixture of reaction products as a tar. TLC analysis of this residue clearly showed the complete absence of the starting material (**5**) and (±)-**1a** in the tarry residue.

In a similar manner, **5** (50 mg, 0.22 mmol) was completely decomposed even when treated with *p*-TsOH–H_2O (410 mg, 2.2 mmol, 10 eq to **5**) in a mixture of AcOH (1.6 ml) and H_2O (1.1 ml) at 110 °C for 20 h.

Treatment of (±)-7-Hydroxy-1,4-dimethoxy-7-methyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-one ((±)-2) and

(±)-6-Hydroxy-1,4-dimethoxy-6-methyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-7-one ((±)-3) under the Conditions for Racemization——a) Reaction with (±)-**3** (Table I, Runs 10 and 11): A solution of (±)-**3** (75 mg, 0.30 mmol) and TsOH–H_2O (4.0 g, 21 mmol, 70 eq to (±)-**3**) in a mixture of AcOH (3.5 ml) and H_2O (2.0 ml) was heated at 110 °C for 20 h. After being cooled, the mixture was diluted with H_2O, and extracted with CH_2Cl_2. The combined organic extracts were washed successively with H_2O, satd. $NaHCO_3$, and H_2O. Filtration and concentration of the filtrate *in vacuo*, followed by purification with PTLC (SiO_2, C_6H_6–EtOAc, 7:1), gave (±)-**1a** as a colorless solid (49.5 mg, 66%), mp 99—101 °C. This was shown to be identical with an authentic sample[3,5,6] by spectral (IR and NMR) and chromatographic (TLC) comparisons.

When (±)-**3** (50 mg, 0.20 mmol) was treated with TsOH–H_2O (380 mg, 2.0 mmol, 10 eq to (±)-**3**) in a mixture of AcOH (1.5 ml) and H_2O (1.0 ml), (±)-**1a** (39.5 mg, 79%), mp 99—101 °C, could be obtained after extractive isolation and chromatographic separation.

b) Reaction with (±)-**2** (Table I, Runs 8 and 9): When (±)-**2** (30 mg, 0.12 mmol) was treated with TsOH–H_2O (1.6 g, 8.4 mmol, 70 eq to (±)-**2**) in a mixture of AcOH (1.4 ml) and H_2O (0.8 ml) or with TsOH–H_2O (228 mg, 1.2 mmol, 10 eq to (±)-**2**) in a mixture of AcOH (0.9 ml) and H_2O (0.6 ml), (±)-**1a** could be obtained in 7% (2.1 mg) or 10% (3.0 mg) yield, respectively, after extractive isolation and chromatographic separation. These products were shown to be identical with an authentic sample[3,5,6] by spectral (IR) and chromatographic (TLC) comparisons.

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11) All melting points were determined with a Büchi 510 melting point apparatus and are uncorrected. All boiling points are uncorrected. A Büchi GKR-50 apparatus was used for bulb-to-bulb distillation. Infrared (IR) spectra measurements were performed with a JASCO DS-402G infrared spectrometer. Nuclear magnetic resonance (NMR) spectra were measured with a JEOL FX-100 spectrometer and a JEOL JNM-PS-100 spectrometer. All signals are expressed as ppm downfield from tetramethylsilane, used as an internal standard (δ value). The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). Mass spectra (MS) were taken with a JEOL JMS-01 SG-2 mass spectrometer. Measurements of optical rotations were carried out using a JASCO DIP-181 digital polarimeter. All reactions were carried out using anhydrous solvent. The combined organic extracts obtained in each experiment were dried over anhyd. $MgSO_4$, filtered, and concentrated *in vacuo* with a rotary evaporator. Wako gel C-200 and Merck Silica gel 60G were used as adsorbents for column chromatography and preparative thin layer chromatography (PTLC), respectively. The following abbreviations are used for solvents and reagents: acetic acid (AcOH), acetone (Me_2CO), benzene (C_6H_6), chloroform ($CHCl_3$), cyclohexane (C_6H_{12}), dichloromethane (CH_2Cl_2), dimethyl sulfoxide (DMSO), ether (Et_2O), ethyl acetate (EtOAc), hexane (C_6H_{14}), isopropanol (iso-PrOH), isopropyl ether (iso-Pr_2O), triethylamine (Et_3N), tetrahydrofuran (THF), *p*-toluenesulfonic acid (TsOH).
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