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Titanium Tetrachloride-Mediated Diels–Alder Reactions of Cyclopentadiene with Di-*l*-menthyl Methylenemalonate and Its Acetoxy Derivative as New Chiral Dienophiles for Asymmetric Induction

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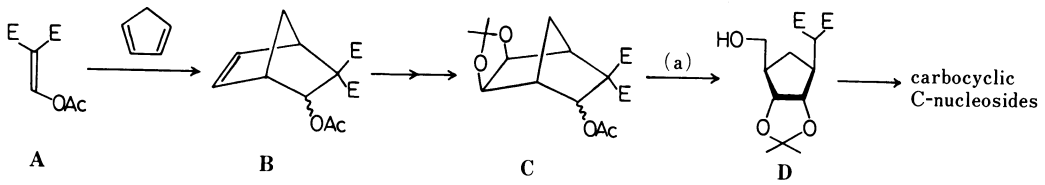
Asymmetric synthesis of [1*S*,2*S*,3*R*,4*R*]-2,3-dihydroxy-4-hydroxymethylcyclopent-1-ylmalonate (its racemic form is already known as a versatile building block for carbocyclic C-nucleosides) was achieved by Diels–Alder reaction of cyclopentadiene with di-*l*-menthyl acetoxymethylenemalonate, followed by retrograde aldol C–C bond fission under reductive conditions. Asymmetric induction in Diels–Alder reactions using the chiral dienophile and its nor-acetoxy derivative is discussed from a mechanistic viewpoint and a new concept for asymmetric induction is proposed.

Keywords——asymmetric synthesis; asymmetric Diels–Alder reaction; carbocyclic C-nucleoside; di-*l*-menthyl acetoxymethylenemalonate; cyclopentadiene; titanium tetrachloride; [4+2]-cycloadduct; reductive retrograde aldol reaction; asymmetric induction; new concept

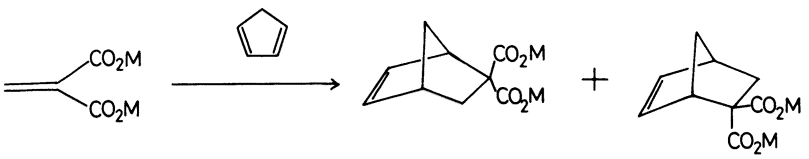
Since the asymmetric Diels–Alder reaction of di-*l*-menthyl fumarate with acyclic dienes was reported by Walborsky *et al.*[1] in 1961, enormous amounts of work on this reaction using enoates of chiral alcohols as dienophiles have been reported. In order to improve the diastereomeric excess (d.e.), many chiral enoates have been examined as dienophiles either in non-catalyzed or in Lewis acid-catalyzed Diels–Alder reactions over the last two decades.[2] Previously, we succeeded in the synthesis of carbocyclic C-nucleoside analogues *via* the adduct **B** obtained by Diels–Alder reaction of dimethyl acetoxymethylenemalonate **A** with cyclopentadiene.[3] The adduct **B** was then converted to the acetonide **C**, whose reductive retrograde aldol C–C bond fission (a) gave the versatile synthetic building block **D** (racemic) with complete stereoselection (Chart 1).

In order to extend this methodology to enantioselective synthesis of the compound **D**, it is necessary to examine the Diels–Alder reaction of chiral methylenemalonates. However,



E = CO_2Me
(a): reductive retrograde aldol C–C bond fission
($NaBH_4/K_2CO_3$/methanol, room temperature)

Chart 1



1 2 2′

M = *l*-menthyl

Chart 2

TABLE I. Diels–Alder Reaction of Di-*l*-menthyl Methylenemalonate (**1**) with Cyclopentadiene

Run	Catalyst	Temp. (°C)	Time (h)	Yield (%)	d.e. (%)
1	$TiCl_4$	−78	1	93	≥80
2	None	−78	4	65[a]	42
3	None	20	4	93	25

a) The starting dienophile **1** was recovered in 30% yield.

most studies have been limited to chiral acrylates and fumarates, and no work on the Diels–Alder reaction using chiral methylenemalonates as dienophiles has yet been reported.

In this paper, we wish to report the successful asymmetric Diels–Alder reactions of di-*l*-menthyl methylenemalonate and its acetoxy derivative with cyclopentadiene, the latter of which provides an enantioselective route to carbocyclic C-nucleoside analogues. During this work, we have also developed a new concept concerning asymmetric induction in the Diels–Alder reaction, which is another subject of this paper. A part of this work has been published as a communication.[4]

A new chiral dienophile **1** was synthesized from di-*l*-menthyl malonate according to the method for the preparation of the corresponding diethyl ester reported by Takagi and Asahara.[5] Thus, when di-*l*-menthyl malonate prepared by the condensation of *l*-menthol and malonic acid in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) was allowed to react with paraformaldehyde in the presence of cupric acetate, the desired dienophile **1** was obtained in 37% yield. Although the reaction was investigated under a variety of conditions, the yield of **1** could not be improved.

The reaction of **1** with cyclopentadiene was carried out under various conditions. The results are shown in Table I. Thus, reaction of cyclopentadiene with **1** in the presence of titanium tetrachloride (0.1 eq) at −78 °C gave the [4+2]cycloadduct as a mixture of diastereoisomers (**2** and **2′**) in 93% yield. Careful examination of the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of the adduct revealed the d.e. to be ≥80%. Namely, the signals of **2** due to two olefinic protons were observed at δ 5.87 (dd) and 6.29 (dd), respectively, whereas those of **2′** appeared at δ 6.29 as a multiplet. The ^{1}H-NMR spectrum of the adduct using tris(heptafluorobutanoylpivaloylmethanato)europium (Eu(FOD)) as a shift reagent further confirmed these observations. Though the isomers were difficult to separate chromatographically from each other, the major isomer **2**, mp 129—130 °C, was isolated by recrystallization from methanol. The yield and d.e. of the adduct were 65% and 42%, respectively, when the reaction was carried out at −78 °C without a catalyst. In this reaction, the starting dienophile **1** was recovered in 30% yield. Although the dienophile **1** reacted with cyclopentadiene at 20 °C without a catalyst to give a high yield of the adduct, the d.e. was, of course, much lower (25%). From the above experimental results, it is evident that titanium

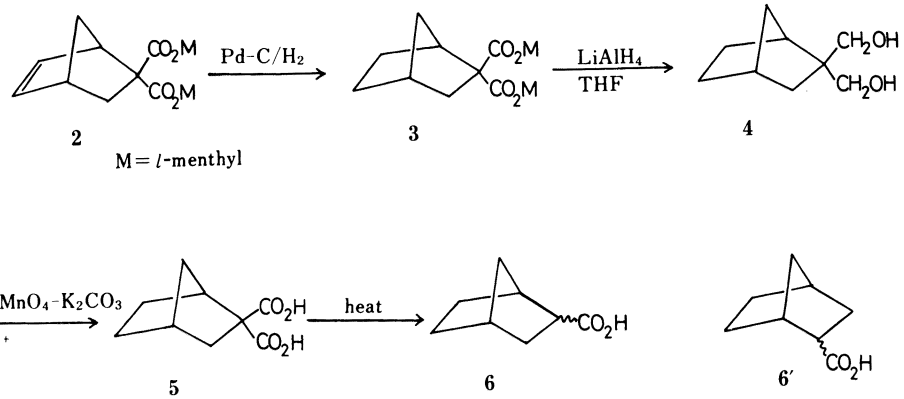


Chart 3

tetrachloride not only enhances the rate of the reaction but also increases the d.e. considerably.

The absolute structure of the major isomer **2** was determined as follows: the dihydro derivative **3** obtained from **2** by catalytic hydrogenation was submitted to lithium aluminum hydride (LAH) reduction to give the diol **4** in 86% yield. Oxidation of **4** with potassium permanganate in an alkaline medium gave a 57% yield of the dicarboxylic acid **5**, which could not be obtained directly from **3** by saponification. Decarboxylation of **5** by heating at 180—190 °C resulted in the formation of bicyclo[2.2.1]heptane-2-carboxylic acid (**6**) in 76% yield as a mixture of *endo*- and *exo*-isomers. The optical rotation of **6** was +36.28° (95% EtOH), indicative of an enantiomer of the known compound **6'** [*endo*: $[\alpha]_D$ −42.8° (95% EtOH), *exo*: $[\alpha]_D$ −39.0° (95% EtOH)].[6]

On the basis of high asymmetric induction in the above Diels–Alder reaction (using **1**) as well as our successful application of the Diels–Alder adduct obtained from achiral acetoxymethylenemalonate[3] and its derivatives[7] to the synthesis (in racemic series) of carbocyclic C-nucleoside analogues (Chart 1), we next examined the Diels–Alder reaction of di-*l*-menthyl acetoxymethylenemalonate (**10**) with cyclopentadiene.

Though we could not synthesize the dienophile **10** according to the method previously reported for the synthesis of dienophile **A**, we have succeeded in its synthesis by using formyl Meldrum's acid (**7**) as the starting material. Thus, reaction of **7** with *l*-menthol in benzene at 55 °C for 2 h gave a half ester **8** in quantitative yield. In this reaction, prolonged heating or higher temperature resulted in the formation of *l*-menthyl formylacetate. Condensation of **8** with *l*-menthol using DCC gave the diester **9** as a crystalline substance, which was acetylated in a usual manner to give the desired dienophile **10**.

Diels–Alder reaction of **10** with cyclopentadiene was investigated under various conditions, and the results are shown in Table II. As shown in run 1, the reaction of **10** with cyclopentadiene in the presence of a catalytic amount of titanium tetrachloride at −78 °C afforded the adduct **11** in 83% chemical yield with a high d.e. (>90%). On raising the reaction temperature, the yield, *endo*/*exo* ratio, and d.e. were decreased. On the other hand, use of diethylaluminum chloride instead of titanium tetrachloride as the catalyst also resulted in decreases of both yield and d.e.

The ratio of *endo*- and *exo*-isomers was determined from the ^{1}H-NMR spectrum, as described in the experimental section.

Since the adduct **11** (as a mixture of *endo*- and *exo*-isomers) was difficult to separate by column chromatography, the d.e. of each product (*endo*- or *exo*-isomer) could not be determined. Therefore, the d.e. of the adduct **11** was determined as follows: catalytic

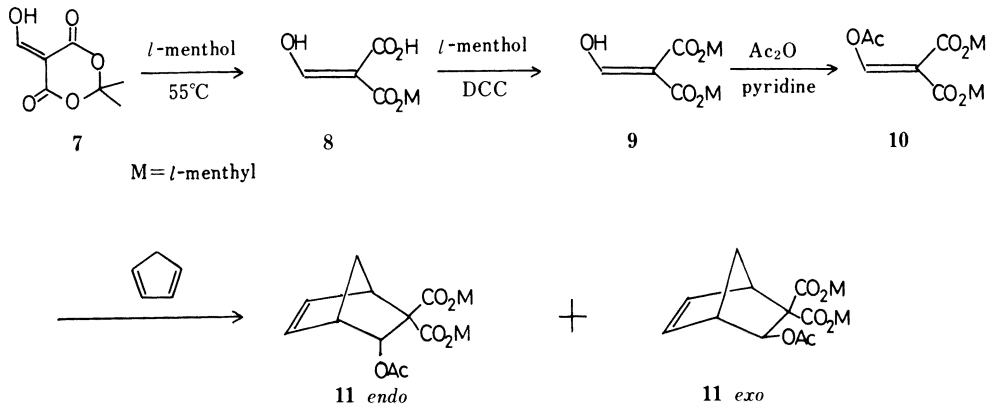


Chart 4

TABLE II. Asymmetric Diels–Alder Reaction of Di-*l*-menthyl Acetoxymethylenemalonate (**10**) with Cyclopentadiene

Run	Catalyst (eq)	Reaction temp. (°C)	Reaction time (h)	Yield (%)	*endo*/*exo*	d.e. (%)
1	$TiCl_4$ (0.1)	−78	5	83	3	≥90
2	$TiCl_4$ (0.1)	−15	0.5	79	2	79
3	$TiCl_4$ (0.1)	Room temp.	0.5	34	1	67
4	Et_2AlCl (1)	−78	3.5	49	5	33
5	Et_2AlCl (1)	−15	3	23	2	0
6	Et_2AlCl (0.1)	−15	3	0[a]	—	—

a) The Diels–Alder reaction under these conditions, as well as at ambient temperature without any catalyst, resulted in complete recovery of the starting materials.

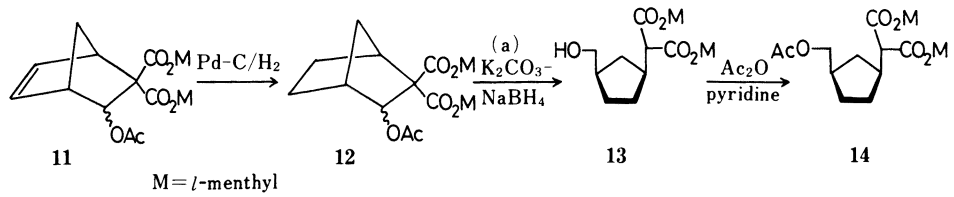


Chart 5

hydrogenation of **11** gave the dihydro derivative **12** as a mixture of *endo*- and *exo*-isomers. Reductive retrograde aldol C–C bond fission of **12** followed by acetylation gave rise to the cyclopentane derivative **14**. The ^{1}H-NMR spectrum of **14** using Eu(FOD) as a shift reagent allowed the d.e. to be obtained precisely by using the acetyl group signal as the criterion.

The absolute structure of **11** was determined by its conversion to the known lactone **23** (Chart 6). According to the method previously described for the synthesis of carbocyclic C-nucleoside precursors in an achiral series using dialkyl acetoxymethylenemalonate as the dienophile,[3] the adduct **11** was treated with osmium tetroxide to give the *exo*-diol derivative **15** which was subsequently protected with an isopropylidene group to produce the acetonide **16**. Compound **16** was submitted to reductive retrograde aldol reaction to give the carbocyclic C-nucleoside precursor **17** in quantitative yield. Saponification of **17** with alkali followed by decarboxylation afforded the unprotected carboxylic acid, which was transformed to the

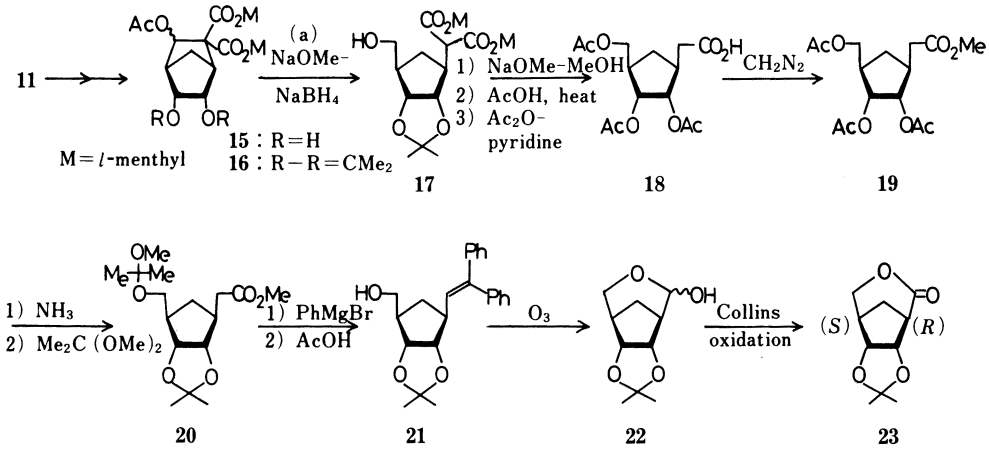


Chart 6

protected ester **19** by acetylation (formation of **18**) and subsequent methylation with diazomethane. Compound **19** was treated successively with ammonia and 2,2-dimethoxypropane to give the acetonide **20**. Barbier–Wieland degradation of **20** followed by Collins oxidation afforded the final product **23** [mp 141—143 °C, $[\alpha]_D^{26}$ +41.1 ° (c=0.19, $CHCl_3$); lit.[8] mp 140—141.5 °C, $[\alpha]_D^{26}$ +44.4 ° (c=1.0, $CHCl_3$)] *via* **21** and **22**.

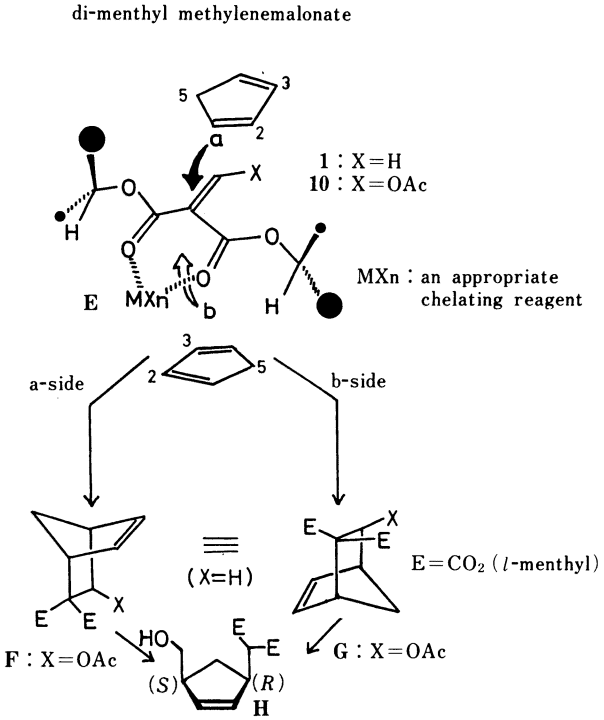
It has thus been proved that the Diels–Alder reaction of di-*l*-menthyl methylenemalonate (**1**) or its acetoxy derivative **10** with cyclopentadiene proceeds with high diastereoselection only if it is carried out in the presence of titanium tetrachloride. In order to account for this remarkable diastereoselectivity in the addition step, we must assume not only that the C_2-C_3-moiety of cyclopentadiene is more bulky than the C_5-moiety but also that the dienophile should be fixed rigidly in a plane having *s-trans* conformation **E**, with the aid of titanium tetrachloride. Then, one would expect predominant formation of either **F** (from a-side attack: X=OAc, *endo*-isomer) or **G** (from b-side attack: X=OAc, *exo*-isomer). In the case of di-*l*-menthyl methylenemalonate (X=H), the adduct **2** (**F**=**G**) forms predominantly, while both adducts (**F** and **G**) derived from the acetoxy derivative (X=OAc) finally afford a single enantiomer **H** after reductive retrograde aldol C–C bond fission (Fig. 1).

This provides further support for the former assumption that Diels–Alder reaction of the dienophile **1** with cyclohexadiene, which should have comparable bulkiness between the C_2-C_3 and C_5-C_6 moieties, does not cause any significant asymmetric induction.

Previously, high diastereoselection in the Diels–Alder reaction has only been observed by using di-menthyl fumarate as the dienophile and this was known by the name of "co-operativity concept."[9] In this case, diastereoselectivity is explained by the plane model, and the a-side is far less hindered than the b-side. Since a C_2 symmetry axis exists perpendicular to the C=C double bond of the dienophile, the diene approaches from the less hindered a-side to give the same diastereoisomer, irrespective of the mode of approach of the diene (Fig. 2).

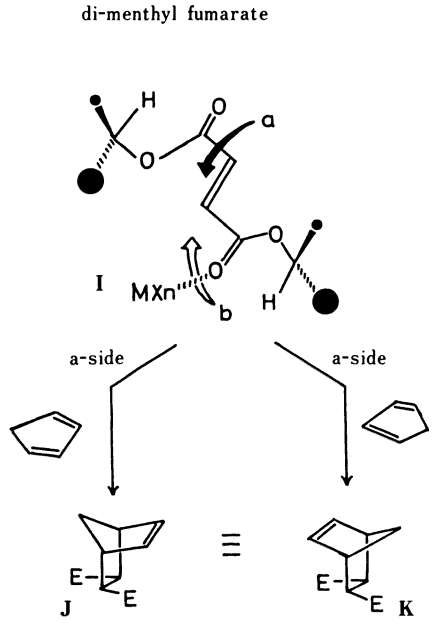
As is evident from the above arguments, the asymmetric Diels–Alder reactions observed with the chiral methylenemalonate **1** or **10** are conceptually different from those of the corresponding fumarates. Therefore, the diastereoselection found in the present study represents a new concept for asymmetric induction in the Diels–Alder reaction.[10]

It should also be noted that in the above reactions only a catalytic amount of titanium tetrachloride is needed, whereas for the corresponding fumarate series the amount of this or other Lewis acid catalysts is 1 mol eq or more with respect to the dienophiles. This supports the conclusions that titanium tetrachloride in the present reactions does chelate with both



(stereofacial selection: a = b)
endo-exo: large difference in preference
a: *endo* ≫ *exo*
b: *exo* ≫ *endo*

Fig. 1



stereofacial selection: a ≫ b
(*endo-exo*)

Fig. 2

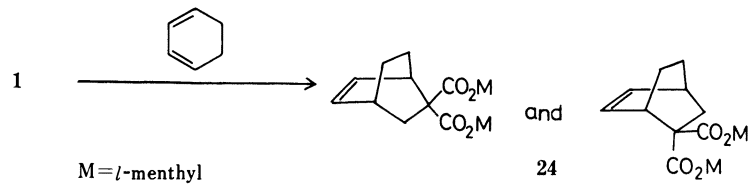


Chart 7

carbonyl groups of the dienophiles (**1** or **10**) at the same time (**E** in Fig. 1)[11] and that this chelated species is the only dienophile in these reactions, affording the high d.e. value.[12]

Experimental

All melting points were determined on a Yanaco model MP instrument, and are uncorrected. Optical rotations were measured with a JASCO DIP-340 digital polarimeter. Infrared (IR) spectra were measured on a JASCO A-102 spectrometer. ^{1}H-NMR spectra at 60 and 100 MHz were recorded with JEOL JNM-PMX 60 si and JEOL JNM-FX100 spectrometers using tetramethylsilane (TMS) as an internal standard, respectively. The abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublet; br, broad; br s, broad singlet. Low- and high-resolution mass spectra (MS) were obtained on Hitachi M-52G and JEOL JMS-01SG-2 instruments, respectively. Wakogel (C-200) and Merck Kiesel-gel 60 F254 were employed for silica gel column and preparative thin layer chromatography (TLC), respectively. The ratio of solvent mixtures for chromatography is shown as volume/volume.

Di-*l*-menthyl Methylenemalonate (1)——A solution of DCC (28.88 g, 0.14 mol) in anhydrous ether (50 ml) was added to a solution of malonic acid (7.28 g, 0.07 mol) and *l*-menthol (21.84 g, 0.14 mol) in anhydrous ether (100 ml) with stirring under ice-salt cooling. After being allowed to stand at room temperature for 2 h, the precipitate was filtered off. The filtrate was concentrated *in vacuo*, and the crystalline residue was recrystallized from MeOH to give di-*l*-menthyl malonate (27.4 g, 100%, mp 55—57 °C). Next, a mixture of paraformaldehyde (0.72 g, 24 mmol) and anhydrous copper(II) acetate (0.5 g) in acetic acid (14 ml) was heated at 60 °C. Then, di-*l*-menthyl malonate (9.12 g, 24 mmol) was added to the solution, and the whole was heated to 100 °C, stirred at 100 °C for 3.5 h, and evaporated *in vacuo*. The residue was subjected to silica gel (300 g) column chromatography. Elution with hexane–ether (40 : 1) gave **1** as a colorless oil, 3.55 g (37%). $[\alpha]_D^{26}$ −85° (c=2.4, $CHCl_3$). High-resolution MS m/z: M^+ − menthyl Calcd for $C_{14}H_{21}O_4$: 253.1440. Found: 253.1442. IR ($CHCl_3$): 1730, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.58—5.11 (2H, m, menthyl 1-H), 6.39 (2H, s, olefinic H).

Di-*l*-menthyl Bicyclo[2.2.1]hept-5-ene-2,2-dicarboxylate (2)——a) $TiCl_4$ (0.2 ml) was added to a solution of **1** (1.46 g, 3.7 mmol) and cyclopentadiene (1.5 ml, 18.5 mmol) in dry toluene (20 ml) with stirring at −78 °C under an argon atmosphere. After being stirred at −78 °C for 2 h, the reaction mixture was poured into water and extracted with benzene. The organic layer was washed with water (20 ml × 3), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was subjected to silica gel (50 g) column chromatography. Elution with hexane–ether (30 : 1) gave a mixture of diastereoisomers **2** and **2'**, 1.57 g (93%, d.e. ≥80%[13]), which was recrystallized from MeOH to give **2** as colorless needles, mp 129—130 °C. $[\alpha]_D^{26}$ +27° (c=2.3, $CHCl_3$). *Anal.* Calcd for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11. Found: C, 76.28; H, 10.47. IR ($CHCl_3$): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.88 (1H, br s, 4-H), 3.45 (1H, br s, 1-H), 4.34—4.98 (2H, m, menthyl 1-H), 5.87 (1H, dd, $J_{5,6}$=6 Hz, $J_{4,5}$=3 Hz, 5-H), 6.29 (1H, dd, $J_{5,6}$=6 Hz, $J_{1,6}$=3 Hz, 6-H).

b) A solution of cyclopentadiene (330 mg, 5 mmol) in dry toluene (4 ml) was added to a solution of **1** (392 mg, 1 mmol) in dry toluene (4 ml) with stirring at −78 °C, and the mixture was stirred at −78 °C for 4 h. Work-up as above gave a mixture of **2** and **2'**, d.e. 42%,[13] 300 mg (65%), and recovered **1**, 130 mg (30%).

c) A solution of cyclopentadiene (330 mg, 5 mmol) in dry toluene (4 ml) was added to a solution of **1** (392 mg, 1 mmol) in dry toluene (4 ml) with stirring at room temperature, and the mixture was stirred at room temperature for 4 h. Work-up as above gave a mixture of **2** and **2'**, d.e. 25%, 440 mg (93%).

Di-*l*-menthyl Bicyclo[2.2.1]heptane-2,2-dicarboxylate (3)——A catalytic amount of 5% Pd–C (40 mg) was added to a solution of **2** (763 mg, 1.67 mmol) in ether (15 ml)–MeOH (8 ml). The suspension was shaken under a hydrogen atmosphere (1 atm) at room temperature for 1 h. Then, Pd–C was filtered off, and the filtrate was concentrated *in vacuo*. The crystalline substance was recrystallized from ether–MeOH to give **3** of mp 123—126 °C, colorless needles, 720 mg (94%). High-resolution MS m/z: M^++1 Calcd for $C_{29}H_{49}O_4$: 461.3631. Found: 461.3651. IR ($CHCl_3$): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.92 (1H, br s, 1-H), 4.44—4.96 (2H, m, menthyl 1-H).

2,2-Dihydroxymethylbicyclo[2.2.1]heptane (4)——A mixture of **3** (444 mg, 0.965 mmol) and $LiAlH_4$ (182 mg, 4.8 mmol) in anhydrous tetrahydrofuran (THF) (10 ml) was heated at reflux with stirring for 1.5 h. After cooling of the reaction mixture, wet ether was added in order to decompose excess $LiAlH_4$. The precipitate was filtered off, and the filtrate was chromatographed on a silica gel column. Elution with hexane–ethyl acetate (4 : 1) gave *l*-menthol (230 mg). Further elution with ethyl acetate gave **4** (130 mg, 86%) as colorless needles (ethyl acetate), mp 107—108 °C. $[\alpha]_D^{23}$ +11.8° (c=1.3, MeOH). *Anal.* Calcd for $C_9H_{16}O_2$: C, 69.18; H, 10.33. Found: C, 68.95; H, 10.01. ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.9 (8H, m), 2.2—2.5 (2H, br d), 3.4—4.1 (6H, m).

Bicyclo[2.2.1]heptane-2,2-dicarboxylic Acid (5)——$KMnO_4$ (240 mg, 152 mmol) and K_2CO_3 (105 mg, 0.76 mmol) were added successively to a suspension of **4** (60 mg, 0.38 mmol) with stirring. The reaction mixture was stirred overnight at room temperature, EtOH (1 ml) was added, and the whole was stirred for a further 1 h. The precipitate was filtered off, and the filtrate was concentrated *in vacuo*. The residue was acidified with diluted HCl, and extracted with ether. The ethereal solution was dried and concentrated, and the residue was chromatographed on a silica gel column. Elution with hexane–ethyl acetate (1 : 1) gave **5** (40 mg, 57%) as colorless needles (benzene–ether), mp 170—173 °C. $[\alpha]_D^{26}$ +152° (c=2.3, MeOH). High-resolution MS m/z: $M^+ - CO_2$ Calcd for $C_8H_{12}O_2$: 140.0837. Found: 140.0826. IR (Nujol): 3400 (br), 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.16—2.41 (9H, m), 2.86 (1H, br s, 1-H), 4.71 (2H, br s, CO_2H).

Bicyclo[2.2.1]heptane-2-carboxylic Acid (6)——The dicarboxylic acid **5** (12 mg, 0.065 mmol) was heated at 180—190 °C in a flask without solvent for 5 min. The reaction mixture was dissolved in $CHCl_3$, and the solution was submitted to silica gel column chromatography. Elution with hexane–ethyl acetate (4 : 1) gave **6** (7 mg, 77%) as a colorless oil. $[\alpha]_D^{26}$ +36.28° (c=0.7, 95% EtOH). IR ($CHCl_3$): 3400—2500, 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.1—1.9 (8H, m), 2.3 (1H, br s), 2.6 (1H, br s), 2.8—3.1 (1H, m).

Di-*l*-menthyl 2-Hydroxymethylenemalonate (9)——A solution of formyl Meldrum's acid[14] (**7**) (1.0 g, 5.81 mmol) and *l*-menthol (0.9 g, 5.81 mmol) in dry benzene (8 ml) was heated at 55 °C for 2 h. Then, *l*-menthol (0.9 g, 5.81 mmol) was added to the mixture at room temperature, and a solution of DCC (1.2 g, 5.81 mmol) in dry benzene (8 ml) was subsequently added dropwise with stirring under ice-salt cooling. The reaction mixture was stirred at room temperature for 2 h, then the precipitate was filtered off, and the filtrate was concentrated *in vacuo*. The residue was subjected to silica gel (80 g) column chromatography. Elution with hexane–chloroform (1 : 2) gave **9** as colorless

needles, mp 58—61 °C, 1.1 g (46%). *Anal.* Calcd for $C_{24}H_{40}O_5$: C, 70.55; H, 9.87. Found: C, 70.38; H, 10.15. IR ($CHCl_3$): 1685 (sh), 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.38—5.16 (2H, m, menthyl 1-H), 8.28 (1H, d, J=13 Hz, olefinic H), 13.45 (1H, d, J=13 Hz, enolic OH).

Di-*l*-menthyl 2-Acetoxymethylenemalonate (10)——Acetic anhydride (5 ml) and pyridine (5 ml) were added to a solution of **9** (898 mg, 2.20 mmol) in dry benzene (4 ml) with stirring under ice cooling. After being kept standing at room temperature for 12 h, the reaction mixture was poured into ice-water (30 ml), and extracted with benzene. The organic layer was washed with water (30 ml × 2), and dried over anhydrous sodium sulfate. The solvent was evaporated off *in vacuo*, and the residue was subjected to silica gel (20 g) column chromatography. Elution with hexane–ethyl acetate (15 : 1) gave **10** (948 mg, quantitative yield). $[\alpha]_D^{24}$ −43.8° (c=4.6, $CHCl_3$). High-resolution MS m/z: M^+ − Ac − menthol Calcd for $C_{14}H_{21}O_4$: 253.1440. Found: 253.1487. IR ($CHCl_3$): 1790, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.20 (3H, s, AcO), 4.47—5.15 (2H, m, menthyl 1-H), 8.43 (1H, s, olefinic H).

Di-*l*-menthyl 3-*endo*- and *exo*-Acetoxybicyclo[2.2.1]hept-5-ene-2,2-dicarboxylate (11)——a) A catalytic amount of $TiCl_4$ (84 mg, 0.44 mmol) was added to a solution of **10** (2.2 g, 4.4 mmol) and cyclopentadiene (1.2 g, 22 mmol) with stirring at −78 °C. After being stirred at −78 °C for 4 h, the reaction mixture was poured into water (10 ml) and extracted with benzene (30 ml). The organic layer was washed with water (30 ml × 2), and dried over anhydrous sodium sulfate. The solvent was evaporated off *in vacuo*, and the residue was subjected to silica gel (110 g) column chromatography. Elution with hexane–ether (10 : 1) gave **11** (*endo*/*exo*=3), 2.1 g (83%). High-resolution MS m/z: M^++1 Calcd for $C_{31}H_{49}O_6$: 517.3529. Found: 517.3484. IR ($CHCl_3$): 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.95 (3H × 3/4, s, AcO, *endo*), 2.03 (3H × 1/4, s, AcO, *exo*), 2.83—3.50 (2H, m, 1, 4-H), 4.37—5.03 (2H, m, menthyl 1-H), 5.58 (1H × 1/4, br s, 3-H, *exo*), 5.93—6.73 (2H, m, olefinic H), 6.17 (1H × 3/4, d, $J_{3,4}$=4 Hz, 3-H, *endo*).

In the same manner, the adduct **11** was obtained from the reaction of **10** with cyclopentadiene at −15 °C and room temperature in 79% (*endo*/*exo*=2) and 34% (*endo*/*exo*=1) yields, respectively.

b) Et_2AlCl (0.8 ml, 1.32 mmol) and cyclopentadiene (175 mg, 6.6 mmol) were added successively to a solution of **10** (595 mg, 1.32 mmol) in dry toluene (10 ml) at −78 °C with stirring. The mixture was stirred at −78 °C for 3.5 h, and poured into water (10 ml). The whole was extracted with benzene, and the organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was chromatographed on a silica gel (20 g) column. Elution with hexane–ether (7 : 1) gave the adduct **11** (332 mg, 49%, *endo*/*exo*=5).

In the same manner, the adduct **11** (23%, *endo*/*exo*=2) was obtained from the reaction of **10** with cyclopentadiene at −15 °C.

Di-*l*-menthyl 3-*endo*- and *exo*-Acetoxybicyclo[2.2.1]heptane-2,2-dicarboxylate (12)——a) A catalytic amount of 10% Pd–C (30 mg) was added to a solution of **11** (271 mg, 0.52 mmol, *endo*/*exo*=3) in absolute EtOH (6 ml)–anhydrous ether (3 ml). The mixture was shaken under a hydrogen atmosphere (1 atm) at room temperature. After being shaken for 1 h, Pd–C was filtered off by suction, and the filtrate was concentrated *in vacuo*. The residue was subjected to silica gel column chromatography. Elution with hexane–ether (10 : 1) gave **12** (*endo*/*exo*=3), 199 mg (74%). High-resolution MS m/z: M^++1 Calcd for $C_{31}H_{51}O_6$: 519.3686. Found: 519.3653. IR ($CHCl_3$): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.97 (3H × 3/4, s, AcO, *endo*), 2.05 (3H × 1/4, s, AcO, *exo*), 2.48—2.98 (2H, m, 1, 4-H), 4.42—4.98 (2H, m, menthyl 1-H), 5.50 (1H × 1/4, d, $J_{3,4}$=2 Hz, 3-H, *exo*), 5.65 (1H × 3/4, d, $J_{3,4}$=5 Hz, 3-H, *endo*).

b) A catalytic amount of 10% Pd–C (30 mg) was added to a solution of **11** (178 mg, 0.34 mmol, *endo*/*exo*=2) in absolute EtOH (6 ml)–anhydrous ether (3 ml), and the mixture was shaken under a hydrogen atmosphere (1 atm) at room temperature for 1 h. Work-up as above gave **12** (*endo*/*exo*=2), 156 mg (88%).

Di-*l*-menthyl 2-(4β-Hydroxymethylcyclopent-1β-yl)malonate (13)——a) $NaBH_4$ (141 mg, 3.8 mmol) and K_2CO_3 (524 mg, 3.8 mmol) were added successively to a solution of **12** (199 mg, 0.38 mmol, *endo*/*exo*=3) in absolute MeOH (5 ml)–anhydrous ether (3 ml) with stirring under ice-salt cooling. After being stirred at room temperature for 12 h, the reaction mixture was neutralized with acetic acid. The solvent was evaporated off *in vacuo*, and the residue was subjected to silica gel (5 g) column chromatography. Elution with hexane–ethyl acetate (20 : 3) gave **13**, 162 mg (89%). High-resolution MS m/z: M^++1 Calcd for $C_{29}H_{51}O_5$: 479.3736. Found: 479.3699. IR ($CHCl_3$): 1740 (sh), 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.20 (1H, d, J=10 Hz, 2-H), 3.53 (2H, d, J=6 Hz, C$\underline{H}_2$OH), 4.45—4.95 (2H, m, menthyl 1-H).

b) $NaBH_4$ (96 mg, 2.63 mmol) and K_2CO_3 (363 mg, 2.63 mmol) were added successively to a solution of **12** (136 mg, 0.26 mmol, *endo*/*exo*=2) in absolute MeOH (5 ml)–anhydrous ether (3 ml) with stirring under ice cooling. The mixture was stirred at room temperature for 12 h. Work-up as above gave **12**, 101 mg (81%).

Di-*l*-menthyl 2-(4β-Acetoxymethylcyclopent-1β-yl)malonate (14)——a) Pyridine (1 ml) was added dropwise to a solution of **13** (141 mg, 0.29 mmol) obtained from **12** (*endo*/*exo*=3) in dry benzene (2 ml)–acetic anhydride (1 ml) with stirring under ice cooling. After being kept standing at room temperature for 2 h, the reaction mixture was poured into ice-water (10 ml) and extracted with benzene. The organic layer was washed with water (10 ml × 3) and dried over anhydrous sodium sulfate. The solvent was evaporated off *in vacuo*, and the residue was subjected to silica gel (5 g) column chromatography. Elution with hexane–ethyl acetate (10 : 1) gave a crystalline substance, which was recrystallized from MeOH–H_2O to give **14** as colorless needles, mp 49—51 °C, 134 mg (89%) (d.e. ≥90%[15]). *Anal.* Calcd for $C_{31}H_{52}O_6$: C, 71.50; H, 10.07. Found: C, 71.68; H, 10.36. IR ($CHCl_3$): 1740, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.04 (3H, s, AcO), 3.19 (1H, d, J=10 Hz, 2-H), 3.98 (2H, d, J=6 Hz, C$\underline{H}_2$OAc), 4.46—4.96 (2H, m, menthyl 1-H).

b) Pyridine (0.5 ml) was added dropwise to a solution of **13** (13 mg, 0.03 mmol) obtained from **12** (*endo*/*exo*=2)

in dry benzene (1 ml)–acetic anhydride (0.5 ml) with stirring under ice cooling. The mixture was allowed to stand at room temperature for 2 h. Work-up as above gave **14** (d.e. 71%[15]), 11 mg (78%).

Di-*l*-menthyl 3-*endo*- and *exo*-Acetoxy-5,6-*exo*-dihydroxybicyclo[2.2.1]heptane-2,2-dicarboxylate (15)——A mixture of 2 ml of OsO_4–*tert*-BuOH solution [prepared from *tert*-BuOH (200 ml), OsO_4 (1 g), and 30% aqueous H_2O_2 (3 drops)] and 60% aqueous 4-methylmorpholine *N*-oxide solution (2 ml) was added to a solution of **11** (1.7 g, 3.10 mmol, *endo*/*exo* = 3) in acetone (5 ml)–ether (10 ml) with stirring. After being stirred at room temperature for 2 h, the reaction mixture was poured into ice-water, and extracted with ether. The organic layer was dried over anhydrous sodium sulfate, and concentrated *in vacuo*, then the residue was subjected to silica gel (50 g) column chromatography. Elution with hexane–ether (2 : 1) gave **15**, 1.67 g (quantitative yield). High-resolution MS *m/z*: $M^+ - AcOH - H_2O$ Calcd for $C_{29}H_{44}O_5$: 472.3188. Found: 472.3204. IR ($CHCl_3$): 3500, 1750, 1730 (sh) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.97 (1H × 1/4, s, AcO, *exo*), 2.02 (1H × 3/4, s, AcO, *endo*), 5.57 (1H × 1/4, s, 3-H, *exo*), 5.83 (1H × 3/4, d, $J_{3,4}$ = 5 Hz, 3-H, *endo*).

Di-*l*-menthyl 3-*endo*- and *exo*-Acetoxy-5,6-*exo*-dihydroxy-di-*O*-isopropylidenebicyclo[2.2.1]heptane-2,2-dicarboxylate (16)——*p*-TsOH · H_2O (50 mg) was added to a solution of **15** (1.2 g, 2.2 mmol) in 2,2-dimethoxypropane (20 ml). After being stirred at room temperature for 30 min, the reaction mixture was neutralized with sodium hydrogen carbonate and the precipitate was filtered off. The filtrate was concentrated *in vacuo*, and the residue was subjected to silica gel (50 g) column chromatography. Elution with hexane–ether (10 : 1) gave **16**, 1.24 g (quantitative yield). High-resolution MS *m/z*: $M^+ - Me$ Calcd for $C_{33}H_{51}O_8$: 575.3584. Found: 575.3591. IR ($CHCl_3$): 1740, 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24, 1.44 (6H × 1/4, s × 2, isopropylidene-Me, *exo*), 1.28, 1.43 (6H × 3/4, s × 2, isopropylidene-Me, *endo*), 5.52 (1H × 1/4, s, 3-H, *exo*), 5.83 (1H × 3/4, d, $J_{3,4}$ = 5 Hz, 3-H, *endo*).

Di-*l*-menthyl 2-(2α,3α-Dihydroxy-di-*O*-isopropylidene-4β-hydroxymethylcyclopent-1β-yl)malonate (17)——$NaBH_4$ (1.02 g, 27 mmol) and NaOMe–MeOH [prepared from MeOH (10 ml) and Na (310 mg, 13.5 mmol)] were added to a solution of **16** (3 g, 5 mmol) in absolute MeOH (20 ml) with stirring under ice cooling. After being stirred under ice cooling for 30 min, the reaction mixture was neutralized with acetic acid under ice-salt cooling. After concentration *in vacuo*, the residue was subjected to silica gel (40 g) column chromatography. Elution with hexane–ethyl acetate (3 : 1) gave **17**, 2.7 g (quantitative yield). $[\alpha]_D^{27}$ −39.7° (*c* = 2.6, $CHCl_3$). *Anal.* Calcd for $C_{32}H_{54}O_7 \cdot 3H_2O$: C, 63.54; H, 10.00. Found: C, 63.72; H, 9.50. IR ($CHCl_3$): 3500, 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26, 1.47 (6H, s × 2, isopropylidene-Me), 3.39 (1H, d, *J* = 8 Hz, C<u>H</u>$(CO_2Me)_2$), 3.67 (2H, d, *J* = 6 Hz, C<u>H</u>$_2$OH), 4.35—4.45 (2H, m, 3, 4-H).

Methyl 2-(2α,3α-Diacetoxy-4β-acetoxymethylcyclopent-1β-yl)acetate (19)——Compound **17** (1 g, 1.8 mmol) was dissolved in NaOMe–MeOH [prepared from MeOH (20 ml) and Na (441 mg, 18 mmol)], and the solution was refluxed for 10 h. The solvent was evaporated off *in vacuo*, and acetic acid (30 ml) was added to the residue. The mixture was refluxed for 10 h, acetic acid was evaporated off, and acetic anhydride (10 ml) and pyridine (10 ml) were added to the residue. The mixture was kept standing at room temperature for 10 h, then the solvent was evaporated off *in vacuo*. The residue was subjected to silica gel column chromatography. Elution with hexane–ethyl acetate (1 : 2) gave a monocarboxylic acid **18** as a colorless oil, 404 mg (71%). This monocarboxylic acid was treated with CH_2N_2–ether to give **19** in quantitative yield.

18: High-resolution MS *m/z*: $M^+ - OAc$ Calcd for $C_{12}H_{17}O_6$: 257.1025. Found: 257.1034. IR ($CHCl_3$): 3500—2800 (br), 1730, 1710 (sh) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (9H, s × 3, OAc), 4.02—4.23 (2H, m, C<u>H</u>$_2$OAc), 4.68—5.24 (2H, m, 2, 3-H), 9.72 (1H, s, CO_2H).

19: $[\alpha]_D^{27}$ −1.6° (*c* = 4.5, $CHCl_3$). High-resolution MS *m/z*: $M^+ - OMe$ Calcd for $C_{14}H_{19}O_7$: 299.1131. Found: 299.1134. IR ($CHCl_3$): 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.05 (3H, s, OAc), 2.08 (6H, s × 2, OAc), 3.68 (3H, s, ester-Me), 4.02—4.23 (2H, m, C<u>H</u>$_2$OAc), 4.74—5.17 (2H, m, 2, 3-H).

Methyl 2-[2α,3α-Dihydroxy-di-*O*-isopropylidene-4β-(2-methoxy-2-propanoxy)methylcyclopent-1β-yl]acetate (20) and Methyl 2-(2α,3α-Dihydroxy-di-*O*-isopropylidene-4β-hydroxymethylcyclopent-1β-yl)acetate (20′)——A solution of **19** in MeOH (10 ml) was saturated with ammonia gas at 0 °C. The solution was allowed to stand at room temperature for 12 h, then the solvent was evaporated off *in vacuo*. Acetone (5 ml), 2,2-dimethoxypropane (5 ml), and *p*-TsOH · H_2O (10 mg) were added to the residue. After being stirred at room temperature for 30 min, the solution was neutralized with sodium hydrogen carbonate and the precipitate was filtered off. The filtrate was concentrated *in vacuo*, and the residue was subjected to silica gel column chromatography. Elution with hexane–ethyl acetate (4 : 1) gave the product **20** (118 mg, 68%) and **20′** (20 mg, 15%).

20: $[\alpha]_D^{22}$ −6.9° (*c* = 1.2, $CHCl_3$). High-resolution MS *m/z*: $M^+ - Me$ Calcd for $C_{15}H_{25}O_6$: 301.1651. Found: 301.1659. IR ($CHCl_3$): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28, 1.48 (6H, s × 2, isopropylidene-Me), 1.32 (6H, s, OC<u>Me</u>$_2$OMe), 3.17 (3H, s, OMe), 3.35—3.46 (2H, m, C<u>H</u>$_2$OCMe$_2$OMe), 3.65 (3H, s, ester-Me), 4.09—4.46 (2H, m, 2, 3-H).

20′: High-resolution MS *m/z*: $M^+ - Me$ Calcd for $C_{11}H_{17}O_5$: 223.1076. Found: 223.1077. IR ($CHCl_3$): 3450, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29, 1.49 (3H, s × 2, isopropylidene-Me), 3.66 (3H, s, ester-Me), 4.16—4.54 (2H, m, 2, 3-H).

2α,3α-Dihydroxy-di-*O*-isopropylidene-1β-hydroxymethyl-4β-(2-phenylstyryl)cyclopentane (21)——PhMgBr–THF solution (0.74 ml of 2 M solution) was added to a solution of **20** (118 mg, 0.37 mmol) in anhydrous ether (5 ml) with

stirring under an argon atmosphere at 0 °C. After being stirred at room temperature for 4 h, the solution was acidified with acetic acid under ice cooling. Stirring was continued at room temperature for 3 h, then the solvent was evaporated off *in vacuo*. The residue was subjected to silica gel column chromatography. Elution with hexane–ethyl acetate (5 : 1) gave **21**, 52 mg (40%). High-resolution MS *m/z*: M^+ Calcd for $C_{23}H_{26}O_3$: 350.1882. Found: 350.1901. IR ($CHCl_3$): 3400, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.31, 1.39 (6H, s × 2, isopropylidene-Me), 3.64 (2H, d, J=6 Hz, C$\underline{H}_2$OH), 4.34—4.56 (2H, m, 2, 3-H), 5.88 (1H, d, J=10 Hz, olefinic H), 7.21, 7.29 (10H, s × 2, ArH).

(1*R*,5*R*,6*R*,7*S*)-6,7-(Dihydroxy-di-*O*-isopropylidene)-3-oxabicyclo[3.2.1]octan-2-ol (22)——Ozone gas was bubbled through a solution of **21** (78 mg, 0.22 mmol) in anhydrous dichloromethane (5 ml) at −78 °C for 3 min. Then, methyl sulfide (1 ml) was added to the reaction mixture and the solvent was evaporated off *in vacuo*. The residue was subjected to silica gel (2 g) column chromatography. Elution with hexane–ethyl acetate (5 : 1) gave **22**, 40 mg (91%). High-resolution MS *m/z*: M^+ − Me Calcd for $C_9H_{13}O_4$: 185.0814. Found: 185.0821. IR ($CHCl_3$): 3400 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.34, 1.44 (6H, s × 2, isopropylidene-Me), 3.32—4.13 (2H, m, –C$\underline{H}_2$O–), 4.43—4.68 (2H, m, 6, 7-H).

(1*R*,5*R*,6*R*,7*S*)-6,7-(Dihydroxy-di-*O*-isopropylidene)-3-oxabicyclo[3.2.1]octan-2-one (23)——Dipyridine–chromium(VI) oxide[16] (450 mg, 1.2 mmol) was added to a solution of **22** (40 mg, 0.2 mmol) in anhydrous dichloromethane (5 ml) with stirring. The mixture was stirred at room temperature for 2 h, the precipitate was filtered off, and the filtrate was concentrated *in vacuo*. The residue was subjected to silica gel (1 g) column chromatography. Elution with hexane–ethyl acetate (6 : 1) gave a crystalline substance, which was recrystallized from hexane–ether–dichloromethane to give **23**, mp 141—143 °C (lit.[8] mp 140—141.5 °C), 24 mg (61%). $[\alpha]_D^{25}$ +41.1° (c=0.19, $CHCl_3$). High-resolution MS *m/z*: M^+ − Me Calcd for $C_9H_{11}O_4$: 183.0657. Found: 183.0648. IR ($CHCl_3$): 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32, 1.48 (6H, s × 2, isopropylidene-Me), 2.92—3.08 (1H, m, 1-H), 4.04—4.52 (2H, m, –C$\underline{H}_2$O–), 4.62 (2H, br s, 2, 3-H).

Di-*l*-menthyl Bicyclo[2.2.2]oct-5-ene-2,2-dicarboxylate (24)——A solution of 1,3-cyclohexadiene (686 mg, 8.6 mmol) in dry toluene (10 ml) and $TiCl_4$ (0.05 ml) were added successively to a solution of **1** (1.680 g, 4.3 mmol) in dry toluene (8 ml) at −78 °C in an argon atmosphere with stirring. The mixture was stirred for 2.5 h at −78 °C, then the temperature was raised to 20 °C. The reaction mixture was diluted with benzene (5 ml), and the whole was poured into water (10 ml), and extracted with benzene (10 ml × 2). The organic layer was washed with water (20 ml × 2), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (50 g) column. Elution with hexane–ether (50 : 1) gave **24** (1.6 g, 79%, d.e. ≤5%) as a colorless oil. The d.e. was determined by high-performance liquid chromatography [column, μPorasil (7.8 mm, 30 cm); eluent, hexane–ethyl acetate (20 : 1); flow rate, 2 ml/min; retention time, 3.2 min, 3.8 min] ^{1}H-NMR ($CDCl_3$) δ: 3.04—3.38 (1H, m, 1-H), 4.24—4.98 (2H, m, menthyl 1-H), 5.97—6.46 (2H, m, olefinic H).

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