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Synthesis of Nucleosides and Related Compounds. XIV.[1] Diels–Alder Reaction of Di-*l*-menthyl Acetoxymethylenemalonate with Cyclopentadiene: Effects of High-Pressure and Catalysts upon Asymmetric Induction[2]

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Asymmetric Diels–Alder reaction of di-*l*-menthyl acetoxymethylenemalonate with cyclopentadiene under high pressure was examined. The yield, proportion of *exo* isomer, and diastereomeric excess (d.e.) of the adduct increased with increase of pressure when the reactions were carried out without any catalyst. The absolute structure of the major diastereoisomer of the *endo* adduct corresponded to the natural configuration, which could be transformed to a precursor of aristeromycin, while the *exo* adduct had the unnatural configuration. The same diastereoselectivity was also observed when diethylaluminum chloride (capable of chelating with only one carbonyl group of the dienophile) was used as the catalyst. On the contrary, both *endo* and *exo* isomers obtained from the high-pressure-mediated Diels–Alder reaction in the presence of zinc chloride or tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium (capable of chelating with the two carbonyl groups of the dienophile at the same time) had the natural configuration. Possible mechanisms of these selectivities are proposed.

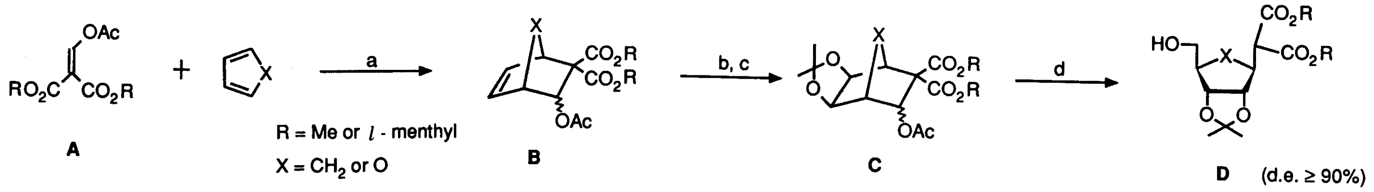
Keywords high pressure; dialkyl acetoxymethylenemalonate; cyclopentadiene; Diels–Alder reaction; asymmetric induction; Lewis acid catalyst; bicyclo[2.2.1]heptane; carbocyclic C-nucleoside

Recently, much attention has been focused on the application of high-pressure techniques in the field of synthetic organic chemistry.[3] A well-known advantage of this technique over reactions carried out under atmospheric pressure is an increase of the reaction rate when the corresponding reaction has a large negative activation volume ($\Delta V^{\neq}$). For example, intermolecular Diels–Alder reactions, known generally to have a large negative activation volume (-25— $-50\,\mathrm{cm}^{-3}/\mathrm{mol}$), are accelerated by the use of high pressure.

Previously, we succeeded in the synthesis of carbocyclic C-nucleoside analogues *via* the adduct B (R = Me, X = CH_2) obtained by Diels–Alder reaction of dimethyl acetoxymethylenemalonate (A: R = Me) with cyclopentadiene.[4] The adduct B was converted to the acetonide C (R = Me, X = CH_2), whose reductive retrograde aldol (RRA) C–C bond fission (d) gave the versatile synthetic block D (R = Me, X = CH_2, racemic) with complete stereoselection.[4] Though the same reaction using di-*l*-menthyl acetoxymethylenemalonate (A: R = *l*-menthyl) did not proceed merely on heating, the reaction proceeded even at $-78\,°C$ when titanium tetrachloride was used as a catalyst. Since remarkable diastereoselection has been attained in this case, a highly enantioselective synthetic route to carbocyclic C-nucleoside has thus been accomplished.[5]

The same methodology has been successfully applied to the synthesis of C-nucleosides (racemic).[6] In this synthesis, the use of a high pressure was the essential requisite for Diels–Alder reaction of furan with dimethyl acetoxymethylenemalonate (A: R = Me). The fact that the adduct (a mixture of *endo*- and *exo*-isomers) thus obtained, when warmed slightly at ordinary atmospheric pressure, cycloreverts to the starting materials indicates clearly that the decrease of molecularity in this reaction not only accelerates the reaction, but also results in the reverse energy relationship of the starting materials and product between the reactions carried out under a high pressure (*i.e.* the product is more stable than the starting materials) and under atmospheric pressure (*i.e.* the product is less stable than the starting materials).

In this paper, we wish to report the high-pressure-mediated asymmetric Diels–Alder reaction of di-*l*-menthyl acetoxymethylenemalonate (**3** = A: R = *l*-menthyl) with cyclopentadiene, which reveals not only the difference in the preferred conformation of the dienophile **3** according to the pressure employed but also how the conformation is affected by the use of appropriate Lewis acid catalysts either at high pressure or at atmospheric pressure.



a : $TiCl_4$ (catalytic amount) / toluene, -78°C or high pressure (13 kbar)

b : OsO_4, 4-methylmorpholine *N*-oxide, acetone-ether

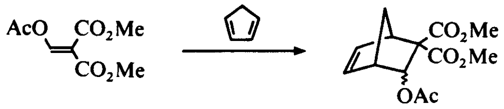
c : $Me_2C(OMe)_2$, *p*-TsOH·H_2O, acetone

d : $NaBH_4$-K_2CO_3 / MeOH [reductive retrograde aldol (RRA) reaction]

Chart 1

Before we investigated the asymmetric Diels–Alder reaction, we examined the reaction of dimethyl acetoxymethylenemalonate **1** (A: $R=Me$) with cyclopentadiene under high pressure in order to see how the rate and *endo*/*exo* ratio are affected. In contrast to the complete recovery of the starting materials if the reaction was carried out at room temperature under atmospheric pressure, the adduct **2** (*endo*/*exo* = 0.39) was obtained in 95% yield when **1** was allowed to react with cyclopentadiene under 13 kbar. As shown in Table I, the yield of **2** was better than that obtained under atmospheric pressure (either by heating alone[4] or with titanium tetrachloride as a catalyst). The ratio (*endo*/*exo*) of the products obtained by the high-pressure reaction of **1** and cyclopentadiene was similar to that of the products obtained simply by heating.

TABLE I. Diels–Alder Reaction of Dimethyl Acetoxymethylenemalonate (**1**) with Cyclopentadiene

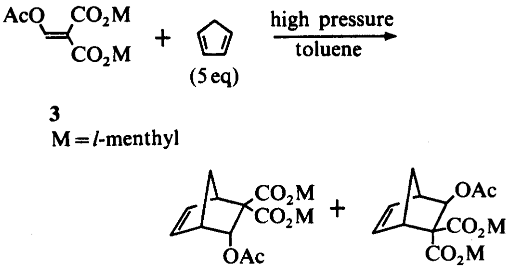


1 **2**

Reaction conditions			Yield (%)	*endo*/*exo*
Temperature (°C) (Pressure)	Time (h)	Solvent (Catalyst)		
80—90	72	Benzene	80	0.33[4]
−15	4	Toluene (TiCl$_4$)	74	1.50
15 (13 kbar)	60	Toluene	95	0.39

High-pressure-mediated Diels–Alder reaction of the chiral dienophile **3** with cyclopentadiene was then investigated under various conditions (using toluene as the common solvent) and the results are shown in Table II. As reported previously, the dienophile **3** dose not react even at high temperature with cyclopentadiene at atmospheric pressure without the use of a suitable Lewis acid catalyst.[5] However, here again, the reaction proceeded smoothly under 13 kbar even at room temperature to give a mixture of *endo* and *exo* isomers (**4** and **5**: hereafter, only the major diastereoisomers

TABLE II. High-Pressure-Mediated Diels–Alder Reaction of Di-*l*-menthyl Acetoxymethylenemalonate (**3**) with Cyclopentadiene



3
M = *l*-menthyl

4 (natural) **5** (unnatural)

Pressure (kbar)	Reaction time (h)	Yield (%)	*endo*/*exo*	d.e. (%)	
				endo	*exo*
13	47	96	0.56	54	60
8	42	89	0.57	52	49
5	65	67	0.76	50	45
1 atm TiCl$_4$ (−78 °C)	4	80	3.00	>99	65[a]

[a] Natural configuration.

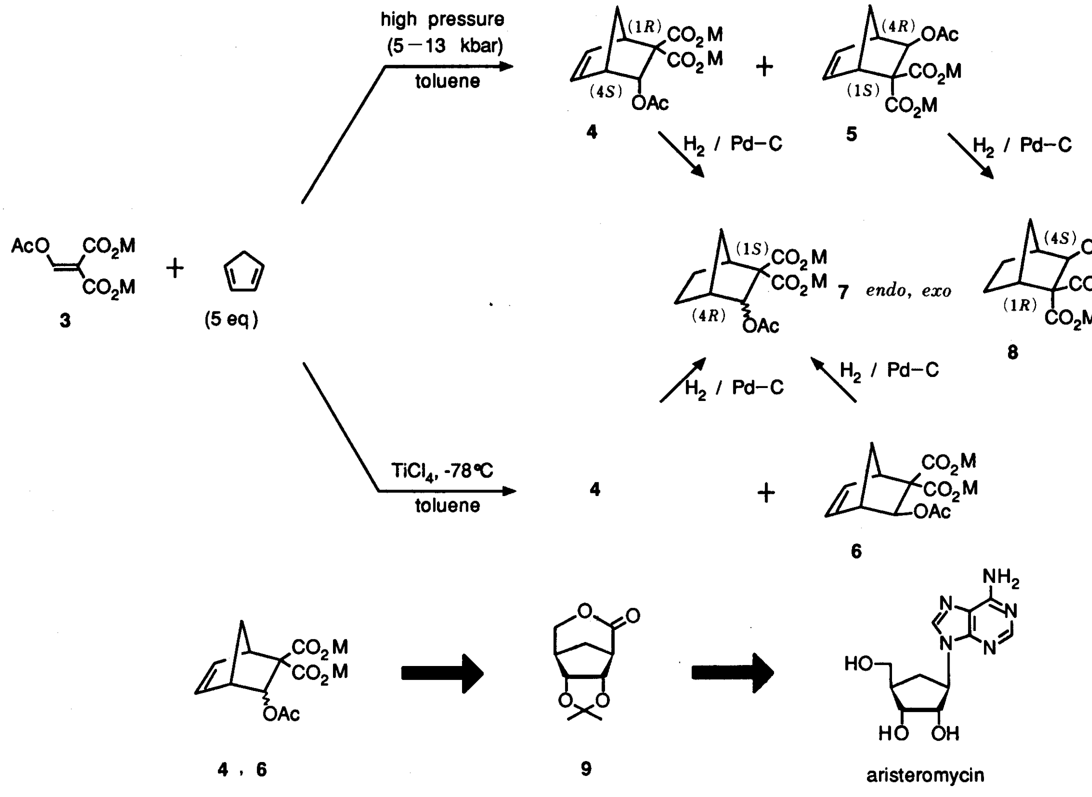


Chart 2

are shown) in 96% chemical yield with respective d.e.s of 54% and 60%. With decreasing pressure, the ratio (*endo*/*exo*) increased, whereas both d.e.s decreased. This means that the negative activation volume (ΔV^{*}) of *exo* addition is larger in magnitude than that of *endo* addition in the reaction of **3** with cyclopentadiene.[7] Though the reaction proceeded at 5 kbar, the rate decreased and the starting dienophile **3** was recovered in a significant amount (20%) even if the reaction was continued longer.

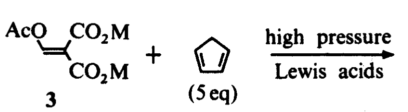
Since the *endo* and *exo* isomers (**4** and **5**) were difficult to separate from each other by column chromatography, their d.e.s could not be determined at this stage. Hence, the d.e.s of **4** and **5** were determined after their conversion to the dihydro derivatives (**7** and **8**), which were chromatographically separable. The proton nuclear magnetic resonance (^{1}H-NMR) spectra of **7** and **8** using tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate)europium [Eu(fod)$_3$] as a shift reagent allowed the determination of d.e.s precisely by using the intensity of methyl signals of the acetyl group as the criterion. In the same manner, the d.e.s of the *endo* and *exo* isomers (**4** and **6**) obtained from the reaction of **3** with cyclopentadiene under atmospheric pressure in the presence of titanium tetrachloride at −78 °C[5] were determined to be ≥99% and 65%, respectively.

Since **4** and **6**, without separation, had already been transformed in our previous study[5] to the chiral lactone **9**, a known precursor of aristeromycin,[8] the absolute structures of both **4** and **6** were assigned as the natural configuration (1*R*,4*S*). On the other hand, by comparing the ^{1}H-NMR spectra of **7** and **8**, the absolute structure of the *exo* adduct **5** (corresponding to the dihydro derivative **8**) formed by the high-pressure reaction was determined as the unnatural one (1*S*,4*R*).

Next, using various Lewis acid catalysts such as diethylaluminum chloride, zinc chloride and tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium [Yb(fod)$_3$], the high-pressure-mediated Diels–Alder reaction of **3** with cyclopentadiene was examined. Though the use of these catalysts in the reactions carried out under atmospheric pressure did not give fruitful results, the reactions carried out under high pressure resulted in the formation of adducts (**4** and **6**) in excellent yields, as shown in Table III. Formation of the *endo* isomer **4** predominated over that of the *exo* isomer **6** under high pressure in the presence of these Lewis acid catalysts, except for diethylaluminum chloride. Though each d.e. is low, it is noteworthy that the reaction of **3** with cyclopentadiene in the presence of zinc chloride or Yb(fod)$_3$ gave the *endo*- and *exo*-isomers both having natural configuration, whereas the *endo*- and *exo*-isomers obtained by using diethylaluminum chloride had the natural and unnatural configurations, respectively.

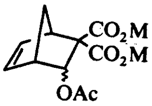
The above results may indicate that diethylaluminum chloride chelates with only one carbonyl group of the diester **3**, whereas zinc chloride or Yb(fod)$_3$ chelates with two carbonyl groups at the same time, just like titanium tetrachloride.[5] If the dienophile **3** assumes the conformation E (*s-cis*, *s-trans*) under high pressure without a catalyst, cyclopentadiene would approach from the less hindered *re*-face. Then the *endo* addition would predominantly give rise to the adduct having the natural configuration, while the *exo* addition would give the one having the unnatural configuration. Such a phenomenon was also observed in the reaction of **3** with furan under high pressure, which provided an efficient route to enantioselective synthesis of C-nucleosides.[9] When diethylaluminum chloride was used as the catalyst, the same situation was found. On the other hand, **3** seems to take the conformation F (*s-trans*, *s-trans*) even under high pressure if a suitable Lewis acid catalyst capable of chelating with both of the carbonyl groups of **3** [*i.e.* zinc chloride or

Table III. High-Pressure-Mediated Diels–Alder Reaction of Di-*l*-menthyl Acetoxymethylenemalonate (**3**) with Cyclopentadiene in the Presence of Lewis Acids

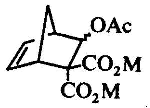


3 (5 eq)

M = *l*-menthyl



4 and 6 (natural)



5 (unnatural)

Pressure (kbar)	Catalyst (mol eq)	Solvent	Time (h)	Yield (%)	*endo*/*exo*	d.e. (%) *endo*	d.e. (%) *exo*
10	Et$_2$AlCl	Toluene	48	84	0.51	52 (N)	51 (UN)
1 atm	(0.1)	Toluene	48	0	—	—	—
11	ZnCl$_2$	CH$_2$Cl$_2$	24	90	1.7	53 (N)	40 (N)
1 atm	(0.1)	CH$_2$Cl$_2$	24	68	1.7	54 (N)	14 (N)
10.8	Yb(fod)$_3$	CH$_2$Cl$_2$	42	90	1.6	44 (N)	25 (N)
1 atm	(0.1)	CH$_2$Cl$_2$	66	27	1.9	37 (N)	37 (N)

N, natural; UN, unnatural.

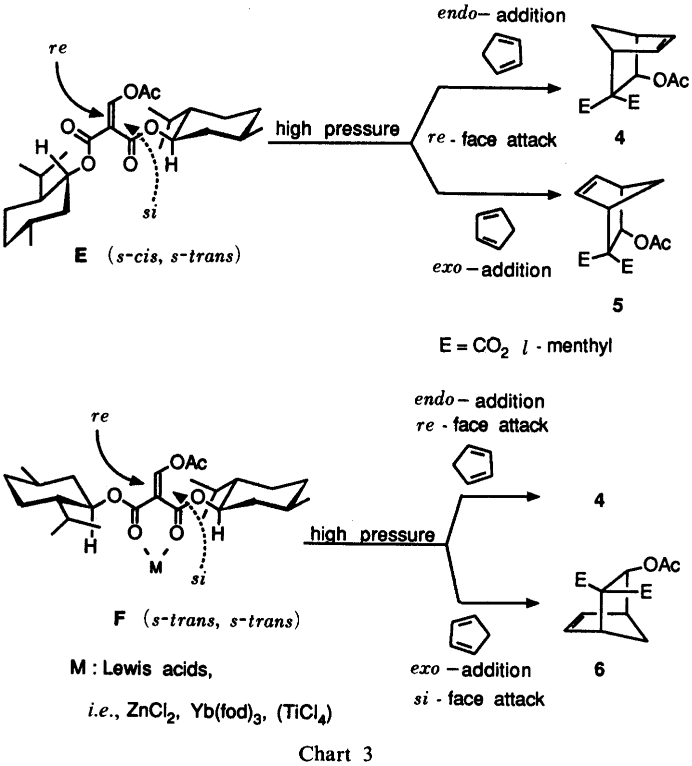


Chart 3

$Yb(fod)_3$] is present in the reaction medium. Though in the conformation F both *re*- and *si*-faces are sterically the same owing to the C_2-symmetry axis parallel to the C–C double bond, F recognizes the difference in bulkiness between the 5-methylene and the C_2–C_3 bond of cyclopentadiene as discussed in the previous paper.[5] As a result, *endo*-addition occurs at the *re*-face and the *exo*-addition occurs at the *si*-face predominantly. Therefore, both additions gave the adducts **4** and **6** having the natural configuration.

The results obtained in the present study may be summarized as follows: 1) The use of high pressure remarkably improves the chemical yield in the Diels–Alder reaction of **3** with cyclopentadiene.

2) The proportion of the *exo* isomer, and degree of asymmetric induction are increased with increase of pressure in the reaction.

3) Irrespective of the pressure employed, use of zinc chloride or $Yb(fod)_3$ as the catalyst gives the diastereoisomers having natural configuration.

4) The use of high pressure without Lewis acid catalysts or with diethylaluminum chloride forms the *endo* diastereoisomer of natural configuration and the *exo* diastereoisomer of unnatural configuration.

5) The degree of asymmetric induction in the reactions of di-*l*-menthyl acetoxymethylenemalonate with cyclopentadiene is lower in the high-pressure-mediated reaction than in the reaction using a catalytic amount of titanium tetrachloride at −78 °C.

Experimental

Infrared (IR) spectra were measured on a JASCO A-102 spectrometer. ^{1}H-NMR spectra were recorded with a JEOL JNM-PMX 60si spectrometer using tetramethylsilane (TMS) as an internal standard. The abbreviations of signal patterns are follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; br, broad; br s, broad singlet. All diastereomeric excess (d.e.) values of the compounds obtained in the present work were determined from the ^{1}H-NMR spectra in $CDCl_3$ (0.3 ml) in the presence of $Eu(fod)_3$ (25 mg). Low- and high-resolution mass spectra (MS) were obtained on a Hitachi M-52G and JEOL JMS-01SG-2 mass spectrometers, respectively. Wakogel (C-200) and Merck Kiesel-gel 60F 254 were employed for silica gel column and thin layer chromatography (TLC), respectively. The ratios of mixtures of solvents for chromatography are shown as volume/volume. High-pressure reactions were carried out by using a piston–cylinder apparatus equipped with a PK. 15. B pump (Hikari Koatsu Kiki Ltd., Co.).

Diels–Alder Reaction of Dimethyl Acetoxymethylenemalonates (1) with Cyclopentadiene in the Presence of Titanium Tetrachloride ($TiCl_4$) $TiCl_4$ (0.1 mmol) was added to a solution of **1** (1 mmol) and cyclopentadiene (5 mmol) in dry toluene (5 ml) with stirring at −15 °C. After being stirred at −15 °C for 1—4 h, the reaction mixture was poured into water and extracted with benzene. The organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography. Elution with hexane–ethyl acetate (6 : 1) gave **2**.[4]

General Procedure for High-Pressure-Mediated Diels–Alder Reaction of Dialkyl Acetoxymethylenemalonates (1 and 3) with Cyclopentadiene without a Catalyst A mixture of **1** or **3** (0.7 mmol) and cyclopentadiene (3.5 mmol) was placed in a Teflon tube (1.2 ml) with a Teflon stopper, and the tube was filled with dry toluene. The tube was placed in a high-pressure reactor and pressurized to 5—13 kbar. The pressure was released and the reaction mixture was concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography using hexane–ethyl acetate (20 : 1 for **4** and **5**) as an eluent to give **2**, **4**, and **5**. The results are shown in Tables I and II.

General Procedure for High-Pressure-Mediated Diels–Alder Reaction of Di-*l*-menthyl Acetoxymethylenemalonate (3) with Cyclopentadiene in the Presence of Lewis Acids A mixture of **3** (0.3 mmol), cyclopentadiene (1.5 mmol) and appropriate Lewis acids (0.03 mmol) was placed in a Teflon tube (0.6 ml) with a Teflon stopper, and the tube was filled with appropriate dry solvents, then placed in a high-pressure reactor and pressurized to 10—11 kbar. The pressure was released and the reaction mixture was poured into ice-water. The resulting mixture was extracted with benzene and the organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give compounds **4**—**6**. The results are shown in Table III.

Di-*l*-menthyl [1*S*,3*R*,4*R*]-3-Acetoxybicyclo[2.2.1]heptane-2,2-dicarboxylate (7 *endo*), Di-*l*-menthyl [1*S*,3*S*,4*R*]-3-Acetoxybicyclo[2.2.1]heptane-2,2-dicarboxylate (7 *exo*), and Di-*l*-menthyl [1*R*,3*R*,4*S*]-3-Acetoxybicyclo[2.2.1]heptane-2,2-dicarboxylate (8) 1) A catalytic amount of 5% Pd–C (30 mg) was added to a solution of a mixture (290 mg) of **4** and **5**, prepared by the reaction of **3** with cyclopentadiene at 13 kbar, in EtOH (10 ml)–ether (5 ml). The mixture was shaken under a hydrogen atmosphere (1 atm) at room temperature for 2 h. Pd–C was filtered off by suction, and the filtrate was concentrated *in vacuo*. The residue was subjected to silica gel (60 g) column chromatography. Elution with hexane–ethyl acetate (20 : 1) gave **7** *endo* as a colorless oil (104 mg, 36%). Further elution with the same solvent gave **8** as a colorless oil (185 mg, 64%).

7 *endo*: ^{1}H-NMR ($CDCl_3$) δ: 2.05 (3H, s, AcO), 4.33—5.07 (2H, m, menthyl 1-H), 5.64 (1H × 77/100, d, $J = 5$ Hz, 3-H, natural), 5.80 (1H × 23/100, d, $J = 5$ Hz, 3-H, unnatural).

8: ^{1}H-NMR ($CDCl_3$) δ: 1.96 (3H, s, AcO), 4.37—5.06 (2H, m, menthyl 1-H), 5.51 (1H, s, 3-H).

2) A catalytic amount of 5% Pd–C (30 mg) was added to a solution of a mixture (470 mg) of **4** and **6**, prepared by the reaction of **3** with cyclopentadiene in the presence of $TiCl_4$ at −78 °C in dry toluene,[5] in EtOH (10 ml)–ether (5 ml). The mixture was shaken under a hydrogen atmosphere (1 atm) at room temperature for 1 h. Work-up as above gave **7** *endo* (352 mg, 75%) and **7** *exo* (118 mg, 25%). The 500 MHz ^{1}H-NMR spectrum (JEOL JNM-FX 500) in $CDCl_3$ revealed that **7** *endo* derived from **4** was a diastereomerically pure compound. No signals corresponding to its isomer were observed in the spectrum. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 2.05 (1H, s, AcO), 2.63 (1H, m, 4-H), 2.84 (1H, m, 1-H), 4.70 (1H, dt, $J = 5$, 11 Hz, menthyl 1-H), 4.75 (1H, dt, $J = 5$, 11 Hz, menthyl 1-H), 5.65 (1H, d, $J = 5$ Hz, 3-H).

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References and Notes

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