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Tetrahedron: *Asymmetry*

A practical improvement of crystallization-induced asymmetric transformation of allene-1,3-dicarboxylates

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Abstract—Enantiomerically pure allene-1,3-dicarboxylates were easily synthesized by using epimerization–crystallization of dissymmetric allene compounds, which were prepared from acetone-1,3-dicarboxylates and naturally abundant chiral alcohols, that is, (−)- and (+)-menthols, borneol, and isoborneol. After scrutinizing the crystallization of several allene-1,3-dicarboxylates in the presence of triethylamine, it was found that allene-1,3-dicarboxylate carrying bornyl groups was the most easily prepared as a single isomer because of it having suitable solubility to be crystallized in hexane at 0 °C to room temperature. Diels–Alder reaction of the enantiomerically pure allene-1,3-dicarboxylates and cyclic dienes, such as *N*-Boc-pyrrole and cyclopentadiene, afforded *endo*-adducts having the same configurations at two newly generated stereogenic centers.

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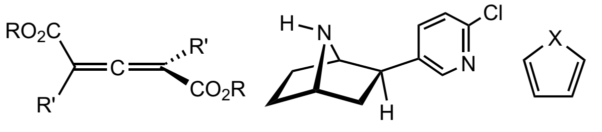
1. Introduction

Allene-1,3-dicarboxylates **1** are useful dienophiles for the Diels–Alder reaction and excellent acceptors in the Michael addition;[1] however, practical methods to prepare optically active allene-1,3-dicarboxylates **1** have not been published except for a few reports. For example, one example has been reported by Kanematsu, who employed resolutional crystallization of a mixture of di-(−)-L-menthyl allene-1,3-dicarboxylates,[2] while another was developed by Naruse, who attained the enantiomerically enriched equilibrium of allene-1,3-dicarboxylates with a chiral organoeuropium reagent.[3] However, the former method does not afford satisfactory yields (<25%), while the latter requires equimolar amounts of expensive Eu(hfc)$_3$ as well as long reaction times with accompanying partial decomposition of the substrate.

We have recently encountered the first example of epimerization-crystallization in dissymmetric allene-1,3-dicarboxylates during a synthetic study of (−)-epibatidine **2**,[4] an excellent candidate for non-opioidal anesthesia, and its derivatives.[5]



1

2

3a: X = NBoc

3b: X = CH$_2$

Figure 1.

Herein, we report a new strategy and details of the crystallization-induced asymmetric transformation of allene-1,3-dicarboxylates and its application to the Diels–Alder reaction with cyclic dienes, such as *N*-Boc-pyrrole **3a** and cyclopentadiene **3b**, since the reaction is applicable to the synthesis of many naturally occurring compounds, for example, α- and β-santalols,[6] as well as epibatidine **2** (Fig. 1).

2. Results and discussion

We started by establishing a new method for the synthesis of allene-1,3-dicarboxylates. At first, dimethyl 1,3-acetonedicarboxylate **4a** was chosen as a starting material to prepare racemic allene-1,3-dicarboxylates **1** on a large scale

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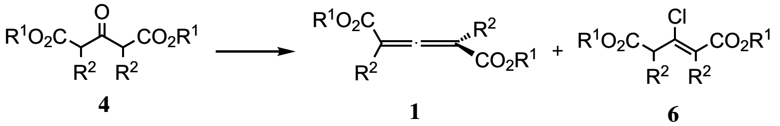
in advance of preparing optically active ones. Initially, we attempted the reaction of **4a** with 2-chloro-1,3-dimethylimidazolinium chloride (DMC) **5a** in the presence of an equimolar amount of triethylamine; this afforded vinyl chloride **6a** as the sole product in moderate yield (Table 1, entry 1).[7] Since the elimination of hydrogen chloride from **6a** should provide dimethyl allene-1,3-dicarboxylate **1a**, the reaction was performed with two equimolar amounts of triethylamine to afford a better result (Table 1, entry 2) and the best result was obtained by reaction in the presence of three equimolar amounts of triethylamine (Table 1, entry 3). Moreover, the use of 2-chloro-1,3-dimethylimidazolinium hexafluorophosphate (CIP) **5b** developed by Kiso for peptide synthesis was effective to avoid the production of **6a**, since pentafluorophosphide is less nucleophilic than chloride to the sp-carbon of **1a** (Table 1, entries 8, 9, and 10). The reaction condition was also effective to prepare **1b–e** from **4b–e** (Table 1, entries 11–14).

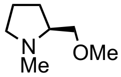
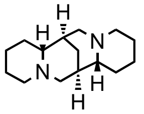
Alternative amines were next employed in place of triethylamine to investigate the effects of bases in the reaction from **4a** to **1a**; however, neither the reactions with diisopropylethylamine nor with pyridine gave more favorable results than the reaction with triethylamine (Table 1, entries 4 and 5). The reactions with optically active amines, for example, (*S*)-2-methoxymethylpyrrolidine and (−)-sparteine, did not afford optically active **1a** at all but instead a racemic mixture (Table 1, entries 6 and 7).

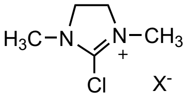
Expecting that chiral induction might occur during the transformation from acetone dicarboxylates to allene-1,3-dicarboxylates, dimenthyl 1,3-acetonedicarboxylate **4f** prepared by the ester exchange of **4a** with (−)-menthol was transformed to allene-1,3-dicarboxylate **1f** by treatment with 1,3-dimethylimidazolium salt **5a** or **5b** in the presence of triethylamine; however, it only afforded a mixture of (*S*)- and (*R*)-(diastereomeric ratio = 5:4) (Table 2, entries 1 and 2).

Since allene-1,3-dicarboxylate diesters are excellent Michael acceptors, we searched for the possibility of epimerization induced by the addition–elimination reaction with bases (Scheme 1). The epimerization of the (*R*)-isomer of **1f** in the presence of a catalytic amount of triethylamine was easily monitored by nuclear magnetic resonance (NMR) spectroscopy and it was observed that the epimerization between the (*R*)- and (*S*)-isomers of the allene moiety can reach an equilibrium within 30 min at room temperature. On the basis of this fact, a mixture of the (*R*)- and (*S*)-epimers was crystallized in pentane, the most non-polar solvent among the ones available, with a catalytic amount of triethylamine (0.01 equiv) at low temperature (−20 °C) to afford the pure (*R*)-isomer as a single crystal. Repeating the same procedure three times gave **1f** with an (*R*)-configuration in 90% total yield. However, the process was too tedious in order to afford high reproducibility because the crystals of **1f** were easily dissolved

Table 1.

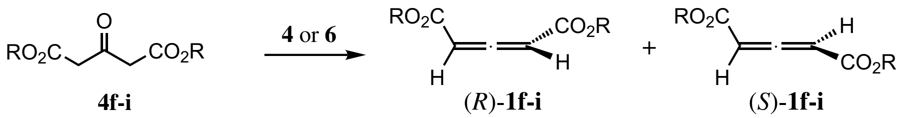


Entry	Reactant	R^1	R^2	Reagent	Base (equiv)	Time (h)	Products (%)	
							1	**6**
1	**4a**	Me	H	**5a**	Et$_3$N (1)	24	—	**6a** (44)
2	**4a**	Me	H	**5a**	Et$_3$N (2)	22	**1a** (72)	**6a** (21)
3	**4a**	Me	H	**5a**	Et$_3$N (3)	1	**1a** (90)	—
4	**4a**	Me	H	**5a**	(i-Pr)$_2$NEt	1.5	**1a** (84)	**6a** (8)
5	**4a**	Me	H	**5a**	Pyridine	15	No reaction	
6	**4a**	Me	H	**5a**		0.5	**1a** (61)	**6a** (23)
7	**4a**	Me	H	**5a**		1	**1a** (78)	—
8	**4a**	Me	H	**5b**	Et$_3$N (1)	1.5	**1a** (32)	**6a** (3)
9	**4a**	Me	H	**5b**	Et$_3$N (2)	1.5	**1a** (80)	—
10	**4a**	Me	H	**5b**	Et$_3$N (3)	1.5	**1a** (88)	—
11	**4b**	Me	Me	**5a**	Et$_3$N (3)	2	**1b** (73)	—
12	**4c**	Et	H	**5a**	Et$_3$N (3)	0.5	**1c** (92)	—
13	**4d**	Bn	H	**5a**	Et$_3$N (3)	2.5	**1d** (70)	—
14	**4e**	t-Bu	H	**5a**	Et$_3$N (3)	0.5	**1e** (71)	—

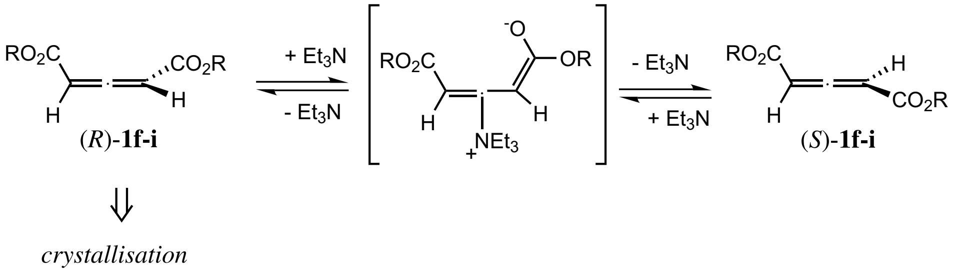


5a: X = Cl (DMC)
5b: X = PF$_6$ (CIP)

Table 2.



Entry	Starting material	R	Reagent (1.2 equiv)	Et_3N	Time (h)	Product (%)
1	**4f**	(−)-Menthyl	**5a**	3	1.5	**1f** (86)
2			**5b**	2	1.5	**1f** (93)
3	**4g**	(+)-Menthyl	**5a**	3	1.5	**1g** (75)
4			**5b**	2	1.5	**1g** (80)
5	**4h**	(−)-Bornyl	**5a**	3	1.5	**1h** (78)
6			**5b**	2	1.5	**1h** (77)
7	**4i**	(−)-Isobornyl	**5a**	3	1.5	**1i** (83)
8			**5b**	2	1.5	**1i** (86)



Scheme 1.

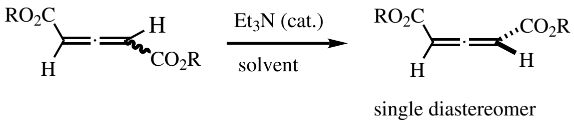
in the organic solvent during filtration, unless the glass ware was well chilled. Furthermore, it was almost impossible to collect crystals once the temperature of the solution rose above 0 °C.

Therefore, we synthesized (−)-bornyl allene-1,3-dicarboxylate **1h** and (−)-isobornyl allene-1,3-dicarboxylate **1i** (Table 2, entries 3–8) and attempted the crystallization-induced asymmetric transformation, based on the speculation that bicyclic terpenes, such as borneol and isoborneol, could form more rigid lattice structures than menthol and this tendency would not change even if the bicyclic moieties of the monoterpenes are involved as a partial structure in the linear derivatives of allene (Table 3).

The crystallization-induced asymmetric transformation of **1h** afforded (−)-bornyl (*R*)-allene-1,3-dicarboxylate **1h** at 0 °C in 85% yield by repeating the procedure four times, while the procedure repeated three times at room temperature afforded a slightly higher yield (92%) (Table 3, entries 1–4). Interestingly, the crystallization of **1i** at 0 °C only gave a mixture of (*R*)- and (*S*)-1,3-dicarboxylate with a maximum ratio of 9:1. The procedure repeated twice at room temperature gave enantiomerically pure (*R*)-**1i** in total 89% yield (Table 3, entry 5), which was as good a result as that of **1h** in spite of the disadvantage that isoborneol is not commercially available. The absolute configuration of allene-1,3-dicarboxylates **1h** and **1i** obtained was determined to be (*R*) by means of X-ray crystallography (Fig. 2).

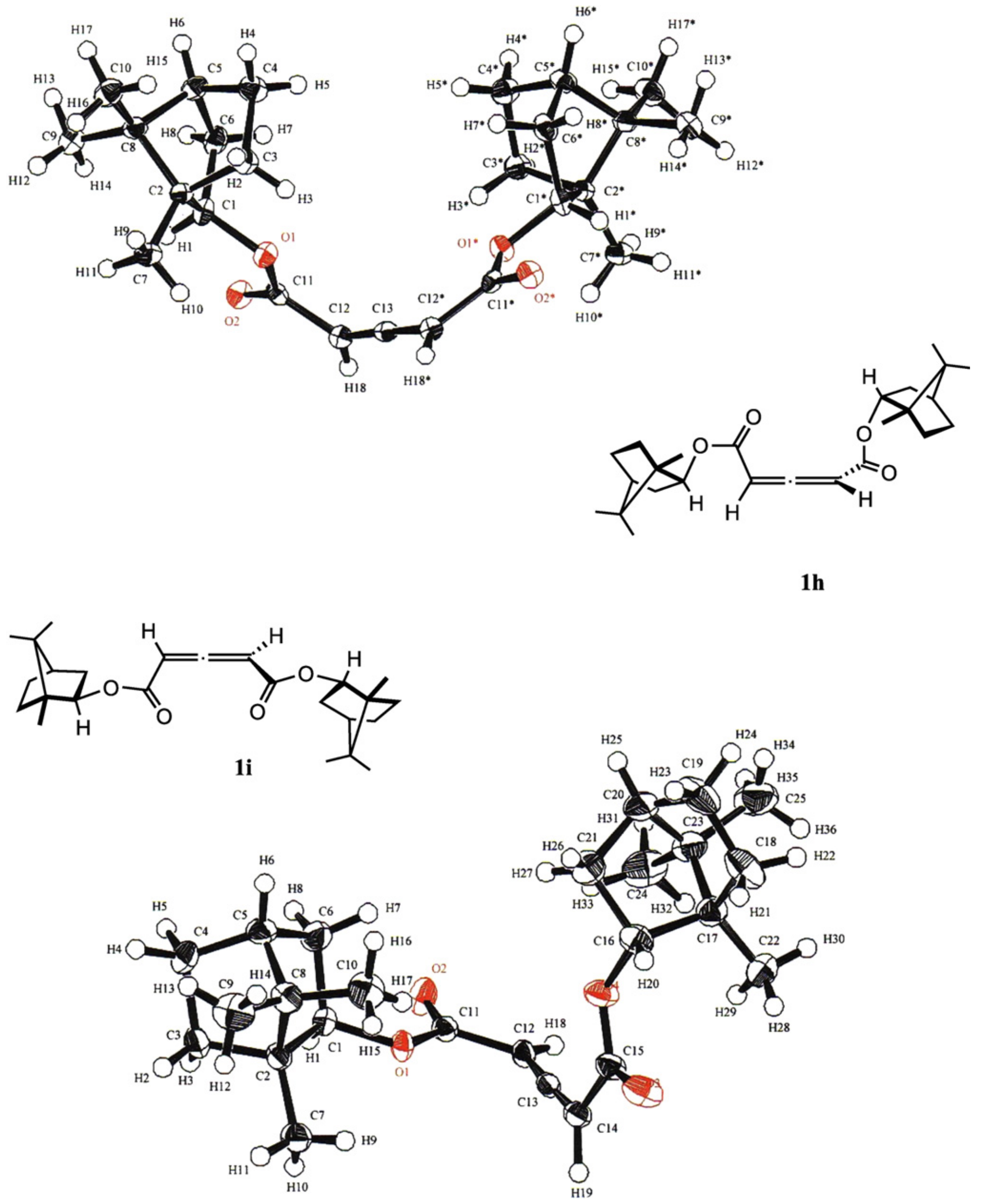
Finally, Diels–Alder reactions of allene-1,3-dicarboxylates **1h** and **1i** with *N*-Boc-pyrrole **3a** and cyclopentadiene **3b** were carried out under the same conditions as the reaction of **1f** and **3a**.[5] As a result, the reaction, respectively, afforded 7-azabicyclo[2.2.1]heptane as a single isomer of

Table 3. Improved crystallization-induced asymmetric transformation



single diastereomer

Entry	Substrate	R	Condition			Yield (%)	Abs. config
			Solvent	Times	Temperature		
1	**1f**	(−)-Menthyl	Pentane	3	−20 °C	90	(*R*)
2	**1h**	(−)-Bornyl	Pentane	4	0 °C	85	(*R*)
3			Hexane	2	rt	89	(*R*)
4			Hexane	3	rt	92	(*R*)
5	**1i**	(−)-Isobornyl	Hexane	2	rt	89	(*R*)



1h

1i

Figure 2. ORTEPs of chiral allene-1,3-dicarboxylates **1h** (CCDC No. 626803) and **li** (CCDC No. 626802).

endo-adducts **7a**–**c** in excellent yields. In addition, the stereochemistry of **7a** and **7c** was confirmed by X-ray crystallography, and the absolute configurations of the newly generated stereogenic centers were revealed to be identical in **7a** and **7b** by comparison of all physical data including $[\alpha]_D$ values of each acetate **8a** and **8b**, which was, respectively, derived by reduction of **7a** and **7b** with $LiAlH_4$ followed by conventional acetylation (Scheme 2).

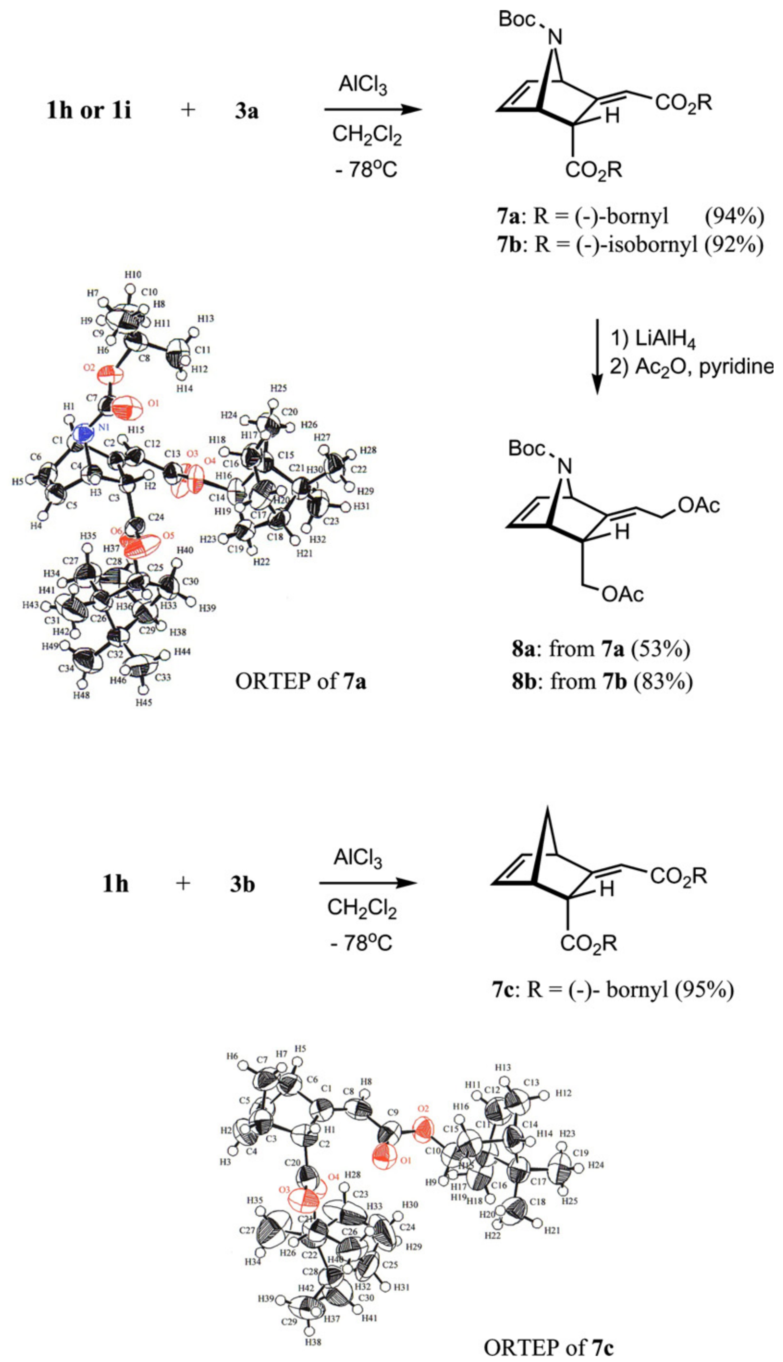
3. Conclusion

In conclusion, we were able to establish a practical method to synthesize chiral allene-1,3-dicarboxylate. Namely, when a bornyl or an isobornyl ester **1h** was employed as the starting material, a crystallization-induced asymmetric transformation was attainable at room temperature to afford enantiomerically pure allene-1,3-dicarboxylate on a gram-scale. Moreover, it was found that the Diels–Alder adducts **7a** and **7b** obtained from **1h**, **1i**, and **3a** had the same absolute configuration at the two newly generated stereogenic centers as the adduct from **1f** and **3a**.[5]

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a Shimadzu FTIR-8300 diffraction grating infrared spectrophotometer and ^1H NMR spectra were obtained on a JEOL JNM-AL 300, a Varian Unity INOVA-400, a JEOL JNM-LA 500 spectrometer with tetramethylsilane as an internal standard. ^{13}C NMR spectra were obtained on a JEOL JNM-AL



Scheme 2. ORTEPs of adducts **7a** (CCDC No. 626804) and **7c** (CCDC No. 626801).

300, a Varian Unity INOVA-400 spectrometer with $CDCl_3$ as an internal standard. Mass spectra (MS) were determined on a JEOL JMS-SX 102A QQ or a JEOL JMS-GC-mate mass spectrometer. Specific rotations were recorded on a Horiba SEPA-200 automatic digital polarimeter. Wakogel C-200 (silica gel) (100–200 mesh, Wako) was used for open column chromatography. Flash column chromatography was performed by using Silica Gel 60N (Kanto Chemical Co., Inc.) as a solid support of immobile phase. Kieselgel 60 F-254 plates (Merck) were used for thin layer chromatography (TLC). Preparative TLC (PTLC) was conducted with Kieselgel 60 F-254 plate (0.25 mm, Merck) or Silica gel 60 F-254 plate (0.5 mm, Merk). Unless purification with silica gel gave a compound pure enough, the compounds were treated further with a recycle HPLC (JAI LC-908) on GPC column (JAIGEL 1H and 2H). When possible, diastereomeric mixtures were also separated by a recycle HPLC (JAI LC-908) on a silica gel column (Kusano Si-10) after the purification procedure mentioned above.

4.2. Dimethyl 2,3-pentadienedioate 1a

Dimethyl 1,3-acetonedicarboxylate **4a** (5.00 g, 28.7 mmol) and triethylamine (11.6 g, 115 mmol) were successively added to a solution of 2-chloro-1,3-dimethylimidazolinium chloride (DMC; 5.80 g, 34.5 mmol) in absolute dichloromethane (100 ml) at 0 °C. After stirring the reaction mixture for 1 h at room temperature, the reaction mixture was directly charged on silica gel column chromatography (hexane/AcOEt = 2:1) to afford **1a** as a pale yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.76 (s, 6H), 6.03 (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 52.3 (2C), 91.9 (2C), 163.5 (2C), 219.5; IR (CHCl$_3$): 3036, 2955, 2359, 1967, 1720, 1439, 1269 cm^{-1}; MS (70 eV) *m*/*z*: 156 (M^{+}, 7), 128 (100), 112 (23), 98 (3); HRMS calcd for $C_7H_8O_4$: 156.0422, found: 156.0420. Anal. Calcd for $C_7H_8O_4$: C, 53.85, H, 5.16. Found: C, 53.68, H, 5.04.

4.3. Dimethyl 2,4-dimethyl-2,3-pentadienedioate 1b

Dimethyl 1,3-dimethyl-1,3-acetonedicarboxylate **4b** (150 mg, 0.74 mmol) was treated as **4a** in the above reaction to afford **1b** (100 mg, 73%) as a pale yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.95 (s, 6H), 3.75 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 14.4 (2C), 52.2 (2C), 98.0 (2C), 166.3 (2C), 216.4; IR (CHCl$_3$): 2955, 1771, 1456, 1263, 1151, 1092 cm^{-1}; MS FAB(+) *m*/*z*: 185 [M^{+}+H]; HRMS calcd for $C_9H_{13}O_4$ [M^{+}+H]: 185.0814, found: 185.0843. Anal. Calcd for $C_9H_{12}O_4$: C, 58.69, H, 6.57. Found: C, 58.39, H, 6.38.

4.4. Diethyl 2,3-pentadienedioate 1c

Diethyl 1,3-acetonedicarboxylate **4c** (100 mg, 0.50 mmol) was treated as **4a** in the above reaction to afford **1c** (84 mg, 92%) as a pale yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.29 (t, $J = 7.1$ Hz, 6H), 4.23 (q, $J = 7.1$ Hz, 4H), 6.04 (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.6 (2C), 61.3 (2C), 92.2 (2C), 163.1 (2C), 219.2; IR (CHCl$_3$): 3032, 2986, 1967, 1716, 1265, 1149 cm^{-1}; MS (70 eV) *m*/*z*: 184 (M^{+}, 11), 157 (3), 156 (31), 128 (24), 112 (100); HRMS calcd for $C_9H_{12}O_4$ (M^{+}): 184.0735, found: 184.0721. Anal. Calcd for $C_9H_{12}O_4$: C, 58.69, H, 6.57. Found: C, 58.67, H, 6.44.

4.5. Dibenzyl 2,3-pentadienedioate 1d

Dibenzyl 1,3-acetonedicarboxylate (**4d**) (50 mg, 0.15 mmol) was treated as **4a** in the above reaction to afford **1d** (32 mg, 70%) as a pale yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.18 (s, 4H), 6.07 (s, 2H), 7.29–7.32 (m, 10H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 67.1 (2C), 92.4 (2C), 128.1 (4C), 128.3 (2C), 128.5 (4C), 135.3 (2C), 163.0 (2C), 219.8: IR (CHCl$_3$): 3069, 1967, 1720, 1288, 1263, 1142, 1003 cm^{-1}; MS FAB(+) *m*/*z*: 331 [M^{+}+Na]; HRMS calcd for $C_{19}H_{16}O_4Na$ [M+Na]$^{+}$: 331.0947, found: 331.0962.

4.6. Di-*tert*-butyl 2,3-pentadienedioate 1e

Di-*tert*-butyl 1,3-acetonedicarboxylate **4e** (100 mg, 0.39 mmol) was treated as **4a** in the above reaction to afford **1e** (66 mg, 71%) as a pale yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.48 (s, 18H), 5.89 (s, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 27.9 (6C), 81.8 (2C), 93.5 (2C), 162.6 (2C), 218.8; IR (CHCl$_3$): 2981, 1963, 1701, 1369, 1302, 1136, 966 cm^{-1}; MS FAB(+) *m*/*z*: 263 [M^{+}+Na]; HRMS calcd for $C_{13}H_{20}ONa$ [M^{+}+Na]: 263.1250, found: 263.1239. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98, H, 8.39. Found: C, 64.70, H, 8.16.

4.7. Dimethyl 3-chloro-2-pentene-1,5-dioate 6a

Dimethyl 1,3-acetonedicarboxylate **4a** (100 mg, 0.57 mmol) and triethylamine (63 mg, 0.63 mmol) were successively added to a solution of 2-chloro-1,3-dimethylimidazolinium chloride (DMC; 146 mg, 0.86 mmol) in absolute dichloromethane (5 ml) at 0 °C. After stirring the reaction mixture for 1 h at room temperature, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl and extracted with diethyl ether. The organic layer was dried over sodium sulfate and condensed in vacuo, and the residue was purified by PTLC (hexane/ethyl acetate = 2:1) to afford **6a** (49 mg, 44%) as a pale yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.73 (s, 3H), 3.74 (s, 3H), 4.11 (s, 2H), 6.27 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 41.0, 51.5, 52.1, 121.4, 146.9, 164.3, 168.0; IR (CHCl$_3$): 3034, 2954, 1720, 1641, 1437, 1321, 1167, 1015 cm^{-1}; MS FAB(+) *m*/*z*: 193 [M+H]$^{+}$; HRMS calcd for $C_7H_{10}O_4{}^{35}Cl$ [M+H]$^{+}$: 193.0267, found: 193.0250. Anal. Calcd for $C_7H_9ClO_4$: C, 43.65, H, 4.71. Found: C, 43.53, H, 4.65.

4.8. (−)-[Bis-(1*R*,2*S*,5*R*)-(−)-menthyl] 1,3-acetonedicarboxylate 4f

(1*R*,2*S*,5*R*)-(−)-Menthol (31.9 g, 0.20 mol) and DMAP (998 mg, 8.17 mmol) were added to a solution of dimethyl 1,3-acetonedicarboxylate **4a** (14.2 g, 81.7 mmol) in toluene (100 ml), and the reaction mixture was refluxed. After 6 h, the resultant mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 12:1) to afford **4f** (32.6 g, 95%) as a pale yellow oil. $[\alpha]_D^{25} = -84.4$ (c 1.0, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.75–1.59 (m, 28H), 1.65–1.70 (m, 4H), 1.84–1.89 (m, 2H), 1.99–2.05 (m, 2H), 3.58 (d, $J = 5.9$ Hz, 4H), 4.68–4.80 (m, 2H); IR (CHCl$_3$): 2961, 2930, 1724, 1653, 1456, 1244, 1180 cm^{-1}; MS FAB(+) *m*/*z*: 423 [M^{+}+H]; HRMS calcd for $C_{25}H_{43}O_5$: 423.3110, found: 423.3119.

4.9. (+)-[Bis-(1*S*,2*R*,5*S*)-(+)-menthyl] 1,3-acetonedicarboxylate 4g

Dimethyl 1,3-acetonedicarboxylate **4a** (5.00 g, 28.7 mmol) and (1*S*,2*R*,5*S*)-(+)-menthol (5.00 g, 28.7 mmol) were treated as **4f** in the above reaction and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10:1) to afford **4g** (8.71 g, 72%) as a pale yellow oil. $[\alpha]_D^{25} = +83.0$ (c 1.0, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.76 (d, $J = 7.0$ Hz, 6H), 0.89 (d, $J = 7.1$ Hz, 6H), 0.91 (d, $J = 6.6$ Hz, 6H), 0.85–0.92 (m, 5H), 0.95–1.01 (m, 4H), 1.35–1.55 (m, 4H), 1.65–1.71 (m, 4H), 1.84–1.89 (m, 2H), 2.00–2.05 (m, 2H), 3.20 (s, 0.5H), 3.57 (d, $J = 15.7$ Hz, 1.5H), 3.59 (d, $J = 15.7$ Hz, 1.5H), 4.73 (dt, $J = 13.2$, 4.3 Hz, 2H), 5.10 (s, 0.25H), 12.18 (s, 0.25H); IR (CHCl$_3$): 2960, 2930, 2872, 1724, 1653, 1456, 1317, 1244 cm^{-1}; MS FAB(+) *m*/*z*: 423 [M+H]$^{+}$; HRMS calcd for $C_{25}H_{43}O_5$ (M^{+}+H): 423.3110, found: 423.3106.

4.10. (−)-[Bis-(1*S*)-(−)-bornyl] 1,3-acetonedicarboxylate 4h

Dimethyl 1,3-acetonedicarboxylate **4a** (2.01 g, 11.5 mmol) and (1*S*)-(−)-borneol (4.45 g, 28.9 mmol) were treated as **4f** in the above reaction and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 7:1) to afford **4h** (3.65 g, 75%) as a pale yellow oil. $[\alpha]_D^{24} = -43.1$ (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.85, 0.88, 0.90 (each s, 6H), 0.99–1.05 (m, 2H), 1.20–1.56 (m, 4H), 1.68–1.95 (m, 6H), 2.33–2.41 (m, 2H), 3.24 (s, 0.5H), 3.63 (s, 3H), 4.92–4.98 (m, 2H), 5.20 (s, 0.25H), 12.14 (s, 0.25H); IR ($CHCl_3$): 3013, 2959, 1728, 1655, 1454, 1327, 1240 cm^{-1}; MS FAB(+) *m*/*z*: 419 (M^++H); HRMS calcd for $C_{25}H_{39}O_5$ (M^++H): 419.2797, found: 419.2801.

4.11. (−)-[Bis-(1*R*)-(−)-isobornyl] 1,3-acetonedicarboxylate (−)-4i

Dimethyl 1,3-acetonedicarboxylate **4a** (1.31 g, 7.52 mmol) and (1*R*)-(−)-isoborneol (2.90 g, 18.8 mmol) were treated as **4f** in the above reaction and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 7:1) to afford **4i** (2.41 g, 76%) as a pale yellow oil. $[\alpha]_D^{24} = -65.3$ (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.83, 0.85, 0.96 (each s, 6H), 1.12 (m, 4H), 1.52–1.56 (m, 2H), 1.66–1.85 (m, 8H), 3.18 (s, 0.6H), 3.57 (s, 3H), 4.70 (dd, $J = 7.3$, 4.0 Hz, 2H), 5.09 (s, 0.2H), 12.11 (s, 0.2H); IR ($CHCl_3$): 3013, 2957, 1728, 1655, 1327, 1219 cm^{-1}; MS FAB(+) *m*/*z*: 441 (M^++Na); HRMS calcd for $C_{25}H_{38}O_5Na$ (M^++Na): 441.2617, found: 441.2624.

4.12. (*R*)-(−)-[Bis-(1*R*,2*S*,5*R*)-(−)-menthyl] 2,3-pentadienedioate 1f

Triethylamine (5.0 mg, 0.05 mmol) was added to a solution of a diastereomeric mixture of **4f** (2.00 g, 4.95 mmol) in pentane (5 ml), and the solution was chilled at −20 °C to afford crystals. Crystallization was repeated three times to afford **1f** (1.8 g, 90%) as colorless crystals. Mp: 83 °C (pentane); $[\alpha]_D^{26} = -244.2$ (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.78, 0.77 (each d, $J = 6.9$ Hz, 3H), 0.91–1.18 (m, 16H), 1.34–1.63 (m, 6H), 1.63–1.77 (m, 4H), 1.84, 1.87 (each dq, $J = 6.9$, 2.6 Hz, 1H), 2.03 (br d, $J = 11.9$ Hz, 2H), 4.75 (dt, $J = 10.8$, 4.4 Hz, 2H), 5.99 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.5 (2C), 20.1 (2C), 21.9 (2C), 23.6 (2C), 26.4 (2C), 31.3 (2C), 34.1 (2C), 40.7 (2C), 46.9 (2C), 75.5 (2C), 92.6 (2C), 162.9 (2C), 219.5; IR ($CHCl_3$): 1945, 1685 cm^{-1}; MS FAB(+) *m*/*z*: 405 [M^++H]; HRMS calcd for $C_{25}H_{41}O_4$: 405.3005, found: 405.3013.

4.13. (*S*)-(+)-[Bis-(1*S*,2*R*,5*S*)-(+)-menthyl] 2,3-pentanedienedioate 1g

A catalytic amount of triethylamine was added to a solution of a diastereomeric mixture of **4g** (917 mg, 2.27 mmol) in a minimum amount of pentane, and the solution was chilled at −20 °C to afford crystals. Crystallization was repeated three times to afford one diastereomer (825 mg, 90%) as colorless crystals. Mp: 87 °C (pentane); $[\alpha]_D = +243.3$ (*c* 0.54, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.78, 0.89, 0.91 (each d, $J = 7.0$ Hz, 6H), 0.83–1.11 (m, 6H), 1.36–1.54 (m, 4H), 1.66–1.71 (m, 4H), 1.82–1.90 (m, 2H), 2.00–2.05 (m, 2H), 4.74 (dt, $J = 10.8$, 4.5 Hz, 2H), 5.99 (s, 1.97H), 6.01 (s, 0.03H); IR ($CHCl_3$) 3028, 2959, 2928, 1965, 1699, 1456, 1290, 1263, 1146 cm^{-1}; MS FAB(+) *m*/*z*: 427 (M^++Na); HRMS calcd for $C_{25}H_{40}O_4Na$ (M^++Na): 427.2824, found: 427.2832.

4.14. (*R*)-(−)-[Bis-(1*S*)-(−)-bornyl] 2,3-pentadienedioate 1i

A catalytic amount of triethylamine was added to a solution of a diastereomeric mixture of **4h** (4.72 g, 11.8 mmol) in a minimum amount of hexane, and the crystallization was attained at room temperature. Crystallization was repeated three times to afford one diastereomer (4.34 g, 92%) as colorless crystals. Mp: 146 °C (hexane); $[\alpha]_D^{26} = -206.8$ (*c* 0.98, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.85, 0.88, 0.91 (each s, 6H), 1.01 (dd, $J = 13.8$, 3.4 Hz, 2H), 1.17–1.23 (m, 2H), 1.25–1.33 (m, 2H), 1.68–1.79 (m, 4H), 1.88–1.94 (m, 2H), 2.35–2.43 (m, 2H), 4.93 (ddd, $J = 9.9$, 3.3, 2.2 Hz, 2H), 6.03 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5 (2C), 18.8 (2C), 19.7 (2C), 26.9 (2C), 28.0 (2C), 36.8 (2C), 44.9 (2C), 47.8 (2C), 49.0 (2C), 81.2 (2C), 92.5 (2C), 163.8 (2C), 219.9; IR ($CHCl_3$): 3032, 3007, 2957, 2880, 1963, 1701, 1454, 1391, 1377, 1366, 1302, 1288, 1261, 1238, 1204, 1151, 1194, 1024 cm^{-1}; MS FAB(+) *m*/*z*: 423 (M^++Na); HRMS calcd for $C_{25}H_{36}ONa$ (M^++Na): 423.2514, found: 423.2508. Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96, H, 9.06. Found: C, 75.17, H, 8.99.

4.15. (*R*)-(−)-Bis[(1*R*)-(−)-isobornyl] 2,3-pentadienedioate 1i

A catalytic amount of triethylamine was added to a solution of a diastereomeric mixture of **4i** (784 mg, 1.96 mmol) in a minimum amount of hexane, and the crystallization was attained at room temperature. Crystallization was repeated twice to afford one diastereomer (698 mg, 89%) as colorless crystals. Mp: 151 °C (hexane); $[\alpha]_D^{21} = -263.8$ (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.83, 0.84, 0.92 (each s, 6H), 1.04–1.18 (m, 4H), 1.52–1.59 (m, 2H), 1.65–1.85 (m, 8H), 4.71 (dd, $J = 7.7$, 3.3 Hz, 2H), 5.95 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.4 (2C), 19.8 (2C), 20.0 (2C), 27.0 (2C), 33.5 (2C), 38.6 (2C), 45.0 (2C), 47.2 (2C), 48.9 (2C), 82.2 (2C), 92.4 (2C), 162.9 (2C), 220.2; IR ($CHCl_3$): 3026, 3013, 2957, 2880, 1962, 1699, 1477, 1454, 1404, 1391, 1371, 1312, 1261, 1244, 1217, 1200, 1163, 1051, 1009 cm^{-1}; MS FAB(+) *m*/*z*: 401 (M^++H); HRMS calcd for $C_{25}H_{37}O_4$ (M^++H): 401.2692, found: 401.2683 Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.92; H, 9.13.

4.16. (1*S*,2*R*,3*E*,4*R*)-(+)-[(1*S*)-(−)-Bornyl] 3-[2-(−)-bornyloxy-2-oxoethylidene]-7-*tert*-butoxycarbonyl-7-azabicyclo-[2.2.1]hept-5-ene-2-carboxylate 7a

Aluminum chloride (199 mg, 1.50 mmol) was added to a solution of **1h** (500 mg, 1.25 mmol) in dichloromethane (20 ml) and the mixture was stirred for 30 min at −78 °C. A solution of **3a** (2.09 g, 12.5 mmol) in dichloromethane (5 ml) was added to the reaction mixture, which was stirred for 48 h while keeping the temperature at −78 °C. The reaction mixture was poured into water and extracted with chloroform. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10:1) to afford **7a** (669 mg, 94%) as colorless crystals. Mp: 138 °C (methanol); $[\alpha]_D^{31} = +19.3$ (*c* 0.64, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 55 °C): δ 0.81, 0.82, 0.86 (each s, 3H), 0.88 (s, 6H), 0.90 (s, 3H), 0.93 (dd, $J = 13.9$, 3.5 Hz, 1H), 0.96 (dd, $J = 13.6$, 3.6 Hz, 1H), 1.11–1.17 (m, 1H), 1.21–1.34 (m, 3H), 1.43 (s, 9H), 1.63–1.68 (m, 2H), 1.70–1.85 (m, 3H), 1.91–1.97 (m, 1H), 2.24–2.37 (m, 2H), 4.10 (dd, $J = 4.3$, 1.9 Hz, 1H), 4.78 (ddd, $J = 3.8$, 5.7, 9.9 Hz, 1H), 4.92 (br m, 1H), 5.03 (br m, 1H), 6.12 (d, $J = 2.2$ Hz, 1H), 6.33 (dd, $J = 5.7$, 2.1 Hz, 1H), 6.41 (dd, $J = 5.7$, 2.6 Hz, 1H); IR ($CHCl_3$): 3028, 2959, 2880, 1707, 1369, 1352, 1273, 1236, 1205, 1196 cm^{-1}; MS FAB(+) *m/z*: 590 (M^++Na); HRMS calcd for $C_{34}H_{49}NO_6$ (M^++Na): 590.3457, found: 590.3463. Anal. Calcd for $C_{34}H_{49}NO_6$: C, 71.93; H, 8.70; N, 2.47. Found: C, 71.84; H, 8.69; N, 2.57.

4.17. (1*S*,2*R*,3*E*,4*R*)-(−)-[(1*R*)-(−)-Isobornyl] 3-[2-(−)-isobornyloxy-2-oxoethylidene]-7-*tert*-butoxycarbonyl-7-azabicyclo[2.2.1]hept-5-ene-2-carboxylate 7b

Aluminum chloride (21 mg, 0.16 mmol) was added to a solution of **1i** (52 mg, 0.13 mmol) in dichloromethane (3 ml) and the mixture was stirred for 30 min at −78 °C. A solution of **3a** (217 mg, 1.30 mmol) in dichloromethane (2 ml) was added to the reaction mixture, which was stirred for 48 h while keeping the temperature at −78 °C. The reaction mixture was poured into water and extracted with chloroform. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10:1) to afford **7b** (68 mg, 92%) as colorless crystals. Mp: 157 °C (methanol); $[\alpha]_D^{27} = -16.7$ (*c* 2.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 55 °C): δ 0.81, 0.82, 0.83, 0.84, 0.85, 0.98 (each s, 3H), 1.16–1.12 (m, 2H), 1.41 (s, 9H), 1.47–1.81 (m, 12H), 4.03 (dd, $J = 3.9$, 2.1 Hz, 1H), 4.60 (ddd, $J = 11.3$, 7.7, 3.4 Hz, 2H), 4.92 (br s, 1H), 4.97 (br m, 1H), 6.01 (d, $J = 2.0$ Hz, 1H), 6.31 (dd, $J = 5.8$, 2.2 Hz, 1H), 6.73 (dd, $J = 5.8$, 2.5 Hz, 1H); IR ($CHCl_3$): 3034, 2957, 1707, 1369, 1352, 1275, 1256, 1186, 1167 cm^{-1}; MS FAB(+) *m/z*: 590 (M^++Na); HRMS calcd for $C_{34}H_{49}NO_6$ (M^++Na): 590.3457, found: 590.3463. Anal. Calcd for $C_{34}H_{49}NO_6$: C, 71.93; H, 8.70; N, 2.47. Found: C, 71.78; H, 8.81; N, 2.59.

4.18. (1*S*,2*R*,3*E*,4*R*)-(+)-7-*tert*-Butoxycarbonyl-2-(2′-acetoxyethylidene)-3-acetoxymethyl-7-azabicyclo[2.2.1]heptane 8a and 8b

A solution of **7a** (200 mg, 0.35 mmol) in tetrahydrofuran (5 ml) was added to a suspension of lithium aluminum hydride (33 mg, 0.88 mmol) and tetrahydrofuran (10 ml) at 0 °C and the mixture was stirred for 1 h while keeping the temperature the same and then for another 48 h at room temperature. The reaction mixture was diluted with diethyl ether and the reaction was quenched by adding saturated aqueous solution of sodium sulfate. Magnesium sulfate was directly added to the mixture, and the filtrate was evaporated. The residue was purified by silica gel column chromatography (chloroform/methanol = 15:1) to afford (1*S*,2*R*,3*E*,4*R*)-7-*tert*-butoxycarbonyl-2-(2′-hydroxyethylidene)-3-hydroxymethyl-7-azabicyclo[2.2.1]heptane (63 mg), which was treated with acetic anhydride and pyridine. After stirring the mixture for 1 h at room temperature, methanol was added and the organic solvents were removed in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 3:1) to afford **8a** (63 mg, 53%) as a colorless oil. $[\alpha]_D^{27} = +73.6$ (*c* 0.64, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 20.7, 20.8, 20.9, 28.06, 28.14, 61.7, 63.0, 65.4, 65.7, 80.1, 80.6, 170.5, 170.6, 170.7, 171.0. **8b** was treated as the same way as **7a**: $[\alpha]_D^{24} = +73.3$ (*c* 0.83, $CHCl_3$).

4.19. (1*S*,2*R*,3*E*,4*R*)-(−)-[(1*S*)-(−)-Bornyl] 3-[2-(−)-bornyloxy-2-oxoethylidene]bicyclo[2.2.1]hept-5-ene-2-carboxylate 7c

Aluminum chloride (88 mg, 0.66 mmol) was added to a solution of **1h** (220 mg, 0.55 mmol) in dichloromethane (6 ml) and the mixture was stirred for 30 min at −78 °C. A solution of **3b** (726 mg, 5.49 mmol) in dichloromethane (4 ml) was added to the reaction mixture, which was stirred for 48 h while keeping the temperature at −78 °C. The reaction mixture was poured into water and extracted with chloroform. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 15:1) to afford **7c** (244 mg, 95%) as colorless crystals. Mp: 115 °C (diethyl ether); $[\alpha]_D^{26} = -31.5$ (*c* 0.64, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.79 (s, 6H), 0.83 (s, 3H), 0.86 (s, 6H), 0.88 (s, 3H), 0.89–0.95 (m, 1H), 0.98 (d, $J = 3.7$ Hz, 1H), 1.05–1.12 (m, 1H), 1.16–1.33 (m, 3H), 1.50–1.81 (m, 7H), 1.92–1.99 (m, 1H), 2.21–2.39 (m, 2H), 3.39 (m, 1H), 3.44 (m, 1H), 3.90 (dd, $J = 3.6$, 2.1 Hz, 1H), 4.73 (ddd, $J = 5.5$, 3.4, 2.2 Hz, 1H), 4.86 (ddd, $J = 5.6$, 3.5, 2.1 Hz, 1H), 6.06 (dd, $J = 2.2$, 0.5 Hz, 1H), 6.14–6.19 (m, 2H); MS FAB(+) *m/z*: 467 (M^++H); HRMS calcd for $C_{30}H_{42}O_4$ (M^++H): 467.3161, found: 467.3169. Anal. Calcd for $C_{30}H_{42}O_4$: C, 77.21; H, 9.07. Found: C, 76.80; H, 9.10.

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