Construction of Tricyclic Enone, a Common Precursor for Aphidicolane and Stemodane B/C/D-Ring System

Tetsuaki TANAKA,* Sachiko YAMAMOTO, Kei HIRAMATSU, Kazuo MURAKAMI, Hitoshi YOSHINO, Debasis PATRA, Chuzo IWATA, and Hiroaki OHNO

Graduate School of Pharmaceutical Sciences, Osaka University; 1–6 Yamadaoka, Suita, Osaka 565–0871, Japan.
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Synthesis of a tricyclic enone (B/C/D ring system), a common key precursor for the aphidicolane- and stemodane-type diterpene, is described. The key reaction for the construction of the quaternary carbon center is allylation of epoxide at the more substituted carbon with an organotitanium reagent. Asymmetric reduction with DIP-Cl followed by stereoselective cyclization of spirocyclic ketone and the functional group modification gave the desired tricyclic enone in good yield.

Key words aphidicolane; stemodane; allylation; organotitanium reagent

The leaves of the rare littoral plant, *Stemodia maritima* L. (fam. Scrophulariaceae), from Jamaica have long been used as a folk medicine for the treatment of venereal disease in the Caribbean Islands.[1)] Attracted by the reported medicinal properties, Manchand and others isolated and characterized structurally unique tetracyclic diterpenes, stemodin **1** and stemodinone **2** (Fig. 1).[2—7)] Aphidicolin (**3**),[8,9)] which has a highly related tetracyclic ring system to stemodanes **1** and **2**, was isolated from *Cephalalosporium aphidicola* by Hesp and co-workers and later found to occur in *Nigrosporum sphaerica*. The fusion of the five-membered C ring to B in stemodanes **1** and **2** is *cis* in contrast to the *trans* fusion in aphidicolin **3**. Aphidicolin is known as a potent antitumor (inhibits DNA replication and growth of several human and neoplastic cells)[10—12)] and antiviral agent (promising activity against Herpes simplex).[13—15)] Stemodanes, with a similar structure to aphidicolanes, is expected to have related pharmacological activities.

Their important medicinal properties as well as the presence of more than six stereocenters and four quaternary carbons, especially the two adjacent quaternary carbons at C-9 and C-10, make these natural products a worthy synthetic challenge.[16)] Although there are several reports on the synthesis of stemodinone,[17—20)] other stemodanes,[21—33)] and aphidicolanes[34—53)] in a racemic form, asymmetric synthesis of this class of compounds is relatively rare.[54—58)] The asymmetric total synthesis of aphidicolin was first achieved by Holton and co-workers in 1987.[54)] After that, formal synthesis of (+)-aphidicolin was reported by Tanis[55)] and Fukumoto.[56)] Recently, total synthesis of aphidicolanes using transannular Diels–Alder reaction was achieved by Deslongchamps and co-workers.[57,58)] These synthetic routes are extremely important in that the complex tetracyclic skeleton was constructed in an enantioenriched form; however, they are limited to the synthesis of a single aphidicolane or stemodane diterpene. Synthesis of other natural products or their analogs is not easily accessible by these routes because in many cases the A-ring having oxygen functionalities was constructed at the earlier stage of the synthetic routes. Therefore, development of a systematic synthetic route leading to various kinds of aphidicolanes, stemodanes, and their analogs in an enantiomerically pure form is desirable.

We then planned a novel flexible synthetic route which can be applied to the synthesis of a variety of aphidicolanes and stemodanes, based on the asymmetric construction of the B/C/D ring system followed by formation of the highly-functionalized A-ring. A tricyclic enone **4** is considered as the key intermediate, which would lead to either natural or non-natural aphidicolanes and stemodanes by stereoselective hydrogenation of the double bond as shown in Chart 1. In this paper, we describe synthesis of the tricyclic enone **4** through allyltitanium-mediated regioselective ring-opening reaction of epoxides at the more substituted carbon,[59—61)] developed by our group (Chart 2).

Synthetic Plan Our basic strategy is shown in Chart 3. The tricyclic enone **4** can be obtained from alcohol **6** by one-

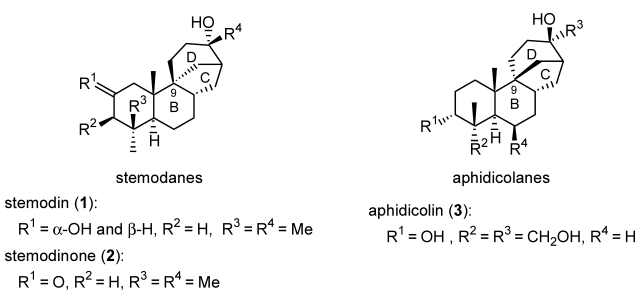


Fig. 1

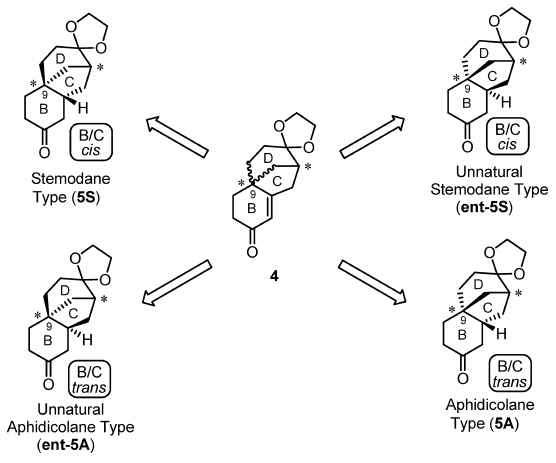


Chart 1

* To whom correspondence should be addressed. e-mail: t-tanaka@phs.osaka-u.ac.jp

carbon elongation followed by cyclization. Access to the alcohol **6** was expected through intramolecular α-alkylation of a ketone derived from the acetal **7**, which would be prepared by the regioselective allylation of the chiral epoxide **8**.

First, we investigated asymmetric preparation of the epoxide **11** by Sharpless asymmetric epoxidation[62—64] (Chart 4). The allylic alcohol **10** was obtained from 1,4-cyclohexanedione **9** according to the literature.[65,66] Epoxidation of the alcohol **10** with L-(+)-diethyl tartrate and titanium tetraisopropoxide gave the epoxide **11**. The hydroxy group of **11** was protected with a methoxymethyl group to afford the corresponding MOM ether **12**, which was subjected to the allyltitanium-mediated ring-opening reaction with allylmagnesium chloride in the presence of chlorotitanium triphenoxide to give the alcohol **13** in 77% yield. Gas chromatography analysis of their MTPA esters,[67,68] **14a** and **14b**, revealed that the alcohol **11** has the desired absolute configuration with 80% ee.

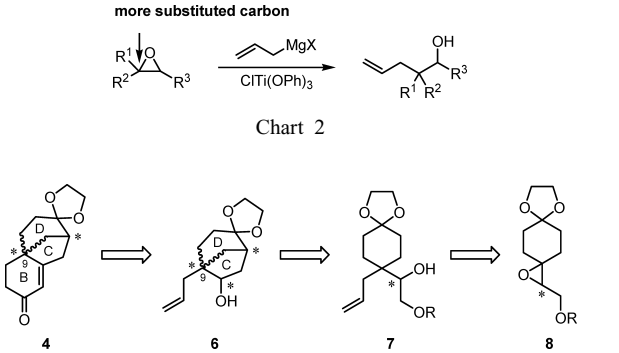
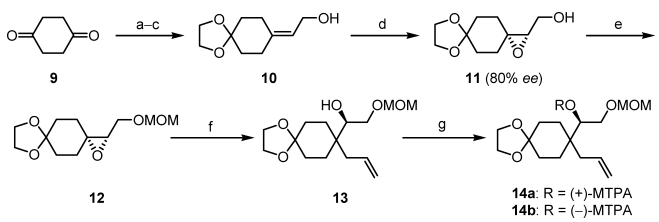


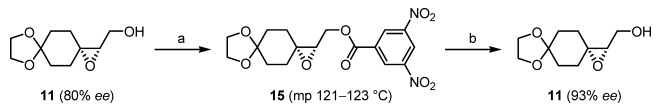
Chart 2

Chart 3. Synthetic Plan of Tricyclic Enone **4**



Reagents and conditions: (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, 0 °C to rt, then **9**, −78 °C; (b) ethylene glycol, *p*-TSA, reflux; (c) DIBAL-H, −78 °C, 45% from **9**; (d) *t*-BuOOH, (+)-diethyl tartrate, $Ti(O\textit{i}\text{-}Pr)_4$, molecular sieves 4A, −20 °C, 82%; (e) MOMCl, $(\textit{i}\text{-}Pr)_2NEt$, rt, 94%; (f) allylMgCl, $ClTi(OPh)_3$, −50 °C to rt, 77%; (g) (+)- or (−)-MTPACl, Et_3N, DMAP, rt.

Chart 4. Synthesis of Chiral Alcohol Derivative **13** *via* Sharpless Epoxidation



Reagents and conditions: (a) 3,5-dinitrobenzoyl chloride, Et_3N, DMAP, 0 °C to rt, then recrystallization, 92%; (b) K_2CO_3, MeOH, 0 °C, 100%.

Chart 5. Synthesis of Enantioenriched Epoxide by Recrystallization

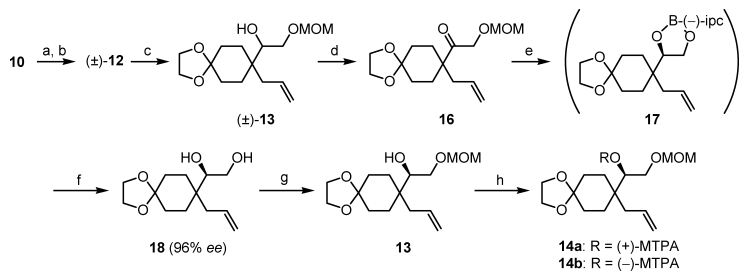
Since the optical yield of the Sharpless epoxidation of **10** was unsatisfactory, the epoxide **11** was converted into 3,5-dinitrobenzoate **15** and recrystallized. Optical purity of the mother liquor was improved to 93% ee after repeated recrystallization (Chart 5). However, this route to **11** is not an ideal process in terms of efficiency and atom economy.

Next, preparation of the alcohol **13** through the asymmetric reduction was investigated (Chart 6). Racemic alcohol (±)-**13** was obtained in high yield by epoxidation of **10** with *t*-BuOOH-$VO(acac)_2$ and protection of the hydroxy group with an MOM group, followed by the allylation with the titanium reagent. Swern oxidation of (±)-**13** gave the corresponding ketone **16**, which was subjected to the asymmetric reduction with (−)-DIP-Cl[69—71] leading to borate **17** without any side reactions of the terminal olefin. Oxidative work-up of the resulting borate **17** afforded diol **18** with 96% ee, which was determined by gas chromatography analysis of the MTPA esters **14a** and **14b**. Thus, the key intermediate **18** was obtained in high enantiomeric excess by use of the asymmetric reduction with DIP-Cl.

We next investigated the stereoselective construction of the C/D-ring system by the intramolecular α-alkylation of keto-tosylate **19** (Chart 7). Keto-tosylate **19** was obtained by tosylation of the primary hydroxy group of the diol **18** and protection of the secondary alcohol. Regioselective α-alkylation of **19** (R=protecting group) under various reaction conditions was unsuccessful. For example, treatment of **19** having a TBDMS group with *t*-BuOK led to bicyclic products, **20** and **21** as a 3 : 1 mixture,[72] which were produced by α-alkylation at carbon a (route a) or carbon b (route b), respectively.

From these observations, stereoselective formation of the D-ring by α-alkylation of the conformationally flexible ketone **19** was proven to be difficult. However, the difficulty has been overcome by the use of a conformationally restricted substrate as shown in Chart 8. Phenylselenenylation[73,74] of the diol **18** led to five-membered ring ether **22**, which was converted to tosylate **23**. Treatment of **23** with NaH gave tricyclic ketone **24** as the single isomer in 82% yield through the stereoselective α-alkylation. Protection of the carbonyl group followed by reductive deselenenylation[75] then afforded the alcohol **6** in good yield.

Finally, the B-ring was constructed by carbon chain elon-



Reagents and conditions: (a) $VO(acac)_2$, *t*-BuOOH, reflux; (b) MOMCl, $(\textit{i}\text{-}Pr)_2NEt$, rt, 88% from **10**; (c) allylMgCl, $ClTi(OPh)_3$, −50 °C to rt, 77%; (d) oxalyl chloride, Et_3N, DMSO, −60 °C, 83%; (e) (−)-DIP-Cl, neat, rt; (f) 2 N NaOH, 30% H_2O_2, 0 °C, 75% from **16**; (g) MOMCl, $(\textit{i}\text{-}Pr)_2NEt$, 0 °C, 32%; (h) (+)- or (−)-MTPACl, Et_3N, DMAP, rt.

Chart 6. Synthesis of Chiral Alcohol Derivatives *via* Asymmetric Reduction

gation and aldol cyclization as shown in Chart 9. Hydroboration of **6** and Swern oxidation of the resulting alcohol **26** led to keto aldehyde **27**. The chemoselective methylation of the aldehyde **27** with methyltitanium triisopropoxide gave ketoalcohol **28** in 94% yield. Swern oxidation of **28** followed by intramolecular aldol cyclization afforded the tricyclic enone **4** in good yield.

In conclusion, we have developed a reliable synthetic method of the tricyclic enone **4** with high optical purity, a common key intermediate for the asymmetric synthesis of stemodane- and aphidicolane-type diterpenes. The quaternary carbon center was efficiently constructed by the allyltitanium-mediated regioselective ring-opening reaction of the epoxide **12**.

Experimental

General Methods Melting points are uncorrected. Nominal (LRMS) and exact mass (HRMS) spectra were recorded on a JEOL JMS-01SG-2 or JMS-HX/HX 110A mass spectrometer. ^{1}H-NMR spectra were recorded in $CDCl_3$. Chemical shifts are reported in parts per million downfield from internal Me_4Si (s=singlet, d=doublet, dd=double doublet, ddd=doublet of double doublet, t=triplet, q=quartet, m=multiplet). Optical rotations were measured in $CHCl_3$ with a JASCO DIP-360 digital polarimeter. For flash chromatography, silica gel 60 H (silica gel for thin-layer chromatography, Merck) or silica gel 60 (finer than 230 mesh, Merck) was employed.

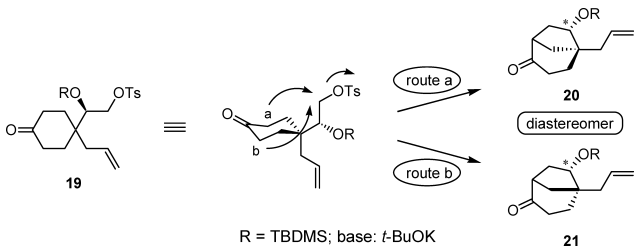
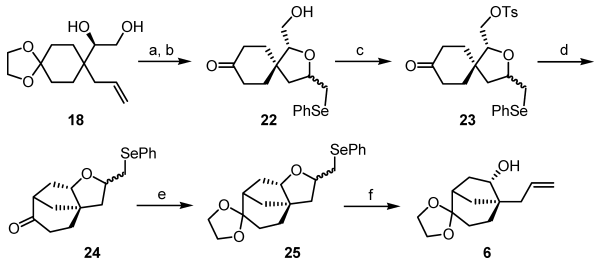


Chart 7



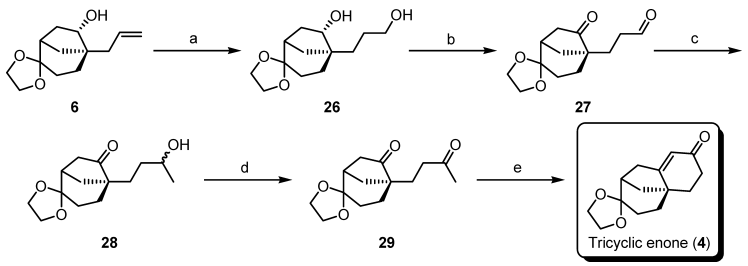
Reagents and conditions: (a) PhSeCl, −78 °C; (b) 10% HCl, rt, 55% from **18**; (c) *p*-TsCl, Et_3N, DMAP, 0 °C to rt, 85%; (d) NaH, 40 °C, 82%; (e) ethylene glycol, PPTS, reflux; (f) Ca, liq. NH_3, −33 °C, 95% from **24**.

Chart 8. Formation of C-Ring *via* Spiro Tetrahydrofuran Derivative

(*S*)-2-(Hydroxymethyl)-1-oxaspiro[2.5]octan-6-one 6,6-Ethylene Acetal (11) To a stirred solution of Ti(O*i*-Pr)$_4$ (9.6 ml, 32.6 mmol) and molecular sieves 4A in dry CH_2Cl_2 (10 ml) was added L-(+)-diethyl tartrate (5.6 ml, 32.6 mmol) at −10 °C. After 10 min, *tert*-butylhydroperoxide (4.0 M in toluene, 16.3 ml, 65.2 mmol) was added dropwise to the mixture under stirring. After 30 min, a solution of the allylic alcohol **10** (3.00 g, 16.3 mmol) in dry CH_2Cl_2 (3 ml) was added dropwise to the mixture at −20 °C, and the mixture was stirred for 4 h at −20 °C. To the mixture were successively added water at 0 °C and 30% NaOH/saturated NaCl, and the mixture was stirred vigorously at room temperature for 2 h. The organic phase was filtered through Celite and dried over $MgSO_4$. Concentration under reduced pressure gave a residual oil, which was purified by column chromatography over silica gel (*n*-hexane : EtOAc=1 : 2) to afford the epoxide **11** (2.67 g, 82% yield) as a colorless oil: $[\alpha]_D^{20}$ −14.7° (*c*=1.20, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3421 (OH); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.54—1.95 (m, 8H), 3.05 (dd, *J*=6.7, 4.3 Hz, 1H, 2-H), 3.68—3.75 (dd, *J*=12.0, 7.0 Hz, 1H, OCHH), 3.83—3.90 (dd, *J*=12.0, 4.0 Hz, 1H, OCHH), 3.98 (t, *J*=2.7 Hz, 4H, OC_2H_4O); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 26.2, 32.0, 32.8 (2C), 61.0, 62.0, 63.6, 63.38, 64.40, 108.1; MS (EI) *m*/*z*: 200 (M^+). *Anal.* Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.04; H, 7.94.

(*S*)-2-(Methoxymethoxymethyl)-1-oxaspiro[2.5]octan-6-one 6,6-Ethylene Acetal (12) To a stirred solution of **11** (1.00 g, 5.00 mmol) in dry CH_2Cl_2 (13 ml) were added (*i*-Pr)$_2$NEt (1.80 ml, 1.00 mmol) and MOMCl (0.75 ml, 10.0 mmol), and the mixture was stirred overnight at room temperature. Saturated $NaHCO_3$ was added to the mixture and the whole was extracted with CH_2Cl_2. The extract was washed with water and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave a residual oil, which was purified by column chromatography over silica gel (*n*-hexane : EtOAc=3 : 1) to afford the MOM ether **12** (1.17 g, 94% yield) as a colorless oil: $[\alpha]_D^{25}$ +0.36° (*c*=1.27, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.55—1.95 (m, 8H), 3.06 (dd, *J*=6.0, 5.1 Hz, 1H, 2-H), 3.38 (s, 3H, OMe), 3.65 (dd, *J*=11.4, 6.0 Hz, 1H, OCHH), 3.73 (dd, *J*=11.4, 5.1 Hz, 1H, OCHH), 3.97 (t, *J*=2.5 Hz, 4H, OC_2H_4O), 4.65 (d, *J*=6.6 Hz, 1H, OCHHO), 4.68 (d, *J*=6.6 Hz, 1H, OCHHO); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 26.2, 32.0, 32.7, 32.8, 55.3, 61.1, 61.8, 64.37, 64.40, 66.0, 96.6, 108.2; MS (EI) *m*/*z*: 244 (M^+). *Anal.* Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.91; H, 8.08.

4-[(*R*)-1-Hydroxy-2-(methoxymethoxy)ethyl]-4-(prop-2-enyl)cyclohexan-1-one 1,1-Ethylene Acetal (13) from 12 To a stirred solution of $ClTi(OPh)_3$ (1.0 M in THF; 14.1 ml, 14.1 mmol) was added dropwise allylmagnesium chloride (2.0 M in THF; 9.4 ml, 18.9 mmol) at −78 °C. The mixture was stirred for 1 h at −50 °C, and a solution of the epoxide **12** (1.15 g, 4.71 mmol) in THF (6 ml) was added to the mixture, and the mixture was gradually warmed to 0 °C. Saturated KF was added to the mixture. The resulting white precipitate was filtered off, and the filtrate was extracted with Et_2O. The extract was washed with 2 N NaOH, water, and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave a residual oil, which was purified by column chromatography over silica gel (*n*-hexane : EtOAc=5 : 1) to afford the alcohol **13** (1.04 g, 77% yield) as a colorless oil: $[\alpha]_D^{24}$ −5.02° (*c*=0.96, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3504 (OH), 1637 (C=C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.46—1.76 (m, 8H), 2.14 (dd, *J*=13.9, 7.5 Hz, 1H, CHHCH=CH_2), 2.34 (dd, *J*=13.9, 7.0 Hz, 1H, CHHCH=CH_2), 2.52 (br s, 1H, OH), 3.37 (s, 3H, OMe), 3.46—3.52 (m, 1H, 1′-H), 3.71—3.79 (m, 2H, 2′-CH_2), 3.93 (s, 4H, OC_2H_4O), 4.66 (s, 2H, OCH_2O), 5.05—5.10 (m, 2H, CH=CH_2), 5.81—5.94 (m, 1H, CH=CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 28.2, 28.6, 30.1, 30.3, 36.3, 38.1, 55.3, 64.1 (2C), 69.2, 74.0, 96.9, 108.7, 117.4, 134.9; MS (EI) *m*/*z*: 286 (M^+). *Anal.* Calcd for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 63.06; H, 9.02.



Reagents and conditions: (a) $BH_3 \cdot SMe_2$, 0 °C to rt then 30% H_2O_2, 3 N NaOH, 0 °C to rt, 82%; (b) oxalyl chloride, Et_3N, DMSO, −60 °C, 82%; (c) MeMgCl, $ClTi(O\textit{i}\text{-}Pr)_3$, −60 °C, 94%; (d) oxalyl chloride, Et_3N, DMSO, −60 °C, 91%; (e) NaOH/MeOH, reflux, 91%.

Chart 9. Synthesis of Tricyclic Enone **4**

4-{(1*R*)-1-[(2*R*)-2-Methoxy-2-(trifluoromethyl)phenylacetoxy]-2-(methoxymethoxy)ethyl}-4-(prop-2-enyl)cyclohexan-1-one 1,1-Ethylene Acetal (14a) To a stirred solution of **13** (8.0 mg, 0.030 mmol) in dry CH_2Cl_2 (0.3 ml) were successively added Et_3N (8.3 μl, 0.059 mmol), 4-dimethylaminopyridine (DMAP; 3.3 mg, 0.030 mmol), and (+)-MTPACl (7.9 μl, 0.045 mmol), and the mixture was stirred for 30 min at room temperature. Saturated $NaHCO_3$ was added to the mixture and the whole was extracted with $CHCl_3$. The extract was washed with brine, and dried over $MgSO_4$. Concentration under reduced pressure gave a residual oil, which was purified by column chromatography over silica gel (*n*-hexane : EtOAc=3 : 1) to afford the MTPA ester **14a** (8.3 mg, 59% yield) as a colorless oil: IR ($CHCl_3$) cm^{-1} 1747 (C=O), 1639 (C=C); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.17—1.54 (m, 8H), 2.04—2.10 (m, 2H), 3.27 (s, 3H), 3.52 (s, 3H), 3.59—3.83 (m, 6H), 4.41 (d, *J*=6.5 Hz, 1H, CHHOMOM), 4.55 (d, *J*=6.5 Hz, 1H, CHHOMOM), 4.95 (m, 2H), 5.37 (d, *J*=7.5 Hz, 1H), 5.64—5.72 (m, 1H), 7.30—7.52 (m, 5H, Ph).

4-{(1*R*)-1-[(2*S*)-2-Methoxy-2-(trifluoromethyl)phenylacetoxy]-2-(methoxymethoxy)ethyl}-4-(prop-2-enyl)cyclohexan-1-one 1,1-Ethylene Acetal (14b) By a procedure identical with that described for the synthesis of **14a** from **13**, the alcohol **13** (9.0 mg, 0.031 mmol) was converted into **14b** (9.6 mg, 61% yield) by the reaction with (−)-MTPACl: colorless oil; IR ($CHCl_3$) cm^{-1} 1747 (C=O), 1639 (C=C); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.47—1.58 (m, 8H), 2.05—2.20 (m, 2H), 3.20 (s, 3H), 3.52—3.75 (m, 5H), 3.85 (s, 4H), 4.37 (d, *J*=6.5 Hz, 1H, CHHOMOM), 4.40 (d, *J*=6.5 Hz, 1H, CHHOMOM), 4.96—5.02 (m, 2H), 5.34 (d, *J*=7.5 Hz, 1H), 5.72—5.75 (m, 1H), 7.32—7.53 (m, 5H, Ph).

(*S*)-2-(3,5-Dinitrobenzoyloxy)methyl-1-oxaspiro[2.5]octan-6-one 6,6-Ethylene Acetal (15) To a stirred solution of **11** (3.00 g, 15.0 mmol) in dry CH_2Cl_2 (150 ml) were successively added Et_3N (8.4 ml, 60.0 mmol), DMAP (366 mg, 3.0 mmol), and 3,5-dinitrobenzoyl chloride (10.4 g, 45.0 mmol), and the stirring was continued for 3 h at room temperature. Saturated $NaHCO_3$ was added to the mixture, and the whole was extracted with $CHCl_3$. The extract was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure gave a residue, which was purified by column chromatography over silica gel (*n*-hexane : EtOAc=3 : 1) to afford the 3,5-dinitrobenzoate **15** (5.44 g, 92% yield) as a colorless solid: mp 121—123 °C (from *n*-hexane–EtOAc); $[\alpha]_D^{24}$ −26.6° (*c*=0.91, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1736 (C=O), 1630 (Ph), 1545 (NO_2); ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.45—1.96 (m, 8H), 3.20 (dd, *J*=7.4, 4.0 Hz, 1H), 3.91 (s, 4H), 4.36 (dd, *J*=12.1, 7.4 Hz, 1H), 4.71 (dd, *J*=12.1, 4.0 Hz, 1H), 9.11 (m, 2H), 9.17 (m, 1H); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 26.3, 31.8, 32.7 (2C), 59.9, 61.7 (2C), 64.4 (2C), 65.4, 107.8, 122.6, 129.4, 129.5, 133.3, 148.6, 162.4; MS (EI) *m*/*z*: 394 (M^+). *Anal.* Calcd for $C_{17}H_{18}N_2O_9$: C, 51.78; H, 4.60; N, 7.10. Found: C, 51.77; H, 4.61; N, 7.13.

(*S*)-2-(Hydroxymethyl)-1-oxaspiro[2.5]octan-6-one 6,6-Ethylene Acetal (11) from 13 To a stirred solution of **15** (150 mg, 0.381 mmol) in MeOH (4 ml) was added saturated aqueous K_2CO_3 (1 ml) at 0 °C, and the mixture was stirred for 5 min at this temperature. Saturated NH_4Cl was added to the mixture, and the solvent was removed *in vacuo*. The residue was diluted with EtOAc and washed with brine, and dried over $MgSO_4$. Concentration under reduced pressure gave a residual oil, which was purified by column chromatography over silica gel (*n*-hexane : EtOAc=1 : 2) to afford the epoxy alcohol **11** (76.0 mg, 100% yield).

(±)-4-(1-Hydroxy-2-methoxymethoxy)ethyl-4-(prop-2-enyl)cyclohexan-1-one 1,1-Ethylene Acetal [(±)-13] To a stirred solution of **10** (1.00 g, 5.43 mmol) in dry benzene (15 ml) were added $VO(acac)_2$ (43.2 mg, 0.163 mmol) and *tert*-butylhydroperoxide (TBHP; 80% aqueous solution; 0.73 ml, 5.97 mmol), and the mixture was stirred under reflux for 5 min. After cooling, the mixture was washed with saturated $NaHCO_3$, water, and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave a residue, which was purified by column chromatography over silica gel (*n*-hexane : EtOAc=1 : 2) to afford the epoxy alcohol (±)-**11** (1.02 g, 94% yield). By a procedure identical with that described for the synthesis of **13** from **11**, (±)-**11** was converted into (±)-**13**.

4-[2-(Methoxymethoxy)-1-oxoethyl]-4-(prop-2-enyl)cyclohexan-1-one 1,1-Ethylene Acetal (16) To a stirred solution of oxalyl chloride (2.53 ml, 29.0 mmol) in dry CH_2Cl_2 (35 ml) was added DMSO (4.11 ml, 57.9 mmol) at −60 °C, and the mixture was stirred for 15 min. To the mixture was added dropwise (±)-**13** (4.14 g, 14.6 mmol) in dry CH_2Cl_2 (43 ml), and the stirring was continued for 1 h. To the mixture was added dropwise Et_3N (12.1 ml, 86.8 mmol), and the mixture was stirred for 2 h. Water was added to the mixture, and the whole was extracted with CH_2Cl_2. The extract was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure gave a residue, which was purified by column chromatography over silica gel (*n*-hexane : EtOAc=2 : 1) to afford the ketone **16** (3.14 g, 83% yield) as a colorless oil: IR ($CHCl_3$) cm^{-1} 1718 (C=O), 1639 (C=C); ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.42—1.65 (m, 6H), 1.96—2.09 (m, 2H), 2.24 (d, *J*=7.3 Hz, 2H), 3.31 (s, 3H), 3.86 (s, 4H), 4.33 (s, 2H), 4.61 (s, 2H), 4.90—5.10 (m, 2H), 5.59 (m, 1H); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 29.8 (2C), 31.5 (2C), 42.4, 49.9, 55.6, 64.2 (2C), 68.4, 96.3, 108.1, 118.5, 132.6, 209.0; MS (EI) *m*/*z*: 284 (M^+). *Anal.* Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.26; H, 8.41.

(*R*)-4-(1,2-Dihydroxyethyl)-4-(prop-2-enyl)cyclohexan-1-one 1,1-Ethylene Acetal (18) A mixture of (−)-DIP-Cl (293 mg, 0.915 mmol) and **16** (200 mg, 0.704 mmol) was stirred for 2 d. The mixture was concentrated under reduced pressure to remove pinene. The residue was diluted with EtOAc, and diethanolamine (192 mg, 1.83 mmol) was added to the mixture. After stirring for 2 h, the mixture was filtered and concentrated *in vacuo*. The residue was diluted with THF (5 ml), and 2 N NaOH (1 ml) and 30% H_2O_2 (1 ml) were added dropwise to the mixture at 0 °C, and the mixture was stirred for 2 h. After salting out, the whole was extracted with $CHCl_3$, and the extract was dried over $MgSO_4$. Concentration under reduced pressure gave a residue, which was purified by column chromatography over silica gel (*n*-hexane : EtOAc=1 : 5) to afford the alcohol **18** (128 mg, 75% yield) as a colorless oil: $[\alpha]_D^{27}$ −5.59° (*c*=1.27, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3439 (OH), 1637 (C=C); ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.35—1.70 (m, 8H), 2.05 (dd, *J*=14.2, 7.4 Hz, 1H), 2.24 (dd, *J*=14.2, 7.2 Hz, 1H), 3.54 (m, 2H), 3.69 (m, 1H), 3.86 (s, 4H), 4.90—5.10 (m, 2H), 5.80 (m, 1H); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 28.4, 29.0, 30.4, 30.6, 36.6, 38.6, 62.9, 64.5 (2C), 76.9, 109.0, 118.0, 135.2; MS (EI) *m*/*z*: 242 (M^+).

(*R*)-4-(1-Hydroxy-2-methoxymethoxy)ethyl-4-(prop-2-enyl)cyclohexan-1-one 1,1-Ethylene Acetal (13) from 18 To a stirred solution of **18** (10 mg, 0.041 mmol) in dry CH_2Cl_2 (0.4 ml) were added (*i*-Pr)$_2$NEt (7.6 μl, 0.083 mmol) and MOMCl (3.1 μl, 0.041 mmol) at 0 °C, and the mixture was stirred for 30 min at this temperature. Saturated $NaHCO_3$ was added to the mixture and the whole was extracted with CH_2Cl_2. The extract was washed with water and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave a residual oil, which was purified by column chromatography over silica gel (*n*-hexane : EtOAc=2 : 1) to afford the MOM ether **13** (3.8 mg, 32% yield).

(1*R*,3*R*)- and (1*R*,3*S*)-1-(Hydroxymethyl)-3-(phenylselenomethyl)-2-oxaspiro[4.5]decan-8-one (22) To a stirred solution of **18** (150 mg, 0.620 mmol) in dry CH_2Cl_2 (4 ml) was added PhSeCl (178 mg, 0.930 mmol) at −78 °C, and the mixture was stirred for 4 h. Saturated $NaHCO_3$ was added to the mixture, and the whole was extracted with CH_2Cl_2. The extract was washed with water and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave a residual oil, which was purified by short column chromatography over silica gel (*n*-hexane : EtOAc=8 : 1) to afford the corresponding THF derivative having an acetal moiety. To a stirred solution of this compound in THF (5 ml) was added 10% HCl (3 ml), and the mixture was stirred for 2 h at room temperature. The mixture was extracted with EtOAc, and the extract was washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave a residue, which was purified by column chromatography over silica gel (*n*-hexane : EtOAc=1 : 1) to afford **22** (120 mg, 55% yield) as a yellow oil: IR ($CHCl_3$) cm^{-1} 3429 (OH), 1713 (C=O); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.70—2.00 (m, 6H), 2.33—2.41 (m, 4H), 3.00—3.28 (m, 2H), 3.60—3.95 (m, 3H), 4.27—4.46 (m, 1H), 7.25—7.57 (m, 5H, Ph).

(1*R*,3*R*)- and (1*R*,3*S*)-1-[(4-Methylphenylsulfonyloxy)methyl]-3-(phenylselenomethyl)-2-oxaspiro[4.5]decan-8-one (23) To a stirred solution of **22** (15.0 g, 42.5 mmol) in dry CH_2Cl_2 (300 ml) were added Et_3N (11.8 ml, 85.0 mmol), DMAP (517 mg, 4.25 mmol), and *p*-TsCl (12.1 g, 63.8 mmol) at 0 °C, and the mixture was stirred for 6 h at room temperature. Water was added to the mixture at 0 °C, and the whole was extracted with CH_2Cl_2. The extract was washed with water and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave a residue, which was purified by column chromatography over silica gel (*n*-hexane : EtOAc=3 : 1) to afford the tosylate **23** (18.4 g, 85% yield) as a yellow oil: IR ($CHCl_3$) cm^{-1} 1720 (C=O); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.61—1.87 (m, 6H), 2.13—2.50 (m, 4H), 2.45 (s, 3H), 2.93—3.16 (m, 2H), 3.80—4.05 (m, 3H), 4.24—4.31 (m, 1H), 7.23—7.86 (m, 9H, 2×Ph).

(1*S*,3*R*,5*S*,7*R*)- and (1*S*,3*S*,5*S*,7*R*)-3-(Phenylselenomethyl)-4-oxatricyclo[5.3.1.0^{1,5}]undecan-8-one (24) To a stirred solution of **23** (18.0 g, 35.5 mmol) in dry THF (400 ml) was added 60% NaH (1.7 g, 35.5 mmol), and the mixture was stirred for 8 h at 40 °C. After cooling, the mixture was poured into water, and the whole was extracted with CH_2Cl_2. The extract was washed with water and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave a residue, which was purified by column chro-

matography over silica gel (*n*-hexane : EtOAc = 4 : 1) to afford the tricyclic compound **24** (9.75 g, 82% yield) as a yellow oil: IR ($CHCl_3$) cm^{-1} 1720 (C=O); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.62—2.38 (m, 10H), 2.83 (m, 1H), 3.03—3.18 (m, 2H), 4.19—4.54 (m, 2H), 7.25—7.52 (m, 5H, Ph).

(1*S*,3*R*,5*S*,7*R*)- and (1*S*,3*S*,5*S*,7*R*)-3-(Phenylselenomethyl)-4-oxatricyclo[5.3.1.0^{1,5}]undecan-8-one 8,8-Ethylene Acetal (25) To a stirred solution of **24** (9.0 g, 26.9 mmol) in dry benzene (300 ml) were added ethylene glycol (30.0 ml, 536 mmol) and pyridinium *p*-toluenesulfonate (PPTS; 2.00 g, 7.96 mmol), and the mixture was stirred under reflux with a Dean-Stark trap for 6 h. After cooling, saturated $NaHCO_3$ was added to the mixture. The whole was extracted with Et_2O, and the extract was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure gave a residue, which was purified by column chromatography over silica gel (*n*-hexane : EtOAc = 3 : 1) to afford **25** (9.99 g, 97% yield) as a yellow oil: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.18—1.35 (m, 2H), 1.40—2.32 (m, 9H), 2.93—3.20 (m, 2H), 3.79—3.99 (m, 4H), 4.10—4.20 (m, 1H), 4.36—4.49 (m, 1H), 7.22—7.53 (5H, Ph).

(1*R*,5*R*,7*S*)-6-Hydroxy-5-(prop-2-enyl)bicyclo[3.2.1]octan-2-one 2,2-Ethylene Acetal (6) Ca (208 mg, 549 mmol) was added to liq. NH_3 (70 ml), and the mixture was stirred for 10 min at −33 °C. To the mixture was added a solution of **25** (208 mg, 549 mmol) in Et_2O (7 ml), and the mixture was stirred for 7 min. Aqueous NH_4Cl was added to the mixture until a blue color disappeared. NH_3 was evaporated at room temperature, and water was added to the residue. The whole was extracted with EtOAc, and the extract was washed with water and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave a residue, which was purified by column chromatography over silica gel (*n*-hexane : EtOAc = 3 : 1) to afford **6** (120 mg, 98% yield) as a colorless oil: $[\alpha]_D^{24}$ +26.8° (*c* = 1.21, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3487 (OH), 1639 (C=C); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.38—1.67 (m, 8H), 2.13—2.29 (m, 4H), 3.81—3.98 (m, 5H), 5.05—5.11 (m, 2H), 5.90 (m, 1H); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 29.1, 31.6, 37.4, 39.1, 39.7, 42.9, 45.5, 64.0, 64.5, 75.9, 110.7, 116.9, 136.1; MS (EI) *m/z*: 224 (M^+). *Anal.* Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.49; H, 8.94.

(1*R*,5*S*,7*S*)-6-Hydroxy-5-(3-Hydroxypropyl)bicyclo[3.2.1]octan-2-one 2,2-Ethylene Acetal (26) To a stirred solution of **6** (3.00 g, 13.4 mmol) in dry THF (60 ml) was added $BH_3 \cdot SMe_2$ (3.81 ml, 40.2 mmol) at 0 °C, and the mixture was stirred for 1 h at room temperature. After the mixture was cooled to 0 °C, 3 N NaOH (26.8 ml) and 30% H_2O_2 (8.21 ml) were added dropwise and the mixture was stirred for 2 h. After salting out, the whole was extracted with $CHCl_3$ and the extract was dried over $MgSO_4$. Concentration under reduced pressure gave a residue, which was purified by column chromatography over silica gel (*n*-hexane : EtOAc = 1 : 2) to afford the diol **26** (2.72 g, 82% yield) as a colorless solid: mp 103—104 °C (from *i*-Pr_2O); $[\alpha]_D^{21}$ +28.5° (*c* = 0.82, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 3400 (OH); ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.29—1.57 (m, 12H), 2.04—2.16 (m, 1H), 2.18—2.24 (m, 1H), 2.69 (br, 1H), 3.50—3.63 (m, 2H), 3.74—3.92 (m, 4H); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 27.9, 29.4, 30.1, 31.4, 38.3, 39.6, 43.0, 45.9, 63.2, 64.3, 64.8, 75.5, 111.2; MS (EI) *m/z*: 242 (M^+), 224 ($M^+ - OH$). *Anal.* Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 63.96; H, 9.11.

3-[(1*S*,5*R*)-7-oxobicyclo[3.2.1]octan-1-yl]propanal 4′,4′-Ethylene Acetal (27) To a stirred solution of oxalyl chloride (3.75 ml, 43.0 mmol) in dry CH_2Cl_2 (20 ml) was added DMSO (6.10 ml, 86.0 mmol) at −60 °C, and the mixture was stirred for 15 min. To the mixture was added dropwise **26** (2.60 g, 10.7 mmol) in dry CH_2Cl_2 (25 ml), and the mixture was stirred for 1 h. Et_3N (17.9 ml, 128 mmol) was added to the mixture, and the mixture was stirred for 2 h. Water was added to the mixture and the whole was extracted with CH_2Cl_2. The extract was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure gave a residue, which was purified by column chromatography over silica gel (*n*-hexane : EtOAc = 2 : 1) to afford the keto aldehyde **27** (2.09 g, 82% yield) as a colorless oil: $[\alpha]_D^{21}$ +4.03° (*c* = 0.89, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1738 (C=O), 1724 (C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.56—2.06 (m, 8H), 2.22—2.40 (m, 5H), 3.87—4.03 (m, 4H), 9.75 (s, 1H); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 25.3, 29.6, 32.1, 36.9, 39.0, 39.1, 42.4, 49.6, 64.4, 64.8, 109.4, 201.7, 219.7; MS (EI) *m/z*: 238 (M^+).

(1*R*,5*S*)-5-(3-Oxobutyl)bicyclo[3.2.1]octane-2,6-dione 2,2-Ethylene Acetal (29) To a stirred solution of $ClTi(O\textit{i}\text{-}Pr)_3$ (2.60 ml, 10.9 mmol) in dry THF (10 ml) was added dropwise methylmagnesium chloride (1.0 M in THF; 10.9 ml, 10.9 mmol) at −40 °C, and the mixture was stirred for 1 h. To the mixture was added a solution of **27** (2.00 g, 8.40 mmol) in dry THF (30 ml) at −60 °C, and the mixture was stirred for 3 h. Saturated NH_4Cl was added to the mixture, and the whole was extracted with EtOAc. The extract was washed with brine, and dried over $MgSO_4$. Concentration under reduced pressure gave a residue, which was purified by column chromatography over silica gel (*n*-hexane : EtOAc = 2 : 1) to afford (1*R*,5*S*)-5-[(*R*)- and (*S*)-3-hydroxybutyl]bicyclo[3.2.1]octane-2,6-dione 2,2-ethylene acetal (**28**) (a mixture of diastereoisomers; 2.01 g, 94% yield).

To a stirred solution of oxalyl chloride (1.24 ml, 1.41 mmol) in dry CH_2Cl_2 (20 ml) was added DMSO (2.01 ml, 28.2 mmol) at −60 °C, and the mixture was stirred for 15 min. A solution of **28** (1.80 g, 7.09 mmol) in dry CH_2Cl_2 (25 ml) was added dropwise to the mixture, and the mixture was stirred for 1 h. To the mixture was added dropwise Et_3N (5.93 ml, 42.4 mmol), and the mixture was stirred for 2 h. Water was added to the mixture, and the whole was extracted with CH_2Cl_2. The extract was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure gave a residue, which was purified by column chromatography over silica gel (*n*-hexane : EtOAc = 3 : 1) to afford **29** (1.63 g, 91% yield) as a colorless oil: $[\alpha]_D^{24}$ +3.54° (*c* = 1.05, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1730 (C=O), 1710 (C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.42—1.81 (m, 7H), 2.00—2.03 (m, 1H), 2.12 (s, 3H), 2.16—2.46 (m, 5H), 3.84—4.04 (m, 4H); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 27.0, 29.6, 29.7, 32.2, 36.9, 38.7, 39.0, 42.4, 49.6, 64.4, 64.7, 109.5, 208.2, 220.0; MS (EI) *m/z*: 252 (M^+), 181 ($M^+ - CH_3COCH_2CH_2$). *Anal.* Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.79; H, 7.94.

(1*R*,8*R*)-Tricyclo[6.3.1.0^{1,6}]dodec-5-ene-4,9-dione 9,9-Ethylene Acetal (4) To a stirred solution of **29** (128 mg, 0.508 mmol) in dry MeOH (5 ml) was added NaOH (56.9 mg, 1.16 mmol), and the mixture was stirred under reflux for 24 h. After cooling, water was added to the mixture, and the solvent was removed *in vacuo.* The residue was diluted with EtOAc and washed with brine, and dried over $MgSO_4$. Concentration under reduced pressure gave a residue, which was purified by column chromatography over silica gel (*n*-hexane : EtOAc = 2 : 1) to afford the tricyclic enone **4** (108 mg, 91% yield) as a colorless solid: mp 188—189 °C (from *i*-Pr_2O); $[\alpha]_D^{23}$ +95.7 (*c* = 1.17, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1658 (C=O), 1620 (C=C); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.45—2.06 (m, 8H), 2.27—2.38 (m, 2H), 2.49—2.61 (m, 3H), 3.85—4.09 (m, 4H), 5.90 (s, 1H, C=C<u>H</u>); ^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 29.9, 31.7, 32.8, 33.5, 35.1, 42.3, 42.4, 43.5, 64.3, 64.7, 110.3, 122.6, 174.5, 199.3; MS (EI) *m/z*: 234 (M^+). *Anal.* Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.62; H, 7.67.

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