Stereoselective Formation of Three Carbon–Carbon Bonds by Cascade Reaction with Enolate Anion: Synthesis of Tricyclo[6.2.2.0^{1,6}]dodecane and Tricyclo[5.3.1.0^{3,8}]undecane Derivatives

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Reaction of 6-[5(*E*)-6-(methoxycarbonyl)hex-5-enyl]-2-cyclohexen-1-one (**1**) with LHMDS, followed by one-pot treatment with CH_2O, resulted in a cascade Michael–Michael–aldol reaction, producing hydroxymethylated tricyclo[6.2.2.0^{1,6}]dodecane **3**. The methylated tricyclo[5.3.1.0^{3,8}]undecane **21** was obtained by a Michael–Michael–substitution reaction, performed by reaction of 5-[4(*E*)-5-(methoxycarbonyl)pent-4-enyl]-2-methyl-2-cyclohexen-1-one (**11**) with LHMDS and one-pot treatment with MeI in the presence of HMPA. Michael–Michael–aldol reactions of **11** were also carried out with LHMDS followed by several aldehydes to provide tricyclo[5.3.1.0^{3,8}]undecane derivatives **22**, **23**, and **24**, respectively. The importance of intramolecular coordination with lithium for the double Michael reaction was supported by an experiment utilizing the corresponding (*Z*)-isomer **13**.

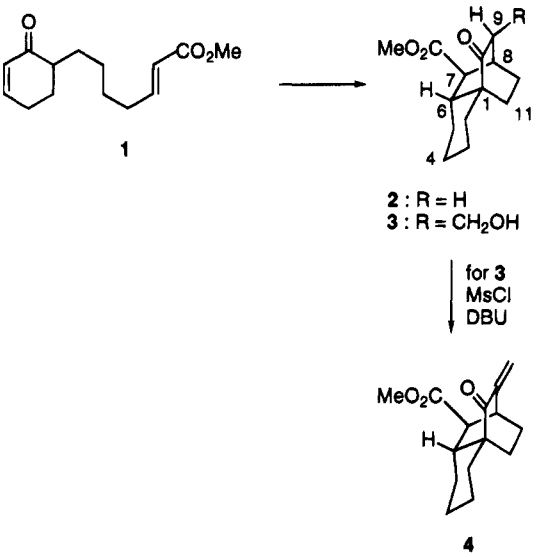
Introduction

It has been demonstrated by us that the intramolecular double Michael reaction[1–3] and the intramolecular Michael–aldol reaction[4] are powerful tools for construction of polycyclic ring systems.[5] These tandem reactions were carried out under four different conditions utilizing base and/or Lewis acid. Among them, the intramolecular double Michael reaction conducted by lithium hexamethyldisilazane (LHMDS) provides a useful methodology for stereoselective assembly of bicyclo[2.2.2]octane systems.[1,6] It was envisaged that the third carbon–carbon bond formation[7] would be feasible by one-pot treatment of an enolate anion, obtained by the tandem reaction, with an electrophile. Here we describe novel cascade reactions forming tricyclo[6.2.2.0^{1,6}]dodecane and tricyclo[5.3.1.0^{3,8}]-undecane systems.

Results and Discussion

When the 6-substituted 2-cyclohexen-1-one **1** was treated with LHMDS at −78 °C to ambient temperature in a mixture of hexane and ether, the tricyclo[6.2.2.0^{1,6}]-dodecane **2** was obtained in 68% yield as a single stereoisomer. The yield was improved compared with the case of the corresponding ethyl ester (50% yield).[6] On successive treatment of the product enolate ion with gaseous CH_2O at −78 °C in the same reaction vessel, the hydroxymethylated compound **3** was produced in 39% yield as a single isomer. The stereochemistry of **3** was tentatively assigned on the basis of an assumption that the electrophile was introduced from the less hindered side. Further reaction of **3** with MsCl in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2 provided the olefin **4** in 80% yield (Scheme 1). Thus, a novel cascade reaction, Michael–Michael–aldol reaction, has been developed. However, treatments of the above enolate with other electrophiles gave no satisfactory result.

Scheme 1



The desired cascade reactions forming a variety of third carbon–carbon bonds were effectively performed in the case of the construction of tricyclo[5.3.1.0^{3,8}]undecane systems from the 5-substituted 2-cyclohexen-1-one **11** as follows. The synthesis of the substrate **11** is shown in

[⊗] Abstract published in *Advance ACS Abstracts,* September 1, 1994.

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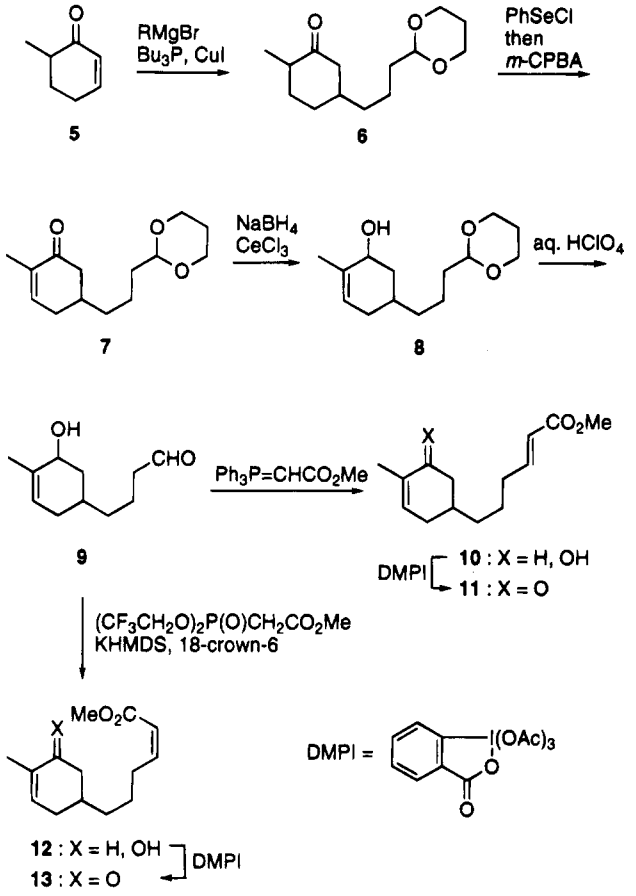
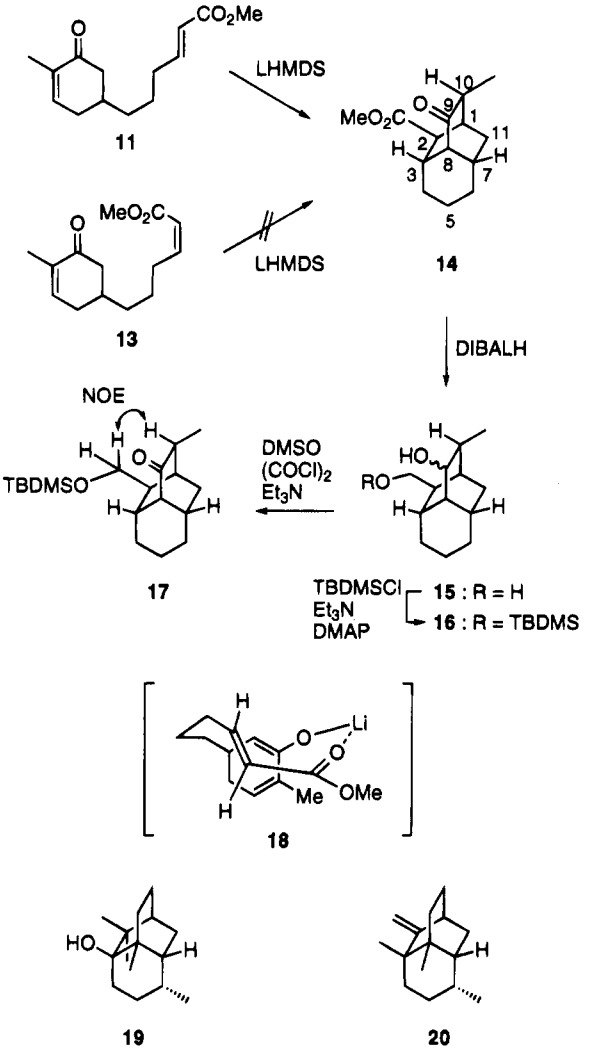
Scheme 2



Scheme 2. The conjugate addition of the Grignard reagent from 2-(3-bromopropyl)-1,3-dioxane to **5**[8] in the presence of CuI and Bu_3P[9] gave **6** in 86% yield. Introduction of the phenylselenyl group under thermodynamically controlled conditions,[10] followed by oxidative elimination, provided **7** in 23% overall yield (55% yield based on the consumed **6**). Since the deprotection of the acetal group of **7** using dilute acid caused an intramolecular aldol reaction, **7** was first reduced with $NaBH_4$ in the presence of $CeCl_3$[11] to afford **8** in 89% yield. After hydrolysis of the acetal group in **8**, reaction of the resulting **9** with Ph_3P=CHCOOMe afforded mainly the (*E*)-unsaturated ester **10** in 56% overall yield (74% yield based on the recovered **8**). Oxidation of **10** with Dess–Martin periodinane (DMPI)[12] furnished **11** in 85% yield. Furthermore, the (*Z*)-isomer **12** was prepared in a selective manner in 63% overall yield (73% yield based on the recovered **8**) using Still's method.[13] Oxidation of the product containing **12** as the major component with the periodinane[12] gave in 69% yield a 2.1:1 mixture of **13** and **11**, which were separated by chromatography.

Scheme 3



The intramolecular double Michael reaction of the (*E*)-isomer **11** smoothly proceeded at −78 °C (Scheme 3). Treatment of **11** with LHMDS for 1 h at −78 °C in THF followed by protic quenching produced a 11:1 mixture of tricyclo[5.3.1.$0^{3,8}$]undecane **14** and its epimer at the C-10 position in 88% yield. The stereochemistry of the major product **14** was determined by the following sequence. After separation from its epimer, **14** was converted into **17** in three steps. Reduction of **14** with DIBALH gave a 6.5:1 mixture of the two epimers of **15** in 87% yield, whose primary hydroxyl groups were protected with the TBDMS group to provide **16** as a mixture of isomers in 54% yield (92% yield based on the consumed **15**). Swern oxidation[14] of **16** gave **17** in 97% yield. A NOE was observed between

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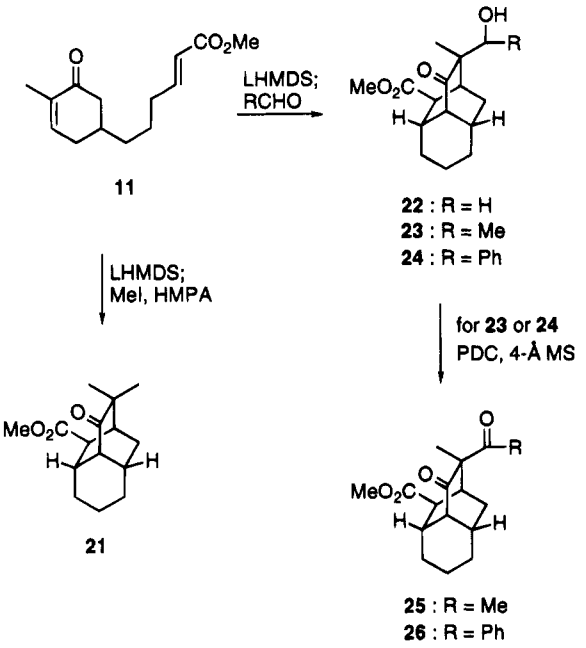
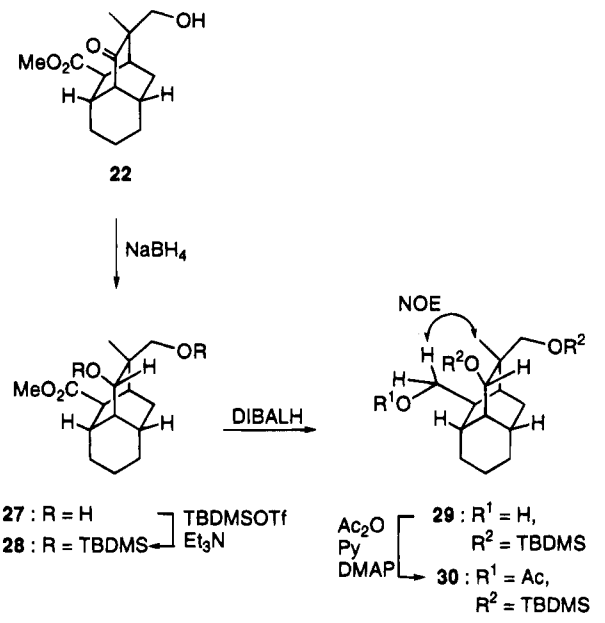
Scheme 4



Scheme 5



CH_2 at the C-2 position and the hydrogen atom at the C-10 position of **17**, but no NOE was detected between CH_2 at the C-2 position and the methyl group at the C-10 position. The tricyclo[5.3.1.$0^{3,8}$]undecane is the key framework of several polycyclic natural products such as patchouli alcohol (**19**)[15] and seychellene (**20**).[16]

It is noteworthy that treatment of the (*Z*)-isomer **13** with LHMDS produced no double Michael product and only an intractable material was obtained. This result supports the importance of an intramolecular coordination with lithium for the double Michael reaction. Specifically, a favorable intermediate **18**, in which two oxygens are held closely to a lithium ion,[17] is responsible for the desired cyclization of the (*E*)-isomer, but such an intermediate is not possible with the (*Z*)-isomer.

Next, we investigated the cascade reaction of **11**. After the intramolecular double Michael reaction of **11**, conducted under the same conditions as above, the resulting enolate anion was treated for 3 h in the one-pot procedure with MeI in the presence of hexamethylphosphoric triamide (HMPA) at −78 °C to ambient temperature to provide **21** in 71% yield. The methylated compound **21** was not produced without HMPA. Thus, creation of a quaternary carbon center was achieved by a Michael−Michael−substitution reaction (Scheme 4).

When the resulting enolate was reacted with gaseous CH_2O for 20 min at −78 °C, **22** was obtained in 83% yield as a single stereoisomer. The one-pot reaction with MeCHO for 3 h at −78 °C produced a 1:1.7 epimeric mixture of **23** in 53% yield. Furthermore, a diastereoisomeric mixture of **24** was obtained in 69% yield, in a reaction with PhCHO, although a higher temperature was required in this case. Oxidation of **23** with pyridinium dichromate (PDC) in the presence of 4-Å molecular sieves gave **25** in 91% yield as a single isomer, while reaction of **24** with the same reagents afforded a 1:2.4 epimeric mixture at the C-10 position of **26** in 95% yield.

The stereostructure of **22**, produced by the selective introduction of hydroxymethyl group from the less hindered side, was determined as follows (Scheme 5). Reduction of **22** with $NaBH_4$ formed **27** as a single stereoisomer in 99% yield. Since there was no NOE between the methine hydrogen at the C-9 position and the methyl group at the C-10 position of **27**, it was assumed that the hydride anion selectively attacked from the side adjacent to the hydroxymethyl group. Treatment of **27** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) in the presence of Et_3N formed **28** in 49% yield. Reduction of **28** with DIBALH gave an 87% yield of **29**, whose acetylation provided **30** in 87% yield. The presence of a NOE between the CH_2 at the C-2 position and the methyl group at the C-10 position supports the stereostructure shown in **30**.

Thus, novel cascade Michael−Michael−substitution and Michael−Michael−aldol reactions, which could provide useful methodology for synthesis of polycyclic compounds, have been exploited.

Experimental Section

General Procedures. All reactions were carried out under a positive atmosphere of dry Ar or N_2. Solvents were distilled prior to use: THF, Et_2O, benzene, toluene, and hexane were freshly distilled from Na benzophenone; DME, CH_2Cl_2, and MeCN were distilled from CaH_2 and kept over 4-Å molecular sieves. Unless otherwise noted, all extracts were dried over $MgSO_4$, and the solvent was removed by rotary evaporation *in vacuo*. Silica gel column chromatography was carried out with Merck Kieselgel 60 Art. 7734, while Merck Kieselgel 60 Art. 9835 was used for flash chromatography. HPLC was carried out using a Gilson HPLC system (Model 302/303), monitored by using UV and refractive index detectors.

6-[5(*E*)-6-(Methoxycarbonyl)hex-5-enyl]-2-cyclohexen-1-one (1). To a solution of 6-(5-hydroxypentyl)-2-cyclohexen-1-one[6] (850 mg, 4.0 mmol) in dry CH_2Cl_2 (15 mL) were added 4-Å molecular sieves (3.0 g) and PDC (2.0 g, 5.3 mmol), and the mixture was stirred for 3 h at ambient temperature. After dilution with Et_2O, followed by filtration through Florisil, the

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filtrate was evaporated to give the crude aldehyde, which was used in the following reaction without purification.

A mixture of the crude product and $Ph_3P{=}CHCO_2Me$ (1.9 g, 5.6 mmol) in MeCN (15 mL) was stirred for 8 h at ambient temperature and then heated 1 h at reflux. Evaporation of the solvent afforded a residue, which was subjected to chromatography on silica gel. Elution with AcOEt/hexane (3:17 v/v) provided **1** (532 mg, 48% for two steps) as a colorless oil: IR (neat) ν 1720, 1675 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.02−6.86 (m, 2H), 5.97 (dt, 1H, J = 9.9, 2.0 Hz), 5.82 (dt, 1H, J = 15.8, 1.5 Hz), 3.72 (s, 3H), 2.43−2.33 (m, 2H), 2.32−2.17 (m, 3H), 2.15−2.04 (m, 1H), 1.92−1.70 (m, 2H), 1.54−1.30 (m, 5H); MS m/z 236 (M^+); HRMS calcd for $C_{14}H_{20}O_3$ 236.1412 (M^+), found 236.1402.

(1*R,6*S**,7*S**,8*R**)-7-(Methoxycarbonyl)tricyclo[6.2.2.0^{1,6}]-dodecan-10-one (2).** To a stirred solution of lithium hexamethyldisilazane (LHMDS) in dry hexane (6 mL), which was prepared from $(Me_3Si)_2NH$ (0.07 mL, 0.33 mmol) and 1.56 M BuLi/hexane (0.18 mL, 0.28 mmol), was slowly added at −78 °C a solution of **1** (56.1 mg, 0.24 mmol) in dry Et_2O (1 mL), and the mixture was stirred for 1 h at −78 °C. The reaction temperature was gradually raised to 20 °C during 3 h and the mixture was further stirred for 10 min at 20 °C. After being cooled to −78 °C, the mixture was poured onto saturated NH_4Cl under cooling with ice. The resulting mixture was thoroughly extracted with Et_2O. The extracts were washed with brine, dried, and evaporated to give a residue, which was chromatographed on silica gel with AcOEt/hexane (1:4 v/v) as eluent to afford **2** (38.2 mg, 68%) as a colorless oil: IR (neat) ν 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 2.49−2.40 (m, 2H), 2.31−2.17 (m, 3H), 2.03−1.06 (m, 12H); MS m/z 236 (M^+); HRMS calcd for $C_{14}H_{20}O_3$ 236.1412 (M^+), found 236.1406.

(1*R,6*S**,7*S**,8*R**,9*R**)-9-(Hydroxymethyl)-7-(methoxycarbonyl)tricyclo[6.2.2.0^{1,6}]dodecan-10-one (3).** To a stirred solution of LHMDS in Et_2O/hexane (1:12 v/v, 13 mL), prepared from $(Me_3Si)_2NH$ (0.12 mL, 0.57 mmol) and 1.56 M BuLi/hexane (0.29 mL, 0.45 mmol), was slowly added at −78 °C a solution of **1** (89.0 mg, 0.38 mmol) in dry Et_2O (1 mL). After being stirred for 1 h at −78 °C, the reaction temperature was gradually raised to 20 °C during 3 h and the mixture was further stirred for 10 min at 20 °C. After being cooled to −78 °C, an excess of gaseous CH_2O, generated by heating paraformaldehyde at 170 °C, was introduced to the reaction mixture. After being stirred for 20 min at −78 °C, Et_2O was added and the mixture was washed with brine, dried, and concentrated. Chromatography of the residue on silica gel with AcOEt/hexane (3:7 v/v) as eluent produced **3** (39.4 mg, 39%) as a colorless oil: IR (neat) ν 3450, 1725, 1710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.94 (ddd, 1H, J = 11.0, 8.0, 2.5 Hz; dd, J = 11.0, 8.0 Hz with D_2O), 3.71 (s, 3H), 3.64 (ddd, 1H, J = 11.0, 9.8, 6.1 Hz; dd, J = 11.0, 6.1 with D_2O), 2.83 (dd, 1H, J = 9.8, 2.5 Hz, disappeared with D_2O), 2.61 (dd, 1H, J = 8.0, 6.1 Hz), 2.37 (br s, 1H), 2.27 (ddd, 1H, J = 14.0, 11.6, 6.1 Hz), 2.22 (dd, 1H, J = 7.6, 1.5 Hz), 2.09−2.03 (m, 1H), 1.93−1.87 (m, 1H), 1.82−1.74 (m, 1H), 1.71−1.60 (m, 3H), 1.57−1.52 (m, 2H), 1.44−1.10 (m, 4H); MS m/z 266 (M^+). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.43; H.8.20.

(1*R,6*S**,7*S**,8*R**)-7-(Methoxycarbonyl)-9-methylenetricyclo[6.2.2.0^{1,6}]dodecan-10-one (4).** To a solution of **3** (8.2 mg, 0.03 mmol) in dry CH_2Cl_2 (1 mL) were added at 0 °C 1,8-diabicyclo[5.4.0]undec-7-ene (DBU) (0.02 mL, 0.13 mmol) and MsCl (0.007 mL, 0.09 mmol), and the mixture was stirred for 1 h at ambient temperature. After dilution with CH_2Cl_2, the mixture was washed with brine, dried, and evaporated to give a residue, which was purified by silica gel column chromatography. Elution with AcOEt/hexane (1:9 v/v) gave **4** (5.1 mg, 80%) as a colorless oil: IR (neat) ν 1730, 1705, 1630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.60 (d, 1H, J = 1.5 Hz), 5.19 (d, 1H, J = 1.5 Hz), 3.66 (s, 3H), 3.07−3.02 (m, 1H), 2.34−2.21 (m, 2H), 2.05−1.96 (m, 1H), 1.93−1.11 (m, 11H); MS m/z 248 (M^+); HRMS calcd for $C_{15}H_{20}O_3$ 248.1412 (M^+), found 248.1400.

5-[3-(1,3-Dioxacyclohexyl)propyl]-2-methylcyclohexan-1-one (6). To a stirred mixture of Mg (729 mg, 30 mmol), which was activated by stirring with a catalytic amount of I_2 prior to use, in dry THF (5 mL) was added a solution of 2-(3-bromopropyl)-1,3-dioxane (4.18 g, 20 mmol) in dry THF (5 mL), and the mixture was heated for 4 h under reflux in order to prepare the Grignard reagent. To a mixture of CuI (2.29 g, 12 mmol) in dry THF (10 mL) was added at 0 °C Bu_3P (2.99 mL, 12 mmol). After being stirred for 2 h at ambient temperature, to the stirred mixture was slowly added at −78 °C the above Grignard reagent. After being stirred for 40 min at −78 °C, a solution of 2-methyl-5-cyclohexen-1-one **5** (1.1 g, 10 mmol) in dry THF (5 mL) was slowly added at −78 °C to the mixture. After being stirred for 2 h at −78 °C, saturated $NaHCO_3$ was added at −78 °C, and the mixture was treated at ambient temperature with H_2O (10 mL) and Et_2O (20 mL). The resulting mixture was filtered through Celite and the aqueous layer was thoroughly extracted with Et_2O. The combined extract was washed with saturated NH_4Cl and brine, dried, and evaporated. Chromatography of the product on silica gel with Et_2O/CH_2Cl_2 (7:93 v/v) provided **6** (2.07 g, 86%) as a pale yellow oil: IR (neat) ν 1706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.50 (dt, 1H, J = 4.9, 1.9 Hz), 4.12−4.07 (m, 2H), 3.79−3.72 (m, 2H), 2.45−2.38 (m, 1H), 2.37−2.30 and 2.24−2.19 [each m, 1H (1.3:1)], 2.12−1.54 (m, 8H), 1.45−1.15 (m, 6H), 1.06 (d, 1.3H, J = 6.8 Hz), 1.01 (d, 1.7H, J = 6.1 Hz); MS m/z 240 (M^+); HRMS calcd for $C_{14}H_{24}O_3$ 240.1725 (M^+), found 240.1756.

5-[3-(1,3-Dioxacyclohexyl)propyl]-2-methyl-2-cyclohexen-1-one (7). To a stirred solution of **6** (980 mg, 4.0 mmol) in dry AcOEt (20 mL) was slowly added at ambient temperature a solution of PhSeCl (860 mg, 4.5 mmol) in dry AcOEt (5 mL), and the mixture was stirred for 7 h at the same temperature. After addition of saturated $NaHCO_3$ (10 mL), the mixture was thoroughly extracted with AcOEt. The extract was washed with saturated $NaHCO_3$ and brine and dried. Evaporation of the solvent afforded the crude phenyl selenide, which was used in the next reaction without purification.

To a stirred mixture of the above product and saturated $NaHCO_3$ (30 mL) in AcOEt (30 mL) was added in small portions at 10 °C *m*-CPBA (840 mg, 4.8 mmol) during 20 min. After being stirred for 45 min at ambient temperature, the mixture was thoroughly extracted with AcOEt. The extract was washed with brine, dried, and evaporated to give a residue, which was purified by chromatography on silica gel. Elution with Et_2O/CH_2Cl_2 (1:9 v/v) provided **7** (223 mg, 23%; 55% yield based on the recovered **6**) as a colorless oil: IR (neat) ν 1670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.72−6.68 (m, 1H), 4.50 (t, 1H, J = 4.4 Hz), 4.09 (dd, 2H, J = 13.4, 4.6 Hz), 3.75 (dt, 2H, J = 12.2, 2.0 Hz), 2.53 (d, 1H, J = 14.0 Hz), 2.45−2.34 (m, 1H), 2.13−1.97 (m, 4H), 1.75 (d, 3H, J = 1.2 Hz), 1.60−1.53 (m, 2H), 1.45−1.26 (m, 5H); MS m/z 238 (M^+); HRMS calcd for $C_{14}H_{22}O_3$ 238.1568 (M^+), found 238.1574. Further elution gave **6** (571 mg, 58%).

5-[3-(1,3-Dioxacylohexyl)propyl]-2-methyl-2-cyclohexen-1-ol (8). To a stirred mixture of **7** (1.27 g, 5.3 mmol) and $CeCl_3{\cdot}7H_2O$ (2.19 g, 5.9 mmol) in MeOH (30 mL) was added in small portions at 0 °C $NaBH_4$ (101 mg, 2.7 mmol), and the mixture was stirred for 15 min at ambient temperature. After evaporation of the solvent, the residue was partitioned between H_2O and Et_2O. The organic layer was washed with brine, dried, and evaporated. The residue was subjected to chromatography on silica gel with AcOEt/hexane (3:7 v/v) as eluent to give **8** (919 mg, 89%) as a colorless oil: IR (neat) ν 3400 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.45 (dd, 1H, J = 5.6, 1.8 Hz), 4.51 (t, 1H, J = 5.0 Hz), 4.18−4.08 (m, 3H), 3.76 (dt, 2H, J = 12.4, 2.2 Hz), 2.15−1.94 (m, 2H), 1.80−1.12 (m, 15H); MS m/z 240 (M^+). Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.71; H, 9.85.

5-[4(*E*)-5-(Methoxycarbonyl)pent-4-enyl]-2-methyl-2-cyclohexen-1-ol (10). A mixture of **8** (919 mg, 3.8 mmol) in 10% $HClO_4$/THF (1:1 v/v, 15 mL) was stirred for 12 h at 30 °C. After extraction with Et_2O, the extract was washed with saturated $NaHCO_3$ and brine, dried, and evaporated to give the crude aldehyde **9**, which was used in the following reaction without purification.

A mixture of the product **9** and $Ph_3P{=}CHCO_2Me$ (1.28 g, 3.8 mmol) in dry MeCN (30 mL) was stirred for 12 h at room

temperature. After evaporation, the residue was purified by silica gel column chromatography with AcOEt/hexane (1:4 v/v) as eluent to give **10** (512 mg, 56% for two steps; 74% yield based on the recovered **8**) as a colorless oil: IR (neat) ν 3400, 1720, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.96 (dt, 1H, J = 15.4, 7.0 Hz), 5.82 (d, 1H, J = 15.4 Hz), 5.57–5.41 (m, 1H), 4.15 and 3.97 [each br s, 1H (1.3:1)], 2.23–1.94 (m, 4H), 1.78 and 1.75 [each s, 3H (1:1.3)], 1.92–1.10 (m, 11H); MS m/z 238 (M^+); HRMS calcd for $C_{14}H_{22}O_3$ 238.1568, found 238.1585. Further elution afforded **8** (217.4 mg, 24%).

5-[4(*E*)-5-(Methoxycarbonyl)pent-4-enyl]-2-methyl-2-cyclohexen-1-one (11). To a stirred mixture of Dess–Martin periodinane (DMPI)[12] (4.1 g, 9.7 mmol) in dry CH_2Cl_2 (30 mL) was slowly added at ambient temperature a solution of **10** (914 mg, 3.8 mmol) in dry CH_2Cl_2 (5 mL), and the mixture was stirred for 90 min at the same temperature. After dilution with Et_2O (10 mL), the resulting mixture was poured onto saturated $NaHCO_3$/0.1 N aqueous $Na_2S_2O_3$ (1:7 v/v, 8 mL). After being stirred for 30 min at ambient temperature, the mixture was thoroughly extracted with Et_2O. The extract was washed with saturated $NaHCO_3$ and brine, dried, and evaporated. Chromatography of the residue on silica gel with AcOEt/hexane (3:17 v/v) provided **11** (774 g, 85%) as a colorless oil: IR (neat) ν 1730, 1675, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.94 (dt, 1H, J = 15.8, 7.0 Hz), 6.75–6.68 (m, 1H), 5.83 (dt, 1H, J = 15.8, 1.2 Hz), 3.73 (s, 3H), 2.58–2.33 (m, 2H), 2.26–1.96 (m, 5H), 1.77 (d, 3H, J = 1.1 Hz), 1.58–1.25 (m, 4H); MS m/z 236 (M^+). Anal. Calcd for $C_{14}H_{20}O_3$; C, 71.16; H, 8.53. Found: C, 70.94; H, 8.57.

5-[4(*Z* and *E*)-5-(Methoxycarbonyl)pent-4-enyl]-2-methyl-2-cyclohexen-1-ols (12 and 10). To a stirred solution of 18-crown-6 (825 mg, 3.1 mmol) and $(CF_3CH_2O)_2P(O)CH_2CO_2Me$[13] (0.44 mL, 2.1 mmol) in dry THF (10 mL) was added at −78 °C 0.5 M KHMDS/toluene (2.0 mL, 1.0 mmol), and the mixture was stirred for 30 min at −78 °C. To the mixture was added at −78 °C a solution of the crude **9**, prepared as above from **8** (250 mg, 1.0 mmol), in dry THF (4 mL). After being stirred for 2 h at −78 °C, followed by dilution with Et_2O, the mixture was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel with AcOEt/hexane (1:4 v/v) to give a 2.1:1 mixture of **12** and **10** (155.0 mg, 63% for two steps: 73% yield based on the recovered **8**) as a colorless oil: IR (neat) 3450, 1720, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 6.96 (dt, 0.32H, J = 15.4, 7.0 Hz), 6.20 (dt, 0.68H, J = 11.4, 7.3 Hz), 5.85–5.72 (m, 1H), 5.50–5.43 (m, 1H), 4.15 (br s, 1H), 3.73 and 3.71 [each s, 3H (1: 2.1)], 2.70–2.50 (m, 2H), 2.25–1.95 (m, 3H), 1.75 (br s, 3H), 1.72–1.10 (m, 7H); MS m/z 238 (M^+); HRMS calcd for $C_{14}H_{22}O_3$; 238.1569 (M^+), found 238.1573. Further elution afforded **8** (50 mg, 20%).

5-[4(*Z*)-5-(Methoxycarbonyl)pent-4-enyl]-2-methyl-2-cyclohexen-1-one (13). According to the similar procedure for the preparation of **11**, the above mixture of **12** and **10** (50.0 mg, 0.2 mmol) was converted into a 2.1:1 mixture of **13** and **11** (34.4 mg, 69%), which was subjected to chromatography on silica gel with AcOEt/hexane (3:17 v/v) to afford **13** as a colorless oil: IR (neat) 1720, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.73–6.68 (m, 1H), 6.21 (dt, 1H, J = 11.4, 7.3 Hz), 5.79 (dt, 1H, J = 11.4, 1.5 Hz), 3.71 (s, 3H), 2.70–2.35 (m, 4H), 2.55–1.96 (m, 3H), 1.78 (d, 3H, J = 1.1 Hz), 1.57–1.36 (m, 4H); MS m/z 236 (M^+); HRMS calcd for $C_{14}H_{20}O_3$ 236.1412 (M^+), found 236.1415.

(1*R,2*S**,3*S**,7*S**,8*R**,10*S**)-2-(Methoxycarbonyl)-10-methyltricyclo[5.3.1.0^{3,8}]undecan-9-one (14).** To a stirred solution of LHMDS in THF (3 mL), prepared from $(Me_3Si)_2NH$ (0.08 mL, 0.38 mmol) and 1.56 M BuLi/hexane (0.23 mL, 0.36 mmol) was slowly added at −78 °C a solution of **11** (42.3 mg, 0.18 mmol) in dry THF (1 mL), and the mixture was stirred for 1 h at −78 °C. After addition of 10% aqueous $KHSO_4$ at −78 °C, the resulting mixture was thoroughly extracted with Et_2O. The extract was washed with brine, dried, and evaporated to give a residue, which was subjected to chromatography on silica gel. Elution with AcOEt/hexane (1:4 v/v) provided a 11:1 mixture of **14** and its diastereoisomer (37.2 mg, 88%). HPLC separation of the mixture using 4 × 250 mm column of Dynamax Microsorb silica (5 μm) with AcOEt/hexane (3:17 v/v; 1 mL min^{-1}) as eluent provided **14** as a colorless oil: IR (neat) ν 1726, 1714 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.69 (s, 3H), 2.79 (br s, 1H), 2.67 (t, 1H, J = 2.4 Hz), 2.44 (dd, 1H, J = 6.4, 2.4 Hz), 2.18–2.12 (m, 1H), 2.12–2.06 (m, 2H), 1.86 (ddd, 1H, J = 14.1, 11.6, 3.2 Hz), 1.66–1.40 (m, 7H), 0.99 (d, 3H, J = 7.7 Hz); MS m/z 236 (M^+). Anal. Calcd for $C_{14}H_{20}O_3$; C, 71.16; H, 8.53. Found: C, 70.84; H, 8.41.

(1*R,2*S**,3*S**,7*S**,8*R**,10*S**)-2-(Hydroxymethyl)-10-methyltricyclo[5.3.1.0^{3,8}]undecan-9-ol (15).** To a stirred solution of **14** (33.3 mg, 0.14 mmol) in dry DME (3 mL) was slowly added at −78 °C 0.93 M DIBALH/hexane (0.76 mL, 0.70 mmol), and the mixture was stirred for 1 h at −78 °C. After dilution with Et_2O, followed by addition of H_2O (0.76 mL), the mixture was stirred for 30 min at ambient temperature and then filtered through Celite. Evaporation of the filtrate gave a residue, which was chromatographed on silica gel with AcOEt/hexane (2:3 v/v) to provide a 6.5:1 mixture of **15** (25.9 mg, 87%) as a colorless oil: IR (neat) 3400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (dd, 1H, J = 8.7, 4.5 Hz), 3.80–3.62 (m, 2H), 3.61–3.35 (m, 1H), 1.95–1.20 (m, 15H), 1.15 and 1.10 [each d, 3H (1:6.5), each J = 9.2 Hz]; MS m/z 192 ($M^+ - H_2O$); HRMS calcd for $C_{13}H_{20}O$ 192.1513 ($M^+ - H_2O$), found 192.1522.

(1*R,2*S**,3*S**,7*S**,8*R**,10*S**)-2-[(*tert*-Butyldimethylsiloxy)methyl]-10-methyltricyclo[5.3.1.0^{3,8}]undecan-9-one (17).** A mixture of **15** (18.4 mg, 0.09 mmol), TBDMSCl (17.2 mg, 0.11 mmol), DMAP (3.1 mg, 0.03 mmol), and Et_3N (0.02 mL, 0.14 mmol) in dry CH_2Cl_2 (5 mL) was stirred for 12 h at ambient temperature. Evaporation of the mixture gave a residue, which was chromatographed on silica gel with AcOEt/hexane (3:17 v/v) to provide the diastereoisomeric mixture of **16** (15.2 mg, 54%; 92% yield based on the recovered **15**) as a colorless oil: IR (neat) ν 3430 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.87 (dd, 1H, J = 8.9, 4.0 Hz), 3.66 (dd, 1H, J = 9.8, 6.5 Hz), 3.62 (dd, 1H, J = 9.8, 6.0 Hz), 2.15 (br s, 1H), 1.94 (br s, 1H), 1.88–1.16 (m, 13H), 1.07 and 1.00 [each d, 3H (6.5:1), each J = 7.5 Hz], 0.91 (s, 9H), 0.07 (s, 6H). Further elution afforded **15** (7.7 mg, 42%).

To a stirred solution of $(COCl)_2$ (0.02 mL, 0.23 mmol) in dry CH_2Cl_2 (3 mL) was slowly added at −78 °C DMSO (0.02 mL, 0.34 mmol).[14] After 10 min of stirring, a solution of **16** (15.0 mg, 0.05 mmol) in dry CH_2Cl_2 (0.5 mL) was slowly added at −78 °C to the mixture. After 1.5 h of stirring at −78 °C, followed by addition of Et_3N (0.06 mL, 0.46 mmol) at −78 °C, the reaction temperature was raised to ambient temperature. The mixture was diluted with Et_2O and then washed with brine. The organic solution was dried and evaporated to afford a residue, which was purified by silica gel chromatography. Elution with AcOEt/hexane (1:20 v/v) gave **17** (14.4 mg, 97%) as a colorless oil: IR (neat) ν 1715 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.49–3.41 (m, 2H), 2.23–2.15 (m, 2H), 2.10 (q, 1H, J = 7.3 Hz), 2.00 (t, 1H, J = 2.4 Hz), 1.88 (ddd, 1H, J = 25.1, 11.5, 2.9 Hz), 1.81–1.67 (m, 2H), 1.65–1.35 (m, 7H), 1.17 (d, 3H, J = 7.3 Hz), 0.88 (s, 9H), 0.02 (s, 6H); MS m/z 322 (M^+); HRMS calcd for $C_{19}H_{34}O_2Si$ 322.2328, found 322.2305.

(1*R,2*S**,3*S**,7*S**,8*R**)-2-(Methoxycarbonyl)-10,10-dimethyltricyclo[5.3.1.0^{3,8}]undecan-9-one (21).** After treatment of **11** (12.0 mg, 0.051 mmol) with LHMDS, prepared from $(Me_3Si)_2NH$ (0.02 mL, 0.09 mmol) and 1.56 M BuLi/hexane (0.04 mL, 0.06 mmol), as in the case of the preparation of **14**, MeI (0.03 mL, 0.5 mmol) and HMPA (0.02 mL, 0.11 mmol) were added to the reaction mixture at -78 °C. The reaction temperature was gradually raised to ambient temperature during 3 h and the mixture was then diluted with Et_2O. The mixture was washed with brine, dried, and evaporated to give a residue, which was chromatographed on silica gel. Elution with AcOEt/hexane (1:4 v/v) provided **21** (9.0 mg, 71%) as a colorless oil: IR (neat) ν 1720, 1712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.69 (s, 3H), 2.81 (br s, 1H), 2.49–2.40 (m, 2H), 2.21–2.09 (m, 2H), 2.06 (t, 1H, J = 2.5 Hz), 1.72–1.14 (m, 7H), 1.10 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.6, 175.4, 51.9, 45.5, 44.1, 41.8, 29.5, 29.1, 29.0, 28.3, 27.4, 24.4, 24.3, 23.5, 23.4; MS m/z 250 (M^+); HRMS calcd for $C_{15}H_{22}O_3$ 250.1569 (M^+), found 250.1555.

(1*R,2*S**,3*S**,7*S**,8*R**,10*R**)-10-(Hydroxymethyl)-2-(methoxycarbonyl)-10-methyltricyclo[5.3.1.0^{3,8}]undecan-9-one (22).** After treatment of **11** (12.3 mg, 0.052 mmol) with LHMDS, prepared from $(Me_3Si)_2NH$ (0.03 mL, 0.14 mmol) and

1.56 M BuLi/hexane (0.07 mL, 0.11 mmol), as the above, an excess of gaseous CH_2O was introduced during 20 min into the stirred mixture at −78 °C. After dilution with Et_2O, the mixture was worked up and purified as above to give **22** (11.5 mg, 83%) as a colorless oil: IR (neat) ν 3450, 1720, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 3H), 3.50 (d, 1H, J = 8.4 Hz), 3.46 (d, 1H, J = 8.4 Hz), 2.84 (br s, 1H), 2.64–2.58 (m, 1H), 2.49 (dd, 1H, J = 6.2, 2.2 Hz), 2.25–2.07 (m, 4H), 1.78–1.22 (m, 7H), 1.04 (s, 3H); MS m/z 266 (M^+); HRMS calcd for $C_{15}H_{22}O_4$ 266.1517 (M^+), found 266.1505.

(1*R,2S*,3S*,7S*,8*R**,10*R**)-10-(1-Hydroxyethyl)-2-(methoxycarbonyl)-10-methyltricyclo[5.3.1.0^{3,8}]undecan-9-one (23).** After treatment of **11** (11.0 mg, 0.047 mmol) with LHMDS, prepared from $(Me_3Si)_2NH$ (0.03 mL, 0.14 mmol) and 1.56 M BuLi/hexane (0.04 mL, 0.06 mmol), as above, MeCHO (0.03 mL, 0.54 mmol) was added to the mixture. After being stirred for 3 h at −78 °C, the mixture was worked up and the product was purified by chromatography on silica gel with AcOEt/hexane (3:7 v/v) as eluent to afford a 1:1.72 epimeric mixture of **23** (6.9 mg, 53%) as a colorless oil: IR (neat) ν 3480, 1725, 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.01–3.92 (m, 1H), 3.75 and 3.72 [each s, 3H (1:1.7)], 2.90–2.80 (m, 1H), 2.64–2.54 (m, 1H), 2.50–2.42 (m, 1H), 2.24–1.95 (m, 3H), 1.89–1.15 (m, 8H), 1.10 (d, 3H, J = 5.9 Hz), 0.93 (s, 3H); MS m/z 280 (M^+); HRMS calcd for $C_{16}H_{24}O_4$ 280.1673 (M^+), found 280.1666.

(1*R,2S*,3S*,7S*,8*R**)-10-(α-Hydroxybenzyl)-2-(methoxycarbonyl)-10-methyltricyclo[5.3.1.0^{3,8}]undecan-9-one (24).** After treatment of **11** (11.0 mg, 0.047 mmol) with LHMDS, prepared from $(Me_3Si)_2NH$ (0.02 mL, 0.09 mmol) and 1.56 M BuLi/hexane (0.04 mL, 0.06 mmol) as above, followed by addition of PhCHO (0.02 mL, 0.19 mmol) at −78 °C, the mixture was stirred for 3 h at between −78 °C and ambient temperature. The mixture was worked up and the product was subjected to silica gel column chromatography. Elution with AcOEt/hexane (3:7 v/v) afforded the diastereoisomeric mixture of **24** (11.0 mg, 69%) as a colorless oil: IR (neat) ν 3440, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.20 (m, 5H), 5.02 (s, 0.52H), 4.62 (s, 0.48H), 3.68 (s, 1.75H), 3.52 (s, 1.25H), 3.73 (s, 0.52H), 3.70 (s, 0.48H), 2.87–2.74 (m, 2H), 2.72–1.20 (m, 11H), 1.00 (s, 0.86H), 0.97 (s, 0.96H), 0.96 (s, 1.18H); MS m/z 236 (M^+ + H − PhCHOH); HRMS calcd for $C_{14}H_{20}O_3$ 236.1411 (M^+ + H − PhCHOH), found 236.1407.

(1*R,2S*,3S*,7S*,8*R**,10*R**)-10-Acetyl-2-(methoxycarbonyl)-10-methyltricyclo[5.3.1.0^{3,8}]undecan-9-one (25).** A mixture of **23** (11.0 mg, 0.03 mmol), 4-Å molecular sieves (30 mg), and pyridinium dichromate (PDC) (20.8 mg, 0.10 mmol) in dry CH_2Cl_2 (5 mL) was stirred for 3 h at ambient temperature. After dilution with Et_2O, the mixture was filtered through Florisil. Evaporation of the solvent, followed by chromatography of the product on silica gel with AcOEt/hexane (1:4 v/v) as eluent, gave **25** (10.0 mg, 91%) as a colorless oil: IR (neat) ν 1720, 1715 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.03 (dd, 1H, J = 5.0, 2.4 Hz), 2.84–2.80 (m, 1H), 2.51–2.48 (m, 1H), 2.20–2.17 (m, 2H), 2.18 (s, 3H), 1.83 (ddd, 1H, J = 13.5, 11.0, 2.5 Hz), 1.65–1.40 (m, 7H), 1.16 (s, 3H); MS m/z 278 (M^+); HRMS calcd for $C_{16}H_{22}O_4$ 278.1518 (M^+), found 278.1509.

(1*R,2S*,3S*,7S*,8*R**)-10-Benzoyl-2-(methoxycarbonyl)-10-methyltricyclo[5.3.1.0^{3,8}]undecan-9-one (26).** Using the same procedure described above for **25**, **24** (3.3 mg, 0.01 mmol) was converted into **26** (3.1 mg, 95%), a colorless oil: IR (neat) ν 1720, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62–7.28 (m, 5H), 3.61 and 3.60 [each s, 3H (1:2.4)], 2.80 (br s, 1H), 2.59–2.29 (m, 4H), 2.15 (t, 1H, J = 2.6 Hz), 1.79–1.76 (m, 1H), 1.64–1.36 (m, 6H), 1.04 (s, 3H); MS m/z 340 (M^+); HRMS calcd for $C_{21}H_{24}O_4$ 340.1674 (M^+), found 340.1669.

(1*R,2S*,3S*,7S*,8*R**,9S*,10*R**)-10-(Hydroxymethyl)-2-(methoxycarbonyl)-10-methyltricyclo[5.3.1.0^{3,8}]undecan-9-ol (27).** To a stirred solution of **22** (43.4 mg, 0.16 mmol) in MeOH (3 mL) was added small portions at 20 °C $NaBH_4$ (30.0 mg, 0.79 mmol). After being stirred for 30 min at ambient temperature, followed by addition of H_2O (3 mL), the mixture was thoroughly extracted with AcOEt. The extract was washed with brine, dried, and evaporated to give a residue, which was purified by chromatography on silica gel. Elution with AcOEt/hexane (2:3 v/v) afforded **27** (43.4 mg, 99%) as a colorless oil: IR (neat) ν 3400, 1710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.40 (dd, 2H, J = 17.6, 10.0 Hz), 3.24 (br s, 1H), 2.78 (br s, 1H), 2.23 (d, 1H, J = 6.0 Hz), 2.21 (d, 1H, J = 2.2 Hz), 1.92–1.77 (m, 1H), 1.71–1.35 (m, 9H), 1.11 (dt, 1H, J = 13.6, 3.2 Hz), 0.94 (s, 3H); MS m/z 250 (M^+ − H_2O): HRMS calcd for $C_{15}H_{22}O_3$ 250.1579 (M^+ − H_2O), found 250.1552.

(1*R,2S*,3S*,7S*,8*R**,9S*,10*R**)-9-(*tert*-Butyldimethylsiloxy)-10-[(*tert*-butyldimethylsiloxy)methyl]-2-(methoxycarbonyl)-10-methyltricyclo[5.3.1.0^{3,8}]undecane (28).** To a stirred solution of **27** (40.0 mg, 0.15 mmol) in dry CH_2Cl_2 (3 mL) were slowly added at 0 °C Et_3N (0.1 mL, 0.71 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) (0.1 mL, 0.43 mmol). After being stirred for 30 min at 0 °C, followed by dilution with CH_2Cl_2, the mixture was washed with saturated $NaHCO_3$ and brine, dried, and evaporated. Chromatography of the product on silica gel with AcOEt/hexane (1:40 v/v) as eluent gave **28** (36.0 mg, 49%) as a pale yellow oil: IR (neat) ν 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.30 (d, 1H, J = 8.9 Hz), 3.20 (d, 1H, J = 8.9 Hz), 3.09 (d, 1H, J = 3.2 Hz), 2.88–2.81 (m, 1H), 2.28–2.22 (m, 1H), 2.18–2.13 (m, 1H), 1.92–1.80 (m, 1H), 1.77–1.64 (m, 1H), 1.58–1.16 (m, 11H), 0.89 and 0.88 (each s, each 9H), 0.28, 0.018, 0.007, and 0.001 (each s, each 3H); MS m/z 481 (M^+ − Me); HRMS calcd for $C_{16}H_{49}O_4Si_2$ 481.3169 (M^+ − Me), found 481.3128.

(1S*,2S*,3S*,7*R,8*R**,9S*,10*R**)-2-(Acetoxymethyl)-9-(*tert*-butyldimethylsiloxy)-10-[(*tert*-butyldimethylsiloxy)methyl]-10-methyltricyclo[5.3.1.0^{3,8}]undecane (30).** To a stirred solution of **28** (5.5 mg, 0.01 mmol) in dry CH_2Cl_2 (1 mL) was slowly added at −78 °C 0.93 M DIBALH/hexane (0.1 mL, 0.09 mmol), and the mixture was stirred for 1 h at −78 °C. After dilution with Et_2O, followed by addition of H_2O (0.1 mL), the mixture was stirred for 30 min at ambient temperature and then filtered through Celite. Evaporation of the filtrate gave a residue, which was chromatographed on silica gel. Elution with AcOEt/hexane (3:17 v/v) provided **29** (5.0 mg, 87%) as a colorless oil: IR (neat) ν 3400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.78–3.60 (m, 2H), 3.29 (d, 1H, J = 9.2 Hz), 3.16 (d, 1H, J = 9.2 Hz), 3.11 (d, 1H, J = 3.9 Hz), 1.91–1.18 (m, 17H), 0.89 and 0.88 (each s, each 9H), 0.028, 0.023, 0.011, and 0.001 (each s, each 3H).

A mixture of **29** (5.0 mg, 0.01 mmol) and Ac_2O (0.1 mL, 1.1 mmol) in dry pyridine (1 mL) was stirred for 1 h at ambient temperature. After evaporation of reagents, the residue was subjected to chromatography on silica gel. Elution with AcOEt/hexane (1:50 v/v) gave **30** (4.0 mg, 87%) as a colorless oil: IR (neat) ν 1715 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.12 (d, 2H, J = 7.9 Hz), 3.29 (d, 1H, J = 9.2 Hz), 3.14 (d, 1H, J = 9.2 Hz), 3.10 (d, 1H, J = 3.7 Hz), 2.04 (s, 3H), 1.92 (br s, 1H), 1.83–1.18 (m 2H), 0.96 (s, 3H), 0.89 and 0.88 (each s, each 9H), 0.028, 0.024, 0.017, and 0.010 (each s, each 3H); MS m/z 453 (M^+ − ^{t}Bu); HRMS calcd for $C_{24}H_{45}O_4Si_2$ 453.2856 (M^+ − ^{t}Bu), found 453.2838.

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Supplementary Material Available: ^1H NMR spectra of compounds **2**, **4**, **7**, **17**, **21–28**, and **30** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.