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Enantio- and diastereoselective construction of 4,9-dimethylspiro[4.4]nonane-2,7-dione using Rh-catalyzed asymmetric cyclization

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Abstract—Asymmetric cyclization using Rh-complexes was applied to the synthesis of 4,9-dimethylspiro[4.4]nonane-2,7-diones. The spiro[4.4]nonane skeleton bearing a chiral quaternary carbon could be stepwisely constructed by using Rh-catalyzed cyclization twice. All diastereomers of the spirodiketone could be stereoselectively prepared from the identical starting material by the combination of a neutral $Rh(PPh_3)_3Cl$ and a cationic $Rh[BINAP]ClO_4$. The cyclization by the neutral $Rh(PPh_3)_3Cl$ proceeded to give *cis*-3,4-disubstituted cyclopentanones, while that by the cationic $Rh[BINAP]ClO_4$ proceeded to afford *trans*-3,4-disubstituted cyclopentanones. Four spirodiketones of six stereoisomers could be prepared in optically active form, and the relationship between the stereochemistry of the spirodiketones and the Rh-complex was discussed based on the plausible acyl-hydride Rh-complexes.

1. Introduction[1]

Some spiro compounds, found as biologically active products from natural sources,[2] have been designed as chiral ligands for asymmetric reactions,[3] and prepared as new materials. Considerable efforts have been already taken to synthesize the chiral spiro compounds because construction of the chiral quaternary carbon in spirane skeletons continues to be fascinating challenge to organic chemists.[4] The chiral quaternary carbon could not yet be easily constructed by a catalytic asymmetric reaction.[5] We have previously reported the construction of spiro compounds using enzymatic methods[6] and diastereoselective and enantioselective methods using cycloalkane-1,2-diols as a chiral auxiliary.[7] We have also reported the Rh-catalyzed cyclization of 4-pentenals,[8] and recently, the cyclization could be applied to the construction of a chiral quaternary carbon.[9] Here, we wish to describe the enantio- and diastereoselective synthesis of 4,9-dimethylspiro[4.4]nonane-2,7-dione using the Rh-catalyzed cyclization.

2. Results and discussion

2.1. Synthetic strategy

We planned two routes to construct 4,9-dimethylspiro[4.4]-nonane-2,7-dione, as shown in Fig. 1. One is a one-step construction, in which the spiro[4.4]nonane skeleton may be directly formed from symmetrical diene-1,5-dial (i) using Rh-catalyzed cyclization. The other is a stepwise method, in which the Rh-catalyzed cyclization would be used twice to construct spiro[4.4]nonane, and the rings would be formed step-by-step. It was expected that the selection between a neutral or a cationic Rh-complex, and the choice of proper phosphin ligands would afford the desired optically active spiro compounds stereoselectively.

2.2. Approach to the construction of spiro[4.4]nonane in one-step

First, we undertook to construct the spirane skeleton from diene-dial **5** in one-step using a Rh-complex. The preparation of **5** was attempted by several routes. Acetylacetone **1** was converted into diester **2** by dialkylation with methyl bromoacetate in 84% yield. Olefination of the 1,3-dicarbonyl function in **2** with Nysted reagent {cyclodibromodi-μ-methylene[μ-(tetrahydrofuran)]trizinc}[10] afforded diene **3** in 30% yield. The conversion of **3** into the diene-dial **5** by reduction with DIBAL-H or $LiAlH_4$/DEA[11] did not proceed at all. Next, the ester function in **3** was once reduced to alcohol, that is to say, the diester **3** was converted to diol **4** in 99% yield. Oxidation of the diol into dialdehyde was attempted by several reagents and conditions such as PCC, PDC, and tetrapropylammonium perruthenate (TPAP).[12] Unfortunately, the diene-dial **5** was not isolated, but only δ-lactone **6** was obtained as a major product in these reactions. This result could be attributable to the fact that

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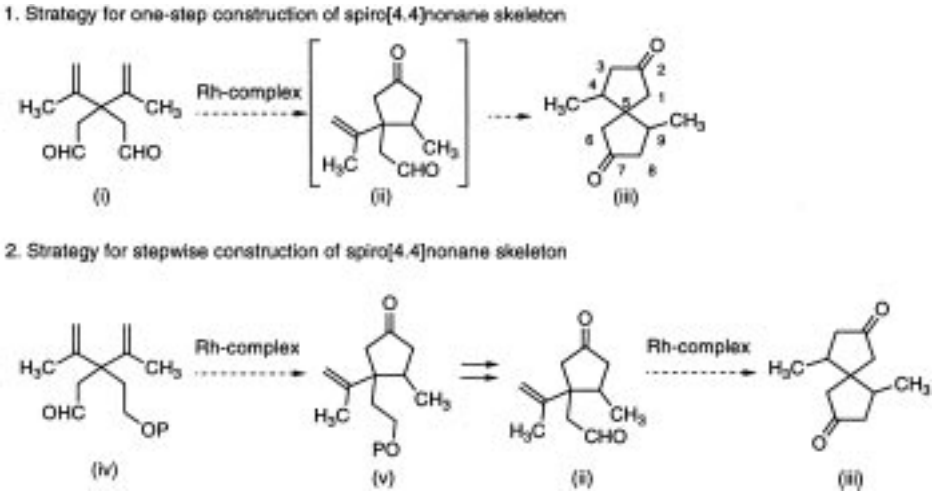


Figure 1.

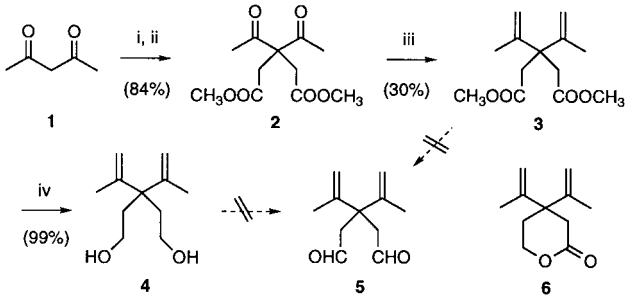
the oxidation of an alcohol afforded not an aldehyde but a lactol due to the cyclization with another alcohol function and subsequent oxidation (Scheme 1).

2.3. Stepwise construction of spiro[4.4]nonane

Next, we examined the construction of spiro[4.4]nonane by a stepwise method. It was considered there were several advantages to the stepwise method as follows: (i) stereochemistry of the cyclized product would be easily expected from the previous results;[8,9] (ii) different diastereomers could be prepared by changing the kind of Rh-complex in the first and second cyclization steps; (iii) a minor diastereomer, which was contaminated as a by-product, may be removed by silica-gel chromatography before the second Rh-cyclization.

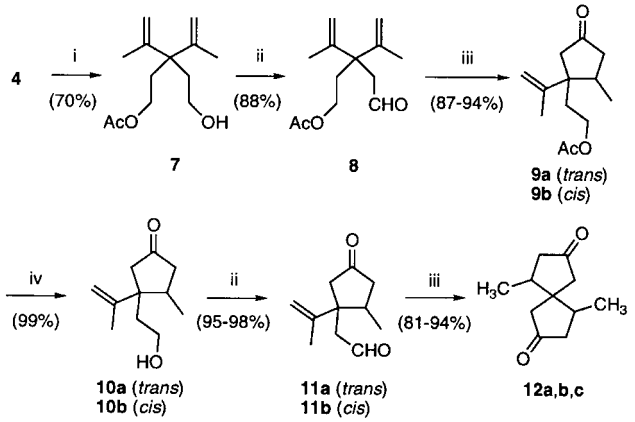
The 4-pentenal **8** for the first Rh-cyclization was prepared from the diol **4** by monoacetylation and subsequent oxidation with PCC in 62% overall yields, as depicted in Scheme 2.

2.3.1. The first Rh-cyclization. The results of cyclization of **8** by Rh-complexes are summarized in Table 1 (entry 1-3). The cyclization by the cationic Rh[(*R*)-BINAP]ClO_4 (0.05 equiv.) afforded cyclopentanone (−)-**9a** in 88% yield and by the Rh[(*S*)-BINAP]ClO_4 gave (+)-**9a** in 94% yield. The ratio of *cis* and *trans* in product cyclized by the cationic Rh[BINAP]ClO_4 was 1 (**9b**, *cis*) to 99 (**9a**, *trans*).



Scheme 1. *Reagents and conditions:* (i) $BrCH_2COOCH_3$, NaH; (ii) $BrCH_2COOCH_3$, *t*-BuOK; (iii) Nysted reagent, $TiCl_4$; (iv) $LiAlH_4$.

The relative stereochemistry of product **9a** was unambiguously determined by the NOESY ^1H–^1H NMR spectrum. Correlation between the methyl proton signals δ 1.06 (d, J=7.3 Hz, 3H) and the methylene signals δ 2.41–2.50 (m, 2H) was observed. The enantiomeric excess of **9a** was determined to be 95% ee by the ^1H NMR and ^{13}C NMR spectra, after conversion of **9a** into the (*R*,*R*)-butane-2,3-diol acetal. Furthermore, the relative and absolute stereochemistries of (+)-**9a** were correlated with those of (3*R*,4*R*)-3,4-dimethyl-3-isopropenylcyclopentanone (−)-**13** which was obtained by the Rh[(*S*)-BINAP]ClO_4-catalyzed cyclization.[9] Therefore, the absolute stereochemistry of (−)-**9a** should be 3*S*,4*S*, and that of (+)-**9a** should be 3*R*,4*R*. Cyclization by the neutral Rh[BINAP]Cl did not proceed at all, due to the low catalytic activity of the neutral Rh-complex and the bulkiness of the BINAP ligand. The cyclization of **8** by an achiral Rh$(PPh_3)_3Cl$ afforded racemic (±)-**9b** in the ratio of 92 (*cis*) and 8 (*trans*) in 87% yield. In the NOESY ^1H–^1H NMR spectra of (±)-**9b**, correlation between the methyl proton signals δ 0.90 (d, J=7.1 Hz, 3H) at C(4)-position and the methyl signals δ 1.78 (br s, 3H) of isopropenyl function was observed, and thus, the stereochemistry of *cis*-3,4 was determined. The obtained cyclopentanones **9a**,**b** were converted into 4-pentenals **11a**,**b** by solvolysis of the acetyl function and subsequent oxidation of primary



Scheme 2. *Reagents and conditions:* (i) Ac_2O, 4-DMAP, pyridine; (ii) PCC; (iii) Rh-complex; (iv) K_2CO_3, MeOH.

Table 1. The first cyclization of **8** and the second cyclization of **11** by the Rh-complexes

Entry	Rh-complex	Product		Entry	Substrate	Rh-complex	Product	
		Yield (%) [**9b** (*cis*)/**9a** (*trans*)]	ee %				Yield (%)	Ratio of **12a**:**12b**:**12c**
1	Rh[(*R*)-BINAP]ClO_4	88 (1/99)	95	1-1	(−)-**11a**	Rh[(*R*)-BINAP]ClO_4	83	97:3:0
				1-2	(−)-**11a**	Rh[(*S*)-BINAP]ClO_4	0	–
				1-3	(−)-**11a**	Rh[(*R*)-BINAP]Cl	0	–
				1-4	(−)-**11a**	Rh[(*S*)-BINAP]Cl	0	–
				1-5	(−)-**11a**	$Rh(PPh_3)_3Cl$	81	4:96:0
2	Rh[(*S*)-BINAP]ClO_4	94 (1/99)	95	2-1	(+)-**11a**	Rh[(*R*)-BINAP]ClO_4	0	-
				2-2	(+)-**11a**	Rh[(*S*)-BINAP]ClO_4	94	97:3:0
				2-3	(+)-**11a**	Rh[(*R*)-BINAP]Cl[a]	0	-
				2-4	(+)-**11a**	Rh[(*S*)-BINAP]Cl[b]	0	-
				2-5	(+)-**11a**	$Rh(PPh_3)_3Cl$	90	5:94:1
3	$Rh(PPh_3)_3Cl$	87 (92/8)		3-1	(±)-**11b**	$Rh(PPh_3)_3Cl$	85	1:17:82

(-)-**9a**

(+)-**9a**

(3*RS*,4*SR*)-(±)-**9b**

(+)-**12a**

(+)-**12b**

(—)-**12a**

(—)-**12b**

(±)-**12c**

Cyclizations were carried out in CH_2Cl_2 using 0.05 equiv. of the cationic Rh-complex or 0.50 equiv. of the neutral Rh-complex at room temperature.

[a] Spirodiketone was not isolated, but decarbonylated product (−)-**13** was obtained.

[b] The reaction in refluxing benzene afforded the cyclized product (−)-**12b** in 30% yield.

(—)-**13**

alcohol, as shown in Scheme 2. The 4-pentenal (−)-**11a** was obtained from (−)-**9a**, (+)-**11a** from (+)-**9a**, and (±)-**11b** from (±)-**9b** in 95–98% yields.

2.3.2. The second Rh-cyclization. The results of the second cyclization by the Rh-complexes are summarized in Table 1 (entry 1-1-5, 2-1-5, and 3-1). The cyclization of (−)-**11a** by the neutral Rh[(*R*)- or (*S*)-BINAP]Cl did not proceed at all because of the bulky quaternary carbon at the C(3)-position and the low reactivity of the neutral Rh[(*R*)- or (*S*)-BINAP]Cl complex. The cyclization of (−)-**11a** by the cationic Rh[(*S*)-BINAP]ClO_4 did not proceed, but the cyclization by the cationic Rh[(*R*)-BINAP]ClO_4 proceeded to afford spirodiketone (+)-**12a** in 83% yield. The cyclization of (−)-**11a** by the achiral Rh(PPh_3)$_3$Cl afforded (+)-**12b** in 81%. The spectroscopic data of (+)-**12a** and (+)-**12b** were apparently different. The cyclization of (+)-**11a**, the enantiomer of (−)-**11a**, by the neutral Rh[(*R*)- or (*S*)-BINAP]Cl or the cationic Rh[(*R*)-BINAP]ClO_4 did not proceed at room temperature, but the cyclization by the cationic Rh[(*S*)-BINAP]ClO_4 afforded (−)-**12a** in 94% yield. The cyclization of (+)-**11a** by the Rh(PPh_3)$_3$Cl afforded (−)-**12b** in 90% yield. In the case that (+)-**11a** and Rh[(*S*)-BINAP]Cl were refluxed in benzene, the cyclized product (−)-**12b** was also obtained in 30% yield. The cyclization of (±)-**11b** by the Rh(PPh_3)$_3$Cl afforded (±)-**12c** in 85% yield. The spectroscopic data of (±)-**12c** were different from those of **12a** and/or **12b**.

The spirodiketones **12** contain three chiral carbons, and the *C*2-axis at the quaternary carbon C(5) exists in some spirodiketones; therefore, six stereoisomers, that is to say, three pairs of enantiomers exist. Thus, the compounds **12a**, **12b**, and **12c** would be diastereomers. The ^{13}C NMR spectra of **12a** and (±)-**12c** showed six peaks, while those of **12b** showed eleven peaks. These results indicate that the *C*2-symmetry exists in the structures **12a** and **12c**, but not in **12b**. In the NOESY-^1H–^1H NMR spectrum of **12a**, correlation between the methyl proton signals δ 1.08 (d, J=6.9 Hz, 6H) at C(4 and 9)-position and the methylene signals δ 2.31 (d, J=17.6 Hz, 2H) at the C(1 and 6)-position was observed. In the spectrum of **12b**, the correlation between the methyl proton signals δ 1.14 (d, J=6.9 Hz, 3H) at the C(9)-positon and the methine signals δ 2.34 (m, 1H) at the C(4)-position and also the methyl signals δ 1.03 (d, J=6.9 Hz, 3H) at the C(4)-position and the methylene signals δ 2.50 (d, J=18.0 Hz, 1H) at the C(6)-position were observed. Moreover, it is already reported that the stereochemistry of 3,4-substituted cyclopentanones cyclized from 4-pentenal by the Rh(PPh_3)$_3$Cl is *cis*-3,4. Furthermore, the relative stereochemistry of (−)-**12a** constructed by using the Rh[(*S*)-BINAP]ClO_4 twice was unambiguously determined to be 4R^*,5S^*,9R^* by the X-ray crystallographic analysis. The X-ray analysis revealed that only a half of the spirodiketone (−)-**12a** existed in the asymmetric unit, due to the *C*2-symmetry of the molecule (Fig. 2). Based on these results, we concluded that the stereochemistry of (+)-**12a** as 4*S*,5*R*,9*S*, (+)-**12b** as 4*S*,5*R*,9*R*, and (±)-**12c** as 4*RS*,5*RS*,9*RS*.

The diasteromeric ratio of spirodiketones **12** in entry (1-1 and 2-2) was determined to be 97 (**12a**), 3 (**12b**), and 0 (**12c**) by the ratio of methyl proton signals of **12a** at δ 1.08 (d, 6H), the signal of **12b** at δ 1.14, 1.03 (each d, total 6H), and **12c** at δ 1.12 (d, 6H) in the ^1H NMR spectrum. The diastereomeric ratio in entry (1-5 and 2-5) was 4 (**12a**), 96 (**12b**), and 0 (**12c**), and that in entry 3-1 was 1 (**12a**), 17 (**12b**), and 82 (**12c**).

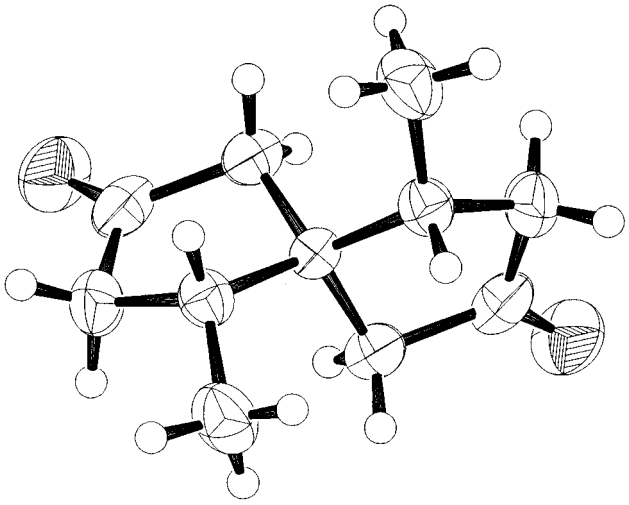


Figure 2. ORTEP drawing of spirodiketone (−)-**12a**.

2.4. Stereoselection in the Rh-catalyzed cyclization

The stereoselectivity for the first cyclization was consistent with the previous experiments.[8,9] That is to say, the cyclization by the neutral Rh(PPh_3)$_3$Cl gave *cis*-3,4-cyclopentanone (±)-**9b** by way of the favorable intermediate, whereas the cyclization by the cationic Rh[(*R*)-BINAP]ClO_4 afforded *trans*-3,4-product (−)-**9a** and its absolute stereochemistry would be 3*S*,4*S* by way of the most unfavorable intermediate.

The outcome in the stereochemistry of spirodiketones **12** could be explained as follows: first, the stereochemistry of C(4)- and C(5)-carbons in the spirodiketones was derived from the C(4)- and C(3)-carbons of cyclopentanone **9** with the retention of its chirality, respectively. Thus, the stereochemistry of the C(9)-carbon in spirodiketones **12** was newly constructed by the second Rh-catalyzed cyclization.

The second cyclization by the neutral Rh(PPh_3)$_3$Cl would be explained by considering the plausible acyl-rhodium intermediates (a–d). The intermediate (a) would be less stable than the intermediate (b) because the repulsion between the methyl function at the C(4)-position and the rhodium metal exists in the intermediate (a). Similarly, the intermediate (c) would be less stable than the intermediate (d). Consequently, the spirodiketones **12b** (entry 1-5, 2-5) and (±)-**12c** (entry 3-1) were formed as a major product by way of the stable intermediates (b and d), as shown in Fig. 3. The relative stereochemistry of **12b** and **12c** was *cis* between the methyl function at the C(9)-position and the C(4)-carbon of the spirane skeleton. The second cyclization by the cationic Rh-complex gave the opposite stereochemistry of the methyl function at the C(9)-position to that by the neutral Rh-complex. These phenomena have been already observed in the Rh-cyclization of 4-pentenals,[8,9] and could be explained by the assumption that the cyclization by the

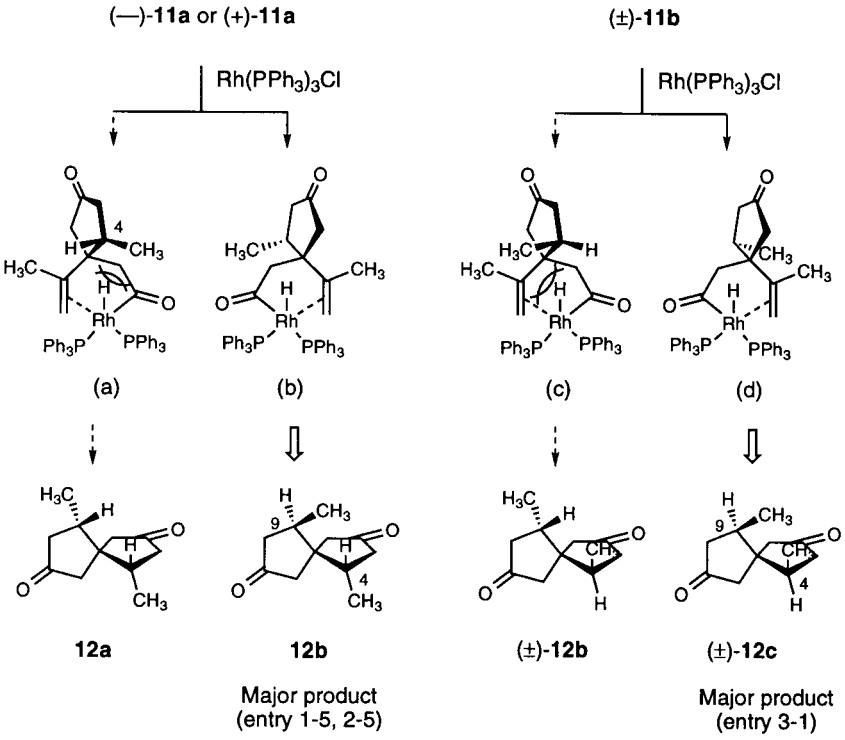


Figure 3. Plausible mechanism for the stereoselection of the second cyclization by the $Rh(PPh_3)_3Cl$.

cationic Rh-complex proceeded by way of an unstable intermediate. The cyclization of (−)-**11a** by the Rh[(*R*)-BINAP]-ClO_4 proceeded to afford (+)-**12a**, but not by the Rh[(*S*)-BINAP]ClO_4. This result would be attributed to the fact that the absolute stereochemistry of (3*S*,4*S*)-(−)-**11a** was matched with (*R*)-BINAP, but mismatched with (*S*)-BINAP.

3. Conclusions

The Rh-catalyzed cyclization was applied to construct the optically active spiro[4.4]nonane-2,7-dione skeleton. All diastereomers **12a**–**c**, bearing a chiral quaternary carbon, could be stereoselectively constructed from the identical 4-pentenal **8** by using the Rh-complex twice. The spirodiketones **12a** and **12b** could be prepared in diastereoselective and enantioselective manner. The strategy described here would be useful for the construction of spirane skeletons.

4. Experimental

4.1. General methods

THF was purchased from Kanto Chemical Co., and used without distillation. Et_2O was distilled from Na/benzophenone before use. Benzene and CH_2Cl_2 were distilled from P_2O_5. (*R*)- and (*S*)-BINAP were purchased from Kanto Chemical Co. Inc. ^1H NMR spectra were determined at 60, 270 or 500 MHz. Infrared spectra were recorded on a JASCO A-100 spectrometer (Nujol or neat). EIMS, FABMS, and HRMS spectra were taken on a JEOL JMS 610H, D300, or SX102 spectrometer. General procedures used for syntheses followed those of the previous reports.[8,9]

4.1.1. Dimethyl 3,3-diacetylglutarate (2). A solution of acetylacetone (6.00 g, 60 mmol) in THF (20 mL) was added to a stirred suspension of NaH (2.40 g, 60%) in THF (60 mL) at 0°C, and the whole was stirred at room temperature for 10 min. Methyl bromoacetate (9.18 g, 60 mmol) in THF (20 mL) was added to the solution at 0°C, and stirred overnight at room temperature. The solution was diluted with brine, extracted with ether, washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (30% EtOAc in hexane) to give an alkylated product (9.50 g, 92%) as a colorless oil: ^1H NMR (60 MHz, $CDCl_3$) δ 4.13 (t, J=7 Hz, 1H), 3.72 (s, 3H), 2.89 (d, J=7 Hz, 2H), 2.22 (s, 6H). A solution of the alkylated product (3.44 g, 20 mmol) in *t*-BuOH (5 mL) was added dropwise to a stirred solution of *t*-BuOK (2.70 g, 24 mmol) in *t*-BuOH (40 mL), and stirred at room temperature for 30 min. Then, a solution of methyl bromoacetate (3.68 g, 24 mmol) in *t*-BuOH (5 mL) was added dropwise, and stirred at room temperature for 18 h. The reaction was quenched with saturated aqueous NH_4Cl, extracted with EtOAc, washed with 5% aqueous $Na_2S_2O_3$, brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 30% EtOAc in hexane gave **2** (4.37 g, 91%) as a colorless oil: IR (neat) 1740, 1710 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.67 (s, 6H), 3.28 (s, 4H), 2.18 (s, 6H); EIMS *m*/*z* 244 (M^+); HRMS calcd for $C_{11}H_{16}O_6$ (M^+) 244.0947, found 244.0940.

4.1.2. Dimethyl 3,3-diisopropenylglutarate (3). A solution of **2** (6.10 g, 25 mmol) in THF (100 mL) was added dropwise to a vigorously stirred suspension of Nysted reagent (20% suspension in THF, 148 g) in THF (100 mL) at

−78°C, and stirred for 15 min. Then, $TiCl_4$ (5.6 mL) was added dropwise to the stirred mixture at −78°C, and then the whole was warmed to room temperature, and stirred for 30 min. The mixture was diluted with water, and extracted with EtOAc. The extract was washed with 5% aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. After removal of the solvent, the oily residue was purified by column chromatography on silica gel (2% EtOAc in hexane) to give **3** (1.74 g, 29%) as a colorless oil: IR (neat) 1740, 1640 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.97 (br s, 2H), 4.77 (br s, 2H), 3.62 (s, 6H), 3.02 (s, 4H), 1.65 (br s, 6H); EIMS *m/z* 240 (M^+, 8), 209 (100); HRMS calcd for $C_{13}H_{20}O_4$ (M^+) 240.1361, found 240.1368.

4.1.3. 3,3-Diisopropenyl-1,5-pentanediol (4). A solution of **3** (1.20 g, 5.0 mmol) in ether (30 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (760 mg, 20 mmol) in ether (70 mL) at room temperature, and stirred for 5 h. The reaction was quenched with EtOAc and H_2O, then filtered through celite, and the filtrate was dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel (2% EtOAc in hexane) to give **4** (718 mg, 78%) as a colorless oil: IR (neat) 3220 (br), 1620 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.99 (m, 2H), 4.89 (br s, 2H), 3.60 (t, *J*=6.8 Hz, 4H), 2.22 (br s, 2H), 1.93 (t, *J*=6.8 Hz, 4H), 1.57 (br s, 6H); FDMS *m/z* 185 (M^++1).

4.1.4. 3,3-Diisopropenyl-δ-valerolactone (6). IR (neat) 1745, 1650 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.05 (br s, 2H), 4.89 (br s, 2H), 4.28 (t, *J*=5.9 Hz, 2H), 2.66 (br s, 2H), 2.04 (t, *J*=5.9 Hz, 2H), 1.61 (br s, 3H), 1.59 (br s, 3H); EIMS *m/z* 180 (M^+, 2), 165 (15), 152 (9), 121 (33), 108 (51), 93 (100); HRMS calcd for $C_{11}H_{16}O_2$ (M^+) 180.1150, found 180.1155.

4.1.5. 5-Acetoxy-3,3-diisopropenylpentanol (7). A mixture of **4** (9.2 g, 50 mmol), Ac_2O (5.1 g, 50 mmol), 4-DMAP (733 mg, 6.0 mmol) and pyridine (4.7 g, 60 mmol) in CH_2Cl_2 (200 mL) was stirred at 0°C for 45 min. After removal of the solvent, the residue was purified by column chromatography on silica gel (20% EtOAc in hexane) to afford **7** (7.9 g, 70%) as a colorless oil: IR (neat) 3435 (br), 1745, 1635 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.99 (br s, 2H), 4.86 (br s, 2H), 3.99 (t, *J*=7.5 Hz, 2H), 3.60 (t, *J*=7.8 Hz, 2H), 2.04 (s, 3H), 1.82–1.99 (m, 4H), 1.75 (br, 1H), 1.59 (br s, 6H); FABMS *m/z* 227 (M^++H); HRFAB(+)MS calcd for $C_{13}H_{23}O_3$ (M^++H) 227.1647, found 227.1650.

4.1.6. 5-Acetoxy-3,3-diisopropenylvaleraldehyde (8). A mixture of **7** (4.52 g, 20 mmol), PCC (5.2 g, 24 mmol), and NaOAc (0.40 g, 4.8 mmol) in CH_2Cl_2 (60 mL) was stirred at room temperature for 3 h. The mixture was diluted with ether, and filtered through florisil to remove chromate. The filtrate was concentrated in vacuo to leave an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 12% ether in pentane afforded **8** (3.94 g, 88%) as a colorless oil: IR (neat) 1745, 1725 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.62 (t, *J*=3.0 Hz, 1H), 5.07 (br s, 2H), 4.87 (br s, 2H), 4.03 (t, *J*=7.2 Hz, 2H), 2.60 (d, *J*=3.0 Hz, 2H), 2.07 (t, *J*=7.2 Hz, 2H), 2.03 (s, 3H), 1.64 (br s, 6H); EIMS *m/z* 224 (M^+, 1), 206 (9), 181 (69), 43 (100); HRMS calcd for $C_{13}H_{20}O_3$ (M^+) 224.1412, found 224.1410.

4.1.7. (3*S*,4*S*)-3-(2-Acetoxyethyl)-3-isopropenyl-4-methylcyclopentanone (−)-(9a). A solution of [Rh(NBD)(*R*)-BINAP]ClO_4 (23 mg, 0.025 mmol) in CH_2Cl_2 (4 mL) was stirred under an H_2 atmosphere at room temperature for 2 h. Then, an Ar gas was bubbled into the solution for 15 min. This bright red solution of [Rh(*R*)-BINAP]ClO_4 was used for the cyclization without isolation. A solution of 4-pentenal **8** (112 mg, 0.50 mmol) in CH_2Cl_2 (3 mL) was added dropwise to the stirred solution of [Rh(*R*)-BINAP]-ClO_4 under an Ar atmosphere. After being stirred for 3 h, the solution was concentrated in vacuo to leave a residue. The residue was dissolved in ether (20 mL), and the precipitated Rh-complex was filtered off. The concentration of filtrate gave an oily residue, which was purified by column chromatography on silica gel to afford (−)-**9a** (92 mg, 88%) as a colorless oil: $[\alpha]^{30}_D$=−86.90 (*c* 2.01, $CHCl_3$); IR (neat) 1745, 1635 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.97 (br s, 1H), 4.75 (br s, 1H), 4.06 (ddd, *J*=5.3, 8.8, 11.1 Hz, 1H), 3.85 (ddd, *J*=6.8, 8.6, 11.1 Hz, 1H), 2.57 (dd, *J*=0.9, 18.3 Hz, 1H), 2.41–2.50 (m, 2H), 2.25 (dd, *J*=1.4, 18.3 Hz, 1H), 2.03 (s, 3H), 2.02 (ddd, *J*=5.2, 8.8, 13.9 Hz, 1H), 1.85 (m, 1H), 1.80 (s, 3H), 1.75 (ddd, *J*=6.6, 8.7, 13.9 Hz, 1H), 1.06 (d, *J*=7.3 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 217.6, 170.9, 146.2, 113.6, 61.9, 48.9, 46.4, 44.4, 36.2, 32.0, 20.9, 19.7, 16.2; EIMS *m/z* 224 (M^+, 2), 181 (4), 164 (13), 140 (20), 122 (41), 94 (71), 79 (100); HRMS calcd for $C_{13}H_{20}O_3$ (M^+) 224.1412, found 224.1408.

4.1.8. (3*R*,4*R*)-3-(2-Acetoxyethyl)-3-isopropenyl-4-methylcyclopentanone (+)-(9a). The cyclization of **8** by the [Rh(*S*)-BINAP]ClO_4 afforded (+)-**9a** in 94% yield. $[\alpha]^{26}_D$=+86.0 (*c* 1.21, $CHCl_3$).

4.1.9. Determination of enantiomeric excess of 9a. The enantiomeric excesses of **9a** were determined by ^1H NMR spectra of acetals derived from (*R*,*R*)-2,3-butandiol. A mixture of cyclopentanone **9a** (67 mg, 0.30 mmol), (*R*,*R*)-butanediol (81 mg, 0.90 mmol), and *p*-TsOH-H_2O (10 mg) in benzene (20 mL) was refluxed for 3 h, fixed with Dean–Stark apparatus. After being cooled to room temperature, the solution was washed with 5% aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. After removal of the solvent, the residue was briefly purified by column chromatography on silica gel to give the crude acetal. The ^1H NMR spectrum of the butanediol acetal of (−)-**9a** cyclized by Rh[(*R*)-BINAP]ClO_4 showed the olefin proton signals at δ 4.846 (br s) and 4.819 (br s) in the ratio of 2 to 98, and the methyl proton signals at δ 0.974 (d, *J*=6.8 Hz) and 0.958 (d, *J*=6.6 Hz) in the same ratio, while that from (+)-**9a** cyclized by Rh[(*S*)-BINAP]ClO_4 showed olefinic signals at δ 4.846 (br s) and 4.819 (br s), and the methyl signals at δ 0.974 (d, *J*=6.8 Hz) and 0.958 (d, *J*=6.6 Hz) in the ratio of 98 to 2. The enantiomeric excesses were also supported by ^{13}C NMR spectra. (*R*,*R*)-2,3-Butanediol acetal of (−)-**9a**: ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.1, 147.5, 115.0, 111.7, 78.4, 78.0, 62.6, 49.9, 47.3, 45.7, 39.7, 29.7, 21.0, 20.6, 17.07, 17.06, 14.8; (*R*,*R*)-2,3-Butanediol acetal of (+)-**9a**: ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.1, 147.4, 115.3, 112.0, 78.3, 78.0, 62.6, 50.0, 46.9, 45.4, 39.4, 31.0, 21.0, 20.4, 17.27, 17.14, 15.2.

4.1.10. (3*RS*,4*SR*)-3-(2-Acetoxyethyl)-3-isopropenyl-4-methylcyclopentanone (±)-(9b). A solution of **8** (112 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of $Rh(PPh_3)_3Cl$ (231 mg, 0.25 mmol) in CH_2Cl_2 (3 mL), and the solution was stirred overnight at room temperature. Removal of the solvent afforded a residue, which was dissolved in ether (30 mL), and the precipitated Rh-complex was filtered off. After removal of ether, the oily residue was purified by column chromatography on silica gel to afford (±)-**9b** (97 mg, 87%) as a colorless oil: IR (neat) 1745, 1645 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.98 (br s, 1H), 4.68 (s, 1H), 4.02 (ddd, J=5.6, 8.6, 11.2 Hz, 1H), 3.82 (ddd, J=5.9, 8.9, 11.2 Hz, 1H), 2.56 (dd, J=7.9, 19.2 Hz, 1H), 2.50 (d, J=17.3 Hz, 1H), 2.28 (m, 1H), 2.23 (d, J=17.3 Hz, 1H), 2.04 (m, 1H), 2.03 (m, 1H), 2.01 (s, 3H), 1.78 (br s, 3H), 1.66 (m, 1H), 0.90 (d, J=7.1 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 217.7, 170.9, 145.0, 113.7, 61.5, 50.4, 44.9, 44.7, 38.6, 35.0, 20.9, 19.4, 16.9; EIMS *m/z* 224 (M^+, 2), 182 (4), 164 (17), 140 (16), 122 (46), 94 (68), 79 (100).

4.1.11. (3*S*,4*S*)-3-Isopropenyl-3-(2-hydroxyethyl)-4-methylcyclopentanone (−)-(10a). A mixture of (−)-**9a** (200 mg, 0.89 mmol) and K_2CO_3 (123 mg, 0.89 mmol) in MeOH (20 mL) was stirred overnight at room temperature. After removal of the solvent, the residue was purified by column chromatography on silica gel (50% EtOAc in hexane) to give (−)-**10a** (163 mg, quant.) as a colorless oil: $[\alpha]^{29}_D$=−109.23 (*c* 1.36, $CHCl_3$); IR (neat) 3450 (br), 1740, 1640 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.95 (br s, 1H), 4.75 (br s, 1H), 3.64–3.46 (m, 2H), 2.57 (d, J=18.1 Hz, 1H), 2.35–2.55 (m, 2H), 2.26 (d, J=18.1 Hz, 1H), 1.99 (m, 1H), 1.81 (br s, 3H), 1.69 (m, 1H), 1.55 (br, 1H), 1.07 (d, J=7.0 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 218.0, 147.3, 113.0, 60.3, 49.0, 46.6, 44.4, 36.3, 36.0, 19.9, 16.3; EIMS *m/z* 182 (M^+, 0.6), 167 (2), 138 (39), 83 (100); HRMS calcd for $C_{11}H_{18}O_2$ (M^+) 182.1307, found 182.1306.

4.1.12. (3*R*,4*R*)-3-Isopropenyl-3-(2-hydroxyethyl)-4-methylcyclopentanone (+)-(10a). $[\alpha]^{28}_D$=+116.2 (*c* 1.04, $CHCl_3$).

4.1.13. (3*RS*,4*SR*)-3-Isopropenyl-3-(2-hydroxyethyl)-4-methylcyclopentanone (±)-(10b). 99% yield from (±)-**9b**: IR (neat) 3450 (br), 1740, 1640 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.95 (br s, 1H), 4.69 (br s, 1H), 3.51–3.58 (m, 2H), 2.57 (dd, J=7.5, 18.1 Hz, 1H), 2.49 (d, J=17.9 Hz, 1H), 2.28 (m, 1H), 2.26 (d, J=17.9 Hz, 1H), 2.03 (m, 1H), 1.99 (m, 1H), 1.79 (br s, 3H), 1.61 (ddd, J=6.0, 7.3, 13.0 Hz, 1H), 1.48 (br, 1H), 0.89 (d, J=7.1 Hz, 3H); EIMS *m/z* 182 (M^+, 16), 138 (36), 83 (100).

4.1.14. (3*S*,4*S*)-3-Formylmethyl-3-isopropenyl-4-methylcyclopentanone (−)-(11a). Compound (−)-**11a** was prepared from (−)-**10a** in a similar manner to that described for the preparation of **8**: 98% yield; a colorless oil; $[\alpha]^{28}_D$=−48.21 (*c* 1.57, $CHCl_3$); IR (neat) 1745, 1725, 1640 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.64 (t, J=2.6 Hz, 1H), 5.04 (br s, 1H), 4.84 (br s, 1H), 2.78 (dd, J=2.9, 15.9 Hz, 1H), 2.69 (d, J=18.1 Hz, 1H), 2.45–2.58 (m, 2H), 2.43 (d, J=18.1 Hz, 1H), 2.33 (dd, J=2.1, 15.9 Hz, 1H), 1.92 (m, 1H), 1.85 (br s, 3H), 1.06 (d, J=6.8 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 216.1, 201.4, 145.7, 113.8, 48.3, 47.4, 46.0, 44.1, 36.7, 20.2, 15.6; EIMS *m/z* 180 (M^+, 1), 138 (52), 82 (100); HRMS calcd for $C_{11}H_{16}O_2$ (M^+) 180.1150, found 180.1156.

4.1.15. (3*R*,4*R*)-3-Formylmethyl-3-isopropenyl-4-methylcyclopentanone (+)-(11a). Compound (+)-**11a** was prepared from (+)-**10a** in a similar manner to that described for the preparation of **8**: $[\alpha]^{27}_D$=+57.0 (*c* 1.01, $CHCl_3$).

4.1.16. (3*RS*,4*SR*)-3-Formylmethyl-3-isopropenyl-4-methylcyclopentanone (11b). Compound **11b** was prepared from **10b** in a similar manner to that described for the preparation of **8**: a colorless oil; IR (neat) 1745, 1725, 1640 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.58 (t, J=2.8 Hz, 1H), 5.05 (br s, 1H), 4.78 (br s, 1H), 2.78 (dm, J=15.6 Hz, 1H), 2.70 (d, J=18.1 Hz, 1H), 2.50 (dd, J=8.24, 19.2 Hz, 1H), 2.38–2.38 (m, 3H), 2.09 (dd, J=3.6, 19.2 Hz, 1H), 1.82 (br s, 3H), 0.94 (d, J=7.1 Hz, 3H); EIMS *m/z* 180 (M^+, 2), 138 (51), 110 (21), 82 (100).

4.1.17. (4*S*,5*R*,9*S*)-4,9-Dimethylspiro[4.4]nonane-2,7-dione (+)-12a. A solution of [Rh(NBD)(*R*)-BINAP]ClO_4 (46 mg, 0.050 mmol) in CH_2Cl_2 (8 mL) was stirred under an H_2 atmosphere at room temperature for 2 h. Then, an Ar gas was bubbled into the red solution for 30 min. This bright red solution of [Rh(*R*)-BINAP]ClO_4 was used for the cyclization without isolation. A solution of 4-pentenal (−)-**11a** (180 mg, 1.00 mmol) in CH_2Cl_2 (3 mL) was added dropwise to the stirred solution of [Rh(*R*)-BINAP]ClO_4 under an Ar atmosphere. After being stirred at room temperature for 2 h, the solution was concentrated in vacuo to leave a residue. The residue was dissolved in ether (20 mL), and the precipitated Rh-complex was filtered off. The concentration of filtrate gave an oily residue, which was purified by column chromatography on silica gel (30% ether in pentane) to afford (+)-**12a** (149 mg, 83%) as a colorless solid. Recrystallization from hexane afforded pure (+)-**12a** as colorless crystals: mp 143–144°C; $[\alpha]^{26}_D$=+301.8 (*c* 0.46, $CHCl_3$); IR (Nujol) 1745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.51 (dd, J=8.0, 18.5 Hz, 2H), 2.38 (m, 2H), 2.31 (d, J=17.6 Hz, 2H), 2.01 (d, J=17.6 Hz, 2H), 1.87 (ddd, J=1.2, 11.6, 18.5 Hz, 2H), 1.08 (d, J=6.9 Hz, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 215.7, 50.7, 45.7, 45.1, 35.1, 14.0; EIMS *m/z* 180 (M^+, 52), 137 (15), 110 (66), 68 (95), 42 (100); HRMS calcd for $C_{11}H_{16}O_2$ (M^+) 180.1150, found 180.1153.

4.1.18. (4*R*,5*S*,9*R*)-4,9-Dimethylspiro[4.4]nonane-2,7-dione (−)-12a. Cyclization of (+)-**11a** by the Rh[(*S*)-BINAP]ClO_4 afforded (−)-**12a** in 94% yield: colorless crystals; mp 143–144°C (recryst. from hexane); $[\alpha]^{22}_D$=−309.8 (*c* 0.47, $CHCl_3$).

4.1.19. X-Ray crystallographic analysis of (−)-12a. Data collection was performed on a Rigaku AFC5R diffractometer, Ni foil filtered CuK_α radiation. The crystal remained stable at room temperature during the X-ray data collection. The structure was solved by direct methods using SHELX 86[13] and expanded using Fourier techniques[14]. All non-hydrogen atoms were given anisotropic thermal parameters and hydrogen atoms included in calculated positions given isotropic thermal parameters. All calculations

were performed using the TEXSAN[15] crystallographic package of Molecular Structure Corporation: solvent of recryst.=hexane, $C_{11}H_{16}O_2$, M_r=180.25, tetragonal, space group $P4_12_12$ (No. 92), a=7.666, c=17.064 Å, V=1002.9 Å^3, Z=4, D_{calcd}=1.194 g cm^{-3}, μ (CuK$_\alpha$)=6.43 cm^{-1}, no. of observation=340 ($I>3.0\sigma(I)$), R=0.043, R_w=0.042.

4.1.20. (4*S*,5*R*,9*R*)-4,9-Dimethylspiro[4.4]nonane-2,7-dione (+)-12b. Cyclization of (−)-**11a** by the $Rh(PPh_3)_3Cl$ afforded (+)-**12b** in 81% yield: a colorless oil; $[\alpha]^{21}_D$=+33.08 (*c* 1.23, $CHCl_3$); IR (neat) 1740 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42–2.58 (m, 3H), 2.50 (d, *J*=18.0 Hz, 1H), 2.40 (d, *J*=18.0 Hz, 1H), 2.34 (m, 1H), 2.21 (d, *J*=18.0 Hz, 1H), 2.06 (d, *J*=18.0 Hz, 1H), 1.96–2.10 (m, 2H), 1.14 (d, *J*=6.9 Hz, 3H), 1.03 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 216.5, 216.2, 50.8, 49.3, 46.0, 45.73, 45.72, 38.2, 34.1, 16.4, 14.9; EIMS *m*/*z* 180 (M$^+$, 48), 137 (7), 110 (61), 82 (50), 68 (92), 42 (100); HRMS calcd for $C_{11}H_{16}O_2$ (M$^+$) 180.1150, found 180.1160.

4.1.21. (4*R*,5*S*,9*S*)-4,9-Dimethylspiro[4.4]nonane-2,7-dione (−)-12b. Cyclization of (+)-**11a** by the $Rh(PPh_3)_3Cl$ afforded (−)-**12b** in 90% yield: a colorless oil; $[\alpha]^{21}_D$=−28.29 (*c* 1.29, $CHCl_3$).

4.1.22. (4*RS*,5*RS*,9*RS*)-4,9-Dimethylspiro[4.4]nonane-2,7-dione (±)-12c. Cyclization of (±)-**11b** by the $Rh(PPh_3)_3Cl$ afforded (±)-**12c** in 85% yield: a colorless oil; IR (neat) 1740 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.26–2.57 (m, 4H), 2.27 (d, *J*=17.6 Hz, 2H), 2.13 (d, *J*=18.0 Hz, 2H), 2.08 (d, *J*=18.0 Hz, 2H), 1.12 (d, *J*=6.6 Hz, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 216.8, 50.0, 47.7, 47.0, 37.1, 16.1; EIMS *m*/*z* 180 (M$^+$, 63), 165 (6), 137 (11), 110 (66), 82 (54), 68 (99), 42 (100); HRMS calcd for $C_{11}H_{16}O_2$ (M$^+$) 180.1150, found 180.1162.

4.1.23. (3*R*,4*R*)-3,4-Dimethyl-3-isopropenylcyclopentanone (13)[9]. $[\alpha]_D^{25}$=−110.0° (*c* 1.10, $CHCl_3$); IR (neat) 1740, 1630 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.89 (m, 1H), 4.84 (br s, 1H), 2.45–2.52 (m, 2H), 2.43 (d, *J*=18.8 Hz, 1H), 2.12 (d, *J*=18.8 Hz, 1H), 1.98 (m, 1H), 1.79 (br s, 3H), 1.05 (s, 3H), 0.99 (d, *J*=6.6 Hz, 3H).

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