First total synthesis of (*R*,*R*,*R*)- and (3*R*,5*S*,9*R*)-bejarol by gold-catalyzed allene cycloisomerization and determination of absolute configuration of the natural product

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The first total synthesis of (*R*,*R*,*R*)-bejarol and its (3*R*,5*S*,9*R*)-isomer has been accomplished which confirms the absolute configuration of the natural products. The key step is the gold-catalyzed cycloisomerization of the enantiomerically pure β-hydroxyallenes **12**/**13** to the corresponding dihydropyrans **14**/**15**.

Introduction

The bejarols **1** are sesquiterpenoid components of the essential oil which was first isolated from *Santolina oblongifolia* in 1983. The initial structural assignment consisted of a 2,5-dihydrofuran core[1a] that was later corrected in favor of a chiral dihydropyran bearing two unsaturated side chains (Fig. 1).[2] Whereas the relative configuration was assigned by NMR spectroscopy, the absolute configuration has not been determined so far. Due to the presence of a stereogenic center in the allylic alcohol side chain, four chiral diastereomers are possible. To the best of our knowledge, no total synthesis of **1** has been reported so far.

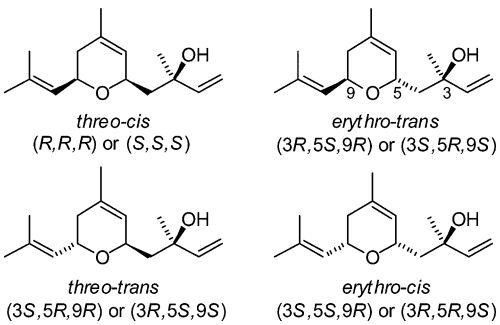
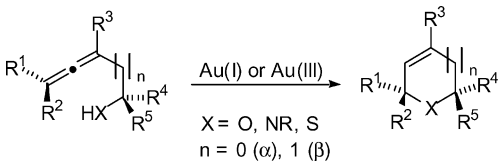


Fig. 1 Structure of diastereomeric bejarols **1**.

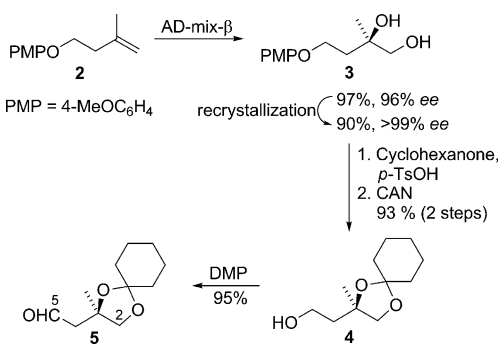
Based on our continued interest in the stereoselective synthesis and transformation of functionalized allenes,[3] we have recently developed the gold-catalyzed[4] cycloisomerization of allenes bearing a hydroxy, amino, or thiol group in the α-position, to the corresponding five-membered heterocycles,[5] a method that combines high reactivity and excellent axis-to-center chirality transfer with a tolerance towards many functional groups (Scheme 1). Moreover, β-hydroxyallenes were also found to undergo a regio- and stereoselective 6-*endo*-cycloisomerization to the corresponding 5,6-dihydro-2*H*-pyrans in the presence of a gold(I) or gold(III) precatalyst.[6] Our methods have already proven to be highly useful in target-oriented synthesis,[7] and we now disclose the first total synthesis of two bejarol stereoisomers which also confirms the absolute configuration of the natural products.



Scheme 1 Gold-catalyzed cycloisomerization of α- or β-hetero-substituted allenes to 5- and 6-membered heterocycles.

Results and discussion

Since the absolute configuration of the bejarols is unknown, we randomly selected (*R*,*R*,*R*)-**1** as target molecule. The key step was envisaged to be the formation of the dihydropyran ring by gold-catalyzed cycloisomerization of a β-hydroxyallene which should be accessible by copper-mediated S_N2'-substitution of a suitable propargyl electrophile.[5–7] Our approach started with the formation of the stereogenic center at C3 by Sharpless dihydroxylation of the protected homoallylic alcohol **2**[8] with AD-mix-β which afforded diol **3** with high yield and enantiomeric excess (Scheme 2). A single recrystallization gave enantiomerically pure material that was converted into alcohol **4** by ketalization with cyclohexanone and oxidative cleavage of the PMP group. Oxidation of **4** with Dess–Martin periodinane[9] afforded the C2–C5 fragment **5** with high yield.



Scheme 2 Synthesis of the C2–C5 fragment **5**.

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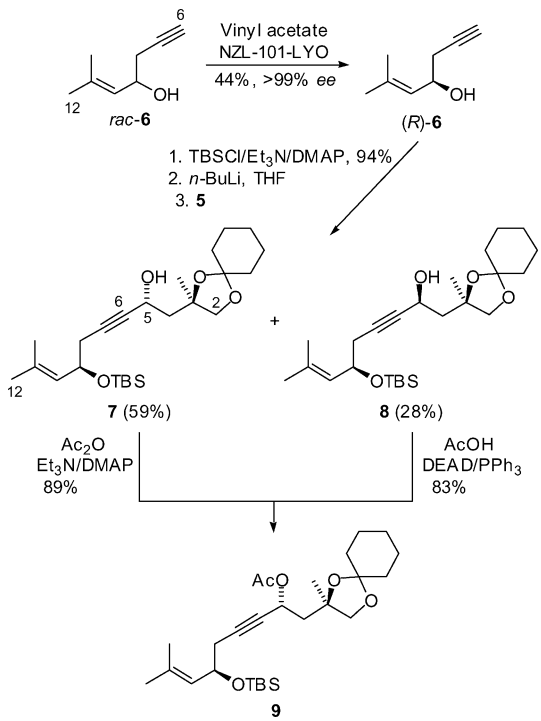
Next, the C6–C12 section of the target molecule was assembled by reaction of propargylzinc bromide with 3-methylbut-2-enal which gave the secondary alcohol *rac*-**6** with 82% yield (Scheme 3).[10] The kinetic resolution of *rac*-**6** was efficiently achieved using Novozyme lipase A from *Candida antarctica* (NZL-101-LYO)[11] which afforded enantiomerically pure alcohol (*R*)-**6**[12] with 44% yield. Protection with TBSCl was followed by addition of the lithium acetylide to aldehyde **5** which gave the diastereomeric alcohols **7** and **8** with 59% and 28% yield, respectively.[13] The assignment of the relative configuration at C3 and C5 is based on the conversion of **7** into **1**, and it is also in line with the preferred formation of the 1,3-*anti* product that is often observed in alkynylations of chiral 3-alkoxyaldehydes.[14] The diastereomers **7** and **8** are easily separable by column chromatography on silica gel, and each of them was converted with good yield into the propargyl acetate **9** by acetylation with Ac_2O, or under Mitsunobu conditions.[15]

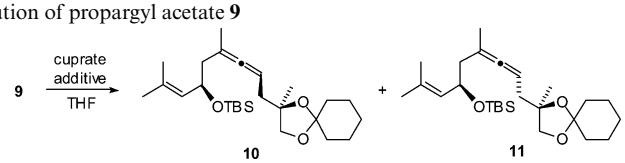


Scheme 3 Synthesis of the C6–C12 fragment **6** and coupling with aldehyde **5**.

Allene formation by treatment of **9** with the magnesium cuprate obtained from MeMgCl, CuI and LiBr in THF[3d,16] gave allenes **10** and **11** with a good chemical yield of 78% (22% of **9** was recovered), but the diastereoselectivity (*anti* : *syn* = 3 : 2) was low, which indicates considerable epimerization of the allene by the copper species (Table 1, entry 1). The addition of phosphorus ligands, which has been used previously to prevent copper-promoted epimerizations of allenes,[3d,16] or using $CuBr{\cdot}Me_2S$ instead of CuI, increased the diastereoselectivity up to 9 : 1, but only at the cost of unacceptable chemical yields (entries 2–5). A fast reaction was observed with the Gilman cuprate $Me_2CuLi{\cdot}LiI$, but it provided a 1 : 1-mixture of allenes **10**–**11** and the corresponding reduced allene bearing a hydrogen atom instead of the methyl group at C7 (entry 6).[3d] This undesired reduction was suppressed with *n*-Bu_3P or $(EtO)_3P$ (entries 7, 8), but the reactivity of these modified cuprate reagents was again insufficient. The same is true for the cyano-Gilman reagent $Me_2CuLi{\cdot}LiCN$ (entry 9), as well as the copper reagent formed from MeLi, CuI, and LiBr (entry 10). Variation of the solvent (Et_2O instead of THF) or the leaving group (*t*-BuOCO or Ts instead of Ac) did not improve this situation.

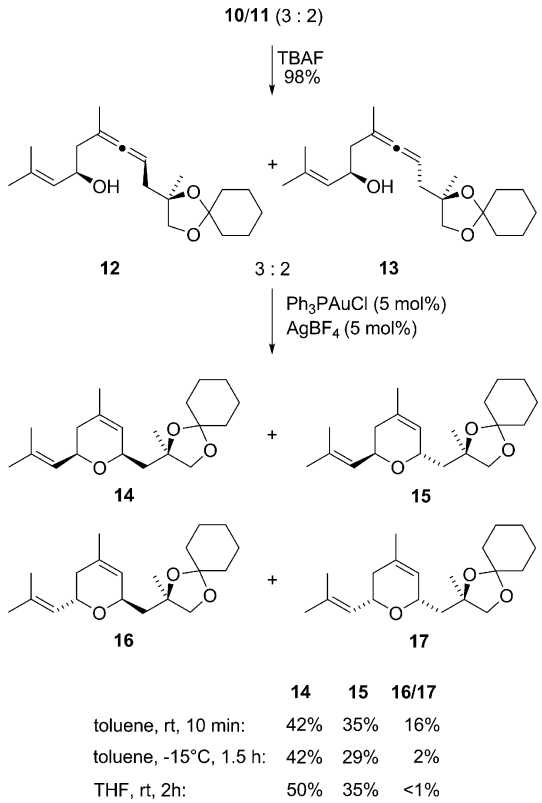
Therefore, we continued our synthesis with the 3 : 2-mixture of allenes **10**–**11** obtained (Table 1, entry 1). Neither these silyl ethers nor the β-hydroxyallenes **12**–**13** obtained after deprotection could be separated chromatographically (Scheme 4). The gold-catalyzed cycloisomerization of the 3 : 2-mixture of **12**–**13** was carried out in the presence of 5 mol% of the cationic catalyst formed *in situ* from Ph_3PAuCl and $AgBF_4$.[6] In toluene, the reaction proceeded smoothly within 10 min at room temperature to afford the desired dihydropyrans **14** and **15** with high yield; however, the diastereomeric heterocycles **16**–**17**, which are a result of an epimerization of the allylic alcohol side chain, were obtained as byproducts with 16% total yield. This undesired side reaction could be prevented by decreasing the reaction temperature, or by using THF as the solvent;[5c] the latter conditions afforded **14** and **15** with 50% and 35% yield, respectively. These isomers could be easily separated by silica gel column chromatography. Since

Table 1 Copper-mediated S_N2'-substitution of propargyl acetate **9**



Entry	Cuprate	Additive	Temp.	Time	Yield (%)	**10** : **11**
1	MeMgCl–CuI–LiBr	—	0 °C–rt	5 h	78	60 : 40
2	MeMgCl–CuI–LiBr	*n*-Bu_3P	0 °C–rt	21 h	30	65 : 35
3	MeMgCl–CuI–LiBr	$(EtO)_3P$	0 °C–rt	5 h	13	90 : 10
4	MeMgCl–CuI–LiBr	$(PhO)_3P$	0 °C–rt	21 h	20	70 : 30
5	MeMgCl–CuBr Me_2S–LiBr	—	0 °C–rt	5 h	12	90 : 10
6	$Me_2CuLi{\cdot}LiI$	—	−40 °C	10 min	40[a]	—
7	$Me_2CuLi{\cdot}LiI$	*n*-Bu_3P	−40 °C–rt	20 h	10	85 : 15
8	$Me_2CuLi{\cdot}LiI$	$(EtO)_3P$	−40 °C–rt	5 h	26	60 : 40
9	$Me_2CuLi{\cdot}LiCN$	—	0 °C–rt	5 h	9	80 : 20
10	MeLi–CuI–LiBr	—	0 °C–rt	2 h	13	70 : 30

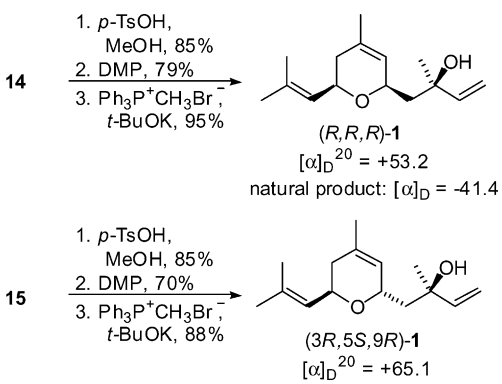
[a] 40% of the reduced allene was obtained as byproduct.



Scheme 4 Gold-catalyzed cycloisomerization of β-hydroxyallenes **12**–**13**

the product ratio is very similar to the ratio of the allenes **12**–**13**, it seems reasonable to assume that the cycloisomerization takes place with complete axis-to-center chirality transfer.[6]

Finally, either isomer was transformed into the corresponding diastereo- and enantiomerically pure bejarol **1** by acetal cleavage, oxidation of the primary alcohol to the aldehyde with Dess–Martin periodinane,[9] and Wittig olefination (Scheme 5). The spectroscopic data of synthetic (*R*,*R*,*R*)-**1** and (3*R*,5*S*,9*R*)-**1** are in excellent agreement with those reported for the natural products.[1,2] Comparison of the optical rotation of our product (*R*,*R*,*R*)-**1** ($[\alpha]_D^{20} = +53.2$, $c = 0.68$, $CHCl_3$) with that reported for naturally occurring *threo-cis*-bejarol ($[\alpha]_D^{20} = -41.4$, $c = 0.756$, $CHCl_3$)[1a] confirms that the absolute configuration of the natural product is (*S*,*S*,*S*). For the (3*R*,5*S*,9*R*)-isomer, we have determined a rotation of $[\alpha]_D^{20} = +65.1$ ($c = 0.53$, $CHCl_3$) whereas the literature value for natural *erythro-trans*-bejarol is $[\alpha]_D^{20} = -9.5$ ($c = 1.1$, $CHCl_3$).[1a]



Scheme 5 Final steps towards (*R*,*R*,*R*)- and (3*R*,5*S*,9*R*)-bejarol.

The discrepancy may indicate that the natural product was not isolated in pure form.

Conclusion

We have achieved the first diastereo- and enantioselective total synthesis of (*R*,*R*,*R*)- and (3*R*,5*S*,9*R*)-bejarol, which is also the first application of the gold-catalyzed cycloisomerization of β-hydroxyallenes to 5,6-dihydro-2*H*-pyrans in natural product synthesis. The absolute configuration of naturally occurring *threo-cis*-bejarol was confirmed to be (*S*,*S*,*S*), whereas natural *erythro-trans*-**1** has the (3*S*,5*R*,9*S*)-configuration. Our modular approach can be easily adapted to the synthesis of any stereoisomeric bejarol. Due to the mildness and carbophilicity of the gold catalyst, labile functionalities such as acetals are tolerated, clearly demonstrating the utility of homogeneous gold catalysis for the synthesis of complex target molecules. Further applications of our methods will be reported in due course.

Experimental

General information

All reactions were performed in oven-dried glassware under argon. Diethyl ether and THF were distilled from sodium–benzophenone. Column chromatography was carried out with Merck silica gel F 60 (70–230 mesh). ^{1}H and ^{13}C NMR spectra were recorded with Bruker DRX 400 and DRX 500 spectrometers at room temperature in $CDCl_3$ as solvent and internal standard (^{1}H NMR: $\delta = 7.27$; ^{13}C NMR: $\delta = 77.0$). Carbon atoms were assigned with APT experiments. IR spectra were measured with a Nicolet Avatar 320 FT-IR as a liquid film between NaCl plates or in the case of solids as KBr pellet. FAB mass spectra (HRMS) were measured with a Jeol SX102A spectrometer.

Synthetic procedures

(*R*)-4-(4-Methoxyphenyl)-2-methylbutane-1,2-diol (3). To a solution of homoallylic alcohol derivative **2** (5.48 g, 28.5 mmol) in a 1 : 1-mixture of *t*-butanol and H_2O (285 mL) was added AD-mix-β (39.9 g) at 4 °C under air. After being stirred at 4 °C for 16 h, the reaction mixture was quenched with Na_2SO_3 and stirred for 30 min at 4 °C. After extraction with CH_2Cl_2, the organic layer was washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane–AcOEt (1 : 3) to give **3** (6.29 g, 27.6 mmol, 97%, 96% ee). After recrystallization from cyclohexane–AcOEt, enantiomerically pure **3** (5.78 g, 24.8 mmol, 90%, >99% ee) was obtained. The ee was determined by chiral HPLC: chiralcel AD; *i*-PrOH : *n*-heptane = 10 : 90; flow rate, 1.2 mL min^{-1}; room temperature; retention time, (*R*)-**3** 14.0 min, (*S*)-**3** 12.9 min. Colorless solid; $[\alpha]_D^{20} = -8.0$ ($c = 2.00$, $CHCl_3$). IR (neat) cm^{-1}: 3252, 2919, 1511, 1469, 1243; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.84 (4H, s), 4.02–4.22 (2H, m), 3.76 (3H, s), 3.53 (1H, d, $J = 11.0$ Hz), 3.46 (1H, d, $J = 11.0$ Hz), 2.75 (2H, brs), 2.08 (1H, ddd, $J = 14.8$, 7.5, 4.8 Hz), 1.90 (1H, ddd, $J = 14.8$, 6.3, 4.8 Hz), 1.24 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.2, 152.4, 115.6, 114.8, 72.5, 70.1, 65.4, 55.8, 37.6, 21.2; EI-HRMS *m*/*z*: 226.1199 (M^+); Calcd for $C_{12}H_{18}O_4$: 226.1200.

(*R*)-2-(2-Methyl-1,4-dioxaspiro[4.5]dec-2-yl)-ethanol (4). To a solution of diol **3** (4.00 g, 17.7 mmol) in cyclohexanone (50 mL) was added *p*-TsOH (673 mg, 3.54 mmol) at room temperature under argon. After being stirred for 5 min, the reaction mixture was quenched with satd. aq. $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under vacuum to give the crude cyclohexylidene ketal. This was dissolved in a 4 : 1-mixture of CH_3CN and H_2O (175 mL) and CAN (19.4 g, 35.4 mmol) was added at 0 °C under air. After being stirred for 5 min, the reaction mixture was quenched with satd. aq. $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane–Et_2O (1 : 1) to give **4** (3.30 g, 16.5 mmol, 93%). Yellow oil; $[\alpha]_D^{20} = +11.2$ ($c = 0.66$, $CHCl_3$). IR (neat) cm^{-1}: 3423, 2935, 2862, 1448, 1367, 1096; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.90 (2H, ddd, $J = 11.0$, 8.8, 3.8 Hz), 3.83 (1H, d, $J = 8.6$ Hz), 3.76 (1H, d, $J = 8.6$ Hz), 3.79–3.70 (1H, m), 2.89 (1H, brs), 1.91 (1H, ddd, $J = 14.3$, 8.8, 4.5 Hz), 1.72 (1H, ddd, $J = 14.3$, 5.5, 3.8 Hz), 1.68–1.50 (8H, m), 1.48–1.30 (2H, m), 1.33 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.4, 81.1, 74.4, 59.6, 41.0, 36.7, 36.4, 25.3, 25.1, 24.1, 23.9; EI-HRMS *m/z*: 200.1409 (M^+); Calcd for $C_{11}H_{20}O_3$: 200.1407.

(*R*)-(2-Methyl-1,4-dioxaspiro[4.5]dec-2-yl)-acetaldehyde (5). To a solution of **4** (412 mg, 2.05 mmol) in CH_2Cl_2 (20 mL) was added Dess–Martin periodinane (1.03 g, 2.42 mmol) at room temperature under air, and the reaction mixture was heated up to 40 °C for 1 h. After cooling to rt, the reaction mixture was quenched with satd. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane–Et_2O (2 : 3) to give **5** (389 mg, 1.95 mmol, 95%). Yellow oil; $[\alpha]_D^{20} = +32.7$ ($c = 2.67$, $CHCl_3$); IR (neat) cm^{-1}: 2936, 2862, 1723, 1449, 1367, 1007; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.79 (1H, s), 3.82 (1H, d, $J = 8.8$ Hz), 3.75 (1H, d, $J = 8.8$ Hz), 2.68 (1H, dd, $J = 15.6$, 1.8 Hz), 2.54 (1H, dd, $J = 15.6$, 2.2 Hz), 1.70–1.42 (8H, m), 1.42–1.20 (2H, m), 1.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.4, 110.4, 78.3, 73.7, 53.5, 36.6, 36.3, 25.7, 25.0, 23.9, 23.8; EI-HRMS *m/z*: 198.1205 (M^+); Calcd for $C_{11}H_{18}O_3$: 198.1250.

6-Methylhept-5-en-1-yn-4-ol (*rac*-6). To a solution of zinc powder (694 mg, 10.6 mmol, activated by treatment with 5% HCl[17]) in dry THF (20 mL) was added propargyl bromide (80% in toluene; 0.93 mL, 8.36 mmol) at 0 °C under argon. After being stirred for 1 h, to reaction mixture was added a solution of 3-methylbut-2-enal (370 mg, 4.40 mmol) in dry THF (10 mL) at 0 °C under argon. After being stirred for 15 min, the reaction mixture was filtered through Celite, the filtrate was quenched with satd. aq. $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane–Et_2O (3 : 1) to give *rac*-**6** (448 mg, 3.60 mmol, 82%). Colorless oil; IR (neat) cm^{-1}: 3384, 3300, 2916, 2862, 2119, 1674, 1445, 1377, 1034; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.23 (1H, d, $J = 8.6$ Hz), 4.54–4.46 (1H, m), 2.43–2.33 (2H, m), 2.02 (1H, t, $J = 2.5$ Hz), 1.72 (3H, s), 1.69 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.8, 125.9, 80.9, 70.5, 66.8, 27.7, 25.8, 18.4.

(*R*)-6-Methylhept-5-en-1-yn-4-ol ((*R*)-6). To a solution of *rac*-**6** (1.39 g, 11.2 mmol) in vinyl acetate (12 mL) was added NZL-101-LYO (485 mg) at room temperature under air. After being stirred for 65 h, the reaction mixture was filtered and NZL-101-LYO (417 mg, 86%) was recovered. The residue was concentrated under vacuum and purified by column chromatography using *n*-pentane–Et_2O (4 : 1) to give (*R*)-**6** (619 mg, 4.92 mmol, 44%, >99% ee). The ee was determined by chiral GC: FS-LIPODEX E (octakis-(2,6-di-*O*-pentyl-3-*O*-butyryl)-γ-cyclodextrin); start temperature, 50 °C; flow rate, 1.0 °C min^{-1}; retention time, (*R*)-**6** 30.0 min, (*S*)-**6** 28.6 min. Colorless oil; $[\alpha]_D^{20} = +38.6$ ($c = 1.05$, $CHCl_3$).

(*R*)-4-(*tert*-Butyldimethylsiloxy)-6-methylhept-5-en-1-yne. To a solution of (*R*)-**6** (350 mg, 2.81 mmol) in CH_2Cl_2 (9 mL) were added TBSCl (820 mg, 5.45 mmol), Et_3N (0.82 mL, 5.88 mmol) and DMAP (144 mg, 1.18 mmol) at room temperature under argon. After being stirred for 21 h, the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography using *n*-pentane–Et_2O (50 : 1) to give the silyl ether (630 mg, 2.64 mmol, 94%). Colorless oil; $[\alpha]_D^{20} = +3.5$ ($c = 1.15$, $CHCl_3$); IR (neat) cm^{-1}: 3307, 2956, 2856, 1472, 1376, 1254; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.14 (1H, d, $J = 8.5$ Hz), 4.54–4.47 (1H, m), 2.38 (1H, ddd, $J = 16.5$, 6.4, 2.5 Hz), 2.26 (1H, ddd, $J = 16.5$, 6.4, 2.5 Hz), 1.94 (1H, t, $J = 2.5$ Hz), 1.70 (3H, s), 1.66 (3H, s), 0.87 (9H, s), 0.05 (3H, s), 0.02 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 133.1, 128.0, 81.9, 69.3, 68.5, 28.7, 25.9, 25.8, 18.5, 18.3, −4.2, −4.6; EI-HRMS *m/z*: 238.1741 (M^+); Calcd for $C_{14}H_{26}OSi$: 238.1747.

(2*R*,6*R*)- and (2*S*,6*R*)-6-(*tert*-Butyldimethylsiloxy)-8-methyl-1-[(2*R*)-2-methyl-1,4-dioxaspiro[4.5]-dec-2-yl]-non-7-en-3-yn-2-ol (7–8). To a solution of (*R*)-4-(*tert*-butyldimethylsiloxy)-6-methylhept-5-en-1-yne (360 mg, 1.37 mmol) in dry THF (8 mL) was added *n*-BuLi (2.5 M in hexane; 0.77 mL, 0.77 mmol) at −80 °C under argon. After being stirred for 30 min at −80 °C, to reaction mixture was added the solution of **5** (272 mg, 1.51 mmol) in dry THF (6 mL) at −80 °C under argon. After warming up to −40 °C for 1 h, the reaction mixture was quenched with H_2O and extracted with Et_2O. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography using CH_2Cl_2–Et_2O (50 : 1) to give **7** (354 mg, 0.80 mmol, 59%) and **8** (170 mg, 0.38 mmol, 28%). **7**: colorless oil; $[\alpha]_D^{20} = +10.2$ ($c = 1.02$, $CHCl_3$); IR (neat) cm^{-1}: 3444, 2932, 2856, 1471, 1462, 1384; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.10 (1H, d, $J = 8.8$ Hz), 4.61–4.35 (1H, m), 4.45 (1H, dd, $J = 15.2$, 6.5 Hz), 3.87 (1H, d, $J = 8.3$ Hz), 3.71 (1H, d, $J = 8.3$ Hz), 2.83 (1H, brs), 2.39 (1H, ddd, $J = 16.5$, 6.5, 1.7 Hz), 2.27 (1H, ddd, $J = 16.5$, 6.5, 1.7 Hz), 2.01 (1H, dd, $J = 14.8$, 8.8 Hz), 1.95 (1H, dd, $J = 14.8$, 3.4 Hz), 1.69 (3H, s), 1.66–1.53 (8H, m), 1.64 (3H, s), 1.45–1.33 (2H, m), 1.34 (3H, s), 0.86 (9H, s), 0.04 (3H, s), 0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 132.9, 128.1, 110.0, 82.6, 82.0, 80.3, 73.8, 68.6, 59.8, 46.6, 37.0, 36.4, 28.9, 26.3, 25.9, 25.8, 25.1, 24.1, 24.0, 18.6, 18.3, −4.2, −4.6; EI-HRMS *m/z*: 436.3008 (M^+); Calcd for $C_{25}H_{44}O_4Si$: 436.3003. **8**: colorless oil; $[\alpha]_D^{20} = -18.5$ ($c = 1.00$, $CHCl_3$); IR (neat) cm^{-1}: 3450, 2932, 2856, 1471, 1461, 1384; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.09 (1H, d, $J = 8.8$ Hz), 4.74–4.69 (1H, m), 4.47 (1H, dd, $J = 15.0$, 6.5 Hz), 3.83 (1H, d, $J = 8.5$ Hz), 3.76 (1H, d, $J = 8.5$ Hz), 3.75 (1H, brs),

2.39 (1H, ddd, $J = 16.6, 6.5, 1.8$ Hz), 2.27 (1H, ddd, $J = 16.6, 6.5, 1.3$ Hz), 2.04 (1H, dd, $J = 14.2, 10.0$ Hz), 1.80 (1H, dd, $J = 14.2, 2.6$ Hz), 1.68 (3H, s), 1.68–1.49 (8H, m), 1.64 (3H, s), 1.42–1.34 (2H, m), 1.33 (3H, s), 0.85 (9H, s), 0.04 (3H, s), 0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 132.8, 128.2, 110.8, 82.3, 81.8, 80.5, 74.9, 68.0, 60.7, 46.9, 36.4, 28.9, 25.9, 25.8, 25.1, 24.5, 24.0, 23.9, 18.6, 18.3, −4.2, −4.6; EI-HRMS m/z: 436.2996 (M^+); Calcd for $C_{25}H_{44}O_4Si$: 436.3003.

(2*R*,6*R*)-6-(*tert*-Butyldimethylsiloxy)-8-methyl-1-[(2*R*)-2-methyl-1,4-dioxaspiro[4.5]-dec-2-yl]-non-7-en-3-yn-2-yl acetate (9). To a solution of **7** (167 mg, 0.38 mmol) in CH_2Cl_2 (2 mL) were added Ac_2O (44 µl, 0.46 mmol), Et_3N (70 µl, 0.50 mmol) and DMAP (3 mg, 0.02 mmol) at 0 °C under air. After being stirred for 30 min, the reaction mixture was quenched with satd. aq. NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane–AcOEt (15 : 1) to give **9** (162 mg, 0.340 mmol, 89%). Alternatively, to a solution of **8** (177 mg, 0.41 mmol) in dry toluene (4 mL) were added Ph_3P (127 mg, 0.49 mmol), AcOH (28 µl, 0.49 mmol) and DEAD (40% in toluene; 0.22 mL, 0.49 mmol) at −20 °C under argon. After being stirred for 1.5 h, the reaction mixture was quenched with satd. aq. $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane–AcOEt (20 : 1) to give **9** (160 mg, 0.336 mmol, 83%). Colorless oil; $[\alpha]_D^{20} = +51.9$ ($c = 1.00$, $CHCl_3$); IR (neat) cm^{-1}: 3155, 2935, 2857, 1737, 1471, 1383; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.44 (1H, dd, $J = 6.9, 6.0$ Hz), 5.08 (1H, d, $J = 8.8$ Hz), 4.43 (1H, dd, $J = 15.1, 6.4$ Hz), 3.87 (1H, d, $J = 8.5$ Hz), 3.63 (1H, d, $J = 8.5$ Hz), 2.37 (1H, ddd, $J = 16.3, 6.4, 1.5$ Hz), 2.25 (1H, ddd, $J = 16.3, 6.4, 1.8$ Hz), 2.15–2.07 (2H, m), 2.03 (3H, s), 1.68 (3H, s), 1.63 (3H, s), 1.65–1.51 (8H, m), 1.43–1.24 (2H, m), 1.25 (3H, s), 0.85 (9H, s), 0.03 (3H, s), 0.00 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.7, 132.9, 128.0, 109.7, 83.4, 79.0, 78.9, 74.1, 68.5, 61.5, 45.3, 36.8, 36.6, 28.9, 25.9, 25.7, 25.2, 25.0, 24.1, 24.0, 21.2, 18.5, 18.2, −4.3, −4.7; EI-HRMS m/z: 463.2869 ($[M - CH_3]^+$); Calcd for $C_{26}H_{43}O_5Si$: 463.2874.

(6*R*)-6-(*tert*-Butyldimethylsiloxy)-4,8-dimethyl-1-[(2*R*)-2-methyl-1,4-dioxaspiro[4.5]dec-2-yl]-nona-2,3,7-triene (10–11). To solution of CuI (4.90 g, 25.7 mmol) and LiBr (2.20 g, 25.7 mmol) in dry THF (15 mL) was added MeMgCl (8.6 mL, 25.7 mmol, 3 M in THF) at 0 °C under argon. After being stirred for 30 min, to the reaction mixture was added a solution of **9** (1.23 g, 2.57 mmol) in dry THF (11 mL) at 0 °C under argon. After being stirred for 5 h at room temperature, the reaction mixture was quenched with satd. aq. NH_4Cl and extracted with Et_2O. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane–AcOEt (50 : 1) to give a 3 : 2-mixture of **10** and **11** (868 mg, 2.00 mmol, 78%) as well as recovered starting material **9** (0.57 mmol, 22%). Colorless oil; IR (neat) cm^{-1}: 2932, 2856, 1965, 1448, 1366; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.13–5.04 (1H, m), 4.96–4.92 (1H, m), 4.47–4.38 (1H, m), 3.83 (1H, d, $J = 8.3$ Hz), 3.65 (1H, d, $J = 8.3$ Hz), 2.19 (2H, d, 7.5 Hz), 2.19–2.09 (1H, m), 2.07–1.96 (1H, m), 1.67 (6H, s), 1.68–1.52 (8H, m), 1.61 (3H, s), 1.38–1.28 (2H, m), 1.28 (3H, s), 0.85 (9H, s), 0.01 (3H, s), −0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.0, 204.7, 131.7, 131.6, 129.3, 109.9, 95.7, 95.4, 84.7, 84.5, 80.7, 80.6, 73.0, 72.9, 69.0, 68.9, 43.7, 43.3, 40.5, 40.4, 36.9, 36.8, 36.7, 26.0, 26.0, 25.8, 25.2, 25.1, 25.1, 24.0, 19.8, 19.5, 18.4, 18.4, 18.3, −4.0, −4.6; EI-HRMS m/z: 434.3211 (M^+); Calcd for $C_{26}H_{46}O_3Si$: 434.3210.

(4*R*)-2,6-Dimethyl-9-[(2*R*)-2-methyl-1,4-dioxaspiro[4.5]dec-2-yl]-nona-2,6,7-trien-4-ol (12–13). To a solution of a 3 : 2-mixture of **10**–**11** (204 mg, 0.469 mmol) in dry THF (2.4 mL) was added TBAF (1 M in THF; 0.66 mL, 0.66 mmol) at room temperature under air. After being stirred for 12 h, the reaction mixture was quenched with H_2O and extracted with Et_2O. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane–AcOEt (3 : 1) to give a 3 : 2-mixture of **12**–**13** (147 mg, 0.460 mmol, 98%). Colorless oil; IR (neat) cm^{-1}: 3434, 2932, 2860, 1965, 1447, 1383; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.22–5.16 (1H, m), 5.11–5.01 (1H, m), 4.52–4.44 (1H, m), 3.85–3.80 (1H, m), 3.67 (1H, d, $J = 8.2$ Hz), 2.28–1.93 (4H, m), 1.73–1.66 (6H, m), 1.67 (3H, s), 1.65–1.51 (8H, m), 1.42–1.29 (2H, m), 1.29 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.8, 203.7, 135.3, 135.0, 127.5, 127.4, 110.1, 110.0, 95.7, 95.7, 86.1, 86.0, 80.6, 80.4, 73.1, 73.1, 66.7, 66.6, 42.6, 42.5, 40.5, 40.3, 36.8, 36.7, 36.6, 36.6, 25.8, 25.2, 25.2, 25.1, 24.9, 24.0, 24.0, 23.9, 19.7, 19.4, 18.3; EI-HRMS m/z: 320.2334 (M^+); Calcd for $C_{20}H_{32}O_3$: 320.2346.

(2*R*)-2-Methyl-2-[(2*R*,6*R*)-4-methyl-6-(2-methylpropenyl)-5,6-dihydro-2*H*-pyran-2-ylmethyl]-1,4-dioxaspiro[4.5]decane (14) and (2*R*)-2-methyl-2-[(2*R*,6*S*)-4-methyl-6-(2-methylpropenyl)-5,6-dihydro-2*H*-pyran-2-ylmethyl]-1,4-dioxaspiro[4.5]decane (15). To a solution of a 3 : 2-mixture of **12**–**13** (52 mg, 0.162 mmol) in dry THF (2.5 mL) was added Ph_3PAuCl (4.0 mg, 0.008 mmol) and $AgBF_4$ (1.6 mg, 0.008 mmol) at room temperature under argon. After being stirred for 2 h, the reaction mixture was filtrated through Celite and the filtrate was concentrated under vacuum The residue was purified by column chromatography using cyclohexane–AcOEt (50 : 1) to give **14** (26 mg, 0.081 mmol, 50%) and **15** (18 mg, 0.057 mmol, 35%). **14**: colorless oil; $[\alpha]_D^{20} = -10.5$ ($c = 1.05$, $CHCl_3$); IR (neat) cm^{-1}: 2933, 2861, 1677, 1447, 1376; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.36 (1H, s), 5.18 (1H, d, $J = 7.5$ Hz), 4.22–4.11 (2H, m), 3.87 (1H, d, $J = 8.8$ Hz), 3.70 (1H, d, $J = 8.8$ Hz), 2.02–1.92 (1H, m), 1.83–1.70 (3H, m), 1.71 (3H, s), 1.66 (3H, s), 1.64 (3H, s), 1.64–1.48 (8H, m), 1.42–1.30 (2H, m), 1.31 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.4, 132.4, 126.3, 124.4, 108.9, 80.1, 74.1, 71.9, 71.9, 46.3, 37.2, 36.5, 36.0, 25.8, 25.3, 24.5, 24.1, 24.0, 23.0, 18.6; EI-HRMS m/z: 320.2339 (M^+); Calcd for $C_{20}H_{32}O_3$: 320.2346. **15**: colorless oil; $[\alpha]_D^{20} = +18.2$ ($c = 0.92$, $CHCl_3$); IR (neat) cm^{-1}: 2932, 2860, 1678, 1448, 1367; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.34 (1H, s), 5.20 (1H, d, $J = 8.3$ Hz), 4.39–4.31 (2H, m), 4.09 (1H, d, $J = 8.2$ Hz), 3.64 (1H, d, $J = 8.2$ Hz), 1.95–1.86 (3H, m), 1.76 (1H, d, $J = 3.2$ Hz), 1.71 (3H, s), 1.68 (6H, s), 1.65–1.50 (8H, m), 1.42–1.31 (2H, m), 1.30 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.2, 131.5, 125.5, 124.2, 109.4, 80.1, 72.2, 68.8, 65.1, 43.1, 37.4, 36.2, 35.4, 27.5, 25.8, 25.2, 24.1, 24.0, 23.3, 18.5.

(*R*,*R*,*R*)-Bejarol ((*R*,*R*,*R*)-1). To a solution of **14** (37 mg, 0.115 mmol) in MeOH (3 mL) was added *p*-TsOH (22 mg,

0.115 mmol) at room temperature under air. After being stirred for 24 h, the reaction mixture was quenched with satd. aq. $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane–Et_2O (1 : 5) to give the diol (23 mg, 0.098 mmol, 85%). Colorless oil; $[\alpha]_D^{20} = +9.8$ ($c = 1.02$, $CHCl_3$); IR (neat) cm^{-1}: 3421, 2968, 2911, 1445, 1382; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.24 (1H, s), 5.16 (1H, d, $J = 8.0$ Hz), 4.36 (1H, s), 4.23 (1H, ddd, $J = 10.5$, 8.0, 3.3 Hz), 3.57 (1H, d, $J = 11.0$ Hz), 3.40 (1H, d, $J = 11.0$ Hz), 2.08–1.98 (1H, m), 1.82–1.70 (3H, m), 1.71 (3H, s), 1.68 (3H, s), 1.66 (3H, s), 1.16 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.7, 132.8, 125.3, 123.5, 72.7, 72.6, 71.4, 69.6, 44.4, 35.8, 25.7, 25.1, 23.0, 18.5; EI-HRMS m/z: 240.1716 (M^+); Calcd for $C_{14}H_{24}O_3$: 240.1720.

To a solution of the diol (23 mg, 0.096 mmol) in CH_2Cl_2 (1 mL) was added Dess–Martin periodinane (53 mg, 0.125 mmol) at room temperature under air. After being stirred for 2 h, the reaction mixture was quenched with satd. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane–Et_2O (3 : 1) to give the aldehyde (18 mg, 0.073 mmol, 79%). Colorless oil; $[\alpha]_D^{20} = +44.1$ ($c = 1.02$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 9.73 (1H, s), 5.23 (1H, s), 5.16 (1H, d, $J = 7.8$ Hz), 4.36 (1H, s), 4.27 (1H, ddd, $J = 10.3$, 8.0, 3.5 Hz), 2.06 (1H, dd, $J = 14.6$, 3.5 Hz), 2.02–1.95 (1H, m), 1.82–1.73 (2H, m), 1.71 (3H, s), 1.66 (3H, s), 1.64 (3H, s), 1.22 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.1, 136.7, 133.0, 125.2, 122.7, 78.0, 72.6, 71.4, 43.2, 35.7, 25.7, 23.9, 22.9, 18.5; EI-HRMS m/z: 238.1559 (M^+); Calcd for $C_{14}H_{22}O_3$: 238.1563.

To solution of $Ph_3P^+CH_3Br^-$ (54 mg, 0.151 mmol) in dry THF (0.5 mL) was added *t*-BuOK (0.15 mL, 0.15 mmol, 1 M in THF) at 0 °C under argon. After being stirred for 30 min, to reaction mixture was added a solution of the aldehyde (18 mg, 0.076 mmol) in dry THF (0.5 mL) at 0 °C under argon. After being stirred for 5 h at room temperature, the reaction mixture was quenched with satd. aq. NH_4Cl and extracted with Et_2O. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane–Et_2O (10 : 1) to give (*R*,*R*,*R*)-**1** (17 mg, 0.072 mmol, 95%). Colorless oil; $[\alpha]_D^{20} = +53.2$ ($c = 0.68$, $CHCl_3$); IR (neat) cm^{-1}: 3490, 2970, 2910, 1674, 1446, 1383; ^1H NMR (500 MHz, $CDCl_3$) δ: 5.88 (1H, dd, $J = 17.1$, 10.8 Hz), 5.33 (1H, d, $J = 17.1$ Hz), 5.17 (1H, brs), 5.09 (1H, dd, $J = 10.8$, 1.6 Hz), 4.43 (1H, brs), 4.31 (1H, d, $J = 10.5$ Hz), 4.15 (1H, ddd, $J = 10.5$, 7.7, 3.3 Hz), 2.08–1.99 (1H, m), 1.81–1.74 (2H, m), 1.71 (3H, s), 1.66 (6H, s), 1.59 (1H, dd, $J = 14.6$, 2.2 Hz), 1.22 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.5, 137.2, 132.8, 125.5, 123.5, 112.5, 73.5, 73.4, 70.9, 46.1, 36.0, 29.6, 25.7, 23.0, 18.6; EI-HRMS m/z: 259.1669 ([M + Na]$^+$); Calcd for $C_{15}H_{24}O_2Na$: 259.1668.

(3*R*,5*S*,9*R*)-Bejarol ((3*R*,5*S*,9*R*)-1). To a solution of **15** (31 mg, 0.097 mmol) in MeOH (3 mL) was added *p*-TsOH (19 mg, 0.097 mmol) at room temperature under air. After being stirred for 24 h, the reaction mixture was quenched with satd. aq. $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane–Et_2O (1 : 5) to give the diol (19 mg, 0.082 mmol, 85%). Colorless oil; $[\alpha]_D^{20} = +29.5$ ($c = 1.03$, $CHCl_3$); IR (neat) cm^{-1}: 3425, 2967, 2913, 1445, 1383; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.27 (1H, s), 5.19 (1H, d, $J = 8.2$ Hz), 4.55 (1H, d, $J = 11.0$ Hz), 4.50 (1H, ddd, $J = 10.5$, 8.2, 4.8 Hz), 3.99 (1H, s), 3.41–3.33 (2H, m), 3.22 (1H, t, $J = 6.5$ Hz), 2.01–1.89 (3H, m), 1.79–1.60 (1H, m), 1.73 (3H, s), 1.71 (6H, s), 1.19 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.4, 132.0, 124.3, 123.0, 71.9, 70.6, 69.0, 65.7, 41.7, 35.2, 25.9, 24.9, 23.3, 18.4; EI-HRMS m/z: 240.1708 (M^+); Calcd for $C_{14}H_{24}O_3$: 240.1720.

To a solution of the diol (13 mg, 0.054 mmol) in CH_2Cl_2 (1 mL) was added Dess–Martin periodinane (36 mg, 0.086 mmol) at room temperature under air. After being stirred for 2 h, the reaction mixture was quenched with sat. $NaHCO_3$ aq. and extracted with CH_2Cl_2. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane–Et_2O (3 : 1) to give the aldehyde (9 mg, 0.038 mmol, 70%). Colorless oil; $[\alpha]_D^{20} = +7.8$ ($c = 0.55$, $CHCl_3$); IR (neat) cm^{-1}: 3466, 2970, 2915, 1729, 1383; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.46 (1H, s), 5.26 (1H, s), 5.13 (1H, d, $J = 8.0$ Hz), 4.42–4.35 (1H, m), 3.90 (1H, s), 2.09 (1H, dd, $J = 14.8$, 10.7 Hz), 1.97 (1H, dd, $J = 16.7$, 2.7 Hz), 1.83 (1H, dd, $J = 16.7$, 6.6 Hz), 1.78–1.73 (1H, m), 1.72 (3H, s), 1.68 (6H, s), 1.25 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.1, 136.5, 132.4, 124.6, 122.4, 76.7, 67.5, 66.0, 42.1, 35.2, 25.8, 23.7, 23.4, 18.4; EI-HRMS m/z: 238.1552 (M^+); Calcd for $C_{14}H_{22}O_3$: 238.1563.

To solution of $Ph_3P^+MeBr^-$ (24 mg, 0.067 mmol) in dry THF (0.5 mL) was added *t*-BuOK (67 μL, 0.067 mmol, 1 M in THF) at 0 °C under argon. After being stirred for 30 min, to the reaction mixture was added a solution of the aldehyde (8 mg, 0.034 mmol) in dry THF (0.5 mL) at 0 °C under argon. After being stirred for 5 h at room temperature, the reaction mixture was quenched with satd. aq. NH_4Cl and extracted with Et_2O. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane–Et_2O (10 : 1) to give (3*R*,5*S*,9*R*)-**1** (7 mg, 0.030 mmol, 88%). Colorless oil; $[\alpha]_D^{20} = +65.1$ ($c = 0.53$, $CHCl_3$); IR (neat) cm^{-1}: 3478, 2968, 2928, 2914, 1447, 1378; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.89 (1H, dd, $J = 17.4$, 10.8 Hz), 5.28 (1H, brs), 5.22 (1H, d, $J = 17.4$ Hz), 5.18 (1H, d, $J = 8.2$ Hz), 4.98 (1H, d, $J = 10.8$ Hz), 4.54 (1H, d, $J = 11.0$ Hz), 4.50 (1H, ddd, $J = 10.8$, 8.2, 4.5 Hz), 4.12 (1H, brs), 2.01–1.93 (1H, m), 1.88 (1H, dd, $J = 14.5$, 11.0 Hz), 1.75-1.68 (1H, m), 1.72 (6H, s), 1.70 (3H, s), 1.51 (1H, dd, $J = 14.5$, 2.3 Hz), 1.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.8, 137.5, 131.9, 124.5, 122.9, 111.1, 72.6, 69.8, 65.5, 43.7, 35.2, 26.6, 25.9, 23.3, 18.5; EI-HRMS m/z: 236.1771 (M^+); Calcd for $C_{14}H_{22}O_2$: 236.1770.

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