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ORIGINAL ARTICLE

Practical synthesis of the C-ring precursor of paclitaxel from 3-methoxytoluene

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The practical synthesis of the C-ring precursor of paclitaxel starting from 3-methoxytoluene is described. Lipase-catalyzed kinetic resolution of a substituted cyclohexane-1,2-diol, derived from 3-methoxytoluene in three steps, successfully afforded a desired enantiomer with >99% ee, which was transformed to a cyclohexenone. 1,4-Addition of a vinyl metal species, followed by Mukaiyama aldol reaction with formalin in the presence of a Lewis acid provided the known C-ring precursor of paclitaxel in a 10 g scale.
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INTRODUCTION

Paclitaxel (taxol, **1**) is a well-known natural diterpenoid that has been used as an anticancer drug.[1–3] The challenging structure as well as important biological activities of **1** have attracted much attention from the synthetic community,[4,5] and nine successful total and formal syntheses of **1** have been documented so far.[6–14] For the creation of novel anticancer agents, development of an efficient synthetic way to chiral **1** and its derivatives starting from readily available materials is still an important issue in the field of organic and medicinal chemistry. In 2015, our group reported the formal synthesis of **1**, in which Takahashi's oxetane intermediate **4** was synthesized using the novel SmI_2-mediated cyclization as the key transformation (Figure 1).[15,16] For the synthesis of **4**, we adopted the convergent approach based on the coupling of A ring **2** with C ring **3** by the Shapiro reaction.[7] The densely functionalized C ring **3** was constructed in a homochiral form from C-ring precursor **6**, which was prepared by the three-component coupling reaction of **5** with a vinyl metal species and formaldehyde.[15,17] The pivotal intermediate, cyclohexenone **5**, was prepared starting from commercially available tri-*O*-acetyl-D-glucal utilizing Hg^{2+}-mediated Ferrier carbocyclization reaction as the key reaction.[17] This chiral pool approach successfully provided chiral C-ring precursor **6** in good overall yield (29% from tri-*O*-acetyl-D-glucal), however, for the preparation of **5**, the relatively long-step reaction sequence (10 steps) and the time- and cost-consuming chromatographic purification processes (nine chromatographic separations) were required. For the large-scale synthesis and the development of more effective second-generation synthesis of **1**, it is necessary to establish the practical synthetic way to **6**. In this paper, we report a chiral and large-scale (10 g scale) synthesis of **6** utilizing the lipase-catalyzed kinetic resolution of a racemic cyclohexane-diol derived from 3-methoxytoluene. Results of three-component coupling reaction of **5** by Mukaiyama aldol reaction under various conditions are also described.

RESULTS AND DISCUSSION

For the practical synthesis of C-ring precursor **6**, we chose readily available 3-methoxytoluene as the starting material. Birch reduction of 3-methoxytoluene, followed by treatment with ethylene glycol and formic acid cleanly afforded ketal derivative **8**,[18–21] which, without isolation, was reacted with catalytic amount of OsO_4 in the presence of *N*-methylmorpholine *N*-oxide to give racemic diol *rac*-**9** in 83% yield from 3-methoxytoluene (Scheme 1).

For the resolution of *rac*-**9**, we chose lipase-catalyzed enantioselective acylation of racemic secondary alcohol in organic solvent,[22–24] in the standpoint of facile experimental operation. After the proper progress of reaction, catalysts are filtered off, and the simple chromatographic separation of ester and unreacted alcohol in the crude residue can provide enantiomerically enriched forms. First, *rac*-**9** was treated with vinyl acetate in the presence of various lipases. Although reactions with lipase AS, lipase AYS and lipase from wheat germ at 40 °C resulted in the no reaction, when *rac*-**9** was treated with lipase PS at 40 °C, enantiomerically enriched (−)-**9** was obtained in 43% yield with modest enantiomeric excess (ee) (Table 1, entry 1). It was found that a use of lipase AK gave better results, providing (−)-**9** in 41% yield with >99% ee (entry 2). After screening the reaction parameters, it was shown the reaction at 35 °C for 85 h gave (−)-**9** in 46% yield with >99% ee (entry 3). However, it was not easy to separate (−)-**9** from (+)-**10a** by silica-gel chromatography due to their similar polarities (SiO_2 TLC: R_f=0.26 for **9** and 0.41 for **10a** and EtOAc–hexane, 2:1 (v/v)), and repeated chromatographic operations were required for their complete separation. To facilitate the separation step, introduction of an acyl group with longer chain have been examined.[25,26] Thus, treatment of *rac*-**9** with vinyl laurate, instead of

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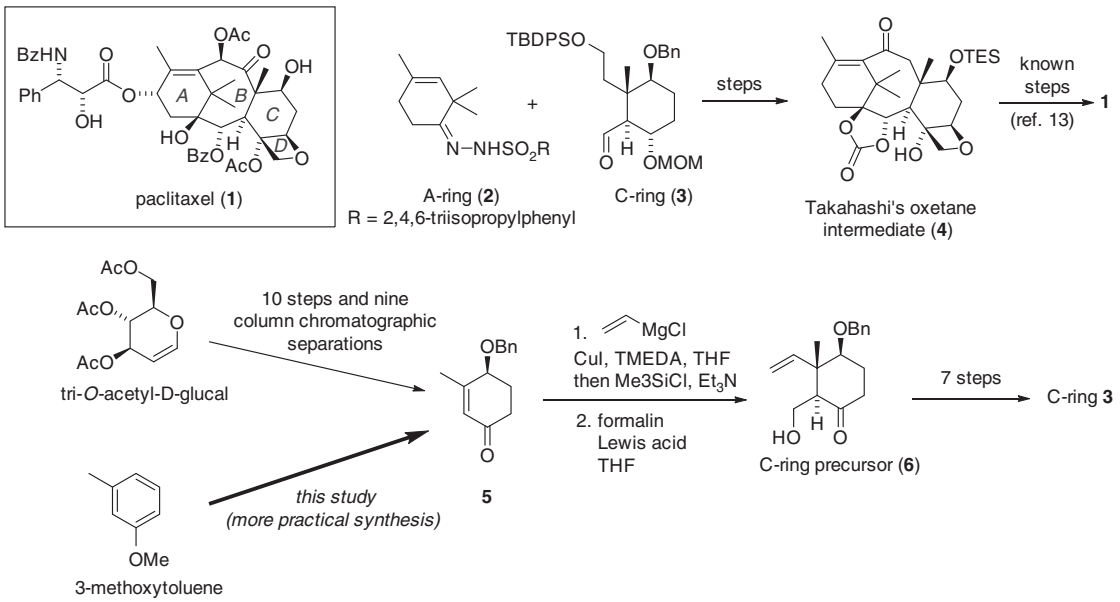
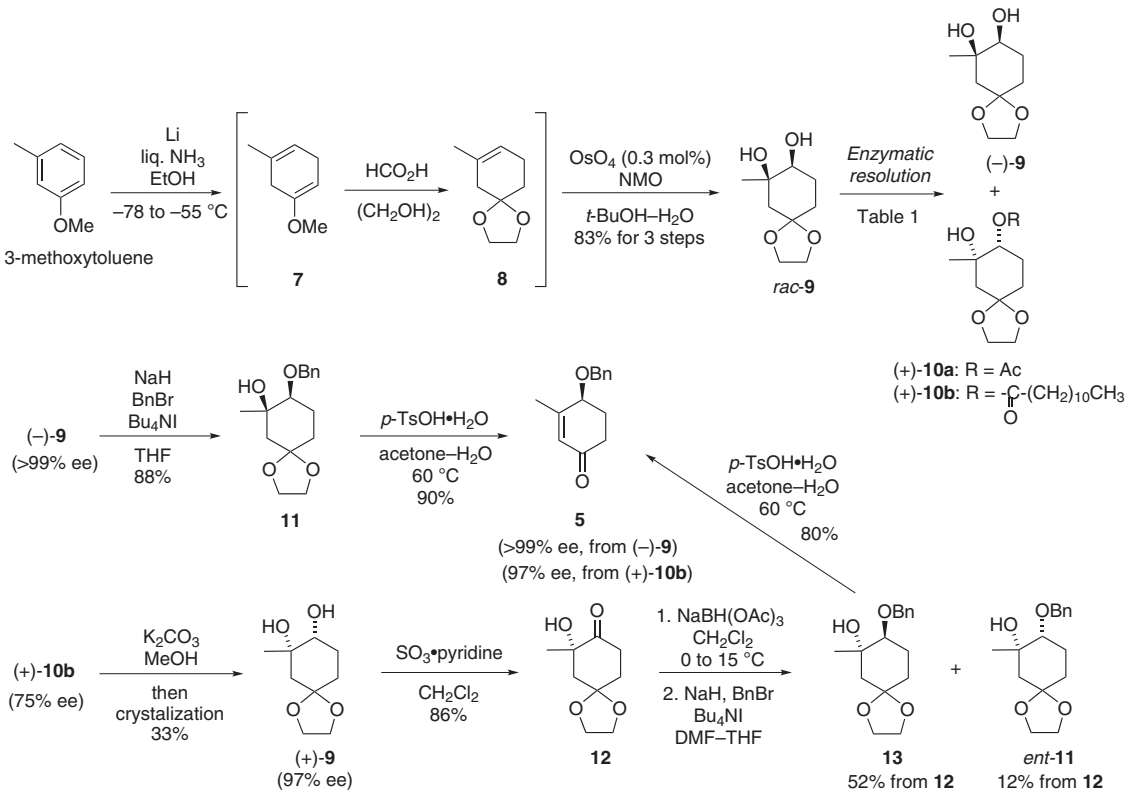


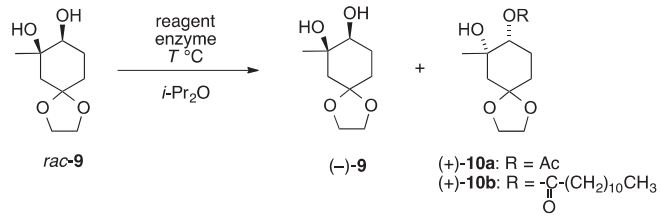
Figure 1 Outline of our first-generation synthesis of paclitaxel and the aim of this study (THF, tetrahydrofuran). A full color version of this figure is available at *The Journal of Antibiotics* journal online.



Scheme 1 Synthesis of cyclohexenone **5** from 3-methoxytoluene (THF, tetrahydrofuran).

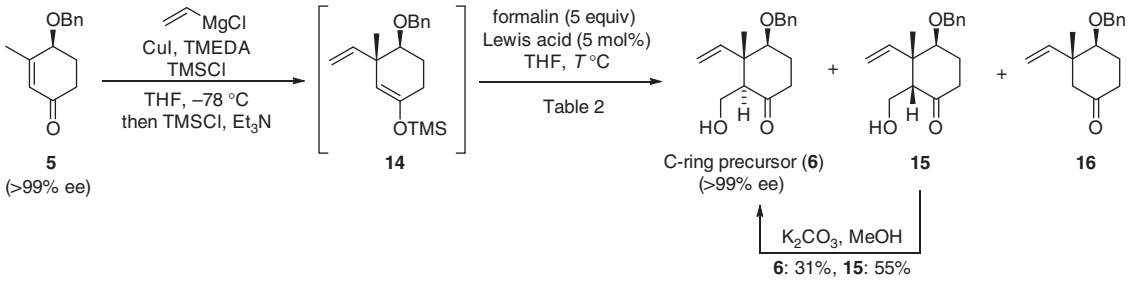
vinyl acetate, in the presence of lipase AK was attempted. Gratifyingly, the kinetic acylation smoothly took place to give (−)-**9** and (+)-**10b** in good yields with high ees, although longer reaction time was required (entry 6). As expected, (+)-**10b** was less polar than (+)-**10a**, and the separation of (−)-**9** from (+)-**10b** could be done without difficulty (SiO_2 TLC: $R_f = 0.26$ for **9**, 0.84 for **10b** and EtOAc–hexane, 2:1 (v/v)). To accelerate the reaction rate, the same reaction was carried out at 60 °C to give (−)-**9** in 49% yield with >99% ee in shorter reaction time (entry 7). By comparing the enantioselectivities (E values[22]) between entry 5 ($E = 32$, with vinyl acetate) and entry 7 ($E = 99$, with vinyl laurate), the selectivity depended upon the length of carbon chain in acylating agent, as had been observed in the literature.[27] On a 20 g scale (entry 8), the reaction at 60 °C afforded (−)-**9** with high enantiomeric purity (>99% ee) in 42% yield and (+)-**10b** (58% yield,

Table 1 Enzymatic resolution of *rac*-9[a]



						Yield % (ee %)[b]		
Entry	*Amount of rac-**9***	*Reagent*	*Lipase*	*T (°C)*	*Time (h)*	*(−)-**9***	*(+)-**10a***	*(+)-**10b***
1	50 mg	Vinyl acetate	Amano PS	40	145	43 (56)	52 (41)	–
2	51 mg	Vinyl acetate	Amano AK	40	147	41 (99)	59 (64)	–
3	53 mg	Vinyl acetate	Amano AK	35	85	46 (99)	54 (82)	–
4	51 mg	Vinyl acetate	Amano AK	45	30	54 (82)	46 (87)	–
5	50 mg	Vinyl acetate	Amano AK	60	19	38 (86)	54 (84)	–
6	48 mg	Vinyl laurate	Amano AK	35	168	48 (99)	–	50 (98)
7	2.11 g	Vinyl laurate	Amano AK	60	48	49 (99)	–	51 (90)
8	20.3 g	Vinyl laurate	Amano AK	60	156	42 (99)	–	58 (75)

Compound (−)-**9** was converted to (−)-**10a** by acetylation (Ac_2O, Et_3N and *N,N*-dimethyl-4-aminopyridine in CH_2Cl_2, at room temperature), and compound (+)-**10b** was converted to (+)-**10a** by basic methanolysis (K_2CO_3, MeOH), followed by acetylation. For detail, see the Experimental section.
[a]Compound *rac*-**9** in *i*-Pr_2O (0.1 M solution) was treated with reagent (3 equivalent) in the presence of enzyme (*ca.* 20 wt% to *rac*-**9**). Yield refers to the isolated yield after chromatographic separation.
[b]Ee was determined by HPLC analyzes with chiral stationary phase of (+)-**10a** and (−)-**10a**.



Scheme 2 Preparation of C-ring precursor **6** by three-component coupling reaction (TMS, trimethylsilyl; THF, tetrahydrofuran).

75% ee), and (−)-**9** could be isolated in pure form by a single-step silica-gel chromatography.

The secondary alcohol function in (−)-**9** was protected as a benzyl ether to give **11** in 88% yield. Treatment of **11** with *p*-toluenesulfonic acid in aqueous acetone cleanly afforded cyclohexenone **5**[28] in 90% yield. The HPLC analysis with chiral stationary phase of **5** showed that the ee of **5** was >99%. By this procedure, the desired cyclohexenone **5** was synthesized in six-step reactions from 3-methoxytoluene with four-column chromatographic separations, affording ample quantities (over 15 g) of optically pure **5** (28% overall yield from 3-methoxytoluene). This route was superior to the so far reported one, based on the esterase-catalyzed enantioselective hydrolysis of the corresponding acetate[28] in terms of scaled-up preparation.

Next, convergence of the undesired enantiomer (+)-**10b** to **5** was investigated. Basic methanolysis of (+)-**10b** afforded (+)-**9** in 96% yield (75% ee) as a mixture of oily product and crystalline residue, which was suspended in EtOAc–hexane, 1:20 (v/v). After removal of the crystals by filtration, the filtrate was concentrated to give enantiomerically enriched (+)-**9** (97% ee) as an oil in 33% yield. Oxidation of (+)-**9** with SO_3-pyridine[29] gave ketone **12** in 86% yield. Hydroxy-directed reduction of **12** with $NaBH(OAc)_3$,[30] followed by *O*-benzylation afforded **13** in 52% yield and *ent*-**11** in 12% yield, respectively. Acid treatment of **13** provided additional amount of **5** in 80% yield (97% ee, 6% overall yield from 3-methoxytoluene).

Finally, three-component coupling reaction of **5** with vinyl metal species and formalin was carried out. In the early stage of our paclitaxel synthesis, we adopted the three-component coupling reaction of **5** with higher order vinylcuprate and formaldehyde, which afforded **6** and **15** in 62% and 33% yields, respectively.[17] However, this procedure required strictly anhydrous conditions as well as a use of freshly prepared gaseous formaldehyde (generated by pyrolysis of paraformaldehyde), thus it was technically unsuitable for the larger-scale synthesis. We investigated the Mukaiyama aldol reaction of a silyl enol ether in the presence of rare earth metal triflates as the reaction could be conducted in aqueous media.[31,32]

Treatment of **5** (>99% ee) with vinyl magnesium chloride in the presence of CuI and *N,N,N′,N′*-tetramethylethylenediamine cleanly afforded a 1,4-addition product, which was trapped with trimethylsilyl (TMS) chloride to give TMS enol ether **14** (Scheme 2). Without purification, enol ether **14** was subjected to conditions for the Mukaiyama aldol reaction with commercially available 35% formalin as an electrophile. Lanthanoid and scandium triflates were examined as the promoter and the results are shown in Table 2. Reactions with $Gd(OTf)_3$ or $Yb(OTf)_3$[33] were found to be sluggish and gave the

Table 2 Mukaiyama aldol reaction of silyl enol ether 14 with formalin[a]

					Yield %[b]		
Entry	*Amount of* ***5***	*Lewis acid*	*T (°C)*	*Time (h)*	***6***	***15***	***16***
1	33 mg	$Gd(OTf)_3$	0	96	15	17	–[c]
2	33 mg	$Yb(OTf)_3$	0	96	22	19	–[c]
3	31 mg	$Sc(OTf)_3$	0	3	53	20	25
4	31 mg	$Sc(OTf)_3$	–20	8	51	15	27
5	31 mg	$Sc(OTf)_3$	rt[d]	0.5	49	21	29
6	15.2 g	$Sc(OTf)_3$	0	3.5	60	27	12

[a]Compound **14** in tetrahydrofuran (0.16 M solution) was reacted with 35% formalin (5 equivalent) in the presence of Lewis acid (5 mol%).
[b]Isolated yield from **5** after chromatographic purification.
[c]A mixture of **14** and **16** was obtained in *ca.* 50% yield.
[d]Room temperature.

desired product **6** in low yields with low stereoselectivities (entries 1 and 2). A reaction with $Sc(OTf)_3$[34] at 0 °C, however, proceeded smoothly to afford **6**, **15**, and protonated product **16** in 53%, 20% and 25% yields, respectively (entry 3). In a 15 g scale reaction (entry 6), the same reaction conditions afforded desired product **6** in 60% yield along with **15** (27%). Treatment of **15** with K_2CO_3 in MeOH provided **6** in 31% yield (8% from **5**): thus the desired isomer **6** was obtained in 68% combined yield after one-cycle epimerization of **15**. HPLC analysis with chiral stationary phase of **6** showed that compound **6** has >99% ee, indicating that the reaction proceeded without loss of enantiomeric purity. Compound **6** was transformed to C-ring **3** by the known procedure[15] to provide **3** in over 5 g scale.

In summary, a new and efficient synthetic way to the C-ring precursor **6** of paclitaxel, employing 3-methoxytoluene as the starting material and utilizing the effective lipase-catalyzed kinetic resolution, has been established. Compared with the previous chiral pool approach to **6** starting from tri-*O*-acetyl-D-glucal,[15,17] the present enzymatic procedure, although the overall yield of **6** was not improved (chiral pool approach: 29% yield, from tri-*O*-acetyl-D-glucal → enzymatic approach: 17% yield with >99% ee, 20% yield with >97% ee, from 3-methoxytoluene), reduced the reaction steps (12 → 8) and number of chromatographic purification processes (10 → 5). By this procedure, it is now possible to conduct the large-scale synthesis and prepare ample quantities of enantiomerically pure **6** in a short-term period. Further efforts for the development of the second-generation synthesis of paclitaxel **1** and its derivatives based on the procedure reported in this paper are ongoing in our laboratory.

EXPERIMENTAL PROCEDURE

General information

Anhydrous reactions were performed in oven-dried glassware fitted with rubber septa under an argon atmosphere. All distilled solvents, CH_2Cl_2 and MeOH were dried over activated **3**-Å molecular sieves. Tetrahydrofuran (dehydrated, stabilizer free) was purchased from Kanto Chemical Co., Inc (Tokyo, Japan). Commercial reagents were used without further purification. Lipases were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan) or Sigma-Aldrich Corporation (St Louis, MO, USA): Lipase AK Amano from *Pseudomonas fluorescens* (Wako), Lipase AS Amano from *Aspergillus niger* (Wako), Lipase AYS Amano from *Candida rugosa* (Wako), Lipase PS Amano SD from *Burkholderia cepacia* (Wako) and Lipase from wheat germ (Sigma-Aldrich). TLC was performed on Merck 60 F254 precoated silica-gel plates. Flash column chromatography was performed on silica gel (Silica Gel 60N; 63–210 mesh, Kanto Chemical Co., Inc or Wakogel 60N, 63–212 μm, Wako Pure Chemical Industries, Ltd.). NMR spectra (^1H at 500 MHz and ^{13}C at 125 MHz) were recorded with JEOL ECA-500 spectrometer (JEOL Ltd., Tokyo, Japan), or ^1H at 400 MHz and ^{13}C NMR at 100 MHz were recorded with JEOL ECS-400 spectrometer (JEOL Ltd.). Chemical shifts are reported in p.p.m. with reference to solvent signals (^1H NMR: $CDCl_3$ (7.26); ^{13}C NMR: $CDCl_3$ (77.16)). Optical rotations were measured with a JASCO P-2100 polarimeter (JASCO Corporation, Tokyo, Japan) with 0.5 dm tube and values of $[\alpha]_D$ are recorded in units of 10^{-1} deg·cm^2·g^{-1}. IR spectra were recorded using a BRUKER ALPHA FT-IR spectrometer (Bruker Corporation, Billerica, MA, USA). Mass spectra (EI) were measured with a JEOL GC-Mate spectrometer (JEOL Ltd.). Mass spectra (ESI–TOF) were measured with a Waters, LCT Premier XE (Waters Corporation, Milford, MA, USA). Melting points were measured with a Mitamura-Riken microhot stage.

*(7*RS*,8*SR*)-7-methyl-1,4-dioxaspiro[4.5]decane-7,8-diol (rac-**9**)*: Lithium (18.9 g, 2.72 mol) was added in portions to a solution of 3-methoxytoluene (50 ml, 397 mmol) in EtOH (300 ml, 5.2 mol) and liquid NH_3 (1.0 l) at −78 °C. After stirring for 20 min, the mixture was allowed to warm to −55 °C. After the blue color of the reaction mixture disappeared, the reaction mixture was cooled to −78 °C and quenched by the addition of solid NH_4Cl (20 g) at −78 °C. The mixture was allowed to warm to room temperature. After being stirred vigorously for 10 h, the resulting mixture was diluted with H_2O and extracted with pentane (3×). The combined organic extracts were washed with brine and dried over Na_2SO_4. The resulting solution was concentrated at 40 °C under atmospheric pressure to give crude 1-methoxy-5-methylcyclohexa-1,4-diene (**7**), which was used in the next reaction without purification: a colorless oil; IR ν_{max} (film) cm^{-1} 3048, 2997, 2965, 2946, 2888, 2824, 1701, 1666, 1439, 1390, 1224, 1135, 1023, 958, 771, 701; ^1H NMR (400 MHz, $CDCl_3$) δ 5.44–5.37 (m, 1H, 4-H), 4.67–4.61 (m, 1H, 2-H), 3.56 (s, 3-H, OCH_3), 2.83–2.73 (m, 2-H, 6-H_2 or 3-H_2), 2.65–2.57 (m, 2-H, 3-H_2 or 6-H_2), 1.73–1.67 (m, 3-H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0 (C), 130.5 (C), 118.9 (CH), 90.3 (CH), 53.8 (CH_3), 33.3 (CH_2), 26.9 (CH_2), 22.9 (CH_3); MS (EI) *m/z* 124 (M^+, 74%), 109 (M–CH_3, 100); HR-MS (EI): M^+ = 124.0883 *m/z*. Calcd for $C_8H_{12}O$ 124.0888 *m/z*.

Formic acid (16 ml, 410 mmol) was added to a solution of crude **7** in ethylene glycol (550 ml) at room temperature. After being stirred for 14 h, the reaction mixture was quenched by saturated aqueous $NaHCO_3$ (350 ml). The resulting mixture was extracted with pentane (3×). The combined organic extracts were washed with H_2O and brine, and dried over Na_2SO_4. The resulting solution was concentrated at 40 °C (at 980 hPa) to give crude 7-methyl-1,4-dioxaspiro[4.5]dec-7-ene (**8**), which was used in the next reaction without purification: a colorless oil; IR ν_{max} (film) cm^{-1} 2881, 1441, 1366, 1254, 1172, 1103, 1064, 949, 861, 805; ^1H NMR (400 MHz, $CDCl_3$) δ 5.45–5.39 (m, 1H, 8-H), 4.01–3.96 (m, 4-H, OCH_2CH_2O), 2.24–2.15 (m, 4-H, 6-H_2, 9-H_2), 1.75–1.65 (m, 5-H, CH_3, 10-H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.7 (C), 120.3 (CH), 108.5 (C), 64.4 (2×CH_2), 40.4 (CH_2), 30.6 (CH_2), 24.1 (CH_2), 23.4 (CH_3); HR-MS (ESI): $(M+H)^+$ = 155.1071 *m/z*. Calcd for $C_9H_{15}O_2$ 155.1072 *m/z*.

Osmium tetraoxide (0.20 M solution in *t*-BuOH, 6.0 ml, 1.2 mmol) was added to a solution of crude **8** in H_2O (140 ml) and *t*-BuOH (650 ml) at room temperature. Then, 4-methylmorpholine *N*-oxide (60.4 g, 516 mmol) was added to the solution at 0 °C. After stirring for 24 h at room temperature, the reaction mixture was quenched by solid $NaHSO_3$ (19.0 g). The resulting mixture was extracted with tetrahydrofuran–EtOAc, 1:1 (v/v), (7×). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica-gel column chromatography (EtOAc–hexane, 1:10–1:5 (v/v), silica gel 1.5 kg) to give 21.2 g of pure *rac*-**9** (28%) and 44.7 g of impure material. A part of impure material (39.1 g) was dissolved in a minimum of EtOAc (about 20 ml) at 60 °C. After standing for 12 h at room temperature, colorless crystals were separated by filtration to give 27.1 g of *rac*-**9** (36%). The mother liquor was concentrated to give 12.1 g of the residue. It was purified by recrystallization in the same way to give 7.56 g of *rac*-**9** (10%). The second filtrate (4.15 g) and the impure material (5.64 g) in the first chromatography were combined and repurified by silica-gel column chromatography to give 5.93 g of *rac*-**9** (8%) (61.79 g, 83% yield in total): R_f = 0.26 (EtOAc–hexane, 2:1 (v/v)); colorless crystals, m.p. 85.0–86.0 °C; IR ν_{max} (KBr) cm^{-1} 3476, 3398, 2986, 2950, 2931, 2895, 1448, 1419, 1397, 1356, 1229, 1120, 1083, 1060, 1013, 952, 840, 696; ^1H NMR (500 MHz, $CDCl_3$) δ 4.02–3.91 (m, 4-H, OCH_2CH_2O), 3.73 (brs, 1H, 7-OH), 3.33 (ddd, *J* = 10.7,

10.6, 4.9 Hz, 1H, 8-H), 2.03 (d, J=10.6 Hz, 1H, 8-OH), 1.94–1.86 (m, 2-H, 6-H and 9-H), 1.78–1.56 (m, 4-H, 6-H, 9-H, 10-H_2), 1.25 (d, J=0.9 Hz, 3-H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 108.7 (C), 74.0 (CH), 72.5 (C), 64.7 (CH_2), 64.4 (CH_2), 44.1 (CH_2), 33.2 (CH_2), 28.4 (CH_2), 26.2 (CH_3); HR-MS (ESI): $(M+Na)^+$=211.0936 *m/z*. Calcd for $C_9H_{16}O_4Na$ 211.0946 *m/z*.

*(7*R*,8S)-7-methyl-1,4-dioxaspiro[4.5]decane-7,8-diol [(−)-**9**] and (7S,8R)-7-hydroxy-7-methyl-1,4-dioxaspiro[4.5]decan-8-yl dodecanoate [(+)-**10b**]*: Vinyl laurate (84 ml, 320 mmol) was added to a mixture of rac-**9** (20.3 g, 108 mmol) and lipase AK (4.06 g) in *i*-Pr_2O (1.08 l) at room temperature. After stirring for 7 days at 60 °C, the reaction mixture was filtered through a pad of silica gel. The pad was washed with EtOAc (3 l). The resulting solution was concentrated, and the residue was purified by silica-gel column chromatography (EtOAc–hexane, 1:9–4:1 (v/v), silica gel 400 g) to give 8.62 g of (−)-**9** (42%, 99% ee) and 23.1 g of (+)-**10b** (58%, 75% ee). (−)-**9**: A colorless oil; $[\alpha]^{27}_D$ −15.3 (c 0.94, $CHCl_3$); IR ν_{max} (film) cm^{-1} 3451, 2950, 2887, 1120, 1086, 1062, 1011, 981, 951; HR-MS (ESI): $(M+Na)^+$=211.0938 *m/z*. Calcd for $C_9H_{16}O_4Na$ 211.0946 *m/z*. Other spectral data, see the preparation of rac-**9**. (+)-**10b**: R_f=0.84 (EtOAc–hexane, 2:1 (v/v)); white crystals, m.p. 47.9–49.8 °C; $[\alpha]^{25}_D$ +2.5 (c 1.08, $CHCl_3$); IR ν_{max} (film) cm^{-1} 3520, 2926, 2855, 1732, 1462, 1361, 1227, 1153, 1118, 1067; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.67 (dd, J=11.2, 4.6 Hz, 1H, 8-H), 4.04–3.90 (m, 4-H, OCH_2CH_2O), 3.86 (brs, 1H, OH), 2.42–2.31 (m, 2-H, $OCOCH_2$), 1.95–1.51 (m, 8-H, 6-H_2, 9-H_2, 10-H_2, CH_2), 1.36–1.20 (m, 16H, 8×CH_2), 1.17 (s, 3-H, 7-CH_3), 0.87 (t, J=6.9 Hz, 3-H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9 (C), 108.5 (C), 76.0 (CH), 71.5 (C), 64.8 (CH_2), 64.3 (CH_2), 44.6 (CH_2), 34.6 (CH_2), 33.1 (CH_2), 32.0 (CH_2), 29.7 (2×CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.0 (CH_3), 25.2 (CH_2), 24.3 (CH_2), 22.8 (CH_2), 14.2 (CH_3); HR-MS (ESI): $(M+Na)^+$=393.2615 *m/z*. Calcd for $C_{21}H_{38}O_5Na$ 393.2617 *m/z*.

*(7*R*,8S)-7-hydroxy-7-methyl-1,4-dioxaspiro[4.5]decan-8-yl acetate [(−)-**10a**] from (−)-**9** and determination of its ee*: *N*,*N*-dimethyl-4-aminopyridine (3.2 mg, 28 μmol) was added to a solution of (−)-**9** (49.1 mg, 261 μmol), triethylamine (89 μl, 0.64 mmol) and Ac_2O (62 μl, 0.65 mmol) in CH_2Cl_2 (5.2 ml) at room temperature. After maintaining for 4 h, the reaction mixture was quenched by saturated aqueous NH_4Cl (3 ml). The resulting mixture was extracted with $CHCl_3$ (2×). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The residue was filtered through a pad of silica gel (1.0 g). The pad was washed with EtOAc (30 ml). The resulting solution was concentrated. The residue was purified by HPLC (PEGASIL Silica 120–5, 250×20 mm, UV 210 nm, *i*-PrOH–hexane, 1:5 (v/v), 10 ml min^{-1}, room temperature=15.1 min) to give 54.3 mg of (−)-**10a** (90%): >99% ee by HPLC (CHIRALCEL OJ-H, 250×4.6 mm, UV 210 nm, *i*-PrOH–hexane, 1:6 (v/v), 1.0 ml min^{-1}, (+)-**10a**: room temperature=8.6 min (not detected), (−)-**10a**: room temerature=11.1 min); R_f=0.41 (EtOAc–hexane, 2:1 (v/v)); a colorless oil; $[\alpha]^{27}_D$ −6.6 (*c* 0.98, $CHCl_3$); IR ν_{max} (film) cm^{-1} 3504, 2958, 2887, 1734, 1368, 1243, 1121, 1087, 1045, 949, 842; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.67 (dd, J=11.2, 4.9 Hz, 1H, 8-H), 4.04–3.88 (m, 5-H, OCH_2CH_2O, OH), 2.12 (s, 3-H, $OCOCH_3$), 1.96–1.65 (m, 6-H, 6-H_2, 9-H_2, 10-H_2), 1.18 (s, 3-H, 7-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2 (C), 108.5 (C), 76.4 (CH), 71.5 (C), 64.8 (CH_2), 64.4 (CH_2), 44.6 (CH_2), 33.2 (CH_2), 26.0 (CH_3), 24.2 (CH_2), 21.4 (CH_3); HR-MS (ESI): $(M+Na)^+$=253.1049 *m/z*. Calcd for $C_{11}H_{18}O_5Na$ 253.1052 *m/z*.

*(7*R*,8S)-8-benzyloxy-7-methyl-1,4-dioxaspiro[4.5]decan-7-ol (**11**)*: Tetrabutylammonium iodide (3.28 g, 8.88 mmol) was added to a mixture of (−)-**9** (16.7 g, 88.7 mmol), benzyl bromide (12 ml, 98 mmol) and sodium hydride (63%, 10.1 g, 265 mmol) in tetrahydrofuran (240 ml) at 0 °C. The solution was allowed to warm up to room temperature. After stirring for 1 day, the reaction mixture was quenched with brine (200 ml) at 0 °C. The resulting mixture was extracted with EtOAc (3×). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by silica-gel column chromatography (EtOAc–hexane, 1:7 (v/v), silica gel 740 g) to give 21.8 g of **11** (88%): a colorless oil; $[\alpha]^{26}_D$ +48.7 (*c* 0.99, $CHCl_3$); IR ν_{max} (film) cm^{-1} 3518, 2952, 2879, 1125, 1085, 739, 699; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.25 (m, 5-H, C_6H_5), 4.70 (d, J=11.7 Hz, 1H, PhC*H*HO-), 4.49 (d, J=11.7 Hz, 1H, PhC*H*HO–), 4.01–3.88 (m, 4-H, OCH_2CH_2O), 3.42 (s, 1H, OH), 3.22 (dd, J=8.0, 4.0 Hz, 1H, 8-H), 1.94–1.77 (m, 4-H, 6-H, 9-H_2, 10-H), 1.68 (dd, J=14.0, 0.9 Hz, 1H, 6-H), 1.52 (dddd, J=12.9, 9.4, 4.3, 0.9 Hz, 1H, 10-H), 1.26 (s, 3-H, 7-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5 (C), 128.4 (2×CH), 127.9 (2×CH), 127.7 (CH), 108.6 (C), 80.9 (CH), 72.2 (C), 71.2 (CH_2), 64.4 (CH_2), 64.2 (CH_2), 44.6 (CH_2), 31.6 (CH_2), 26.0 (CH_3), 23.0 (CH_2); HR-MS (ESI): $(M+Na)^+$=301.1403 *m/z*. Calcd for $C_{16}H_{22}O_4Na$ 301.1416 *m/z*.

*(S)-4-benzyloxy-3-methylcyclohex-2-en-1-one (**5**)*: *p*-Toluenesulfonic acid monohydrate (14.9 g, 78.3 mmol) was added to a solution of **11** (21.8 g, 78.4 mmol) in acetone (390 ml) and H_2O (390 ml) at room temperature. After stirred for 72 h at 60 °C, the reaction solution was quenched by solid $NaHCO_3$ (28 g) at 0 °C. The resulting mixture was extracted with EtOAc (3×). The combined organic extracts were washed with H_2O and brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica-gel column chromatography (EtOAc–hexane, 1:7 (v/v), silica gel 510 g) to give 15.2 g of **5** (90%): >99% ee by HPLC (CHIRALCEL OD-H, 250×4.6 mm, UV 254 nm, *i*-PrOH–hexane, 1:22 (v/v), 1.0 ml min^{-1}, *ent*-**5**: room temperature=16.1 min (peak area: 0.3%), **5**: room temperature=18.6 min (peak area: 99.7%)); a colorless oil; $[\alpha]^{26}_D$ +8.1 (*c* 1.01, $CHCl_3$); IR ν_{max} (film) cm^{-1} 2951, 2869, 1672, 1092, 1068, 740, 699; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5-H, C_6H_5), 5.86 (q, J=0.9 Hz, 1H, 2-H), 4.74 (d, J=11.7 Hz, 1H, PhC*H*HO–), 4.56 (d, J=11.7 Hz, 1H, PhC*H*HO–), 4.11–4.05 (m, 1H, 4-H), 2.64–2.56 (m, 1H, 6-H), 2.35–2.22 (m, 2-H, 5-H, 6-H), 2.16–2.06 (m, 1H, 5-H), 2.02 (dd, J=1.2, 0.9 Hz, 3-H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8 (C), 161.4 (C), 138.0 (C), 128.6 (2×CH), 128.1 (CH), 128.0 (2×CH), 127.8 (CH), 75.1 (CH), 71.9 (CH_2), 34.5 (CH_2), 27.7 (CH_2), 21.2 (CH_3); HR-MS (ESI): $(M+Na)^+$=239.1040 *m/z*. Calcd for $C_{14}H_{16}O_2Na$ 239.1048 *m/z*.

*(7S,8R)-7-methyl-1,4-dioxaspiro[4.5]decane-7,8-diol [(+)-**9**]*: Potassium bicarbonate (5.39 g, 39.0 mmol) was added to the solution of (+)-**10b** (2.89 g, 7.80 mmol, 75% ee) in MeOH (78 ml) at room temperature. After stirring for 18 h, the reaction mixture was diluted with H_2O (20 ml). The resulting mixture was extracted with EtOAc (11×). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica-gel column chromatography (EtOAc/hexane 1:8–2:1, silica gel 29 g) to give 1.41 g of (+)-**9** (96%) as a mixture of slightly yellow crystals and oil, which was co-distilled twice with hexane (5 ml). The resulting residue was suspended in EtOAc–hexane (1:20 (v/v), 21 ml) and gently stirred for 30 s. The crystals were removed by filtration and washed with hexane (5 ml). The filtrate was concentrated to give 478 mg of enantiomerically enriched (+)-**9** (33%, 97% ee): a colorless oil; $[\alpha]^{24}_D$ +13.7 (*c* 1.01, $CHCl_3$); HR-MS (ESI): $(M+Na)^+$=211.0938 *m/z*. Calcd for $C_9H_{16}O_4Na$ 211.0946 *m/z*. Other spectral data, see the preparation of *rac*-**9**. Compound (+)-**9** was converted to (+)-**10a** by the same procedure as described for the preparation of (−)-**10** from (−)-**9**, and ee of (+)-**10a** was determined by HPLC analysis (CHIRALCEL OJ-H, 250×4.6 mm, UV 210 nm, *i*-PrOH–hexane, 1:6 (v/v), 1.0 ml min^{-1}).

*(S)-7-hydroxy-7-methyl-1,4-dioxaspiro[4.5]decan-8-one (**12**)*: Sulfur trioxide–pyridine complex (2.50 g, 15.7 mmol) was added to a solution of (+)-**9** (1.52 g, 8.08 mmol) and triethylamine (6.5 ml, 47 mmol) in DMSO (10 ml) and CH_2Cl_2 (71 ml) at room temperature. After maintaining for 17 h, the solution was quenched by H_2O (30 ml). The resulting mixture was extracted with $CHCl_3$ (3×). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by silica-gel column chromatography (EtOAc–hexane, 1:9 to 1:4 (v/v), silica gel 150 g) to give 1.29 g of **12** (86%): a slightly yellow oil; $[\alpha]^{26}_D$ − 32.6 (*c* 0.98, $CHCl_3$); IR ν_{max} (film) cm^{-1} 3482, 2967, 2934, 2890, 1720, 1110, 1069, 1027; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (s, 1H, OH), 4.08–3.96 (m, 4-H, OCH_2CH_2O), 2.75–2.60 (m, 2-H, 9-H_2), 2.18 (dd, J=13.9, 2.5 Hz, 1H, 6-H), 2.11–1.95 (m, 3-H, 6-H, 10-H_2), 1.41 (s, 3-H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.1 (C), 107.4 (C), 74.9 (C), 64.9 (CH_2), 64.6 (CH_2), 47.7 (CH_2), 35.4 (CH_2), 33.9 (CH_2), 25.8 (CH_3); HR-MS (ESI): $(M+H)^+$=187.0968 *m/z*. Calcd for $C_9H_{15}O_4$ 187.0970 *m/z*.

*(7S,8S)-8-(benzyloxy)-7-methyl-1,4-dioxaspiro[4.5]decan-7-ol (**13**)*: Sodium triacetoxyborohydride (128 mg, 0.605 mmol) was added to a solution of **12** (74.4 mg, 400 μmol) in CH_2Cl_2 (8.0 ml) at 0 °C. After stirring for 3 h at 15 °C, further sodium triacetoxyborohydride (127 mg, 0.599 mmol) was added to the reaction mixture at 0 °C. After stirring for 2 h at 15 °C, further sodium triacetoxyborohydride (84.7 mg, 400 μmol) was added to the reaction mixture at 0 °C. After stirring for 2 h at 15 °C, the reaction mixture was quenched by saturated aqueous $NaHCO_3$ (8 ml) at 0 °C. The resulting mixture was extracted with EtOAc (10×). The combined organic extracts were washed with H_2O

and brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica-gel column chromatography (EtOAc/hexane 1:4–2:1, silica gel 2.3 g) to give an inseparable mixture of (7*S*,8*S*)-7-methyl-1,4-dioxaspiro[4.5]decan-7,8-diol and its 8-epimer, which was used in the next reaction without further purification. Benzyl bromide (52 µl, 440 µmol) was added to a solution of a mixture of (7*S*,8*S*)-7-methyl-1,4-dioxaspiro[4.5]decan-7,8-diol and its 8-epimer, tetrabutylammonium iodide (14.7 mg, 39.8 µmol) and sodium hydride (64%, 44.6 mg, 1.19 mmol) in DMF–tetrahydrofuran (1:5, 1.1 ml) at 0 °C. The solution was allowed to warm to room temperature. After stirring for 12 h, the reaction mixture was quenched with brine (3 ml) at 0 °C. The resulting mixture was extracted with EtOAc (6×). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by silica-gel column chromatography (EtOAc/hexane 1:8, silica gel 7.5 g) to give 58.1 mg of **13** (52% from **12**) and 13.1 mg of *ent*-**11** (12% from **12**): **13**: a colorless oil; $[\alpha]^{24}_D$ +67.8 (*c* 0.92, $CHCl_3$); IR (film) 3509, 2962, 2932, 2882, 1195, 1089, 966, 738, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.25 (m, 5-H, C_6H_5), 4.62 (d, *J*=11.7 Hz, 1H, PhC*H*HO–), 4.44 (d, *J*=11.7 Hz, 1H, PhC*H*HO–), 4.07 (brs, 1H, OH), 4.01–3.92 (m, 4-H, OCH_2CH_2O), 3.28 (dd, *J*=2.6, 2.6 Hz, 1H, 8-H), 2.00 (d, *J*=13.8 Hz, 1H, 6-H), 1.97–1.81 (m, 3-H, 9-H_2, 10-H), 1.60 (ddd, *J*=13.8, 2.6, 0.9 Hz, 1H, 6-H), 1.53 (dddd, *J*=12.0, 3.7, 3.2, 2.6 Hz, 1H, 10-H), 1.26 (s, 3-H, 7-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9 (C), 128.4 (2xCH), 127.6 (3xCH), 109.7 (C), 79.9 (CH), 73.0 (C), 71.3 (CH_2), 64.5 (CH_2), 64.2 (CH_2), 41.1 (CH_2), 28.9 (CH_2), 26.0 (CH_3), 21.9 (CH_2); HR-MS (ESI): $(M+Na)^+$=301.1419 *m/z*. Calcd for $C_{16}H_{22}O_4Na$ 301.1416 *m/z*. *ent*-**11**: a colorless oil; $[\alpha]^{25}_D$ –47.5 (*c* 1.14, $CHCl_3$).

(S)-4-(benzyloxy)-3-methylcyclohex-2-en-1-one (5) from ***13*****:** *p*-Toluenesulfonic acid monohydrate (90.7 mg, 477 µmol) was added to a solution of **13** (130 mg, 466 µmol) in acetone (2.3 ml) and H_2O (2.3 ml) at room temperature. After stirred for 3 days at 60 °C, the reaction solution was quenched by solid $NaHCO_3$ (123 mg) at 0 °C. The resulting mixture was extracted with EtOAc (3×). The combined organic extracts were washed with H_2O and brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica-gel column chromatography (EtOAc–hexane, 1:6 (v/v), silica gel 10 g) to give 80.7 mg of **5** (80%): 97% ee by HPLC (CHIRALCEL OD-H, 250×4.6 mm, UV 254 nm, *i*-PrOH–hexane, 1:22 (v/v), 1.0 ml min^{-1}).

*(2R,3S,4S)-4-benzyloxy-2-(hydroxymethyl)-3-methyl-3-vinylcyclohexan-1-one (****6****), its (2R,3S,4S)-isomer (****15****) and (3R,4S)-4-benzyloxy-3-methyl-3-vinylcyclohexan-1-one (****16****)*: Vinyl magnesium chloride (1.5 M in tetrahydrofuran, 82 ml, 120 mmol) was added to a mixture of **5** (15.2 g, 70.3 mmol), CuI (4.02 g, 21.1 mmol), *N,N,N',N'*-tetramethylethylenediamine (21 ml, 140 mmol) and trimethylsilyl chloride (22 ml, 180 mmol, neutralized over 10 mg of poly-4-vinyl-pyridine) in tetrahydrofuran (230 ml) at −78 °C. After maintaining for 30 min, trimethylsilyl chloride (31 ml, 250 mmol) and Et_3N (34 ml, 250 mmol) were added to the solution at −78 °C. This solution was allowed to warm to room temperature. After maintaining for 14 h, the solution was cooled to −78 °C and then quenched by saturated aqueous NH_4Cl (200 ml). The resulting mixture was extracted with hexane (3×). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. The solution was filtered through a pad of Celite (300 cm^3). The pad was washed with hexane (1.5 l). The resulting solution was concentrated to give a crude TMS enol ether **14**, which was used in the next reaction without purification.

Scandium trifluoromethanesulfonate (1.73 g, 3.52 mmol) was added to a solution of crude **14** and formalin (35%, 28 ml, 350 mmol) in tetrahydrofuran (440 ml) at 0 °C. After maintaining for 3.5 h, the reaction solution was quenched by saturated $NaHCO_3$ (300 ml) at 0 °C. The resulting mixture was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica-gel column chromatography (EtOAc–hexane, 1:10–1:1 (v/v), silica gel 580 g) to give 11.5 g of **6** (60%), 5.29 g of **15** (27%) and 2.08 g of **16** (12%): **6**: >99% ee by HPLC (CHIRALCEL OD-H, 250×4.6 mm, UV 254 nm, *i*-PrOH–hexane, 1:30 (v/v), 1.0 ml min^{-1}, *ent*-**6**: room temperature=21.5 min (not detected), **6**: room temperature=23.2 min); a colorless oil; $[\alpha]^{26}_D$ +10.3 (*c* 0.99, $CHCl_3$); IR ν_{max} (film) cm^{-1} 3447, 2947, 1711, 1100, 1025, 738, 698; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5-H, C_6H_5), 5.80 (dd, *J*=17.5, 10.6 Hz, 1H, C*H*=CH_2), 5.23 (dd, *J*=10.6, 0.6 Hz, 1H, CH=C*H*H), 5.12 (dd, *J*=17.5, 0.6 Hz, 1H, CH=C*H*H), 4.62 (d, *J*=11.7 Hz, 1H, PhC*H*HO–), 4.54 (d, *J*=11.7 Hz, 1H, PhC*H*HO–), 3.92 (dd, *J*=11.6, 8.6 Hz, 1H, C*H*HOH), 3.64 (dd, *J*=10.6, 4.3 Hz, 1H, 4-H), 3.49 (dd, *J*=11.6, 2.9 Hz, 1H, C*H*HOH), 2.49 (ddd, *J*=8.6, 2.9, 1.2 Hz, 1H, 2-H), 2.48 (brs, 1H, OH), 2.46 (ddd, *J*=15.6, 5.4, 3.4 Hz, 1H, 6-H), 2.39 (dddd, *J*=15.6, 12.8, 6.4, 1.2 Hz, 1H, 6-H), 2.23 (dddd, *J*=13.5, 6.4, 4.3, 3.4 Hz, 1H, 5-H), 1.88 (dddd, *J*=13.5, 12.8, 10.6, 5.4 Hz, 1H, 5-H), 0.98 (s, 3-H, 3-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.4 (C), 143.8 (CH), 138.4 (C), 128.4 (2×CH), 127.8 (CH), 127.7 (2×CH), 115.2 (CH_2), 81.1 (CH), 72.4 (CH_2), 58.9 (CH_2), 58.0 (CH), 47.9 (C), 38.8 (CH_2), 26.6 (CH_2), 13.1 (CH_3); HR-MS (ESI): $(M+Na)^+$=297.1460 *m/z*. Calcd for $C_{17}H_{22}O_3Na$ 297.1467 *m/z*. **15**: a colorless oil; $[\alpha]^{24}_D$ +14.4 (*c* 0.99, $CHCl_3$); IR ν_{max} (film) cm^{-1} 3469, 2968, 2941, 2882, 1702, 1071, 1038, 1029, 739, 698; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.29 (m, 5-H, C_6H_5), 5.64 (dd, *J*=17.3, 10.9 Hz, 1H, C*H*=CH_2), 5.11 (dd, *J*=10.9, 0.9 Hz, 1H, CH=C*H*H), 5.06 (dd, *J*=17.3, 0.9 Hz, 1H, CH=C*H*H), 4.72 (d, *J*=11.5 Hz, 1H, PhC*H*HO–), 4.54 (d, *J*=11.5 Hz, 1H, PhC*H*HO–), 3.91 (ddd, *J*=11.8, 9.2, 3.4 Hz, 1H, C*H*HOH), 3.51 (ddd, *J*=11.8, 10.3, 3.4 Hz, 1H, C*H*HOH), 3.24 (dd, *J*=2.0, 2.0 Hz, 1H, 4-H), 3.05 (ddd, *J*=9.2, 3.4, 0.9 Hz, 1H, 2-H), 2.73 (ddd, *J*=14.2, 14.0, 6.9 Hz, 1H, 6-H), 2.62 (dd, *J*=10.3, 3.4 Hz, 1H, OH), 2.28 (dddd, *J*=14.2, 5.2, 3.2, 0.9 Hz, 1H, 6-H), 2.20 (dddd, *J*=14.3, 6.9, 3.2, 2.0 Hz, 1H, 5-H), 2.00 (dddd, *J*=14.3, 14.0, 5.2, 2.0 Hz, 1H, 5-H), 1.32 (s, 3-H, 3-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.3 (C), 140.6 (CH), 138.5 (C), 128.6 (2×CH), 127.9 (CH), 127.6 (2×CH), 116.2 (CH_2), 81.8 (CH), 71.8 (CH_2), 59.0 (CH_2), 56.0 (CH), 48.8 (C), 36.8 (CH_2), 25.2 (CH_2), 21.2 (CH_3); HR-MS (ESI): $(M+Na)^+$=297.1462 *m/z*. Calcd for $C_{17}H_{22}O_3Na$, 297.1467 *m/z*. **16**: a colorless oil; $[\alpha]^{25}_D$ +41.3 (*c* 1.07, $CHCl_3$); IR ν_{max} (film) cm^{-1} 2958, 2870, 1710, 1092, 1073, 739, 698; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41–7.28 (m, 5-H), 5.71 (dd, *J*=17.5, 10.6 Hz, 1H, C*H*=CH_2), 5.05 (d, *J*=10.6 Hz, 1H, CH=C*H*H), 5.04 (d, *J*=17.5 Hz, 1H, CH=C*H*H), 4.71 (d, *J*=11.7 Hz, 1H, PhC*H*HO–), 4.54 (d, *J*=11.7 Hz, 1H, PhC*H*HO–), 3.44 (dd, *J*=4.0, 2.3 Hz, 1H, 4-H), 2.61 (d, *J*=14.6 Hz, 1H, 2-H), 2.51 (dddd, *J*=14.8, 12.0, 6.3, 0.9 Hz, 1H, 6-H), 2.40–2.34 (m, 1H, 2-H), 2.22–2.15 (m, 1H, 6-H), 2.10 (dddd, *J*=14.3, 6.3, 4.6, 4.0 Hz, 1H, 5-H), 1.95 (dddd, *J*=14.3, 12.0, 5.2, 2.3 Hz, 1H, 5-H), 1.16 (s, 3-H, 3-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.2 (C), 144.0 (CH), 138.6 (C), 128.5 (2×CH), 127.8 (CH), 127.6 (2×CH), 114.3 (CH_2), 79.2 (CH), 71.6 (CH_2), 47.3 (CH_2), 46.1 (C), 36.1 (CH_2), 25.0 (CH_2), 24.2 (CH_3); HR-MS (ESI): $(M+H)^+$=245.1532 *m/z*. Calcd for $C_{16}H_{21}O_2$ 245.1542 *m/z*.

Base-induced epimerization of ***15*****:** To a solution of **15** (4.66 g, 17.0 mmol) in MeOH (140 ml) at room temperature was added K_2CO_3 (305 mg, 2.21 mmol), and the resulting mixture was stirred for 2.5 h. After addition of 1M HCl (100 ml), products were extracted with EtOAc (3×). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica-gel column chromatography (EtOAc–hexane, 1:7–1:4 (v/v), silica gel 230 g) to give 1.45 g of **6** (31%) and 2.56 g of the starting material (**15**, 55%).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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