Asymmetric Reduction of an Enantiomerically Pure γ-Polyketone

Kyoko Nozaki,* Naoyuki Kosaka, Shin-ichi Muguruma, and Tamejiro Hiyama

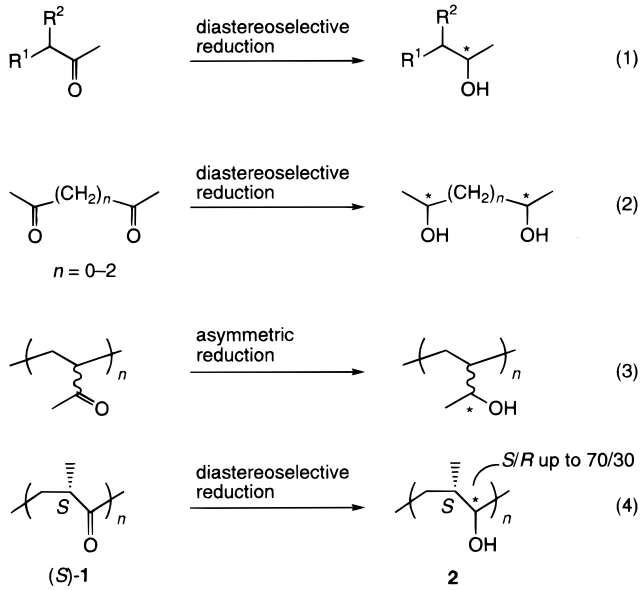
Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Sakyo-ku, Kyoto 606-8501

Received March 8, 2000; Revised Manuscript Received May 10, 2000

ABSTRACT: Diastereoselective reduction of enantiomerically pure polymer is described. Reduction of poly((*S*)-1-oxo-2-methylpropylene) [(*S*)-**1**] with tetrabutylammonium borohydride ($Bu_4N{\cdot}BH_4$) provided the corresponding polyol, poly(1-hydroxy-2-methylpropylene) (**2**), in a quantitative yield. The absolute configuration of the local structure was determined by the unambiguous synthesis of four diastereomers of 3-methyl-2,5-hexanediol. The newly formed asymmetric carbon was controlled to *S*-configuration with *S*/*R* ratio of 70/30. The *S*-selectivity contradicts to the conventional Cram-selectivity with which *R*-configuration is predicted from (*S*)-**1**. The origin of the selectivity is discussed by comparing the results with the reduction of a model molecule, 3-methyl-2,5-hexanedione.

Introduction

Diastereoselective nucleophilic addition to α-chiral carbonyl compounds has been studied since 1950s (eq 1).[1] Although the arguments have been expanded to more complicated systems, such as α-, *β*-, and *γ*-diketones which contain multiple reactive centers,[2] the chemistry still stays in molecular size of so-called low molecular weight compounds after half a century (eq 2).



Meanwhile, studies on the enantioselective reduction of polymeric ketones have been reported since 1960s. Chiral reductants or catalysts were employed to reduce ketonic groups in the side chains (eq 3).[3] In these studies, however, the main chain of the substrate polyketones contain multiple asymmetric centers whose absolute configurations are not well-controlled. Thus, the starting materials are of low tacticity, in other words, diastereomerically impure. In addition, determination of the magnitude of selectivities is generally difficult when a substrate is polymeric, and thus, optical rotation is often the only measurable value to estimate the selectivities.

Here we report the diastereoselective reduction of poly(1-oxo-2-methylpropylene) [(*S*)-**1**], a *γ*-polyketone bearing an asymmetric carbon at the α-position of each carbonyl group (eq 4). To the best of our knowledge, this is the first example of investigating the diastereoselectivity in a transformation of an enantiomerically pure polymer, a polymer with configurational homosequence. Polyketone (*S*)-**1** which is given by the asymmetric alternating copolymerization of propene and carbon monoxide[4] is of great interest as an artificially formed optically active polymer with main-chain chirality. Chemical modification of the carbonyl group, a versatile precursor for other functional groups, would provide new classes of chiral polymers. For achiral poly(ethene-*co*-CO) or atactic poly(propene-*alt*-CO), several examples[5] have appeared for the transformation of ketones into, e.g., furans,[6a] thiophenes,[6a] oximes,[5,6d,7] cyanohydrins,[5,6d] alcohols,[5,6] acetals,[8] amines,[5,9] α-hydroxy-phosphonic acids,[5,10] thiols,[5,11] and amides via Schmidt reaction[5,12] or via a Beckmann rearrangement of oximes.[5,12] On the other hand, only one example is reported by Sen et al. on the functionalization of enantiomerically pure polyketone.[4d] Sen reduced (*S*)-**1** by lithium aluminum hydride but the stereochemistry of the product, polyol **2**, was not defined. Using tetrabutylammonium borohydride as a reductant, here we reduced polyketone (*S*)-**1** into polyol **2** with the *S*/*R* ratio of 70/30 for the absolute configuration of the newly created chiral carbon (eq 4).

Results and Discussions

Diastereoselective Reduction of Polyketone (*S*)-1. Sen reported that the polyol **2** given by the reduction of optically pure (*S*)-**1** exhibits four methyl peaks in ^{13}C NMR at *δ* 14.5, 15.2, 16.4, and 17.1. In their study, the integration of each peak was essentially equal to each other. The four peaks have been attributed to the four diastereomeric structures described in Chart 1. In polyol **2**, each of the methyl group is neighbored by two newly formed chiral carbons. Here in this report, we call the local structure "*RSS*" when the chiral centers at the 3- and 2-positions from the original asymmetric carbon (1 position) are *R* and *S*, respectively. Thus, the four diastereomeric structures are named *SSS*, *RSS*, *SSR*, and *RSR*. Each ^{13}C NMR peak will be identified to the four diastereomeric structures later in this report, by

10.1021/ma000424d CCC: $19.00
Published on Web 07/08/2000

Chart 1

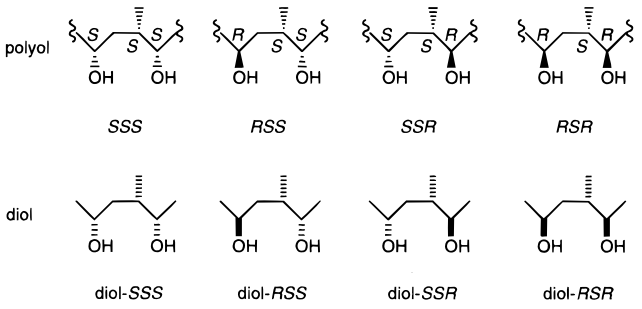


Table 1. Diastereoselective Reduction of Polyketone (*S*)-1

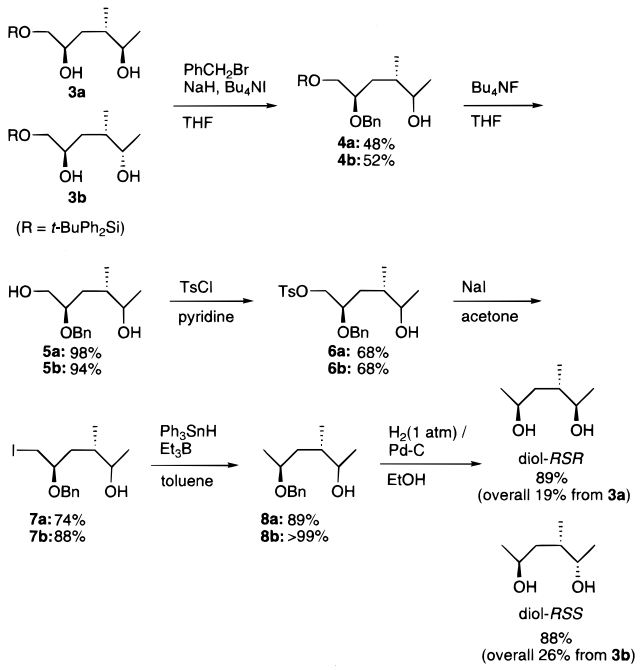
			^{13}C NMR of Me (δ)			
run	reductants and conditions	yield (%)	14.4 (*SSS*)	15.2	16.4	17.1 (*RSR*)
1	$LiBH_4$/THF, 40 °C, 52 h	95	39	21	22	18
2	$LiBH_4/CH_2Cl_2$, 25 °C, 29 h	96	37	23	23	17
3	$Zn(BH_4)_2/CH_2Cl_2$, 25 °C, 5 d	96	36	25	25	14
4	Bu_4NBH_4/CH_2Cl_2, 25 °C, 9 d	95	48	22	22	8

comparing their shifts with those of the four diastereomeric diols described in Chart 1. The diols are named as diol-*SSS*, diol-*RSS*, diol-*SSR*, and diol-*RSR*, corresponding to the local diastereomeric structure of the polyol, although the names do not represent the absolute configuration of the diols.

We first examined several reductants and compared the integration of the four methyl peaks. Substrate polyketone (*S*)-**1** (M_n = 20 200, M_w/M_n = 1.3, $[\Phi]_D^{23}$ = −39.2 in $CHCl_3$) was prepared by asymmetric alternating copolymerization of propene with CO. The results of the reduction are summarized in Table 1. A THF-soluble reductant, $LiBH_4$, was first employed. Since polyketone (*S*)-**1** is insoluble in THF, the reaction was carried out under a heterogeneous condition (run 1). To accelerate the reaction, the mixture was treated with ultrasonication at 40 °C for 52 h. After aqueous work up, the organic solvents were removed *in vacuo*, and the inorganic residues were washed away by 1 M HCl. From the residue, polyol **2** was extracted by MeOH and reprecipitated from MeOH/H_2O in its pure form. The conversion of ketone to alcohol was complete and no trace of a carbonyl group was observed by IR. Analysis with ^{13}C NMR revealed that the peak at δ 14.4 was the major one occupying 38% out of the four peaks. In CH_2Cl_2, polyketone (*S*)-**1** was soluble but $LiBH_4$ was not (run 2). In this case, ultrasonication was not necessary to complete the reaction. Polyol **2** was obtained with selectivity similar to that in THF. In spite of the fact that $Zn(BH_4)_2$[13] is known as a better chelating reductant for α-hydroxyketones,[13a−e] β-hydroxyketones,[13a,f−h] and β-keto esters,[13a,c,i−k] no significant change was observed for the selectivity in the polyketone reduction (run 3). The negligible difference between runs 2 and 3 implies that metal chelation between the neighboring two carbonyl oxygens is unlikely influential. With Bu_4NBH_4, the selectivity for the peak at δ 14.4 has risen up to 48% (run 4). In all runs, the peak at δ 17.1 was the smallest. It should be noted that the integration of the peaks at δ 15.2 and 16.4 are always equal to each other.

Identification of the Local Configurations. Here we assume that the neighboring functional group, either ketone or alcohol, does not affect the enantiofacial selectivity of a ketone. When the newly formed chiral carbon possesses *S* configuration with the possibility of *x*, the possibility that a methyl group exist between two

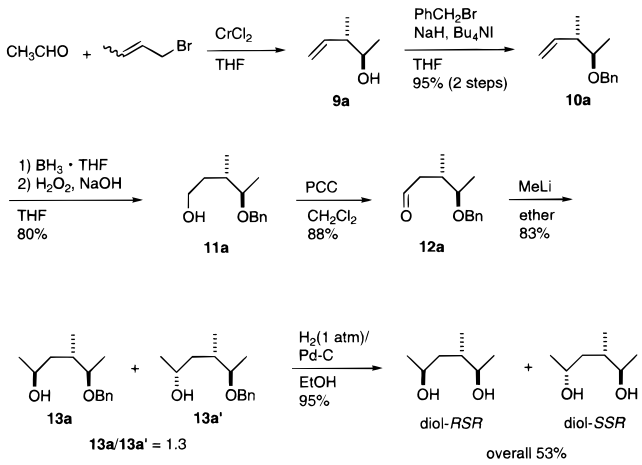
Scheme 1



S configurations, that is *SSS* in our definition, can be expressed as x^2. Meanwhile, the possibility for *RSR* is $(1 - x)^2$ and those for *RSS* and *SSR* are $(1 - x)x$ and $x(1 - x)$, respectively. The equality of integration between the two peaks at δ 15.2 and 16.4 in all runs allows us to assign one of these peaks to local structure *RSS* and the other to *SSR*.

Furthermore, the other two peaks at δ 14.4 and 17.1 can be assigned as follows. As models, four diastereomers of 3-methyl-2,5-hexanediol were synthesized. The structures and the names are drawn in Chart 1. Each compound of diol-*RSR* and diol-*RSS* was prepared in its enantiomerically pure form, as shown in Scheme 1, from enantiomerically pure triol derivatives **3a** and **3b**. A mixture of **3a** and **3b** was prepared from (*R*)-dihydro-5-(hydroxymethyl)-2(3*H*)-furanone according to the literature[14] and separated by HPLC. One of the two secondary alcohols was selectively benzylated in each of the diastereomers to give **4a** and **4b**. The selective monobenzylation may be explained that the side-chain methyl caused a significant steric repulsion to keep the −OH at its β-position from benzyl ether formation. After deprotection of the *tert*-$BuPh_2Si$, the primary alcohol was deoxigenated in four steps to afford diol-*RSR* and diol-*RSS*, respectively. Although neither diol-*SSR* nor diol-*SSS* could be obtained as a single diastereomer, a mixture of diol-*SSR* and diol-*RSR* was synthesized as described in Scheme 2. *anti*-Homoallylic alcohol **9a** was prepared from a crotylcromium reagent and acetaldehyde.[15] Hydroboration of the C−C double bond was followed by oxidation to aldehyde **12a**. Addition of MeLi to **12a** took place in a nonselective manner providing **13a** and **13a′** in a ratio of **13a**/**13a′** = 1.3.[14,16] Similarly, a mixture of diol-*SSS* and diol-*RSS* was given as shown in Scheme 3 from *syn*-homoallylic alcohol **9b** which was prepared from a crotyltin reagent and acetaldehyde by the aid of $BF_3{\cdot}Et_2O$.[17] All the diols were obtained as racemic mixtures in Schemes 2 and 3. The information obtained above together, ^{13}C NMR spectra of the four diastereomeric diols were determined unambiguously. The chemical shifts of the methyl carbons are listed in Table 2.

Scheme 2



Scheme 3

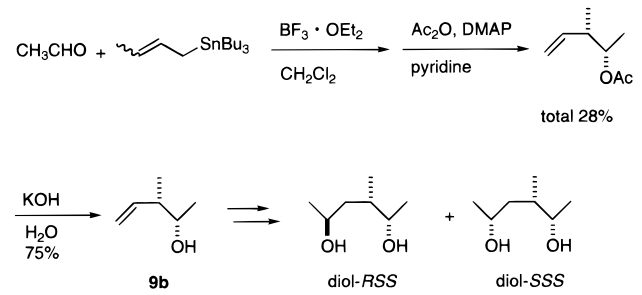
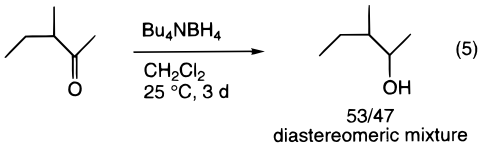


Table 2. ^{13}C NMR Chemical Shifts of the Methyl Groups of the Four Diastereomeric Diols

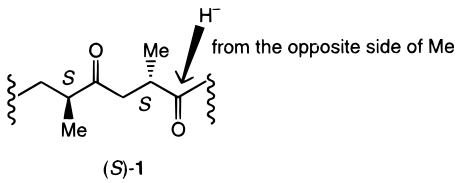
diols	diol-*RSS*	diol-*SSS*	diol-*SSR*	diol-*RSR*
^{13}C NMR of Me (δ)	14.9	15.0	15.4	15.8

Referring to the chemical shifts of the diols, we speculate that the peak of polyol **2** at the higher chemical shift corresponds to the peak of diol at the higher chemical shift and the lower corresponds to the lower. Accordingly, the peaks of polyol **2** at δ 14.4 and δ 17.1 are assignable to the peaks of diols at δ 15.0 (diol-*SSS*) and 15.8 (diol-*RSR*), respectively.

Selectivity in the Reduction of Polyketone and Diketone. On the basis of the above identification, the possibility of *S* for the newly built asymmetric center, value *x*, can be calculated as 0.7 in run 4 of Table 1. The 70/30 selectivity is rather high, as a simple asymmetric induction shown in an α-chiral carbonyl reduction. As a reference, for example, the reduction of 3-methyl-2-butanone under the common conditions of Table 1, run 4, gave a 53/47 diastereomeric mixture of 3-methyl-2-butanol (eq 5). Furthermore, the *S*-selectivity observed in the polymer reduction is an *anti*-Cram selectivity.[1] The Cram's rule premises the rapid rotation of the C−C bond between the α-asymmetric carbon and the carbonyl carbon so that the nucleophile can approach with the least steric repulsion. When a carbonyl is included in a polymer, however, the rotation must be limited. Thus, for the discussion of the asymmetric induction in polymer transformation, a new working



(5)



(*S*)-**1**

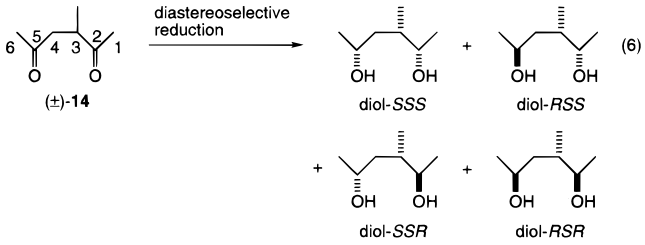
Figure 1. *S*-Selectivity for the newly created asymmetric carbon explained by the hydride attack from the opposite side of the neighboring side-chain methyl group when the main-chain takes a zigzag conformation.

Table 3. Diastereoselective Reduction of 3-Methyl-2,5-hexanedione

			^{13}C NMR of Me (δ)			
run	reductants and conditions	yield (%)	15.0 (*SSS*)	14.9 (*RSS*)	15.4 (*SSR*)	15.8 (*RSR*)
1	$LiBH_4$/THF, 25 °C, 21 h	63	34	15	15	36
2	$LiBH_4/CH_2Cl_2$, 25 °C, 23 h	68	34	19	21	26
3	Bu_4NBH_4/CH_2Cl_2, 25 °C, 3 d	58	37	18	31	14

hypothesis seems to be required. In crystals, poly(ethene-*alt*-CO) is known to form a zigzag linear conformation.[18] While replacing up to 15 mol % of ethene by propene influences the packing pattern to increase the *β*-form rather than the α-form, the zigzag linear conformation of one chain is not influenced.[19] Isotactic poly(styrene-*alt*-CO) is also reported to take the linear conformation.[20] Here, if we suppose that polyketone (*S*)-**1** keeps the linear conformation in solid state in THF (Table 1, run 1) or even in solutions (runs 2−4), it would be likely that the hydride prefers to approach the carbonyl group from the opposite side of the side chain methyl in order to avoid the steric repulsion (Figure 1). This hypothesis matches the *anti*-Cram selectivity observed in all runs of Table 1.

In relation to the studies on the polyketone, diastereoselectivities were investigated in the reduction of (±)-3-methyl-2,5-hexanedione ((±)-**14**) (eq 6). The same



(6)

reductants and conditions were employed as for polyketone (*S*)-**1** (Table 3). The distributions of the four diastereomers differ from the ones observed with polyketone **1** (compare Tables 1 and 3). The difference may be accounted for as follows. First, the rapid free rotations around all the C−C bonds are possible only in a low-molecular weight compound. In addition, the two carbonyls in **14** are nonequivalent, unlike polyketone **1**. In **14**, it is probable to assume that the less crowded C(5)-carbonyl tend to get reduced prior to the more crowded one at the C(2). The reduction of C(5)-carbonyl is under the control of the side-chain methyl on C(3), the *β*-position of C(5). Meanwhile, the carbonyl in polyketone **1** is always neighbored by an α-asymmetric carbon which influences the diastereoselectivity.

Conclusion

Diastereoselective reduction of enantiomerically pure poly((*S*)-1-oxo-2-methylpropylene) [(*S*)-**1**] provided polyol

2 in which the absolute configuration of the newly formed asymmetric carbon was controlled in preference to *S* with an *S*/*R* ratio of 70/30. Thus, we created an additional chiral center stereoselectively in the polymer main chain. Although the selectivity is not extremely high, this is the first example of investigating diastereoselective transformation of an enantiomerically pure polymer. The difficulty that often arises in the characterization of the absolute configuration of local structure was demonstrated to be overcome by the unambiguous synthesis of four diastereomeric diols.

Experimental Section

Apparatus. Nuclear magnetic resonance spectra were taken with a JEOL EX-270 (^{1}H 270 MHz; ^{13}C 68 MHz) or a Varian Mercury 200 (^{1}H 200 MHz; ^{13}C 50 MHz) spectrometer using tetramethylsilane as an internal standard, and coupling constants are given in hertz. Infrared spectra were recorded on a JASCO IR-810. Optical rotation and melting points were measured on a JASCO DIP-360 and a Yanako MP-500D. Microanalysis was performed at Microanalysis Center of Kyoto University.

Chemicals. Most of the reagents were available from Wako Pure Chemical Industries Ltd. or Nacalai Tesque Ltd. All of solvents used for the reactions and recrystallizations were distilled under argon after drying over an appropriate drying agent. For silica gel column chromatography, Wako-gel C-200 was used.

Reduction of Poly(CO-*alt*-propene) ((*S*)-1) with Lithium Borohydride in THF. Poly(CO-*alt*-propene) ((*S*)-**1**), prepared by the procedure of our previous reports,[4e,f] was dissolved in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP, 2 mL), and the solvent was removed by rotary evaporator to form a film of the polyketone. This process is necessary to transform a partially formed spiroketal structure into a pure polyketone.[4a] A mixture of (*S*)-**1** (59.8 mg, 0.853 mmol of unit), lithium borohydride (94.5 mg, 4.34 mmol) in THF (12 mL) was stirred under ultrasonication at 40 °C for 52 h. The polymer was insoluble in THF at the beginning. As the reduction proceeded, the mixture became cloudy and the polymer films disappeared. The reaction was quenched by the addition of 1 M HCl(aq) (10 mL), and the solvent was removed by evaporation. To the residue was added 1 M HCl(aq) (30 mL), and the resulting mixture was filtered by a glass filter (G4). After washing with H_2O (25 mL), the remaining solid was eluted with methanol (60 mL) and the solution was concentrated. The residue was purified by reprecipitation in CH_3OH/H_2O to afford polyol **2** (58.2 mg, 0.807 mmol, 95% yield): mp 331 °C; T_g 145 °C; ^{1}H NMR (CD_3OD) δ 0.85−1.10 (br m, 3H), 1.10−1.48 (br m, 1H), 1.48−1.92 (br m, 2H), 3.49−3.78 (br m, 1H); ^{13}C NMR (CD_3OD) δ 14.2−17.4 (m, CH_3), 36.2−39.8 (m), 72.2−75.2 (m); IR (neat): 3340, 2932, 1455, 1379, 984, 933, 840 cm^{-1}. Anal. Calcd for C_4H_8O: C, 66.63; H, 11.18. Found: C, 66.60; H, 11.03.

Reduction of (*S*)-1 with Lithium Borohydride in Dichloromethane. A mixture of polyketone (*S*)-**1** (41.5 mg, 0.592 mmol) and lithium borohydride (67.1 mg, 3.08 mmol) in dichloromethane (10 mL) was stirred at room temperature for 29 h. The polymer was soluble while $LiBH_4$ remained insoluble. Workup as common to the reaction in THF afford polyol **2** (40.9 mg, 0.567 mmol, 96% yield). The purity of polyol **2** was confirmed by microanalysis. Anal. Calcd for C_4H_8O: C, 66.63; H, 11.18; Found: C, 66.68; H, 11.07.

Reduction of (*S*)-1 with Tetrabutylammonium Borohydride in Dichloromethane. A mixture of polyketone (*S*)-**1** (38.1 mg, 0.544 mmol) and tetrabutylammonium borohydride (562 mg, 2.19 mmol) in dichloromethane (15 mL) was stirred at room temperature for 9 d. As the reaction proceeded, polyol **2** precipitated from the clear homogeneous solution. Aqueous workup gave polyol **2** (37.2 mg, 0.516 mmol, 95% yield).

Reduction of (*S*)-1 with Zinc Borohydride in Dichloromethane. A mixture of the polyketone (39.0 mg, 0.556 mmol) and zinc borohydride (275 mg, 2.89 mmol) in dichloromethane (15 mL) was stirred at room temperature for 5 d. Aqueous workup followed by reprecipitation in aqueous MeOH/EDTA·2Na gave polyol **2** (38.6 mg, 0.535 mmol, 96% yield).

Preparation of (2*R*,3*S*,5*R*)-5-Benzyloxy-6-(*tert*-butyldiphenylsiloxy)-3-methyl-2-hexanol (4a). A mixture of **3a** and **3b** was prepared by the literature method.[14] Diastereomers **3a** and **3b** were separated by HPLC (column, JAIGEL-SIL. S-043-15; eluent, hexane:ethyl acetate = 3:2,; flow rate, 1.20 mL/min). Benzyl bromide (0.317 mL, 2.67 mmol) was added to a suspension of **3a** (516 mg, 1.33 mmol), sodium hydride (178 mg, 60%, 4.45 mmol) and tetrabutylammmonium iodide (25.0 mg, 0.068 mmol) in THF (9 mL) at room temperature, and the resulting mixture was stirred at room temperature for 3.5 h. After cooling to 0 °C, 1 M HCl(aq) (6 mL) was added, and the mixture was poured into H_2O (15 mL)/ether (15 mL). The separated aqueous layer was extracted with ether (4 × 10 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (15 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane: ether = 3:1 then 5:2) to afford **4a** (307 mg, 0.644 mmol, 48% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.87 (d, J = 6.8 Hz, 3H), 1.07 (s, 9H), 1.10 (d, J = 6.4 Hz, 3H), 1.51−1.70 (m, 3H), 2.31−2.46 (br, 1H), 3.39−3.84 (m, 4H), 4.46 (d, J = 11.5 Hz, 1H), 4.64 (d, J = 11.5 Hz, 1H), 7.20−7.51 (m, 11H), 7.64−7.79 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 16.3, 19.2, 19.8, 26.8, 35.1, 37.4, 65.9, 71.1, 71.9, 77.6, 127.6, 127.7, 127.9, 128.3, 129.7, 133.4, 133.4, 135.6, 138.2; R_f 0.33 (hexane: ether = 1:1). Anal. Calcd for $C_{30}H_{40}O_3Si$: C, 75.58; H, 8.46; Found: C, 75.30; H, 8.61. The above procedure was also applied to the preparation of **4b**.

(2*S*,3*S*,5*R*)-5-Benzyloxy-6-(*tert*-butyldiphenylsiloxy)-3-methyl-2-hexanol (4b): 52% yield; ^{1}H NMR ($CDCl_3$) δ 0.85 (d, J = 6.8 Hz, 3H), 1.03−1.13 (s,d, 12H), 1.34−1.93 (m, 4H), 3.50−3.86 (m, 4H), 4.49 (d, J = 11.7 Hz, 1H), 4.68 (d, J = 11.7 Hz, 1H), 7.20−7.57 (m, 11H), 7.63−7.80 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.7, 19.2, 19.9, 26.8, 35.0, 35.9, 66.1, 70.3, 71.9, 77.9, 127.5, 127.7, 127.8, 128.3, 129.7, 133.4, 133.5, 135.6, 138.5; R_f 0.33 (hexane:ether = 1:1). Anal. Calcd for $C_{30}H_{40}O_3Si$: C, 75.58; H, 8.46; Found: C, 75.51; H, 8.66.

Deprotection of 4a to (2*R*,4*S*,5*R*)-2-Benzyloxy-4-methyl-1,5-hexanediol (5a). Tetrabutylammonium fluoride (1.0 M in THF, 3.20 mL, 3.20 mmol) was added to a solution of **4a** (307 mg, 0.644 mmol) in THF (8 mL) and stirred at room temperature for 18 h. The reaction was quenched by addition of H_2O (25 mL) and ethyl acetate (30 mL). The separated organic layer was washed with H_2O (15 mL) and the combined aqueous layers were extracted with ethyl acetate (4 × 15 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, concentrated, and purified by silica gel column chromatography (hexane:ethyl acetate = 1:1 and then 1:3) to afford **5a** (150 mg, 0.629 mmol, 98% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 6.4 Hz, 3H), 1.13 (d, J = 6.4 Hz, 3H), 1.47−1.70 (m, 3H), 2.05−2.38 (br, 2H), 3.48−3.85 (m, 4H), 4.56 (d, J = 11.5 Hz, 1H), 4.62 (d, J = 11.5 Hz, 1H), 7.24−7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.1, 20.0, 34.1, 37.1, 63.9, 71.3, 71.6, 78.0, 127.9, 127.9, 128.5, 138.1; R_f 0.25 (hexane:ethyl acetate = 1:4). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30; Found: C, 70.29; H, 9.59.

(2*R*,4*S*,5*S*)-2-Benzyloxy-4-methyl-1,5-hexanediol (5b): 94% yield; ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 6.6 Hz, 3H), 1.12 (d, J = 6.4 Hz, 3H), 1.40−1.77 (m, 3H), 2.05 (s, 2H), 3.49−3.82 (m, 4H), 4.56 (d, J = 11.7 Hz, 1H), 4.62 (d, J = 11.7 Hz, 1H), 7.24−7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.8, 19.7, 33.6, 35.9, 63.8, 70.7, 71.2, 77.9, 127.9, 128.5, 138.2; R_f 0.25 (hexane: ethyl acetate = 1:4). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30; Found: C, 70.64; H, 9.39.

Preparation of (2*R*,3*S*,5*R*)-5-Benzyloxy-3-methyl-6-tosyloxy-2-hexanol (6a). To a solution of **5a** (150 mg, 0.629 mmol) in pyridine (6 mL) was added tosyl chloride (180 mg, 0.944 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 17 h. After quenching with 1 M HCl(aq) (40 mL) and ethyl acetate (40 mL), the separated organic layer was washed with 1 M HCl(aq) (3 × 15 mL) and the combined aqueous layers were extracted with ethyl acetate (3 × 20 mL). The organic layers were dried over anhydrous magnesium sulfate,

filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1 then 1:1) to afford **6a** (167 mg, 0.425 mmol, 68% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.85 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 6.2 Hz, 3H), 1.45−1.66 (m, 3H), 1.89−2.03 (br, 1H), 2.44 (s, 3H), 3.39−3.57 (m, 1H), 3.64−3.82 (m, 1H), 3.97−4.11 (m, 2H), 4.48 (d, J = 11.5 Hz, 1H), 4.58 (d, J = 11.4 Hz, 1H), 7.22−7.43 (m, 7H), 7.75−7.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 16.1, 20.0, 21.6, 34.8, 37.1, 71.2, 71.4, 72.1, 74.8, 127.9, 128.0, 128.4, 129.8, 132.8, 137.5, 144.9; R_f 0.54 (hexane:ethyl acetate = 1:2). Anal. Calcd for $C_{21}H_{28}O_5S$: C, 64.26; H, 7.19; Found: C, 64.15; H, 7.19.

(2*S*,3*S*,5*R*)-5-Benzyloxy-3-methyl-6-tosyloxy-2-hexanol (6b). 68% yield: ^{1}H NMR ($CDCl_3$) δ 0.84 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.4 Hz, 3H), 1.32−1.76 (m, 4H), 2.44 (s, 3H), 3.55−3.84 (m, 2H), 3.97−4.16 (m, 2H), 4.46 (d, J = 11.5 Hz, 1H), 4.58 (d, J = 11.5 Hz, 1H), 7.19−7.38 (m, 7H), 7.75−7.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.6, 19.7, 21.6, 34.4, 35.6, 69.9, 71.5, 72.0, 74.8, 127.8, 127.9, 128.4, 129.8, 132.8, 137.7, 144.9; R_f 0.53 (hexane:ethyl acetate = 1:2). Anal. Calcd for $C_{21}H_{28}O_5S$: C, 64.26; H, 7.19; Found: C, 64.37; H, 7.35.

Preparation of (2*R*,3*S*,5*R*)-5-Benzyloxy-6-iodo-3-methyl-2-hexanol (7a). A mixture of **6a** (160 mg, 0.408 mmol) and sodium iodide (260 mg, 1.73 mmol) in acetone (12 mL) was heated at reflux with stirring for 21 h. The solvent was removed by rotary evaporator. Ethyl acetate (20 mL), H_2O (11 mL), 1 M HCl(aq) (1 mL) and then 10% $Na_2S_2O_3$(aq) (10 mL) were added to the residue. The separated organic layer was washed with H_2O (9 mL) and the combined aqueous layers were extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1) to afford **7a** (104 mg, 0.299 mmol, 74% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 6.8 Hz, 3H), 1.13 (d, J = 6.2 Hz, 3H), 1.50−1.78 (m, 3H), 1.98−2.18 (br, 1H), 3.24−3.37 (m, 2H), 3.37−3.65 (m, 2H), 4.48 (d, J = 11.4 Hz, 1H), 4.65 (d, J = 11.4 Hz, 1H), 7.25−7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 9.8, 16.1, 19.9, 37.2, 37.9, 71.2, 71.3, 75.8, 128.0, 128.1, 128.5, 137.5; R_f 0.53 (hexane:ethyl acetate = 1:1). Anal. Calcd for $C_{14}H_{21}O_2I$: C, 48.29; H, 6.08; Found: C, 48.04; H, 6.06.

(2*S*,3*S*,5*R*)-5-Benzyloxy-6-iodo-3-methyl-2-hexanol (7b). 88% yield: ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 6.6 Hz, 3H), 1.12 (d, J = 6.4 Hz, 3H), 1.40−1.91 (m, 4H), 3.23−3.52 (m, 3H), 3.64−3.79 (m, 1H), 4.46 (d, J = 11.4 Hz, 1H), 4.66 (d, J = 11.5 Hz, 1H), 7.25−7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 10.0, 14.7, 19.9, 35.8, 37.7, 70.3, 71.2, 75.7, 127.9, 128.0, 128.5, 137.7; R_f 0.49 (hexane:ethyl acetate = 1:1). Anal. Calcd for $C_{14}H_{21}O_2I$: C, 48.29; H, 6.08; Found: C, 49.14; H, 6.32. (A slightly yellowish color implied the contamination of an impurity, e.g., iodine.)

Dehalogenation of 7a to (2*R*,3*S*,5*S*)-5-Benzyloxy-3-methyl-2-hexanol (8a). To a solution of **7a** (90.1 mg, 0.258 mmol) and triphenyltin hydride (222 mg, 0.633 mmol) in toluene (4.5 mL) was added triethylborane (1.0 M in hexane, 0.100 mL, 0.100 mmol) at room temperature, and the reaction was stirred for 0.5 h.[21] The reaction was quenched by the addition of saturated KF(aq) (8 mL). The resulting mixture was stirred for 1.5 h and filtered through a Celite pad and the filter cake was washed with ethyl acetate (20 mL). The separated organic layer of the filtrate was washed with brine (2 × 20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1) to afford **8a** (51.1 mg, 0.230 mmol, 89% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.89 (d, J = 6.6 Hz, 3H), 1.13 (d, J = 6.4 Hz, 3H), 1.22 (d, J = 6.0 Hz, 3H), 1.40−1.78 (m, 3H), 2.20−2.32 (br, 1H), 3.48−3.77 (m, 2H), 4.45 (d, J = 11.5 Hz, 1H), 4.60 (d, J = 11.5 Hz, 1H), 7.22−7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.3, 19.6, 20.0, 37.5, 40.0, 70.4, 71.3, 72.8, 127.6, 127.8, 128.4, 138.4; R_f 0.22 (hexane:ethyl acetate = 3:1). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97; Found: C, 75.62; H, 10.18.

(2*S*,3*S*,5*S*)-5-Benzyloxy-3-methyl-2-hexanol (8b): quantitative yield; ^{1}H NMR ($CDCl_3$) δ 0.89 (d, J = 6.8 Hz, 3H), 1.12 (d, J = 6.4 Hz, 3H), 1.22 (d, J = 6.2 Hz, 3H), 1.39−1.85 (m, 3H), 2.02 (br s, 1H), 3.55−3.81 (m, 2H), 4.44 (d, J = 11.7 Hz, 1H), 4.61 (d, J = 11.7 Hz, 1H), 7.19−7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.5, 19.3, 19.8, 36.0, 39.9, 70.2, 70.5, 73.0, 127.5, 127.7, 128.4, 138.5; R_f 0.21 (hexane:ethyl acetate = 3:1). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97; Found: C, 75.52; H, 10.22.

Deprotection of 8a to (2*R*,3*S*,5*S*)-3-Methyl-2,5-hexanediol (diol-*RSR*). A mixture of **8a** (18.3 mg, 0.0823 mmol), Pd−C (5% Pd, 140 mg), ethanol (4 mL) was stirred under H_2 atmosphere at room temperature for 42 h and then filtered through a pad of Celite. The filter cake was washed with ethanol (20 mL). The filtrate was concentrated and the residue was purified by silica gel TLC (ethyl acetate only) to afford **diol-*RSR*** (9.7 mg, 0.073 mmol, 89% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.95 (d, J = 6.8 Hz, 3H), 1.19 (d, J = 6.2 Hz, 3H), 1.20 (d, J = 6.2 Hz, 3H), 1.38−1.79 (m, 3H), 2.69 (s, 2H), 3.57−3.77 (m, 1H), 3.90−4.09 (m, 1H); (CD_3OD) δ 0.90 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 6.4 Hz, 3H), 1.14 (d, J = 6.2 Hz, 3H), 1.23−1.70 (m, 3H), 3.51−3.70 (m, 1H), 3.71−3.93 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.6, 20.7, 23.8, 37.3, 42.1, 65.1, 71.6; (CD_3OD) δ 15.8 (CH_3), 19.3, 23.4, 38.2, 43.3, 66.8, 72.2; R_f 0.30 (ethyl acetate only).

The above procedure was applied to the preparation of **(2*S*,3*S*,5*S*)-3-methyl-2,5-hexanediol (diol-*RSS*)**: 88% yield; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 7.0 Hz, 3H), 1.16 (d, J = 6.4 Hz, 3H), 1.20 (d, J = 6.4 Hz, 3H), 1.36−1.90 (m, 3H), 3.09 (s, 2H), 3.78−4.09 (m, 2H); (CD_3OD) δ 0.89 (d, J = 6.8 Hz, 3H), 1.12 (d, J = 6.6 Hz, 3H), 1.14 (d, J = 6.2 Hz, 3H), 1.26−1.70 (m, 3H), 3.61−3.95 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.6, 23.6, 36.0, 42.6, 65.1, 70.9; (CD_3OD) δ 14.9 (CH_3), 20.1, 23.6, 37.7, 43.3, 66.6, 71.2; R_f 0.30 (ethyl acetate only).

Preparation of (3*S*,4*R*)-4-Benzyloxy-3-methyl-1-pentene (10a). To a suspension of sodium hydride (1.50 g, 60%, 37.5 mmol) in THF (10 mL) was added a solution of homoallyl alcohol **9a**[15] (0.938 g, 9.37 mmol) in THF (38 mL) at room temperature and the mixture was stirred for 15 min. Benzyl bromide (1.25 mL, 10.5 mmol) and tetrabutylammonium iodide (140 mg, 0.378 mmol) were added to this mixture, and the resulting mixture was stirred at room temperature for 4 h. The reaction was quenched by the careful addition of 1 M HCl(aq) (50 mL) and ether (50 mL) at 0 °C. The separated aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were washed with H_2O (2 × 50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 55:1) to afford **10a** (1.75 g, 9.20 mmol, 98% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.04 (d, J = 7.0 Hz, 3H), 1.12 (d, J = 6.4 Hz, 3H), 2.30−2.54 (m, 1H), 3.33−3.55 (m, 1H), 4.47 (d, J = 11.9 Hz, 1H), 4.58 (d, J = 11.9 Hz, 1H), 4.95−5.12 (m, 2H), 5.74−5.93 (m, 1H), 7.20−7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.7, 16.1, 42.5, 70.6, 78.2, 114.4, 127.3, 127.5, 128.2, 139.1, 141.1; R_f 0.40 (hexane:ethyl acetate = 20:1). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53; Found: C, 81.99; H, 9.53.

(3*S*,4*S*)-4-Benzyloxy-3-methyl-1-pentene (10b): 86% yield from **9b**;[17] ^{1}H NMR ($CDCl_3$) δ 1.05 (d, J = 6.8 Hz, 3H), 1.14 (d, J = 6.4 Hz, 3H), 2.29−2.50 (m, 1H), 3.28−3.49 (m, 1H), 4.48 (d, J = 11.7 Hz, 1H), 4.59 (d, J = 11.7 Hz, 1H), 4.95−5.12 (m, 2H), 5.73−5.94 (m, 1H), 7.19−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.9, 16.6, 43.0, 70.6, 78.4, 114.5, 127.3, 127.6, 128.3, 139.0, 140.8; R_f 0.40 (hexane:ethyl acetate = 20:1). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53; Found: C, 81.80; H, 9.54.

Hydroboration of 10a to (3*S*,4*R*)-4-Benzyloxy-3-methyl-1-pentanol (11a). To a solution of **10a** (1.75 g, 9.20 mmol) in THF (15 mL) was added dropwise BH_3·THF (1.0 M in THF, 18.0 mL, 18.0 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. To this were carefully added cold H_2O (8 mL), 3 M NaOH(aq) (15 mL), and 30% H_2O_2 (15 mL) at 0 °C. The resulting mixture was stirred at 50 °C for 1 h and poured into ether (50 mL)/H_2O (30 mL). The separated aqueous layer was extracted with ether (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 4:1 then 7:2) to afford

11a (1.54 g, 7.39 mmol, 80% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.95 (d, J = 6.8 Hz, 3H), 1.18 (d, J = 6.2 Hz, 3H), 1.41−1.95 (m, 3H), 1.99 (br s, 1H), 3.30−3.50 (m, 1H), 3.50−3.89 (m, 2H), 4.45 (d, J = 11.7 Hz, 1H), 4.60 (d, J = 11.7 Hz, 1H), 7.21−7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.3, 15.9, 34.9, 35.7, 60.5, 70.5, 78.7, 127.4, 127.6, 128.2, 138.6; R_f 0.15 (hexane:ethyl acetate = 3:1). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68; Found: C, 75.06; H, 9.87.

(3*S*,4*S*)-4-Benzyloxy-3-methyl-1-pentanol (11b): 83% yield; ^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 6.8 Hz, 3H), 1.16 (d, J = 6.4 Hz, 3H), 1.33−2.02 (m, 3H), 2.24 (s, 1H), 3.38−3.79 (m, 3H), 4.48 (d, J = 11.9 Hz, 1H), 4.61 (d, J = 11.7 Hz, 1H), 7.22−7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.8, 16.7, 35.0, 35.3, 61.5, 70.6, 78.6, 127.5, 127.5, 128.3, 138.6; R_f 0.15 (hexane:ethyl acetate = 3:1). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68; Found: C, 75.13; H, 9.48.

Oxidation of 11a to (3*S*,4*R*)-4-Benzyloxy-3-methyl-1-pentanal (12a). A solution of **11a** (1.51 g, 7.26 mmol) in dichloromethane (15 mL) was added to a mixture of PCC (3.14 g, 14.6 mmol) in dichloromethane (45 mL) at room temperature, and the resulting mixture was stirred at room temperature for 4 h. To the reaction mixture was added dry ether (50 mL). The resulting mixture was filtered through a short silica gel column, and the remaining black solid was washed with dry ether (3 × 15 mL) through the column. The filtrate was concentrated and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1) to afford **12a** (1.32 g, 6.40 mmol, 88% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.97 (d, J = 6.6 Hz, 3H), 1.19 (d, J = 6.0 Hz, 3H), 2.10−2.37 (m, 2H), 2.44−2.68 (m, 1H), 3.19−3.43 (m, 1H), 4.38 (d, J = 11.5 Hz, 1H), 4.56 (d, J = 11.5 Hz, 1H), 7.21−7.50 (m, 5H), 9.69−9.82 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.6, 34.6, 48.1, 70.7, 78.7, 127.5, 127.8, 128.3, 138.4, 202.4 (1 unresolved); R_f 0.44 (hexane:ethyl acetate = 3:1). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80; Found: C, 75.47; H, 8.90.

(3*S*,4*S*)-4-Benzyloxy-3-methyl-1-pentanal (12b): 85% yield; ^{1}H NMR ($CDCl_3$) δ 0.96 (d, J = 7.0 Hz, 3H), 1.14 (d, J = 6.4 Hz, 3H), 2.15−2.69 (m, 3H), 3.42−3.57 (m, 1H), 4.42 (d, J = 11.9 Hz, 1H), 4.57 (d, J = 11.9 Hz, 1H), 7.19−7.41 (m, 5H), 9.71−9.76 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 15.2, 15.5, 32.7, 46.5, 70.4, 77.2, 127.4, 127.5, 128.3, 138.7, 202.7; R_f 0.44 (hexane:ethyl acetate = 3:1). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80; Found: C, 75.74; H, 9.07.

Preparation of (2*S*,4*S*,5*R*)-5-Benzyloxy-4-methyl-2-hexanol (13a) and (2*R*,4*S*,5*R*)- 5-Benzyloxy-4-methyl-2-hexanol (13a′). A solution of **12a** (1.15 g, 5.55 mmol) in ether (15 mL) was cooled to −78 °C. Methyllithium (1.14 M in ether, 22.0 mL, 25.1 mmol) was slowly added to the solution, and the resulting mixture was gradually warmed to ambient temperature during 12 h. The reaction was quenched by the careful addition of 1 M HCl(aq) (45 mL) and ether (50 mL) at 0 °C. The separated organic layer was washed with 1 M HCl-(aq) (2 × 40 mL) and the combined aqueous layers were extracted with ether (3 × 40 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 5:1) to afford a mixture of **13a** and **13a′** (**13a**: **13a′** = 1:1, total 532 mg). In another fraction, a mixture of **13a** and **13a′** (**13a**: **13a′** = 1.6:1) was obtained with <10 wt % of impurity, presumably (3*S*,4*R*)-4-benzyloxy-2,3-dimethyl-2-pentanol, originating from the opposite regioselectivity in the hydroboration (total 537 mg). The total yield of **13a** and **13a′** was 83% (1.02 g, 4.59 mmol). Data for **13a**: ^{1}H NMR ($CDCl_3$) δ 0.96 (d, J = 7.0 Hz, 3H), 1.13−1.22 (d, d, 6H), 1.45−1.64 (m, 2H), 1.71−1.96 (m, 1H), 1.96−2.20 (br, 1H), 3.28−3.54 (m, 1H), 3.75−4.00 (m, 1H), 4.44 (d, J = 11.5 Hz, 1H), 4.62 (d, J = 11.5 Hz, 1H), 7.20−7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.0, 16.2, 23.5, 35.3, 42.5, 65.1, 70.8, 78.9, 127.6, 127.7, 128.4, 138.5; R_f 0.20 (hexane:ethyl acetate = 3:1). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97; Found: C, 75.68; H, 9.82 (1:1 mixture of **13a** and **13a′**). Data for **13a′**: ^{1}H NMR ($CDCl_3$) δ 0.94 (d, J = 6.8 Hz, 3H), 1.13−1.22 (d, d, 6H), 1.45−1.64 (m, 2H), 1.71−1.96 (m, 1H), 1.96−2.20 (br, 1H), 3.28−3.54 (m, 1H), 3.75−4.00 (m, 1H), 4.46 (d, J = 11.7 Hz, 1H), 4.59 (d, J = 11.7 Hz, 1H), 7.20−7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.8, 16.2, 24.6, 35.1, 43.1, 66.2, 70.5, 79.2, 127.5, 127.7, 128.3, 138.8; R_f 0.20 (hexane:ethyl acetate = 3:1).

The same procedure was applied for the synthesis of **(2*R*,4*S*,5*S*)-5-benzyloxy-4-methyl-2-hexanol (13b) and (2*S*,4*S*,5*S*)-5-benzyloxy-4-methyl-2-hexanol (13b′):** 93% yield (mixture of **13b** and **13b′**, **13b**: **13b′** = 1:1.1). Data for **13b**: ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 7.0 Hz, 3H), 1.12−1.20 (d, d, 6H), 1.25−1.68 (m, 2H), 1.89−2.10 (m, 1H), 2.55−2.87 (br, 1H), 3.41−3.58 (m, 1H), 3.83−3.98 (m, 1H), 4.50 (d, J = 11.9 Hz, 1H), 4.61 (d, J = 11.9 Hz, 1H), 7.21−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.5, 17.4, 24.2, 35.4, 41.6, 66.7, 70.5, 78.9, 127.5, 127.5, 128.3, 138.5; R_f 0.20 (hexane:ethyl acetate = 3:1). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97; Found: C, 75.85; H, 10.10 (1:1.1 mixture of **13b** and **13b′**). Data for **13b′**: ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 7.0 Hz, 3H), 1.12−1.20 (d, d, 6H), 1.25−1.68 (m, 2H), 1.89−2.10 (m, 1H), 2.55−2.87 (br, 1H), 3.41−3.58 (m, 1H), 3.83−3.98 (m, 1H), 4.43 (d, J = 11.9 Hz, 1H), 4.62 (d, J = 11.9 Hz, 1H), 7.21−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.6, 16.7, 23.2, 34.4, 41.9, 65.6, 70.5, 78.4, 127.5, 127.5, 128.3, 138.6; R_f 0.20 (hexane:ethyl acetate = 3:1).

Debenzylation of a Mixture of 13a and 13a′ to (2*R*,3*S*,5*R*)-3-Methyl-2,5-hexanediol (diol-*RSR*) and (2*R*,3*S*,5*S*)-3-Methyl-2,5-hexanediol (diol-*SSR*). A mixture of **13a 13a′** (**13a**: **13a′** = 1:1, 505 mg, 2.27 mmol), and Pd−C (5% Pd, 204 mg) in ethanol (10 mL) was stirred under H_2 atmosphere at room temperature for 39 h and then filtered through a pad of Celite, and the filter cake was washed with methanol (30 mL). The filtrate was concentrated and the residue was purified by silica gel column chromatography (ethyl acetate only) to afford a mixture of **diol-*RSR*** and **diol-*SSR*** (**diol-*RSR***: **diol-*SSR*** = 1:1, 284 mg, 2.15 mmol, 95% yield) as colorless oils. Data for **diol-*SSR***: ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 6.8 Hz, 3H), 1.17 (d, J = 6.4 Hz, 3H), 1.21 (d, J = 6.2 Hz, 3H), 1.42−1.80 (m, 3H), 3.08 (s, 2H), 3.43−3.65 (m, 1H), 3.78−3.96 (m, 1H); (CD_3OD) δ 0.90 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 6.4 Hz, 3H), 1.17 (d, J = 6.0 Hz, 3H), 1.25−1.80 (m, 3H), 3.49−3.71 (m, 1H), 3.71−3.92 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 17.1, 20.6, 24.6, 38.6, 44.4, 66.6, 72.5; (CD_3OD) δ 15.4 (CH_3), 19.5, 24.7, 37.8, 43.5, 66.4, 72.7; R_f 0.30 (ethyl acetate only). Anal. Calcd for $C_7H_{16}O_2$: C, 63.60; H, 12.20; Found: C, 63.80; H, 12.39 (1:1 mixture of **diol-*RSR*** and **diol-*SSR***).

(2*S*,3*S*,5*R*)-3-Methyl-2,5-hexanediol (diol-*SSS*) and (2*S*,3*S*,5*S*)-3-methyl-2,5-hexanediol (diol-*RSS*) were similarly produced: 99% yield. Data for **diol-*SSS***: ^{1}H NMR ($CDCl_3$) δ 0.89 (d, J = 7.0 Hz, 3H), 1.13 (d, J = 6.4 Hz, 3H), 1.22 (d, J = 6.2 Hz, 3H), 1.30−1.90 (m, 3H), 2.31−2.98 (br, 2H), 3.71−4.10 (m, 2H); (CD_3OD) δ 0.89 (d, J = 6.8 Hz, 3H), 1.11 (d, J = 6.2 Hz, 3H), 1.16 (d, J = 6.2 Hz, 3H), 1.24−1.81 (m, 3H), 3.52−3.95 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 16.5, 18.2, 24.6, 37.5, 41.4, 66.9, 70.9; (CD_3OD) δ 15.0 (CH_3), 19.8, 24.6, 37.6, 43.3, 66.5, 72.4; R_f 0.30 (ethyl acetate only). Anal. Calcd for $C_7H_{16}O_2$: C, 63.60; H, 12.20; Found: C,63.57; H, 12.30 (1.1:1 mixture of **diol-*RSS*** and **diol-*SSS***).

Preparation of 3-Methyl-2,5-hexanedione ((±)-14). To a solution of methylsuccinic acid (792 mg, 6.00 mmol) in THF (45 mL) was added methyllithium (1.20 M in ether, 25.0 mL, 30.0 mmol) at once at 0 °C. The reaction mixture was stirred at room temperature for 23 h and then at 75 °C for 17 h. The reaction was quenched by the addition of H_2O (30 mL) and ether (40 mL) at 0 °C and neutralizad with 1 M HCl(aq). The separated aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were washed with H_2O (2 × 50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 5:1) to afford diketone (±)-**14** (165.1 mg, 1.29 mmol, 21% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.11 (d, J = 7.1 Hz, 3H), 2.15 (s, 3H), 2.22 (s, 3H), 2.32−2.46 (m, 1H), 2.91−3.15 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 16.4, 28.4, 29.8, 41.6, 46.2, 207.1, 211.3; R_f 0.20 (hexane:ethyl acetate = 3:1).

Reduction of Diketone 14. To a solution of $LiBH_4$ (48.6 mg, 2.23 mmol) in THF (3 mL) was added a solution of diketone **14** (47.0 mg, 0.367 mmol) in THF (4 mL) at 0 °C. The reaction mixture was stirred at room temperature for 21

h and the reaction was quenched by the addition of 1 M HCl-(aq) (8 mL) and ethyl acetate (20 mL) at 0 °C. The separated aqueous layer was extracted with ethyl acetate (5 × 50 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate) to afford a mixture of 3-methyl-2,5-hexanediols (29.8 mg, 0.225 mmol, 63% yield) as a colorless oil. The diastereomer ratio is shown in Table 3, run 1. The same procedure was used for Table 3, runs 2 and 3. Using the diketone (52.0 mg, 0.406 mmol), $LiBH_4$ (51.4 mg, 2.36 mmol) and CH_2Cl_2 (7 mL) gave the diols (35.8 mg, 0.271 mmol, 68% yield) (run 2). From the diketone (62.0 mg, 0.484 mmol), Bu_4NBH_4 (1.00 g, 3.89 mmol) and CH_2Cl_2 (10 mL), the diols was obtained (37.1 mg, 0.281 mmol, 58% yield) (Run 3).

References and Notes

(1) (a) Cram and Elhafez, *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *30*, 2199. (c) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145. (d) *Asymmetric Organic Reactions*; Morrison, J. D., Mosher, H. S., Eds.; Prentice Hall Inc.: Upper Saddle River, NJ, 1969. (e) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1983; Vol. 2.

(2) (a) Maier, G.; Roth, C.; Schmitt, R. K. *Chem. Ber.* **1985**, *118*, 704. (b) Maier, G.; Schmitt, R. K.; Seipp, U. *Chem. Ber.* **1985**, *118*, 722. (c) Maier, G.; Seipp, U. *Tetrahedron Lett.* **1987**, *28*, 4515. (d) Barluenga, J.; Resa, J. G.; Olano, B.; Fustero, S. *J. Org. Chem.* **1987**, *52*, 1425. (e) Hanamoto, T.; Hiyama, T. *Tetrahedron Lett.* **1988**, *29*, 6467. (f) Yamada, M.; Horie, T.; Kawai, M.; Yamamura, H.; Araki, S. *Tetrahedron* **1997**, *53*, 15685. (g) Bartoli, G.; Bosco, M.; Bellucci, M. C.; Dalpozzo, R.; Marcantoni, E.; Sambri, L. *Org. Lett.* **2000**, *2*, 45.

(3) (a) Schulz, R. C.; Mayerhöfer, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 216. (b) Masuda, T.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 268. (c) Kawai, M.; Masuda, T. *Polym. J.* **1981**, *13*, 573.

(4) (a) Jiang, Z.; Adams, S. E.; Sen, A. *Macromolecules* **1994**, *27*, 2694. (b) Bronco, S.; Consiglio, G.; Hutter, R.; Batistini, A.; Suter, U. W. *Macromolecules* **1994**, *27*, 4436. (c) Brookhart, M.; Wagner, M. I.; Balavoine, G. G. A.; Haddou, H. A. *J. Am. Chem. Soc.* **1994**, *116*, 3641. (d) Jiang, Z.; Sen, A. *J. Am. Chem. Soc.* **1995**, *117*, 4455. (e) Nozaki, K.; Sato, N.; Takaya, H. *J. Am. Chem. Soc.* **1995**, *117*, 9911. (f) Nozaki, K.; Sato, N.; Tonomura, Y.; Yasutomi, M.; Takaya, H.; Hiyama, T.; Matsubara, T.; Koga, N. *J. Am. Chem. Soc.* **1997**, *119*, 12779.

(5) Sen, A. *CHEMTECH* **1986**, 48.

(6) Hydride reduction: (a) Jiang, Z.; Sanganeria, S.; Sen, A. *J. Polym. Sci., Part A: Polym. Chem.* **1994**, *32*, 841. (b) Wong, P.; Drent, E.; Smaardijk, A. A.; Kramer, A. H. Eur. Pat. Appl. EP 322,976; *Chem. Abstr.* **1989**, *111*, 195667p. (c) Smaardijk, A. A.; Kramer, A. H. Eur. Pat. Appl. EP 372,602; *Chem. Abstr.* **1990**, *113*, 173476q. Hydrogenation: (d) Brubaker, M. M.; Coffman, D. D.; Hoehn, H. H. *J. Am. Chem. Soc.* **1952**, *74*, 1509. (e) Scott, S. L. U.S. Patent 2,495,292; *Chem. Abstr.* **1952**, *46*, 3294c. (f) Watanabe, Y.; Takeda, M.; Ookago, J.; Seo, S. Jpn. Kokai Tokkyo Koho JP 01,149,828; *Chem. Abstr.* **1990**, *112*, 57079t. (g) Ito, C.; Takatani, K. Jpn. Kokai Tokkyo Koho JP 05,339,367, *Chem. Abstr.* **1994**, *120*, 299571e. See also ref 6a.

(7) (a) Lu, S.; Paton, R. M.; Green, M. J.; Lucy, A. R. *Eur. Polym. J.* **1996**, *32*, 1285. (b) Khansawai, P.; Paton, R. M.; Reed, D. *J. Chem. Soc., Chem. Commun.* **1999**, 1297.

(8) Green, M. J.; Lucy, A. R.; Lu, S.; Paton, R. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2063.

(9) Coffman, D. D.; Hoeln, H. H.; Maynard, J. T. *J. Am. Chem. Soc.* **1954**, *76*, 6394.

(10) Upson, R. W. U.S. Patent 2,599,501, *Chem. Abstr.* **1952**, *46*, 8416f.

(11) Scott, S. L. U.S. Patent 2,495,293, *Chem. Abstr.* **1952**, *46*, 3299i.

(12) Michel, R. H.; Murphey, W. A. *J. Polym. Sci.* **1961**, *55*, 741.

(13) (a) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338. (b) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2653. (c) Nakata, T.; Fukui, M.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2657. (d) Fujisawa, T.; Kohama, H.; Tajima, K.; Sato, T. *Tetrahedron Lett.* **1984**, *25*, 5155. (e) Sayo, N.; Nakai, E.; Nakai, T. *Chem. Lett.* **1985**, 1723. (f) Nakata, T.; Tani, Y.; Hatozaki, M.; Oishi, T. *Chem. Pharm. Bull.* **1984**, *32*, 1411. (g) Kathawala, F. G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M. J.; Stabler, R. S.; Widler, L. *Helv. Chim. Acta* **1986**, *69*, 803. (h) Kashihara, H.; Suemune, H.; Fujimoto, K.; Sakai, K. *Chem. Pharm. Bull.* **1989**, *37*, 2610. (i) Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1980**, *21*, 1641. (j) Nakata, T.; Kuwabara, T.; Tani, Y.; Oishi, T. *Tetrahedron Lett.* **1982**, *23*, 1015. (k) Taber, D. F.; Deker, P. B.; Gaul, M. D. *J. Am. Chem. Soc.* **1987**, *109*, 7488.

(14) Tomooka, K.; Okinaga, T.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1989**, *30*, 1563.

(15) (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. (b) Hiyama, T.; Kimura, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1037. (c) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561.

(16) Reetz, M. T.; Kesseler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 989.

(17) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107.

(18) (a) Lommerts, B. J.; Klop, E. A.; Aerts, J. *J. Polym. Sci., Part B: Polym. Phys.* **1993**, *31*, 1319. (b) Chatani, Y.; Takizawa, T.; Murahashi, S.; Sakata, Y.; Nishimura, Y. *J. Polym. Sci.* **1961**, *55*, 811. (c) Wittwer, H.; Pino, P.; Suter, U. W. *Macromolecules* **1988**, *21*, 1262. (d) Aerts, J. *Polym. Bull.* **1996**, *36*, 645.

(19) Klop, E. A.; Lommerts, B. J.; Veurink, J.; Aerts, J.; van Puijenbroek, R. R. *J. Polym. Sci., Part B: Polym. Phys.* **1995**, *33*, 315.

(20) Brückner, S.; De Rosa, C.; Corradini, P.; Porzio, W.; Musco, A. *Macromolecules* **1996**, *29*, 1535.

(21) Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn* **1989**, *62*, 143.

MA000424D