Asymmetric Bis(alkoxycarbonylation) Reaction of Homoallylic Alcohols Catalyzed by Palladium in the Presence of Cu(I) Triflate Using the Chiral Bioxazoline Ligand

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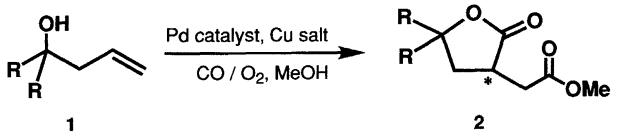
Palladium-catalyzed asymmetric intra- and intermolecular bis(alkoxycarbonylation) reactions of homoallylic alcohols in the presence of copper(I) triflate were achieved by using the chiral bioxazoline ligand, (*S*,*S*)-4,4′-dibenzyl-4,4′,5,5′-tetrahydro-2,2′-bioxazole, under normal pressure of carbon monoxide and oxygen at 25 °C to give the corresponding optically active γ-butyrolactones in 19—65% ee.

We recently reported on selective mono- and bis(alkoxycarbonylation) reactions catalyzed by palladium in the presence of copper(II) or copper(I) chloride under remarkably mild conditions to prepare esters from terminal olefins and γ-butyrolactones from homoallylic alcohols.[1] Our attention has then turned to designing of the enantioselective alkoxycarbonylation reaction.

Concerning enantioselective carbonylation catalyzed by palladium, only limited methods have been developed. The enantioselective hydrocarboxylation of styrene derivatives catalyzed by $PdCl_2$ was carried out in the presence of $CuCl_2$ using 1,1′-binaphthalene-2,2′-diyl hydrogenphosphate.[2] The palladium-catalyzed bis(alkoxycarbonylation) of styrene using atropisomeric diphosphanes gave phenylsuccinic acid ester enantioselectively.[3] Optically active poly(1,4-ketones) were synthesized by the copolymerization of olefins with carbon monoxide using palladium catalysts based on bis(oxazoline) ligands[4] and 1,2-bis(2,5-dimethylphospholano)benzene.[5] Further, enantioselective hydroformylation catalyzed by platinum and rhodium compounds gave optically active aldehydes and their acetals.[6] On the other hand, the enantioselective intramolecular carbonylation of olefinic alcohols could give optically active lactones, the synthesis of which is of considerable interest. 2-Methyl-4-butanolide was reported to be prepared by the palladium-catalyzed carbonylation of 2-buten-1-ol using diethyl tatrate or polyleucine in moderate optical purity.[7] Herein, we wish to report on the asymmetric intra- and intermolecular bis(alkoxycarbonylation)s of homoallylic alcohols catalyzed by palladium(II) and copper(I) salts under normal pressure of carbon monoxide and oxygen atmosphere to afford the corresponding optically active γ-butyrolactones.



1 2

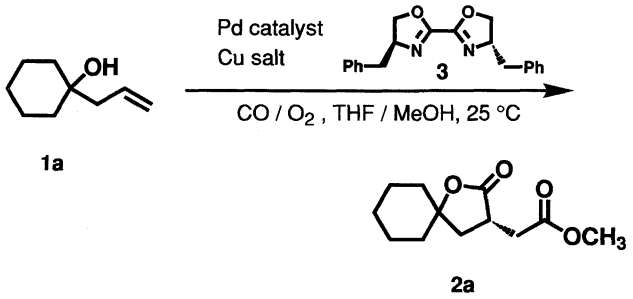
(1)

As a chiral ligand for the intra-and intermolecular bis(alkoxycarbonylation) reactions, the bioxazoline ligand[8—10] was chosen. The reaction of 1-allylcyclohexanol (**1a**) using 0.02 molar amounts of $PdCl_2$ and 1.5 molar amounts of CuCl in the presence of (*S*,*S*)-4,4′-dibenzyl-4,4′,5,5′-tetrahydro-2,2′-bioxazole (**3**) was first examined under a carbon monoxide and oxygen (ca. 1/1, v/v, 1 atm) atmosphere in MeOH and THF (1/1, v/v) at 25 °C. After the usual workup, the corresponding γ-butyrolactone **2a** was isolated in 62% yield. The optical yield of the obtained lactone, however, was determined to be 1% ee by an ^1H NMR analysis using $Eu(hfc)_3$ (Entry 1 in Table 1). When the carbonylation reaction was performed utilizing $CuOTf(C_6H_6)_{0.5}$ instead of CuCl, the optically active lactone **2a** was obtained in 50% ee (Entry 2). Furthermore, when allylpalladium chloride dimer was used instead of $PdCl_2$, the enhanced stereoselectivity was realized to produce lactone **2a** in 65% ee (Entry 6). The combination of the allylpalladium chloride dimer with CuCl resulted in a slight stereoselection (Entry 3). A reaction using $Cu(OTf)_2$ as a copper salt proceeded with lower stereoselectivity (Entry 8). The amount of $CuOTf(C_6H_6)_{0.5}$ influenced the stereoselectivity; i.e., using 0.04 molar amounts of $CuOTf(C_6H_6)_{0.5}$ resulted in poor stereoselection, and the use of 1.0 molar amount of $CuOTf(C_6H_6)_{0.5}$ was not very effective (Entries 4—7). In order to obtain optically active lactone **2a**, each allylpalladium chloride dimer and $CuOTf(C_6H_6)_{0.5}$ appeared to be necessary (Entries 9 and 10). In the reaction described above, monocarbonylated lactone **4** was scarcely obtained.

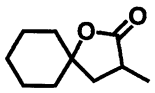
Table 1. Asymmetric Bis(alkoxycarbonylation) Reaction of 1-Allylcyclohexanol (**1a**) under Various Conditions[a)]

Entry	Pd catalyst	(molar amounts)	Cu Salt	(molar amounts)	Time/d	Yield of **2a**/%	ee/%[b)]
1[c)]	$PdCl_2$	(0.02)	CuCl	(1.5)	12	62	1
2	$PdCl_2$	(0.04)	$CuOTf(C_6H_6)_{0.5}$	(0.5)	6	78	50
3	$(C_3H_5PdCl)_2$	(0.02)	CuCl	(1.5)	19	81	2
4	$(C_3H_5PdCl)_2$	(0.02)	$CuOTf(C_6H_6)_{0.5}$	(0.04)	13	40	9
5	$(C_3H_5PdCl)_2$	(0.02)	$CuOTf(C_6H_6)_{0.5}$	(0.25)	7	60	51
6	$(C_3H_5PdCl)_2$	(0.02)	$CuOTf(C_6H_6)_{0.5}$	(0.5)	9	57	65
7	$(C_3H_5PdCl)_2$	(0.02)	$CuOTf(C_6H_6)_{0.5}$	(1.0)	3	22	52
8	$(C_3H_5PdCl)_2$	(0.02)	$Cu(OTf)_2$	(0.5)	4	55	18
9	—		$CuOTf(C_6H_6)_{0.5}$	(0.5)	5	—	—
10	$(C_3H_5PdCl)_2$	(0.02)	—		6	—	—

a) The reactions were performed in the presence of 0.08 molar amounts of **3** as a ligand otherwise noted. b) Enantiomeric excess was determined by ^{1}H NMR analysis using $Eu(hfc)_3$. c) The molar amount of **3** was 0.04.



1a **2a** (2)



4 (3)

The solvent effect was also examined, the results of which are summarized in Table 2. The carbonylation reaction in MeOH alone also gave optically active lactones (Entry 1). The use of Et_2O, DME, CH_2Cl_2, or C_6H_6 instead of THF showed moderate stereoselectivity (Entries 3—6), and little stereoselection was observed using CH_3CN (Entry 7), probably due to the coordination of CH_3CN toward palladium instead of the olefinic moiety of **1a**. Among these solvents, THF together with MeOH realized a higher stereoselection (Entry 2).

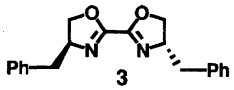
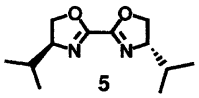
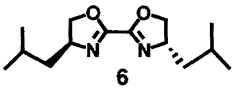
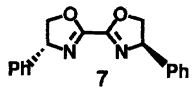
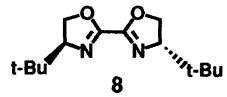
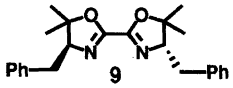
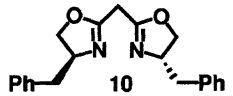
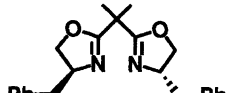
Next, the effect of substituents at the 4 and 4′ positions in the bioxazoline ligands was investigated. As shown in Table 3, a carbonylation reaction using isopropyl- and isobutyl-substituted bioxazoline ligands **5**,**6** proceeded with moderate stereoselectivity. Phenyl- and *t*-butyl-substituted ligands **7**,**8** were unpromising. The 5,5,5′,5′-tetramethyl analogue **9** disappointingly appeared to be less selective than **3**. In the case of bis(oxazoline) ligands **10**, **11**, the optical purities were

Table 2. Asymmetric Bis(alkoxycarbonylation) Reaction of 1-Allylcyclohexanol (**1a**) in Various Solvents[a)]

Entry	Solvent		Time/d	Yield of **2a**/%	ee/%[b)]
1	MeOH		5	36	50
2	MeOH+THF	(1/1)	9	57	65
3	MeOH+Et_2O	(1/1)	5	51	52
4	MeOH+DME	(1/1)	5	65	56
5	MeOH+CH_2Cl_2	(1/1)	6	67	45
6	MeOH+C_6H_6	(1/1)	3	36	36
7	MeOH+CH_3CN	(1/1)	9	51	1

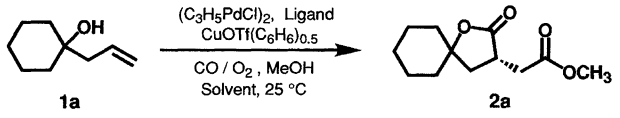
a) The reactions were performed using 0.02 molar amounts of $(C_3H_5PdCl)_2$ and 0.5 molar amounts of $CuOTf(C_6H_6)_{0.5}$ in the presence of 0.08 molar amounts of **3**. b) Enantiomeric excess was determined by ^{1}H NMR analysis using $Eu(hfc)_3$.

Table 3. Asymmetric Bis(alkoxycarbonylation) Reaction of 1-Allylcylohexanol (**1a**) Using Various Ligands[a)]

Entry	Ligand	Time/d	Yield of **2a**/%	ee/%[b)]
1	 **3**	9	57	65
2	 **5**	4	53	46
3	 **6**	3	52	53
4	 **7**	4	64	0
5	 **8**	5	65	18
6	 **9**	5	43	20
7	 **10**	3	25	2
8	 **11**	5	56	9

a) The reactions were performed using 0.02 molar amounts of $(C_3H_5PdCl)_2$ and 0.5 molar amounts of $CuOTf(C_6H_6)_{0.5}$ in the presence of 0.08 molar amounts of ligand in THF/MeOH. b) The absolute configuration of the product was *S* except Entry 4. Enantiomeric excess was determined by ^{1}H NMR analysis using $Eu(hfc)_3$.

poor. On the other hand, chiral ligands other than oxazolines were not effective for the present bis(alkoxycarbonylation) reaction. For example, the reaction using chiral phosphines (+)-DIOP and (+)-BINAP, chiral phosphoric acid (−)-1,1′-binaphthalene-2,2′-diyl hydrogenphosphate, and (+)-diethyl tatrate as chiral ligands, gave the corresponding lactone **2a** in <10% optical yield.



(4)

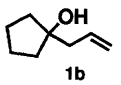
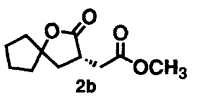
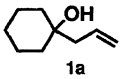
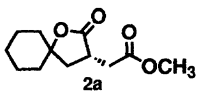
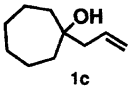
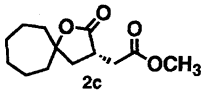
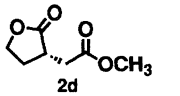
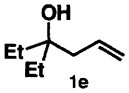
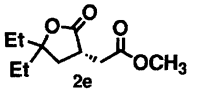
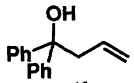
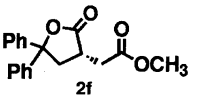
Then, the bis(alkoxycarbonylation) reaction of several homoallylic alcohols **1** was carried out using 0.02 molar amounts of allylpalladium chloride dimer and 0.5 molar amounts of $CuOTf(C_6H_6)_{0.5}$ in the presence of 0.08 molar amounts of bioxazoline **3** under a carbon monoxide and oxygen (ca. 1/1, v/v, 1 atm) atmosphere in MeOH and THF (1/1, v/v) at 25 °C; the results are summarized in Table 4. In the reaction of cyclopentanol and cycloheptanol derivatives **1b**, **1c**, comparable results were obtained (Entries 1 and 3). Unsubstituted homoallylic alcohol, 3-buten-1-ol (**1d**), showed low selectivity (Entry 4). In the cases of acyclic tertiary homoallylic alcohols, a bis(alkoxycarbonylation) reaction also proceeded enantioselectively (Entries 5 and 6). 1,1-Diphenyl-3-buten-1-ol (**1f**) afforded the corresponding γ-butyrolactone **2f** in 64% ee.

The absolute configuration of the lactone **2a** was confirmed based on the transformation to **16**, which was compared with the authentic **16** derived from **12**. That is, optically active alcohol **12** (68% ee), obtained by asymmetric esterification of 2-allyl-1,3-propanediol by PPL (Pig pancreatic lipase),[11,12] was converted to **16** according to the pathway shown in Scheme 1 (MEMCl means 2-methoxyethoxymethyl chloride). On the other hand, γ-butyrolactone **2a** (56% ee), obtained by the present asymmetric carbonylation reaction, was also transformed into **16**. By comparing the specific optical rotations of both alcohols **16** derived from **2a** and **12**, the absolute configuration of the γ-butyrolactone **2a** obtained by the present asymmetric carbonylation reaction was determined to be *S*. Furthermore, the ^{13}C NMR spectra in the presence of $Eu(hfc)_3$ of the major enantiomer **16** derived from **2a** and the major enantiomer of **16** derived from **12** were identical to each other.

Although the precise mechanism of the present reaction is still an open question,[13—15] the role of $CuOTf(C_6H_6)_{0.5}$ and the stereochemical course might be explained as follows: Copper(I) triflate reacts with palladium chloride complex **17** to afford a cationic palladium intermediate **18**,[16] in which the olefinic moiety could more strongly coordinate to the palladium metal, as illustrated in Fig. 1. At this stage, a steric hindrance between the substituent R in homoallylic alcohol and the substituent at C_4 of the bioxazoline ligand would disfavor the transition state T_2, and, thus, transition state T_1 was favored to produce (*S*)-γ-butyrolactones (Fig. 2).

In summary, palladium-catalyzed asymmetric bis(alkoxycarbonylation) of homoallylic alcohols was achieved utiliz-

Table 4. Asymmetric Bis(alkoxycarbonylation) Reaction of Homoallylic Alcohols **1** in the Presence of **3**[a]

Entry	Substrates	Time/d	Products	Yield/%	ee/%
1	 **1b**	3	 **2b**	56	52[b]
2	 **1a**	9	 **2a**	57	65[b]
3	 **1c**	5	 **2c**	40	49[b]
4	 **1d**	10	 **2d**	42	19[b]
5	 **1e**	7	 **2e**	40	48[b]
6	 **1f**	8	 **2f**	68	64[c]

a) The reactions were performed using 0.02 molar amounts of $(C_3H_5PdCl)_2$ and 0.5 molar amounts of $CuOTf(C_6H_6)_{0.5}$ in the presence of 0.08 molar amounts of **3**; see Experimental. On the basis of the absolute configuration of (*S*)-**2a**, the absolute configuration of products **2b**—**f** were tentatively determined to be *S*. b) Enantiomeric excess was determined by ^1H NMR analysis using $Eu(hfc)_3$. c) Enantiomeric excess was determined by HPLC analysis (Daicel Chiralcel OD-H).

ing the chiral bioxazoline ligand. This method provides a new entry for preparing optically active γ-butyrolactones.

Experimental

All of melting points were determined with a micro melting-point apparatus (Yanagimoto-Seisakusho) and were uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-GX 400 spectrometer with tetramethylsilane as an internal standard. The IR spectra were measured with a JASCO IRA-1 or a JASCO FT/IR-230 spectrometer. The MS spectra were measured with a Hitachi M-80 mass spectrometer. The HRMS spectrum was measured with a JMS-SX102A spectrometer. The specific optical rotations were recorded on a JASCO DIP-370 spectrometer. All of the solvents were distilled and stored over drying agents. Column chromatography and thin-layer chromatography (TLC) were performed on Wakogel C-300 and Merck's silica gel 60 PF_{254} (Art 7749), respectively.

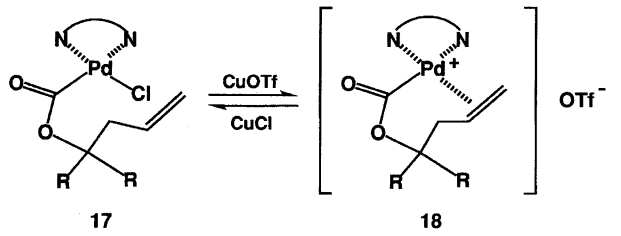


Fig. 1.

Chiral ligands **3**,[8a,10] **5**,[8a,9,10] **7**,[10] **8**,[8a,10] **10**,[8a] and **11**[17] were prepared by the methods reported in the literature. Ligand **6** was prepared according to the procedure for the preparation of **3**.[8a]

(*S*,*S*)-4,4′-Diisobutyl-4,4′,5,5′-tetrahydro-2,2′-bioxazole (6): Mp 59—60 °C (hexane); $[\alpha]_D^{25}$ −175° (*c* 0.9, MeOH); IR (KBr) 2950, 1615, 1460, 1375, 1360, 1105, 1060, 930, 810, 720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.93 (d, *J*=6.71 Hz, 6H), 0.96 (d, *J*=6.72 Hz, 6H), 1.35 (dt, *J*=13.42, 7.32 Hz, 2H), 1.70 (dt, *J*=13.42, 6.87 Hz, 2H), 1.85 (m, 2H), 3.99 (dd, *J*=8.54, 8.24 Hz, 2H), 4.34 (m, 2H), 4.52 (dd, *J*=9.56, 8.24 Hz, 2H). Found: C, 66.37; H, 9.64; N, 11.03%. Calcd for $C_{14}H_{24}N_2O_2$: C, 66.63; H, 9.59; N, 11.10%.

Preparation of Ligand 9: (*S*)-*N*-(Trifluoroacetyl)phenylalanine Methyl Ester: To a suspension of (*S*)-phenylalanine methyl ester hydrochloride (26.5 g, 123 mmol) in CH_2Cl_2 (150 ml) were added triethylamine (37.5 ml, 270 mmol) and trifluoroacetic anhydride (20.8 ml, 148 mmol) at −78 °C under a nitrogen atmosphere; the reaction mixture was stirred at room temperature overnight. After evaporation of CH_2Cl_2, the residue was extracted with ether; the combined extracts were then washed with water and brine, dried over Na_2SO_4, and condensed in vacuo to give crude (*S*)-*N*-(trifluoroacetyl)phenylalanine methyl ester in 58% yield (14.5 g), which was used for the following reaction without further purification. MS *m*/*z* 275 (M^+; 11.49%), 216 (11.10), 162 (100.00), 131 (28.02), 103 (15.37), 91 (99.38), 65 (15.40), 43 (18.61); IR (KBr)

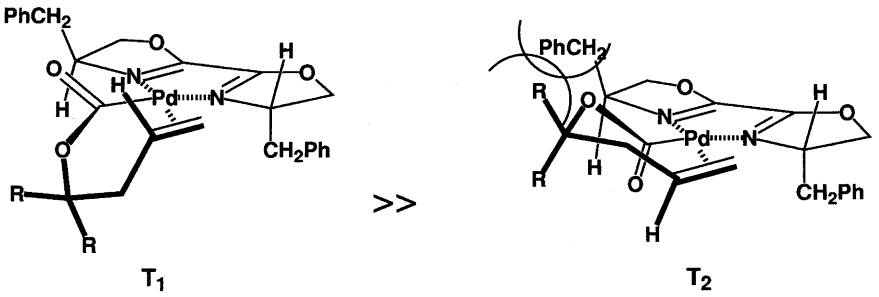
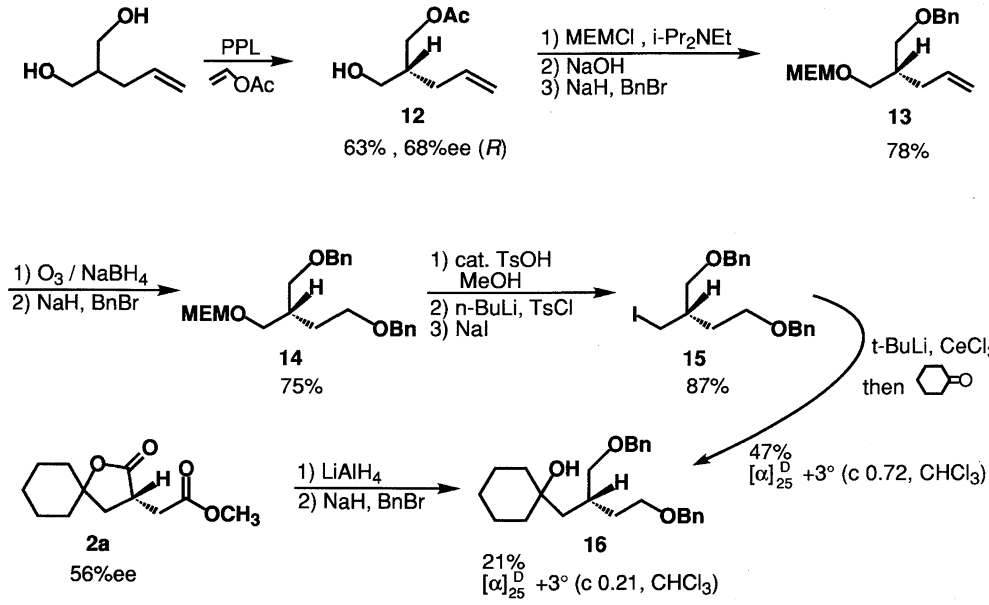


Fig. 2.



Scheme 1.

3320, 3070, 3040, 2940, 1750, 1700, 1600, 1540, 1500, 1440, 1360, 1280, 1210, 1160, 1025, 880, 740, 720, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.17 (dd, J=14.04, 5.49 Hz, 1H), 3.24 (dd, J=14.04, 5.49 Hz, 1H), 3.79 (s, 3H), 4.88 (ddd, J=7.63, 5.80, 5.49 Hz, 1H), 6.81 (br, 1H), 7.07 (dd, J=7.63, 1.53 Hz, 2H), 7.27—7.35 (m, 3H).

(*S*)-3-Amino-2-methyl-4-phenyl-2-butanol: To an ether (134 ml) solution of methylmagnesium iodide, prepared from magnesium (3.1 g, 128 mmol) and methyl iodide (7.9 ml, 128 mmol), was added a THF (15 ml) solution of the crude (*S*)-*N*-(trifluoroacetyl)-phenylalanine methyl ester (7.0 g, 25.5 mmol) obtained above at 0 °C under a nitrogen atmosphere; the mixture was stirred for 1 d.[18] The reaction mixture was poured into a sat. aqueous NH_4Cl solution, and the resulting precipitate was filtered off through Celite. The filtrate was extracted with ethyl acetate; the combined extracts were then washed with water and brine, dried over Na_2SO_4, and condensed in vacuo to give crude (*S*)-2-methyl-4-phenyl-3-(trifluoroacetylamino)-2-butanol. The obtained alcohol was dissolved in MeOH (50 ml) and then treated with a 1 M (1 M=1 mol dm^{-3}) NaOH solution (50 ml, 50 mmol) with stirring for 3 d. Extraction with CH_2Cl_2 and the combined extracts were washed with water and brine, dried over Na_2SO_4, and condensed in vacuo. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH=10/1, v/v) to give (*S*)-3-amino-2-methyl-4-phenyl-2-butanol in 24% yield (1.06 g). Mp 71 °C (toluene); $[\alpha]_D^{25}$ −46° (*c* 0.32, $CHCl_3$); IR (KBr) 3450, 3370, 3120, 3080, 3040, 2990, 2920, 1620, 1560, 1520, 1485, 1420, 1375, 1120, 1070, 1040, 955, 900, 730, 720, 685 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.21 (s, 3H), 1.26—1.60 (br, 3H), 1.30 (s, 3H), 2.27 (dd, J=13.42, 11.29 Hz, 1H), 2.81 (dd, J=11.29, 2.75 Hz, 1H), 3.03 (dd, J=13.42, 2.75 Hz, 1H), 7.20 (d, J=7.02 Hz, 2H), 7.24—7.36 (m, 3H). Found: *m/z* 180.1402. Calcd for $C_{11}H_{18}NO$: M+H, 180.1388.

(*S,S*)-4,4′-Dibenzyl-4,4′,5,5′-tetrahydro-5,5,5′,5′-tetramethyl-2,2′-bioxazole (9): (*S*)-3-Amino-2-methyl-4-phenyl-2-butanol (906 mg, 5.06 mmol) was treated with a slight excess amount of 1 M hydrochloric acid, and excess hydrochloric acid was evaporated. To the residue was added a $ClCH_2CH_2Cl$ (10 ml) solution of diethyl oxalimidate (364 mg, 2.53 mmol) under a nitrogen atmosphere; the solution was refluxed for 1 d.[8a] After cooling and adding water, the reaction mixture was extracted with CH_2Cl_2, and the combined extracts were washed with water and brine, dried over Na_2SO_4, and condensed in vacuo to give almost pure **9** in 20% yield (190 mg). The pure **9** was obtained by recrystallization from toluene. Mp 181—183 °C; $[\alpha]_D^{25}$ −166° (*c* 0.39, MeOH); IR (KBr) 3027, 2976, 1612, 1495, 1451, 1374, 1307, 1197, 1119, 1069, 970, 908, 787, 748, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.33 (s, 6H), 1.36 (s, 6H), 2.80 (dd, J=14.35, 8.85 Hz, 2H), 3.24 (dd, J=14.35, 6.11 Hz, 2H), 4.22 (dd, J=8.85, 6.11 Hz, 2H), 7.18—7.34 (m, 10H). Found: C, 76.73; H, 7.55; N, 7.46%. Calcd for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.50; N, 7.44%.

The Representative Procedure of Asymmetric Bis(alkoxycarbonylation) for 1-Allylcyclohexanol (1a): After a mixture of allylpalladium chloride dimer (3.66 mg, 0.010 mmol as dimer), $CuOTf(C_6H_6)_{0.5}$ (63 mg, 0.25 mmol), and (*S,S*)-4,4′-dibenzyl-4,4′,5,5′-tetrahydro-2,2′-bioxazole (**3**) (13 mg, 0.040 mmol) in THF (1.5 ml) was stirred for 30 min under a nitrogen atmosphere, a THF (1.5 ml) solution of 1-allylcyclohexanol (**1a**) (70 mg, 0.5 mmol) and MeOH (3 ml) was added successively. The nitrogen atmosphere was replaced with CO/O_2 (ca. 1/1, v/v), and the mixture was stirred for 9 d at 25 °C. Sat. aqueous $NaHCO_3$ was added and the insoluble substance was filtered off through Celite. After the filtrate was extracted with ethyl acetate, the combined extracts were washed with water and brine, dried over Na_2SO_4, and condensed in vacuo. The residue was purified by TLC (SiO_2, hexane/ethyl acetate=4/1, v/v) to give (*S*)-3-(methoxycarbonylmethyl)-1-oxaspiro[4.5]decan-2-one (**2a**) (65 mg, 57%, 65% ee) and 3-methyl-1-oxaspiro[4.5]decan-2-one (**4**) (2 mg, 2%).[1b,19]

(*S*)-3-(Methoxycarbonylmethyl)-1-oxaspiro[4.5]decan-2-one (2a): An oil; $[\alpha]_D^{25}$ −11° (*c* 0.60, $CHCl_3$; 65% ee); MS *m/z* 227 (M^++1; 13.04%), 226 (M^+; 79.63), 195 (48.56), 166 (100.00), 155 (66.80), 153 (58.32), 151 (35.84), 150 (82.71), 132 (27.67), 123 (22.69), 108 (25.87), 100 (27.57), 67 (25.13); IR (neat) 2960, 2880, 1770, 1740, 1205 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.34—1.86 (m, 10H), 1.68 (t, J=12.52 Hz, 1H), 2.43 (dd, J=12.52, 9.46 Hz, 1H), 2.52 (dd, J=17.09, 9.15 Hz, 1H), 2.91 (dd, J=17.09, 4.28 Hz, 1H), 3.12 (m, 1H), 3.71 (s, 3H).

In a similar manner, other lactones **2b—f** were prepared from the corresponding homoallylic alcohols **1b—f**.

(*S*)-3-(Methoxycarbonylmethyl)-1-oxaspiro[4.4]nonan-2-one (2b): An oil; $[\alpha]_D^{25}$ −7° (*c* 0.63, $CHCl_3$; 52% ee); MS *m/z* 212 (M^+; 1.89%), 183 (41.69), 181 (39.00), 155 (37.14), 152 (100.00), 136 (74.62), 110 (37.98), 94 (56.60), 55 (29.20); IR (neat) 2900, 2840, 1760, 1720, 1420, 1360, 1320, 1260, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.62—1.78 (m, 4H), 1.78—1.94 (m, 2H), 1.94—2.14 (m, 3H), 2.45 (dd, J=12.51, 8.55 Hz, 1H), 2.50 (dd, J=17.09, 9.15 Hz, 1H), 2.93 (dd, J=17.09, 4.27 Hz, 1H), 3.08—3.20 (m, 1H), 3.71 (s, 3H).

(*S*)-3-(Methoxycarbonylmethyl)-1-oxaspiro[4.6]undecan-2-one (2c): An oil; $[\alpha]_D^{25}$ −16° (*c* 0.36, $CHCl_3$; 49% ee); MS *m/z* 240 (M^+; 37.72%), 209 (45.73), 183 (60.80), 180 (100.00), 155 (64.11), 151 (20.44), 123 (35.70), 122 (27.71), 95 (24.25), 81 (19.47), 67 (17.98), 55 (24.55), 41 (27.32), 28 (14.71); IR (neat) 2928, 2859, 1766, 1374, 1237, 1164, 1018, 966, 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.30—1.50 (m, 2H), 1.50—1.64 (m, 2H), 1.64—1.84 (m, 7H), 1.84—1.94 (m, 1H), 2.06 (dd, J=12.51, 8.85 Hz, 1H), 2.44 (dd, J=12.51, 8.85 Hz, 1H), 2.50 (dd, J=17.09, 9.16 Hz, 1H), 2.90 (dd, J=17.09, 3.96 Hz, 1H), 3.11 (m, 1H), 3.71 (s, 3H).

(*S*)-2-(Methoxycarbonylmethyl)-4-butenolide (2d): An oil; $[\alpha]_D^{25}$ −5° (*c* 0.29, $CHCl_3$; 19% ee); MS *m/z* 159 (M^++1; 1.97%), 127 (37.80), 114 (16.88), 82 (16.91), 72 (22.41), 59 (57.33), 55 (100.00); IR (neat) 2945, 2910, 1760, 1725, 1430, 1360, 1260, 1200, 1145, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.05 (m, 1H), 2.51—2.59 (m, 2H), 2.89—3.01 (m, 2H), 3.72 (s, 3H), 4.24 (m, 1H), 4.41 (dt, J=8.85, 1.83 Hz, 1H).

(*S*)-4, 4- Diethyl- 2- (methoxycarbonylmethyl)- 4- butenolide (2e): An oil; $[\alpha]_D^{25}$ −10° (*c* 0.43, $CHCl_3$; 48% ee); MS *m/z* 185 (M^+−Et; 100.00%), 183 (25.41), 153 (65.37), 138 (23.78), 125 (43.43), 111 (36.01), 96 (24.65), 81 (21.75), 57 (63.86), 43 (26.26), 28 (40.46); IR (neat) 2972, 2884, 1763, 1439, 1372, 1173, 1037, 953 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.93 (t, J=7.33 Hz, 3H), 0.95 (t, J=7.33 Hz, 3H), 1.60—1.84 (m, 5H), 2.35 (dd, J=12.82, 9.46 Hz, 1H), 2.52 (dd, J=17.09, 8.85 Hz, 1H), 2.90 (dd, J=17.09, 3.96 Hz, 1H), 3.04—3.18 (m, 1H), 3.71 (s, 3H).

(*S*)-2-(Methoxycarbonylmethyl)-4,4-diphenyl-4-butenolide (2f): An oil; $[\alpha]_D^{25}$ −19° (*c* 0.69, $CHCl_3$; 64% ee); MS *m/z* 310 (M^+; 100.00%), 233 (53.80), 205 (47.54), 183 (83.68), 165 (37.07), 128 (49.44), 115 (26.39), 105 (96.92), 77 (48.64); IR (neat) 3060, 3035, 3000, 2960, 2845, 1960, 1890, 1780, 1740, 1600, 1495, 1450, 1375, 1240, 1180, 1090, 1040, 975, 750, 700, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.52—2.64 (m, 2H), 2.93 (dd, J=17.09, 3.97 Hz, 1H), 2.96—3.06 (m, 1H), 3.36 (dd, J=12.51, 7.93 Hz, 1H), 3.70 (s, 3H), 7.22—7.44 (m, 8H), 7.44—7.50 (m, 2H).

Transformation of 12 to 16: (*R*)-2-Acetoxymethyl-4-penten-1-ol (12): Under a nitrogen atmosphere, a centrifuged solution of Pig pancreatic lipase (Sigma, Type II) (1.278 g, 50 wt%) was added

to a THF (175 ml) solution of 2-allyl-1,3-propanediol (2.56 g, 22 mmol) at 0 °C; to the resulting suspension was added vinyl acetate (2.84 g, 33 mmol). After stirring for 1 d, the mixture was filtered through Celite. The condensed filtrate was separated by silica-gel column chromatography (hexane/ether=1/2—0/1, v/v) to give **12** (2.20 g, 63%), the unreacted diol (0.35 g, 14%), and diacetate (1.02 g, 23%). Mono acetate **12**: An oil; $[\alpha]_D^{25}$ +8° (*c* 0.92, $CHCl_3$) [lit,[11] (*S*)-**12**; $[\alpha]_D^{23}$ −7.65° (95% ee)]; MS *m/z* 158 (M^+; 0.47%), 141 (13.99), 111 (10.25), 89 (100.00), 81 (26.44), 80 (16.32), 59 (88.35), 58 (10.30), 45 (26.28), 44 (13.36), 43 (72.10), 41 (17.13), 31 (15.99), 29 (13.29); IR (neat) 3500, 2980, 2880, 2820, 1735, 1710, 1630, 1440, 1380, 1360, 1230, 1190, 1100, 1030, 975, 910, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.86—1.99 (m, 1H), 2.08 (s, 3H), 2.03—2.20 (m, 3H), 3.54 (dd, *J*=11.29, 6.10 Hz, 1H), 3.62 (dd, *J*=11.29, 4.88 Hz, 1H), 4.09 (dd, *J*=11.29, 6.41 Hz, 1H), 4.19 (dd, *J*=11.29, 4.88 Hz, 1H), 5.06 (ddd, *J*=10.07, 2.13, 1.22 Hz, 1H), 5.09 (ddd, *J*=17.09, 3.35, 1.52 Hz, 1H), 5.79 (ddt, *J*=17.09, 10.07, 7.02 Hz, 1H). The optical purity of the obtained **12** was determined to be 68% ee by an ^1H NMR analysis of the (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) ester derivative using $Eu(hfc)_3$.[11]

(*R*)-5-Acetoxy-4-[(2-methoxyethoxy)methoxymethyl]-1-pentene: Under a nitrogen atmosphere, a mixture of **12** (2.06 g, 13 mmol), *N,N*-diisopropylethylamine (2.52 g, 19.5 mmol), and chloro(2-methoxyethoxy)methane (2.43 g, 19.5 mmol) in CH_2Cl_2 (160 ml) was stirred at room temperature for 1 d. To the reaction mixture were added *N,N*-diisopropylethylamine (0.84 g, 6.5 mmol) and chloro(2-methoxyethoxy)methane (0.810 g, 6.5 mmol) again; the resulting solution was then further stirred for 1 d. To the solution was added sat. aqueous NH_4Cl, and the resulting solution was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, and condensed under reduced pressure. Purification by silica-gel column chromatography (hexane/ether=4/1—3/1, v/v) gave (*R*)-5-acetoxy-4-[(2-methoxyethoxy)methoxymethyl]-1-pentene in 90% yield (3.03 g). An oil; $[\alpha]_D^{25}$ +1° (*c* 1.40, $CHCl_3$); MS *m/z* 187 (M^+−OAc; 0.18%), 141 (17.60), 89 (78.46), 81 (42.38), 67 (18.60), 59 (100.00), 45 (22.24), 43 (96.94), 41 (18.33); IR (neat) 3540, 3080, 2990, 2900, 2820, 1735, 1710, 1630, 1460, 1440, 1360, 1230, 1160, 1100, 1020, 910, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.96—2.08 (m, 1H), 2.05 (s, 3H), 2.08—2.24 (m, 2H), 3.39 (s, 3H), 3.48—3.58 (m, 4H), 3.64—3.70 (m, 2H), 4.08—4.12 (m, 2H), 4.69 (s, 2H), 5.05 (ddd, *J*=10.07, 2.14, 1.22 Hz, 1H), 5.06 (ddd, *J*=17.09, 3.36, 1.52 Hz, 1H), 5.77 (ddt, *J*=17.09, 10.07, 7.02 Hz, 1H).

(*S*)-2-[(2-Methoxyethoxy)methoxymethyl]-4-penten-1-ol: After (*R*)-5-acetoxy-4-[(2-methoxyethoxy)methoxymethyl]-1-pentene (2.98 g, 12 mmol) was treated with excess 1 M NaOH for 1 d, the product was extracted with ether. The combined extracts were then washed with brine, dried over Na_2SO_4, and condensed under reduced pressure to give crude (*S*)-2-[(2-methoxyethoxy)-methoxymethyl]-4-penten-1-ol (2.420 g, 98%), which was used for the following reaction without further purification. An oil; MS *m/z* 205 (M^++1; 0.30%), 105 (25.03), 89 (97.77), 81 (49.61), 80 (20.67), 77 (29.47), 68 (38.47), 67 (36.56), 59 (100.00), 57 (27.52), 55 (28.83), 45 (62.11), 43 (40.28), 41 (47.68), 39 (22.18), 31 (44.78), 29 (38.62); IR (neat) 3440, 3080, 2900, 2820, 1720, 1630, 1460, 1435, 1360, 1225, 1190, 1160, 1080, 1030, 900, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.84—1.96 (m, 1H), 2.04—2.16 (m, 2H), 2.50 (brs, 1H), 3.40 (s, 3H), 3.53—3.66 (m, 4H), 3.66—3.75 (m, 4H), 4.70 (s, 2H), 5.03 (d, *J*=10.07 Hz, 1H), 5.06 (d, *J*=17.09 Hz, 1H), 5.80 (ddt, *J*=17.09, 10.07, 7.02 Hz, 1H).

(*S*)-4-(Benzyloxymethyl)-5-(2-methoxyethoxy)methoxy-1-pentene (13): Under a nitrogen atmosphere, a DMF (40 ml) solution of (*S*)-2-[(2-methoxyethoxy)methoxymethyl]-4-penten-1-ol (0.429 g, 2.1 mmol) was treated with sodium hydride (60% dispersion in mineral oil) (0.42 g, 10.5 mmol); the suspension was then stirred for 1 h at room temperature. To the solution, benzyl bromide (0.375 ml, 3.2 mmol) was added. After stirring overnight, water was added and the mixture was extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, and condensed in vacuo. The residue was purified by TLC (SiO_2, hexane/ethyl acetate=4/1, v/v) to give **13** in 89% yield (0.547 g). An oil; $[\alpha]_D^{25}$ +1° (*c* 0.96, $CHCl_3$) [lit,[11] (*R*)-**13**; $[\alpha]_D^{23}$ −1.97° (95% ee)]; MS *m/z* 294 (M^+; 0.13%), 293 (M^+-1; 0.58), 205 (16.18), 107 (37.72), 105 (25.57), 91 (100.00), 89 (42.09), 81 (16.38), 59 (83.43); IR (neat) 3495, 3389, 3063, 3030, 2927, 2877, 2489, 2237, 1884, 1651, 1454, 1365, 1200, 1173, 1048, 849, 740, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.92—2.06 (m, 1H), 2.12—2.24 (m, 2H), 3.38 (s, 3H), 3.42—3.51 (m, 2H), 3.51—3.65 (m, 4H), 3.65—3.71 (m, 2H), 4.49 (s, 2H), 4.69 (s, 2H), 5.00 (d, *J*=10.07 Hz, 1H), 5.03 (d, *J*=17.09 Hz, 1H), 5.78 (ddt, *J*=17.09, 10.07, 7.02 Hz, 1H), 7.26—7.40 (m, 5H).

(*S*)-3-(Benzyloxymethyl)-4-(2-methoxyethoxy)methoxy-1-butanol: Under an oxygen atmosphere, ozone containing oxygen was bubbled into a CH_2Cl_2 (20 ml) solution of (*S*)-**13** (1.18 g, 4 mmol) for 100 min at −78 °C. After confirmation of the complete consumption of (*S*)-**13** by TLC, a MeOH (9 ml) solution of sodium borohydride (1.21 g, 32 mmol) was added. The reaction mixture was gradually warmed to room temperature and stirred overnight. The mixture was quenched with water and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, and condensed in vacuo. The residue was separated by silica-gel column chromatography (ethyl acetate) to give (*S*)-3-(benzyloxymethyl)-4-(2-methoxyethoxy)methoxy-1-butanol and the intermediary ozonide. Then, the ozonide was again treated with excess $NaBH_4$ in MeOH overnight. After a similar workup, (*S*)-3-(benzyloxymethyl)-4-(2-methoxyethoxy)methoxy-1-butanol was obtained in 75% total yield (980 mg). An oil; $[\alpha]_D^{25}$ −0.6° (*c* 0.96, $CHCl_3$); MS *m/z* 298 (M^+; 0.05%), 121 (39.15), 108 (26.08), 103 (91.46), 101 (31.23), 92 (34.29), 89 (64.53), 85 (49.64), 84 (25.29), 79 (22.75), 59 (100.00), 43 (33.31); IR (neat) 3460, 3070, 3040, 2940, 2860, 1710, 1590, 1570, 1440, 1355, 1260, 1190, 1160, 1090, 1030, 830, 720, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.60—1.74 (m, 2H), 2.09 (m, 1H), 2.65 (brs, 1H), 3.37 (s, 3H), 3.42 (d, *J*=6.41 Hz, 1H), 3.45 (d, *J*=6.41 Hz, 1H), 3.50—3.62 (m, 4H), 3.64—3.70 (m, 4H), 4.51 (s, 2H), 4.69 (s, 2H), 7.26—7.36 (m, 5H).

(*S*)-4-Benzyloxy-2-(benzyloxymethyl)-1-[(2-methoxyethoxy)-methoxy]butane (14): Under a nitrogen atmosphere, a DMF (10 ml) solution of (*S*)-3-(benzyloxymethyl)-4-(2-methoxyethoxy)-methoxy-1-butanol (1.31 g, 4.4 mmol) was treated with sodium hydride (60% dispersion in mineral oil) (0.528 g, 13.2 mmol) at 0 °C and the suspension was stirred for 1 h at room temperature. To the solution, benzyl bromide (1.05 ml, 8.8 mmol) was added. After stirring overnight, water was added and the mixture was extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, and condensed in vacuo. The residue was purified by silica-gel column chromatography (hexane/ethyl acetate=4/1—0/1, v/v) to give **14** in quantitative yield (1.71 g). An oil; $[\alpha]_D^{25}$ +2° (*c* 1.0, $CHCl_3$); MS *m/z* 313 ($M^+-CH_3OCH_2CH_2O$; 3.53%), 299 (1.15), 207 (14.98), 193 (13.37), 191 (14.61), 115 (46.37), 105 (63.62), 101 (33.19), 92 (20.99), 91 (100.00), 89 (55.29), 85 (23.75), 83 (28.35), 59 (68.85); IR (neat) 3500, 3060, 3050, 2940, 2880, 1735, 1600, 1580, 1490, 1450, 1360, 1240, 1200, 1170, 1100, 1040, 840, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.71 (q, *J*=6.71

Hz, 2H), 2.01—2.14 (m, 1H), 3.36 (s, 3H), 3.43—3.60 (m, 8H), 3.61—3.66 (m, 2H), 4.47 (s, 4H), 4.67 (s, 2H), 7.22—7.40 (m, 10H).

(*R*)-4-Benzyloxy-2-(benzyloxymethyl)-1-butanol: A MeOH (40 ml) solution of (*S*)-**14** (895 mg, 2.3 mmol) and a catalytic amount of TsOH was refluxed for 2 d. After cooling to room temperature, sat. aqueous $NaHCO_3$ was added and the mixture was extracted with ethyl acetate. The combined extracts were washed with water and brine, dried over Na_2SO_4, and condensed in vacuo. The residue was purified by silica-gel column chromatography (hexane/ethyl acetate=4/1—1/1, v/v) to give (*R*)-4-benzyloxy-2-(benzyloxymethyl)-1-butanol in 87% yield (602 mg). An oil; $[\alpha]_D^{25}$ +8° (*c* 0.95, $CHCl_3$); MS *m/z* 301 (M^++1; 0.19%), 300 (M^+; 0.06), 107 (41.75), 103 (81.00), 101 (20.48), 92 (24.98), 91 (100.00), 85 (32.80), 57 (10.13); IR (neat) 3420, 3080, 3040, 2940, 2860, 1490, 1445, 1360, 1200, 1090, 1020, 725, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.68 (q, *J*=6.10 Hz, 2H), 1.96—2.10 (m, 1H), 2.89 (brs, 1H), 3.24—3.60 (m, 4H), 3.60—3.74 (br, 2H), 4.49 (s, 4H), 7.24—7.40 (m, 10H).

(*S*)-4-Benzyloxy-2-(benzyloxymethyl)-1-tosyloxybutane: Under a nitrogen atmosphere, butylithium (1.24 ml in hexane, 2.1 mmol) was added to a THF (10 ml) solution of (*R*)-4-benzyloxy-2-(benzyloxymethyl)-1-butanol (512 mg, 1.7 mmol) at 0 °C and the solution was stirred for 1 h. To the solution, a THF solution (10 ml) of tosyl chloride (486 mg, 2.5 mmol) was added, and the reaction mixture was stirred for 1 h. Sat. aqueous NH_4Cl was added and the mixture was extracted with CH_2Cl_2. The combined extracts were washed with water and brine, dried over Na_2SO_4, and condensed in vacuo. The residue was purified by silica-gel column chromatography (hexane/ethyl acetate=8/1—0/1, v/v) to give (*S*)-4-benzyloxy-2-(benzyloxymethyl)-1-tosyloxybutane in quantitative yield (994 mg). An oil; $[\alpha]_D^{25}$ −0.3° (*c* 1.24, $CHCl_3$); MS *m/z* 363 (M^+ − Bn; 2.20%), 2.57 (30.13), 192 (31.85), 191 (17.76), 173 (8.85), 156 (8.55), 155 (12.12), 145 (9.52), 120 (26.38), 107 (100.00), 92 (88.77), 91 (93.30), 65 (62.76); IR (neat) 3080, 3050, 2940, 2880, 2800, 1590, 1490, 1450, 1360, 1300, 1285, 1210, 1180, 1170, 1090, 1020, 1015, 950, 910, 830, 810, 780, 730, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.64 (q, *J*=6.41 Hz, 2H), 2.12—2.22 (m, 1H), 2.40 (s, 3H), 3.36—3.48 (m, 4H), 4.07 (dd, *J*=9.46, 5.80 Hz, 1H), 4.13 (dd, *J*=9.46, 4.88 Hz, 1H), 4.37 (s, 2H), 4.42 (s, 2H), 7.21 (d, *J*=8.24 Hz, 2H), 7.24—7.36 (m, 10H), 7.75 (d, *J*=8.24 Hz, 2H).

(*S*)-4-Benzyloxy-2-(benzyloxymethyl)-1-iodobutane (15): Under a nitrogen atmosphere, an acetone (10 ml) solution of (*S*)-4-benzyloxy-2-(benzyloxymethyl)-1-tosyloxybutane (615 mg, 1.35 mmol) and sodium iodide (607 mg, 4.04 mmol) was refluxed for 7 h. After cooling to room temperature, sat. aqueous $NaHSO_3$ was added and the mixture was extracted with ether. The combined extracts were washed with water and brine, dried over Na_2SO_4, and condensed in vacuo. The residue was purified by TLC (SiO_2, hexane/ethyl acetate=8/1, v/v) to give **15** in quantitative yield (554 mg). An oil; $[\alpha]_D^{25}$ +3° (*c* 1.03, $CHCl_3$); MS *m/z* 410 (M^+; 0.58%), 319 (75.99), 283 (2.65), 211 (100.00), 183 (5.70), 181 (61.33), 149 (56.32), 127 (5.66), 92 (97.40), 77 (43.95), 65 (97.63); IR (neat) 3062, 3029, 2857, 2792, 1950, 1872, 1810, 1726, 1604, 1586, 1496, 1453, 1362, 1204, 1185, 1099, 1028, 949, 908, 801, 737, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.56—1.74 (m, 2H), 1.74—1.86 (m, 1H), 3.32 (dd, *J*=9.46, 5.18 Hz, 1H), 3.34 (dd, *J*=9.46, 7.33 Hz, 1H), 3.43—3.53 (m, 4H), 4.48 (s, 2H), 4.50 (s, 2H), 7.24—7.44 (m, 10H).

(*R*)-1-[4-Benzyloxy-2-(benzyloxymethyl)butyl]cyclohexanol (16): Under a nitrogen atmosphere, to an ether (1 ml) solution of **15** (205 mg, 0.5 mmol) was added *t*-butyllithium (0.65 ml in pentane, 1.1 mmol) at −78 °C and the solution was stirred for 0.5 h. To the solution was introduced a THF (2 ml) suspension of cerium(III) chloride (98 mg, 0.4 mmol) which has been previously stirred overnight.[20] After 30 min, a THF solution of cyclohexanone (39 mg, 0.4 mmol) was added and the reaction mixture was gradually warmed to −40 °C over a 1 h period. The reaction was quenched by sat. aqueous NH_4Cl and the mixture was extracted with ether. The combined extracts were washed with water and brine, dried over Na_2SO_4, and condensed in vacuo. The residue was separated by TLC (SiO_2, hexane/ethyl acetate=8/1, v/v) to give **16** in 47% yield (72 mg). An oil; $[\alpha]_D^{25}$ +3° (*c* 0.72, $CHCl_3$); MS *m/z* 382 (M^+; 0.52%), 364 (1.90), 273 (15.49), 256 (43.46), 185 (29.74), 165 (79.08), 147 (45.82), 121 (68.75), 105 (83.38), 91 (100.00), 77 (43.36), 71 (47.06), 67 (36.48), 65 (30.16), 55 (22.12), 41 (18.12); IR (neat) 3460, 3080, 3040, 2940, 2870, 1490, 1450, 1360, 1250, 1200, 1080, 1065, 1020, 965, 725, 685 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.26—1.76 (m, 14H), 2.06—2.18 (br, 1H), 3.30 (dd, *J*=8.85, 8.24 Hz, 1H), 3.43 (s, 1H), 3.46 (dd, *J*=8.85, 4.73 Hz, 1H), 3.50 (t, *J*=6.46 Hz, 2H), 4.47 (s, 2H), 4.51 (s, 2H), 7.24—7.46 (m, 10H).

Transformation of 2a to 16: (*R*)-1-[4-Hydroxy-2-(hydroxymethyl)butyl]cyclohexanol: Under a nitrogen atmosphere, lithium aluminum hydride was added to a THF (5 ml) solution of (*S*)-**2a** (67 mg, 0.28 mmol, 56% ee) and the suspension was stirred overnight. The reaction mixture was quenched with sat. aqueous Na_2SO_4 (0.24 ml); the precipitate was then filtered off and washed with ether. The combined filtrates were washed with water and brine, dried over Na_2SO_4, and condensed in vacuo. On the other hand, the precipitate was further washed with hot ethyl acetate; the filtrate of ethyl acetate was washed with water and brine, dried over Na_2SO_4, and condensed in vacuo. Both residues were combined and separated by TLC (SiO_2, ethyl acetate/MeOH=9/1, v/v) to give (*R*)-1-[4-hydroxy-2-(hydroxymethyl)butyl]cyclohexanol in 41% yield (23 mg). Mp 90—91 °C (toluene); $[\alpha]_D^{25}$ +5° (*c* 0.56, $CHCl_3$); IR (KBr) 3400—3140, 2960—2860, 1440, 1360, 1320, 1280, 1260, 1250, 1190, 1150, 1100, 1090, 1030, 1000, 960, 940, 825, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.24—1.38 (m, 2H), 1.38—1.70 (m, 12H), 1.92—2.08 (m, 1H), 2.20—2.60 (br, 3H), 3.53 (dd, *J*=10.99, 6.10 Hz, 1H), 3.66 (dd, *J*=10.99, 4.89 Hz, 1H), 3.64—3.79 (m, 2H). Found: C, 65.44; H, 10.92%. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96%.

(*R*)-1-[4-Benzyloxy-2-(benzyloxymethyl)butyl]cyclohexanol (16): Under a nitrogen atmosphere, a DMF (10 ml) solution of (*R*)-1-[4-hydroxy-2-(hydroxymethyl)butyl]cyclohexanol (22 mg, 0.11 mmol) was treated with sodium hydride (60% dispersion in mineral oil) (22 mg, 0.55 mmol) at 0 °C and the suspension was stirred for 0.5 h at room temperature. To the suspension, benzyl bromide (0.065 ml, 0.55 mmol) was added. After stirring overnight, water was added and the mixture was extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, and condensed in vacuo. The residue was separated by silica-gel column chromatography (hexane/ethyl acetate=4/1—0/1, v/v) to give **16** in 50% yield (21 mg). $[\alpha]_D^{25}$ +3° (*c* 0.21, $CHCl_3$).

(*R*)-2-(Benzyloxymethyl)-4-penten-1-ol:[12] A MeOH (10 ml) solution of (*S*)-4-benzyloxymethyl-5-(2-methoxyethoxy)methoxy-1-pentene **13** (236 mg, 0.8 mmol) and a catalytic amount of *p*-toluenesulfonic acid (TsOH) was refluxed for 2 d. After cooling to room temperature, sat. aqueous $NaHCO_3$ was added and the mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and condensed in vacuo. The residue was purified by TLC (SiO_2, hexane/ethyl acetate=4/1, v/v) to give (*R*)-2-(benzyloxymethyl)-4-penten-1-ol in 70% yield (116 mg). An oil; $[\alpha]_D^{25}$ +9° (*c* 1.16, $CHCl_3$) [lit,[11] *S*-isomer; $[\alpha]_D^{23}$ −11.8° (95% ee), lit,[21] *S*-isomer; $[\alpha]_D^{22}$ −12.1° (*c* 0.68, $CHCl_3$)]; MS *m/z* 207

(M^++1; 0.96%), 206 (M^+; 5.91), 205 (M^+-1; 2.58), 175 (31.70), 107 (95.28), 92 (47.47), 91 (100.00), 79 (20.75), 67 (23.02), 65 (29.33), 41 (31.63); IR (neat) 3260, 3050, 3020, 2880, 1620, 1480, 1435, 1350, 1190, 1070, 1010, 975, 890, 710, 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.90—2.04 (m, 1H), 2.09 (t, J=7.02 Hz, 2H), 2.45 (brs, 1H), 3.49 (dd, J=9.16, 7.63 Hz, 1H), 3.62 (dd, J=9.16, 4.28 Hz, 1H), 3.60—3.78 (m, 2H), 4.50 (d, J=15.87 Hz, 1H), 4.53 (d, J=15.87 Hz, 1H), 5.02 (ddd, J=10.07, 1.83, 0.91 Hz, 1H), 5.06 (ddd J=17.09, 3.36, 1.53 Hz, 1H), 5.78 (ddt, J=17.09, 10.07, 7.02 Hz, 1H), 7.26—7.39 (m, 5H).

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