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Oxirane Ring-Opening with Alcohol Catalyzed by Organotin Phosphate Condensates. Complete Inversion at Tertiary and Benzylic Centers

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Abstract: Regio- and stereospecific ring-opening of chiral oxiranes has been effected by organotin phosphate condensates catalyst. Alcohols attack on the tertiary and benzylic positions exclusively. Despite seemingly acidic character of the catalyst in terms of regioselectivity the chiral centers are completely inverted The new methodolgy is applied to synthesis of enantiomerically pure linalool and to conversion of commercially available (R)-styrene oxide into the (S)-counterpart

INTRODUCTION

Nucleophilc substitution at a tertiary carbon proceeds usually by an S_N1 mechanism, thus resulting in racemization of the tertiary center Despite some exceptions which suggest S_N2-like reactions,[2] little is known about the stereochemistry. The only example, to our konwledge, is the study by Doering and Zeiss in which methanolysis of optically active hydrogen 1-ethyl-1,3-dimethylbutyl phthalate gave rise to 54% inversion and 46% racemization [3] In this relation, ring-opening of oxiranes attracted extensive attention[4] and provided useful information in cases of cyclic olefin oxides.[5] In particular, Rickborn lent an unambigous proof for the inversion of a tertiary center through hydration of 2,3-dimethyl-2-octalin oxide having a *trans* fused carbocycle which furnished the *trans* diaxial 2,3-diol [5c] Intramolecular version of the ring-opening also has proved to induce complete inversion [6] Unfortunately, however, more general intermolecular reaction between acyclic olefin oxides and a nucleophile has been missed so far Aryl-substituted oxiranes are also liable to form a carbocation at the benzylic position under acidic conditions Nucleophilic attack on these oxides gives rise to diversity of the stereospecificity from inversion to retention depending on reaction conditions, and thus a variety of mechanistic explanations have been implicated [7] As far as the inversion is concerned, acid-catalyzed ring-opening by HCl was reported to give rise to at most 83% and 60% selectivities with styrene and *trans*-stilbene oxides, respectively [7c] Moreover, methanolysis of the former under acidic conditions induced 89% inversion [7d]

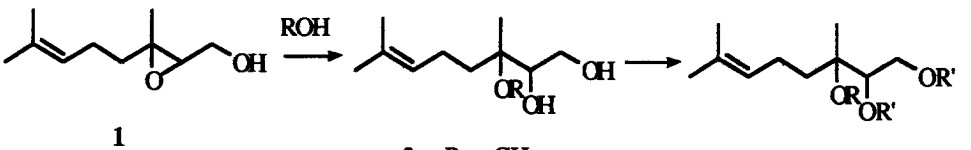
We previously reported that organotin phosphate condensates (OPC) catalyzed regio- and stereospecific ring-opening of oxiranes by alcohol [8] Namely, alcoholysis of 2-alkyloxiranes occurs at the primary carbon while 2-phenyl-, 2,2-dialkyl-, and 2,2,3-trialkyloxiranes undergo the alcohol attack at the more hindered sites. On the other hand, cyclohexene oxide provides *trans* α-alkoxy cyclohexanol stereospecifically These results have led us to expect that even tertiary and benzylic centers are possibly inverted We disclose herein that this is indeed the case Of more importance is that the present reaction offers practical routes for enantiomerically pure tertiary and

benzylic alcohols in unsymmetrically protected forms. The utility is exemplified by novel syntheses of linalool and (S)-styrene oxide [9]

RESULTS AND DISCUSSION

The ring-opening proceeded smoothly by heating enantiomerically almost pure samples of 2,3-epoxy-3,7-dimethyl-6-octen-1-ol (**1**)[10] in the presence of OPC in refluxing methanol[11] as well as with 1.5 equiv of benzyl alcohol in refluxing hexane (Scheme 1) The reaction products were isolated as acetates **3** because of readiness of

Scheme 1

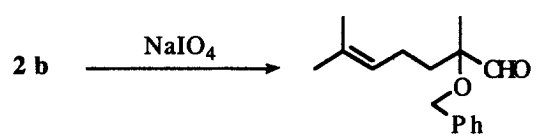


1

2a· R = CH_3
2b R = $PhCH_2$

3a R' = Ac (72%)
3b R' = Ac (54%)
4a: R' = Bn

chromatographic purification Usual alkaline hydrolysis, of course, transforms **3** to pure diols **2** No regioisomers were detected on TLC and GLC analyses The optical purity of the methanol adduct **2a** was determined on the basis of chiral HPLC as the benzoate **4a** The benzyl alcohol adduct **2b** was converted to the corresponding aldehyde **5** (eq 1), enatiomeric excess of which was measured by means of ^1H NMR spectra in the



(1)

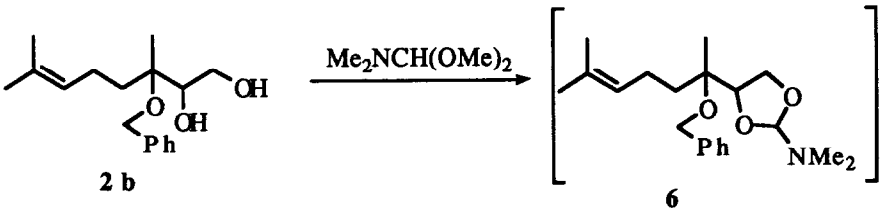
5

presence of $Eu(hfc)_3$ It is evident from Table 1 that the reaction is virtually stereospecific since the optical purity of **1** employed is 98 %ee for the 2S,3S and 2S,3R isomers and 99 %ee for the 2R,3R and 2R,3S isomers, respectively In order to assign the stereochemistry of the tertiary center, the benzyl alcohol adduct was converted to linalool[12] as illustrated in Scheme 2 The diol **2b** was treated with N,N-dimethylformamide dimethyl acetal and exposure of the resulting acetal **6** to acetic anhydride gave benzyl linalyl ether **7** [13] Removal of the benzyl group with Na/NH_3 provided linalool **8** The $[\alpha]_D$ values of **8** were found to be -17 2 (*c* 7 31, $CHCl_3$) and 16 5 (*c* 7 43, $CHCl_3$) for those derived from (2S, 3S)- and (2S, 3R)-**1**, respectively Comparison with the $[\alpha]_D$ value of (R)-linalool (-19 4, *c* 8.15, $CHCl_3$) unequivocally indicates that the tertiary carbon in **1** has been inverted upon the ring-opening by benzyl alcohol

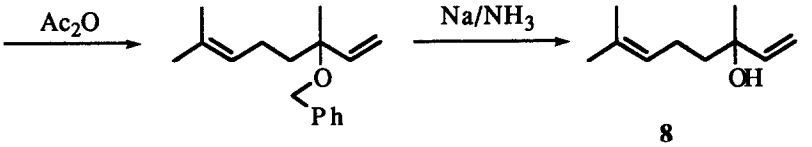
Table 1 The ee's of **4a** and **5**

4a or **5**	%ee
4a form (2S,3S)-**1**	98
4a from (2S,3R)-**1**	98
4a from (2R,3R)-**1**	99
4a from (2R,3S)-**1**	99
5 from (2S,3S)-**1**	96
5 from (2S,3R)-**1**	95

Scheme 2

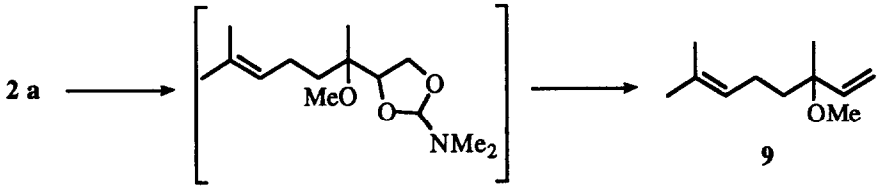


2 b **6**



7 **8**

Scheme 3

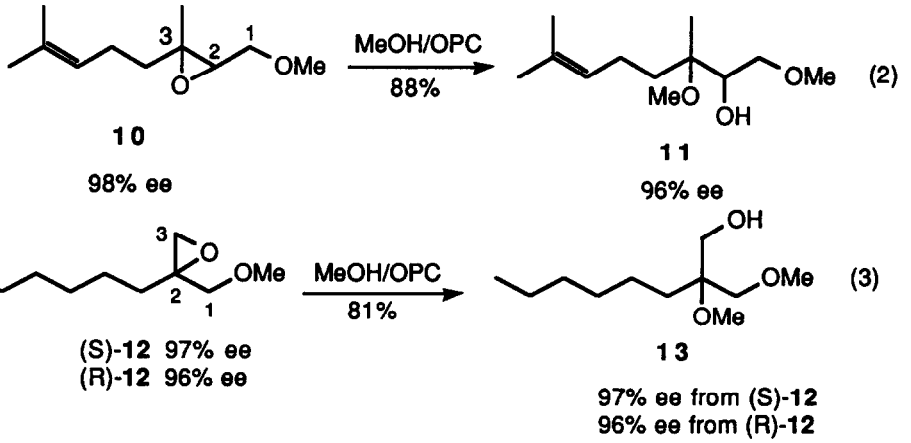


9

9 derived from	$[\alpha]_D$
(2S,3S)-**1**	13 0
(2S,3R)-**1**	-12 8
(R)-**8**	12.3
(S)-**8**	-11 9

The stereochemistry in methanolysis was confirmed with linalyl methyl ether **9** which was obtained by the similar method described above (Scheme 3) Comparison with authentic samples is again in accord with the inversion at the tertiary carbon

One may attribute the stereospecificity to the presence of the hydroxy group in **1** since the $Ti(OR)_4$-promoted ring-opening of allylic alcohol epoxides at the C(3)-O bond is initiated by replacement of the RO group by the substrate allylic alcohol.[14] Invalidity of such interaction in our case was attested by employing the methyl ether **10** (eq 2) The high ee was attained although the absolute configuration was not determined. Moreover, exclusive C-2 ring-opening was observed with **12** (eq 3) From (S)-**12** (97% ee), the ring-opening product **13** (97% ee) was obtained in 81% yield, whereas (R)-**12** (96% ee) provided **13** (96% ee), the absolute configuration being not determined in both cases. Apparently, the ring-opening at the tertiary carbon with complete inversion predominates It is concluded therefore that the OPC catalyst serves as a Lewis acid which attacks on the oxirane oxygen atom without prior substitution by an allylic alcohol.

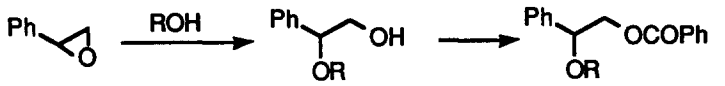


Upon treatment with benzyl alcohol (1 5 equiv) in hexane, (R)-styrene oxide (**14**) (>98% ee) afforded the adduct **15a** in 79% yield without contamination by the regioisomer (Scheme 4). The ee of **15a** was determined to be 98% on the basis of HPLC analysis of its benzoate **16a** The absolute configuration was assigned by conversion to (S)-**14** (vide infra) The reaction with the (S)-**14** gave the similar outcome Methanolysis, on the other hand, gave lower ee values of 74-76% We presumed that these disfavorable results were ascribed to coexistence of strongly acidic sites on the catalyst which induced carbocation formation from the oxirane. Thus, the catalyst was stirred with a small amount of pyridine in methanol at room temperature before subjection to the reaction As a result, the almost optically pure adducts **15b** were obtained (98% and 96% ee's as their benzoates **16b**) The absolute configuration was apparent by comparison with the literature data [15]

The methanolysis of (2S,3S)-2,3-epoxy-3-phenylpropanol (**17**) (98% ee) which is readily accessible through the Sharpless oxidation of (*E*)-cinnamyl alcohol[16] proceeded smoothly to give the desired adduct **18** in 67% yield (Scheme 5) The satisfactory ee value was attained in this case even without recourse to the pyridine-modified catalyst The conversion to (R)-**15b** through oxidation followed by reduction disclosed that **18** possessed the (2S,3R)-configuration It follows unambiguously from these results that the benzylic centers are specifically inverted

Scheme 6 illustrates new access to (S)-**14** starting from the (R)-counterpart that is synthetically significant since microbial methods by which commercial **14** is produced usually provide the latter isomer only [17]

Scheme 4

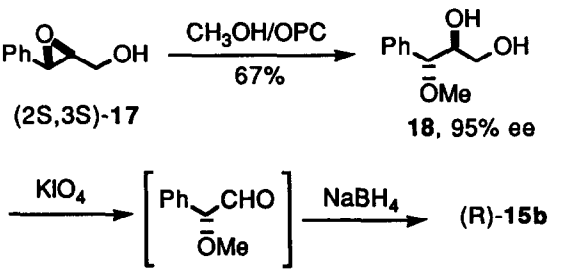


14 **15a** R = $PhCH_2$ **16a** R = $PhCH_2$
15b R = CH_3 **16b** R = CH_3

oxirane	alcohol	yield (%) of **15**	%ee of **16**
(R)-**14**	$PhCH_2OH$	79	98
(S)-**14**	$PhCH_2OH$	79	96
(R)-**14**	MeOH	84	76
		76[a]	98
(S)-**14**	MeOH	82	74
		76[a]	96

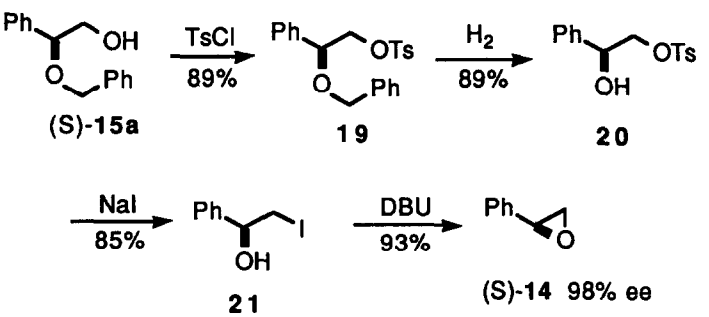
[a] The pyndine-modified catalyst was used

Scheme 5



(2S,3S)-**17** **18**, 95% ee

Scheme 6

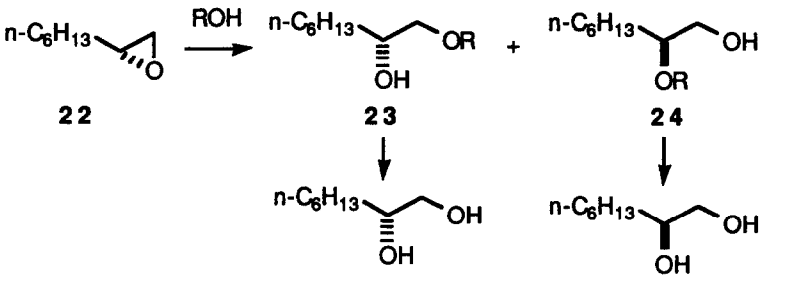


(S)-**15a** **19** **20**

21 (S)-**14** 98% ee

It seems of interest to note further the results with 1,2-epoxyoctane (**22**) for comparison The reaction of (R)-**22** under standard conditions described above afforded the normal ring-opening product **23** and the abnormal product **24** (Scheme 7) The ee values were measured with ^1H NMR spectra and the absolute configuration was assigned based on the $[\alpha]_D$ value of the corresponding diol.[18] Quite naturally, no decrease in optical purity was detected during the normal ring-opening Moreover, the secondary carbon center was perfectly inverted in the abnormal ring-opening

Scheme 7



ROH	yield (%) of		%ee (Configuration)	
	23	**24**	**23**	**24**
CH_3OH	**23a** 51	**24a** 31	>99 (R)	>99 (S)
Ph_2CHOH	**23b** 64	**24b** 15	>99 (R)	>99 (S)

The results which have been disclosed in this study demonstrate that OPC enables an alcohol to attack at the tertiary or benzylic position in preference to primary and secondary carbons and the stereochemistry of the substituted carbon is totally inverted Particularly remarkable is the capability of a tertiary center to undergo a high degree of inversion under seemingly acidic conditions [19] Furthermore, the present method is synthetically promising for providing practical routes for optically pure tertiary and benzylic alcohols

EXPERIMENTAL SECTION

NMR spectra were recorded on Hitachi R-24B and JEOL GSX-400 spectrometers Mass spectra were obtained with a JEOL JMS-DX 303-HF mass spectrometer using electron impact ionization HPLC analysis was performed on a Shimadzu LC-8A machine equipped with a Daicel Chiralcel OD column Column chromatography was carried out on Kieselgel 60 (70-230 mesh) (E Merck) All the solvents were purified according to the standard methods (R)- and (S)-**14** were products of Aldrich Co and E Merck Co, respectively and their optical purity was found to be >98% (R)-**18** (>98% ee) was purchased from Nippon Mining Co The preparation of OPC has already been described [20]

Preparation of 12. Sharpless oxidation of 2-methylene-1-octanol provided the corresponding oxirane in 87% yield (97% and 96% ee's for the (S)- and (R)-isomers, respectively) The oxirane thus obtained (319 mg, 2 02 mmol) and NaH (60% paraffin suspension, 89 mg, 2 22 mmol) were stirred in THF (5 mL) at 0 °C for 1 h MeI (430 mg, 3 03 mmol) was added to this suspension The mixture was stirred at room temperature for 1 h Water was added and the mixture was extracted with ether The organic layer was washed with water, dried (Na_2SO_4), and evaporated Column chromatography of the residue (10 1 hexane-ethyl acetate) afforded **12** (278 mg, 80%)

Reaction of 1, 10, or 12 with methanol (typical procedure) A reaction flask containing OPC (217 mg) was heated at 150 °C in vacuo for 1 h, charged with argon, and cooled to room temperatrue In this flask were added methanol (10 mL) and (2S,3S)-**1** (170 mg, 1 mmol) The reaction mixture was heated under reflux for 2 h while being stirred After removal of the catalyst by filtration, the filtrate was concentrated The residue was stirred in 1 1 acetic anhydride-pyridine (each 2 mL) at room temperature for 2 h Workup and column chromatography on silica gel (10 1 hexane-ethyl acetate) afforded (2S,3R)-1,2-diacetoxy-3,7-dimethyl-3-methoxy-6-octene (**3a**) (206 mg, 72%) ^1H NMR ($CDCl_3$) δ 1 17 (s, 3H), 1 42-1 58 (m, 2H), 1 60 (s, 3H), 1 68 (s, 3H), 1 97-2 01 (m, 2H), 2 02 (s, 3H), 2 10 (s, 3H),3 23 (s, 3H), 4 08 (dd, 1H, J = 9 0 and 12 1 Hz),

4 50 (dd, 1H, J = 2.2 and 12 1 Hz), 5.06 (t, 1H, J = 7 3 Hz), 5 26 (dd, 1H, J = 2 2 and 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 17 43, 18 48, 20 66, 20 83, 21 36, 25 53, 34.79, 49.43, 63 25, 73.38, 76.64, 123.74, 131 66, 170 05, 170 77, HRMS. *m/z* calcd for $C_9H_{17}O$ (M^+ - $CH(OAc)CH_2OAc$) 141 1279; found 141.1254.

To a methanol solution (5 mL) of the diacetate **3a** (206 mg, 0 72 mmol) was added 1 M NaOH (2 mL) The solution was stirred for 5 min and extracted with dichloromethane. The organic layer was washed with water, dried (Na_2SO_4), and evaporated Column chromatography (1·1 heaxane-ethyl acetate) afforded (2S,3R)-**2a** (131 mg, 90%): ^1H NMR ($CDCl_3$) δ 1 14 (s, 1 5H), 1 15 (S, 1 5H), 1 39-1.46 (m, 2H), 1.61 (s, 3H), 1 67 (s, 3H), 1 97-2 00 (m, 2H), 3 21 (s, 3H), 3.59-3 70 (m, 5H), 5 09 (t, 1H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 17 48, 18 32, 21.60, 25.51, 34.27, 48.92, 63 04, 74.52, 78.28, 124 14, 131.44, HRMS *m/z* calcd for $C_{10}H_{18}O_2$ (M^+ - MeOH) 170 1307, found 170.1295. The reaction with other diastereomers of **1** were conducted similarly.

The similar reaction with (2S,3S)-**10** and (S)- or (R)-**12** afforded **11** and **13** in 88 and 81% yields, respectively **11**. ^1H NMR ($CDCl_3$) δ 1.11 (s, 3H), 1 20-1.83 (m, 2H), 1 63 (s, 3H), 1.69 (s, 3H), 1 97-2 00 (m, 2H), 2.86 (br s, 1H), 3.20 (s, 3H), 3 34-3 89 (m, 3H), 3 39 (s, 3H), 5 11 (br t, 1H), MS *m/z* 216 (M^+), 96% ee based on the chiral HPLC (99 1 hexane-isopropyl alcohol) as the benzoate **13** from (S)-**12**: ^1H NMR ($CDCl_3$) δ 0 89 (t, 3H, J = 6 6 Hz), 1 23-1 25 (m, 8H), 1 38-1 54 (m, 2H), 2 42 (br s, 1H), 3 27 (s, 3H), 3 37 (s, 3H), 3 46 (ABq, 2H, J = 9.5 Hz, $\Delta\nu_{AB}$ = 16 5 Hz), 3.61 (ABq, 2H, J = 11 4 Hz, $\Delta\nu_{AB}$ = 19 7 Hz), ^{13}C NMR ($CDCl_3$) δ 14 01, 22.48, 22 57, 29 84, 29 91, 31 71, 49 52, 59 42, 64 37, 75 18, 77 83, MS *m/z* 173 (M^+ - MeO), 97% ee based on ^1H NMR with Eu(hfc)$_3$. **13** from (R)-**12** ^1H NMR ($CDCl_3$) δ 0 87 (t, 3H, J = 6 6 Hz), 1 22-1 35 (m, 8H), 1 38-1 54 (m, 2H), 2 44 (br s, 1H), 3.27 (s, 3H), 3 37 (s, 3H), 3 43 (ABq, 2H, J = 9 9 Hz, $\Delta\nu_{AB}$ = 17 1 Hz), 3 60 (ABq, 2H, J = 11 4 Hz, $\Delta\nu_{AB}$ 19 7 Hz), ^{13}C NMR ($CDCl_3$) δ 13 99, 22 45, 22 55, 29 82, 29 87, 31 69, 49 49, 59 39, 64 30, 75 10, 77 82, MS *m/z* 204 (M^+); 96% ee based on ^1H NMR with Eu(hfc)$_3$

Reaction of 1 with benzyl alcohol (typical procedure) To a reaction flask containing OPC (217 mg) which had been dried as described above was added hexane (10 mL), (2S,3S)-1 (170 mg, 1 mmol), and benzyl alcohol (162 mg, 1 5 mmol) The mixutre was heated at reflux for 3 h while being stirred. After removal of the catalyst by filtration, the solvent was evaporated. The remaining oil was heated at 100 °C/2 mm to remove the benzyl alcohol The residue was stirred in 1 1 acetic anhydride-pyridine (each 2 mL) at room temperature for 2 h Workup and column chromatography (10·1 hexane-ethyl acetate) afforded (2S,3R)-3-benzyloxy-1,2-diacetoxy-3,7-dimethyl-6-octene (**3b**) (195 mg, 54%) ^1H NMR ($CDCl_3$) δ 1 28 (s, 3H), 1 51-1 71 (m, 2H), 1 59 (s, 3H), 1 67 (s, 3H), 2 02 (s, 3H), 2 05-2 10 (m, 2H), 2 14 (s, 3H), 4 17 (dd, 1H, J = 9.0 and 11 7 Hz), 4 49 (s, 2H), 4 57 (dd, 1H, J = 2 6 and 11 7 Hz), 5 08 (t, 1H, J = 7 1 Hz), 5.36 (dd, 1H, J = 2 6 and 9 0 Hz), 7 23-7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 17 51, 19.30, 20 81, 20.98, 21.57, 25 65, 35 58, 63 46, 63 87, 73 73, 77 32, 123 80, 127 14, 127 27, 128 28, 131 90, 138 83, 170 21, 170.97, HRMS *m/z* calcd for $C_{14}H_{22}O_4$ (M^+ - $PhCH_2OH$) 254 1518, found 254 1499

Alkaline hydrolysis of the diacetate as described above affoded diol (2S,3R)-**2b** ^1H NMR ($CDCl_3$) δ 1 30 (s, 3H), 1 50-1 58 (m, 1H), 1 61 (s, 3H), 1 68 (s, 3H), 1 74-1 82 (m, 1H), 2 02-2.09 (m, 2H), 2.84 (br s, 2H), 3 68-3 78 (m, 3H), 4.45 (s, 2H), 5 11 (t, 1H, J = 7 1 Hz), 7 24-7 34 (m, 5H), ^{13}C NMR ($CDCl_3$) δ 17 57, 19 15, 21 86, 25 58, 35 05, 63 07, 63 54, 74 80, 79 06, 124 07, 127 20, 127 30, 128 28, 131 64, 138 82, HRMS *m/z* calcd for $C_{15}H_{21}O$ (M^+ - $CH(OH)CH_2OH$) 217 1592, found 217 1623 The reaction with (2S,3R)-**1** was conducted similarly.

Preparation of benzoate 4a (typical procedure) A pyridine solution (3 mL) of (2S,3R)-**2a** (101 mg, 0 5 mmol) and benzoyl chloride (281 mg, 2 mmol) was stirred at room temperature for 1 h The solution was poured into water and the mixture was extracted with ethyl acetate The organic layer was washed with water, dried (Na_2SO_4), and evaporated Column chromatography (50.1 hexane-ethyl acetate) afforded (2S,3R)-**4a** (156 mg, 76%) ^1H NMR ($CDCl_3$) δ 1 26 (s, 3H), 1 46-1 64 (m, 2H), 1 51 (s, 3H), 1 56 (s, 3H), 1 93-2 10 (m, 2H), 3 25 (s, 3H), 4 45 (dd, 1H, J = 9 0 and 12 0 Hz), 4 73 (dd, 1H, J = 2 4 and 12 0 Hz), 4 99 (t, 1H, J = 7 0 Hz), 5 63 (dd, 1H, J = 2 4 and 9 0 Hz), 7 26-7 98 (m, 10H) Benzoylation of other diastereomers of **2a** was carried out similarly

Optical purity of **4a** was measured with the chiral HPLC (99 1 hexane-isopropyl alcohol)

Preparation of aldehyde 5 A mixture of **2b** (139 mg, 0.5 mmol) and $NaIO_4$ (214 mg, 1 mmol) in dioxane (4 mL)-water (1 mL) was stirred at room temperature for 1 h The mixture was extracted with ether The organic layer was washed with $Na_2S_2O_3$ solution, $NaHCO_3$ solution, and water Drying (Na_2SO_4) and evaporation left an oil which was subjected to column chromatography (5 1 hexane-ethyl acetate) to give **5** (102

mg, 80%). ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.58 (s, 3H), 1.67 (s, 3H), 1.68-1.82 (m, 2H), 2.00-2.10 (m, 2H), 4 49 (ABq, 2H, J = 11.5 Hz, $\Delta\nu_{AB}$ = 20.0 Hz), 5 09 (t, 1H, J = 7.7 Hz), 7.21-7.33 (m, 5H), 9.53 (s, 1H). The ee was determined on the basis of ^{1}H NMR by using a shift reagent, Eu(hfc)$_3$.

Benzyl linalyl ether (7) To a dichloromethane solution (20 mL) of (2S,3R)-**2b** (980 mg, 3.5 mmol) was added N,N-dimethylformamide dimethylacetal (4.23 g, 35.3 mmol) and the mixture was heated under reflux for 12 h. After evaporation of the solvent, the residue was combined with acetic anhydride (10 mL). The mixture was heated under reflux for 1 h. Ether was added to this mixture and the ether layer was washed with water. Drying (Na_2SO_4) and evaporation left an oil Column chromatography (50:1 hexane-ethyl acetate) afforded **7** (490 mg, 57%). (R)-**7**: ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 3H), 1.46 (s, 3H), 1.47-1.52 (m, 2H), 1 53 (s, 3H), 1 93-1 95 (m, 2H), 4.21 (s, 2H), 4 93-5.01 (m, 2H), 5.04 (dd 1H, J = 1.5 and 8.0 Hz), 5 66 (dd 1H, J = 11.0 and 18 0 Hz), 7 01-7.17 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 17.37, 22.04, 22.24, 25.49, 39 92, 64.09, 77.20, 114 29, 124.50, 126.67, 126.76, 127 88, 130.70, 139.61, 143 01; HRMS *m/z* calcd for $C_{10}H_{16}$ (M^+ - $PhCH_2OH$) 136 1252, found 136.1207; $[\alpha]_D$ -2 78 (*c* 2 80, EtOH). (S)-**7**· ^{1}H NMR ($CDCl_3$) δ 1 24 (s, 3H), 1 51 (s, 3H), 1 53-1 62 (m, 2H), 1 59 (s, 3H),.1.98-2.01 (m, 2H), 4.29 (s, 2H), 5.04 (t, 1H, J = 7 0 Hz), 5 09-5.13 (m, 2H), 5.78 (dd, 1H, J = 11.0 and 18 Hz), 7.19-7.25 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 17.58, 22.25, 22 39, 25 65, 39.89, 64 33, 77 55, 114.63, 124.50, 126.95, 127 08, 128 16, 131 25, 139.75, 143.11; MS *m/z* 244 (M^+), $[\alpha]_D$ 2.84 (*c* 2.39, EtOH)

Linalool (8) Sodium metal (132 mg) was added to liq. NH_3 (10 mL) at -78 °C To this solution was added an ether solution (0.5 mL) of **7** (466 mg, 1.9 mmol) and the sloution was stirred at this temperature for 30 min NH_4Cl (1.0 g) was added to this mixture, which then was warmed to room temperature. Extraction with ether and evapoartion left an oil Column chromatography (30:1 hexane-ethyl acetate) afforded **8** (257 mg, 88%) which was identified by comparison with an authentic specimen· $[\alpha]_D$ of **8** derived from (2S,3S)-**1** -17.24 (*c* 7.31, $CHCl_3$), $[\alpha]_D$ of **8** derived from (2S,3R)-**1** 16.51 (*c* 7 43, $CHCl_3$).

Linalyl methyl ether (9). A dichloromethane solution (20 mL) of **2a** (713 mg, 3.5 mmol) and N,N-dimethylformamide dimethylacetal (4.23 g, 35.3 mmol) was heated under reflux for 12 h. The dichloromethane was distilled off and Ac_2O (10 mL) was added to the residue. The mixture was heated under reflux for 1 h and then extracted with ether water The organic layer was washed with water and column chromatography (50:1 hexane-ethyl acetate) of the residue gave **9** (388 mg, 66%). ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 3H), 1.44-1 51 (m, 2H), 1 52 (s, 3H), 1.60 (s, 3H), 1.90 (diastereotopic dt, 2H, J = 8 Hz), 3 08 (s, 3H), 5.02 (t, 1H, J = 7Hz), 5 03-5 11 (m, 2H), 5 65-5 71 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 17 57, 21 52, 22.32, 25.64, 39.27, 49.94, 77 14, 114.59, 124 44, 131.35, 142 81, HRMS *m/z* calcd for $C_{11}H_{20}O$ (M^+) 168.1514, found 168.1471 $[\alpha]_D$ of **9** derived from (2S,3S)-**1**: 13 00 (*c* 2 26, EtOH) $[\alpha]_D$ of an authentic sample prepared from (R)-linalool 12 25 (*c* 2.05, EtOH). $[\alpha]_D$ of **9** derived from (2S,3R)-**1**: -12 81 (*c* 2 30, EtOH). $[\alpha]_D$ of an authentic sample prepared from (S)-linalool. -11 92 (*c* 2.39, EtOH)

Reaction of 14 with benzyl alcohol A hexane solution (5 mL) of (R)-**14** (120 mg, 1.0 mmol) and benzyl alcohol (162 mg, 1 5 mmol) in the presence of OPC (217 mg) was heated under reflux for 5 h The workup as described above followed by column chromatography (5·1 hexane-ethyl acetate) afforded (S)-**15a** (180 mg, 79%): ^{1}H NMR ($CDCl_3$) δ 2.93 (br s, 1H), 3.55 (dd, 1H, J = 3 7 and 11.7 Hz), 3.68 (dd, 1H, J = 8 4 and 11 7 Hz), 4 38 (ABq, 2H, J = 7 3 Hz, $\Delta\nu_{AB}$ = 12.6 Hz), 4 46 (dd, 1H, J = 3 7 and 8.1 Hz), 7.27-7 34 (m, 10H), ^{13}C NMR ($CDCl_3$) δ 67.00, 70 40, 82 10, 126 80, 127 50, 127 60, 127.90, 128.20, 128 30, 137 80, 138 40, m/z 228 (M^+), $[\alpha]_D$ 86 78 (*c* 2 58, EtOH) The corresponding benzoate **16a** was proved to be 98% ee based on the chiral HPLC analysis (99 1 hexane-isopropyl alcohol) The reaction of (S)-**14** was conducted analogously.

Reaction of 14 with methanol To a suspension of OPC (217 mg) in methanol (5 mL) was added pyridine (8 mg, 0 11 mmol) and the mixture was stirred for 30 min at room temperature. Then, (R)-**14** (120 mg, 1 0 mmol) was added to this mixture. The mixture was heated under reflux for 2 h. The workup and column chromatography (5 1 hexane-ethyl acetate) provided (S)-**15b** (116 mg, 76%) $[\alpha]_D$ 116.87 (*c* 2 70, EtOH); *lit* [17]127 00 (*c* 6.40, EtOH) The corresponding benzoate **16b** was subjected to the chiral HPLC analysis to show 98 %ee (99·1 hexane-isopropyl alcohol) The reaction of (S)-**14** was conducted analogously. Without premixing of OPC with pyridine, the ee's of **16b** were found to be 76 or 74%

Reaction of (2S,3S)-17 with methanol To a methanol suspension (5 mL) containing OPC (217 mg) was added (2S,3S)-**17** (98 %ee) (150 mg, 1 0 mmol). The mixture was heated under reflux for 3 h and then filtered The filtrate was concentrated and the residue was stirred in Ac_2O (2 mL)-pyridine (3 mL) at room

temperature for 3 h. The reaction mixture was extracted with ethyl acetate and the organic layer was washed with 1M HCl solution three times, $NaHCO_3$ solution twice, and water Drying ($MgSO_4$), evaporation, and column chromatography (10·1 hexane-ethyl acetate) of the crude product afforded (2S,3R)-1,2-diacetoxy-3-methoxy-3-phenylpropane (196 mg, 67%): ^1H NMR (CCl_4) δ 1 93 (s, 3H), 2 07 (s, 3H), 3 40 (s, 3H), 4 37-4 60 (m, 3H), 5 20-5 53 (m, 1H), 7.70 (br s, 5H). Alkaline hydrolysis of this compound gave **18**, whose ee value was determined to be 95% as its benzoate by means of the chiral HPLC analysis.

Conversion of 18 to (R)-15b. To an ethanol solution (10 mL) of **18** (81 mg, 0 48 mmol) was added H_2SO_4 solution (2 mL) of KIO_4 (115 mg, 0 50 mmol) at 40 °C. The solution was stirred for 10 min at this temperature and cooled to room tempearture The reaction was quenched with water The mixture was extracted with ether The organic layer was washed with water, dried ($MgSO_4$), and evaporated The residue thus obtained (70 mg) was dissolved in EtOH (5 mL) To this solution was added $NaBH_4$ (0.48 mmol, 18 mg) The mixture was stirred for 2 h at room temperature and extracted with ether. The organic layer was washed with water twice, dried ($MgSO_4$), and evaporated Column chromatography (5 1 hexane-ethyl acetate) of the residue afforded (R)-**15b** (41 mg, 58%). $[\alpha]_D$ -107.05 (*c* 1.00, EtOH)

(S)-1-Benzyloxy-1-phenyl-2-(*p*-toluenesulfonyloxy)ethane (19): A pyridine solution (5 mL) of (S)-**15a** (123 mg, 0 54 mmol) and *p*-toluenesulfonyl chloride (309 mg, 1.62 mmol) was stirred at room temperature for 4 h The solution was extracted with benzene-water The organic layer was washed with water and dried ($MgSO_4$) Evaporation left an oil which was subjected to column chromatography (5 1 hexane-ethyl acetate) to give **19** (183 mg, 89%)· ^1H NMR ($CDCl_3$) δ 2 41 (s, 3H), 4 09 (dd, 1H, J = 4 0 and 10 6 Hz), 4 18 (dd, 1H), J = 8 0 and 10 6 Hz), 4 40 (ABq, 2H, J = 11 7 Hz, $\Delta\nu_{AB}$ = 20 Hz), 4 61 (dd, 1H, J = 4 0 and 8 0 Hz), 7 23-7 35 (m, 12H), 7 69-7 71 (m, 2H), ^{13}C NMR ($CDCl_3$) δ 21 50, 70 60, 72 70, 78 60, 126 90, 127 53, 127 55, 127 80, 128 20, 128.50, 128 60, 129 60, 132 90, 136 90, 137 60, 144 50, m/z 274 (M^+ - $PhCH_2OH$), $[\alpha]_D$ 66 63 (*c* 2 20, $CHCl_3$)

(S)-1-Phenyl-2-(*p*-toluenesulfonyloxy)ethanol (20) A glass autoclave was charged with ethanol (5 mL), **19** (200 mg, 5 2 mmol), Pd-C (5%) (20 mg), and H_2 (3 bar) The mixture was stirred at room temperature for 72 h and then filtered. The filtrate was concentrated and column chromatography of the residue (5 1 hexane-ethyl acetate) afforded **20** (136 mg, 89%) ^1H NMR ($CDCl_3$) δ 2 41 (s, 3H), 3 02 (br s, 1H), 4 01 (dd, 1H, J = 8 0 and 10 0 Hz), 4 10 (dd, 1H, J = 4 0 and 10 0 Hz), 4 92 (dd, 1H, J = 4 0 and 8 0 Hz), 7 24-7 30 (m, 7H), 7 71-7 73 (m, 2H), ^{13}C NMR ($CDCl_3$) δ 21 50, 71 60, 74 10, 126 10, 127 80, 128 20, 128 40, 130 00, 132 40, 138 30, 144.90, *m/z* 274 (M^+ - H_2O)

(S)-2-Iodo-1-phenylethanol (21) An acetone solution (15 mL) of **20** (383 mg, 1 3 mmol) and NaI (1 57 g, 9 6 mmol) was heated under reflux for 4 h The acetone was evaporated, and the residue was combined with ether and water The organic layer was washed with $Na_2S_2O_3$ solution and water Drying ($MgSO_4$), evaporation, and column chromatography (5 1 hexane-ethyl acetate) provided **21** (276 mg, 85%) ^1H NMR ($CDCl_3$) δ 2 91 (br s, 1H), 3.30-3.46 (m, 2H), 4 74 (br t, 1H), 7 31 (s, 5H), ^{13}C NMR ($CDCl_3$) δ 15 00, 73 80, 125 70, 128 20, 128 50, 141 00; HRMS calcd for C_8H_9IO (M^+) 247 9698, found 247 9720

(S)-Styrene oxide A dichloromethane solution (10 mL) of **21** (250 mg, 1 0 mmol) and DBU (306 mg, 2 0 mmol) was stirred at room temperature for 30 min The solution was poured into water The organic layer was washed with water, dried ($MgSO_4$), and evaporated Column chromatography of the residue (20 1 hexane-ethyl acetate) afforded (S)-**14** (143 mg, 93%) $[\alpha]_D$ -45 68 (*c* 1 25, benzene), *lit* [17d] -44 90 (*c* 1 02, benzene)

Reaction of (R)-22 with methanol or benzyl alcohol The reaction was conducted analogously as described already Column chromatography of the crude product afforded **23** and **24** The yields are given in Scheme 7 **23a** ^1H NMR ($CDCl_3$) δ 0 87 (br t, 3H), 1.09-1 57 (m, 10H), 2 91 (br s, 1H), 3 17-3 54 (m, 2H), 3 37 (s, 3H), 3 63-3 91 (m, 1H), $[\alpha]_D$ 10 47 (*c* 2 505, EtOH), >99 %ee based on ^1H NMR with $Eu(hfc)_3$ **24a** ^1H NMR ($CDCl_3$) δ 0 89 (br t, 3H), 1 03-1 69 (m, 10H), 3 09 (br s, 1H), 3 17-3 80 (m, 3H), 3 40 (s, 3H), $[\alpha]_D$ -3 29 (*c* 2 50, EtOH), >99 %ee based on ^1H NMR with $Eu(hfc)_3$

To an acetonitrile solution (10 mL) of **23a** (170 mg, 1 0 mmol) and NaI (329 mg, 2 2 mmol) was added chlorotrimethylsilane (239 mg, 2 2 mmol) The solution was heated under reflux for 8 h and extracted with dichloromethane The organic layer was washed with water and dried ($MgSO_4$). Column chromatography of the residue (3 1 hexane-ethyl acetate) afforded (R)-octane-1,2-diol (117 mg, 80%) $[\alpha]_D$ 14 49 (*c* 2 21, EtOH), *lit* [18] 17 10 (*c* 1 57, EtOH) The similar reaction converted **24a** to (S)-octane-1,2-diol $[\alpha]_D$ -16 31 (*c* 2 095, EtOH)

23b ^1H NMR ($CDCl_3$) δ 0 86 (br t, 3H), 1 09-1 46 (m, 10H), 2 80 (br s, 1H), 3 17-3 51 (m, 2H), 3 60-3 84 (m, 1H), 4 49 (s, 2H), 7 26 (s, 5H), $[\alpha]_D$ 7 13 (*c* 2 71, EtOH), >99 %ee based on ^1H NMR with

$Eu(hfc)_3$ **24b** ^1H NMR ($CDCl_3$) δ 0 90 (br t, 3H), 1 03-1 60 (m, 10H), 2 88 (br s, 1H), 3 07-3 47 4.35 (s, 2H), 7.08 (s, 5H); $[\alpha]_D$ -18.35 (*c* 2 64, EtOH), >99 %ee based on ^1H NMR with $Eu(hfc)_3$

Hydrogen was bubbled into an ethanol solution (5 mL) of **23b** (300 mg, 1 27 mmol) in the presei C (5%) (30 mg) at room temperature for 8 h Filtration of the reaction mixture and concentration of th layer provided (R)-octane-1,2-diol ($[\alpha]_D$ 16 72, *c* 2 42, EtOH) The similar reaction converted **24b** t isomer ($[\alpha]_D$ 14 49, *c* 2 21, EtOH)

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