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A HIGHLY EFFICIENT KINETIC RESOLUTION OF γ- AND β- TRIMETHYLSILYL SECONDARY ALLYLIC ALCOHOLS BY THE SHARPLESS ASYMMETRIC EPOXIDATION

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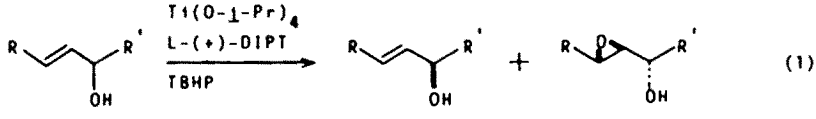
Abstract - Kinetic resolution of γ- and β-trimethylsilyl secondary allylic alcohols proceeds with very large and synthetically satisfactory rate differences for the two enantiomers, respectively, thus providing a convenient and widely applicable method for preparation of various kinds of homochiral compounds.

Shortly after the discovery of unusually efficient asymmetric epoxidation reaction of primary allylic alcohols by tert-butyl hydroperoxide (TBHP) using titanium-tartrate catalysts,[1] Sharpless has demonstrated that the same system could be used to resolve kinetically racemic secondary allylic alcohols[2] (Eq. 1). In this kinetic resolution, in which one enantiomer reacts faster than the



(1)

L-(+)-DIPT = L-(+)-diisopropyl tartrate

other, the parameter of interest is the ratio of the rates of epoxidation of the fast- (k_{fast}) and slow-reacting enantiomers (k_{slow}), termed as the "relative rate" ($k_{rel} = k_{fast}/k_{slow}$), because the efficiency of the resolution is closely related to the magnitude of k_{rel}. The magnitude of k_{rel} depends upon the substitution patterns in the allylic alcohols and the largest magnitude of k_{rel} reported so far was 138 (at -20 °C) for 2-methyl-1-hepten-3-ol.[2]

In relation to our studies on the syntheses of metabolites of arachidonic acid and their related compounds[3-6] we needed optically pure γ-halo allylic alcohols with both E- and Z-configuration,[7] and we were interested in the kinetic resolution of (E)-1-trimethylsilylalk-1-en-3-ol (1) by the Sharpless asymmetric epoxidation, because both epoxysilanes and vinylsilanes are useful precursors of vinyl halides.[8] As a result, fortunately, we found that the resolution of 1 proceeds with very large k_{rel} value of more than 1000 in contrast to the usual secondary allylic alcohols.[2] Herein we report in full our studies on the kinetic resolution of various γ-trimethylsilyl secondary allylic alcohols[9a] and also the kinetic resolution of β-trimethylsilyl secondary allylic alcohols.[9b]

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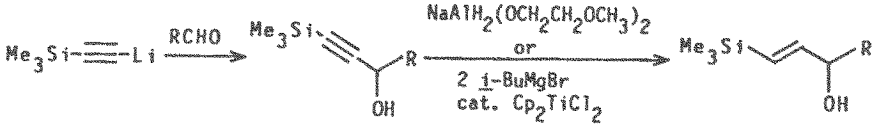
† Fellow of the Japan Society for the Promotion of Science for Japanese Junior Scientists, 1987-1989.

RESULTS AND DISCUSSION

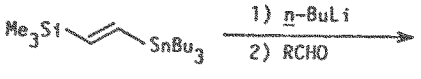
Kinetic resolution of 1

The allylic alcohols 1 which have E-configuration can be readily prepared specifically by the reaction of lithium trimethylsilylethylide with aldehydes followed by reduction of the resulting adducts with sodium bis-(2-methoxyethoxy)aluminium hydride[10] or Cp_2TiCl_2 - i-BuMgBr[11], or by the reaction of the vinyllithium prepared from (E)-1-tributylstannyl-2-trimethylsilylethylene with aldehydes[12] (Scheme 1).



1

a, R = n-Am (89% yield based on the aldehyde)
b, R = i-Pr (90%)
c, R = t-Bu (85%)
d, R = Ph (70%)
e, R = CH_2OPh (97%)
f, R = CH_2OBn (84%)
g, R = [illegible] (79%)

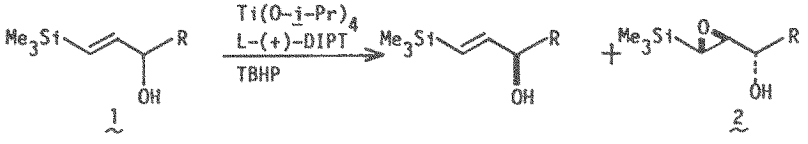


1

h, R = CH_2CH_2OBn (92% yield)
i, R = [illegible]CO_2Me (56%)

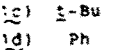
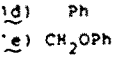
Scheme 1.

Firstly we carried out the kinetic resolution of 1 thus prepared by using 0.6 equiv of TBHP which is the usual condition of the kinetic resolution[2] and found that the reaction proceeded with very large rate differences for the two enantiomers. Thus, to speed up the reaction, the kinetic resolution was carried out using rather large excess of TBHP (Eq. 2). Table 1 summarizes the results



1 2 (2)

Table 1. Results of the kinetic resolution of 1[a]

Entry	Substrate 1, R	Reaction time (h)	Optical purity (% e.e.)[b] 1[c]	2[d]
1	(1a) n-Am	7	>99	>99
2	(1a) n-Am	18	>99	97.6
3[e]	(1a) n-Am	2	>99	94.9
4	(1b) i-Pr	6	>99[f]	99
5[e]	(1c) t-Bu	40	13[f,g]	-
6	(1d) Ph	13.5	>99[f]	97.3
7	(1e) CH_2OPh	13	>99	>99
8	(1f) CH_2OBn	9.5	>99	>99
9	(1g) 	3.5	>99	>99
10	(1h) CH_2CH_2OBn	9	>99	>99
11[h]	(1i) 	20	>99	>99

[a]All reactions were carried out at -20 °C with 1.0 equiv of $Ti(O\text{-}i\text{-}Pr)_4$, 1.2 equiv of L-(+)-DIPT, 1.0 equiv of racemic 1 and 1.5 equiv of TBHP in CH_2Cl_2, unless otherwise noted. [b]Optical purities were determined by the conversion to the MTPA ester followed by ^{1}H-NMR analysis and/or by conversion to the acetate followed by ^{1}H-NMR analysis in the presence of either (-)-Pr(dfpm)$_3$ or (+)-Eu(dfpm)$_3$ (dfpm = di(perfluoro-2-propoxypropionyl)methanato)(see Experimental). Total yields of 1 and 2 were >98% checked by ^{1}H-NMR analysis. The isolated yield of 1 and 2 ranged from 40-48%, respectively, except for entry 5 (see Experimental). [c]Absolute configurations were confirmed by chemical correlations.[13] [d]No threo isomer was detected except for entry 5. [e]3 Å molecular sieves, 0.2 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ and 0.24 equiv of L-(+)-DIPT were used. [f]Although the absolute configuration was not determined, the face selection rule of the Sharpless kinetic resolution strongly suggests the structure.[2] [g]66% conversion checked by ^{1}H-NMR analysis. [h]Employed D-(-)-DIPT instead of L-(+)-DIPT.

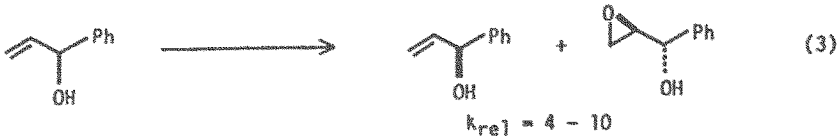
of the kinetic resolution of various 1 in which a substituent is a prim-, sec-, or tert-alkyl group, aryl group, or alkyl group having various functional groups using L-(+)-DIPT as chiral source. Examination of the results shown in Table 1 reveals that the rate of epoxidation between two enantiomers of 1 differs significantly except for 1c which has sterically demanding tert-butyl group. Thus, in most cases it is possible to obtain the allylic alcohols 1 with more than 99% e.e. and the epoxy alcohols 2 with more than 99% e.e., simultaneously[15]: This result indicates that the magnitude of k_{rel} of 1 is more than 1000‡ which is calculated from the equation which relates the k_{rel} to the optical purities of 1 and 2.[2]

Since the reaction proceeds with these large k_{rel} value, even allowing the resolution to run for additional several hours after the completion of the kinetic resolution scarcely alters the enantiomeric purity of 2 nor the yield of 1 as is exemplified by the reaction shown in entry 2 in Table 1, thus making the reaction practicable and operationally very simple. Moreover, the kinetic

‡If the optical purities of both the epoxy alcohol and the remaining allylic alcohol are just 99.0% e.e., respectively, the calculated k_{rel} value is 1057.

resolution can also be effected under catalytic conditions[16] (entry 3 in Table 1), though the efficiency seems to be decreased a little compared to the use of stoichiometric amount of the catalyst.

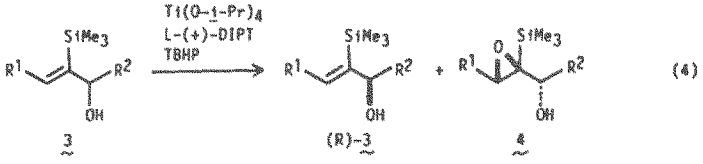
It was reported that 1-phenyl-2-propen-1-ol is not a good substrate for the kinetic resolution; the reaction rate was very slow and the k_{rel} was ~10[1b] (Eq. 3). However, the kinetic resolution of the corresponding allylic alcohol



k_{rel} = 4 - 10 (3)

possessing trimethylsilyl group at γ-position, i.e., 1d, proceeds not only with a very large k_{rel} value but also at a more rapid rate. Thus it is evident that the presence of trimethylsilyl group at γ-position in the allylic alcohols resulted in the increase of both the rate of epoxidation and the magnitude of k_{rel}.

With the results that the presence of trimethylsilyl group at γ-position in the allylic alcohols increases the efficiency of the kinetic resolution significantly, we next turned our attention to the kinetic resolution of β-trimethylsilyl secondary allylic alcohols 3 (Eq. 4). Table 2 summarizes the



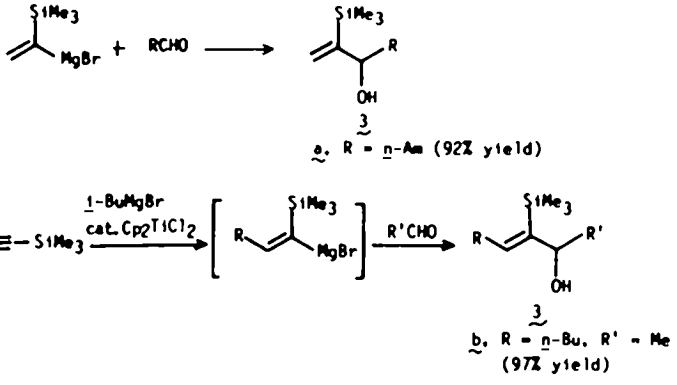
(4)

Table 2. Results of the kinetic resolution of 3[a]

Entry	Substrate 3	R^1	R^2	Reaction time (h)	Optical purity (% e.e.)[b] (R)-3	4[c]
1	(3a)	H	n-Am	24	87.4[d,e]	79.2[d]
2	(3b)	n-Bu	Me	1	95.4[f]	92.4[f]
3	(3b)	n-Bu	Me	2	>99[f,g]	83.8[f]

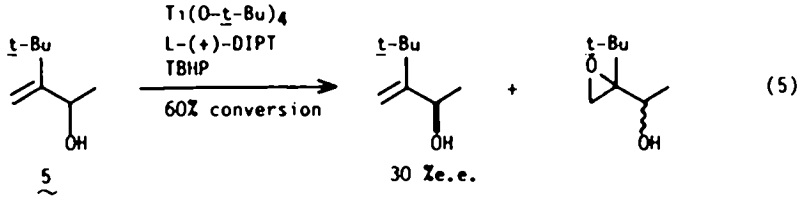
[a]Reactions were carried out at -23 °C with 1.0 equiv of Ti(O-i-Pr)$_4$, 1.2 equiv of L-(+)-DIPT, 1.0 equiv of racemic 3, and 0.6 equiv of TBHP. [b]Total yields of (R)-3 and 4 were >98% checked by ^{1}H-NMR analysis. [c]No threo isomer was detected (^{1}H-NMR analysis). [d]Optical purities were determined by HPLC analysis after conversion into the benzoate derivatives of 7a and 8a (see Scheme 3 and Experimental). [e]Absolute configuration was confirmed by conversion into 7a[17] by epoxidation[18] followed by protodesilylation.[19] [f]Optical purities were determined by ^{1}H-NMR analysis of the corresponding allylic acetate of (R)-3b in the presence of (-)-Pr(dfpm)$_3$ and of the corresponding epoxy acetate of 4b in the presence of (+)-Eu(dfpm)$_3$. [g]Absolute configuration was confirmed by conversion into (R)-(-)-2-octanol[20] by protodesilylation[21] followed by hydrogenation.

results of the kinetic resolution of 3 using L-(+)-DIPT as chiral source, while the alcohols 3 were prepared by the procedure shown in Scheme 2. It can be seen from the Table that the relative rates of fast and slowly reacting isomers



Scheme 2.

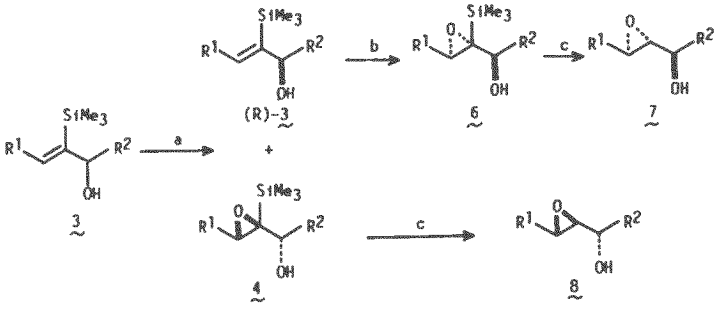
for 3 are not so great as for 1, but have synthetically satisfactory magnitudes of 24 for 3a, and near 100 for 3b. The high efficiency of the kinetic resolution of 3 is especially noteworthy because it has been reported that the secondary allylic alcohols with bulky tertiary groups in the β-position are not good kinetic resolution substrates and in the reaction of 5 the enantiomeric excess of the recovered starting alcohol was only 30% at 60% conversion[22] (Eq. 5).



5 (5)

Since the kinetic resolution of 3 proceeds effectively, it is possible to obtain both enantiomers of erthro-epoxy alcohol by using a single chiral source according to the procedure shown in Scheme 3. Thus, after the kinetic resolution of 3b (1.0 equiv $Ti(O\text{-}i\text{-}Pr)_4$, 1.2 equiv L-(+)-DIPT, -23 °C, 2 h), the products were separated by column chromatography on silica gel,[23] to give 4b with 83.8% e.e. (42% yield) and optically pure (R)-3b (41% yield) which was converted into epoxy alcohol 6b (>99% e.e., the enantiomer of 4b) specifically by V^{5+}-catalyzed epoxidation with TBHP[18] in 93% yield. Treatment of 4b and 6b with t-BuOK and $n\text{-}Bu_4NF$ in THF at 0°C for 5 min resulted in a near quantitative protodesilylation[19] to afford 8b and 7b, respectively (Scheme 3). As the starting racemic alcohols 3 are readily available by hydromagnesiation of 1-trimethylsilylalk-1-ynes followed by reaction with aldehydes[21,24] (Scheme 2), the present reaction offers a convenient method for preparation of both

enantiomers of erythro-epoxy alcohols, one of which is optically pure.



Scheme 3. (a) $Ti(O\text{-}i\text{-}Pr)_4$, L-(+)-DIPT, TBHP, -23 °C; (b) TBHP, $VO(acac)_2$, CH_2Cl_2; (c) t-BuOK, n-Bu_4NF, THF.

In summary, owing to the presence of trimethylsilyl group at the vinylic position, the kinetic resolution of γ-trimethylsilyl secondary allylic alcohols proceeds with very large magnitude of k_{rel}, while the kinetic resolution of β-trimethylsilyl secondary allylic alcohols proceeds with synthetically satisfactory magnitude of k_{rel}. The high efficiency of the kinetic resolution observed here may be attributed to the two factors of trimethysilyl group, i.e., the steric effect and the electronic effect. The electronic effect, however, seems to be more important, since there are significant difference of the efficiency of the kinetic resolution of 3a and 5.

Since both epoxysilanes and vinylsilanes are useful precursors of epoxides, carbonyl compounds and substituted alkenes,[8] the present reaction provides a convenient and widely applicable method for preparation of various kinds of homochiral compounds. The several synthetic uses of the reaction have been reported which includes the preparation of four possible stereoisomers of secondary allylic alcohols,[9a] γ-halo secondary allylic alcohols with E- or Z-configuration,[7] and eventually lipoxygenase metabolites of unsaturated fatty acids.[5,6] Further uses of the reaction are being studied.

EXPERIMENTAL

General. ^{1}H-NMR spectra were recorded on either HITACHI R-40 (90 MHz) or a JOEL FX-90Q (90 MHz) instrument, whereas ^{13}C-NMR spectra were recorded on a JOEL FX-90Q (22.5 MHz). Both ^{1}H-NMR and ^{13}C-NMR spectra were obtained with CCl_4 or $CDCl_3$ as solvent and values are reported in ppm (δ) downfield from TMS using TMS or residual $CHCl_3$ as internal standard, except as noted. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Coupling constants (J) are given in Hz. Optical rotations were measured on a YANAKO OR-50 porarimeter, using 20-cm^3 capacity (5-dm path length) cell. Infrared (IR) spectra were recorded on a JASCO A-100 spectrometer and are reported in wave numbers (cm^{-1}). Dichloromethane was distilled from calcium hydride. All reactions sensitive to oxygen or moisture were conducted

under argon atmosphere. In order to determine the optical purity, in some cases, the alcoholic products were converted into the (S)- or (R)-β,β,β-trifluoro-α-methoxy-α-phenylpropionates (MTPA esters) according to Mosher's procedure[25] by using (S)- or (R)-MTPACl. A chiral shift reagent, (-)-Pr(dfpm)$_3$ [dfpm = di(perfluoro-2-propoxypropyonyl)methanato] or (+)-Eu(dfpm)$_3$ was also employed for determining optical purity of the products after converting into the corresponding acetates. High-performance liquid chromatography (HPLC) analysis carried out on a NSP-800-9DX (Nihon Seimitsu Kagaku Co., Ltd.) instrument with a chiral column (CHIRALPAK OT(+), Daicel Chemical Ind., Ltd.) and a Shodex RI detector for determining optical purity of the products.

Preparation of γ-trimethylsilyl allylic alcohols, 1a-g

1-trimethylsilylalk-1-yn-3-ol - General procedure. To an ice-cooled soln of MeLi (1.0 equiv) in Et_2O (1.0 M) was added dropwise trimethylsilyl acetylene (1.3 equiv). The resulting soln was stirred for 1 h at room temp. To this was added dropwise the aldehyde (1 equiv) at -30 °C. The mixture was allowed to warm up to room temp and poured into ice cooled sat NH_4Cl (1.2 ml/mmol aldehyde), the mixture was extracted with hexane (2 X 0.6 ml/mmol aldehyde). The combined org layers were dried ($MgSO_4$) and evaporated to afford the product. The acetylenic alcohols are fully characterized compounds, but due to space limitations the spectroscopic and physical data will not be given here.

Reduction with $NaAlH_2(OCH_2CH_2OCH_3)_2$- Preparation of 1a,d-g - General procedure. To an ice-cooled soln of $Na[AlH_2(OCH_2CH_2OCH_3)_2]$ (1.7 equiv, 3.56 M in toluene) in Et_2O (1.0 M) was added dropwise the acetylenic alcohol (and 20 v/v% THF for 1-trimethylsilyl-1-octyne-3-ol) and the resulting soln was refluxed overnight and cooled to 0 °C. To this soln were added slowly water (9 equiv) and 3N HCl (1.2 ml/mmol acetylenic alcohols), and the org layers were separated and the aq layer was extracted with hexane-Et_2O (1:1) repeatedly. The combined org layers were washed with aq $NaHCO_3$ and brine successively, dried (Na_2SO_4), and concentrated to give the crude product which was distilled or chromatographed (1d was chromatographed and distilled).

1a, Yield 89%; b.p. 90 °C/3 Torr; IR (neat) 3330, 2930, 1645, 1285; ^{1}H-NMR (CCl_4, PhH, D_2O) δ 0.07 (s, 9H), 0.94 (t, J = 6.0, 3H), 1.10-1.75 (m, 8H), 3.93 (q, J = 4.8, 1H), 5.67 (d, J = 18.0, 1H), 6.00 (dd, J = 4.8, 18.0, 1H); ^{13}C-NMR ($CDCl_3$) δ 148.9, 128.8, 74.6, 36.9, 31.8, 25.0, 22.5, 13.9, -1.3.

1d, Yield 70%; b.p. 108-111 °C/0.32 Torr; IR (neat) 3320, 2960, 1605, 1250, 839, 695; ^{1}H-NMR (CCl_4) δ 0.17 (s, 9H), 5.05 (d, J = 4.6, 1H), 5.93 (d, J = 19.8, 1H), 6.23 (dd, J = 4.6, 19.8, 1H), 7.10-7.54 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 147.3, 142.7, 129.7, 128.4, 127.4, 126.4, 76.6, -1.4.

1e, Yield 97%; b.p. 150-160 °C/0.15 Torr; IR (neat) 3430, 1598, 1585; ^{1}H-NMR (CCl_4) δ 0.25 (s, 9H), 2.83 (br s, 1H), 3.93 and 4.04 (2dd, J = 7.8, 10.2 and 4.0, 10.2, 2H), 4.48-4.82 (m, 1H), 6.21 (s, 2H), 6.85-7.05 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 158.5, 143.4, 131.9, 129.3, 121.0, 114.6, 72.3, 71.7, -1.4.

1f, Yield 84%; IR (neat) 3400, 1245, 830, 730, 690; ^{1}H-NMR (CCl_4, D_2O) δ 0.15 (s, 9H), 3.32 (dd, J = 7.8, 10.3, 1H), 3.42 (dd, J = 4.1, 10.3, 1H), 4.15-4.36

(m, 1H), 4.50 (s, 2H), 5.95-6.10 (m, 2H), 7.23-7.40 (m, 5H).

1g, Yield 79%; IR (neat) 3340, 1610, 1240, 830; ^{1}H-NMR (CCl_4) δ 0.10 (s, 9H), 0.90 (t, J = 6.6, 3H), 1.10-1.60 (m, 6H), 1.86-2.14 (m, 2H), 2.22 (t, J = 6.0, 2H), 3.98 (dt, J = 4.0, 6.0, 1H), 5.14-5.60 (m, 2H), 5.74 (d, J = 18.6, 1H), 6.02 (dd, J = 18.6, 3.8, 1H); ^{13}C-NMR ($CDCl_3$) δ 148.0, 133.3, 129.2, 124.5, 73.8, 35.1, 31.5, 29.3, 27.4, 22.4, 14.0, -1.4.

Reduction with i-BuMgBr-Cp_2TiCl_2 - Preparation of 1b,c - General procedure. To an ice cooled soln of i-BuMgBr (3.8 equiv) in Et_2O (1.4 M) was added Cp_2TiCl_2 (5 mol%) and the mixture was stirred for 30 min at 0 °C. To this mixture was added dropwise the acetylenic alcohol at 0 °C. The resulting mixture was stirred at 27 °C. When the reaction was completed (monitored by TLC, 7 h - 12 h), the mixture was poured into 3N HCl soln (1.5 ml/mmol Grignard). The org layers were separated and the aq layer was extracted with hexane-Et_2O (1:1) repeatedly. The combined org layers were washed with aq $NaHCO_3$ and brine successively, dried (Na_2SO_4) and concentrated to give the crude product which was purified by distillation (1c was purified by chromatography on silica gel).

1b, Yield 90%; b.p. 42-48 °C/0.1 Torr; IR (neat) 3340, 2870, 1615, 1240, 985, 840; ^{1}H-NMR (CCl_4, CH_2Cl_2) δ 0.07 (s, 9H), 0.88 (d, J = 7.0, 6H), 1.33-1.96 (m, 1H), 2.58 (br s, 1H), 3.74 (t, J = 5.0, 1H), 5.70 (d, J = 19.0, 1H), 5.95 (dd, J = 5.0, 19.0, 1H).

1c, Yield 85%; ^{1}H-NMR (CCl_4, PhH) δ 0.06 (s, 9H) 0.89 (s, 9H), 1.60 (br s, 1H), 3.62 (d, J = 5.8, 1H), 5.74 (d, J = 19.5, 1H), 6.08 (dd, J = 19.5, 5.8, 1H).

Preparation of γ-trimethylsilyl allylic alcohol, 1h. To a soln of 1-tributylstannyl-2-trimethylsilylethylene (28.5 g, 73.2 mmol) in THF (70 ml) was added n-BuLi (41.9 ml, 67.1 mmol, 1.6 M in hexane) at -78 °C and the resulting soln was warmed up to -40 °C over 1 h, and recooled to -78 °C. To this was added a soln of 3-benzyloxypropanal[14] (10.0 g, 61 mmol) in THF (10 ml). The soln was warmed up to room temp and stirred for 2 h. The soln was poured into sat NH_4Cl (100 ml). Extraction with hexane (2 X 100 ml) followed by drying ($MgSO_4$) afforded the crude product which was chromatographed on silica gel to yield 1h (14.8 g, 92%). IR (neat) 3400, 1090, 835, 730, 690; ^{1}H-NMR (CCl_4, D_2O) δ 0.08 (s, 9H) 1.60-1.90 (m, 2H), 3.53 (dt, J = 2.5, 6.1, 2H), 4.04-4.26 (m 1H), 4.42 (s, 2H), 5.73 (d, J = 19.9, 1H), 5.99 (dd, J = 4.0, 19.9, 1H), 7.08-7.30 (m, 5H).

Preparation of γ-trimethylsilyl allylic alcohol, 1i. The vinyl lithium in THF prepared in the same manner described above, from 1-tributylstannyl-2-trimethylsilylethylene (21.0 g, 54 mmol) in THF (100 ml) and n-BuLi (36 ml, 54 mmol, 1.50 M in hexane) was added to a soln of methyl 6-formylbutyrate[26] (7.0 g, 54 mmol) in THF (30 ml) at -78 °C. The resulting soln was stirred for 30 min at -78 °C and poured into a mixture of benzene and sat NH_4Cl and extracted with benzene. The extracts were dried ($MgSO_4$) and concentrated. Chromatography on silica gel afforded 2i (6.29 g, 55.9%). IR (neat) 3400, 1727, 842; ^{1}H-NMR (CCl_4) δ 0.07 (s, 9H), 2.05-1.25 (m, 4H), 2.26 (t, J = 7.0, 2H), 3.02 (br s, 1H), 3.58 (s, 3H), 4.08-3.86 (m, 1H), 5.77 (d, J = 18.3, 1H), 5.97 (dd, J = 18.3, 3.6, 1H).

^{13}C-NMR ($CDCl_3$) δ 174.0, 148.3, 129.4, 74.0, 51.4, 36.2, 33.8, 20.8, -1.4.

Kinetic resolution of 1 - General procedure. To a soln of $Ti(O\text{-}i\text{-}Pr)_4$ (1.0 equiv) in CH_2Cl_2 (8.8 ml/mmol allylic alcohol) were added L-(+)-DIPT (1.2 equiv)(D-(-)-DIPT for 1i) and the resulting soln was stirred for 10 mim at -20 °C. After addition of 1 (1 equiv) the resulting soln was stirred for additional 10 min. TBHP (1.5 equiv) in anhydrous CH_2Cl_2 was added slowly and the soln was stirred at -20 °C for the prescribed time in Table 1. After completion, Me_2S (3 equiv) was added slowly and the mixture was stirred for 30 min at -20 °C. 10% tartaric acid aq soln (twice the volume of $Ti(O\text{-}i\text{-}Pr)_4$ in the reaction), Et_2O (the same volume of CH_2Cl_2), NaF (ca 0.7 g/mmol allylic alcohol) and Celite (ca 0.4 g/mmol allylic alcohol) were added sequencially. The resulting mixture was stirred for 30 min at room temp and filtered through a pad of Celite with Et_2O and concentrated. The isolation of 1 and 2 was carried out as follows, for 1a, 1b, 1d and 1g; the residue was chromatographed on triethylamine-deactivated silica gel, for 1e, 1f, and 1h; the residue was treated with aq NaOH in Et_2O at 0 °C[1a] and chromatographed, for 1i; chromatography separation gave 1i and the mixture of 2i and D-(-)-DIPT (2i and DIPT could be separated by chromatography on silica gel after converting DIPT into DMT by treatment with NaOMe in MeOH).

(R)-1a, >99% e.e. (by ^{1}H-NMR shift analysis of the corresponding acetate with (-)-Pr(dfpm)$_3$ in CCl_4 and ^{1}H-NMR analysis of the derived MTPA ester); Yield 42%, $[\alpha]_D^{25}$ -9.8° (c 1.10, $CHCl_3$).

2a, >99% e.e. (by ^{1}H-NMR shift analysis of the corresponding acetate with (+)-Eu(dfpm)$_3$ in $CDCl_3$ and ^{1}H-NMR analysis of the derived MTPA ester) ; Yield 42%; $[\alpha]_D^{25}$ -7.5° (c 1.04, $CHCl_3$); IR (neat) 3420, 2930, 1247; ^{1}H-NMR (CCl_4, PhH, D_2O) δ 0.03 (s, 9H), 0.93 (t, J = 4.8, 3H), 1.07-1.72 (m, 8H), 2.26 (d, J = 4.0, 1H), 2.71 (t, J = 4.0, 1H), 3.30-3.70 (m, 1H).

(R)-1b, >99% e.e. (by ^{1}H-NMR analysis of the derived MTPA ester); Yield 40% $[\alpha]_D^{25}$ -21.8° (c 1.14, $CHCl_3$).

2b, 99% e.e. (by ^{1}H-NMR shift analysis of the corresponding acetate with (+)-Eu(dfpm)$_3$ in $CDCl_3$); Yield 41%, $[\alpha]_D^{25}$ -1.07° (c 1.49, $CHCl_3$). IR (neat) 3425, 2950, 1250, 840; ^{1}H-NMR ($CDCl_3$) δ 0.04 (s, 9H), 0.94 and 0.95 (2d, J = 6.6 and 6.8, 6H), 1.48-2.05 (m, 1H), 1.98 (br s, 1H), 2.35 (d, J = 3.7, 1H), 2.87 (dd, J = 3.1, 3.7, 1H), 3.48-3.68(m, 1H).

(S)-1d, >99% e.e. (by ^{1}H-NMR analysis of derived MTPA ester); Yield 44%; $[\alpha]_D^{25}$ -10.8° (c 1.06, $CHCl_3$).

2d, 97.3% e.e. (by ^{1}H-NMR analysis of the derived MTPA ester); Yield 42%;, $[\alpha]_D^{25}$ +25.7° (c 1.58, $CHCl_3$); IR (neat) 3400, 2975, 1940, 1605, 1250, 838, 695. ^{1}H-NMR (CCl_4, D_2O) δ 0.05 (s, 9H), 2.44 (d, J = 4.0, 1H), 2.95 (t, J = 4.0, 1H), 4.63-4.83 (m, 1H), 7.16-7.46 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 140.2, 128.3, 127.9, 126.4, 72.1, 58.9, 47.8, -3.8.

(S)-1e, >99% e.e. (by ^{1}H-NMR analysis of derived MTPA ester); Yield 47%; $[\alpha]_D^{25}$ +8.0° (c 1.55, $CHCl_3$); m.p. 49.0-50.0 °C (recrystallized from pentane-Et_2O).

2e, >99% e.e. (by ^{1}H-NMR analysis of the derived MTPA ester); Yield 46%; $[\alpha]_D^{25}$

-17.0° (c 0.98, $CHCl_3$); m.p. 61.5-62.5 °C (recrystallized from pentane-Et_2O); IR (nujol) 3400, 1598, 1585; ^{1}H-NMR (CCl_4, CH_2Cl_2) δ 0.19 (s, 9H), 2.36 (d, J = 3.7, 1H), 2.80 (br s, 1H), 2.95-3.12 (m, 1H), 3.73-4.37 (m, 3H), 6.74-7.45 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 158.6, 129.5, 121.3, 114.7, 69.8, 69.5, 55.7, 48.8, -3.7.
(S)-1f, >99% e.e. (by ^{1}H-NMR analysis of the derived MTPA ester); Yield 43%; $[\alpha]_D^{25}$ -1.9° (c 1.06, $CHCl_3$).
2f, >99% e.e. (by ^{1}H-NMR analysis of the derived MTPA ester); Yield 48%; $[\alpha]_D^{25}$ -2.2° (c 1.20, $CHCl_3$); IR (neat) 3400, 1240, 1100, 840, 730, 690; ^{1}H-NMR (CCl_4, D_2O) δ 0.05 (s, 9H), 2.17 (d, J = 3.6, 1H), 2.78 (dd, J = 3.6, 4.2, 1H), 3.43-3.73 (m, 3H), 4.46 (s, 2H), 7.13-7.34 (m, 5H).
(R)-1g, >99% e.e. (by ^{1}H-NMR analysis of the derived MTPA ester); Yield 44%; $[\alpha]_D^{25}$ +7.59° (c 1.37, $CHCl_3$).
2g, >99% e.e. (by ^{1}H-NMR analysis of the derived MTPA ester); Yield 43%; $[\alpha]_D^{25}$ +4.23° (c 1.13, $CHCl_3$); IR (neat) 3420, 1243, 840; ^{1}H-NMR (CCl_4, PhH) δ 0.05 (s, 9H), 0.90 (t, J = 6.0, 3H), 1.10-1.70 (m, 6H), 1.87-2.18 (m, 2H), 2.15-2.38 (m, 3H), 2.62 (br s, 1H), 2.73 (t, J = 3.0, 1H), 2.65 (dt, J = 4.0, 6.0, 1H), 5.20-5.70 (m, 2H).
(R)-1h, >99% e.e. (by ^{1}H-NMR analysis of the derived MTPA ester); Yield 43%; $[\alpha]_D^{25}$ -3.2° (c 1.00, $CHCl_3$).
2h, >99% e.e. (by ^{1}H-NMR analysis of the derived MTPA ester); Yield 45%; $[\alpha]_D^{25}$ -10.1° (c 0.97, $CHCl_3$); IR (neat) 3400, 1240, 1080, 835, 730, 690; ^{1}H-NMR (CCl_4, D_2O) δ 0.03 (s, 9H), 1.58-1.90 (m, 2H), 2.13 (d, J = 3.6, 1H), 2.68 (t, J = 3.6, 1H), 3.43-3.82 (m, 3H), 4.42 (s, 2H), 7.10-7.33 (m, 5H).
(S)-1i, >99% e.e. (by ^{1}H-NMR analysis of the derived MTPA ester); Yield 43%; $[\alpha]_D^{25}$ +6.78° (c 1.15, $CHCl_3$).
2i, >99% e.e. (by ^{1}H-NMR analysis of the derived MTPA ester); Yield 45%; $[\alpha]_D^{25}$ +6.74° (c 1.75, $CHCl_3$); IR (neat) 3410, 1726, 1248, 843; ^{1}H-NMR ($CDCl_3$) δ -0.08 (s, 9H), 1.20-1.80 (m, 4H), 2.08-2.29 (m, 3H), 2.62 (t, J = 5.1, 1H), 2.82 (br d, J = 2.4, 1H), 3.46 (s, 3H), 3.40-3.62 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 173.4, 69.5, 58.1, 50.9, 47.5, 33.6, 33.0, 20.5, -4.1.

Catalytic kinetic resolution of 1a,c. To a mixture of crushed molecular sieves 3A (1.4 g), Ti(O-i-Pr)$_4$ (1.52 ml, 5.12 mmol) in CH_2Cl_2 (16 ml) was added L-(+)-DIPT (1.29 ml, 6.14 mmol) at -20 °C and the resulting mixture was stirred for 30 min at -15 °C. To this mixture was added 1a (5.12 g, 25.6 mmol) in CH_2Cl_2 (16 ml) and the resulting mixture was stirred for 1 h at -20 °C. The mixture was cooled to -40 °C and TBHP (11 ml, 38.4 mmol, 3.49 M in CH_2Cl_2) was slowly added. After 2 h of stirring at -20 °C, Me_2S (4 ml, 54.5 mmol) was added slowly and the mixture was stirred for 30 min. Usual workup and followed by column chromatography on triethylamine-deactivated silica gel afforded (R)-1a (2.15 g, 42%, >99% e.e. (by ^{1}H-NMR analysis of the derived MTPA ester)) and 2a (2.43 g, 44%, 94.9% e.e. (by ^{1}H-NMR analysis of the derived MTPA ester)). The kinetic resolution of 1c was perfomed on 7.63 mmol scale (1.42 g) in the same manner described above. After 40 h, usual workup afforded the mixture of 2c (64% yield

checked by ^{1}H-NMR anlysis using an internal standard) and (S)-1c (34% ^{1}H-NMR yield, 13% e.e. (by ^{1}H NMR analysis of the derived MTPA ester)).

Preparation of β-trimethylsilyl allylic alcohol 3a. To an ice-cooled soln of CH_2=C(SiMe$_3$)MgBr (68.8 mmol) in THF (210 ml) was added hexanal (8.3 ml, 69.0 mmol) at 0 °C. The soln was stirred for 1 h at 0 °C and for 30 min at room temp. The soln was poured into ice-cooled 3N HCl (70 ml) and extracted with hexane-Et_2O (5:1, 2 X 100 ml). Combined org solvents were washed with sat $NaHCO_3$ and brine and dried ($MgSO_4$). The crude product was purified by distillation to give 5b (12.7 g, 92%). IR (neat) 3350, 2920, 1245, 838; ^{1}H-NMR (CCl_4) δ 0.07 (s, 9H), 0.70-1.04 (m, 3H), 1.07-1.96 (m, 9H), 4.01-4.30 (m, 1H), 5.20-5.39 and 5.60-5.76 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 155.6, 123.6, 76.3, 37.4, 31.8, 25.5, 22.6, 13.9, -0.5.

Preparation of β-trimethylsilyl allylic alcohol 3b. To an ice-cooled soln of i-BuMgBr (75 mmol) in Et_2O (55 ml) was added Cp_2TiCl_2 (0.37 g, 1.5 mmol). After stirring for 20 min, 1-trimethylsilyl-1-hexyne (10.5 ml, 50 mmol) was added and the resulting soln was stirred at 25 °C for 6 h and then cooled to 0 °C. To this soln was added acetaldehyde (5.4 ml, 76.6 mmol). The resulting mixture was stirred at room temp for 30 min and poured into ice-cooled 3N HCl (60 ml). The mixture was extracted with hexane (3 X 20 ml) and the extracts were dried ($MgSO_4$) and concentrated. The crude product was chromatographed on silica gel to give 3b (9.7 g, 97%). IR (neat) 3320, 2920, 1610, 1250, 830; ^{1}H-NMR (CCl_4, PhH) δ 0.10 (s, 9H), 0.83 (t, J = 6.0, 3H), 1.09 (d, J = 6.0, 3H), 1.18-1.48 (m, 4H), 2.05 (q, J = 6.0, 2H), 2.22 (br s, 1H), 4.19 (q, J = 6.0, 1H), 6.10 (t, J = 7.0, 1H); ^{13}C-NMR ($CDCl_3$) δ 143.7, 140.,9, 72.1, 32.1, 31.3, 24.3, 22.4, 14.0, 0.7.

Kinetic resolution of 3a. To a soln of Ti(O-i-Pr)$_4$ (1.86 ml, 6.25 mmol) was added L-(+)-DIPT (1.58 ml, 7.51 mmol) at -20 °C and the soln was stirred for 10 min. To this soln was added a soln of 3a (1.25 g, 6.25 mmol) in CH_2Cl_2. After stirring for 10 min at -20 °C, TBHP (1.6 ml, 3.75 mmol, 2.33 M in CH_2Cl_2) was added to the soln and stirred for 24 h at -23 °C. Workup was performed as indicated in the procedure of the kinetic resolution of 1. The products were purified by chromatography on silica gel to afford (R)-3a (554 mg, 44%) and 4a (642 mg, 48%). The optical purities of (R)-3a and 4a were 87.4% e.e. and 79.2% e.e. respectively, determined by HPLC analysis after conversion into the benzoate derivatives of 7a and 8a (see Scheme 3). (R)-3a, 87.4% e.e.; $[\alpha]_D^{25}$ +6.8° (c 1.02, $CHCl_3$). 4a, 79.2% e.e.; $[\alpha]_D^{25}$ -7.0° (c 1.00, $CHCl_3$); IR (neat) 3450, 2920, 1245, 1060, 838; ^{1}H-NMR (CCl_4, CH_2Cl_2) δ 0.07 (s, 9H), 0.92 (t, J = 6.0, 3H), 1.10-1.79 (m, 8H), 2.22 (br s, 1H), 2.44 and 2.82 (2d, J = 5.8, 2H), 3.56-3.85 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 69.6, 53.9, 46.2, 33.8, 31.9, 25.5, 22.5, 13.9, -3.0. The absolute configuration of (R)-3a was determined after conversion into 7a: To a soln of the recovered allylic alcohol (540 mg, 2.7 mmol, 87.4% e.e.) in CH_2Cl_2 (20 ml) were added TBHP (2.2 ml, 4.3 mmol, 1.96 M in CH_2Cl_2) and

$VO(acac)_2$ (40 mg). The resulting soln was stirred for 4 h at 0 °C and Me_2S (0.5 ml, 6.8 mmol) was added. The mixture was stirred for 30 min at room temperature and poured into $NaHCO_3$ (30 ml). Extraction followed by chromatography on silica gel gave the epoxy alcohol (500 mg, 86%). To an ice-cooled soln of the epoxy alcohol (107 mg, 0.49 mmol) in THF (7 ml) were added t-BuOK (55 mg, 0.49 mmol) and n-Bu_4NF (0.74 ml,0.49 mmol, 0.66 M in THF). The resulting soln was stirred for 5 min at 0 °C and sat NH_4Cl (10 ml) was added. Extraction followed by chromatography on silica gel afforded 7a (61 mg, 86%). $[\alpha]_D^{25}$ -20.5° (c 0.41, $CHCl_3$) (lit[17] $[\alpha]_D^{25}$ -22.8° (c 2.46, $CHCl_3$)).

Kinetic resolution of 3b. The reaction was performed on 5.4 mmol scale (1.08 g) in the same manner described above. After 2 h, usual workup followed by chromatography on silica gel afforded the mixture of (R)-3b and 4b. To this mixture were added Ac_2O (1 ml, 10.8 mmol) and C_5H_5N (1 ml) and stirred for 6 h at room temp and poured into sat $NaHCO_3$. Extraction with hexane (3 X 5 ml) followed by purification by chromatography on silica gel to afford the acetates of (R)-3b and 4b which were individually treated with K_2CO_3 (1.5 g) in MeOH and H_2O (4:1, 10 ml) at room temp for 4 h. Extraction followed by chromatography on silica gel to give (R)-3b (445 mg, 41%) and 4b (490 mg, 42%).
(R)-3b, >99% e.e. (by ^{1}H-NMR shift analysis of the acetate with (-)-Pr(dfpm)$_3$ in CCl_4); $[\alpha]_D^{25}$ +17.5° (c 0.96, $CHCl_3$).
4b, 83.8% e.e. (by ^{1}H-NMR shift analysis of the acetate with (+)-Eu(dfpm)$_3$ in $CDCl_3$); $[\alpha]_D^{25}$ -4.86° (c 1.03, $CHCl_3$); IR (neat) 3450, 1250, 845; ^{1}H-NMR (CCl_4, PhH) δ 0.10 (s, 9H), 0.90 (t, J = 6.0, 3H), 1.06 (d, J = 6.0, 3H), 1.20-1.60 (m, 6H), 2.21 (br s, 1H), 2.85-3.04 (m, 1H), 3.79 (q, J = 6.0, 1H); ^{13}C-NMR ($CDCl_3$) δ 65.1, 59.2, 57.2, 29.7, 29.0, 22.3, 19.1, 13.7, -1.4. The absolute configuration of (R)-3b was determined after conversion into (R)-(-)-2-octanol: A mixture of the recovered allylic alcohol (382 mmg, 1.91 mmol) and NaH (380 mg, 50% in oil, 1.91 mmol) in HMPA (10 ml) was stirred at room temp for 30 min and poured into 3N HCl (10 ml). Extraction followed by filtration through a column of silica gel gave the protodesilylated allylic alcohol (230 mg, 94%). A mixture of this allylic alcohol and 10% Pd/C (150 mg) in pentane (10 ml) was stirred at room temp under hydrogen atomosphere for 30 min. Filtration of the mixture through a column of silica gel afforded (R)-(-)-2-octanol (205 mg, 82%). $[\alpha]_D^{21}$ -9.95° (c 1.91, EtOH)(lit[20] (S)-(+)-2-octanol, $[\alpha]_D^{21}$ +10.1° (c 5.57, EtOH)).

Preparation of 6b. To an ice-cooled soln of (R)-3b (2.0 g, 10.0 mmol, >99% e.e.) in CH_2Cl_2 (30 ml) was added TBHP (2.7 ml, 20.0 mmol, 70 wt% in H_2O) and $VO(acac)_2$ (133 mg, 0.50 mmol). The resulting soln was stirred for 3 h at 0 °C and Me_2S (1.5 ml, 20.0 mmol) was added. The mixture was stirred for 30 min at room temp and poured into sat $NaHCO_3$ (30 ml). Extraction with hexane and Et_2O (3:1, 2 X 20 ml) followed by chromatography on silica gel yielded 6b (2.0 g, 93%). $[\alpha]_D^{25}$ +5.74° (c 1.00, $CHCl_3$).

Preparation of 7b. To an ice-cooled soln of 6b (490 mg, 2.27 mmol) in THF (10 ml) was added t-BuOK (280 mg, 2.50 mmol) and n-Bu_4NF (4.1 ml, 2.72 mmol, 0.67 M in THF) and the resulting soln was stirred for 5 min at 0 °C. After addition of sat NH_4Cl (10 ml), the product was extracted with Et_2O (3 X 5 ml). The org layers were dried ($MgSO_4$) and concentrated to afford an oil which was chromatographed on silica gel to give 7b (280 mg, 95%). $[\alpha]_D^{25}$ +4.40° (c 1.00, $CHCl_3$); ^{1}H-NMR (CCl_4) δ 0.62-1.10 (m, 3H), 1.14 (d, J = 6.2, 3H), 1.15-1.70 (m, 6H), 2.56 (dd, J = 2.4, 3.6, 1H), 2.70-2.95 (m, 1H), 3.09 (br s, 1H), 3.68 (dq, 3.6, 6.2, 1H).

Preparation of 8b. 4b (310 mg, 1.44 mmol, 83.8% e.e.) was converted into 8b (180 mg, 96%) in the same manner as described for the preparation of 7b. $[\alpha]_D^{25}$ -3.67° (c 0.98, $CHCl_3$).

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