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Bovine Liver Acetone Powder (BLAP) Catalyzed Synthesis of Chiral C-8 Allyl Alcohols: An Application of Substrate Specificity Approach

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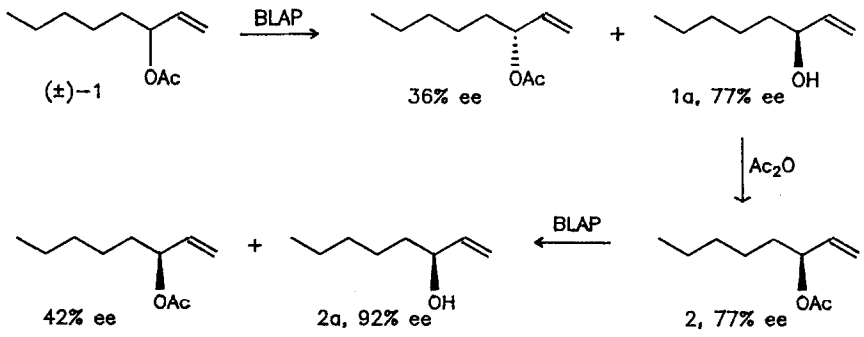
Abstract: (S)-Matsutake alcohol is synthesized by enzymatic hydrolysis in 92% optical purity using bovine liver acetone powder (BLAP). The principle of substrate specificity approach is applied to the synthesis of C-8 allyl alcohols in 46-93% enantiomeric purities using BLAP.

The C-8 allyl alcohol moiety is an important structural unit in the synthesis of biologically active molecules. For example oct-1-en-3-ol is a well known pheromone matsutake alcohol,[1] a flavor component of the mushroom *Tricholoma matsutake* and 1,7-octadien-3-ol is an important synthon[2] for lipoic acid, a co-enzyme associated with α-ketoacid dehydrogenases.[3,4]

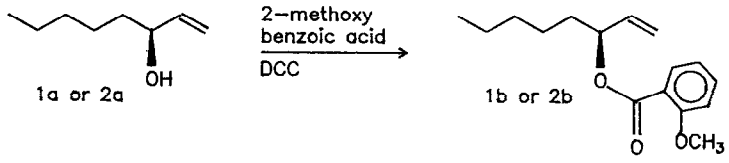
Recent years have witnessed an exponential growth of chemico-enzymatic methodology for obtaining enantiomerically enriched molecules.[5-8] In continuation of our interest on chemico-enzymatic methodology,[9-11] we herein report our studies based on substrate specificity approach for synthesis of chiral C-8 allylic alcohols using bovine liver acetone powder (BLAP).

Applications of crude enzymes[9-15] gained importance in organic transformations because they are cheap, easy to prepare and handle. Recently we have reported a simple convenient methodology for synthesis of 1-aryl-1-alkanols in high enantiomeric purities using crude bovine liver acetone powder.[11] It occurred to us that this crude enzyme would be useful for resolution of C-8 allyl alcohol derivatives. Accordingly we have first selected 1-octen-3-ol for kinetic resolution with BLAP. The biocatalytic hydrolysis of 3-acetoxy-1-octene with BLAP was carried out in biphasic medium (ether : phosphate buffer) and the resulting (S)-3-hydroxy-1-octene was obtained in 77% enantiomeric purity (Scheme 1).

Scheme 1



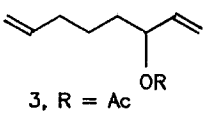
Attempted determination of the enantiomeric purity of this molecule by ^1H NMR analysis of alcohol and its acetate in the presence of $Eu(hfc)_3/Eu(tfc)_3$ was not successful. The analysis of the benzoate and Mosher's ester of this alcohol on HPLC with chiralcel OD (Diacel) chiral column was also not useful for determining the enantiomeric purity. However the enantiomeric purity was determined by the HPLC analysis (base line separation for R,S isomers) of the corresponding 2-methoxybenzoate derivative (**1b** or **2b**) (eq 1) using chiralcel OD (Diacel) column (method A in experimental section).



(eq 1)

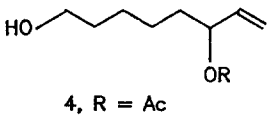
The enantiomeric purity of this molecule was enhanced by converting this enantiomerically enriched alcohol into its corresponding acetate and again subjecting this acetate to enzymatic hydrolysis using bovine liver acetone powder thus producing the desired (S)-matsutake alcohol in 92% enantiomeric purity.

It is well known that enzymes are highly specific for substrates. Enantioselectivity in enzymatic hydrolysis depends on how best substrate fits in the cavity of the enzyme. We have therefore selected four C-8 allylic alcohol units **3-6** which have different substitution pattern, as substrates to examine the substrate specificity leading to better selectivity.



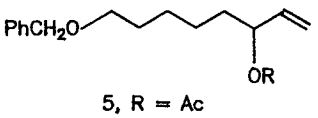
3, R = Ac

3a, R = H



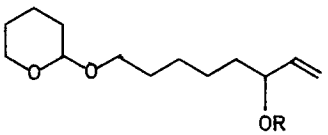
4, R = Ac

4a, R = H



5, R = Ac

5a, R = H



6, R = Ac

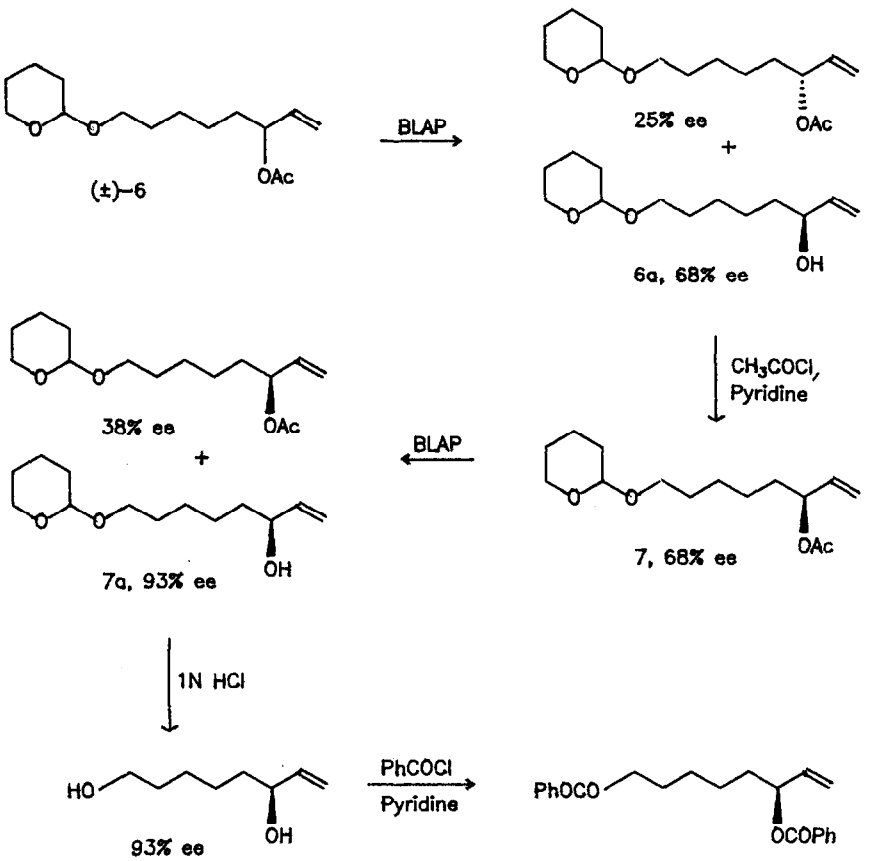
6a, R = H

First we have examined the hydrolysis of 3-acetoxy-1,7-octadiene (3) with a view that C-7 double bond might influence the enantioselectivity. The resulting 3-hydroxy-1,7-octadiene (**3a**) has only 56% enantiomeric purity as determined by the HPLC analysis of the corresponding 2-methoxybenzoate derivative on chiral column, chiralcel OD (Diacel) (method A). Thus the introduction of a double bond at C-7 position has reduced the enantioselectivity from 77% ee (in the case of oct-1-en-3-ol) to 56% ee.

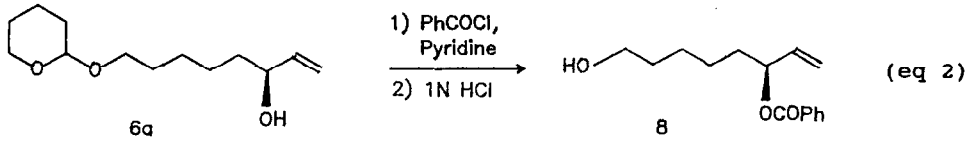
Next we have examined the hydrolysis of 8-hydroxy-3-acetoxy-1-octene (**4**) with BLAP. The resulting oct-1-en-3,8-diol (**4a**) is obtained in 49% ee. The enantiomeric purity was determined by converting the diol into dibenzoate and analyzing by HPLC using chiralcel OD (Diacel) column (method B in experimental section). This indicates that 7-hydroxy substitution is not suitable for better selecitivity. A similar hydrolysis of 8-benzyloxy-3-acetoxy-1-octene (5) with BLAP provided the desired 8-benzyloxy-3-hydroxy-1-octene (**5a**) in 46% ee (as determined by method A). Finally we have selected 8-(tetrahydropyran-2-yloxy)-3-acetoxy-1-octene (6) for BLAP hydrolysis. The resulting alcohol **6a** was produced in 68% enantiomeric purity as determined by converting this molecule into the corresponding diol which inturn was converted into dibenzoate and analyzed by HPLC using chiralcel OD (Diacel) column (method B). These results indicate that 8-(tetrahydropyran-2-yloxy) group allows the molecule to better fit in the cavity of the enzyme.

We have converted this enantiomerically enriched alcohol **6a** into corresponding acetate which was again subjected to hydrolysis with BLAP. The resulting (S)-(+)-alcohol **7a** was obtained in 93% ee (scheme 2).

Scheme 2



The absolute configuration was established by converting the molecule **6a** into a known compound **8** (eq 2) and comparing the specific rotation.[16]



(eq 2)

The molecule **7a** was transformed into (4S)-2-methyl-4-(4-carbomethoxybutyl)-1,3-dioxane (**12**) (Scheme 3) an important synthon for lipoic acid[2].

Scheme 3

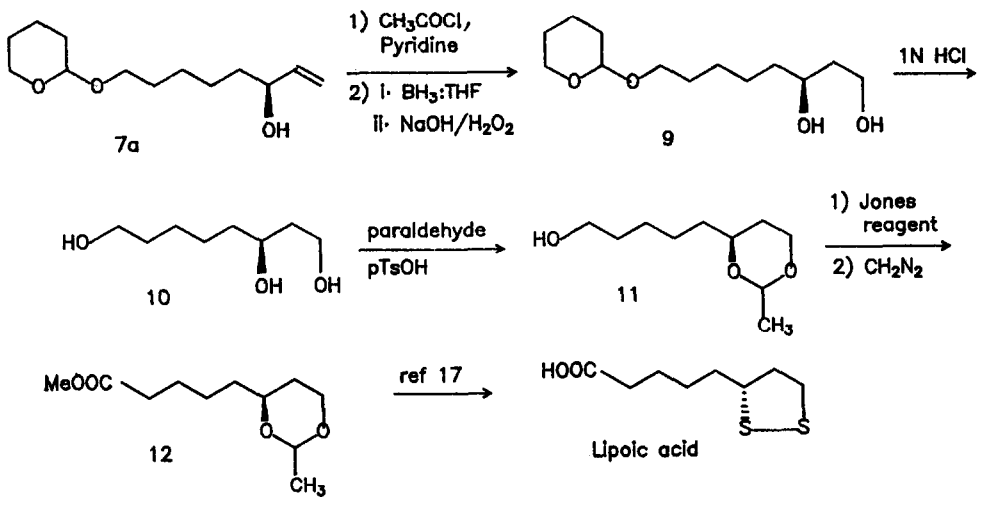


Table 1. BLAP catalyzed resolution of C-8 allylic acetates 1-7.[a]

substrate	reaction time(h)	% hydrolysis[b] OH:OAc	(+)-alcohol yield[c]	% ee[d]	config	Recovered acetate yield[c]	E[e]
1	52	37:63	70	77	S	76	12
2	44	32:68	65	92	S	72	12
3	28	30:70	72	56	S[f]	84	5
4	6	44:56	84	49	S	71	4
5	9	25:75	67	46	S[f]	95	3
6	10	30:70	64	68	S	85	7
7	10	35:65	85	93	S	86	7

a) All reactions were performed on 5 mM scale. Substrates 1 and 6 are performed on 30 mM scale for preparative purpose.

b) Percentage of hydrolysis (conversion ratio) was determined by GC analysis. (For substrate 5, by HPLC analysis)

c) Yields are of isolated and pure compounds and based on percentage of hydrolysis.

d) Determined by HPLC equipped with chiralcel OD (Diacel) column.

e) Caleculated according to the Sih equation.[18]

f) Tentatively assigned based on the sign of the optical rotation.

In conclusion, our methodology provides a simple synthesis of optically active (S)-matsutake alcohol and (4S)-2-methyl-4-(4-carbomethoxybutyl)-1,3-dioxane an important synthon in the synthesis of lipoic acid. Our study also throws light on the importance of tetrahydropyran-2-yloxy group in enzymatic hydrolysis. Further studies on the use of tetrahydropyran-2-yloxy group in enzymatic methodology are in progress in our laboratory.

Experimental section:

^{1}H and ^{13}C NMR spectra are recorded on JEOL-FX-100 (100 MHz) or Bruker-200 (200 MHz) spectrometers in chloroform-d solution with TMS as internal standard. IR spectra are recorded on Perkin-Elmer 1310 spectrophotometer. HPLC analysis was performed on Shimadzu LC-10AD equipped with SPD-10A detector. GC analysis was performed on Chemito gas chromatograph equipped with SE-30 column. Column chromatography was carried out using Acme's silica gel (100-200 mesh) and Acme's aluminum oxide neutral. Optical rotations were measured on Autopol II automatic polarimeter. BLAP was prepared using freshly purchased bovine liver.[11]

3-Hydroxy-1-octene was prepared by treating n-hexanal with vinylmagnesium bromide. 3-Hydroxy-1,7-octadiene was prepared by the reaction of pent-4-enylmagnesium bromide on acrolein. 3-Hydroxy-8-benzyloxy-1-octene was prepared by treating 6-benzyloxyhexanal with vinylmagnesium bromide. Acetates were prepared by treating the racemic alcohols with acetic anhydride in presence of pyridine. 3-Hydroxy-8-(tetrahydropyran-2-yloxy)-1-octene was prepared by treating 5-(tetrahydropyran-2-yloxy)pentylmagnesium bromide with acrolein. The corresponding acetate, 3-acetoxy-8-(tetrahydropyran-2-yloxy)-1-octene, was prepared by the action of acetyl chloride on the racemic alcohol in presence of pyridine. 3-Acetoxy-8-hydroxy-1-octene was prepared by treating 3-acetoxy-8-(tetrahydropyran-2-yloxy)-1-octene with 1N HCl in methanol. Recovered acetates were hydrolyzed with KOH/MeOH at room temperature for 2 h to provide the corresponding optically active alcohols.

Determination of optical purity:

Method A: The enantiomeric purities were determined by HPLC analysis (chiralcel OD, 4.5mm x 25cm (Diacel) column, solvent system / hexane : isopropanol) of 2-methoxybenzoate derivatives of optically active

alcohols with reference to the corresponding 2-methoxybenzoate derivatives of racemic alcohols.

Preparation of 2-methoxybenzoate derivative: A solution of racemic alcohol (1-3, 5) (0.1 mM), 2-methoxybenzoic acid (0.1 mM), dicyclohexylcarbodiimide (0.125mM) and DMAP (cat.) in dichloromethane was stirred at room temperature for 4 h. Usual workup followed by column purification provided the desired 2-methoxybenzoate derivatives. Similarly optically active alcohols ((+)-1-3, 5) were converted into corresponding 2-methoxybenzoate derivatives.

Method B: The enantiomeric purities were determined by HPLC analysis (chiralcel OD 4.5mm x 25cm (Diacel) column, solvent system / hexane : isopropanol) of dibenzoate derivatives of optically active diols with reference to the corresponding dibenzoate derivatives of racemic diols.

Preparation of dibenzoate derivative: A solution of racemic diol (0.1mM), benzoyl chloride (0.2 mM), pyridine (0.2mM) and DMAP (cat.) in benzene was stirred for 3 h at room temperature. Usual workup followed by column purification provided the corresponding dibenzoate.

BLAP catalyzed hydrolysis of racemic acetates 1-7:
General procedure: To the solution of racemic acetate (5 mM) in ether (10 mL), 40 mL of 0.5 M pH 8 phosphate buffer (K_2HPO_4/KH_2PO_4) was added. To this stirred solution 1 g of BLAP was added and stirring was continued at room temperature. Hydrolysis was monitored by GC (or HPLC) analysis. After appropriate hydrolysis (Table 1) the reaction was quenched with 2N HCl. The enzyme was filtered and the aqueous layer was extracted with dichloromethane. Organic layer was dried over sodium sulphate and concentrated. The crude product containing optically active alcohol and acetate was separated by column chromatography (neutral aluminium oxide, hexane : ethyl acetate / 90 : 10).

The enzymatic hydrolysis results are summarized in Table 1. IR, ^1H and ^{13}C NMR spectra, optical rotations, methods of ee determination are given below.

(S)-(+)-3-hydroxy-1-octene (1a): Obtained by the enzymatic hydrolysis of the corresponding acetate 1, Yield 70%, $[\alpha]_D^{20}$ + 8.67 (c3.09, $CHCl_3$) 77% ee. [Lit[1] $[\alpha]_D$ + 8.1 (c1.46, $CHCl_3$) >94% ee, config. S]. IR (neat): 3345, 1620 cm^{-1}, ^1H NMR (200 MHz) δ: 0.92 (t, 3H, J=6Hz), 1.20-1.68 (m, 9H, 1H D_2O washable), 4.14 (q, 1H, J=6Hz), 5.06-5.31 (m, 2H),

5.76-5.94 (m, 1H). ^{13}C NMR (25 MHz) δ: 13.82, 22.47, 24.94, 31.70, 36.88, 73.00, 114.24, 141.47.
2-methoxybenzoate derivative of **1a**: IR (neat): 1715, 1620 cm^{-1}, ^{1}H NMR (200 MHz) δ: 0.88 (t, 3H, J=6Hz), 1.22-1.82 (m, 8H), 3.89(s, 3H), 5.12-5.61 (m, 3H), 5.76-5.98 (m, 1H), 6.92-7.04 (m, 2H), 7.42-7.52 (m, 1H), 7.80 (m, 1H). HPLC analysis (method A, solvent system hexane : isopropanol / 98 : 2) shows 77% enantiomeric purity.

(R)-(-)-3-hydroxy-1-octene : The recovered acetate was hydrolyzed with KOH / MeOH to provide (-)-alcohol, Yield 74%, $[\alpha]_D^{20}$- 3.88 (c3.61, $CHCl_3$) 34% ee. The ee was determined by comparing the optical rotation with that of (+)-3-hydroxy-1-octene (**1a**).

(S)-(+)-3-hydroxy-1-octene (2a): Obtained by the enzymatic hydrolysis of the corresponding acetate **2**, Yield 65%, $[\alpha]_D^{20}$ + 10.56 (c2.61, $CHCl_3$) 92% ee. The enantiomeric purity was determined by method A.

(S)-(+)-3-hydroxy-1-octene: The recovered acetate was hydrolyzed with KOH / MeOH to provide (+)-alcohol, Yield 72%, $[\alpha]_D^{20}$+4.72 (c2.41, $CHCl_3$) 42% ee. The ee was determined by comparing the optical rotation with that of (+)-3-hydroxy-1-octene (**1a**).

(S)-(+)-3-hydroxy-1,7-octadiene (3a): Obtained by the enzymatic hydrolysis of corresponding acetate **3**, Yield 72%, $[\alpha]_D^{20}$ + 8.19 (c2.44, Et_2O) 56% ee, IR (neat): 3300, 1620 cm^{-1}. ^{1}H NMR (200 MHz): δ 1.41-1.68 (m, 5H, 1H D_2O washable), 2.14 (m, 2H), 4.12 (m, 1H), 4.92-5.28 (m, 4H), 5.68-5.95 (m, 2H). ^{13}C NMR (200 MHz): δ 24.59, 33.59, 36.41, 73.06, 114.71, 138.77, 141.42.
2-methoxybenzoate derivative of **3a**: IR (neat): 1705, 1620 cm^{-1}, ^{1}H NMR (200 MHz): δ 1.46-1.92 (m, 4H), 2.10 (m, 2H), 3.90(s, 3H) 4.92-5.62 (m, 5H), 5.74-6.00 (m, 2H), 6.94-7.06 (m, 2H), 7.42-7.55 (m, 1H), 7.82 (m, 1H). HPLC analysis (method A, solvent system hexane : isopropanol / 99.5 : 0.5) shows 56% enantiomeric purity.

(R)-(-)-3-hydroxy-1,7-octadiene: The recovered acetate was hydrolyzed with KOH / MeOH to provide (-)-alcohol, Yield 68%, $[\alpha]_D^{20}$- 3.36 (c2.11, Et_2O) 23% ee. The ee was determined by comparing the optical rotation with that of (+)-3-hydroxy-1,7-octadiene (**3a**).

(S)-(+)-3,8-dihydroxy-1-octene (4a): Obtained by enzymatic hydrolysis of corresponding monoacetate **4**, Yield 84%, $[\alpha]_D^{20}$ + 3.25, (c2.76, $CHCl_3$), 49% ee, IR(neat): 3325, 1620 cm^{-1}. ^{1}H NMR (200 MHz):δ 1.22-1.72 (m, 10H,

2H D_2O washable), 3.63 (t, 2H, J=6.5 Hz), 4.08 (m, 1H), 5.05-5.30 (m, 2H), 5.74-5.95 (m, 1H). ^{13}C NMR (50 MHz): δ 25.01, 25.60, 32.49, 36.86, 62.58, 72.98, 114.48, 141.25.
Dibenzoate derivative of **4a**: IR (neat): 1720, 1620 cm^{-1}, ^1H NMR (200 MHz): δ 1.44-1.56 (m, 4H), 1.70-1.88 (m, 4H), 4.32 (t, 2H, J=6.5 Hz), 5.18-5.38 (m, 2H), 5.52 (m, 1H), 5.81-5.98 (m, 1H), 7.40-7.74 (m, 6H), 7.92-8.18 (m, 4H). HPLC analysis (method B, solvent system hexane : isopropanol / 99 : 1) shows 49% enantiomeric purity.

(R)-(-)-3,8-dihydroxy-1-octene: The recovered acetate was hydrolyzed with KOH / MeOH to provide (-)-alcohol, Yield 78%, $[\alpha]_D^{20}$ - 2.51 (c3.2, $CHCl_3$) 40% ee. The enantiomeric purity was determined by method B.

(S)-(+)-3-hydroxy-8-benzyloxy-1-octene (5a): Obtained by the enzymatic hydrolysis of the corresponding acetate 5, Yield 67%, $[\alpha]_D^{20}$ + 2.96 (c2.01, $CHCl_3$) 46% ee. IR (neat): 3335, 1620 cm^{-1}. ^1H NMR (200 MHz) : δ 1.28-1.72 (m, 9H, 1H D_2O washable), 3.46 (t, 2H, J=7Hz), 4.08(m, 1H) 4.49 (s, 2H), 5.05-5.28 (m, 2H), 5.76-5.94 (m, 1H), 7.32 (m, 5H). ^{13}C NMR (50 MHz) : δ 25.11, 26.08, 29.61, 36.92, 70.28, 72.78, 72.94, 114.37, 127.45, 127.59, 128.29, 138.58, 141.34.
2-Methoxybenzoate derivative of 5a: IR (neat): 1725, 1620 cm^{-1}, ^1H NMR (200 MHz): δ 1.34-1.86 (m, 8H), 3.44 (t, 2H, J=7Hz), 3.88 (s, 3H), 4.48 (s, 2H), 5.14-5.61 (m, 3H), 5.78-5.96 (m, 1H), 6.91-7.04 (m, 2H), 7.24-7.52 (m, 6H), 7.78 (m, 1H). HPLC analysis (method A, solvent system hexane : isopropanol / 90 : 10) shows 46% enantiomeric purity.

(R)-(-)-3-hydroxy-8-benzyloxy-1-octene: The recovered acetate was hydrolyzed with KOH / MeOH to provide (-)-alcohol, Yield 80%, $[\alpha]_D^{20}$ - 0.71 (c5.51, $CHCl_3$) 11% ee. The enantiomeric excess was determined by comparing the optical rotation with that of (+)-3-hydroxy-8-benzyloxy-1-octene (5a).

(S)-(+)-3-hydroxy-8-(tetrahydropyran-2-yloxy)-1-octene (6a): Obtained by the enzymatic hydrolysis of the corresponding acetate 6, Yield 64%, $[\alpha]_D^{20}$ + 1.93 (c3.12, $CHCl_3$) 68% ee. IR (neat): 3365 cm^{-1}, ^1H NMR (200 MHz): δ 1.24-1.92 (m, 15H, 1H D_2O washable), 3.30-4.25 (m, 5H), 4.56 (m, 1H), 5.06-5.31 (m, 2H), 5.78-5.95 (m, 1H). ^{13}C NMR (50 MHz): δ 19.66, 25.15, 25.50, 26.19, 29.66, 30.77, 36.99, 62.32, 67.52, 73.06, 98.84, 114.45, 141.38. The enantiomeric excess was determined by converting this alcohol into diol, which inturn was converted into dibenzoate and analyzed on HPLC (method B, hexane:isopropanol / 99:1).

(R)-(-)-3,8-dihydroxy-1-octene: (from 6) The recovered acetate was hydrolyzed with KOH / MeOH and THP ether was cleaved with 1N HCl in methanol to provide (-)-diol, Yield 60%, $[\alpha]_D^{20}$ - 1.70 (c3.16, $CHCl_3$) 25% ee. The enantiomeric excess was determined by method B.

(S)-(+)-3-hydroxy-8-(tetrahydropyran-2-yloxy)-1-octene (7a): Obtained by the enzymatic hydrolysis of the corresponding acetate 7, Yield 85%, $[\alpha]_D^{20}$ + 2.61 (c3.15, $CHCl_3$) 93% ee. The enantiomeric excess was determined by method B.

(R)-(+)-3,8-dihydroxy-1-octene: (from 7) The recovered acetate was hydrolyzed with KOH / MeOH and THP ether was cleaved with 1N HCl in methanol to provide (+)-diol, Yield 73%, $[\alpha]_D^{20}$ + 2.44 (c3.68, $CHCl_3$) 38% ee.The enantiomeric excess was determined by method B.

Preparation of (S)-3-benzoyloxy-8-hydroxy-1-octene (8): The optically active 3-hydroxy-8-(tetrahydropyran-2-yloxy)-1-octene (**6a**, 68% ee) (0.083 g, 0.36 mM) was treated with benzoyl chloride (0.051 g, 0.36 mM) in presence of pyridine (0.5 mM, 0.04 g) in benzene (1 mL) for 4 h at room temperature. The reaction mixture was washed successively with water and aqueous potassium carbonate solution. Organic layer was dried over anhydrous sodium sulphate and evaporated. The crude product was dissolved in methanol (0.5 mL) and treated with 1N HCl (0.1 mL) with stirring at room temperature for 1 h. Usual workup followed by column chromatography (silica gel, hexane : ethyl acetate / 90 : 10) provided 3-benzoyloxy-8-hydroxy-1-octene (**8**) (0.057 g, 63%). $[\alpha]_D^{20}$ + 13.6 (c2.75, $CHCl_3$). [Lit[16] $[\alpha]_D^{25}$ - 18.2 (c1.7, $CHCl_3$) R config. ee 95%]. IR (neat): 3325, 1700, 1620 cm^{-1}, ^1H NMR (200 MHz): δ 1.22-1.86 (m, 9H, 1H D_2O washable), 3.62 (t, 2H, J=6.5Hz), 5.17-5.35 (m, 2H), 5.54 (m, 1H), 5.80-5.98 (m, 1H), 7.38-7.62 (m, 3H), 8.00-8.09 (m, 2H), ^{13}C NMR (50 MHz): δ 24.86, 25.50, 32.57, 34.30, 62.73, 75.19, 116.66, 128.35, 129.58, 132.89, 136.53, 165.94.

Preparation of (S)-3-acetoxy-8-(tetrahydropyran-2-yloxy)-1-octene : To a solution of **7a** (0.3 g, 1.31 mM), pyridine (1.5 mM, 0.118 g) in benzene (5 mL) was added acetyl chloride (0.93 mL, 1.31 mM) at 0°C and stirred for 3 h at room temperature. The reaction mixture was washed successively with aqeuous potassium carbonate solution and water. Organic layer was dried over anhydrous sodium sulphate and concentrated to give the corresponding acetate (0.3 g, 85%). IR (neat): 1735, 1620 cm^{-1}, ^1H NMR (200 MHz): δ 1.26-1.84 (m, 14H), 2.06 (s, 3H), 3.28-3.94 (m, 4H), 4.55 (m, 1H), 5.10-5.28 (m, 3H), 5.69-5.86 (m, 1H). ^{13}C NMR

(50 MHz): δ 19.64, 21.16, 24.88, 25.50, 26.04, 29.58, 30.75, 34.11, 62.25, 67.39, 74.71, 98.80, 116.47, 136.60, 170.22.

Preparation of (S)-8-(tetrahydropyran-2-yloxy)-1,3-octanediol (9) : The acetate obtained above (0.3 g, 1.1 mM) was treated with BH_3:THF[19] (2M, 0.5 mM) at room temperature for 2 h. Then 5N NaOH solution (0.5mL) was carefully added followed by 29% H_2O_2 solution (1 mL) and the reaction mixture was stirred at room temperature for 2 h. Usual work up followed by column chromatography (silica gel, hexane : ethyl acetate / 90 : 10) provided the desired product 9 (0.17 g, 63%). $[\alpha]_D^{20}$ + 3.74 (c3.80, $CHCl_3$), IR (neat): 3345 cm^{-1}, ^1H NMR (200 MHz): δ 1.24-2.45 (m, 18H, 2H D_2O washable), 3.35-3.96 (m, 7H), 4.58 (m, 1H). ^{13}C NMR (50 MHz): δ 19.68 , 25.29, 25.44, 26.19, 29.60, 30.74, 37.63, 38.31, 61.41, 62.42, 67.52, 71.71, 98.93.

(4S)-2-Methyl-4-(4-carbomethoxybutyl)-1,3-dioxane (12): Compound 9 (0.17 g, 0.69 mM) was converted into 1,3,8-octanetriol (10) by treating with 1N HCl followed by usual workup. This crude triol was converted into 12 according to Tsuji[2] procedure as described for the corresponding racemic molecule. The crude triol as such was dissolved in dichloromethane (1 mL), and paraldehyde (0.3 mL) was added followed by p-toluenesulphonic acid (cat.). After stirring 2 h at room temperature under nitrogen the reaction mixture was poured into sat. sodium carbonate solution. Organic layer was washed with water and brine, dried over anhydrous sodium sulphate. Removal of solvent furnished (4S)-2-methyl-4-(5-hydroxypentyl)-1,3-dioxane (11). This alcohol 11 as such was dissolved in acetone (0.5 mL), Jones reagent was added dropwise at 0^oC until the red brown colour remained in the solution. Water is added to the reaction mixture and extracted with ether. Ether layer was dried over anhydrous sodium sulphate and solvent was evaporated. The crude acid was treated with diazomethane in ether. Usual workup followed by column chromatography (silica gel, hexane:ether / 10:1) provided the methyl ester 12 (0.053 g, over all yield 36% from 9). $[\alpha]_D^{20}$ + 3.01 (c2.65, $CHCl_3$). IR (neat): 1715 cm^{-1}, ^1H NMR (200 MHz): δ 1.20-1.82 (m, 11H), 2.34 (t, 2H, J=6Hz), 3.52-3.84 (m, 5H), 4.02-4.14 (m, 1H), 4.62 (q, 1H, J=5Hz). ^{13}C NMR (50 MHz): δ 21.16, 24.48, 24.79, 31.08, 33.90, 35.57, 51.35, 66.44, 76.29, 98.88, 173.99.

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