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Lipase-Catalyzed Resolution of 1-[4-(Benzyloxy)phenyl]hex-5-en-3-ol: Synthesis of (-)-Centrolobine

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A practical and efficient method for the preparation of homoallylic alcohol and its successful enzymatic resolution has been developed. This lipase-catalyzed resolution process has been optimized with respect to different lipases and solvents. Moreover, Mitsunobu strategy has been applied to recover the unwanted isomer. Further optically enriched homoallylic alcohol has been employed for the synthesis of (-)-centrolobine.

Keywords: Kinetic resolution, Lipases, Enantioselectivity, Mitsunobu reaction and Metathesis.

INTRODUCTION

The natural products containing of 2,5-disubstituted tetrahydrofuran and 2,6-disubstituted tetrahydropyran units exhibits different biological activities. These motifs can also be found in various monocyclic and polycyclic compounds, cyclic ethers or spiroketals [1-7]. (-)-Centrolobine (**1**) is a six membered heterocyclic natural product in which tetrahydropyran ring is present in *syn*-fashion. Basically it is isolated from the heartwood of *Centrolobium robustum* and from the stem of *Broginum potabile* in the Amazon forest. It is active ingredient in an herbal tea made from the wood of *Centrolobum robustum* and is used by the native people of the Amazon as a tonic cure for a variety of ailments [8-13]. Moreover, it exhibits various therapeutic activities like antibiotic and antifungal. Furthermore, it exhibits activity against *Leishmania amazonensis* promastigotes, a parasite associated with leishmaniasis, a major health problem in Brazil.

However, the structure of centrolobine was elucidated in 1964 and its absolute configuration was assigned in 2002 by its enantioselective synthesis [14]. Owing to excellent biological activities and its simple chemical structure, many research groups have been paid attention for its synthesis in racemic form [15-19] as well as in enantiomerically form [14,20-38].

The enantiomerically pure core unit of tetrahydropyran unit has been constructed by various methods like Prins-cyclization [39,40], ring rearrangement metathesis [41], asymmetric allylation [42-45], asymmetric hydrogenation [46-48], chelation controlled diastereoselective synthesis from carbohydrate [49], intramolecular amide enolate alkylation [50], enantioselective hetero Diels-Alder reaction (HDA) [51], the reduction of a β-ketosulfoxide [52,53], intra molecular reductive etherification [54], asymmetric reduction [55]. However, most of these reported methods have certain limitations like use of expensive chiral reagents, low selectivity and moderate yields. Herein, we demonstrated the synthesis of optically pure (-)-centrolobine using lipase catalyzed resolution protocol.

EXPERIMENTAL

Unless specified all solvents and reagents were reagent grade and used without further purification. Reactions involving moisture-sensitive reagents were performed under an atmosphere of nitrogen in glassware, which had been oven dried. *Pseudomonas cepacia* lipase immobilized on diatomite (PS-D), *Pseudomonas cepacia* (PS), *Pseudomonas cepacia* lipase immobilized on modified ceramic particals (PS-C), *Pseudomonas fluorescens* lipase (AK)are obtained from Amano Pharmaceutical company, Japan, *Pseudomonas fluorescens* lipase immobilized in Sol-Gel-AK on sintered glass (P), lipase immobilized from *Mucormeihei* (Lipozyme), *Candida antartica* lipase immobilized in Sol-Gel-AK on sintered glass (CAL B) are from Fluka, *Candida rugosa* lipase (CRL) (Sigma).

Melting points were recorded on an S.D. Fine 9100 Electrothermal melting point apparatus and are uncorrected. Infrared

spectra were recorded on Perkin-Elmer model 683 or 1310 spectrometers and are reported in wave numbers (cm^{-1}). ^1H NMR spectra were recorded as solutions in $CDCl_3$, or acetone (d_6) and chemical shifts were reported in parts per million (ppm) on a Varian Gemini 200 MHz or AV 300 MHz, instrument using tetramethylsilane (TMS) as an internal standard. Coupling constants were reported in hertz (Hz). Low-resolution mass spectra were recorded on CEC-21-100B Finnigan Mat 1210 or VG 7070H micromass spectrometers. Analytical TLC of all the reactions were performed on Merck prepared plates (silica gel 60F-254 on glass). Column chromatography was performed using Acme silica gel (100–200 mesh). Percentage yields were given for all the isolated compounds. HPLC analysis was performed on an instrument that consisted of a Shimadzu SIL-10AD auto injector, system controller with an SPD-M10A UV monitor as detector. The chiral purity was determined using Chiracel AS-H coloumn (Diacel). E-values were calculated based on the enantiomeric excess of the products (ee_p) and the conversion (c). Optical rotations were measured using SEPA-300 (Horiba) digital polarimeter.

3-(4-Benzyloxy)phenylpropan-1-ol (3): To a stirred solution of 4-(3-hydroxypropyl)phenol (**2**) (2.0 g, 13.5 mmol) in acetone (50 mL), K_2CO_3 (3.6 g, 26.3 mmol), benzyl bromide (2.3 g, 13.5 mmol) were added sequentially and stirred under reflux conditions for 10 h. After completion of the reaction, the reaction was taken into CH_2Cl_2 (25 mL), washed with brine (1 × 10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue was purified by column chromatography using EtOAc-hexane (15:85) as eluant to give the required benzyl ether **3** as a solid (3.0 g, 90 %); m.p.: 54-56 °C; IR (KBr, ν_{max}, cm^{-1}): 3362, 2927, 2860, 1510, 1241; ^1H NMR (200 MHz, $CDCl_3$): δ 1.40 (bs, 1H), 1.76-1.94 (m, 2H), 2.66 (t, 2H, *J* = 6.9 Hz), 3.64 (t, 2H, *J* = 6.0 Hz), 5.04 (s, 2H), 6.86 (d, 2H, *J* = 8.6 Hz), 7.09 (d, 2H, *J* = 7.8 Hz), 7.20-7.50 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.2, 34.4, 62.2, 70.1, 114.9, 127.5, 127.9, 128.4, 129.4, 134.3, 137.3, 157.1 ppm; Mass (EI): 242 $(M)^+$, 141, 91, 77, 65, 51.

3-(4-Benzyloxy)phenylpropanal (4): To a stirred solution of oxalyl chloride (1.1 mL, 12.4 mmol) in CH_2Cl_2 (50 mL), DMSO (1.8 mL, 24.8 mmol) was added slowly at –78 °C and stirred the reaction mixture at the same temperature for 30 min. Compound **3** (2.0 g, 8.3 mmol) in CH_2Cl_2 (10 mL) was added to the reaction mixture slowly at –78 °C and stirred at the same temperature for 2.5 h. To the reaction mixture triethylamine (6.9 mL, 49.6 mmol) was added slowly at 0 °C and stirred for another 30 min. The reaction mixture was taken into CH_2Cl_2 (20 mL), washed with 5 % HCl (1 × 5 mL), brine (1 × 5 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated. Purification of the crude residue was accomplished by column chromatography using EtOAc-hexane (10:90) as eluant to give the required aldehyde **4** as a solid (1.8 g, 88 %); m.p.: 46-48 °C; IR (KBr, ν_{max}, cm^{-1}): 2924, 1722, 1682, 1510, 1240; ^1H NMR (300 MHz, $CDCl_3$): δ 2.70 (t, 2H, *J* = 7.5 Hz), 2.87 (t, 2H, *J* = 7.5 Hz), 5.01 (s, 2H), 6.84 (d, 2H, *J* = 8.3 Hz), 7.05 (d, 2H, *J* = 8.3 Hz), 7.23-7.41 (m, 5H), 9.78 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.1, 45.3, 69.9, 114.9, 127.3, 127.8, 128.5, 129.2, 132.5, 137.1, 157.2, 201.6; Mass: (EI): 240 $(M)^+$, 239, 91, 77.

1-[4-(Benzyloxy)phenyl]hex-5-en-3-ol (5): To a stirred solution of allyl bromide (1.5 g, 12.5 mmol) in dry THF (20 mL), zinc powder (0.8 g, 12.5 mmol) was added and stirred at room temperature for 1 h. To the reaction mixture aldehyde **4** (1.2 g, 5 mmol) in THF (5 mL) was added and stirred at room temperature for 1.5 h. After completion of the reaction, the reaction mixture was washed with 5 % HCl (1 × 5 mL), dried over anhydrous Na_2SO_4. Purification was accomplished by column chromatography using EtOAc-hexane (30:70) as eluant to give the required homoallylic alcohol **5** as a solid (1.3 g, 90 %); m.p. : 68-70 °C; IR (KBr, ν_{max}, cm^{-1}): 3361, 2925, 1510, 1236, 1008; ^1H NMR (300 MHz, $CDCl_3$): δ 1.55 (bs, 1H), 1.70 (q, 2H, *J* = 8.3 Hz), 2.08-2.33 (m, 3H), 2.54-2.77 (dddd, 2H, *J* = 7.5, 13.5, 21.1, 28.7 Hz), 3.54-3.65 (m, 1H), 5.01 (s, 2H), 5.11 (d, 2H, *J* = 12.0 Hz), 5.70-5.85 (m, 1H), 6.83 (d, 2H, *J* = 9.0 Hz), 7.06 (d, 2H, *J* = 8.3 Hz), 7.23-7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.2, 38.7, 42.1, 70.0, 70.2, 114.9, 118.2, 127.6, 127.9, 128.7, 129.4, 134.5, 134.7, 137.4, 157.2 ppm; Mass (EI): 305 $(M+Na)^+$, 265, 223, 197, 91.

Kinetic resolution of 1-[4-(benzyloxy)phenyl]hex-5-en-3-ol (5): To the compound **5** (1.0 g, 3.5 mmol) in diisopropyl ether (25 mL), lipase (1.0 g, w/w) and vinyl acetate (1.8 g, 21 mmol) were added successively and the mixture was stirred at room temperature for nearly 17 h. After conversion to about 50 % which was monitored by HPLC on AS-H chiral Daicel column, the reaction mixture was filtered and the two compounds alcohol (*S*)-**5a** and acetate(*R*)-**7a** were separated by column chromatography using EtOAc-hexane (85:15) as eluent.

1-[4-(Benzyloxy)phenyl]hex-5-en-3ylacetate (6): To a stirred solution of homoallylic alcohol **5** (0.3 g, 0.9 mmol) in CH_2Cl_2 (20 mL), acetic anhydride (0.3 g, 2.6 mmol), Et_3N (0.3 g, 2.6 mmol) and DMAP (cat.) were added successively at 0 °C. After completion of the reaction, the reaction mixture was taken into CH_2Cl_2 (10 mL), washed with 5 % HCl (1 × 5 mL), brine (1 × 5 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude residue was purified by column chromatography using EtOAc-hexane (20:80) as eluant to give the required acetate **7** as a liquid (0.2 g, 80 %); IR (KBr, ν_{max}, cm^{-1}): 2927, 1736, 1511, 1375, 1240, 1171, 1024; ^1H NMR (300 MHz, $CDCl_3$): δ 1.75-1.92 (m, 2H), 2.10 (s, 3H), 2.30-2.42 (t, 2H, *J* = 9.0 Hz), 2.52-2.70 (m, 2H), 4.90-5.00 (m, 1H), 5.05 (s, 2H), 5.10-5.20 (d, 2H, *J* = 4.5 Hz), 5.60-5.80 (m, 1H), 6.82-6.92 (d, 2H), 7.00-7.15 (d, 2H), 7.25-7.50 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 30.8, 35.4, 38.6, 70.0, 72.8, 114.8, 117.7, 127.4, 127.8, 128.5, 129.2, 133.5, 133.8, 137.2, 157.1, 170.6; Mass (EI): 325 $(M)^+$, 265, 223, 197, 147, 91.

(*S*)-1-[4-(Benzyloxy)phenyl]hex-5-en-3-yl-4-nitrobenzoate (*S*)-7: To solution of *p*-nitrobenzoic acid (0.7 g, 4.3 mmol) in toluene (20 mL), powdered PPh_3 (1.1 g, 4.25 mmol) was added followed by a solution of alcohol (*S*)-**5a** (1.0 g, 3.5 mmol) in toluene (5 mL) at –30 °C. To this, a solution of diethyl azodicarboxylate solution (DEAD) (1 mL, 7 mmol) in toluene (3 mL) was added slowly and stirred at the same temperaturefor 10 h. After completion of the reaction as indicated by TLC, the reaction mixture was poured into saturated $NaHCO_3$ (20 mL). The phases were separated and the aqueous phase was further extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4

and concentrated. Purification of the crude product by flash chromatography (4 % EtOAc: hexane) provided *p*-nitrobenzoate (*R*)-**7** (1.4 g, 95 %) as a yellow solid; m.p. : 61-63 °C; $[\alpha]_D^{29.8}$ -32.76° (c 1.9, $CHCl_3$); IR (KBr, ν_{max}, cm^{-1}): 2949, 2221, 1714, 1607, 1524, 1515, 1281; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.89-2.13 (m, 2H), 2.40-2.70 (m, 4H), 4.97 (s, 2H), 5.01-5.29 (m, 3H), 5.64-5.84 (m, 1H), 6.80 (d, 2H, *J* = 8.9 Hz), 7.02 (d, 2H, *J* = 8.2 Hz), 8.12 (d, 2H, *J* = 8.9 Hz), 8.27 (d, 2H, *J* = 8.9 Hz), 8.30-8.42 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.8, 35.3, 38.5, 69.9, 74.8, 114.8, 118.3, 123.4, 127.3, 127.8, 128.5, 129.1, 130.6, 132.9, 133.4, 135.8, 137.1, 150.4, 157.2, 164.2 ppm; LCMS: 454 $(M+Na)^+$.

(*S*)-1-[4-(Benzyloxy)phenyl]hex-5-en-3-ol [(*S*)-5b]: To a solution of *p*-nitrobenzoate (*R*)-**7** (1.0 g, 2.3 mmol) in MeOH (15 mL), K_2CO_3 (1.3 g, 9.3 mmol) was added at 0 °C and the suspension was stirred for 15 min at room temperature. After completion of the reaction, neutralized the reaction mass with acetic acid (5 mL) and the solvent in the reaction mass was removed. The resulting crude mixture was diluted with H_2O (15 mL) and extracted with EtOAc (2 × 25 mL). The combined organic extracts were washed with brine (1 × 10 mL), dried (Na_2SO_4) and concentrated. The crude residue was purified by flash chromatography (10 % EtOAc:hexane) to provide the alcohol (*R*)-**5b** (0.6 g, 90 %) as a yellow solid; $[\alpha]_D^{25.2}$ -15.33° (c 1.0, $CHCl_3$).

(*R*)-1-[4-(Benzyloxy)phenyl]hex-5-en-3-ol [(*R*)-5a]: $[\alpha]_D^{25.2}$ + 14.66° (c 1.25, $CHCl_3$).

(*S*)-1-(4-(Benzyloxy)phenyl)hex-5-en-3-ol [(*R*)-5b]: $[\alpha]_D^{25.2}$ -14.31° (c 1.0, $CHCl_3$).

(*S*)-1-[4-(Benzyloxy)phenyl]hex-5-en-3-ylacetate [(*S*)-6a]: $[\alpha]_D^{25.2}$ +7.0° (c 1.0, $CHCl_3$).

(*S*)-1-[4-(Benzyloxy)phenyl]hex-5-en-3-ylacrylate [(*S*)-8]: To a stirred solution of (*R*)-**5b** (1 g, 3.54 mmol) in dry CH_2Cl_2 (20 mL), Et_3N (1.0 mL, 7.1 mmol), DMAP (cat.) and acryloyl chloride (0.3 g, 3.54 mmol) were added successively under ice-cold conditions. The reaction mixture was stirred at room temperature for 1 h. After completion of the reaction, the reaction mixture was taken into CH_2Cl_2 (15 mL), washed with 5 % HCl (1 × 5 mL), brine (1 × 5 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography using EtOAc-hexane (10:90) as eluant to give the acryl ester (*R*)-**8** as a liquid (1.1 g, 90 %); $[\alpha]_D^{25.2}$ -3.2° (c 1.0, $CHCl_3$); IR (KBr, ν_{max}, cm^{-1}): 2925, 1720, 1510, 1195, 1045; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.77-1.92 (m, 2H), 2.35 (t, 2H, *J* = 6.7 Hz), 2.45-2.65 (m, 2H), 5.0 (s, 2H), 5.02-5.10 (m, 3H), 5.65-5.83 (m, 2H), 6.03-6.14 (m, 1H), 6.38 (d, 1H, *J* = 17.3 Hz), 6.82 (d, 2H, *J* = 8.3 Hz), 7.02 (d, 2H, *J* = 8.3 Hz), 7.21-7.42 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.6, 35.4, 38.6, 70.0, 72.9, 114.8, 117.8, 127.3, 127.8, 128.5, 128.7, 129.2, 130.4, 133.3, 133.7, 137.2, 157.1, 165.8 ppm; Mass (EI): 337 $(M+H)^+$, 265, 223, 197, 147, 91.

(*S*)-6-[(4-Benzyloxy)phen]ethyl-5,6-dihydropyran-2-one [(*S*)-9]: To a stirred solution of (*R*)-**8** (0.1 g, 0.3 mmol) in CH_2Cl_2 (20 mL), Grubbs' 2nd generation catalyst (0.01 g, 0.015 mmol) was added and the mixture was stirred under reflux conditions for 30 h. After completion of the reaction, the reaction mixture was directly adsorbed on silica and purified by column chromatography using EtOAc-hexane (30:70) as eluent to give (*R*)-**9** as a solid (0.07 g, 80 %); m. p.: 103-105 °C; $[\alpha]_D^{25.2}$ +19.5° (c 1.0, $CHCl_3$); IR (KBr, ν_{max}, cm^{-1}): 2924, 1720, 1511, 1238, 1018, 749; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.75-2.39 (m, 5H), 2.61-2.88 (m, 2H), 4.30-4.46 (m, 1H), 5.03 (s, 2H), 6.01 (d, 1H, *J* = 9.3 Hz), 6.80 (d, 2H, *J* = 7.6 Hz), 7.10 (d, 2H, *J* = 8.4 Hz), 7.23-7.47 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.6, 30.1, 36.8, 70.2, 77.6, 115.0, 121.6, 127.5, 128.0, 128.7, 129.4, 133.4, 137.3, 145.1, 157.9, 164.5 ppm; Mass (EI): 309 $(M-1)^+$, 297, 197, 91.

(*R*)-6-(4-Hydroxyphenethyl)-tetrahydropyran-2-one [(R)-10]: To a solution of (*R*)-**9** (50 mg, 0.16 mmol) in ethyl acetate (10 mL), Pd/C (50 mg) was added under hydrogen atmosphere and stirred at room temperature for 4 h. After completion of the reaction, filtered the reaction mass through the celite pad and washed with ethyl acetate (3 × 20 mL). The solvent was evaporated and the residue was purified by column chromatography using EtOAc-hexane (40:60) as eluent to give the required product (*R*)-**10** as a solid (32 mg, 90 %); m.p. : 120-124 °C; $[\alpha]_D^{25.2}$-57.75° (c 1.0, $CHCl_3$); IR (KBr, ν_{max}, cm^{-1}): 3296, 2954, 2926, 1707, 1516, 1256; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44-2.06 (m, 6H), 2.35-2.80 (m, 4H), 4.16-4.28 (m, 1H), 5.72 (bs, 1H), 6.74 (d, 2H, *J* = 8.3 Hz), 6.99 (d, 2H, *J* = 8.3 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.6, 27.1, 28.7, 29.4, 36.8, 79.2, 114.7, 128.7, 131.7, 153.8, 172.6 ppm; Mass (EI): 221 $(M-1)^+$, 203, 185, 127, 107.

(2R,6R)-6-(4-Hydroxyphenethyl)-2-(4-methoxyphenyl)-tetrahydro-2*H*-pyran-2-ol (11): To a stirred solution of (*R*)-**10** (0.1 g, 0.5 mmol) in dry THF (15 mL), *p*-MeO-C_6H_4-MgBr (4 mL, 0.5 M in THF, 2 mmol) was added at –78 °C over 1 h. After completion of the reaction as indicated by TLC, the reaction mixture was taken into CH_2Cl_2 (15 mL), washed with 5 % HCl (1 × 5 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude residue was purified by column chromatography using EtOAc-hexane (1:1) as eluant to give the required product **11** as a liquid (0.1 g, 76 %); $[\alpha]_D^{25.1}$ +28.0° (c 1.5, $CHCl_3$); IR (KBr, ν_{max}, cm^{-1}): 3386, 2926, 1599, 1514, 1258, 1173, 829; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46-1.96 (m, 6H), 2.50-3.08 (m, 4H), 3.57-3.67 (m, 1H), 3.87 (s, 3H), 6.75 (d, 2H, *J* = 8.3 Hz), 6.93 (d, 2H, *J* = 9.0 Hz), 7.03 (d, 2H, *J* = 8.3 Hz), 7.94 (d, 2H, *J* = 9.0 Hz); Mass (EI): 329 $(M+H)^+$, 311, 279, 152, 102.

(-)-Centrolobine (1): To a stirred solution of (*R*)-**11** (60 mg, 0.18 mmol) in dry dichloromethane (5 mL), $BF_3{\cdot}Et_2O$ (0.1 g, 0.73 mmol), Et_3SiH (0.1 g, 0.73 mmol) were added successively at -78 °C and the reaction mixture was stirred at room temperature for 1 h. After completion of the reaction, the organic layer was washed with aq. $NaHCO_3$ (2 × 5 mL), brine (1 × 5 mL), dried over anhydrous Na_2SO_4. Purification of the crude residue was accomplished by column chromatography using EtOAc-hexane (1:1) as eluant to afford the required product **1** as a solid (0.04 g, 65 %); m.p.: 81-84 °C; {Lit. [1] 85.5-86.5 °C}; $[\alpha]_D^{25.1}$-90.0° (c 1.0, $CHCl_3$) {Lit. [1] $[\alpha]_D^{24}$-91.7° (c 0.77, $CHCl_3$)}; IR (neat, ν_{max}, cm^{-1}): 3401, 2934, 1613, 1513, 1247; ^{1}H NMR (400 MHz, acetone-d_6): δ 1.23-1.34 (m, 1H), 1.36-1.46 (m, 1H), 1.60-1.92 (m, 6H), 2.57-2.72 (m, 2H), 3.40-3.46 (m, 1H), 3.78 (s, 3H), 4.30 (dd, 1H, *J* = 11.2, 11.8 Hz), 6.74 (d, 2H, *J* = 8.5 Hz), 6.88 (d, 2H, *J* = 8.7 Hz), 7.02 (d,

2H, *J* = 8.5 Hz), 7.31 (d, 2H, *J* = 8.6 Hz), 8.07 (s, OH); ^{13}C NMR (75 MHz, acetone-d_6): δ 25.5, 32.2, 32.8, 35.4, 40.3, 56.2, 78.4, 80.5, 114.9, 116.7, 128.5, 130.9, 134.7, 137.8, 156.9, 160.4 ppm; LCMS: 313 $(M+H)^+$, 335 $(M+Na)^+$.

RESULTS AND DISCUSSION

In continuation of our earlier efforts towards [56-65] the synthesis of optically active biologically important compounds using lipase-catalyzed resolution, herein we wish to report the synthesis of (-)-centrolobine (Fig. 1) using this method. The synthesis of (-)-centrolobine has been commenced from 4-(3-hydroxypropyl)phenol (**2**) as a starting material. The aromatic alcohol **2** has been protected as benzyl ether (**3**) using benzyl bromide (K_2CO_3, acetone, reflux, 10 h) in quantitative yield and this on further oxidation to give the aldehyde (**4**) under Swern conditions. The aldehyde (**4**) on Barber allylation using allyl bromide and zinc in THF yielded the homoallylic alcohol (**5**). The racemic homoallylic alcohol (**5**) has been subjected for lipase screening for resolution. The screening has been accomplished with different lipases using vinyl acetate as acyl donor in diisopropylether as solvent. Amongst all the lipases screened, *Pseudomonas cepacia* lipase adsorbed on ceramic particles (PS-C) which is also known as *Buckoldia cepacia* has given good conversion and high enantiomeric excess in shorter reaction time (Table-1). By selecting lipase PS-C as the best of choice, the effect of different solvents has also been studied. Amongst all the solvents screened hydrophobic solvents like hexane, diisopropyl ether, *t*-butyl methyl ether and toluene provided better conversion compared to hydrophilic solvents like acetone, THF, acetonitrile (Table-2). After the resolution, the two optically pure compounds acetate (*S*)-**6a** and alcohol (*R*)-**5a** have been separated by column chromatography. Enantiomeric excess has been calculated using chiral AS-H column on HPLC. The enantiomeric excess of alcohol (*R*)-**5a** is > 99 % and acetate (*S*)-**6a** is > 99 % (*E* = 1046) respectively. The stereochemical preference of lipase PS-C during lipase catalyzed resolution was in line with Kazlauskas' rule (Fig. 2) [70].

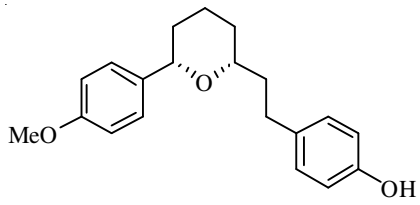


Fig. 1. (-)-Centrolobine (**1**)

After separation of the two compounds alcohol and acetate by coloumn chromatography, the alcohol (*R*)-**5a** was subjected for Mitsunobu esterification [71,72] followed by hydrolysis to give the alcohol (*S*)-**5b**. The acetate (*S*)-**6a** was hydrolyzed using potassium carbonate in methanol to give the alcohol (*S*)-**5b**. The compound (*S*)-**5b** upon esterificaton using acryloyl

TABLE-1
TRANSESTERIFICATION OF 1-[4-(BENZYLOXY)PHENYL]HEX-5-EN-3-OL (**5**) WITH VARIOUS LIPASES IN DIISOPROPYLETHER[a]

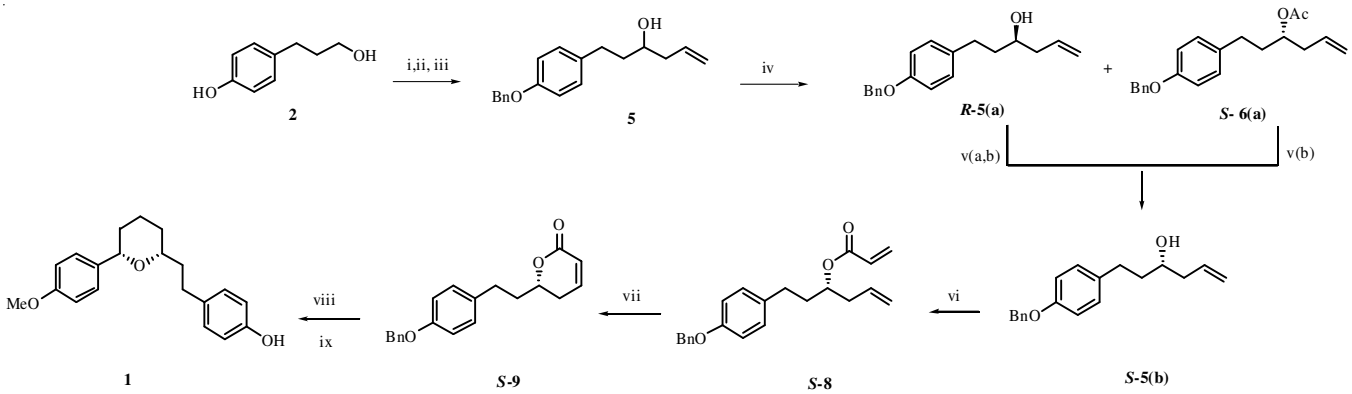
Entry	Lipase	Time (h)	Alcohol		Acetate		Conversion (%)	E[d]
			Yield[b] (%)	ee[c] (%)	Yield[b] (%)	ee[c] (%)		
1	PS-C	5	46	> 99	46	> 99	0.5	1046
2	PS-D	12	45	> 99	45	> 99	0.5	1046
3	PS	24	40	81	44	> 99	0.45	440
4	CRL	120	82	21	5	> 99	0.18	45
5	PPL	120	85	22	5	> 99	0.18	322
6	CAL-B	15	42	95	43	97	0.18	117
7	PF	120	4	21	6	> 99	0.18	45
8	MML	120	88	–	4	> 99	–	–

[a]Conditions: Reactions were carried out in diisopropylether (15 mL), **5** (50 mg, 0.18 mmol), vinyl acetate (0.9 g, 1.08 mmol) and lipase (50 mg, w/w) at 30 °C, 200 rpm; [b]Isolated yields; [c]Determined by HPLC (Chiracel AS-H column; Daicel) employing *n*-hexane:iso-propanol (9:1) as mobile phase at 0.5 mL/min and monitored at UV (254 nm); [d]Calculated according to Chen *et al.* [69,70] using the equation: $E = (\ln[1-c(1 + ee_p)])/(\ln[1-c(1-ee_p)])$.

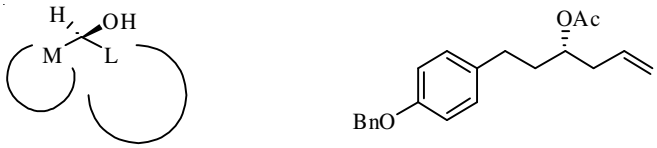
TABLE-2
EFFECT OF DIFFERENT SOLVENTS ON THE TRANSESTERIFICATION
1-[4-(BENZYLOXY)PHENYL]HEX-5-EN-3-OL (**5**) BY LIPASE PS-C[a]

Entry	Solvent	log P[b]	Time (h)	Alcohol		Acetate		Conversion (%)	E[e]
				Yield[c] (%)	ee[d] (%)	Yield[c] (%)	ee[d] (%)		
1	$^{i}Pr_2O$	3.5	5	44	> 99	46	> 99	0.5	1046
2	*n*-Hexane	2.5	12	43	> 99	45	> 99	0.5	1046
3	^{t}BuOMe	1.9	65	40	89	42	> 99	0.47	281
4	Toluene	2.5	5	41	95	40	97	0.18	117
5	CH_3CN	-0.33	65	69	13	23	54	19	4
6	Acetone	-0.23	65	80	15	12	98	13	10
7	THF	0.49	20	85	–	6	94	–	–
8	$CHCl_3$	-1.1	120	88	–	5	> 99	–	–

[a]Conditions: Reactions were carried out in diisopropylether (15 mL), **5** (50 mg, 0.18 mmol), vinyl acetate (0.9 g, 1.08 mmol) and lipase (50 mg, w/w) at 30 °C, 200 rpm; [b]Source of data: references [71,72]; [c]Isolated yields; [d]Determined by HPLC (Chiracel AS-H column; Daicel) employing *n*-hexane:*iso*-propanol (9:1) as mobile phase at 0.5 mL/min and monitored at UV (254 nm); [e]Calculated according to Chen *et al.* [69,70] using the equation: $E = (\ln[1-c(1+ee_p)])/(\ln[1-c(1-ee_p)])$.



Scheme-I: Reagents and conditions: (i). BnBr, K_2CO_3, acetone, reflux, 10 h, 95 %; (ii). $(COCl)_2$, DMSO, -78 °C, 2 h, then NEt_3, -78 to -10 °C, 80 %; (iii). Allyl bromide, Zn, THF, 3 h, 90 %; (iv). Lipase PS-C, vinylacetate, diisopropyl ether; (v). (a) 4-Nitrobenzoic acid, PPh_3, DEAD, toluene, –30 °C, 95 %; (b) K_2CO_3, MeOH, r.t., 1 h, 90 %; (vi). Acryloyl chloride, NEt_3, CH_2Cl_2, 1 h, 90 %; (vii). Grubb's catalyst-2nd generation, CH_2Cl_2, reflux, 30 h, 80 %; (viii). Pd/C, H_2, EtOAc, 4 h, 80 %; (ix). (a) *p*-MeO-Ph-MgBr, THF, -78 °C, 1 h, 76 %; (b) $BF_3{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2, -78 °C then r.t., 1 h, 65 %



M = medium sized group
L = large gruop

(Resolved using PS-C
preferred enantiomer shown)

Fig. 2

chloride followed by ring closing metathesis using Grubbs' 2nd generation catalyst to provide the α,β-unsaturated lactone (*S*)-**9**. This upon hydrogenation in the presence of Pd/C in ethyl acetate resulted (*S*)-**10** *via* debenzylation and hydrogenation of the double bond in one pot. The lactone (*S*)-**10** upon treatment with *p*-MeO-Ph-MgBr gave lactol **11**, which on further reduction with Et_3SiH in the presence of $BF_3{\cdot}Et_2O$ afforded the optically pure (-)-centrolobine **1** (**Scheme-I**). The spectral data of ^1H and ^{13}C NMR as well as its optical rotation closely match with the previously reported data of the natural product **1** [54,55].

Conclusion

In summary, a practical and efficient method for the preparation of homoallylic alcohol and its successful enzymatic resolution has been described. This lipase-catalyzed resolution process has been optimized with respect to different lipases and solvents. Further, optically enriched homoallylic alcohol has been employed in the synthesis of (-)-centrolobine. This method has potential for the synthesis of similar natural products.

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