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Chemoenzymatic synthesis of calcilytic agent NPS-2143 employing a lipase-mediated resolution protocol

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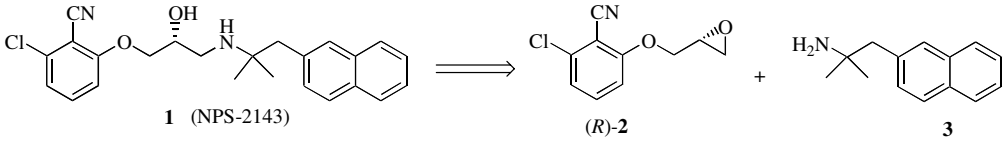
Abstract—The kinetic resolution of chlorohydrin (±)-**6** has been successfully carried out via a lipase-mediated transesterification with vinyl acetate in organic as well as ionic liquid media to yield (*R*)-alcohol **6** and (*S*)-acetate **7** in high enantioselectivity. An enantioconvergent synthesis has also been achieved by a Mitsunobu esterification of a mixture of (*R*)-alcohol **6** and (*S*)-acetate **7** in one pot to convert the (*R*)-alcohol **6** to (*S*)-acetate **7**. (*S*)-Acetate **7** has been hydrolyzed by $LiOH{\cdot}H_2O$ to give epoxide (*R*)-**2**. This enantiopure epoxide has been used as a chiral precursor for the synthesis of calcilytic agent NPS-2143.

1. Introduction

Osteoporosis is becoming a major disease that affects over 28 million people, especially post-menopausal women. Presently, anti-resorptive agents such as estrogen, bisphosphonates, calcitonin and selective estrogen receptor modulators (SERMs) are used in the treatment of osteoporosis. These anti-resorptive agents can prevent bone loss but have limited effects on new bone formation and each has been associated with efficacy, safety, tolerability and/or cost limitation. A synthetic 1–34 amino acid peptide fragment of human parathyroid hormone (PTH), has been used to treat severe osteoporosis as an alternative subcutaneous injection.[1] As an alternative to a daily PTH injection, one could envision stimulating the release of endogenous PTH from the parathyroid glands. It is well established that PTH secretion is inversely related to plasma calcium concentration[2] and regulated by the extracellular calcium-sensing receptor (CaSR). Thus, the compound that blocks the activity of the CaSR (CaSR 'antagonists') leads to increased plasma levels of PTH. These increased PTH levels are associated with bone formation,[3] hence CaSR antagonists could provide a practical approach to the treatment of osteoporosis; such compounds are known as calcilytic agents. NPS-2143 is an orally active low molecular weight calcilytic agent that stimulates the secretion of endogenous PTH by antagonizing the CaSR on the surface of parathyroid cells,[4] resulting in the stimulation of new bone growth. Studies have suggested that the (*R*)-enantiomer of NPS-2143 is 10- to 100-fold more potent than the corresponding (*S*)-enantiomer.[5] To the best of our knowledge, there has been only one report for the preparation[6] of NPS-2143 that involves the synthesis of enantiomerically pure (*S*)-oxirane and its coupling with 1,1-dimethyl-2-(2-naphthyl)ethylamine **3**.

In an effort to develop an efficient preparation of enantiomerically pure NPS-2143, we considered enantiomerically pure chlorohydrin **6** as one of a number of suitable precursors for the synthesis of this compound.[7] In continuation of our previous studies towards the preparation of biologically important chiral compounds or their intermediates by the application of enzymes,[8] we



1 (NPS-2143) (*R*)-**2** **3**

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herein report a lipase-mediated kinetic resolution of chlorohydrin (±)-**6** and its application in the synthesis of optically active calcilytic agent NPS-2143 **1**.

2. Results and discussion

2.1. Synthesis of racemic epoxide (±)-2 and chlorohydrin (±)-6

Racemic epoxide (±)-**2** was prepared by a reaction with excess of epichlorohydrin in the presence of K_2CO_3 and 18-crown-6 in refluxing acetone (Scheme 1). Upon completion of the reaction, the solids were filtered and the filtrate evaporated under vacuum. The resulting crude epoxide (±)-**2** was then purified by column chromatography. Ring opening of the epoxide (±)-**2** by LiCl and $CuCl_2$ in tetrahydrofuran afforded the desired chlorohydrin (±)-**6**.[9] Additionally, this reaction has also been carried out in ionic liquid [bmim]PF_6. Interestingly, the use of ionic liquid media not only provides a quantitative yield with regioselectivity but has potential for its reuse and recycle in further runs.[10,11]

2.2. Lipase-mediated resolution of racemic chlorohydrin (±)-6

Enantiomerically pure epoxide (*R*)-**2** is an important precursor towards the synthesis of NPS-2143 and other related calcium-sensing receptor antagonists.[7] In the literature, there have been some reports on the preparation of optically active epoxide **2** in its (*R*)-form.[6,7] Herein, we have resolved the racemic chlorohydrin (±)-**6** by employing various lipases (Scheme 2).

2.2.1. Screening of lipases. The primary requirement for a successful kinetic resolution is the selection of a suitable lipase and solvent. Initially, six different commercially available lipases were screened for the transesterification of 2-chloro-6-(3-chloro-2-hydroxypropoxy)benzonitrile (±)-**6** with vinyl acetate in diisopropyl ether with the results being summarized in Table 1. Amongst the lipases screened, lipase from *Pseudomonas cepacia*, that is, PS and PS-D gave good conversion and high enantioselectivity.

Table 1. Transesterification of chlorohydrin (±)-**6** with various lipases in diisopropyl ether[a]

Lipase[b]	Amount (equiv w/w)	Time (h)	c[c] (%)	ee_6[d] (%)	ee_7[d] (%)
PS-D	0.5	3	50	96	93
PS	1	24	46	84	98
PS-C	0.5	3	49	77	80
AK	1	24	27	30	82
CCL	1	24	19	18	74
PF	1	24	13	15	99

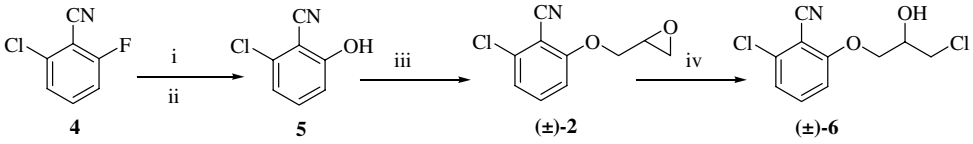
[a] Conditions: 0.25 mmol of (±)-**6**, 2.5 mL of solvent, 0.75 mmol vinyl acetate at 35 °C.

[b] PS-D (*Pseudomonas cepacia* lipase immobilized on diatomite), PS (*Pseudomonas cepacia* lipase), PS-C (*Pseudomonas cepacia* lipase immobilized on ceramic particles), AK (Amano 20), CCL (*Candida cylindracea* lipase from Sigma), PF (*Pseudomonas fluorescens* lipase immobilized in sol–gel–AK on sintered glass).

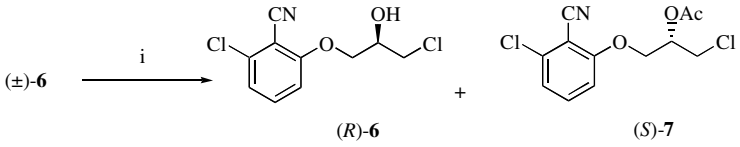
[c] Conversions were calculated from the enantiomeric excess of substrate **6** (ee_s) and product **7** (ee_p) using the formula: Conv. = $ee_s/(ee_s + ee_p)$.

[d] Determined by HPLC analysis (Daicel chiralcel AD-H column) 90:10; hexane/2-propanol, 0.5 mL/min flow rate at 254 nm.

2.2.2. Effect of solvents. In order to investigate the effect of solvents on the transesterification reaction process, different organic solvents as well as ionic liquids (Fig. 1) were studied by using vinyl acetate as acyl donor with lipase PS-D with the results described in Table 2. Hydrophobic solvents diisopropyl ether and toluene gave excellent results when compared with hydrophilic solvents such as tetrahydrofuran. Water-immiscible ionic liquids have been shown to be excellent non-aqueous media for enzyme-catalyzed reactions (especially for lipases), not only because of the high level of activity and stereoselectivity displayed by enzymes in chemical transformations,[12,13] such as ester synthesis, kinetic resolution of *sec*-alcohols, etc., but also because of their now well identified stabilization effects on the biocatalysts.[14,15] In continuation of our interest in the area of biocatalysis, particularly in the use of ionic liquid as a medium,[9] we investigated the effect of different ionic liquids on this transesterification process. Four ionic liquids containing different cations/anions were utilized for the transesterification of chlorohydrin (±)-**6** using vinyl acetate employing lipase PS-D.



Scheme 1. Reagents and conditions: (i) KOAc, 18-crown-6, CH_3CN, reflux 24 h; (ii) NaOH, H_2O, rt, 1 h; (iii) epichlorohydrin, K_2CO_3, 18-crown-6, acetone, reflux 24 h; (iv) $CuCl_2$/LiCl, THF, rt, 14 h, or $CuCl_2$/LiCl, [bmim]PF_6, 65 °C, 5 h.



Scheme 2. Reagents: (i) lipase, vinyl acetate.

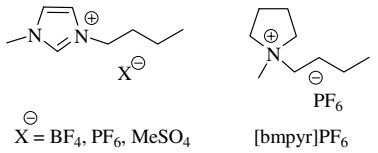


Figure 1.

Table 2. The effect of solvent and ionic liquid on the enantioselectivity in the resolution of chlorohydrin (±)-**6** with lipase PS-D[a]

Solvent	Time (h)	c[b] (%)	ee_6[c] (%)	ee_7[c] (%)	E[d]
DIPE	3	50	96	93	108
THF	5	23	30	99	>200
Hexane	5	35	53	99	>200
Toluene	6	50	98	99	>200
[bmpyr]PF_6	9	36	53	94	54
[bmim]PF_6	9	48	92	98	>200

[a] Conditions: 0.25 mmol of (±)-**6**, 2.5 mL of solvent, 0.5 mL ionic liquid, lipase (0.5 equiv w/w), 0.75 mmol vinyl acetate at 35 °C, PS-D = *Pseudomonas cepacia* lipase immobilized on diatomite.

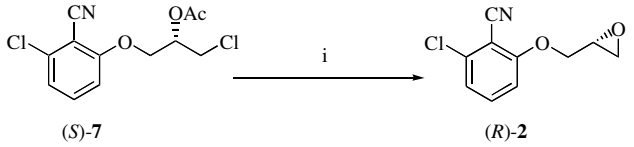
[b] Conversions were calculated from the enantiomeric excess of substrate **6** (ee_s) and product **7** (ee_p) using the formula: Conv. = $ee_s/(ee_s + ee_p)$.

[c] Determined by HPLC analysis (Daicel chiralcel AD-H column) 90:10; hexane/2-propanol, 0.5 mL/min flow rate at 254 nm.

[d] E values were calculated using the formula: $E = [\ln(1 - c)(1 - ee_s)]/[\ln(1 - c)(1 + ee_s)]$.

The conversion is negligible when using the ionic liquids 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]-BF_4 and 1-butyl-3-methylimidazolium methane sulfonate [bmim]$MeSO_4$. However, the use of the ionic liquid 1-butyl-1-methyl-pyrrolidinium hexafluorophosphate [bmpyr]PF_6 gave about 36% conversion in 9 h with >94% ee of (*S*)-**7**. Interestingly, the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate [bmim]PF_6 not only provides good conversion but also high enantioselectivity for both the (*R*)-alcohol **6** and (*S*)-acetate **7** as shown in Table 2. Moreover, the recyclability of the ionic liquid-lipase system was also investigated for this transesterification processes by recycling it for 2–3 subsequent runs without any appreciable effect on the conversion or the enantioselectivity.

2.2.3. Mitsunobu esterification and synthesis of enantiopure epoxide (*R*)-2. A mixture of (*R*)-alcohol **6** and (*S*)-acetate **7** was dissolved in dry THF and treated with PPh_3 and acetic acid followed by DEAD for 24 h, to give (*S*)-acetate **7** in 80% yield and 94% ee. The hydrolysis of acetate (*S*)-**7** with $LiOH{\cdot}H_2O$ in ethanol gave the corresponding epoxide (*R*)-**2** in an almost quantitative yield (>95%) and good enantiomeric excess (>95% ee) (Scheme 3).



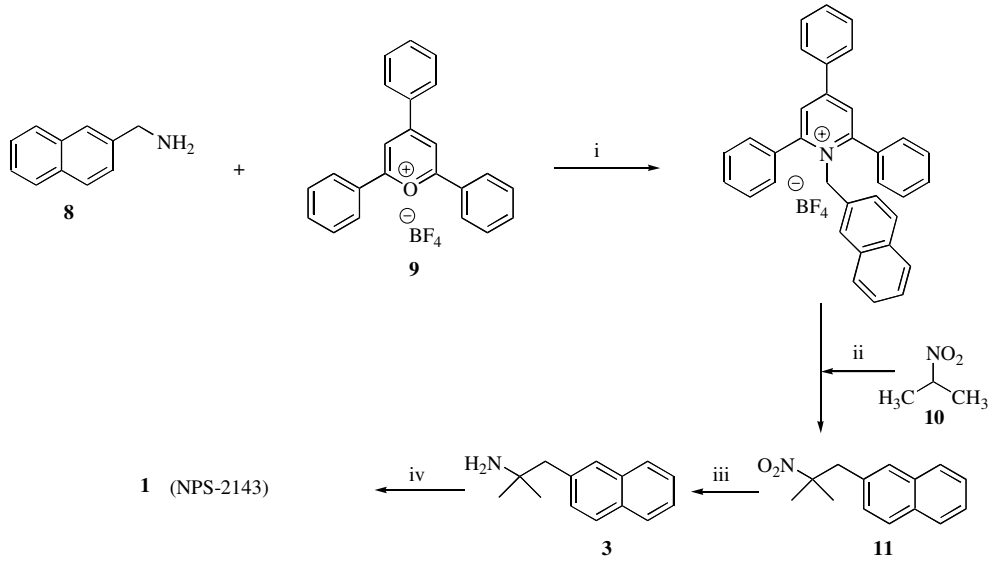
Scheme 3. Reagents and conditions: (i) $LiOH{\cdot}H_2O$, EtOH, 20 min.

2.3. Synthesis of NPS-2143

NPS-2143 was synthesized by the coupling of 2-chloro-6-[2-(*R*)-oxiranylmethoxy]benzonitrile (*R*)-**2** with 1,1-dimethyl-2-(2-naphthyl)ethylamine **3** in ethanol. Amine **3** was prepared by treatment of 2-(aminomethyl)naphthalene **8** with 2,4,6-triphenylpyrylium tetrafluoroborate **9** in ethanol. The resulting compound was dissolved in DMSO and treated with the sodium salt of 2-nitropropane **10** to give the nitro derivative **11**,[16] which on reduction by hydrogenation over Pd/C in ethanol gave the amine **3** (Scheme 4).

3. Conclusion

In summary, we have developed an efficient method for the resolution of chlorohydrin (±)-**6** in good yield and



Scheme 4. Reagents and conditions: (i) EtOH, Et_3N, overnight; (ii) NaH, MeOH; (iii) Pd/C, H_2; (iv) (*R*)-**2**, EtOH, 60 °C.

high enantioselectivity employing lipase-mediated transesterification process. Moreover, an enantioconvergent strategy has also been used by the Mitsunobu esterification of alcohol **6**. Furthermore, we have utilized this enantiopure (*S*)-chlorohydrin **7** for the preparation of the calcilytic drug NPS-2143. Additionally, the effect of using ionic liquids on this transesterification process has also been investigated.

4. Experimental

4.1. Material and methods

Enzymatic reactions were carried out on a 'Labline Environ-shaker' at 170 rpm. ^{1}H NMR spectra were recorded at 200 MHz or 300 MHz, chemical shifts are given in δ units relative to the tetramethylsilane (TMS) signal as an internal reference in $CDCl_3$. Coupling constants (J) are reported in Hertz (Hz). Electron-impact (EI) mass spectra were recorded in the form of m/z (intensity relative to base 100) on a VG 7070H Micromass mass spectrometer at 200 °C, 70 eV, with a trop current of 200 μA and 4 kV acceleration. FAB+ mass spectra were recorded on AutoSpec mass spectrometer with 7 kV acceleration voltage and 25 kV gun voltage. Melting points were recorded on an electrothermal melting point apparatus. IR spectra were recorded on a refractive spectrophotometer and are reported in wave numbers (cm^{-1}). Analytical TLC of all the reactions was performed on Merck prepared plates (silica gel 60 F-254 on glass). Column chromatography was performed using Acme silica gel (100–200 mesh). HPLC analyses were performed on 'Shimadzu LC-10AT' system controller, and UV monitor as detector. Specific rotations were recorded on SEPA-300 Horiba high sensitive polarimeter, fixed with a sodium lamp of wavelength 589 nm.

4.2. Chemicals and enzymes

All reagents were obtained from commercial sources and used without further purification. Solvents for extraction were of technical grade and distilled before use. Racemic chlorohydrin acetate **7** was prepared by the acetylation of racemic compound **6** with acetic anhydride in the presence of triethylamine and catalytic DMAP in DCM. *P. cepacia* lipase immobilized on diatomite (PS-D), *P. cepacia* lipase (PS), *P. cepacia* lipase immobilized on ceramic particles (PS-C) and AK (Amano 20) was purchased from Amano (Nagoya, Japan). *Candida cylindracea* lipase (CCL) was purchased from Sigma. *Pseudomonas fluorescens* lipase immobilized in sol–gel–AK on sintered glass (PF) was purchased from Fluka.

4.3. *rac*-2-Chloro-6-(oxiran-2-ylmethoxy)benzonitrile (±)-2

To a solution of 2-chloro-6-fluorobenzonitrile **4** (3.12 g, 20 mmol) in 40 mL of acetonitrile were added 18-crown-6 (7.92 g, 30 mmol) and dry potassium acetate (2.94 g, 30 mmol) and the reaction mixture refluxed under nitrogen for 24 h, and then cooled to room temperature. Sodium hydroxide (4 mL of a 10 M solution, 40 mmol) and water (10 mL) were added, and the reaction mixture stirred at room temperature for 2 h. The acetonitrile was removed on a rotary evaporator, and the residue was taken up in diethyl ether and water. The basic aqueous layer was washed three times with diethyl ether. The aqueous layer was then made acidic with HCl, and the product extracted into ether. The combined diethyl ether layers were dried over anhydrous sodium sulfate, filtered, and concentrated to give 2.20 g of 3-chloro-2-cyanophenol **5**. This was dissolved in acetone (60 mL) and treated with potassium carbonate (5.96 g, 43.13 mmol), 18-crown-6 (3.79 g, 14.37 mmol), and refluxed under nitrogen for 15 min. Epichlorohydrin (6.53 g, 70.6 mmol) was then added by syringe, and the mixture was refluxed for 24 h. The mixture was cooled and filtered and the filtrate evaporated to dryness. The residue was partitioned between ether/water, and the layers separated. The diethyl ether layer was washed with saturated NaCl, dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by silica gel column chromatography [eluent: ethyl acetate/*n*-hexane (20:80)] to give (±)-**2** as a white solid; yield: 2.7 g (90%); mp 119–120 °C; IR: 3421, 2231, 1590, 1452, 1284, 1034, 862, 778 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.75–2.82 (1H, dd, $J = 2.4$, 4.8 Hz), 2.86–2.93 (1H, t, $J = 4$ Hz), 3.25–3.30 (1H, m), 4.03–4.14 (1H, dd, $J = 5.6$, 12 Hz), 4.35–4.44 (1H, dd, $J = 2.4$, 11.2 Hz), 6.85–6.95 (1H, d, $J = 8.8$ Hz), 7.0–7.20 (1H, d, $J = 8.8$ Hz), 7.70–7.50 (1H, t, $J = 8.8$ Hz); EIMS (m/z): 209 (M^+); Anal. Calcd for $C_{10}H_8ClNO_2$: C, 57.3; H, 3.85; N, 6.68. Found: C, 57.21; H, 3.76, N, 6.5.

4.4. *rac*-2-Chloro-6-(3-chloro-2-hydroxypropoxy)benzonitrile (±)-6

To a stirred solution of (±)-**2** (209 mg, 1 mmol) taken in ionic liquid [bmim]PF_6 (1.5 mL) was added $CuCl_2$ (85 mg, 0.63 mmol) and LiCl (55 mg, 1.3 mmol) at room temperature. The reaction mixture was stirred at 60 °C for 5 h. After completion of the reaction as indicated by TLC, diethyl ether (3 × 5 mL) was added to the reaction mixture with stirring for 5 min. The mixture was allowed to stand for a further 5 min and the clear supernatant liquid then decanted. The combined ether layers were dried over sodium sulfate and concentrated in vacuum to obtain the crude product, which was purified by silica gel column chromatography [eluent: ethyl acetate/*n*-hexane (15:85)] to furnish chlorohydrin (±)-**6**. The ionic liquid layer was treated with phosphate buffer (4 mL, 0.1 M, pH = 7), and dissolved in dichloromethane (1 × 5 mL), dried in high vacuum and recycled in subsequent runs. (±)-**6** white solid; yield: 240 mg (97%); mp 101–102 °C; IR: 3499, 2231, 1592, 1471, 1447, 1290, 1092, 1038, 964, 780 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.85–3.90 (2H, d, $J = 5.0$ Hz), 4.15–4.40 (3H, m), 6.90–7.0 (1H, d, $J = 8.4$ Hz), 7.10–7.20 (1H, d, $J = 7.6$ Hz), 7.40–7.55 (1H, t, $J = 8.4$ Hz); EIMS (m/z): 245 ($M^+ - 1$); Anal. Calcd for $C_{10}H_9Cl_2NO_2$: C, 48.81; H, 3.69; N, 5.69. Found: C, 48.78; H, 3.66, N, 5.5.

4.5. Lipase-mediated resolution: preparation of optically active (*R*)-6 and (*S*)-7

To a solution of 2-chloro-6-(3-chloro-2-hydroxypropoxy)benzonitrile (±)-**6** (500 mg, 2.03 mmol), in toluene (30 mL) were added lipase PS-D (250 mg) and vinyl acetate (3 equiv). The suspension was shaken at 170 rpm at 35 °C and monitored by HPLC analysis until it reached 50% conversion (6 h). Then the reaction mixture was filtered and washed with water, followed by brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by silica gel column chromatography [eluent: ethyl acetate/*n*-hexane (15:85)] to give (*R*)-**6** 220 mg (45%) and (*S*)-**7** 270 mg (47%).

(*R*)-**6**: White solid, 98% ee [chiral HPLC analysis; Daicel chiralcel AD-H (0.46 × 25 cm) column; eluent: hexane/isopropanol = 90/10; flow rate: 0.5 mL/min; detector: 254 nm; $[\alpha]_D^{25} = -3.1$ (*c* 1, $CHCl_3$).

(*S*)-**7**: White solid, 99% ee [chiral HPLC analysis; Daicel chiralcel AD-H (0.46 × 25 cm) column; eluent: hexane/isopropanol = 90/10; flow rate: 0.5 mL/min; detector: 254 nm.; $[\alpha]_D^{25} = +33.8$ (*c* 1.2, $CHCl_3$); IR: 2233, 1746, 1591, 1451, 1375, 1236, 1046, 984, 776 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.15 (3H, s), 3.75–3.95 (2H, m), 4.3 (2H, d, $J = 5.2$ Hz), 5.3 (1H, quint, $J = 5.2$ Hz), 6.85 (2H, d, $J = 8.9$ Hz), 7.10 (2H, d, $J = 7.4$ Hz), 7.45 (2H, t, $J = 8.1$ Hz); FAB+ (*m*/*z*): 289 (M^++1); Anal. Calcd for $C_{12}H_{11}Cl_2NO_3$: C, 50.02; H, 3.85. N, 4.86. Found: C, 49.98; H, 3.68, N, 4.74.

4.6. Lipase-mediated resolution in ionic liquid [bmim]PF_6

To a stirred solution of (±)-**6** (50 mg) taken in an ionic liquid (0.5 mL) were added vinyl acetate (3 equiv) and lipase PS-D (0.5 equiv w/w) at room temperature. The mixture was stirred at room temperature. After about 48% conversion of the reaction as indicated by HPLC/TLC, diethyl ether (3 × 3 mL) was added to the reaction mixture with stirring for 5 min. The mixture was allowed to stand for a further 5 min and the clear supernatant liquid decanted. The combined diethyl ether layers were concentrated in vacuum to obtain an oily residue, which was purified by short silica gel column chromatography [eluent: ethyl acetate/*n*-hexane (15:85)] to obtain the products (*R*)-alcohol **6** and (*S*)-acetate **7**. The products were analyzed by HPLC using a chiral column to determine their enantiomeric excess (see Section 4.5).

4.7. Mitsunobu esterification of the mixture (*R*)-alcohol 6 and (*S*)-acetate 7

The transesterification processes were repeated by reacting (±)-**6** (100 mg), vinyl acetate (3 equiv) and lipase PS-D (0.5 equiv) in toluene (10 mL). The products (*R*)-alcohol **6** and (*S*)-acetate **7** were not separated. The evaporated mixture was dissolved in dry THF (5 mL), after which PPh_3 (1.5 equiv), and then acetic acid (1.5 equiv) were added. The mixture was cooled to 0–5 °C and DEAD (1.5 equiv) added. The mixture was stirred at room temperature for 24 h. Evaporation of solvent and purification by column chromatography [eluent: ethyl acetate/*n*-hexane (15:85)], yields (*S*)-acetate **7** (80%), ee = 94%.

4.8. 2-Chloro-6-[(2*R*)-oxyrane-2-ylmethoxy]benzonitrile (*R*)-2

To a solution of (*S*)-**7** (144 mg, 0.5 mmol) in ethanol (2 mL) was added $LiOH{\cdot}H_2O$ (65 mg, 1.5 mmol). The mixture was stirred at room temperature for 20–30 min. Evaporation of ethanol followed by dichloromethane extraction, water wash, drying and removal of the solvent afforded epoxide (*R*)-**2** as a white solid; yield: 100 mg (95%); >95% ee [chiral HPLC analysis; Daicel chiralcel OD (0.46 × 25 cm) column; eluent: hexane/isopropanol = 90/10; flow rate: 0.5 mL/min; detector: 254 nm.; $[\alpha]_D^{25} = -11.2$ (*c* 0.5, $CHCl_3$).

4.9. 1,1-Dimethyl-2-(2-naphthyl)ethylamine 3

A solution of 2,4,6-triphenylpyrylium tetrafluoroborate **9** (2.51 g, 6.33 mmol) in ethanol (15 mL) was treated with 2-(aminomethyl)naphthalene **8** (1 g, 6.33 mmol) and Et_3N (0.63 mmol). The reaction was stirred overnight at room temperature and diluted with diethyl ether to precipitate the product. The product was recrystallized from ethanol/diethyl ether to give *N*-(2-methyl naphthalene)-2,4,6-triphenylpyridinium tetrafluoroborate as a tan coloured solid. This tetrafluoroborate salt was dissolved in dimethyl sulfoxide (20 mL) and treated with the sodium salt of 2-nitropropane **10** (prepared by the reaction of sodium hydride (383 mg, 60% oil dispersion, 9.5 mmol) and 2-nitropropane **10** (0.858 mL, 9.5 mmol) in methanol (3 mL) at 0 °C). The mixture was stirred at 70 °C overnight under nitrogen. The reaction was diluted with water, and the product extracted into diethyl ether. The combined ether layers were washed with saturated NaCl and dried over sodium sulfate. The ether solution was treated with an Amberlyst 15 ion-exchange resin to absorb the 2,4,6-triphenylpyridine. The resin was filtered and the filtrate evaporated to give pure 2-(2-methyl-2-nitropropyl)naphthalene **11**. The 2-(2-methyl-2-nitropropyl)naphthalene **11** was hydrogenated in ethanol (30 mL) in presence of 10% Pd/C (500 mg) overnight. Removal of the catalyst by filtration and evaporation of the solvent gave an oil, which was purified by silica gel column chromatography [eluent: methanol/ethyl acetate (15:85)] to obtain 0.95 g of 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine **3** as a clear oil. IR: 3043, 2963, 2928, 1593, 1387, 782 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.2 (6H, s), 1.60–1.85 (2H, br s), 3.15 (2H, s), 7.22–7.50 (4H, m), 7.60–7.80 (2H, m), 8.15 (1H, d, $J = 8.4$ Hz); FAB+ (*m*/*z*): 200 (M^++1); Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.60; N, 7.03. Found: C, 84.28; H, 8.56; N, 6.85.

4.10. Synthesis of NPS-2143

2-Chloro-6-[2-(*R*)-oxiranylmethoxy]benzonitrile (*R*)-**2** (209 mg, 1 mmol) and 1,1-dimethyl-2-(2-naphthyl)ethylamine **3** (300 mg, 1.5 mmol) were stirred at 60 °C in ethanol overnight. The methanol was evaporated at

reduced pressure, and the resulting thick liquid purified by silica gel column chromatography [eluent: methanol/ethyl acetate (10:90)] to furnish the NPS-2143. $[\alpha]_D^{25} = +13.3$ (c 1.2, $CHCl_3$); IR: 3355, 2927, 2857, 2231, 1590, 1451, 1377, 1285, 1038, 781 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.20 (6H, s), 2.90–3.20 (2H, m), 3.30 (2H, s), 4.1–4.2 (2H, m), 4.30–4.50 (2H, m), 6.85 (1H, d, $J = 8.9$ Hz), 6.90–7.0 (1H, d, $J = 7.4$ Hz), 7.20–7.50 (5H, m), 7.60–7.80 (2H, m), 8.10–8.20 (1H, d, $J = 8.9$ Hz); FAB+ (m/z): 409 (M^++1); Anal. Calcd for $C_{24}H_{26}ClN_2O_2$: C, 70.49; H, 6.16; N, 6.85. Found: C, 70.38; H, 6.15; N, 6.74.

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