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The influence of microwave irradiation on lipase-catalyzed kinetic resolution of racemic secondary alcohols

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Abstract—The influence of microwave irradiation on the Novozyme 435® (*Candida antarctica* lipase) catalyzed kinetic resolution of secondary alcohols with different functional groups was studied in comparison to the use of conventional heating at 60 °C. *p*-Chlorophenyl acetate was used as an acyl donor and toluene as the solvent. (±)-1-Phenyl-1-propanol **1**, (±)-1-(4-bromophenyl)-propan-1-ol **3**, (±)-1-phenylbut-3-en-1-ol **5** and (±)-3-bromo-2-(2-hydroxypropyl)-1,4-dimethoxynaphthalene **7** were successfully resolved into their (*S*)-alcohols and (*R*)-esters, respectively, in good enantiomeric excess. Resolution of (±)-ethyl-5-(4-methoxybenyloxy)-3-hydroxypentanoate **9** afforded its (*R*)-alcohol and (*S*)-ester using this method. In addition, microwave-assisted lipase transesterification of *meso*-symmetric diol **11** effected desymmetrization to ester **12** with high enantiomeric excess. In all cases studied, the conversion value for the microwave-assisted lipase kinetic resolution of secondary alcohols was higher than that obtained using conventional heating.

1. Introduction

Biocatalysts are an attractive alternative to conventional methods for effecting asymmetric organic transformations, offering unique characteristics when compared to chemical (homogeneous and heterogeneous) catalysts. Very high enantio-, regio- and chemoselectivities can be achieved using biocatalysts due to the strict recognition of the substrate by the enzyme. Biocatalytic reactions are also generally safe and the reaction conditions are mild.[1–3]

Lipases (triacylglycerol acyl hydrolases, EC 3.1.1.3) can be used as biocatalysts in hydrolysis reactions, acylation reactions, ester aminolysis and peracid formation.[4–7] Applications of lipase-catalyzed reactions include efficient syntheses of chiral building blocks, drugs and fragrances.[8–14] The kinetic resolution of secondary alcohols or their carboxylates either via esterification or hydrolysis has been extensively studied with different lipases, where the enzyme discriminates between the two enantiomers present in a racemic mixture.[2] Microwave-assisted high speed synthesis has also attracted considerable interest in recent years.[15] The advantages of microwave-assisted organic synthesis (MAOS) include reduced chemical reaction time, reduced side reactions, increased yields and improved reproducibility. MAOS has been applied to the synthesis of several natural products as well as peptides, peptoids and carbohydrates.[16–19]

Microwave-assisted lipase-catalyzed transesterification has emerged as a useful tool in organic synthesis. To date few reports are available that have been limited to the use of a relatively small number of secondary alcohol substrates.[20–23] A recent paper investigating microwave-assisted lipase-catalyzed transesterification of methyl acetoacetate in toluene suggested that microwave heating in fact had no noticeable effect on the reaction.[23] Studies on the kinetic resolution of alcohols that contain additional functionality and the position of the hydroxyl group relative to an aromatic ring have not been reported. Previous studies on the microwave-assisted kinetic resolution of alcohols have also used potentially toxic and explosive solvents with reaction temperatures varying from 35 °C to 95 °C.[20–22]

We herein report our studies on microwave-assisted lipase kinetic resolution of secondary alcohols which contain additional functionality. The position of the hydroxyl group relative to the aromatic ring is also investigated.

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2. Results and discussion

Immobilized *Candida antarctica* lipase (CALB) was chosen for these transesterification studies. *C. antarctica*, available under the trade name of Novozyme 435® (immobilized on a macroporous acrylic resin), has proven to be an efficient biocatalyst for lipase transesterifications[22,25–27] demonstrating good thermal stability with a maximum activity in the range of 70–90 °C.[22]

The use of vinyl acetate or isopropenyl acetate as the acyl donor is disadvantageous due to its propensity to cause undesired side reactions.[24] To date, *p*-chlorophenyl acetate **13** has not been used for microwave-assisted lipase transesterifications, despite the fact that it is a versatile acyl donor for use in conventional lipase (Novozyme 435®) transesterifications.[24] *p*-Chlorophenol is released as a non-interfering by-product,[28] thus prompting us to employ *p*-chlorophenyl acetate **13** as the acyl donor in the present work.

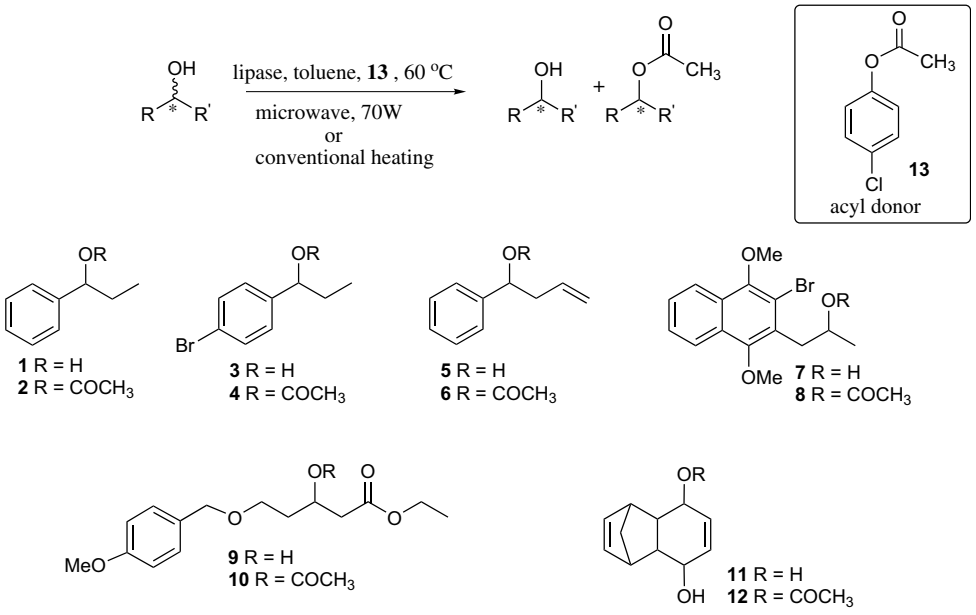
The choice of solvent is important, as it can influence the enantioselectivity observed for a given reaction. Toluene is an efficient solvent compared to other solvents, with respect to the enantiopurity of the products obtained.[29–32] Kazlauskas and Park demonstrated that the trend is towards higher reaction rates in less polar solvents.[32] With its higher boiling point, toluene appeared to be an excellent solvent for the investigation of microwave-assisted kinetic resolution.

Our objective was to study the influence of microwave irradiation on Novozyme 435® catalyzed kinetic resolution of several secondary alcohols **1**, **3**, **5**, **7**, **9** and **11** which contain different functional groups on the aryl ring and which also vary in the position of the hydroxyl group relative to the aryl ring. The Novozyme 435® catalyzed kinetic resolution of several different racemic secondary alcohols was carried out (Scheme 1) using *p*-chlorophenyl acetate **13** in toluene at 60 °C. For these microwave-assisted reactions, the CEM Discover system® with a circular single mode and focused waves was used, resulting in formation of a homogeneous field pattern surrounding the sample. Conventional heating reactions were carried out for the same reaction time as the microwave-assisted lipase reactions. The enantiomeric excess of the substrate (ee_s) and the product (ee_p) was measured using chiral HPLC. For each transesterification, the conversion (Conv) was calculated according to Sih and Chen.[28] The results obtained are summarized in Table 1.

Under microwave irradiation for 4 h, lipase kinetic resolution of racemic alcohol **1** afforded (−)-(*S*)-alcohol **1** (42%, 99% ee) and (+)-(*R*)-ester **2** (45%, 99% ee) with a conversion value of 50%. Under conventional heating for the same period, racemic alcohol **1** proceeded to (−)-(*S*)-alcohol **1** (81%, 55% ee) and (+)-(*R*)-ester **2** (17%, >99% ee) with a lower conversion value of 36%.

It was next decided to investigate the influence of a halogen substituent at the *para*-position on alcohol **3**. Under microwave irradiation for 5 h, lipase kinetic resolution of racemic alcohol **3** afforded (−)-(*S*)-alcohol **3** (48%, 92% ee) and (+)-(*R*)-ester **4** (39%, 99% ee). Under conventional heating, racemic alcohol **3** was converted into (−)-(*S*)-alcohol **3** (62%, 56% ee) and (+)-(*R*)-ester **4** (30%, >99% ee). The microwave irradiation method gave a higher conversion value of 48% when compared to the 35% obtained using conventional heating.

Having secured an efficient approach for the resolution of secondary alcohols **1** and **3**, our subsequent efforts focussed on the use of allyl alcohol **5**. In this case, microwave-assisted lipase kinetic resolution for 6 h effected resolution



Scheme 1. Lipase-catalyzed kinetic resolution of racemic secondary alcohols.

Table 1. Comparison of microwave-assisted lipase kinetic resolution and conventional heating assisted lipase kinetic resolution of secondary alcohols

Substrate	Time[d] (h)	Microwave heating			Conventional heating		
		Ester ee %[a] (yield %)	Alcohol ee %[a] (yield %)	Conv.[b] (%)	Ester ee %[a] (yield %)	Alcohol ee %[a] (yield %)	Conv.[b] (%)
1	4	>99 (45)	99 (42)	50	>99 (81)	55 (17)	36
3	5	>99 (39)	92[c] (48)	48	>99 (30)	53[c] (62)	35
5	6	>99 (24)	58 (71)	37	>99 (2)	6 (89)	6
7	6	>99 (44)	93 (40)	48	99 (26)	26 (73)	21
9	12	99 (38)	43 (48)	30	94 (9)	6 (73)	6
11	12	99 (81)	—	—	No reaction	—	—

[a] Determined by HPLC (Chiralcel OD–H, hexane–*i*-PrOH).
[b] Conversion was calculated according to the formula $\text{Conv} = ee_s/(ee_s + ee_p)$.[29] ee_p = enantiomeric excess of ester. ee_s = enantiomeric excess of alcohol.
[c] Calculation based on specific rotation.
[d] Reaction time for both microwave heating method and conventional heating method.

of racemic alcohol **5** into (−)-(*S*)-alcohol **5** (71%, 58% ee) and (+)-(*R*)-ester **6** (24%, >99% ee) with a conversion value of 37%. Under conventional heating, racemic alcohol **5** was converted into (−)-(*S*)-alcohol **5** (89%, 6% ee) and (+)-(*R*)-ester **6** (2%, >99% ee) with a conversion value of 6%. Thus, the microwave-assisted kinetic resolution proceeded with a sixfold higher conversion than conventional heating.

Next, the presence of an additional aromatic ring with the hydroxyl group β to the aryl ring was investigated using naphthyl alcohol **7**. Using microwave-assisted lipase kinetic resolution for 6 h, racemic alcohol **7** was resolved into (+)-(*S*)-alcohol **7** (40%, 93% ee) and (+)-(*R*)-ester **8** (44%, 99% ee). Under conventional heating, racemic alcohol **7** was resolved into (+)-(*S*)-alcohol **7** (73%, 26% ee) and (+)-(*R*)-ester **8** (26%, >99% ee). This reflected a twofold higher conversion value for the microwave method over conventional heating.

In order to test the utility of our approach for the resolution of multifunctional secondary alcohols, our attention next turned to the resolution of β-hydroxy ester **9** (Scheme 1). Using the microwave-assisted lipase kinetic resolution method, racemic alcohol **9** was resolved into (+)-(*R*)-alcohol **9** (48%, 43% ee) and (+)-(*S*)-ester **10** (38%, 99% ee) after 12 h. Under conventional heating, racemic alcohol **9** was resolved into (+)-(*R*)-alcohol **9** (73%, 6% ee) and (+)-(*S*)-ester **10** (9%, >94% ee). The microwave irradiation method proved to be the optimum method with a conversion value of 30%, which is a fivefold increase over conventional heating.

Desymmetrization of *meso*-compounds or prochiral diols and diacetates using a lipase enzyme has become a practical approach for the preparation of chiral compounds due to its high specificity and reproducibility. *meso*-Diol **11** has been used as a starting material for the enantioselective synthesis of (+)-panepophenanthrin,[8] hygromycin A[9] and (+)-Sch642305.[10] Takano et al.[33] also reported the monoacetylation of *meso*-symmetric diol **11** with vinyl acetate in the presence of lipase PS in 79% yield with the reaction stirred for 16 days at 28 °C.

We therefore evaluated the use of microwave-assisted lipase-catalyzed desymmetrization of *meso*-symmetric diol **11**. Ester **12** was obtained in 81% yield (99% ee) after microwave irradiation for 12 h at 60 °C in toluene using Novozyme 435® and *p*-chlorophenyl acetate **13** as the acyl donor. The rate of reaction was enhanced 32-fold over conventional heating which mainly afforded the recovered starting material. This example thus provides an excellent illustration of the considerable rate enhancement observed for lipase kinetic resolutions carried out using microwave irradiation.

In all cases, except for **9**, the enzymatic resolution fits Kazlauskas rule with the (*R*)-ester and (*S*)-alcohols being obtained. In alcohol **9**, the size of the substituents attached to the carbon atom bearing the hydroxyl group may be the reason for the deviation from this pattern.

Some conclusions can be derived from these experiments; the conversions observed using this microwave-assisted lipase kinetic resolution varied depending on the nature of the substituent attached to the secondary alcohol. The observed conversion increased in the order: $\mathbf{9} < \mathbf{5} < \mathbf{7} \leqslant \mathbf{3}$, **1**.

The position of the hydroxyl group was also found to be an important factor in these lipase kinetic resolutions. Based on these experiments, it can be concluded that the presence of a substituent α- to the hydroxyl group in the secondary alcohol substrates resulted in a higher conversion than the presence of a substituent at a position more remote to the hydroxyl group. Thus, α-substituted alcohol **1** showed a higher conversion than β-substituted alcohol **7**. The γ-substituted alcohol **9** showed even less conversion than both α-substituted alcohol **1** and β-substituted alcohol **7**.

The effect of the position of the substituents present on the aromatic ring was also found to be important. The observed conversion rate in the order $\mathbf{7} < \mathbf{3} < \mathbf{1}$ supports the notion that the presence of a halogen substituent at the *ortho*- or *para*-position on the aromatic ring results in decreased conversion.

The nature of the aromatic ring system was also investigated. Naphthyl substituted alcohol **7** afforded less selectivity than the phenyl substituted alcohols **1** and **3**. The presence of an allyl group also had an effect in that alcohol **5** resulted in less conversion than **1**, even though **5** still contains an α-substituted phenyl ring. Longer substituents

resulted in lower conversion rates as demonstrated by the conversion rates **9** < **5** < **3**, **1**. Notably during the kinetic resolution of **9**, no intramolecular lactonization or hydrolysis of the ester functionality was observed.

3. Conclusion

Microwave-assisted Novozyme 435® kinetic resolution of secondary alcohols in toluene using 4-chlorophenyl acetate **13** as an acyl donor at a temperature of 60 °C at 70 W has proven to be a versatile method to effect the kinetic resolution of secondary alcohols of varying substitution patterns compared to conventional heating.

4. Experimental

4.1. General details

All reactions were carried out in either oven-dried or flame-dried glassware under a nitrogen atmosphere unless otherwise stated. Analytical thin layer chromatography was performed using 0.2 mm Kieselgel F_{254} (Merck) silica plates and compounds were visualized under 365 nm ultraviolet irradiation followed by staining with either alkaline permanganate or ethanolic vanillin solution. Flash chromatography was performed using Riedel-de Häen Kieselgel or Merck Kieselgel 60 F (both 230–400 mesh) with the indicated solvents. Infrared spectra were obtained using a Perkin–Elmer Spectrum One Fourier Transform Infrared spectrometer as a thin film between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}). Optical rotations were measured using a Perkin–Elmer 341 polarimeter at $\lambda = 598$ nm and are given in 10^{-1} deg cm^2 g^{-1}. Melting points were recorded on an Electrothermal® melting point apparatus and are uncorrected. NMR spectra were recorded as indicated on either a Bruker DRX-400 spectrometer operating at 400 MHz for ^1H nuclei and 100 MHz for ^{13}C nuclei or on a Bruker Avance 300 spectrometer operating at 300 MHz and 75 MHz for ^1H and ^{13}C nuclei, respectively. Chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane peak recorded as δ 0.00 ppm in $CDCl_3$/TMS solvent, or the residual chloroform peak at δ 7.25 ppm. The ^{13}C NMR values were referenced to the residual chloroform peak at δ 77.0 ppm. ^{13}C NMR values are reported as chemical shift δ, multiplicity and assignment. ^1H NMR shift values are reported as chemical shift δ, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (J in Hz) and assignment. High resolution mass spectra were recorded on a VG-70SE mass spectrometer at a nominal accelerating voltage of 70 eV.

4.2. General procedure for microwave-assisted lipase-catalyzed kinetic resolution

A mixture of racemic alcohol (1.0 mmol) and *p*-chlorophenyl acetate (3.0 mmol) in toluene (5 mL) was flushed with argon for 1 min followed by the addition of Novozyme 435® (Sigma–Aldrich) (50 mg). The resulting mixture was stirred at 60 °C in a microwave reactor (single mode CEM Discover® Focused Microwave Synthesis System) at 70 W for the time shown in Table 1. When the reaction was complete (as indicated by TLC analysis) the mixture was filtered through cotton wool to remove the enzyme and washed with dichloromethane (2 × 3 mL). The combined organic extracts were concentrated under reduced pressure and the residue was purified by flash chromatography using hexane–ethyl acetate as eluent to yield the corresponding alcohol and ester.

4.3. General procedure for lipase-catalyzed kinetic resolution using conventional heating

A mixture of racemic alcohol (1.0 mmol) and *p*-chlorophenyl acetate (3.0 mmol) in toluene (5 mL) was flushed with argon for 1 min followed by the addition of Novozyme 435® (Sigma–Aldrich) (50 mg). The resulting mixture was stirred at 60 °C with heating on a sand bath for the time shown in Table 1. When the reaction was complete (as indicated by TLC analysis) the mixture was filtered through cotton wool to remove the enzyme and washed with dichloromethane (2 × 3 mL). The combined organic extracts were concentrated under reduced pressure and the residue purified by flash chromatography using hexane–ethyl acetate as eluent to yield the corresponding alcohol and ester.

4.3.1. (−)-(*S*)-1-Phenyl-1-propanol 1[34] and (+)-(*R*)-1-phenyl-1-propyl acetate 2.[34] Using the microwave-assisted kinetic resolution procedure described above with racemic alcohol **1** (113 mg, 0.8 mmol), the title compound **1** (47 mg, 0.33 mmol, 42%) was afforded as a colourless liquid, $[\alpha]_D^{20} = -46.0$ (*c* 0.80, $CHCl_3$) {lit.[35] $[\alpha]_D^{22} = -43.9$ (*c* 1.7, $CHCl_3$)}, 99% ee. The enantiomeric excess (ee) was determined by high pressure liquid chromatography (Waters-600) using a chiral column (Chiralcel OD–H, 0.43 cm × 1 cm, Daicel Chemical Ind. Ltd) and 2-propanol–hexane (1:99) as eluent with a flow rate of 0.5 mL/min. The retention time for the minor peak was 23 min and the retention time for the major peak was 33 min; υ_{max} (film)/cm^{-1}: 3406 (OH); δ_H (400 MHz, $CDCl_3$): 0.77 (3H, t, $J_{3,2} = 7.5$ Hz, 3-H), 1.54–1.68 (2H, m, 2-H), 3.79 (1H, br s, OH), 4.34 (1H, t, $J_{1,2} = 6.6$ Hz, 1-H), 7.11–7.22 (5H, m, Ar-H); δ_C (100 MHz, $CDCl_3$): 9.7 (CH_3, C-3), 31.4 (CH_2, C-2), 75.2 (CH, C-1), 125.7 (CH, C-2 and C-6), 126.7 (CH, C-4), 127.8 (CH, C-3 and 5), 144.4 (quat., C-1). The spectroscopic data were in agreement with that reported in the literature.[34]

(+)-(*R*)-1-Phenyl-1-propyl acetate **2** (66 mg, 0.37 mmol, 45%) was also obtained as a colourless liquid, $[\alpha]_D^{20} = +98.2$ (*c* 1.308, $CHCl_3$), 99% ee. The enantiomeric excess (ee) was determined by high pressure liquid chromatography (Waters-600) using a chiral column (Chiralcel OD–H, 0.43 cm × 1 cm, Daicel Chemical Ind. Ltd) and 2-propanol–hexane (1:99) as eluent with a flow rate of 0.5 mL/min. The retention time for the minor peak was 7 min and the retention time for the major peak was 10 min; υ_{max} (film)/cm^{-1}: 1735 (C=O), 1236 (C–O); δ_H (400 MHz, $CDCl_3$): 0.87 (3H, t, $J_{3,2} = 7.4$ Hz, 3-H), 1.65–1.86 (1H, m, 2-H), 1.87–1.96 (1H, m, 2-H), 2.07 (3H, s,

OCOCH_3), 5.67 (1H, t, $J_{1,2} = 6.8$ Hz, H-1), 7.25–7.34 (5H, m, Ar-H); δ_C (100 MHz, $CDCl_3$): 9.8 (CH_3, C-3), 21.2 (CH_3, C-2), 29.2 (CH_2, C-2), 77.3 (CH, C-1), 126.5 (CH, C-2 and C-6), 127.8 (CH, C-4), 128.3 (CH, C-3 and 5), 140.5 (quat., C-1), 170.4 (quat., C-1). The spectroscopic data were in agreement with that reported for the racemic material in the literature.[34]

4.3.2. (−)-(*S*)-1-(4-Bromophenyl)propan-1-ol 3[35,36] and (+)-(*R*)-1-(4-bromophenyl)-1-propyl acetate 4. Using the microwave-assisted kinetic resolution procedure with racemic alcohol **3** (107 mg, 0.5 mmol), the title compound **3** (51 mg, 0.24 mmol, 48%) was afforded as a colourless liquid, $[\alpha]_D^{20} = -38.9$ (*c* 1.91, $CHCl_3$) {lit.[35] $[\alpha]_D^{20} = -35.2$ (*c* 1.9, $CHCl_3$), 83% ee}, 92% ee;[†] v_{max} (film)/cm^{-1}: 3375 (OH), 1009 (C–Br); δ_H (400 MHz, $CDCl_3$): 0.83 (3H, t, $J_{3,2} = 6.4$ Hz, 3-H), 1.60–1.73 (2H, m, 2-H), 3.00 (1H, br s, OH), 4.43 (1H, t, $J_{1,2} = 6.5$ Hz, 1-H), 7.11 (2H, d, $J = 8.4$ Hz, 2-H and 6-H), 7.41 (2H, d, $J = 8.4$ Hz, 3-H and 5-H); δ_C (100 MHz, $CDCl_3$): 9.8 (CH_3, C-3), 31.6 (CH_2, C-2), 75.0 (CH, C-1), 120.9 (quat., C-4), 127.6 (CH, C-2 and C-6), 131.2 (CH, C- 3 and C-5), 143.4 (quat., C-1) The spectroscopic data were in agreement with that reported in the literature.[35,36]

(+)-(*R*)-1-(4-Bromophenyl)-1-propyl acetate **4** (50 mg, 0.19 mmol, 39%) was also obtained as a colourless liquid, $[\alpha]_D^{20} = +85.0$ (*c* 0.50, $CHCl_3$), 99% ee. The enantiomeric excess (ee) was determined by high pressure liquid chromatography (Waters-600) using a chiral column (Chiralcel OD–H, 0.43 cm × 1 cm, Daicel Chemical Ind. Ltd) and 2-propanol–hexane (1:99) as eluent with a flow rate of 0.5 mL/min. The retention time for the minor peak was 7 min and the retention time for the major peak was 10 min; HRMS (EI): Found M^+, 256.0092, 258.0077; $C_{11}H_{13}{}^{79}BrO_2$, $C_{11}H_{13}{}^{81}BrO_2$ requires 256.0099, 258.0078; v_{max} (film)/cm^{-1}: 1735 (C=O), 1236 (O–C); δ_H (300 MHz, $CDCl_3$): 0.86 (3H, t, $J_{3,2} = 7.4$ Hz, 3-H), 1.72–1.93 (2H, m, 2-H), 2.06 (3H, s, OCOCH_3), 5.60 (1H, t, $J_{1,2} = 6.9$ Hz, 1-H), 7.17–7.21 (2H, m, 2-H and 6-H), 7.44–7.47 (2H, m, 3-H and 5-H); δ_C (75 MHz, $CDCl_3$): 9.7 (CH_3, C-3), 21.1 (CH_3, C-2), 29.1 (CH_2, C-2), 76.6 (CH, C-1), 121.7 (quat., C-4), 128.3 (CH, C-2 and C-6), 131.5 (CH, C-3 and C-5), 139.6 (quat., C-1), 170.2 (quat., C-1); *m*/*z* (EI, %): 258 (M^+, ^{81}Br, 13), 256 (M^+, ^{79}Br, 13), 229 (17), 227 (17), 187 (26), 185 (30), 43 (100).

4.3.3. (−)-(*S*)-1-Phenylbut-3-en-1-ol 5[37,38] and (+)-(*R*)-1-Phenylbut-3-en-1-yl acetate 6.[27,38] Using the microwave-assisted kinetic resolution procedure with racemic alcohol **5** (112 mg, 0.8 mmol), the title compound **5** (80 mg, 0.57 mmol, 71%) was afforded as a colourless liquid, $[\alpha]_D^{20} = -46.0$ (*c* 0.80, $CHCl_3$) {lit.[38] $[\alpha]_D = -28.5$ (*c* 1.2, $CHCl_3$)}, 58% ee. The enantiomeric excess (ee) was determined by high pressure liquid chromatography (Waters-600) using a chiral column (Chiralcel OD–H, 0.43 cm × 1 cm, Daicel Chemical Ind. Ltd) and 2-propanol–hexane (1:99) as eluent with a flow rate of 0.5 mL/min. The retention time for the minor peak was 19 min and the retention time for the major peak was 28 min; v_{max} (film)/cm^{-1}: 3406 (OH); δ_H (400 MHz, $CDCl_3$): 2.21 (1H, br s, OH), 2.47–2.51 (2H, m, 2-H), 4.70 (1H, t, $J_{1,2} = 6.1$ Hz, 1-H), 5.11–5.17 (2H, m, 4-H), 5.78 (1H, dd, $J = 6.3$ Hz, $J = 7.7$ Hz, 3-H), 7.23–7.34 (5H, m, Ar-H); δ_C (100 MHz, $CDCl_3$): 43.7 (CH_2, C-2), 73.2 (CH, C-1), 118.3 (CH, C-4), 125.8 (CH, C-2 and C-6), 127.5 (CH, C-4), 128.3 (CH, C-3 and C-5), 134.4 (CH, C-3), 143.83 (quat., C-1). The spectroscopic data were in agreement with that reported in the literature.[37,38]

(+)-(*R*)-1-Phenylbut-3-en-1-yl acetate **6** (35 mg, 0.16 mmol, 24%) was also obtained as a colourless liquid, $[\alpha]_D^{20} = +67.4$ (*c* 0.45, $CHCl_3$) {lit.[38] $[\alpha]_D = +30.4$ (*c* 1.2, $CHCl_3$)}, >99% ee. The enantiomeric excess (ee) was determined by high pressure liquid chromatography (Waters-600) using a chiral column (Chiralcel OD–H, 0.43 cm × 1 cm, Daicel Chemical Ind. Ltd) and 2-propanol–hexane (1:99) as eluent with a flow rate of 0.5 mL/min. The retention time for the minor peak was 8 min and the retention time for the major peak was 10 min; v_{max} (film)/cm^{-1}: 1739 (C=O), 1215 (O–C); δ_H (400 MHz, $CDCl_3$): 2.06 (3H, s, OCOCH_3), 2.55–2.69 (2H, m, 2-H), 5.03–5.10 (2H, m, 4-H), 5.66–5.73 (1H, m, 1-H), 5.81 (1H, dd, $J = 6.1$ Hz, $J = 7.7$ Hz, 3-H), 7.25–7.36 (5H, m, Ar-H); δ_C (100 MHz, $CDCl_3$): 21.2 (CH_3, C-2), 40.7 (CH_2, C-2), 75.1 (CH, C-1), 117.9 (CH_2, C-4), 126.5 (CH, C-2 and C-6), 127.9 (CH, C-4), 128.4 (CH, C-3 and C-5), 133.3 (CH, C-3), 140.1 (quat., C-1), 170.2 (quat., C-1). The spectroscopic data were in agreement with that reported in the literature.[27,38]

4.3.4. (+)-(*S*)-3-Bromo-2-(2-hydroxypropyl)-1,4-di methoxynaphthalene 7[39] and (+)-(*R*)-3-bromo-2-(2-acetoxypropyl)-1,4-dimethoxynaphthalene 8. Using the microwave-assisted kinetic resolution procedure with racemic alcohol **7** (200 mg, 0.6 mmol), the title compound **7** (80 mg, 0.24 mmol, 40%) was afforded as a white solid, mp 118–120 °C (lit.[39] mp 118–120 °C), $[\alpha]_D^{20} = +40.8$ (*c* 0.001, $CHCl_3$) {lit.[39] $[\alpha]_D = +8.1$ (*c* 2.05, $CHCl_3$)}, 93% ee. The enantiomeric excess (ee) was determined by high pressure liquid chromatography (Waters-600) using a chiral column (chiralcel OD–H, 0.43 cm × 1 cm, Daicel Chemical Ind. Ltd) and 2-propanol–hexane (1:99) as eluent with a flow rate of 0.5 mL/min. The retention time for major peak was 32 min and the retention time for the minor peak was 41 min; HRMS (EI): Found M^+, 324.0360, 326.0347; $C_{15}H_{17}{}^{79}BrO_3$, $C_{15}H_{17}{}^{81}BrO_3$ requires 324.0361, 326.0341; v_{max} (film)/cm^{-1}: 3433 (OH); δ_H (400 MHz, $CDCl_3$): 1.32 (3H, d, $J_{3,2} = 6.4$ Hz, 3-H), 3.17 (2H, d, $J_{1,2} = 8.0$ Hz, 1-H), 3.93 (3H, s, 4-OMe), 3.96 (3H, s, 1-OMe), 4.14–4.20 (1H, m, 2-H), 7.49–7.57 (2H, m, 6-H and 7-H), 8.01–8.11 (2H, m, 5-H and 8-H); δ_C (100 MHz, $CDCl_3$): 23.5 (CH_3, C-3), 39.8 (CH_2, C-1), 61.3 (CH_3, 1-OMe or 4-OMe), 62.0 (CH_3, 4-OMe or 1-OMe), 68.1 (CH, C-2), 116.6 (quat., C-3), 122.6 (CH, C-5 or C-8), 122.6 (CH, C-8 or C-5), 126.7 (CH, C-6 or C-7), 126.7 (CH, C-6 or C-7), 127.6 (quat., C-2), 127.8 (quat., C-4a or C-8a), 128.2 (quat., C-4a or C-8a), 150.3 (quat., C-1 or C-4), 151.1 (quat., C-1 or C-4); *m*/*z* (EI, %): 326 (M^+, ^{81}Br, 38), 324 (M^+, ^{79}Br, 38), 282 (40), 280 (44), 267 (74), 265 (77), 185 (100), 186 (50), 171 (48),

[†] The enantiomeric excess was calculated based on the observed specific rotation.

127 (67), 115 (70), 77 (25). The spectroscopic data were in agreement with that reported in the literature.[39]

3-Bromo-2-(2-acetoxypropyl)-1,4-dimethoxynaphthalene **8** (100 mg, 0.27 mmol, 44%) was also obtained as a colourless liquid, $[\alpha]_D^{20} = +17.8$ (*c* 0.17, $CHCl_3$), 99% ee. The enantiomeric excess (ee) was determined by high pressure liquid chromatography (Waters-600) using a chiral column (Chiralcel OD–H, 0.43 cm × 1 cm, Daicel Chemical Ind. Ltd) and 2-propanol–hexane (0.25:99.75) as eluent with a flow rate of 0.5 ml/min. The retention time for the minor peak was 47 min and the retention time for the major peak was 55 min; HRMS (EI): Found M^+, 366.0466, 368.0447; $C_{17}H_{19}{}^{79}BrO_4$, $C_{17}H_{19}{}^{81}BrO_4$ requires 366.0467, 368.0446; υ_{max} (film)/cm^{-1}: 1732 (C=O), 1239 (C–O–C); δ_H (400 MHz, $CDCl_3$): 1.29 (3H, d, $J_{3,2}$ 6.3 Hz, 3-H), 1.94 (3H, s, OCOCH_3), 3.19 (1H, dd, $J_{gem} = 13.3$ Hz, $J_{1A,2} = 6.2$ Hz, 1-H_A), 3.34 (1H, dd, $J_{gem} = 13.3$ Hz, $J_{1B,2} = 6.2$ Hz, 1-H_B), 3.92 (3H, s, 4-OMe), 3.96 (3H, s, 1-OMe), 5.34–5.46 (1H, m, 2-H), 7.49–7.56 (2H, m, 6-H and 7-H), 8.01–8.09 (2H, m, 5-H and 8-H); δ_C (75 MHz, $CDCl_3$): 19.7 (CH_3, C-3), 21.2 (CH_3, C-5), 36.2 (CH_2, C-1), 61.3 (O–CH_3, 1-OMe or 4-OMe), 62.2 (O–CH_3, 4-OMe or 1-OMe), 70.3 (CH, C-2), 116.7 (quat., C-3), 122.5 (CH, C-6 or C-7), 122.7 (CH, C-7 or C-6), 126.6 (CH, C-5 or C-8), 126.6 (CH, C-8 or C-5), 126.9 (quat., C-2), 127.6 (quat., C-4a or C-8a), 128.2 (quat., C-8a or C-4a), 150.1 (quat., C-4 or C-1), 151.6 (quat., C-1 or C-4), 170.36 (quat., C-4); *m*/*z* (EI, %): 368 (M^+, ^{81}Br, 48), 366 (M^+, ^{79}Br, 48), 308 (100), 306 (100), 293 (27), 291 (30), 281 (15), 279 (20), 212 (50), 200 (45), 185 (50).

4.3.5. (+)-(*R*)-Ethyl-5-(4-methoxybenyloxy)-3-hydroxypentanoate 9[40] and (+)-(*S*)-ethyl-5-(4-methoxybenzyloxy)-3-acetoxypentanoate 10. Using the microwave-assisted kinetic resolution procedure described above with racemic alcohol **9** (180 mg, 0.6 mmol), title compound **9** (86 mg, 0.29 mmol, 48%) was afforded as a colourless liquid, $[\alpha]_D^{20} = +4.5$ (*c* 3.44, $CHCl_3$), 43% ee. The enantiomeric excess (ee) was determined by high pressure liquid chromatography (Waters-600) using a chiral column (Chiralcel OD–H, 0.43 cm × 1 cm, Daicel Chemical Ind. Ltd) and 2-propanol–hexane (1:99) as eluent with a flow rate of 0.5 ml/min. The retention time for the minor peak was 42 min and the retention time for the major peak was 59 min; υ_{max} (film)/cm^{-1}: 3448 (OH), 1735 (C=O), 1248 (C–O); δ_H (400 MHz, $CDCl_3$): 1.27 (3H, t, $J_{2,1} = 7.24$ Hz, 2-H), 1.77–1.82 (2H, m, 4-H), 2.48 (2H, d, $J_{2,3} = 6.3$ Hz, 2-H), 3.38 (1H, br s, OH), 3.61–3.67 (2H, m, 5-H), 3.80 (3H, s, 4-OMe), 4.15 (2H, q, $J_{1,2} = 7.0$ Hz, 1-H), 4.19 (1H, m, 3-H), 4.45 (2H, s, 7-H), 6.86–6.88 (2H, m, 5-H and 3-H), 7.23–7.26 (2H, m, 6-H and 2-H); δ_C (100 MHz, $CDCl_3$): 14.2 (CH_3, C-2), 36.0 (CH_2, C-4), 41.6 (CH_2, C-2), 55.3 (CH_3, 4-OMe), 60.6 (CH_2, C-1), 67.1 (CH, C-3), 67.7 (CH_2, C-5), 72.9 (CH_2, C-7), 133.8 (CH, C-3 and C-5), 129.3 (CH, C-2 and C-6), 130.1 (quat., C-1), 159.2 (quat., C-4), 172.5 (quat., C-1). The spectroscopic data were in agreement with that reported for the (*S*)-enantiomer in the literature.[40]

(+)-(*S*)-Ethyl-5-(4-methoxybenzyloxy)-3-acetoxypentanoate **10** (80 mg, 0.25 mmol, 38%) was also obtained as a colourless liquid, $[\alpha]_D^{20} = +6.0$ (*c* 5.08, $CHCl_3$), 99% ee. The enantiomeric excess (ee) was determined by high pressure liquid chromatography (Waters-600) using a chiral column (chiralcel OD–H, 0.43 cm × 1 cm, Daicel Chemical Ind. Ltd) and 2-propanol–hexane (1:99) as eluent with a flow rate of 0.5 ml/min. The retention time for the major peak was 29 min and the retention time for the minor peak was 43 min; HRMS (EI): Found M^+, 324.1576, $C_{17}H_{24}O_6$ requires 324.1573; υ_{max} (neat)/cm^{-1}: 1737 (C=O), 1246 (C–O); δ_H (400 MHz, $CDCl_3$): 1.23 (3H, t, $J_{2,1} = 7.2$ Hz, 2-H), 1.91 (2H, q, $J = 6.4$ Hz, 4-H), 2.0 (3H, s, OCOCH_3), 2.59 (2H, d, $J_{2,3} = 6.4$ Hz, 2-H), 3.43–3.52 (2H, m, 5-H), 3.79 (3H, s, 4-OMe), 4.12 (2H, q, $J_{1,2} = 6.8$ Hz, 1-H), 4.39 (2H, s, 7-H), 5.34 (1H, p, $J = 6.5$ Hz, 3-H), 6.84–6.88 (2H, m, 5-H and 3-H), 7.21–7.25 (2H, m, 2-Hand 6-H); δ_C (100 MHz, $CDCl_3$): 14.2 (CH_3, C-2), 21.0 (CH_3, $OCOCH_3$), 34.0 (CH_2, C-4), 39.4 (CH_2, C-2), 55.3 (CH_3, 4-OMe), 60.6 (CH_2, C-1), 66.0 (CH_2, C-5), 68.5 (CH, C-3), 72.7 (CH_2, C-7), 113.8 (CH, C-5 and C-3), 129.3 (CH, C-2 and C-6), 130.3 (quat., C-1), 159.2 (quat., C-4), 170.2 (quat., $OCOCH_3$), 170.3 (quat., C-1); *m*/*z* (EI, %): 324 (M^+, 5), 281 (3), 263 (3), 233 (3), 176 (60), 137 (35), 121 (100), 97(6), 77 (10).

4.3.6. (+)-(1*S*,4*R*,4a*S*,5*S*,8*R*,8a*S*)-5-Acetoxy-1,4,4a,5,8,8a-hexahydro-8-hydroxy-endo-1,4-methano naphthalene 12.[33] Using the microwave-assisted kinetic resolution procedure described above with racemic alcohol **11** (35 mg, 0.2 mmol), the title compound **12** (35 mg, 0.16 mmol, 81%) was afforded as colourless crystals, mp 87–88 °C (lit.[33] mp 87–88 °C), $[\alpha]_D^{20} = +30.5$ (*c* 0.67, $CHCl_3$) {lit.[33] $[\alpha]_D^{30} = +70.1$ (*c* 1.02, $CHCl_3$)}, 99% ee. The enantiomeric excess (ee) was determined by high pressure liquid chromatography (Waters-600) using a chiral column (Chiralcel OD–H, 0.43 cm × 1 cm, Daicel Chemical Ind. Ltd) and 2-propanol–hexane (1:99) as eluent with a flow rate of 0.5 ml/min. The retention time for the minor peak was 24 min and the retention time for the major peak was 33 min; δ_H (300 MHz, $CDCl_3$): 1.29 (2H, q, $J = 8.1$ Hz, 9-H), 1.92 (1H, br s, OH), 2.08 (3H, s, OCOCH_3), 2.79–2.85 (2H, m, 4a-H and 8a-H), 2.95–3.03 (2H, m, 4-H and 1-H), 4.41–4.45 (1H, m, 8-H), 5.25 (1H, d, $J = 10.3$ Hz, 7-H or 6-H), 5.30–5.36 (1H, m, 5-H), 5.43 (1H, d, $J = 10.3$ Hz, 6-H or 7-H), 5.78 (1H, dd, $J = 2.8$ Hz, $J = 5.4$ Hz, 2-H or 3-H), 5.85 (1H, dd, $J = 2.8$ Hz, $J = 5.4$ Hz, 3-H or 2-H); δ_C (75 MHz, $CDCl_3$): 21.07 (CH_3, OCO*C*H_3), 38.48 (CH, C-4a or C-8a), 41.73 (CH, C-8a or C-4a), 44.94 (CH, C-4 or C-1), 45.65 (CH, C-1 or C-4), 48.88 (CH_2, C-9), 66.45 (CH, C-8), 69.82 (CH, C-5), 126.79 (CH, C-6 or C-7), 132.02 (CH, C-7 or C-6), 135.40 (CH, C-2 or C-3), 135.54 (CH, C-3 or C-2), 170.73 (quat., O*C*OCH$_3$). The spectroscopic data were in agreement with that reported in the literature.[33]

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