Organic & Biomolecular Chemistry

PAPER

Cite this: *Org. Biomol. Chem.*, 2016, **14**, 2742

Synthesis and characterization of chiral aza-macrocycles and study of their enantiomer recognition ability for organo-phosphoric acid and phosphonic acid derivatives by ^{31}P NMR and fluorescence spectroscopy†

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Received 20th December 2015,
Accepted 28th January 2016

DOI: 10.1039/c5ob02616d

www.rsc.org/obc

Two diastereomers of optically active *N,O*-containing new macrocycles with dual chirality of the ring and pendent group were synthesized and characterized. The difference in the accessibility of the cavity was explored to discriminate the enantiomers of the derivatives of organo-phosphoric and phosphonic acids by ^{31}P NMR and fluorescence spectroscopy.

Introduction

Crown ethers and other macrocyclic compounds have a unique place in the field of supramolecular chemistry. These host molecules interact with guest entities in a predictable and non-covalent manner. This phenomenon has been well studied over the last several decades.[1] The importance of optically active molecules in the field of medicine, fragrance and flavours, material science and supramolecular chemistry has already been well established. The supramolecular interactions in biological systems between the chiral receptors and guest substrates are in general more enantiospecific. Many studies have been conducted on large complex biological assemblies and their interactions based on supramolecular principles.[2] Optically active crown ethers and other macrocyclic compounds can be prepared by introducing chirality in the backbone of the ring itself or by attaching chiral pendent groups to the achiral framework of the crown. Chiral macrocyclic hosts can selectively recognize isomers of optically active guest molecules based on supramolecular interactions. Few such macrocyclic compounds with a chiral ring[3] or with suitable chiral pendent groups[4] have been reported and their molecular recognition ability with chiral guests has been investigated.

The optical purity of chiral materials is usually confirmed by more than one analytical method such as chromatography (GC or HPLC with a chiral stationary phase), spectroscopy (NMR, CD), capillary electrophoresis *etc*. For accurate determination of the ratio of enantiomers by NMR spectroscopy, it is necessary to convert the analyte to the diastereomers, quantitatively. This can be achieved by making diastereomeric derivatives of the analyte with appropriate chiral derivatizing agents (CDA), such as Mosher's acid,[5] involving a covalent bond. In other approach, a chiral solvating agent (CSA)[6] can be mixed during the NMR analysis where it may bind temporarily with the chiral analyte, creating *in situ* diastereomers. Their ratio can be established by detecting the signals. This has been achieved by chiral crown ethers[7] or macrocyclic[8] CSAs capable of having supramolecular interactions with optically active analytes. Also some crown ethers with chiral pendent groups have been used as CSAs for determination of optical purity.[9] The molecular recognition of chiral macrocycles with optically active guests has also been measured by analyzing the change in their fluorescence properties.[10] Here we report the synthesis of new macrocycles **1** with a chiral backbone along with chiral pendent groups. We evaluate their ability to discriminate chiral organic compounds by NMR and fluorescence spectroscopy (Scheme 1). Two chiral elements will allow the study of the match, mismatch effect to fine tune the CSA for such applications for different analytes. In this report we have screened derivatives of 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate, α-hydroxy phosphonic acid and α-amino phosphonic acid as analytes employing ^{31}P NMR analysis. Chiral BINOL derived phosphoric acid derivatives have acquired significant interest in asymmetric catalysis. Chiral phosphoric acids have cemented their status as an efficient synthetic tool in Brønsted acid catalysis.[11] α-Hydroxy phosphonic acids and α-amino phosphonic acids have received considerable attention in the

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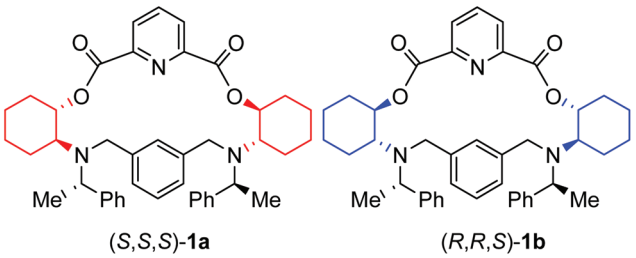
†Electronic supplementary information (ESI) available: Copies of the spectral data, details of the crystal structure including cif files, and spectra from the CSA study (as PDF). CCDC 1004162 and 1016922. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob02616d



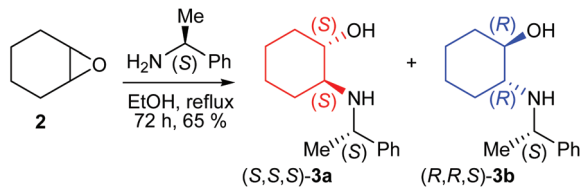
Scheme 1 New macrocycles with a chiral backbone and chiral pendent groups.

field of medicinal chemistry. Aminophosphonic acid derivatives, being structurally analogous to amino acids, have been incorporated into many drug molecules due to their physiological activity as antiviral, antibacterial, anticancer and neuroactive compounds.[11a]

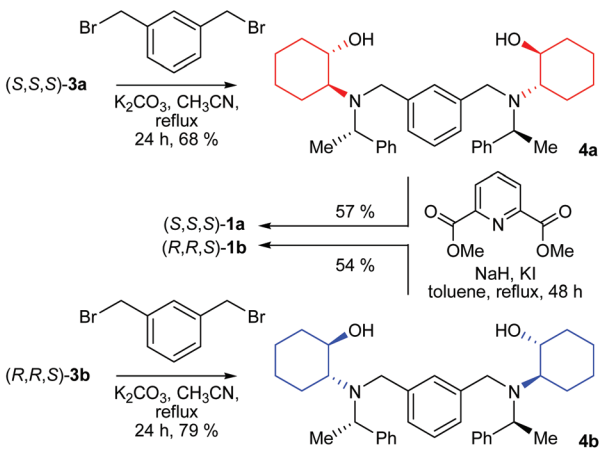
Results and discussion

The two diastereomers of the aminocyclohexanol, **3a** and **3b**, were obtained by the ring opening reaction of cyclohexene oxide **2** with (*S*)-2-phenylethyl amine (Scheme 2).[12]

The two separated diastereomers were condensed with *m*-xylene dibromide to afford two diastereomers of diol **4a** and **4b** (Scheme 3). The final eighteen member macrocycles were



Scheme 2 Preparation of amino alcohols from cyclohexeneoxide.



Scheme 3 Synthesis of the macrocycle.

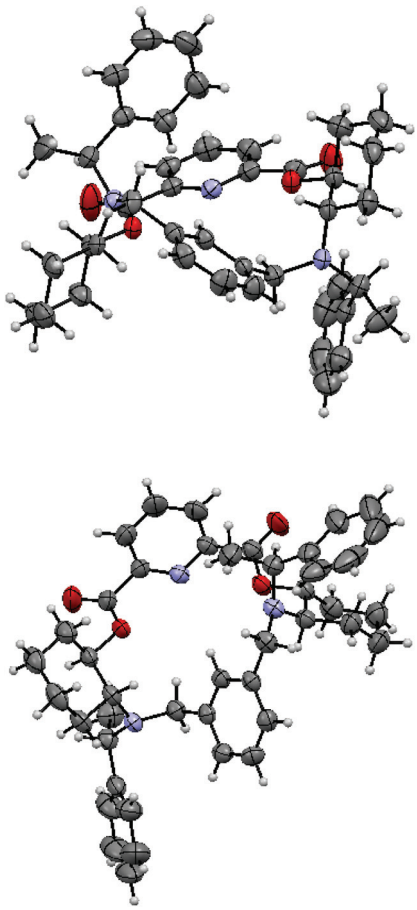


Fig. 1 X-ray structure of (*S*,*S*,*S*)-**1a** [top] (CCDC No. 1004162) and (*R*,*R*,*S*)-**1b** [bottom] (CCDC No. 1016922).

prepared by transesterification with dimethyl 2,6-pyridinedicarboxylate by a slightly modified procedure.

Single crystal X-ray analysis of both the diastereomers of macrocycles revealed interesting features. In the case of (*S*,*S*,*S*)-**1a** the phenyl units of the pendent groups were seen to lie on the top and cover the bottom of the macrocyclic cavity while in the case of (*R*,*R*,*S*)-**1b** they appear to be away (Fig. 1).

Recently chiral Brønsted acids such as the phosphoric acid derivative 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate **5a** and its analogues have found wide use as chiral catalysts.[11b,c] There can be three different types of chiral organic phosphorus containing acid derivatives (Chart 1).

The two derivatives of **1** were screened to study their ability to discriminate the ^{31}P NMR signals[13] of the derivatives of **5** by

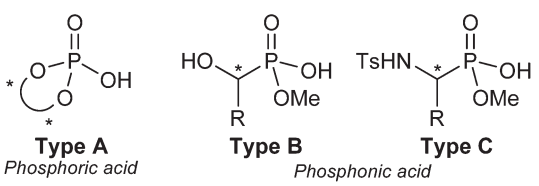
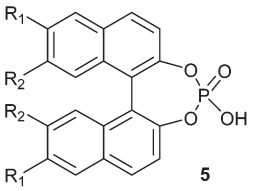


Chart 1 Types of phosphorus containing analytes.

Table 1 Discrimination of binaphthyl phosphoric acids 5 [a]



5

No.	Comp. no.	R_1	R_2	$\Delta\Delta\delta$ (ppm) (*S*,*S*,*S*)-**1a**	$\Delta\Delta\delta$ (ppm) (*R*,*R*,*S*)-**1b**
1	**5a**	H	H	0.03	0.74
2	**5b**	H	OMe	—[b]	0.68
3	**5c**	H	O-iPr	—[b]	0.76
4	**5d**	NO_2	H	—[b]	0.81
5	**5e**	Br	H	—[b]	0.40

[a] In $CDCl_3$ (20 mM), 162 MHz (^{31}P NMR), ratio of 5 : 1 (2 : 1). [b] Not resolved.

measuring the chemical shift non-equivalence ($\Delta\Delta\delta$) (Table 1). A clear pattern of better discrimination for (*R*,*R*,*S*)-**1b** was observed in all the examples, while the other derivative (*S*,*S*,*S*)-**1a** with a closed cavity was found ineffective (Fig. 2).

The separation of signals was further studied to establish a linear relationship between experimental and actual values of optical purity for establishing the practical utility of CSAs (see the ESI†).

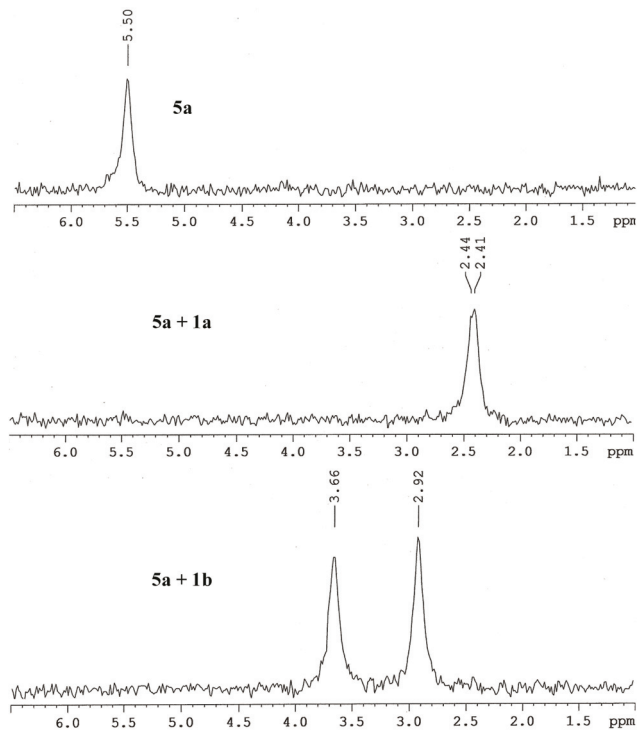


Fig. 2 ^{31}P NMR signals for (±)-**5a** with **1a** and **1b**.

The nature of the complex between **5** and the isomers of the macrocycle was determined by IR spectroscopy. The complex of **5** with **1a** showed a weak band at 1098 cm^{-1} for phosphoryl bond stretching,[14] but appears much stronger for **1b** (see the ESI†). This may indicate a better complexation in the case of **1b** supporting the observation.

The use of fluorescence spectroscopy for understanding the recognition of chiral molecules has received considerable attention.[15] Many chiral fluorescent host molecules have been known to exhibit enantioselective quenching[15c] or enhancement[15g] on interaction with chiral guests. In this study the fluorescence properties of the analyte **5a** were utilized to evaluate the interactions with the two isomers of macrocycle. Such chirality dependent quenching of both the enantiomers of **5a** in the presence of macrocycles **1a** and **1b** has been investigated. The recognition ability of macrocycles towards the phosphoric acid was evident from the extent of quenching (Fig. 3). The static quenching is probably attributed to the deprotonation of phosphoric acid **5a**, which is indicated by the appearance of a new peak in the UV-Vis spectra[15c] (at a higher wavelength of 327 nm; see the ESI†).

The response of quenching the emission of enantiomers of **5a** with **1a** follows the Stern–Völmer equation. The fluorescence quenching efficiency can be expressed as a ratio of $K_{sv}^{R\text{-}5a}/K_{sv}^{S\text{-}5a}$ which was observed to be 1.05 (Fig. 3, A-2). On the other hand quenching of enantiomers of **5a** with the other macrocycle **1b** indicated the ratio $K_{sv}^{R\text{-}5a}/K_{sv}^{S\text{-}5a}$ to be 1.40 (Fig. 3, B-2), indicating its higher quenching ability.[16] This data confirms the recognition observed in ^{31}P NMR analysis. These observations substantiate the assumption that the relatively open cavity of **1b** facilitates efficient complexation between the protonated macrocycle and the phosphate ion as well as π–π interaction of the naphthyl ring of **5** (see the ESI† for the geometrical model).

Preliminary investigation was made to determine the effective stoichiometric ratio of host–guest association in the present system (Table 2). Although each macrocycle contains three basic sites, out of which the two tertiary nitrogens undergo protonation to generate ion pairs, as evident from entry 2 of Table 2. While the third site of pyridine is expected to show π–π interaction with the naphthyl ring of the guest molecule.

Chiral phosphonic acid derivatives, which resemble closely with amino acids, have also been found useful in medicinal chemistry and in asymmetric transformations.[17] It was noteworthy to see a reverse trend for a second group of analytes of α-substituted phosphonic acids (**6** to **10**) with the same set of macrocyclic CSAs (Table 3). These analytes, being smaller in size are better accommodated in the partially closed cavity of macrocycle **1a**. The presence of the hydrogen bond donor group at the α position of phosphonic acid is essential to effect the discrimination. In the case of α-chloro derivative **8** both the macrocycles are found to be ineffective in the discrimination.

In both the cases protonation of nitrogen of macrocycles results in electrostatic interactions holding the diastereomers together effecting the chiral discrimination. In the second set of analytes there could be additional H-bonding interaction

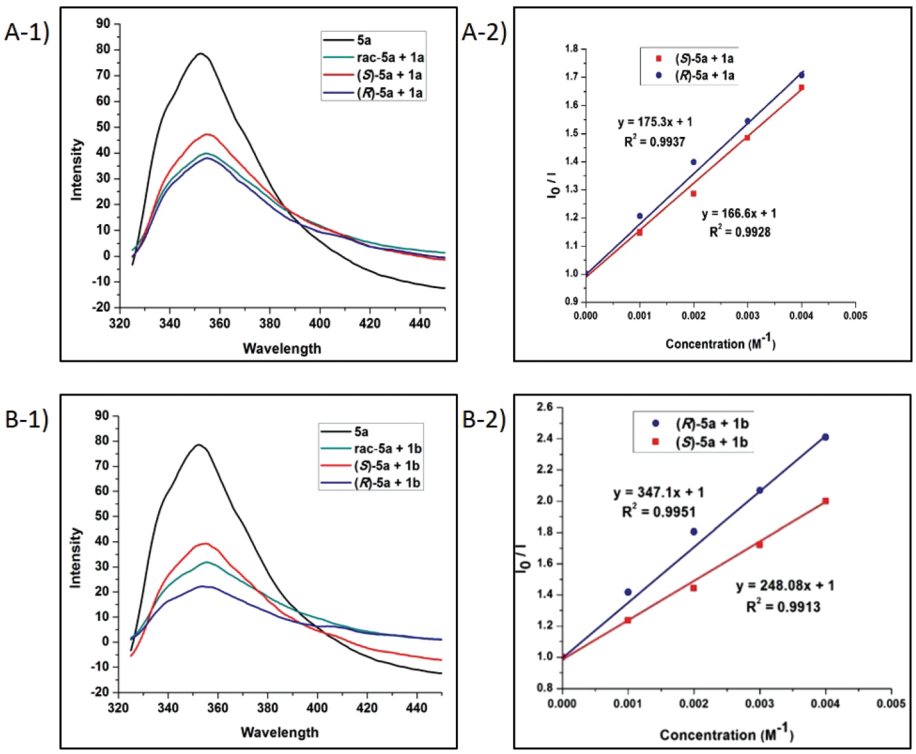


Fig. 3 Quenching study: (A-1) fluorescence spectra of **5a** (10^{-5} M, $CHCl_3$); (±)-**5a**, (*S*)-**5a** and (*R*)-**5a** in the presence of **1a** (λ_{ex} = 305 nm); (A-2) Stern–Völmer plots of (*S*)-**5a** and (*R*)-**5a** with **1a**; (B-1) fluorescence spectra of **5a** (10^{-5} M, $CHCl_3$); (±)-**5a**, (*S*)-**5a** and (*R*)-**5a** in the presence of **1b** (λ_{ex} = 305 nm); (B-2) Stern–Völmer plots of (*S*)-**5a** and (*R*)-**5a** with **1b**.

Table 2 Determination of stoichiometry of host (**1b**) and guest (**5a**) association

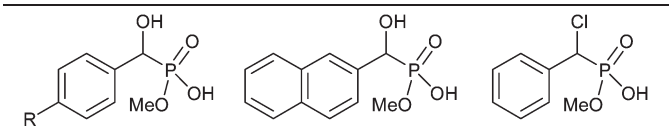
No.	Ratio[a] **1b** : **5a**	ΔΔδ (ppm)
1	1 : 3	0.58
2	1 : 2	0.74
3	1 : 1	0.66
4	1 : 0.5	0.63

[a] In $CDCl_3$ (20 mM), 162 MHz (^{31}P NMR).

working in tandem. The formation of the H-bond between the phosphonic acid analyte and H-bond acceptor sites of the macrocyclic CSA is probably favored by the partially closed cavity of **1a**. This could also explain better discrimination for the α-amino derivatives (**9** and **10**) where the H-bonding will be stronger.

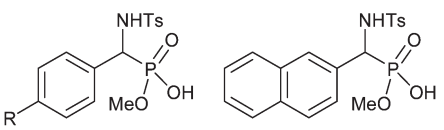
In summary, two diastereomers of eighteen member *N*,*O*-macrocycles are synthesized and evaluated as CSAs for effective discrimination of ^{31}P NMR signals and fluorescence quenching of several organo-phosphoric and phosphonic acid derivatives. Combination of chirality on the backbone of the macrocycle and of the pendant group was explored for molecular recognition of optically active hosts for quantifiable discrimination. Further studies on the binding between

Table 3 Discrimination of monomethyl esters of substituted phosphonic acids **6** to **10** [a]



6 **7** **8**

No.	Comp. no.	R	ΔΔδ (ppm) (*S*,*S*,*S*)-**1a**	(*R*,*R*,*S*)-**1b**
1	**6a**	H	0.17	0.04
2	**6b**	Me	0.19	—[b]
3	**6c**	Cl	0.16	—[b]
4	**7**	—	0.17	—[b]
5	**8**	—	—[b]	—[b]



9 **10**

6	**9a**	H	0.40	—[b]
7	**9b**	Me	0.42	—[b]
8	**9c**	Cl	0.45	0.10
9	**9d**	OMe	0.43	—[b]
10	**9e**	NO_2	0.40	0.12
11	**10**	—	0.37	—[b]

[a] In CD_3OD (5%), in $CDCl_3$ (20 mM), 162 MHz (^{31}P NMR), ratio of **6** to **10** : **4** (2 : 1). [b] Not resolved.

isomers of macrocycles and two sets of guest molecules are in progress.

Experimental section

Reagents were purchased from Sigma-Aldrich Chemicals Limited, SD Fine, Sisco, Qualigens, Avara Chemicals Limited, *etc*. All the glassware were flame dried before the experiment. All solvents that were used were stored on oven dried molecular sieves (4 Å). All commercial products were used without further purification. Toluene was distilled and dried by passing over sodium wire. Thin Layer Chromatography was performed on Merck 60 F254 Aluminium coated plates. The spots were visualized under UV light or with iodine vapour. All the compounds were purified by column chromatography using SRL silica gel (60–120 mesh). All reactions were carried out under an inert atmosphere (nitrogen) unless other conditions are specified. ^{1}H, ^{13}C and ^{31}P NMR spectra are recorded on a 400 MHz Bruker Avance 400 Spectrometer (100 MHz for ^{13}C and 162 MHz for ^{31}P, respectively) with $CDCl_3$ as a solvent and TMS as an internal standard. Signal multiplicity is denoted as singlet (s), doublet (d), doublet of doublet of doublets (ddd), triplet (t), doublet of triplet (dt), quartet (q) and multiplet (m). Mass spectra were recorded on a Thermo-Fischer DSQ II GCMS instrument. IR spectra were recorded on a Perkin-Elmer FTIR RXI spectrometer as KBr pallets or neat in the case of liquids. UV-vis spectra were recorded on Perkin-Elmer Lambda-35. Fluorescence spectra were recorded on a Jasco FP-6300 Spectrofluorometer. The 1,1′-binaphthyl-2,2′-diylhydrogen phosphate derivatives **5a–5e** were synthesized by the reported procedure.[18a] Monomethyl esters of α-hydroxy and α-amino phosphonic acids **6–10** were synthesized by following the literature procedure.[18b] All ^{31}P CSA NMRs were recorded by mixing 1 equiv. (10 mmol) of **1a** or **1b** and 2 equiv. (20 mmol) of hosts (**5–10**) in 0.6 ml $CDCl_3$ or indicated otherwise.

Synthesis of (1*S*,2*S*)-*trans*-2-(*N*-benzoyl-*N*-methyl)amino-1-cyclohexanol (3a)

A mixture of (*S*)-phenylethyl amine (1.0 g, 8.3 mmol) and cyclohexeneoxide (0.97 g, 9.9 mmol), in 15 mL dry ethanol, was refluxed under a nitrogen atmosphere for 72 h. The solvent was then evaporated under vacuum and the reaction mixture was subjected to column chromatography (ethyl acetate/petroleum ether, 3 : 7) yielding compound **3a** as colourless oil. (0.63 g, 35%);

$[\alpha]_D^{25}$ = +11.5 (*c* = 1.0 in MeOH) (Lit[12] +20.9 *c* = 1.64, MeOH)

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80–0.91 (1H, m), 1.15–1.35 (3H, m), 1.34–1.36 (3H, d, *J* = 6.4 Hz), 1.66–1.73 (2H, m), 1.94–1.98 (1H, m), 2.09–2.06 (1H, m), 2.32–2.38 (1H, ddd, *J* = 13.2, 9.2, 4.0 Hz), 3.08–3.14 (1H, dt, *J* = 9.2, 4.4), 3.91–3.96 (1H, q, *J* = 6.4 Hz), 7.24–7.28 (1H, m), 7.32–7.36 (4H, m).

^{13}C NMR (100 MHz, $CDCl_3$):δ 23.5, 24.2, 25.4, 31.3, 33.0, 55.2, 61.5, 74.0, 126.4, 127.1, 128.5, 146.7.

IR (neat): ν 3412, 2980, 1449, 1370, 1062, 762, 700.

Mass (ESI): *m*/*z* 242 (30), 221 (50), 220 (94), 158 (30), 116 (99), 106 (24), 105 (100).

Synthesis of (1*R*,2*R*)-*trans*-2-[(*S*)-(α-methylbenzyl)amino]-1-cyclohexanol (3b)

As described above, compound **3b** was obtained from the later fractions from column chromatography (ethyl acetate/petroleum ether, 2 : 3) as a white solid. (0.54 g, 30%);

Mp: 53–54 °C.

$[\alpha]_D^{25}$ = −99.6 (*c* = 1.0 in MeOH) (Lit.[12] −100.2 *c* = 1.20, MeOH)

^{1}H NMR (400 MHz, $CDCl_3$): 0.88–1.01 (1H, m), 1.07–1.13 (2H, m), 1.19–1.30 (1H, m), 1.36–1.38 (3H, d, *J* = 6.4 Hz), 1.64–1.69 (2H, m), 1.99–2.05 (2H, m), 2.14–2.20 (1H, m), 3.14–3.20 (1H, m), 3.99–4.04 (1H, q, *J* = 6.4 Hz), 7.25–7.27 (1H, m), 7.31–7.35 (4H, m).

^{13}C NMR (100 MHz, $CDCl_3$):δ 24.2, 25.0, 25.6, 30.3, 32.9, 54.1, 60.0, 74.0, 126.7, 127.1, 128.6, 145.0.

IR (KBr): ν 3480, 2924, 1452, 1368, 1350, 1127, 1064, 762, 698.

Mass (ESI): *m*/*z* 242 (7), 221 (48), 220 (96), 116 (96), 106 (24), 105 (100).

(1*S*,1′*S*,2*S*,2′*S*)-2,2′-((*S*)-(1,3-Phenylenebis(methylene))bis(((*S*)-1-phenylethyl)azanediyl))-dicyclohexanol (4a)

A solution of amino alcohol **3a** (0.5 g, 2.2 mmol) in 10 mL acetonitrile was added K_2CO_3 (0.69 g, 5.0 mmol) and α,α′-dibromo-*m*-xylene (0.33 g, 1.3 mmol). The mixture was then refluxed under nitrogen for 24 h. The solvent was then evaporated under vacuum and the mixture was poured in cold water and extracted from ethyl acetate (3 × 50 mL) and the combined extracts were washed with water (2 × 25 mL). The organic layer was dried over anh. Na_2SO_4, evaporated under vacuum and then subjected to column chromatography on silica gel (ethyl acetate/petroleum ether, 1 : 4) to afford compound **4a** as a white solid.(0.42 g, 68%);

Mp: 58–60 °C.

$[\alpha]_D^{25}$ = +83.9 (*c* = 1.0 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21–1.28 (3H, m), 1.27–1.39 (1H, m), 1.47–1.49 (3H, d, *J* = 6.4 Hz), 1.64–1.66 (1H, m), 1.76–1.78 (1H, m), 1.92–1.93 (1H, m), 1.96–2.03 (1H, m), 2.34–2.39 (1H, m), 3.33–3.68 (1H, m), 3.64–3.67 (1H, d, *J* = 13.6 Hz), 3.86–3.89 (1H, d, *J* = 13.6 Hz), 4.02–4.07 (1H, q, *J* = 6.8 Hz), 7.13–7.25 (6H, m), 7.29–7.38 (1H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 24.2, 25.9, 27.7, 33.3, 49.9, 55.9, 62.3, 69.4, 127.1, 127.6, 128.0, 128.4, 128.8, 130.2, 140.7, 143.8.

IR (KBr): ν 3465, 2934, 1603, 1450, 1374, 1218, 1076, 759, 701.

Mass (ESI): *m*/*z* 542 (40), 541 (100), 349 (10), 348 (46), 234 (13).

HRMS: calculated for $C_{36}H_{49}N_2O_2$ (M + 1) = 541.3788. Found 541.3789.

(1*R*,1′*R*,2*R*,2′*R*)-2,2′-((*S*)-(1,3-Phenylenebis(methylene))bis(((*S*)-1-phenylethyl)azanediyl))-dicyclohexanol (4b)

The title compound was obtained by following the same procedure as for compound **4a** from the corresponding amino alcohol **3b**. The organic extract was column chromatographed (ethyl acetate/petroleum ether, 1 : 4) to yield compound **4b** as a white solid. (0.49 g, 79%);

Mp: 111–112 °C.

$[\alpha]_D^{25}$ = −161.4 (*c* = 1.0 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22–1.38 (4H, m), 1.45–1.47 (3H, d, *J* = 6.8 Hz), 1.70–1.71 (1H, m), 1.77–1.99 (1H, m), 1.95–1.98 (1H, m), 2.09–2.11 (1H, m), 2.59–2.65 (1H, m), 3.41–3.47 (1H, m), 3.67–3.69 (1H, d, *J* = 13.2 Hz), 3.96–4.02, (2H, m), 5.34 (1H, s), 6.67–6.69 (1H, d, *J* = 8.0), 7.09–7.17 (3H, m), 7.19–7.22 (2H, m), 7.25–7.29 (1H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1, 24.2, 25.6, 25.8, 33.4, 50.2, 57.4, 62.8, 69.2, 127.1, 127.3, 127.8, 128.3, 128.7, 128.9, 140.9, 142.0.

IR (KBr): ν 3440, 2928, 1603, 1449, 1373, 1349, 1198, 1084, 761, 699.

Mass (ESI): *m*/*z* 542 (37), 541 (100), 523 (5).

HRMS: calculated for $C_{36}H_{49}N_2O_2$ (M + 1) = 541.3788. Found 541.3789.

Synthesis of aza-macrocycle (1a)

In a three neck round bottom flask fitted with septa, a mixture of diamino diol **4a** (0.4 g, 0.74 mmol), NaH (0.15 g, 3.7 mmol) and KI (0.13 g, 0.74 mmol) was heated to reflux under nitrogen in 30 mL dry toluene for 0.5 h. To this mixture a solution of dimethyl 2,6-pyridinedicarboxylate (0.17 g, 0.89 mmol) in 10 mL dry toluene was added dropwise with a syringe over a period of 0.5 h. The mixture was then refluxed for 48 h. After completion of reaction the solvent was removed under vacuum and the reaction mixture was subjected to column chromatography (ethyl acetate/petroleum ether, 1 : 9) resulting in a white solid. (0.28 g, 57%);

Mp: >200 °C.

$[\alpha]_D^{25}$ = −162.7 (*c* = 1.0 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.9–1–1.10 (2H, m), 1.26–1.42 (4H, m), 1.53–1.54 (1H, m), 1.57–1.59 (6H, d, *J* = 6.4 Hz), 1.59–1.69 (5H, m), 1.69–1.99 (2H, m), 2.29–2.31 (2H, m), 3.04–3.10 (2H, dt, *J* = 10.8, 3.2 Hz), 4.01–4.04 (2H, d, *J* = 13.6 Hz), 4.07–4.10 (2H, d, *J* = 13.6 Hz), 4.28–4.30 (2H, q, *J* = 6.4 Hz), 5.12–5.16 (2H, dt, *J* = 10.8, 3.6 Hz), 6.98–7.01 (6H, m), 7.17–7.26 (3H, m), 7.64 (4H, s), 7.87–7.91 (1H, t, *J* = 4.0 Hz), 8.22–8.24 (2H, d, *J* = 7.6 Hz), 8.51 (1H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 24.6, 25.5, 29.4, 32.0, 50.5, 53.6, 58.7, 77.4, 125.9, 126.5, 127.6, 127.8, 128.5, 130.7, 136.9, 140.6, 145.8, 148.8, 165.3.

IR (KBr): ν 2940, 1704, 1602, 1585, 1448, 1368, 1330, 1243, 1144, 957, 701.

Mass (ESI): *m*/*z* 672 (100), 568 (60), 464 (70), 462(20), 105 (20).

HRMS: calculated for $C_{43}H_{50}N_3O_4$ (M + 1) = 672.3790. Found 672.3796.

Synthesis of aza-macrocycle (1b)

The title compound was obtained by following the same procedure as for compound **1a** from the corresponding diamino diol **4b**. The organic extract was column chromatographed (ethyl acetate/petroleum ether, 1 : 9) to yield compound **1b** as a white solid. (0.27 g, 54%);

Mp: >200 °C.

$[\alpha]_D^{25}$ = +36.8 (*c* = 1.0 in $CHCl_3$).

The ^{1}H and ^{13}C NMR spectra of compound **1b** exhibit broad signals. This type of observation for a macrocyclic system has been reported earlier by Periasamy *et al.*[3i]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26–1.28 (4H, m), 1.30–1.43 (7H, m), 1.59–1.69 (9H, m), 2.23 (2H, s), 2.97–3.32 (2H, m), 3.61–3.64 (2H, d, *J* = 13.6 Hz), 4.26 (4H, m), 5.31 (2H, s), 7.07 (2H, br s), 7.19–7.20 (4H, m), 7.28–7.30 (4H, m), 7.54 (3H, s), 8.04–8.08 (1H, t, *J* = 8 Hz), 8.47 (3H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ 18.3, 24.4, 25.4, 30.0, 31.9, 50.7, 52.2, 53.4, 57.8, 79.2, 126.2, 126.8, 127.6, 127.9, 129.2, 133.6, 137.8, 140.1, 146.5, 149.4, 165.9.

IR (KBr): ν 2941, 1705, 1559, 1449, 1369, 1333, 1245, 1082, 700.

Mass (ESI): *m*/*z* 695 (45), 694 (80), 672 (M + 1, 100), 568 (10).

HRMS: calculated for $C_{43}H_{50}N_3O_4$ (M + 1) = 672.3790. Found 672.3797.

Acknowledgements

We wish to thank the Council of Scientific and Industrial Research (CSIR), New Delhi for the award of a fellowship to ANK (JRF and SRF) and the Department of Science and Technology (DST-FIST), New Delhi for the grant to purchase single crystal X-ray diffraction facility in the faculty. We also thank Dr S. Sahoo of Sun Pharma Industries for some NMR analysis. We are also grateful to Prof. Jean-Marie Lehn, of the University of Strasbourg, Strasbourg for his helpful discussion and suggestions.

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ChemComm

COMMUNICATION

Cite this: *Chem. Commun.*, 2018, **54**, 11037

Received 1st August 2018,
Accepted 7th September 2018

DOI: 10.1039/c8cc06245e

rsc.li/chemcomm

Optically pure 2-(quinolin-8-yloxy)cyclohexan-1-ol as a practical agent for molecular recognition by NMR and fluorescence spectroscopy†

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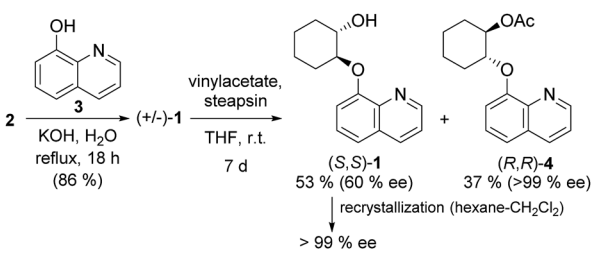
Optically pure 2-(quinolin-8-yloxy)cyclohexan-1-ol 1, obtained *via* simple chemical and bio-catalytic steps, was used as a chiral solvating agent for molecular recognition of the enantiomers of acids. The discrimination of isomers was detected by NMR or fluorescence spectroscopy. Isomers of α-substituted carboxylic acids, phosphoric acids, unprotected amino acids and dipeptides were efficiently detected, while the method can be used for quantitative determination for practical applications. Analysis of the crystal of (*R*,*R*)-1 (*R*)-mandelic acid established a three point supramolecular interaction.

Determination of the ratio of enantiomers of chiral molecules is an important consideration and often separation techniques (HPLC or GC) utilizing special columns with chiral solid phases are employed.[1] The proper separation of isomers for the accurate analysis is based on precise molecular recognition, which often is substrate specific. Small structural changes in similar types of analytes result in poor or no recognition under comparable conditions. The enantiomer ratio may also be determined by other techniques such as mass spectrometry,[2] IR & UV spectroscopy,[3] CD & electrophoresis,[4] competitive immunoassay,[5] *etc.* Fluorescence spectroscopy based methods for the determination of optical purity have also been developed[6,7] and information is compiled in few good reviews.[8] Enantiomers in an achiral environment in nuclear magnetic resonance spectroscopy show indistinguishable sets of signals, while diastereomers may show separate signals. Hence, converting enantiomeric analytes to diastereomers may lead to separation of signals for effective measurement of their composition. This has been achieved by different methods such as addition of chiral shift reagents[9] or by preparation of derivatives by attaching another chiral moiety.[10] The diastereomer formation may also be achieved by *in situ* supramolecular interactions with addition of some chiral agents. Since the interactions are similar to the phenomenon of solvolysis, these agents are often referred to as Chiral Solvating Agents (CSAs).[11] In our earlier studies we have also explored few molecules as CSAs for supramolecular discrimination of chiral analytes.[12] Recently, we have also reported new chiral aza-macrocycles, capable of exhibiting a dual mode of detection, NMR and fluorescence spectroscopy,[13] for discrimination of a range of acids. Considerable work has been done on searching chiral fluorescent sensors, such as natural product like cinchona alkaloid based[7d] or synthetic ones designed from BINOL derivatives.[7e]

In this work we report the preparation of a simple chiral molecule, which has three distinct binding sites along with the aromatic quinoline moiety for effective supramolecular interactions as well as is capable of exhibiting good fluorescence response. It will be useful as a sensor which can work in the dual mode of analysis to get more accurate results. The proposed sensor 2-(quinolin-8-yloxy)cyclohexan-1-ol (**1**) is a derivative of 8-hydroxyquinoline (**3**), which itself is known to exhibit good fluorescence properties.[14] The racemic sample of **1** was prepared by stereoselective opening of cyclohexene oxide (**2**) (Scheme 1). Its enantiomers were separated using a kinetic resolution protocol;[15] several conditions were investigated, and the best one is presented here. The unreacted alcohol (*S*,*S*)-**1**, obtained in moderate optical purity, was recrystallized to give a pure sample.

The absolute configuration of **1** was established by making its derivative with a compound of known optical configuration.



Scheme 1 Synthesis and resolution of **1**.

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† Electronic supplementary information (ESI) available: Experimental details, spectral analysis, reproductions of spectra and details of X-ray data. CCDC 1853111, 1853113, 1853115 and 1853116. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc06245e

The alcohol (*R*,*R*)-**1**, obtained by the hydrolysis of (*R*,*R*)-**4**, was coupled with (*R*)-*O*-acetyl mandelic acid,[12a] while the relative absolute configuration of the ester was established by its single crystal X-ray diffraction analysis (see the ESI†).

We tested our hypothesis by scanning it as a chiral solvating agent to measure the discrimination of signals by NMR spectroscopy. The design of alcohol **1** suggests the possibility of three point interaction with acidic substrates like mandelic acid (**A-I**). We envisage protonation of the quinoline nitrogen, along with two sets of intermolecular hydrogen bonding with the carboxylate. This was checked by ^{1}H NMR of (*R*,*R*)-**1** with racemic **A-I** (20 mM in $CDCl_3$, 400 MHz). The spectrum indicates a well resolved signal of $C_\alpha H$ with a considerable chemical shift non-equivalence ($\Delta\Delta\delta$) (Table 1); salt formation by deprotonation was supported by FT-IR.[16] The capability for the molecular recognition of other derivatives of α-substituted phenyl acetic acids (Types **A** and **B**) was further investigated, with moderate to good levels of discrimination (by ^{1}H-NMR & ^{19}F-NMR). Structurally similar acid **C**, an intermediate of Nebivolol, a beta blocker drug,[17] was also screened with good separation of signals in ^{19}F-NMR.

To understand the interactions between (*R*,*R*)-**1** and the isomers of mandelic acid, the crystal of its salt with both isomers of **A-I** was studied.[12c] Suitable quality crystals of (*R*,*R*)-**1** and (*R*)-**A-I** could be obtained from acetonitrile, while the other pair resulted in an amorphous salt. The single crystal X-ray analysis of (*R*,*R*)-**1** (*R*)-**A-I** confirmed the three point supramolecular interactions (Fig. 1). The deprotonation of mandelic acid is further confirmed by the shorter length of the (C–O) bond (1.22–1.28 Å) of the carboxylate. The salt shows an (NH···O) hydrogen bond (1.789 Å) between the protonated quinoline 'NH' and (C–O), and an (OH···O) hydrogen bond (2.049 Å) between the alcoholic 'OH' and (C–O) of the carboxylate of mandelic acid. The mandelic acid shows further (CO···O) interaction (2.889 Å) with the ether 'O' of (*R*,*R*)-**1**. In addition, the other 'O' of the carboxylate shows strong (CH–O) interaction (2.491 Å) with the C–H of the quinoline ring. Furthermore, the alcoholic OH of mandelic acid shows lateral (OH–C) interaction (2.851 Å) with the carbon of the cyclohexyl ring and the (O–HC) (2.716 Å) of the quinoline ring.

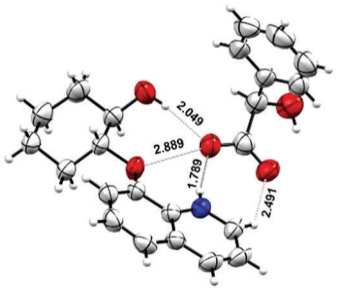
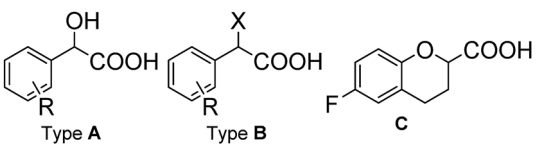


Fig. 1 ORTEP diagram of (*R*,*R*)-**1** (*R*)-**A-I**.

The scope of (*R*,*R*)-**1** was further explored for the discrimination of isomers of BINOL (Type-**D**), 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (Type **E**) and cyclic phosphoric acids (Type **F**) (Table 2). Due to the considerable interest in the applications of these molecules in asymmetric synthesis,[18] it is crucial to develop an efficient method for establishing their optical purity. For this study ^{1}H-NMR of **D-I** with (*R*,*R*)-**1** exhibited excellent separation for two hydrogens (H6 and H8) (Fig. 2), whereas **D-II** showed moderate separation (H5). In the case of **E** the resolution of signals in ^{1}H-NMR could not be detected due to overlap; however, the ^{31}P-NMR indicated a good base line separation. The cyclic phosphoric acid analogues (Type **F**), which have not been commonly analysed for such molecular recognition,[19] resulted in good separation of signals, in both ^{1}H- and ^{31}P-NMR spectroscopy. In general, the presence of electron withdrawing substituents resulted in better separation, probably due to their increased acidic nature (**F-II** and **F-III**).

One of the objectives of the design of (*R*,*R*)-**1** was to explore the fluorescence properties of 8-hydroxyquinoline in tandem with the structural rigidity and hydrogen bonding ability of the cyclohexanol moiety. Amino acids, essentially utilized in their

Table 1 Application of (*R*,*R*)-**1** as a Chiral Solvating Agent for discrimination of signals of α-substituted carboxylic acids by NMR

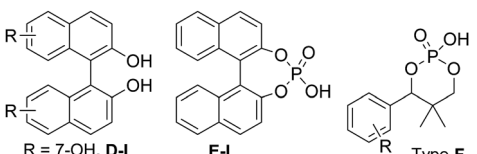


Type **A** Type **B** **C**

No.	Analyte	R =	$\Delta\Delta\delta^a$ (^{1}H)	$\Delta\Delta\delta^a$ (^{19}F)
1	**A-I**	H	0.026	—
2	**A-II**	4-CF_3	0.032	0.036
3	**A-III**	2-Cl	0.019	—
4	**A-IV**	3,4-O-CH_2-O	0.029	—
5	**A-V**	4-Br	0.033	—
6	**B-I**	R = H; X–Br	0.030	—
7	**B-II**	R = H; X–Cl	0.016	—
8	**B-III**	R = 2-Cl; X–Cl	0.024	—
9	**B-IV**	R = 4-CF_3; X–Cl	0.014	0.026
10	**C**	—	—[b]	0.033

[a] Chemical shift non-equivalence ($\Delta\Delta\delta$) in ppm. [b] Not resolved completely. The (*R*,*R*)-**1**:**A–C** ratio is 1:1 (20 mM in $CDCl_3$).

Table 2 Application of (*R*,*R*)-**1** as a CSA for discrimination of signals of BINOLs and phosphoric acids by NMR spectroscopy



R = 7-OH, **D-I**
R = 6-Br, **D-II**
E-I
Type **F**

No.	Analyte	R =	$\Delta\Delta\delta^a$ (^{1}H)	$\Delta\Delta\delta^b$ (^{31}P)
1	**D-I**	—	0.058 (H8)	—
			0.038 (H6)	
2	**D-II**	—	0.016 (H5)	
3	**E**	—	—	0.56
4	**F-I**	H	0.020 (C*H*)	0.37
5	**F-II**	4-Cl	0.042 (C*H*)	0.39
6	**F-III**	4-NO_2	0.043 (C*H*)	0.35
7	**F-IV**	4-OMe	0.047 (C*H*)	—[b]
			0.011 (OCH_3)	

[a] Chemical shift non-equivalence ($\Delta\Delta\delta$) in ppm. [b] Not resolved completely. The (*R*,*R*)-**1**:**D–F** ratio of is 1:1 (20 mM in $CDCl_3$).

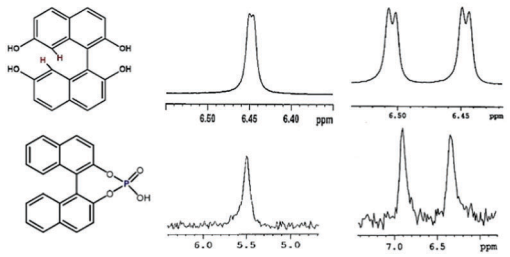


Fig. 2 ^{1}H NMR spectra of **D-I** with (*R*,*R*)-**1** (top) and ^{31}P NMR spectra of **E** with (*R*,*R*)-**1** (bottom).

optically pure form, are generally analysed by HPLC on chiral columns.[19] There are some reports of fluorescence spectroscopy based analytical methods, involving prior *N*-protection or involving the use of complex sensors.[20] At the same time, few reports are available where amino acids are directly analyzed;[21] hence we examined our sensor (*R*,*R*)-**1** for fluorescence recognition of amino acids.

Fluorescence recognition of **AA-I** to **AA-IV** with (*R*,*R*)-**1** in EtOH showed significant enhancement, indicating selectivity towards one enantiomer (Fig. 3). The fluorescence spectrum of (*R*,*R*)-**1** in the presence of **AA-I** resulted in a marked enhancement in short wavelength emission with the L-isomer, while an insignificant change was seen with the other isomer. Similar experiments with isomers of **A-I** did not result in any marked difference in fluorescence, indicating the essential role of the amino group. The sensor exhibited highly enantioselective fluorescence recognition towards **AA-I** (ef = 14.4). Further NMR titration of (*R*,*R*)-**1** with (L)-**AA-I** in CD_3OD was performed with a maximum at 0.5, indicating a 1 : 1 complex between the sensor and **AA-I** (see the ESI†). The nitrogen of the quinoline ring of the sensor interacts with the acid due to protonation, thereby making the lone pair unavailable for PIET, leading to an enhancement in fluorescence. The binding of (L)-**AA-I** with the sensor (*R*,*R*)-**1** must be stronger than (D)-**AA-I** due to favourable hydrogen bonding and π−π interactions.[22] Furthermore, the other isomer of the sensor (*S*,*S*)-**1** when screened with **AA-I** exhibited fluorescence enhancement for the other isomer (D)-**AA-I**,

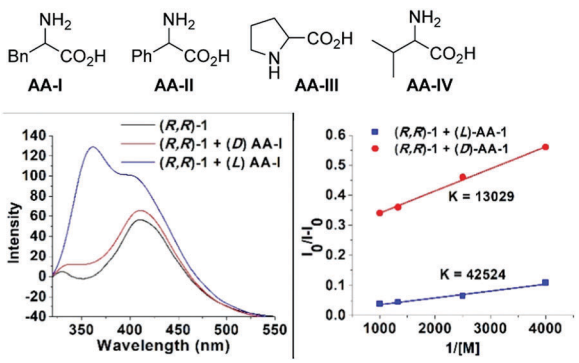


Fig. 3 List of amino acids investigated (top). Fluorescence spectra of (*R*,*R*)-**1** (1.0×10^{-5} M in EtOH) in the presence of D- and L-phenyl alanine (**AA-I**) (1.0×10^{-3} M in EtOH) (bottom left) [λ_{ex} 300 nm]. Benesi–Hildebrand plots of (*R*,*R*)-**1** (1.0×10^{-5} M in EtOH) in the presence of D- and L-phenyl alanine (**AA-I**) (bottom right).

Table 3 Enantioselective fluorescence responses and association constants of (*R*,*R*)-**1** with AA (I to IV) and DP (I & II)

No.	Analyte	Enantioselective fluorescence (ef)	K_L/K_D	K_D/K_L
1	**AA-I**	14.4	3.26	—
2	**AA-II**	6.9	1.86	—
3	**AA-III**	3.5	—	2.22
4	**AA-IV**	4.8	—	6.86
5	**DP-I**	1.3	1.38	—
6	**DP-II**	1.5	1.53	—
7	**DP-III**	1.6	—	—

thus confirming the mirror image relationship (see the ESI†). Similar behaviour was observed for **A-II**, but for the aliphatic analogues **AA-III** and **AA-IV**, the D-isomer showed higher fluorescence enhancement (see the ESI†). This perhaps indicates a favourable π–π interaction between the aromatic ring of the L-amino acid and the quinoline unit of the sensor in the case of **AA-I** and **AA-II**, which will be lacking in the other cases. The enantioselective fluorescence response of the sensor towards amino acids has been discussed (Table 3). To establish this, **AA-I** was treated with (*R*,*R*)-**1** at varying concentrations and it followed the Benesi–Hildebrand equation (Fig. 3).[6f]

For establishing the practical application of (*R*,*R*)-**1** as a tool for determining the optical purity of chiral analytes, it is essential to follow linear enantioselective response. This ability to quantitatively determine the ee of samples of optically active analytes was established by NMR analysis of a scalemic mixture of mandelic acid (see the ESI†). However, such studies of establishing optical purity by florescence spectroscopy have not been widely reported in the literature.[7b,–d]

We explored the sensor (*R*,*R*)-**1** for determining the ee of **AA-I** by recording its fluorescence spectra with different samples of enantiomeric purity (Fig. 4). The optical purity of samples of **AA-I** was determined from the plot of I/I_0 *vs.* % ee of L-**AA-I** (see the ESI†); from this % ee was obtained and compared with the actual values. A linear relationship was observed between the actual and observed ee values. Furthermore, two samples of unknown purity were analysed in the same way and their ee's were validated with the actual and the SOR values.

Molecular recognition of peptides using chiral fluorescence sensors is rare, although some studies on fluorescence markers for peptides and proteins are known.[23] Hence, the possibility of using (*R*,*R*)-**1** for determining fluorescence response with

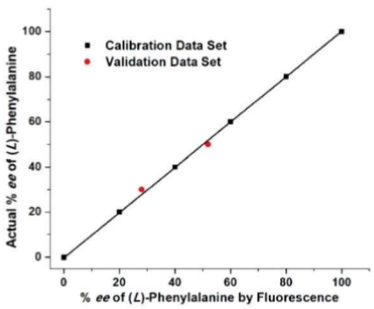


Fig. 4 Plot of the fluorescence response of (*R*,*R*)-**1** (1.0×10^{-5} M in EtOH) in the presence of **AA-I** (1.0×10^{-3} M in EtOH) with varying ee ratio.

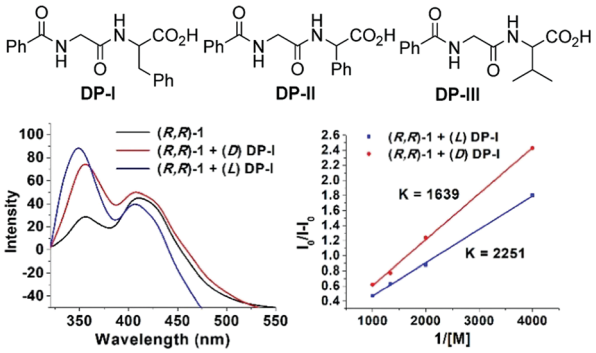


Fig. 5 Dipeptides investigated as analytes for the fluorescence response of (*R*,*R*)-**1** (top). Fluorescence spectra of (*R*,*R*)-**1** (5.0×10^{-6} M in EtOH) in the presence of D- and L-**DP-I** (1.0×10^{-3} M in EtOH) [λ_{ex} 300 nm] (bottom left). Benesi–Hildebrand plots of (*R*,*R*)-**1** (5.0×10^{-6} M in EtOH) in the presence of D- and L-**DP-I** (bottom right).

isomers of peptides is investigated. Few dipeptides as analytes for this study were chosen (**DP-I** to **DP-III**, Fig. 5). The fluorescence study of (*R*,*R*)-**1** with isomers of **DP-I** showed greater enhancement for L-**DP-I**, showing selective recognition. This behavior was similar in the case of both dipeptides (**DP-I** and **DP-II**) containing amino acids with aromatic groups, which was consistent with the observation for the amino acid series (**AA-I** and **AA-II**). The comparison of the molecular recognition for amino acids and dipeptides is summarized in Table 3. The behaviour of these analytes containing aromatic side chains supports the role of π–π interactions with the quinoline unit of sensor **1**. At the same time, the responses for aliphatic side chain containing analytes were similar.

We have presented the design, synthesis and molecular recognition study of a new chiral sensor and established its selectivity using NMR as well as fluorescence spectroscopy. Single crystal X-ray analysis indicates the possible mode of molecular recognition, while the practical utility was confirmed by performing control experiments by both techniques.

We thank the Council of Scientific and Industrial Research (CSIR), New Delhi, for the award of a Senior Research Fellowship to ANK and DST-PURSE for the Single Crystal X-Ray Diffraction facility available in the Faculty of Science.

Conflicts of interest

There are no conflicts to declare.

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Organic & Biomolecular Chemistry

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Cite this: *Org. Biomol. Chem.*, 2019, **17**, 2670

Applications of chiral naphthyloxycyclohexanols in deracemization of α-substituted carboxylic acids by dynamic thermodynamic resolution†

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Received 20th November 2018,
Accepted 8th February 2019

DOI: 10.1039/c8ob02896f

rsc.li/obc

Two derivatives of *trans*-2-naphthyloxycyclohexanol were synthesized, their enantiomers were separated by enzyme mediated kinetic resolution and their absolute configuration was established by synthesizing their diastereomers with esters of known chiral description. Chiral alcohols were then used as chiral auxiliaries for the preparation of esters by coupling with racemic α-halo acids. During the coupling reactions with DCC and a suitable base, an efficient dynamic thermodynamic resolution was observed and the products were isolated in high diastereomeric purity. The effect of several parameters on the reaction was studied and the absolute configuration of a newly created chiral centre was established by single crystal X-ray analysis; the correlation of the structure of chiral auxiliary and diastereoselectivity was investigated. The observed diastereoselectivity was in accordance with the relative energy profile of the products. The chirally pure α-halo acid could be separated from the auxiliary, without any loss of optical purity of both components.

Introduction

The synthesis of optically pure organic compounds containing diverse functional groups is an important consideration in modern synthetic endeavours. Optically pure compounds can be obtained by several approaches, either from prochiral substrates by asymmetric synthesis or from racemic samples by various techniques of resolution of enantiomers. The separation of enantiomers can be achieved by crystallization as salts with chiral components, by chiral chromatography, crystallization as enantiomorphic solids or spontaneous resolution,[1] subjecting to enantioselective reactions based on difference in their kinetics, such as enzyme mediated kinetic or dynamic kinetic resolutions,[2] in combination with other catalysts[3] or by catalytic parallel kinetic resolution reactions.[4] Many of these procedures are complex, resulting in the maximum yield of 50%, or need for continuous separation of unwanted isomers. At the same time there are other strategies involving isomerization of the unwanted isomer in the reaction medium, therefore theoretically increasing the yield to a quantitative level. The mechanism of isomerization of the unwanted enantiomer, may differ in such approaches like dynamic kinetic resolution (DKR),[5] dynamic kinetic asymmetric transformations (DYKAT)[6] or dynamic thermodynamic resolution (DTR),[7] where ultimately an optically pure product is formed in an efficient manner.

The developments in the area of DTR have mostly been in the electrophilic substitution reactions of organolithium reagents leading to the generation of chiral products of diverse functionalities.[8] The same approach of DTR has also been occasionally employed in deracemization of α-substituted derivatives of carboxylic acids. The optically pure α-substituted carboxylic acids are either part of the structural motifs of biologically significant compounds or are important intermediates for the synthesis of functional molecules, including amino acids. Several methods are available for their synthesis in optically pure form involving isomer separation and asymmetric synthesis.[9] The synthesis of optically enriched α-substituted derivatives of carboxylic acids by the DTR procedure involves two protocols. In one of the approaches the α-halo ester substrates undergo epimerization in favour of a thermodynamically stable isomer and undergo a nucleophilic substitution reaction to produce optically active derivatives, while in the other one, the epimerization of these α-substituted derivatives produces enrichment of the enantiomer for separate and stepwise functional group manipulations. Few chiral alcohols have been utilised as auxiliaries to anchor the

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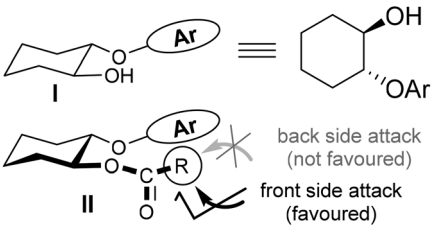
†Electronic supplementary information (ESI) available: Copies of the spectral data, details of the crystal structure including cif files, and computational study data (as PDF). CCDC 1854338, 1854339, 1854340, 1854341, 1854342 and 1854344. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ob02896f

α-substituted acid unit to form esters,[10,11] which were subjected to the suitable conditions of DTR to control the stereochemical output.

Another class of important chiral alcohols used in asymmetric synthesis is *trans*-2-aryloxy cyclohexanol. The aromatic ring of the ether unit (in **I**) provides an effective shield to control the stereochemistry in the asymmetric reactions using such auxiliaries.[12] The prochiral group attached on R (in **II**) can be attacked from both the faces. However, the aryl unit of the ether should block the back side attack and favour the front attack. This type of auxiliary is effectively employed to introduce chirality by the nucleophile addition reaction of PhZnCl on the prochiral ketone group attached in the form of phenylglyoxylate.[12b] The optically pure *trans*-2-aryloxycyclohexanol derivatives are structurally analogous to more popular auxiliaries like 8-phenylmenthol[13] and 2-arylcyclohexanol,[14a] particularly 2-tritylcyclohexanol.[14b]

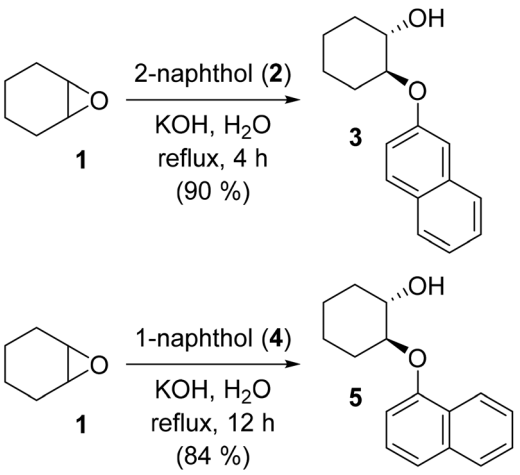


However, not many applications of chiral 2-aryloxycyclohexanol in asymmetric synthesis are explored. Recently we have demonstrated the ability of molecular recognition of chiral substrates using optically pure 2-(quinolin-8-yloxy)cyclohexan-1-ol, detected by NMR as well as fluorescence spectroscopy.[14c] In this paper, we shall present our studies on the synthesis, resolution and applications of *trans*-2-naphthyloxycyclohexanol as a chiral auxiliary in the synthesis of optically active α-halo esters by a DTR driven deracemization procedure.

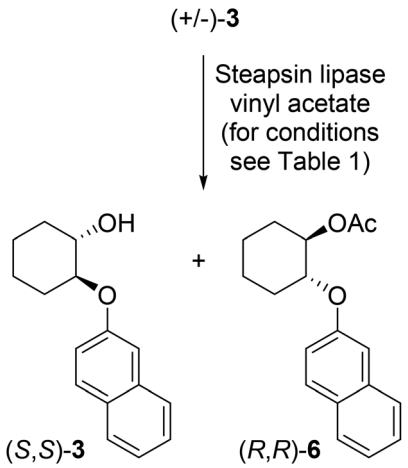
Results and discussion

The title compound *trans*-2-aryloxycyclohexanol derivatives in racemic form can be easily obtained by epoxide ring opening of cyclohexene oxide **1** with the corresponding phenoxides.[15] We have designed our auxiliaries, **3** and **5** (Scheme 1), by choosing a naphthalene unit as the aryl moiety due to its steric considerations as well as π–π interactions during the key step of a stereoselection process. The two possible isomers of *trans*-2-naphthyloxycyclohexanol are known in the literature.[16] Accordingly, we obtained *trans*-2-(naphthalen-2-yloxy)cyclohexanol **3** and *trans*-2-(naphthalen-1-yloxy)cyclohexanol **5** by the reaction of cyclohexene oxide **1** with the corresponding naphthoxides, **2** or **4**, prepared *in situ* with aqueous potassium hydroxide under reflux conditions (Scheme 1).

Having obtained the required racemic samples of alcohols **3** and **5**, we subjected them for separation of enantiomers by a well-established enzyme mediated kinetic resolution protocol.[2] The selective acylation of one enantiomer can be achieved by



Scheme 1 Synthesis of *trans*-2-naphthyloxycyclohexanols **3** and **5**.



Scheme 2 Resolution of (±)-**3**.

Table 1 Searching conditions for kinetic resolution of (±)-**3** with steapsin lipase

Entry	Eq. of VA[a]	Solvent	Lipase w/w eq.	Time (d)	% ee of **6** (%)[b]	% ee of **3** (%)[b]
1	3.0	THF	1.5	3	>99 (17)	13 (57)
2	10.0	THF	1.5	3	>99 (22)	27 (60)
3	10.0	EA	1.5	6	>99 (36)	51 (53)
4	10.0	Dioxane	1.5	6	>99 (22)	13 (46)
5	10.0	EA	3.0	6	>99 (45)	83 (52)
6	10.0	EA	3.0	9	>99 (47)	92 (51)
7	10.0	EA[c]	3.0	9	>99 (48)	>99 (49)

[a] Vinyl acetate. [b] Isolated yield. [c] High dilution; (E > 200 in all cases); EA = ethyl acetate.

adopting appropriate conditions using a combination of a suitable biocatalyst, acyl donor, solvent *etc*. The standardization procedure was performed on (±)-**3** as a model substrate (Scheme 2 and Table 1). The initial experiment was performed in THF with steapsin lipase as an immobilized biocatalyst and

vinyl acetate as an acyl donor, resulting in the formation of acetate **6** with high optical purity, but with low chemical yield. Increasing the amount of vinyl acetate resulted in better conversion without loss in selectivity. However, good overall yield and high selectivity were also achieved by increasing the amount of enzyme and changing the solvent to ethyl acetate. Furthermore we observed that performing the resolution procedure at high dilution resulted in near perfect selectivity and conversion.

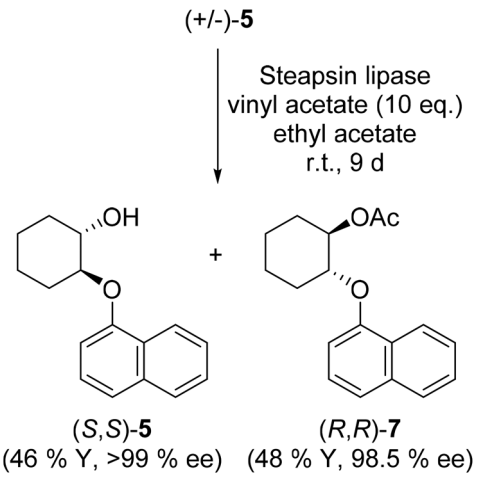
The above optimized experimental conditions were extended for the resolution of other alcohol (±)-**5** with similar success (Scheme 3). The optical purity of all the products of resolution was established by chiral solid phase HPLC analysis without any derivatization.

The correlation of absolute configuration of both the optically pure alcohols **3** and **5** could not be established due to the lack of literature reference. Hence, we prepared their ester derivatives with an acid of known chiral element, purified the corresponding diastereomeric esters, and established their optical description by single crystal X-ray analysis. The optically pure alcohols, obtained by careful hydrolysis of *O*-acetyl derivatives **6** and **7**, were treated with (*R*)-*O*-acetyl mandelic acid under Steglich esterification conditions[17] where the corresponding esters **8** and **9** were obtained in pure form. Their suitable crystals were grown from hexane–dichloromethane and subjected to X-ray diffraction analysis (Fig. 1).

The analysis established the configuration of the unreacted isomer of the alcohols as well the acylated products (Scheme 4).

The objective of the present study is to establish the scope of these two optically pure derivatives of *trans*-2-naphthyloxycyclohexenols as chiral auxiliaries for deracemization of α-halo esters. In this endeavour the optically pure alcohol (*R*,*R*)-**3** was treated with racemic 2-chloropropanoic acid **10** under the standard coupling conditions[17] (Scheme 5). The formation of an ester was a smooth process, the pure product **11** was isolated in near quantitative yield, and its NMR analysis indicated the presence of a single diastereomer. The $C_\alpha H$ of **11** appeared as a q (4.29–4.34 δ) in ^{1}H NMR analysis ($CDCl_3$, 400 MHz). The stereochemistry of the product was determined by its X-ray diffraction analysis (Fig. 2).

The other isomer (*R*,*R*,*R*)-**11**, where the newly generated chiral center should possess opposite stereochemistry, was prepared by coupling (*R*,*R*)-**3** with (*R*)-**10** and its ^{1}H NMR spectra were recorded. The $C_\alpha H$ of (*R*,*R*,*R*)-**11** showed a q at 4.23–4.28 δ, which was distinguishable and quantifiable for further optimization study. Furthermore the configuration of $C_\alpha H$ of (*R*,*R*,*S*)-**11** was confirmed by its acid hydrolysis and isolation of (*S*)-2-chloropropanoic acid, (*S*)-**10**, without loss of optical purity, by comparing the sign of optical rotation with the lit-



Scheme 3 Resolution of (±)-**5**.

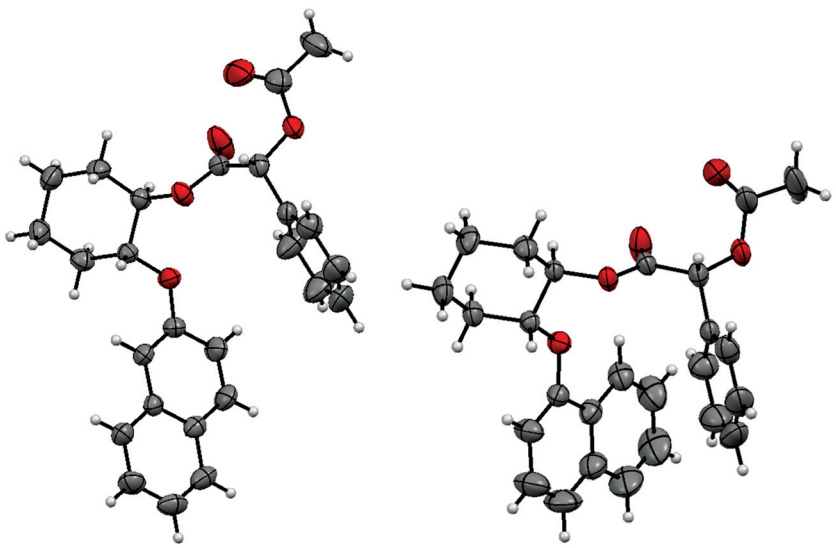
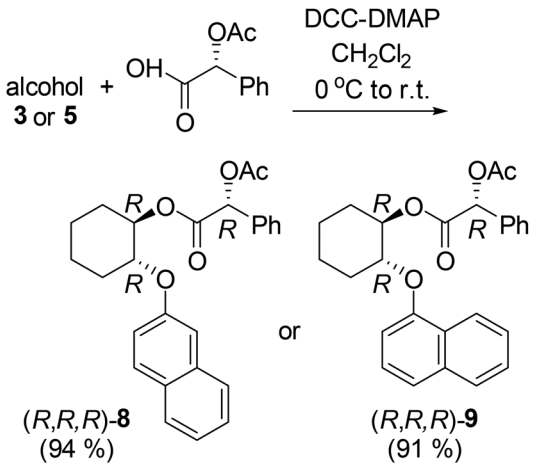
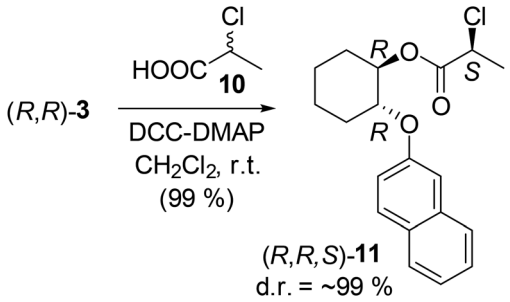


Fig. 1 Determination of absolute configuration of (*R*,*R*,*R*)-**8** (ORTEP diagram; CCDC 1854344; left) and (*R*,*R*,*R*)-**9** (ORTEP diagram; CCDC 1854340;† right).



Scheme 4 Determination of absolute configuration of optically pure alcohols.



Scheme 5 Deracemization of α-halo acid.

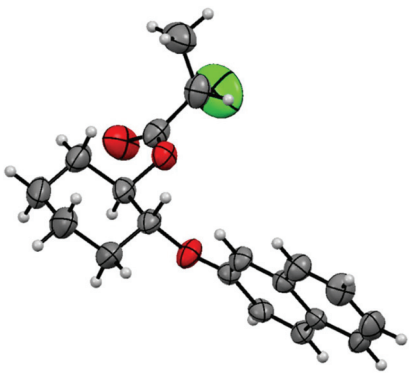
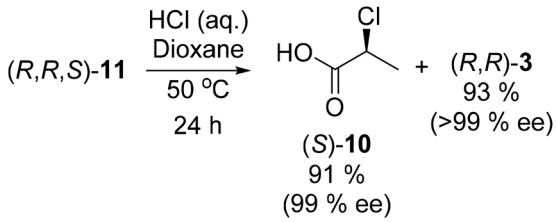


Fig. 2 Determination of absolute configuration of (*R*,*R*,*S*)-**11** (ORTEP diagram; CCDC 1854341†).

erature value (Scheme 6). It was also noted that there was no substantial loss in chemical yield as well as the optical purity of the recovered chiral auxiliary (*R*,*R*)-**3**.

The choice of a base in stereochemical consideration in the deracemization of similar substrates plays a crucial role in the final outcome of such reactions.[10d,18] The role of the base in this deracemization was also investigated in detail (Table 2). It



Scheme 6 Generation of chirally pure (*S*)-**10**.

Table 2 Effect of base in deracemization of **11**

Entry	Base[a]	% dr of **11**[b] (α-*R* : α-*S*)
1	DMAP	0.5 : 99.5
2	DABCO	0.5 : 99.5
3	Et_3N	1.0 : 99.0
4	K_2CO_3	1.5 : 98.5

[a] 20.0 mol% along with DCC (1.0 eq.). [b] Determined by CSP-HPLC.

was observed that organic bases show consistently good dr, while potassium carbonate too showed a comparable result.

The process of deracemization may involve two possible pathways, depending on the kinetic (DKR) or thermodynamic (DTR) aspect. The possible mechanism of deracemization may favour dynamic resolution, as in all the cases, the chemical yield is observed to be near quantitative. To further strengthen this possibility, the reaction was performed at varying temperatures (Table 3). The reaction was performed at three different reaction temperatures to investigate this aspect. A racemic sample of acid **10** showed the formation of ester **11**, as almost a single diastereomer (>99% de), within the temperature range of 0 °C to reflux temperature of CH_2Cl_2. The reaction was then performed using a scalemic mixture of (*R*)-**10**, (67 : 33) in a similar temperature range; however, in this study, the reaction product **11** at ambient and reflux temperature showed a de of around 72%, which dropped to 50% at low temperature (0 °C). This observation probably suggests the possibility of the mechanism to be a dynamic thermodynamic resolution (DTR).[7a]

Table 3 Effect of temperature on diastereoselectivity of **11** (see Scheme 5)[a]

Entry	Initial composition of **10** (*R* : *S*)	Temperature (°C)	% dr of **11**[b] (α-*R* : α-*S*)
1	50 : 50	Reflux	0.5 : 99.5
2	50 : 50	r.t.	0.5 : 99.5
3	50 : 50	0 °C	0.5 : 99.5
4	67 : 33	Reflux	14.0 : 86.0
5	67 : 33	r.t.	14.0 : 86.0
6	67 : 33	0 °C	25.0 : 75.0

[a] DMAP (20.0 mol%), DCC (1.0 eq.). [b] Determined by CSP-HPLC.

Table 4 Effect of time on diastereoselectivity of **11** (see Scheme 5)[a]

Entry	Time (h)	dr of **11** [b] (α-*R* : α-*S*)	% de of (*R*,*R*,*S*)-**11** [b]
1	0.5	16.0 : 84.0	68.0
2	1.0	16.0 : 84.0	68.0
3	3.0	15.5 : 84.5	69.0
4	6.0	15.0 : 85.0	70.0
5	12.0	14.0 : 86.0	72.0
6	18.0	11.0 : 89.0	78.0
7	24.0	10.0 : 90.0	80.0
8	48.0	8.0 : 92.0	84.0

[a] DMAP (20.0 mol%), DCC (1.0 eq.), initial composition of **10** (*R* : *S* was 67 : 33). [b] Determined by CSP-HPLC.

The reaction of (*R*,*R*)-**3** with a scalemic mixture of **10** which initially had the ratio in favour of the *R* isomer (*R* : *S* was 67 : 33), under the standard coupling conditions (DCC, DMAP, CH_2Cl_2 or $CHCl_3$), was monitored at different time intervals. The diastereomeric ratio of the product **11** was monitored. The acid **10** which had an enantiomeric ratio in favour of the *R* isomer (33% ee) on coupling with (*R*,*R*)-**3** underwent inversion at $C_\alpha H$ chiral carbon. It was observed that the ratio of diastereomer (*R*,*R*,*S*)-**11** improved with the progress of the reaction (Table 4). This also suggests that the epimerization process at the chiral centre of $C_\alpha H$ of **11** proceeds after the ester formation step. This observation helps us to further establish the mode of deracemization *via* the epimerization process, which must be controlled by the stereochemistry of the chiral *trans*-2-aryloxycyclohexanol auxiliary.

The effect of initial composition of 2-chloropropanoic acid **10** on the final stereochemical outcome of the deracemization reaction was studied by conducting a series of experiments with varying enantiomeric ratios (Table 5). As we progress from higher optical purity of **10** in favour of the *R*-isomer [80% ee of (*R*)-**10**] to its racemic sample, the diastereomeric ratio of the product gradually increases in favour of (*R*,*R*,*S*)-**11**. This suggests the dependence of initial composition of the coupling partner 2-chloropropanoic acid on the ultimate diastereoselectivity of ester **11**. Such observation of the relationship of initial composition of acid **10** and the final stereochemical output of deracemization is in accordance with the reported example.[10f]

Table 5 Effect of initial composition of acid **10** on diastereoselectivity of **11** (see Scheme 5)[a]

Entry	Initial composition of **10** (*R* : *S*)	Product ratio[b] (*R*,*R*,*R*)-**11** : (*R*,*R*,*S*)-**11**	% de[b] of (*R*,*R*,*S*)-**11**
1	90 : 10	47.5 : 52.5	5
2	75 : 25	23.5 : 76.5	53
3	67 : 33	14 : 86	72
4	60 : 40	10 : 90	80
5	55 : 45	4 : 96	92
6	50 : 50	0.5 : 99.5	99

[a] DMAP (20.0 mol%), DCC (1.0 eq.), reaction time was 12 h. [b] Determined by CSP-HPLC.

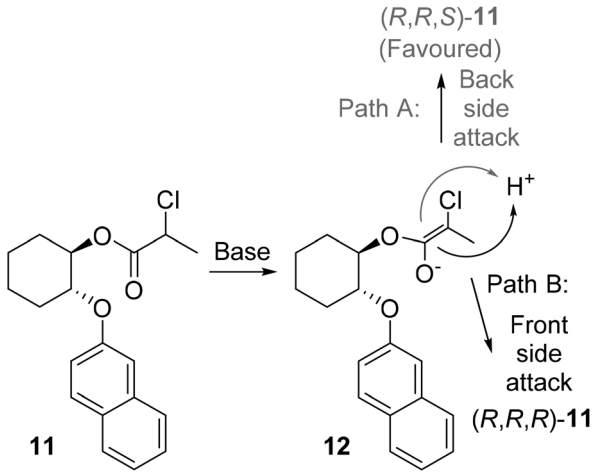


Fig. 3 Probable mechanism of selective deracemization.

Based on these detailed investigations, we can summarise the possible reaction pathway in Fig. 3. The base deprotonates the initially coupled ester **11** to form enolate intermediate **12**, which on re-protonation from the two possible sides leads to the formation of its two diastereomers. The re-protonation of **12** from Path-A involving the back side attack will furnish the observed (*R*,*R*,*S*)-**11**, while that from the front side by Path-B should result in the formation of its epimer (*R*,*R*,*R*)-**11**. Probably due to the steric crowding offered by the naphthyloxy moiety, the former mode of attack in Path-A is more feasible and supports the experimental observation.

This observation of deracemization in favour of (*R*,*R*,*S*)-**11** was further validated by the density functional theory (DFT) study of the final diastereomers of **11** at the B3LYP/6-31+G(d) level.[19] Fig. 4 depicts the relative energies of both the diastereomers of **11**. The difference in energy between (*R*,*R*,*S*)-**11** and (*R*,*R*,*R*)-**11** is about 2.1 kJ mol^{-1} which is in agreement with the experimental results and the stereochemical outcome of the deracemization reaction (for detailed discussion on DFT calculations, see the ESI†).

In the present study we have also prepared another derivative of naphthyloxycyclohexanol (*S*,*S*)-**5**, prepared from 1-naphthol **4** and cyclohexene oxide **1** (Scheme 1). The reaction of optically pure alcohol (*S*,*S*)-**5** and (±)-2-chloropropanoic acid **10** under optimized esterification and deracemization conditions resulted in the formation of ester **14a** with moderate selectivity (68% de; Table 6). The ratio of diastereomers of **14a** was established by ^{1}H NMR, where the $C_\alpha H$ hydrogen appeared as a distinguishable q signal in the range of 4.1–4.3 δ (see the ESI† for more details). The much lower selectivity in this case of deracemization could be attributed to two aspects, the steric factors pertaining to the orientation of the naphthalene unit of the auxiliary and the relative energy difference of the diastereomers of **14a** (1.6 kJ mol^{-1}; for details see the ESI†). In both these examples, **11** and **14a**, we have observed the formation of a thermodynamically more stable diastereomer as a major product, strengthening the probability of the dynamic thermodynamic resolution mechanism in this reaction.

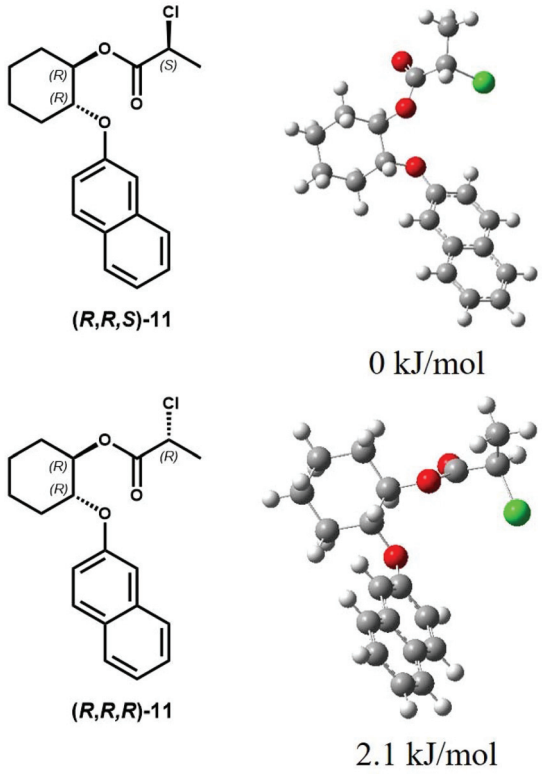
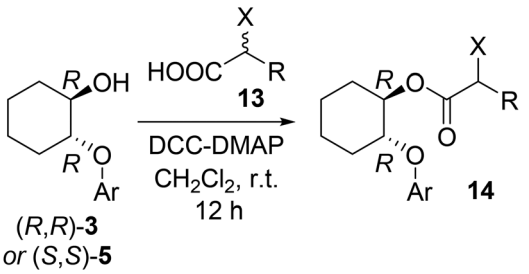


Fig. 4 Optimized structures of the diastereomers (*R*,*R*,*S*)-**11** and (*R*,*R*,*R*)-**11** and their relative energies.

Table 6 Effect of substituents on diastereoselectivity of α-halo esters[a]



Entry	Chiral auxiliary	R in α-halo acid (**10**/**13**)	X in α-halo acid (**10**/**13**)	Yield (%)	% de[b] [**14**]
1	(*S*,*S*)-**5a**	Me	Cl	98	68 [(*S*,*S*,*S*)-**14a**]
2	(*R*,*R*)-**3a**	Me	Cl	99	>99 [(*R*,*R*,*S*)-**11**]
3	(*R*,*R*)-**3a**	Me	Br	98	66 [(*R*,*R*,*S*)-**14b**]
4	(*R*,*R*)-**3a**	Et	Cl	97	50 [**14c**][c]
5	(*R*,*R*)-**3a**	Et	Br	98	40 [**14d**][c]
6	(*R*,*R*)-**3a**	i-Pr	Cl	98	42 [**14e**][c]
7	(*R*,*R*)-**3a**	i-Pr	Br	96	46 [**14f**][c]
8	(*R*,*R*)-**3a**	Bn	Cl	94	43 [**14g**][c]
9	(*R*,*R*)-**3a**	Bn	Br	92	38 [**14h**][c]
10	(*S*,*S*)-**5a**	Ph	Br	95	8 [**14i**][c]
11	(*R*,*R*)-**3a**	Ph	Br	98	65 [(*R*,*R*,*R*)-**14j**]
12	(*R*,*R*)-**3a**	Ph	Cl	94	34 [**14k**][c]

[a] DMAP (20.0 mol%), DCC (1.0 eq.), reaction time was 12 h. [b] Determined by CSP-HPLC. [c] Absolute configuration was not established.

The better selectivity with auxiliary (*R*,*R*)-**3** led us to select it for further screening of examples of deracemization (Table 6). The reaction of alcohol (*R*,*R*)-**3** with 2-bromopropanoic acid resulted in the formation of ester **14b** (66% de), which is lower as compared to its chloro analogue, which could be attributed to the higher acidity of $C_\alpha H$, making its abstraction a more facile process. Replacing a methyl group with an ethyl group in the next example, **14c**, led to a decrease in diastereoselectivity (50% de), which is in agreement with the earlier reports.[10d,f] Furthermore, introducing a bulkier group in **14e** resulted in diminished selectivity for the chloro analogue (42% de); however marginal reversal was detected for the bromo analogue **14f** (46% de). We also examined the case of 2-halo-3-phenylpropanoic acid and 2-halophenylacetic acid as coupling partners in this deracemization study. In the case of 2-chloro-3-phenylpropanoic acid the diastereomeric **14g** was isolated with moderate selectivity (43%, de), while for its bromo derivative, **14h**, a small drop in selectivity was seen (38% de). In the case of 2-chlorophenylacetic acid, the selectivity of **14k** was observed to be much reduced (34% de), while for its bromo derivative **14j**, it was much improved (65% de). In the two sets of examples with bulkier substituents, isopropyl and phenyl, the trend was similar. The lower selectivity in the case of (*S*,*S*)-**5** was also observed in the example with 2-bromophenylacetic acid, as the product **14i** was isolated in poor selectivity (8% de). In some of the examples (**14a**, **14b** and **14j**) we could observe a considerable enrichment of optical purity (98–99 de) on the recrystallization, which is an expected phenomenon.[10d] The structures of all the α-halo esters prepared in this study are presented in Chart 1.

Absolute configuration at the enriched chiral carbon of few of the optically pure α-halo esters, **14a**, **14b** and **14j**, was established by their single crystal diffraction analysis, and a representative example is presented in Fig. 5 (see the ESI† for details of other crystals).

Thus with these examples we have demonstrated the ability of the present chiral derivative of *trans*-2-naphthyloxycyclohexanol as an efficient auxiliary to introduce chirality into the α-halo acids by a suitable base mediated DTR procedure.

Conclusion

We have reported the preparation of two derivatives of chiral 2-aryloxycyclohexanol, *trans*-2-(naphthalen-2-yloxy)cyclohexanol **3** and *trans*-2-(naphthalen-1-yloxy)cyclohexanol **5**, and their isomers were separated by enzyme mediated kinetic resolution. The absolute configuration was confirmed by single crystal X-ray diffraction analysis of their esters prepared by coupling with chiral acids of known optical description. The optically pure alcohols were used as chiral auxiliaries for coupling with racemic α-halo acids, where an efficient deracemization resulted in the formation of the product almost as a single diastereomer. The study of different reaction parameters and the relative energies of the two possible diastereomers indicates towards the dynamic thermodynamic resolution to

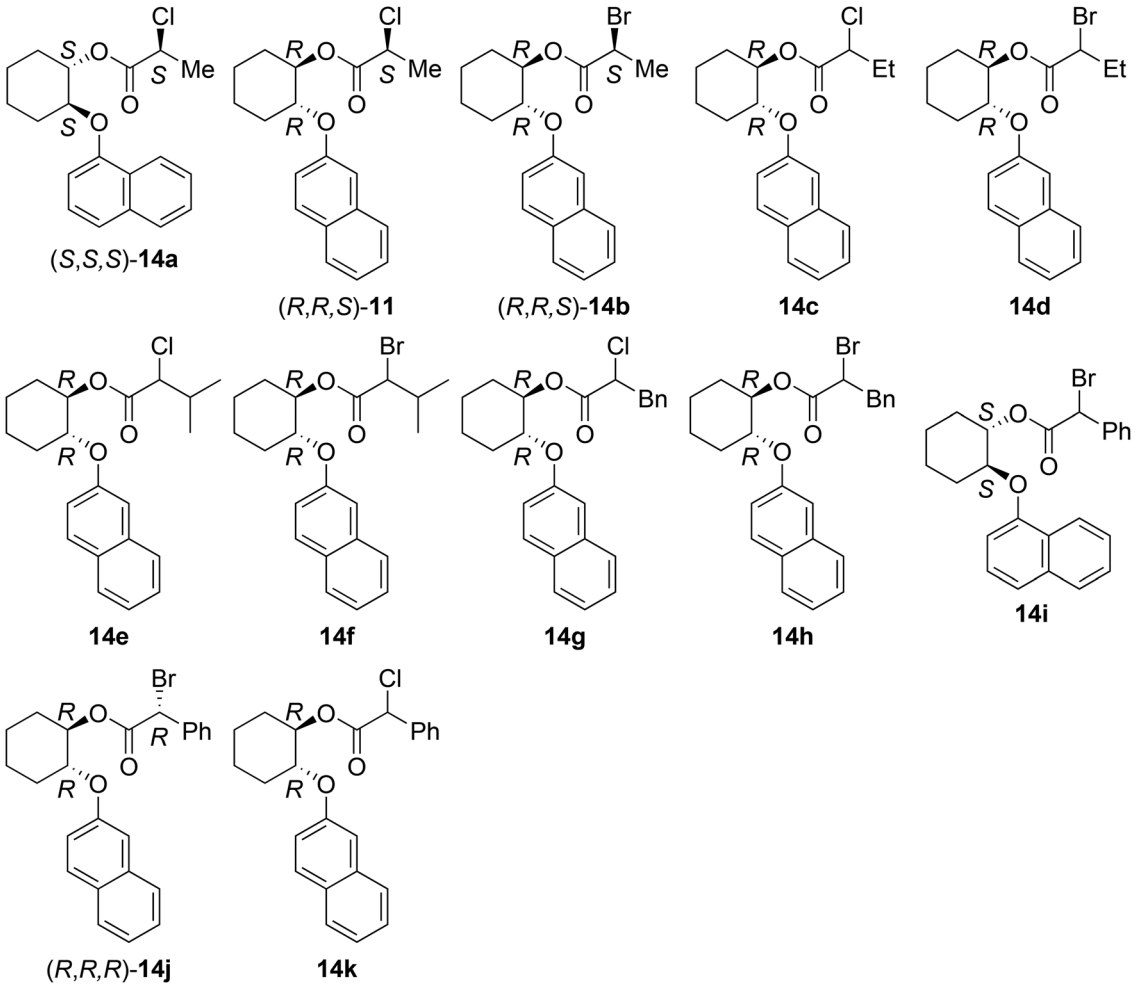


Chart 1 Examples of enantiomer enrichment reaction by DTR.

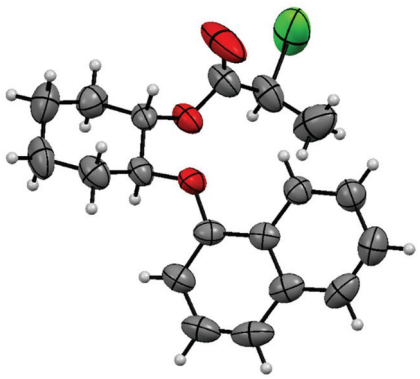


Fig. 5 ORTEP diagram of (*S*,*S*,*S*)-**14a** (CCDC 1854339†).

be the possible mode of deracemization. The acid mediated cleavage of the diastereomeric ester product affords both the components in optically pure form, hence this could be a useful method to access chiral α-halo acids of considerable importance.

Experimental section

General information

Reagents were purchased from Sigma-Aldrich Chemicals Limited, SD Fine, Sisco, Qualigens, Avra Chemicals Limited *etc*. All solvents that were used were stored on oven dried molecular sieves (4 Å). All commercial products were used without further purification. Thin layer chromatography was performed on Merck 60 F254 aluminium coated plates. The spots were visualized under UV light or with iodine vapour. All the compounds were purified by column chromatography using SRL silica gel (60–120 mesh). All reactions were carried out under an inert atmosphere (nitrogen) unless other conditions are specified. ^{1}H and ^{13}C NMR spectra are recorded on a 400 MHz Bruker Avance 400 spectrometer (100 MHz for ^{13}C) with $CDCl_3$ as the solvent and TMS as the internal standard. Signal multiplicity is denoted as singlet (s), doublet (d), doublet of doublet of doublets (ddd), triplet (t), doublet of triplets (dt), quartet (q) and multiplet (m). NMR spectra of **14a–k** were recorded after passing the mixture through a short column of silica gel. For the ^{13}C NMR spectra of **14c–14i** and

14k only peaks corresponding to a major diastereomer have been considered. Mass spectra were recorded on a Thermo-Fischer DSQ II GCMS instrument. IR spectra were recorded on a PerkinElmer FTIR RXI spectrometer and a Bruker Alpha as KBr pellets or neat in the case of liquids, while the X-ray data collection was carried out on an Xcalibur, Eos, Gemini diffractometer.[20] Specific optical rotations were recorded on a Jasco P-2000 polarimeter. Computational studies were performed with Gaussian 16 Revision A.03 using the B3LYP/6-31+G(d) basis set.

Synthesis of (±) *trans*-2-(naphthalen-2-yloxy)cyclohexan-1-ol (3)

Into a solution containing potassium hydroxide (1.68 g, 30 mmol) in water (16 mL) was added β-naphthol (4.32 g, 30 mmol) and heated at 100 °C. To this solution was added cyclohexene oxide (1.0 g, 10 mmol) in 15 min. A heavy precipitation made it necessary to add more water (8 mL) to facilitate stirring. After an additional 40 min, the mixture was allowed to cool to room temperature, filtered and precipitates were washed with 1 M KOH solution and water. The dried product (**3**) was further recrystallized from toluene to afford a white solid.[16a] (2.21 g, 90%).

M.p. 143–145 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.79–7.73 (m, 3H), 7.48–7.44 (t, J = 7.2 Hz, 1H), 7.38–7.34 (t, J = 7.2 Hz, 1H), 7.25 (m, 1H), 7.21–7.18 (dd, J = 8.8, 2.4 Hz, 1H), 4.19–4.17 (m, 1H), 3.84–3.78 (m, 1H), 2.68 (bs, 1H, –O*H*), 2.29–2.14 (m, 2H), 1.80–1.53 (m, 4H), 1.50–1.38 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 155.6, 134.5, 129.6, 129.2, 127.6, 126.8, 126.4, 123.9, 119.6, 109.3, 82.2, 73.5, 32.1, 29.0, 24.0, 23.9.

IR (KBr) ν cm^{-1}: 3458, 3004, 1629, 1468, 1391, 1235, 1181, 838, 709.

Mass (ESI): m/z 242.3 $[M]^+$, 213, 144.1 (100%), 114.

Synthesis of (±) *trans*-2-(naphthalen-1-yloxy)cyclohexan-1-ol (5)

Into a solution containing potassium hydroxide (0.56 g, 10 mmol) in water (16 mL) was added α-naphthol (1.44 g, 10 mmol) and heated at 100 °C. To this solution was added cyclohexene oxide (1.5 g, 15 mmol) over 15 min. The reaction mixture was then allowed to reflux for 12 h and then allowed to cool. The mixture was then extracted with ethyl acetate (3 × 25 mL) and then washed with water (2 × 25 mL). The combined extract was dried over anh. Na_2SO_4, concentrated under vacuum and subjected to column chromatography on silica gel (ethyl acetate/petroleum ether 3 : 7) resulting in a yellowish solid (**5**).[16c] (1.42 g, 84%).

M.p. 63–65 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.35–8.33 (m, 1H), 7.86–7.85 (m, 1H), 7.56–7.50 (m, 3H), 7.44–7.41 (m, 1H), 7.00–6.99 (d, J = 7.2 Hz, 1H), 4.32–4.28 (m, 1H), 3.98–3.93 (m, 1H), 2.80 (bs, 1H, –O*H*), 2.29–2.19 (m, 2H), 1.81 (m, 2H), 1.57–1.37 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 153.3, 134.8, 127.7, 126.6, 126.4, 125.9, 125.3, 122.0, 120.7, 107.3, 82.4, 73.4, 32.1, 29.1, 24.0, 23.9.

IR (KBr) ν cm^{-1}: 3410, 2929, 1575, 1460, 1269, 1099, 1076, 763.

HRMS (ESI): calcd for $C_{16}H_{18}KO_2$ $[M + K]^+$ 281.0938 found 281.0944.

General procedure for enzymatic resolution of alcohol

To a solution of racemic alcohol (**3**) (0.30 g, 1.24 mmol) in ethyl acetate, lipase (0.9 g, 3 eq. w/w, steapsin lipase) and vinyl acetate (1.14 mL, 12.4 mmol) were added and the reaction mixture was stirred for 9 days at room temperature. The reaction material was filtered through a Celite bed and the filtrate was concentrated under vacuum. The crude mixture was then separated by column chromatography over silica gel using ethyl acetate and petroleum ether as the eluent. The acetate (**4**) was eluted with 10% ethyl acetate/petroleum ether (0.17 g, 48%).

M.p. 99–101 °C. ee = >99%.

$[\alpha]_D^{25}$ = +39.4 (c = 1.0 in $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.80–7.75 (m, 3H), 7.48–7.45 (m, 1H), 7.38–7.35 (m, 1H), 7.33–7.29 (m, 1H), 7.20–7.18 (dd, J = 8.8, 2.4 Hz, 1H), 5.12–5.07 (m, 1H, –C*H*–OAc), 4.45–4.40 (ddd, J = 12.4, 8.0, 4.0 Hz, 1H, –C*H*–O–Ar), 2.27–2.24 (m, 1H), 2.15–2.11 (m, 1H), 1.96 (s, 3H, –CO–CH_3), 1.86–1.78 (m, 2H), 1.66–1.61 (m, 1H), 1.58–1.43 (m, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 170.6, 156.0, 134.5, 129.4, 129.1, 127.6, 126.7, 126.3, 123.7, 119.6, 109.1, 77.6, 74.1, 29.8, 29.6, 23.2, 23.1, 21.2.

IR (KBr) ν cm^{-1}: 2943, 1734, 1625, 1506, 1246, 1033, 835.

Mass (ESI): m/z 285.1 $[M + 1]^+$, 284.1 $[M]^+$, 225, 144.1, 141.1 (100%), 81.

HRMS (ESI): calcd for $C_{18}H_{21}O_3$ $[M + H]^+$ 285.1491 found 285.1496.

HPLC conditions: Chiralcel OD-H column, 10% isopropyl alcohol–hexane, UV = 254 nm, flow rate = 0.5 mL min^{-1}. R_t = 8.9 min, major peak (*R*,*R*-isomer), 9.7 min (*S*,*S*-isomer).

Alcohol (*S*,*S*-3) was eluted with 20% ethyl acetate/petroleum ether. (0.15 g, 49%). ee = >99%. $[\alpha]_D^{25}$ = +66.2 (c = 1.0 in $CHCl_3$). HPLC conditions: ChiralCel OD-H column, 10% isopropyl alcohol–hexane, UV = 254 nm, flow rate = 1 mL min^{-1}. R_t = 10.9 min (*R*,*R*-isomer), 16.7 min, major peak (*S*,*S*-isomer).

Enzymatic resolution of alcohol (5)

The title compound was obtained by following the same procedure as that for alcohol (**3**) from the racemic alcohol (**5**). The crude mixture was separated by column chromatography over silica gel using ethyl acetate and petroleum ether as the eluent. The acetate (**7**) was eluted with 20% ethyl acetate/petroleum ether as a colorless oil. (0.17 g, 48%). ee = 98.5%.

$[\alpha]_D^{25}$ = −88.3 (c = 1.0 in $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.26–8.23 (m, 1H), 7.81–7.79 (m, 1H), 7.51–7.47 (m, 2H), 7.46–7.44 (d, J = 7.6 Hz, 1H), 7.40–7.36 (m, 1H), 6.97–6.95 (d, J = 7.2 Hz, 1H), 5.24–5.19 (m, 1H, –C*H*–OAc), 4.48–4.42 (ddd, J = 12.4, 8.4, 4.4 Hz, 1H, –C*H*–OAr), 2.32–2.28 (m, 1H), 2.14–2.11 (m, 1H), 1.92 (s, 3H, –COCH_3), 1.88–1.78 (m, 2H), 1.70–1.62 (m, 1H), 1.57–1.43 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 170.7, 153.9, 134.7,

127.4, 126.4, 126.3, 125.8, 125.3, 122.3, 120.4, 106.7, 78.0, 73.8, 29.8, 29.5, 23.2, 23.1, 21.2.

IR (KBr) ν cm^{-1}: 2939, 1735, 1579, 1234, 1097, 738.

Mass (ESI): m/z 308.3 $[M + 23]^+$, 307.3 $[M + Na]^+$ (100%), 285.3, 225.2, 158.1.

HRMS (ESI): calcd for $C_{18}H_{20}O_3Na$ $[M + H]^+$ 307.1304 found 307.1303.

HPLC conditions: ChiralCel OD-H column, 2.5% isopropyl alcohol–hexane, UV = 254 nm, flow rate = 1.0 mL min^{-1}. R_t = 13.0 min (*S*,*S*-isomer), 13.9 min, major peak (*R*,*R*-isomer).

Alcohol (*S*,*S*-5) was eluted with 30% ethyl acetate/petroleum ether. (0.14 g, 46%). ee = ~99%. $[\alpha]_D^{25}$ = +93.6 (c = 1.0 in $CHCl_3$). HPLC conditions: ChiralCel OD-H column, 25% isopropyl alcohol–hexane, UV = 254 nm, flow rate = 1 mL min^{-1}. R_t = 8.6 min, major peak (*S*,*S*-isomer), 10.7 min (*R*,*R*-isomer).

General procedure for hydrolysis of acetate

To a solution of chiral acetate (**4**) (0.1 g, 0.35 mmol) in methanol, conc. HCl (0.05 mL, 0.53 mmol) was added. The resulting mixture was then refluxed for 3 h. The solvent was removed under vacuum and subjected to column chromatography over silica gel using ethyl acetate and petroleum ether to afford chiral alcohol (*R*,*R*)-**3** as a white solid. (0.081 g, 95%). ee = >99%. $[\alpha]_D^{25}$ = (−66.7) (c = 1.0 in $CHCl_3$).

HPLC conditions: ChiralCel OD-H column, 10% isopropyl alcohol–hexane, UV = 254 nm, flow rate = 1 mL min^{-1}. R_t = 10.9 min, major peak (*R*,*R*-isomer), 16.7 min (*S*,*S*-isomer).

Hydrolysis of acetate (7)

The chiral alcohol (**5**) was obtained by following the same procedure as that for alcohol (**3**) from the chiral acetate (**7**). The crude mixture was separated by column chromatography over silica gel using ethyl acetate and petroleum ether as the eluent resulting in chiral alcohol (*R*,*R*)-**5** as a low melting yellow solid. (0.078 g, 93%). ee = 98.5%.

$[\alpha]_D^{25}$ = −93.2 (c = 1.0 in $CHCl_3$).

HPLC conditions: ChiralCel OD-H column, 25% isopropyl alcohol–hexane, UV = 254 nm, flow rate = 1 mL min^{-1}. R_t = 8.6 min (*S*,*S*-isomer), 10.7 min, major peak (*R*,*R*-isomer).

Determination of absolute configuration: synthesis of (1*R*,2*R*)-2-(naphthalen-2-yloxy)cyclohexyl-(*R*)-2-acetoxy-2-phenylacetate (*R*,*R*,*R*)-8

Alcohol (*R*,*R*)-**3** (0.10 g, 4.1 mmol), DCC (0.084 g, 4.1 mmol) and DMAP (0.010 g, 0.8 mmol) were dissolved in CH_2Cl_2 (10 mL) in a two-necked flask under a nitrogen atmosphere and cooled to 0 °C. A solution of (*R*)-*O*-acyl mandelic acid (0.079 g, 4.1 mmol) in dichloromethane (5 mL) was then added dropwise. The reaction mixture was stirred at rt for 4 h. The reaction mixture was then filtered through a Celite bed, washed with dichloromethane and purified by column chromatography over silica gel (10% ethyl acetate/petroleum ether) affording a white solid (*R*,*R*,*R*-**8**)(0.16 g, 94%).

M.p. 95–97 °C.

$[\alpha]_D^{25}$ = −73.8 (c = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.79–7.77 (d, J = 8.0 Hz, 1H), 7.71–7.65 (m, 2H), 7.47–7.43 (m, 1H), 7.38–7.34 (m, 3H), 7.13–7.05 (m, 4H), 6.90–6.87 (dd, J = 9.2, 2.4 Hz, 1H), 5.91 (s, 1H, $C_\alpha H$), 5.11–5.10 (m, 1H, –C*H*OCO–), 4.32–4.30 (m, 1H, –C*H*OAr), 2.21–2.18 (m, 1H), 2.14–2.10 (m, 1H, s of $-COCH_3$ merged), 1.80–1.79 (m, 2H), 1.69–1.40 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 170.4, 168.1, 155.5, 134.4, 133.4, 129.3, 129.0, 128.9, 128.5, 127.6, 127.4, 126.8, 126.2, 123.6, 119.5, 108.3, 75.3, 74.7, 29.6, 29.3, 23.0, 22.9, 20.7. IR (KBr) ν cm^{-1}: 2935, 1749, 1737, 1627, 1209, 1174, 1045, 835.

Mass (ESI): m/z 441.2 $[M + Na]^+$ (100%), 359.1, 301.1.

HRMS (ESI): calcd for $C_{26}H_{26}O_5Na$ $[M + Na]^+$ 441.1678 found 441.1659.

Synthesis of (1*R*,2*R*)-2-(naphthalen-1-yloxy)cyclohexyl(*R*)-2-acetoxy-2-phenylacetate (*R*,*R*,*R*)-9

The title compound was obtained by the same procedure as that for ester (*R*,*R*,*R*)-**8** from alcohol (*R*,*R*)-**5**. The mixture was purified by column chromatography on silica gel using 10% ethyl acetate/petroleum ether as a white solid (*R*,*R*,*R*)-**9** (0.15 g, 91%).

M.p. 113–115 °C.

$[\alpha]_D^{25}$ = −135.0 (c = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.97–7.94 (d, J = 8.4 Hz, 1H), 7.69–7.67 (d, J = 8.0 Hz, 1H), 7.40–7.36 (m, 1H), 7.32–7.27 (m, 2H), 7.20–7.16 (m, 1H), 7.14–7.12 (m, 2H), 6.85–6.81 (t, J = 7.2 Hz, 1H), 6.72–6.69 (t, J = 7.6 Hz, 1H), 6.61–6.59 (d, J = 7.6 Hz, 1H), 5.82 (s, 1H, $C_\alpha H$), 5.20–5.14 (ddd, J = 12.4, 8.0, 4.4 Hz, 1H, –C*H*OCO–), 4.27–4.21 (dt, J = 8.8, 4.0 Hz, 1H, –C*H*OAr), 2.12–2.07 (m, 1H), 1.73–1.68 (m, 2H), 1.56–1.52 (m, 1H), 1.46–1.38 (m, 2H), 1.33–1.27 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 170.4, 168.4, 152.9, 134.6, 133.2, 128.6, 127.2, 127.1, 126.3, 126.1, 125.6, 125.1, 122.4, 120.0, 105.1, 76.8, 74.6, 74.5, 29.5, 28.8, 23.0, 22.8, 20.7. IR (KBr) ν cm^{-1}: 2957, 1751, 1739, 1570, 1458, 1371, 1269, 1232, 1059, 794.

Mass (ESI): m/z 441.2 $[M + Na]^+$ (100%), 413.3, 359.2.

HRMS (ESI): calcd for $C_{26}H_{26}O_5Na$ $[M + Na]^+$ 441.1678 found 441.1655.

Deracemization of α-halo acid: synthesis of (1*R*,2*R*)-2-(naphthalen-2-yloxy)cyclohexyl (*S*)-2-chloropropanoate (*R*,*R*,*S*)-11

Alcohol (*R*,*R*)-**3** (0.1 g, 0.4 mmol), DCC (0.13 g, 0.61 mmol) and DMAP (0.01 g, 0.082 mmol) were placed in a two neck round bottom flask under an N_2 atmosphere, dissolved in 5 mL of CH_2Cl_2 and cooled to 0 °C. A solution of 2-chloropropanoic acid (0.04 mL, 0.4 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then filtered through a Celite bed and washed with CH_2Cl_2 and purified by column chromatography over silica gel by eluting with 5% ethyl acetate/petroleum ether. (0.14 g, 99%).

M.p. 93–95 °C.

$[\alpha]_D^{25}$ = +10.6 (c = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.79–7.73 (m, 3H), 7.47–7.44 (m, 1H), 7.37–7.34 (m, 1H), 7.27–7.26 (m, 1H), 7.18–7.15 (dd, J = 8.8, 2.4 Hz, 1H), 5.16–5.11 (ddd, J = 12.4, 8.0, 4.4 Hz, 1H, –C*H*OCO–), 4.49–4.44 (ddd, J = 12.4, 8.4, 4.4 Hz, 1H, –C*H*OAr), 4.34–4.29 (q, J = 7.2 Hz, 1H, $C_\alpha H$), 2.29–2.25 (m, 1H), 2.16–2.12 (m, 1H), 1.88–1.78 (m, 2H), 1.67–1.57 (m, 5H, d of $-CH_3$ merged), 1.56–1.45 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 169.5, 155.8, 134.4, 129.5, 129.1, 127.6, 126.8, 126.3, 123.8, 119.6, 108.9, 75.6, 52.8, 29.4, 29.3, 23.0, 22.8, 21.4.

IR (KBr) ν cm^{-1}: 2957, 1751, 1739, 1570, 1458, 1371, 1269, 1232, 1059, 794.

Mass (ESI): m/z 331.8 $[M]^+$, 188.9, 144.2 (100%), 143.5, 114.9.

HRMS (ESI): calcd for $C_{19}H_{21}ClO_3Na$ $[M + Na]^+$ 355.1071 found 355.1070.

HPLC conditions: Chiralpak IA column, 1.0% isopropyl alcohol–hexane, UV = 254 nm, flow = 0.5 mL min^{-1}. R_t = 17.2 min (*R*,*R*,*R*)-**11** and R_t = 18.2 min (*R*,*R*,*S*)-**11**.

Synthesis of (1*S*,2*S*)-2-(naphthalen-1-yloxy)cyclohexyl (*S*)-2-chloropropanoate (*S*,*S*,*S*)-14a

The title compound was obtained by following the same procedure as that for (*R*,*R*,*S*)-**11** from alcohol (*S*,*S*)-**5** and 2-chloropropanoic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in the formation of a white solid. (0.13 g, 98%).

M.p. 81–83 °C. de = 68%.

$[\alpha]_D^{25}$ = +85.8 (c = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) after crystallization: δ ppm 8.23–8.21 (d, J = 6.4 Hz, 1H), 7.81–7.80 (d, J = 6.4 Hz, 1H), 7.51–7.45 (m, 3H), 7.41–7.37 (m, 1H), 6.96–6.94 (d, J = 6.4 Hz, 1H), 5.31–5.27 (dt, J = 7.2, 3.6 Hz, 1H, –C*H*OCO–), 4.53–4.49 (dt, J = 7.2, 3.6 Hz, 1H, –C*H*OAr), 4.23–4.19 (q, J = 7.2, 1H, $C_\alpha H$), 2.35–2.33 (m, 1H), 2.20–2.18 (m, 1H), 1.90–1.84 (m, 2H), 1.74–1.66 (m, 1H), 1.64–1.59 (m, 2H), 1.57–1.50 (m, 1H), 1.46–1.45 (d, J = 6.4 Hz, 3H, $-CH_3$).

^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 169.8, 153.6, 134.7, 127.4, 126.4, 126.2, 125.7, 125.3, 122.2, 120.6, 106.4, 75.6, 52.6, 29.6, 29.5, 23.2, 23.0, 21.3.

IR (KBr) ν cm^{-1}: 3058, 2942, 1752, 1627, 1458, 1332, 1172, 1085.

Mass (ESI): m/z 355.1 $[M + Na]^+$.

HRMS (ESI): calcd for $C_{19}H_{21}ClO_3Na$ $[M + Na]^+$ 355.1071 found 355.1068.

HPLC conditions: Chiralpak IA column, 1.0% isopropyl alcohol–hexane, UV = 254 nm, flow = 0.5 mL min^{-1}. R_t = 10.6 min (*S*,*S*,*S*)-**14a** and R_t = 11.1 min (*S*,*S*,*R*)-**14a**.

Synthesis of (1*R*,2*R*)-2-(naphthalen-2-yloxy)cyclohexyl (*S*)-2-bromopropanoate (*R*,*R*,*S*)-14b

The title compound was obtained by following the same procedure as that for (*R*,*R*,*S*)-**11** from alcohol (*R*,*R*)-**3** and 2-bromopropanoic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in the formation of a white solid. (0.15 g, 98%).

M.p. 92–94 °C. de = 66%. $[\alpha]_D^{25}$ = −12.4 (c = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) after crystallization: δ ppm 7.78–7.73 (m, 3H), 7.47–7.43 (m, 1H), 7.37–7.33 (m, 1H), 7.27–7.25 (m, 1H), 7.18–7.16 (dd, J = 8.8, 2.4 Hz, 1H), 5.15–5.08 (m, 1H, –C*H*OCO), 4.50–4.43 (m, 1H, –CHOAr), 4.33–4.28 (q, J = 6.8 Hz, 1H, $C_\alpha H$), 2.29–2.24 (m, 1H), 2.16–2.11 (m, 1H), 1.86–1.80 (m, 2H), 1.72–1.70 (d, J = 6.8 Hz, 3H, $-CH_3$), 1.68–1.59 (m, 2H), 1.58–1.54 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 169.6, 155.8, 134.5, 129.5, 129.1, 127.6, 126.8, 126.3, 123.7, 119.6, 108.9, 75.3, 40.5, 29.3, 29.1, 22.9, 22.8, 21.6.

IR (KBr) ν cm^{-1}: 3057, 2935, 1737, 1628, 1598, 1446, 1353, 1218, 1160, 1097.

Mass (ESI): m/z 377 $[M]^+$, 375, 234, 144 (100%), 114.

HRMS (ESI): calcd for $C_{19}H_{21}BrO_3Na$ $[M + Na]^+$ 399.0566 found 399.0564.

HPLC conditions: Chiralpak IA column, 1.0% isopropyl alcohol–hexane, UV = 254 nm, flow = 0.5 mL min^{-1}. R_t = 10.9 min (*R*,*R*,*S*)-**14b** and R_t = 11.4 min (*R*,*R*,*R*)-**14b**.

Synthesis of (1*R*,2*R*)-2-(naphthalen-2-yloxy)cyclohexyl-2-chlorobutanoate (14c)

The title compound was obtained by following the same procedure as that for (*R*,*R*,*S*)-**11** from alcohol (*R*,*R*)-**3** and 2-chlorobutanoic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in a colorless oil. (0.14 g, 97%) de = 50%.

$[\alpha]_D^{25}$ = 9.63 (c = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) diastereomeric mixture: δ ppm 7.79–7.73 (m, 3H), 7.47–7.43 (m, 1H), 7.37–7.33 (m, 1H), 7.26–7.24 (m, 1H), 7.17–7.12 (m, 1H), 5.16–5.10 (m, 1H, –C*H*OCO–), 4.49–4.44 (m, 1H, –C*H*OAr), 4.14–4.09 (m, 1H, $-C_\alpha H$), 2.29–2.17 (m, 1H), 2.16–2.13 (m, 1H), 1.92–1.79 (m, 4H), 1.68–1.54 (m, 3H), 1.50–1.39 (m, 2H), 0.94–0.91 (t, J = 7.2 Hz, 3H, major diastereomer), 0.89–0.85 (t, J = 7.2 Hz, 3H, minor diastereomer).

^{13}C NMR ($CDCl_3$, 100 MHz) major diastereomer: δ ppm 169.0, 155.8, 134.5, 129.5, 129.2, 127.6, 126.8, 126.7, 126.4, 126.3, 123.8, 119.6, 119.5, 108.9, 75.7, 59.2, 29.5, 29.4, 28.4, 23.0, 22.9, 10.4.

IR (KBr) ν cm^{-1}: 3057, 2939, 1738, 1628, 1464, 1388, 1180, 1081.

HRMS (ESI): calcd for $C_{20}H_{23}ClO_3Na$ $[M + Na]^+$ 369.1233 found 369.1228.

HPLC conditions: Chiralcel OD-H column, 1.5% isopropyl alcohol–hexane, UV = 254 nm, flow = 0.5 mL min^{-1}. R_t = 11.8 min major isomer and R_t = 12.3 min minor isomer.

Synthesis of (1*R*,2*R*)-2-(naphthalen-2-yloxy)cyclohexyl-2-bromobutanoate (14d)

The title compound was obtained by following the same procedure as that for (*R*,*R*,*S*)-**11** from alcohol (*R*,*R*)-**3** and 2-bromobutanoic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in a colorless oil. (0.16 g, 98%) de = 40%.

$[\alpha]_D^{25}$ = +2.13 (*c* = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) diastereomeric mixture: δ ppm 7.78–7.74 (m, 3H), 7.74–7.43 (m, 1H), 7.37–7.33 (m, 1H), 7.26–7.24 (m, 1H), 7.17–7.13 (m, 1H), 5.15–5.09 (m, 1H, –C*H*OCO–), 4.49–4.45 (m, 1H, –C*H*OAr), 4.12–4.08 (t, *J* = 7.2 Hz, 1H, –C$_\alpha$*H*, major diastereomer), 4.02–3.99 (t, *J* = 7.2 Hz, 1H, –C$_\alpha$*H*, minor diastereomer), 2.29–2.25 (m, 1H), 2.17–2.13 (m, 1H), 2.0–1.80 (m, 5H), 1.80–1.71 (m, 1H), 1.66–1.60 (m, 4H), 1.58–1.48 (m, 2H), 1.46–1.27 (m, 2H), 0.92–0.90 (t, *J* = 7.2 Hz, 3H, major diastereomer), 0.87–0.83 (t, *J* = 7.2 Hz, 3H, minor diastereomer).

^{13}C NMR ($CDCl_3$, 100 MHz) major diastereomer: δ ppm 169.1, 155.8, 134.5, 129.5, 127.6, 126.7, 126.4, 123.8, 119.6, 108.9, 75.7, 47.9, 29.6, 29.3, 28.3, 23.1, 23.0, 11.6.

IR (KBr) ν cm^{-1}: 3057, 2936, 1736, 1629, 1465, 1387, 1216, 1156, 1053.

HRMS (ESI): calcd for $C_{20}H_{23}BrO_3Na$ $[M + Na]^+$ 413.0723 found 413.0720.

HPLC conditions: Chiralpak IC column, 0.8% isopropyl alcohol–hexane, UV = 254 nm, flow = 0.5 mL min^{-1}. R_t = 11.2 min major isomer and R_t = 11.7 min minor isomer.

Synthesis of (1*R*,2*R*)-2-(naphthalen-2-yloxy)cyclohexyl-2-chloro-3-methylbutanoate (14e)

The title compound was obtained by following the same procedure as that for (*R*,*R*,*S*)-**11** from alcohol (*R*,*R*)-**3** and 2-chloro-3-methylbutanoic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in a colorless oil. (0.14 g, 98%) de = 42%.

$[\alpha]_D^{25}$ = +3.63 (*c* = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) diastereomeric mixture: δ ppm 7.78–7.73 (m, 3H), 7.47–7.43 (m, 1H), 7.37–7.33 (m, 1H), 7.25–7.22 (m, 1H), 7.16–7.10 (m, 1H), 5.15–5.10 (m, 1H, –C*H*OCO–), 4.49–4.36 (m, 1H, –C*H*OAr), 4.07–4.05 (d, *J* = 6.8 Hz, 1H, minor diastereomer), 4.02–4.00 (d, *J* = 6.8 Hz, 1H, major diastereomer), 2.30–2.22 (m, 1H), 2.20–2.13 (m, 2H), 1.85–1.80 (m, 2H), 1.54–1.13 (m, 3H), 0.96–0.95 (d, *J* = 6.8 Hz, 3H), 0.94–0.92 (d, *J* = 6.8 Hz, 3H, major diastereomer), 0.91–0.89 (d, *J* = 6.8 Hz, 3H, minor diastereomer).

^{13}C NMR ($CDCl_3$, 100 MHz) major diastereomer: δ ppm 168.8, 155.7, 134.5, 129.5, 129.1, 127.6, 126.7, 126.3, 123.8, 119.6, 108.9, 75.7, 64.6, 32.6, 29.7, 29.5, 23.1, 22.9, 19.5, 18.1.

IR (KBr) ν cm^{-1}: 3058, 2939, 1744, 1629, 1466, 1390, 1217, 1120, 1019.

HRMS (ESI): calcd for $C_{21}H_{25}ClO_3Na$ $[M + Na]^+$ 383.1384 found 383.1384.

HPLC conditions: Chiralpak IC column, 0.8% isopropyl alcohol–hexane, UV = 254 nm, flow = 0.5 mL min^{-1}. R_t = 12.4 min major isomer and R_t = 13.1 min minor isomer.

Synthesis of (1*R*,2*R*)-2-(naphthalen-2-yloxy)cyclohexyl-2-bromo-3-methylbutanoate (14f)

The title compound was obtained by following the same procedure as that for (*R*,*R*,*S*)-**11** from alcohol (*R*,*R*)-**3** and 2-bromo-3-methylbutanoic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in a colorless oil. (0.16 g, 96%) de = 46%.

$[\alpha]_D^{25}$ = −7.13 (*c* = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) diastereomeric mixture: δ ppm 7.78–7.73 (m, 3H), 7.47–7.43 (m, 1H), 7.39–7.33 (m, 1H), 7.25–7.23 (m, 1H), 7.16–7.12 (m, 1H), 5.14–5.09 (m, 1H, –C*H*OCO–), 4.49–4.44 (ddd, *J* = 12.4, 5.8, 4.4 Hz, 1H, –C*H*OAr), 3.97–3.95 (m, 1H, C$_\alpha$*H*), 2.30–2.26 (m, 1H), 2.18–2.09 (m, 1H), 1.85–1.80 (m, 2H), 1.63–1.60 (m, 1H), 1.50–1.43 (m, 3H), 1.02–1.00 (d, *J* = 6.4 Hz, 3H, –C*H*$_3$), 0.93–0.91 (d, *J* = 6.4 Hz, 3H, –C*H*$_3$, major diastereomer), 0.90–0.89 (d, *J* = 6.4 Hz, 3H, minor diastereomer).

^{13}C NMR ($CDCl_3$, 100 MHz) major diastereomer: δ ppm 168.8, 155.7, 134.5, 129.4, 129.1, 127.6, 126.7, 126.3, 123.7, 119.6, 118.8, 75.5, 55.1, 32.3, 29.4, 23.0, 22.9, 19.9, 19.8.

IR (KBr) ν cm^{-1}: 3057, 2939, 1737, 1629, 1466, 1389, 1252, 1216, 1152, 1053.

HRMS (ESI): calcd for $C_{21}H_{25}BrO_3Na$ $[M + Na]^+$ 427.0879 found 427.0883.

HPLC conditions: Lux amylose column, 2.5% isopropyl alcohol–hexane, UV = 254 nm, flow rate = 0.5 mL min^{-1}. R_t = 14.4 min (minor diastereomer), 16.0 min, (major diastereomer).

Synthesis of (1*R*,2*R*)-2-(naphthalen-2-yloxy)cyclohexyl-2-chloro-3-phenylpropanoate (14g)

The title compound was obtained by following the same procedure as that for (*R*,*R*,*S*)-**11** from alcohol (*R*,*R*)-**3** and 2-chloro-3-phenylpropanoic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in a colorless oil. (0.16 g, 94%) de = 43%.

$[\alpha]_D^{25}$ = +4.83 (*c* = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) diastereomeric mixture: δ ppm 7.78–7.71 (m, 3H), 7.47–7.43 (m, 1H), 7.37–7.33 (m, 1H), 7.27–7.01 (m, 2H), 7.21–7.14 (m, 1H), 7.13–7.01 (m, 2H), 5.11–5.06 (m, 1H, –C*H*OCO–), 4.47–4.41 (m, 1H, –C*H*OAr), 4.36–4.32 (dd, *J* = 7.2 Hz, 1H, C$_\alpha$*H*, major diastereomer), 4.30–4.27 (dd, *J* = 6.8 Hz, 1H, C$_\alpha$*H*, minor diastereomer), 3.26–3.22 (dd, *J* = 14.0, 6.8 Hz, 1H, major diastereomer), 3.14–3.12 (dd, *J* = 14.0, 6.8 Hz, 1H, minor diastereomer), 3.07–2.96 (m, 1H), 2.25–2.21 (m, 1H), 2.04–2.02 (m, 1H),

1.81–1.80 (m, 1H), 1.75–1.73 (m, 1H), 1.65–1.62 (m, 1H), 1.47–1.42 (m, 3H), 1.30–1.27 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) major diastereomer: δ ppm 168.7, 155.8, 135.9, 134.5, 129.5, 129.3, 128.5, 127.6, 127.2, 126.8, 123.8, 119.6, 109.1, 75.9, 57.7, 41.0, 29.4, 29.2, 22.9, 22.8. IR (KBr) ν cm^{-1}: 3059, 2748, 1741, 1628, 1460, 1253, 1215, 1145, 1026.

HRMS (ESI): calcd for $C_{25}H_{25}ClO_3Na$ $[M + Na]^+$ 431.1389 found 431.1386.

HPLC conditions: Chiralcel OD H column, 1.0% isopropyl alcohol–hexane, UV = 254 nm, flow = 0.5 mL min^{-1}. R_t = 23.1 min major isomer and R_t = 24.3 min minor isomer.

Synthesis of (1*R*,2*R*)-2-(naphthalen-2-yloxy)cyclohexyl-2-bromo-3-phenylpropanoate (14h)

The title compound was obtained by following the same procedure as that for (*R*,*R*,*S*)-**11** from alcohol (*R*,*R*)-**3** and 2-bromo-3-phenylpropanoic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in a colorless oil. (0.17 g, 92%) de = 38%.

$[\alpha]_D^{25}$ = −7.0 (c = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) diastereomeric mixture: δ ppm 7.78–7.70 (m, 3H), 7.48–7.43 (m, 1H), 7.38–7.32 (m, 1H), 7.27–7.11 (m, 6H), 7.06–7.01 (m, 1H), 5.13–5.04 (m, 1H, –C*H*OCO–), 4.48–4.47 (m, 1H, –C*H*OAr, major diastereomer), 4.46–4.44 (m, 1H, –C*H*OAr, minor diastereomer), 4.34–4.30 (dd, J = 8.4, 7.2 Hz, 1H, C$_\alpha$*H*, major diastereomer), 4.24–4.20 (dd, J = 6.8 Hz, 1H, C$_\alpha$*H*, minor diastereomer), 3.38–3.33 (dd, J = 14.0, 8.4 Hz, 1H, major diastereomer), 3.26–3.20 (dd, J = 14.0, 8.4 Hz, 1H, minor diastereomer), 3.16–3.09 (m, 1H), 2.27–2.23 (m, 1H), 2.22–2.13 (m, 1H), 2.03–2.00 (m, 1H), 1.82–1.80 (m, 1H), 1.76–1.72 (m, 1H), 1.46–1.42 (m, 3H), 1.30–1.26 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) major diastereomer: δ ppm 168.9, 155.9, 136.7, 134.5, 129.5, 129.1, 128.6, 127.7, 126.8, 126.4, 123.8, 119.7, 108.9, 75.6, 45.8, 41.1, 29.3, 29.0, 22.9, 22.8. IR (KBr) ν cm^{-1}: 3058, 2939, 1739, 1628, 1462, 1388, 1255, 1174, 1050.

HRMS (ESI): calcd for $C_{25}H_{25}BrO_3Na$ $[M + Na]^+$ 475.0885 found 475.0879.

HPLC conditions: Chiralcel OD H column, 1.0% isopropyl alcohol–hexane, UV = 254 nm, flow = 0.5 mL min^{-1}. R_t = 20.3 min major isomer and R_t = 21.7 min minor isomer.

Synthesis of (1*R*,2*R*)-2-(naphthalen-1-yloxy)cyclohexyl-2-bromo-3-phenylacetate (14i)

The title compound was obtained by following the same procedure as that for (*R*,*R*,*S*)-**11** from alcohol (*S*,*S*)-**5** and 2-bromo-3-phenylacetic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in a white solid. (0.17 g, 95%).

M.p. 110–112 °C. de = 8%.

$[\alpha]_D^{25}$ = +61.6 (c = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) diastereomeric mixture: δ ppm 8.17–8.13 (m, 1H), 7.80–7.78 (m, 1H), 7.49–7.42 (m, 2H), 7.41–7.37 (m, 3H), 7.36–7.30 (m, 1H), 6.90–6.88 (d, J = 7.2 Hz, 1H, major diastereomer), 6.84–6.82 (d, J = 7.6 Hz, 1H, minor diastereomer), 5.31–5.26 (m, 1H, –C*H*OCO–), 5.27 (s, 1H), 5.25 (s, 1H), 4.54–4.49 (m, 1H, –C*H*OAr, major diastereomer), 4.47–4.42 (m, 1H, –C*H*OAr, minor diastereomer), 2.41–2.19 (m, 2H), 1.86–1.68 (m, 2H), 1.66–1.44 (m, 3H), 1.28–1.24 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) major diastereomer: δ ppm 167.9, 153.4, 135.7, 134.7, 128.9, 128.5, 127.3, 126.4, 126.3, 125.7, 125.3, 122.4, 120.5, 106.1, 75.8, 47.3, 29.2, 22.9, 22.8.

IR (KBr) ν cm^{-1}: 3063, 2948, 1726, 1576, 1456, 1398, 1274, 1182, 1096.

HRMS (ESI): calcd for $C_{24}H_{23}BrO_3$ $[M + Na]^+$ 461.0723 found 461.0717.

HPLC conditions: Chiralpak IC column, 1.0% isopropyl alcohol–hexane, UV = 254 nm, flow = 0.5 mL min^{-1}. R_t = 14.2 min major isomer and R_t = 14.9 min minor isomer.

Synthesis of (1*R*,2*R*)-2-(naphthalen-2-yloxy)cyclohexyl-(*R*)-2-bromo-3-phenylacetate (*R*,*R*,*R*)-14j

The title compound was obtained by following the same procedure as that for (*R*,*R*,*S*)-**11** from alcohol (*R*,*R*)-**3** and 2-bromo-3-phenylacetic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in a white solid. (0.18 g, 98%).

M.p. 80–82 °C. de = 65%.

$[\alpha]_D^{25}$ = −37.5 (c = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) after crystallization: δ ppm 7.78–7.76 (d, J = 8.0 Hz, 1H), 7.71–7.66 (m, 2H), 7.47–7.43 (m, 1H), 7.38–7.34 (m, 3H), 7.20–7.14 (m, 4H), 6.99–6.96 (m, 1H), 5.26 (s, 1H, –C$_\alpha$*H*), 5.16–5.11 (m, 1H, –C*H*OCO–), 4.42–4.36 (m, 1H, –C*H*OAr), 2.20–2.18 (m, 2H), 1.81–1.80 (m, 2H), 1.58–1.51 (m, 2H), 1.49–1.37 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 167.7, 155.7, 134.3, 129.3, 129.1, 129.0, 128.6, 128.5, 127.6, 126.8, 126.3, 123.7, 119.5, 108.9, 47.2, 29.5, 29.3, 23.0, 22.9.

IR (KBr) ν cm^{-1}: 3058, 2933, 1746, 1626, 1461, 1352, 1283, 1141, 1057.

MS: 461.1 $[M + Na]^+$, 413.2.

HRMS (ESI): calcd for $C_{24}H_{24}BrO_3$ (M + H) 439.0903 found 439.0901.

HPLC conditions: Chiralpak IA column, 1.0% isopropyl alcohol–hexane, UV = 254 nm, flow = 0.5 mL min^{-1}. R_t = 18.7 min (*R*,*R*,*R*-**14j**) and R_t = 19.8 min (*R*,*R*,*S*-**14j**).

Synthesis of (1*R*,2*R*)-2-(naphthalen-2-yloxy)cyclohexyl-2-chloro-3-phenylacetate (14k)

The title compound was obtained by following the same procedure as that for (*R*,*R*,*S*)-**11** from alcohol (*R*,*R*)-**3** and 2-chloro-3-phenylacetic acid. The mixture was filtered and concentrated under vacuum. The crude mixture was further purified by column chromatography on silica gel with 10% ethyl acetate/petroleum ether resulting in a colorless oil. (0.16 g, 94%) de = 34%.

$[\alpha]_D^{25}$ = +4.73 (*c* = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) diastereomeric mixture: δ ppm 7.80–7.73 (m, 2H), 7.70–7.66 (m, 1H), 7.49–7.45 (m, 1H), 7.43–7.32 (m, 4H), 7.27–7.22 (m, 2H), 7.16–7.09 (m, 2H), 5.29 (s, 1H, –$C_\alpha H$, major diastereomer), 5.23 (s, 1H, $C_\alpha H$, minor diastereomer), 5.23–5.09 (m, 1H, –C*H*OCO–), 4.47–4.41 (m, 1H, –C*H*OAr, major diastereomer), 4.38–4.30 (m, 1H, –C*H*OAr, minor diastereomer), 2.26–2.06 (m, 2H), 1.83–1.71 (m, 2H), 1.64–1.50 (m, 1H), 1.48–1.36 (m, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) major diastereomer: δ ppm 167.6, 155.7, 135.8, 134.4, 129.4, 129.1, 129.0, 128.7, 127.8, 127.6, 126.7, 126.3, 123.7, 119.5, 108.9, 76.0, 59.3, 29.4, 29.1, 23.0, 22.9, 22.8.

IR (KBr) ν cm^{-1}: 3058, 2935, 1752, 1628, 1453, 1351, 1016, 840.

HRMS (ESI): calcd for $C_{24}H_{23}ClO_3Na$ $[M + Na]^+$ 417.1233 found 417.1219.

HPLC conditions: Chiralpak IC column, 1.5% isopropyl alcohol–hexane, UV = 254 nm, flow = 0.5 mL min^{-1}. R_t = 15.2 min major isomer and R_t = 17.2 min minor isomer.

General procedure for hydrolysis of esters: hydrolysis of (1*R*,2*R*)-2-(naphthalen-2-yloxy)cyclohexyl (*S*)-2-chloropropanoate (*R*,*R*,*S*)-11

Into a two neck round bottom flask, fitted with a guard tube and condenser, containing freshly prepared chiral ester (*R*,*R*,*S*)-**11** (0.5 g, 1.5 mmol) in dioxane (8 mL), was added conc. HCl (0.3 mL) and heated at 50 °C for 24 h. The reaction mixture was then concentrated under vacuum and subjected to column chromatography on silica gel. The alcohol was eluted with 10% ethyl acetate/petroleum ether as a white solid (0.33 g, 93%). ee > 99%. The acid was eluted with 30% ethyl acetate/petroleum ether as a colorless liquid (0.14 g, 91%). ee > 99% $[\alpha]_D^{25}$ = 13.9 (neat).[11]

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the Council of Scientific and Industrial Research (CSIR), New Delhi for the award of Senior Research Fellowship to ANK, DST-PURSE for the purchase of Single Crystal X-Ray Diffraction and DST-FIST of the NMR machine.

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20 Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Centre [CCDC 1854338, 1854339, 1854340, 1854341, 1854342 and 1854344].†