Resolution of (RS)-Binol through co-crystal formation with 3-n-propyl-4-((RS)-1′-phenylethylamino)butanoic acid

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A method for the optical resolution of (RS)-Binol to obtain optically pure (S)-Binol (99% ee) through co-crystal formation with (RS)-3-n-propyl-4-((S)-1′-phenylethylamino)butanoic acid (3RS, 1′S) and similarly optically pure (R)-Binol (99% ee) through co-crystal formation with (RS)-3-n-propyl-4-((R)-1′-phenylethylamino)butanoic acid (3RS,1′R), in high yield is reported. The individual co-crystal of optically pure (S)-3-n-propyl-4-((S)-1′-phenylethylamino)butanoic acid (3S,1′S) (99% ee) with (S)-Binol, and (R)-3-n-propyl-4-((S)-1′-phenylethylamino)butanoic acid (3R,1′S) (90% ee) with (S)-Binol have been analyzed by single crystal X-ray diffraction to understand hydrogen bonding in the crystal structure and the chiral recognition parameters.

Keywords: Co-crystal, resolution, Binol, γ-amino acid

Both optically pure (S)-(−)-1,1′-bi-2-naphthol ((S)-Binol) and (R)-(+)1,1′-bi-2-naphthol ((R)-Binol) have wide applications in synthetic chemistry and are used as building blocks for the manufacture of several important chemicals including natural products. They are used as chiral auxiliaries in asymmetric synthesis and enantioselective reduction, catalytic asymmetric Diels-Alder reactions, ene reactions, asymmetric Michael additions, alkylations, oxidations, epoxidations, Henry reactions, etc. Recently, optically active Binol has been used for resolution of active pharmaceutical compounds such as omeprazole, lamivudine, and as a chiral shift reagent. Other uses of optically pure Binol include the preparation of BINAP, a very useful chiral diphosphine ligand developed by Noyori, chiral 1,1′-binaphthyls, chiral crown ethers, chiral stationary phases for HPLC, chiral chromogenic receptors, and chiral materials for nonlinear optics.

The synthesis of enantiomerically pure (R) or (S)-Binol has been investigated with essentially two major approaches, resolution and asymmetric synthesis. Asymmetric synthesis involves the oxidative coupling of 2-naphthol in the presence of chiral vanadium and iron catalysts, but these methods are not feasible on an industrial scale. Generally, resolution of (RS)-Binol has been carried out by employing the following strategies: (a) enzymatic kinetic resolution of the appropriate derivative of (RS)-Binol; (b) through esterification of racemic (RS)-Binol with the appropriate tri-basic acid, such as phosphoric or boric acid followed by resolution through diastereomeric salt formation with optically active amines; (c) conglomerate crystallization of an appropriate derivative of (RS)-Binol; and (d) co-crystal formation with suitable coformers. However, none of the above mentioned processes has been found to be attractive in terms of efficiency, cost and scalability.

A co-crystal is defined as a crystal structure that contains two different molecules in the same crystal lattice. There is no ionic interaction between the molecules in a co-crystal and both molecules are solids at ambient temperature and pressure.
In the present work, homologous series of novel compounds of 3-alkyl-4-(1′-phenylethylamino)butanoic acid i.e. γ-amino butyric acid derivatives were synthesized and evaluated for the resolution of (RS)-Binol via co-crystal formation. Among the homologs studied, (S)-3-n-propyl-4-((S)-1′-phenylethylamino)butanoic acid (3S,1′S), (R)-3-n-propyl-4-((S)-1′-phenylethylamino)butanoic acid (3R,1′S), and (RS)-3-n-propyl-4-((S)-1′-phenylethylamino)butanoic acid (3RS,1′S) formed a co-crystal with (S)-Binol. Similarly, 3-(R)-n-propyl-4-((R)-1′-phenylethylamino)butanoic acid (3R,1′R), (S)-3-n-propyl-4-((R)-1′-phenylethylamino)butanoic acid (3S,1′R), and (RS)-3-n-propyl-4-((R)-1′-phenylethylamino)butanoic acid (3RS,1′R) formed a co-crystal with (R)-Binol. Single crystal X-ray analysis of individual co-crystal of optically pure (S)-3-n-propyl-4-((S)-1′-phenylethylamino)butanoic acid (3S,1′S) with optically pure (S)-Binol and (R)-3-n-propyl-4-((S)-1′-phenylethylamino)butanoic acid (3R,1′S) (90% ee) with optically pure (S)-Binol was carried out to understand hydrogen bonding, chiral recognition, and molecular packing.

Results and Discussions

Synthesis of 3-alkyl-4-(1′-phenylethylamino)butanoic acids [γ-amino butyric acid derivatives]

5-Hydroxy-4-R-5H-furan-2-one22 (I, R = H, alkyl) was reacted with (S or R)-(α)-methyl benzyl amine (IIa/IIb) to give the corresponding 1,5-dihydro-pyrrol-2-one derivatives (IIIa/IIIb). Hydrogenation gave the diastereomeric products IVa-d which were separated by fractional crystallization (Figure 1). Synthesis of homologues of 3-alkyl-4-(1′-phenylethylamino)butanoic acids i.e. γ-amino butyric acid derivatives [IVa-d] are reported in experimental section.

Co-crystals of γ-amino butyric acid derivatives IVa-d and optically pure Binol

Derivatives of γ-amino butyric acid [compounds IVa-d] were evaluated towards the co-crystal formation with optically pure Binol. It was observed that only the compound having propyl chain yielded good quality crystals and high optical purity of
product. Hence, \(n\)-propyl (\(R = n\)-Pr) series was investigated in detail for resolution of (RS)-Binol to obtain optically pure Binol and their single crystal structures are discussed in detail.

Resolution of (RS)-Binol through co-crystal formation

Optically pure compound IVa4 (3S,1’S, 99% ee) was treated with (S)-Binol in methanol at 40°C to give a crystalline precipitate (Figure 2a), having sharp DSC melting point at 182.68°C; compound IVb4 (3R,1’S, 90% ee) similarly gave a crystalline product (Figure 2b) with (S)-Binol, having sharp DSC melting point at 175.17°C. However, the same compounds IVa4 or IVb4 gave no precipitate with (R)-Binol in methanol at 40°C; a clear solution was observed. IVc4 (3R,1’R) and IVd4 (3S,1’R) gave the opposite results: solid complexes with (R)-Binol and clear solution with (S)-Binol. The physical properties of co-crystals are summarized in Table I. The compounds IVa4 to IVd4 of \(n\)-propyl series are thus useful for the resolution of (RS)-Binol through co-crystal formation to obtain optically pure (S)-Binol or (R)-Binol by suitable choice of co-formers.

Compound IVb4 (90% ee) containing 5% of compound IVa4 as impurity was used to obtain the co-crystal with (S)-Binol which showed a product ratio of 90:10 by HPLC. Single crystals were isolated by slow evaporation of a methanol solution. HPLC analysis of the single crystal showed IVb4:IVa4 ratio of 65:35, and this was confirmed by single crystal X-ray analysis. The co-crystal with (S)-Binol is a solid-solution with 0.65 and 0.35 site occupancy factor (s.o.f.) of IVb4 and IVa4 by site occupancy of least squares refinement of atoms. Thus, a diastereomeric mixture of IVa4 and IVb4 was used for the resolution of (RS)-Binol to obtain optically pure (S)-Binol in 99% ee. Similarly, a mixture of IVc4 and IVd4 gave optically pure (R)-Binol in 99% ee. Eliminating the step involving physical separation of diastereomers IVa4/IVb4 and IVc4/IVd4, makes the present process (summarized in Figure 3) inexpensive, efficient, green, and scalable.

Single crystal X-ray analysis

The co-crystal structures were analyzed on Bruker Smart Apex CCD X-ray diffractometer using Cu-Kα radiation at 100 K and detailed crystal analysis data is given in Tables II and III.

The single crystals of co-crystal of compound IVa4 with (S)-Binol were isolated by slow evaporation of a methanol solution of compound IVa4 and (S)-Binol (1:1 ratio). The X-ray crystal structure in orthorhombic \(P2_12_12_1\) space group (Table II) contains one molecule each of IVa4 and (S)-Binol (Figure 4). O–H···O hydrogen bonds between the O–H donor of (S)-Binol with the carboxylate acceptor of compound IVa4 (Table III) (O1–H1⋯O3’, 1.66 Å, 174.6° and O2–H2⋯O4’, 2.22 Å, 122.9°), intramolecular N+−H⋯O hydrogen bond (N1’−H1A⋯O4’, 1.79 Å, 157.1°) and intermolecular N+−H⋯O hydrogen bonding (N1’−H1A⋯O3’, 1.79 Å, 174.9°) between ionic NH2 group and carboxylate group form a ring motif R2(13) (Figure 5, molecule packing diagram). This motif continues along the b-axis assisted by C–H⋯O hydrogen bonds (C23–H23⋯O1, 2.44 Å, 122.4°; C27–H27⋯O2, 2.43 Å, 148.4°; and C33–H33B⋯O3’, 2.50 Å, 131.6°). The absolute
Table I — Physical and powder XRD data of co-crystals

<table>
<thead>
<tr>
<th>Co-crystal</th>
<th>DSC $T_{\text{peak}}$ (°C) (@ 10 °C/min heating rate)</th>
<th>$\left[\alpha\right]_{D}^{20}$ (°) (c 1 in MeOH)</th>
<th>Solubility in MeOH at 33 °C (g/100 mL)</th>
<th>PXRD lines at 2θ (°) (Cu-Kα = 1.5 Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound IVc4 – (R)-Binol</td>
<td>182.54</td>
<td>(+)17.02</td>
<td>3.85</td>
<td>9.34, 10.35, 12.18, 15.51, 17.55, 17.86, 17.96, 20.37, 21.76, 22.54, 24.53 and 27.24, 27.79, 31.34, 33.59, 34.49 and 35.46</td>
</tr>
</tbody>
</table>

Figure 3 — Process for the resolution of (RS)-Binol through co-crystal formation to give (S)-Binol or (R)-Binol in excellent enantiomeric excess.
Table II — Crystal data and X-ray structure refinement of co-crystals

<table>
<thead>
<tr>
<th></th>
<th>Co-crystal of <strong>IVa</strong> (99% ee) with (S)-Binol</th>
<th>Co-crystal of <strong>IVb</strong> (90% ee) with (S)-Binol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>C_{35}H_{37}NO_{4}</td>
<td>C_{35}H_{37}NO_{4}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>535.66</td>
<td>535.66</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Orthorhombic</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>P_{2_1}2_1</td>
<td>P_{2_1}2_1</td>
</tr>
<tr>
<td>T/ K</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>a/ Å</td>
<td>10.0289(3)</td>
<td>9.9317(5)</td>
</tr>
<tr>
<td>b/ Å</td>
<td>11.2460(3)</td>
<td>11.0600(7)</td>
</tr>
<tr>
<td>c/ Å</td>
<td>25.6127(9)</td>
<td>26.3136(14)</td>
</tr>
<tr>
<td>α/ °</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>β/ °</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>γ/ °</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>V/ Å³</td>
<td>2888.71(16)</td>
<td>2890.4(3)</td>
</tr>
<tr>
<td>D_{calc}/ g cm(^{-3})</td>
<td>1.232</td>
<td>1.231</td>
</tr>
<tr>
<td>μ/ mm(^{-1})</td>
<td>0.631</td>
<td>0.631</td>
</tr>
<tr>
<td>Reflns. collected</td>
<td>11458</td>
<td>10064</td>
</tr>
<tr>
<td>Observed reflns.</td>
<td>5092</td>
<td>5106</td>
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<tr>
<td>Total reflns.</td>
<td>5628</td>
<td>5444</td>
</tr>
<tr>
<td>R(_1)(I&gt;2σ(I))</td>
<td>0.0340</td>
<td>0.0392</td>
</tr>
<tr>
<td>wR(_2)(all)</td>
<td>0.0865</td>
<td>0.1005</td>
</tr>
<tr>
<td>Flack parameter</td>
<td>0.01(15)</td>
<td>0.1(2)</td>
</tr>
<tr>
<td>Goodness-of-fit</td>
<td>0.987</td>
<td>1.093</td>
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</table>

Table III — Hydrogen bond interactions

<table>
<thead>
<tr>
<th>Interaction</th>
<th>H⋯A /Å</th>
<th>D⋯A /Å</th>
<th>θ /º</th>
<th>Symmetry code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-crystal of <strong>IVa</strong> (99% ee):(S)-Binol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O(1)−H(1)−O(3)</td>
<td>1.66</td>
<td>2.645(2)</td>
<td>174.6</td>
<td>1-x, -1/2+y, 1/2-z</td>
</tr>
<tr>
<td>N(1)−H(1A)−O(3)</td>
<td>1.79</td>
<td>2.793(2)</td>
<td>174.9</td>
<td>1-x, -1/2+y, 1/2-z</td>
</tr>
<tr>
<td>N(1)−H(1B)−O(4)</td>
<td>1.79</td>
<td>2.746(2)</td>
<td>157.1</td>
<td>Intramolecular</td>
</tr>
<tr>
<td>O(2)−H(2)−O(4)</td>
<td>2.22</td>
<td>2.875(2)</td>
<td>122.9</td>
<td>x, y, z</td>
</tr>
<tr>
<td>C(23)−H(23)−O(1)</td>
<td>2.44</td>
<td>3.157(2)</td>
<td>122.4</td>
<td>1-x, 1/2+y, 1/2-z</td>
</tr>
<tr>
<td>C(27)−H(27)−O(2)</td>
<td>2.43</td>
<td>3.403(2)</td>
<td>148.4</td>
<td>1-x, -1/2+y, 1/2-z</td>
</tr>
<tr>
<td>C(33)−H(33B)−O(3)</td>
<td>2.50</td>
<td>3.316(2)</td>
<td>131.6</td>
<td>1-x, -1/2+y, 1/2-z</td>
</tr>
<tr>
<td>Co-crystal of <strong>IVb</strong> (90% ee):(S)-Binol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O(1)−H(1)−O(3)</td>
<td>1.70</td>
<td>2.661(2)</td>
<td>165.8</td>
<td>1-x, 1/2+y, 1/2-z</td>
</tr>
<tr>
<td>N(1)−H(1A)−O(4)</td>
<td>1.72</td>
<td>2.716(2)</td>
<td>167.2</td>
<td>Intramolecular</td>
</tr>
<tr>
<td>N(1)−H(1B)−O(4)</td>
<td>1.75</td>
<td>2.748(2)</td>
<td>168.7</td>
<td>1-x, -1/2+y, 1/2-z</td>
</tr>
<tr>
<td>O(2)−H(2)−O(4)</td>
<td>2.09</td>
<td>2.831(2)</td>
<td>130.7</td>
<td>x, y, z</td>
</tr>
<tr>
<td>C(23)−H(23)−O(1)</td>
<td>2.38</td>
<td>3.182(3)</td>
<td>129.2</td>
<td>1-x, -1/2+y, 1/2-z</td>
</tr>
<tr>
<td>C(27)−H(27)−O(2)</td>
<td>2.39</td>
<td>3.355(3)</td>
<td>147.2</td>
<td>1-x, 1/2+y, 1/2-z</td>
</tr>
</tbody>
</table>
**Figure 4** — ORTEP diagram of co-crystal of compound IVa4 and S-Binol

**Figure 5** — Molecule Packing Diagram of co-crystal of IVa4 with (S)-Binol. (a) Infinite chains formed by hydrogen bonded Rigidity motif between IVa4 with(S)-Binol runs along b-axis. (b), (c) Such infinite chains are inter-connected by C−H⋯π interactions to complete the 3D packing. Non-hydrogen bonded hydrogen atoms are removed for clarity.
**Figure 6** — ORTEP diagram of co-crystal of compound IVb4 and S-Binol. Hydrogen atoms on the disordered components were removed for clarity.

**Figure 7** — Molecule Packing Diagram of co-crystal of IVb4 with (S)-Binol. (a) Hydrogen bonded $R_{2}^{2}(13)$ ring motif formed between molecules IVb4 and (S)-Binol runs along the $b$-axis forming an infinite chain. Such infinite chains are interconnected by various C–H–π interactions to complete the 3D packing (b), (c). Minor component of the disorder and non-hydrogen bonded hydrogen atoms were removed for clarity.
Table IV — Equivalent isotropic thermal parameters

<table>
<thead>
<tr>
<th>Atom</th>
<th>B (Å²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C29A</td>
<td>0.0276(8)</td>
</tr>
<tr>
<td>C30A</td>
<td>0.0267(8)</td>
</tr>
<tr>
<td>C31A</td>
<td>0.0368(9)</td>
</tr>
<tr>
<td>C32A</td>
<td>0.0430(10)</td>
</tr>
<tr>
<td>C34A</td>
<td>0.0295(8)</td>
</tr>
<tr>
<td>C29B</td>
<td>0.0253(14)</td>
</tr>
<tr>
<td>C30B</td>
<td>0.0273(14)</td>
</tr>
<tr>
<td>C31B</td>
<td>0.0387(9)</td>
</tr>
<tr>
<td>C32B</td>
<td>0.0422(18)</td>
</tr>
<tr>
<td>C34B</td>
<td>0.0331(15)</td>
</tr>
</tbody>
</table>

Table V — Bond distances involving the disordered atoms

<table>
<thead>
<tr>
<th>Atom</th>
<th>Bond Distance (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C28 — C29A</td>
<td>1.432(4) Å</td>
</tr>
<tr>
<td>C28 — C29B</td>
<td>1.796(6) Å</td>
</tr>
<tr>
<td>C29A — C30A</td>
<td>1.538(4) Å</td>
</tr>
<tr>
<td>C29A — C34A</td>
<td>1.550(4) Å</td>
</tr>
<tr>
<td>C30A — C31A</td>
<td>1.528(5) Å</td>
</tr>
<tr>
<td>C31A — C32A</td>
<td>1.53(5) Å</td>
</tr>
<tr>
<td>C29B — C30B</td>
<td>1.537(8) Å</td>
</tr>
<tr>
<td>C29B — C34B</td>
<td>1.557(8) Å</td>
</tr>
<tr>
<td>C30B — C31B</td>
<td>1.539(8) Å</td>
</tr>
<tr>
<td>C31B — C32B</td>
<td>1.510(9) Å</td>
</tr>
</tbody>
</table>

configuration of IVa4 was found to be (S,S) in the crystal structure with Flack parameter 0.01(15). Since there are no heavy atoms the estimated standard deviation of Flack parameter is high.

**Co-crystal of compound IVb4 (90% ee) with (S)-Binol**

Single crystal obtained from above co-crystal was analyzed as a co-crystal of solid solution of compound IVb4 and IVa4 with (S)-Binol in the orthorhombic space group P2₁2₁2₁ (Table II). It is isostructural with co-crystal IVa4:(S)-Binol (Figure 6) and their PXRD line patterns are identical. O−H···O hydrogen bonds from O−H donor of (S)-Binolto carboxylate acceptor (Table III) (O1−H1···O3², 1.70 Å, 165.3°; O2−H2···O4³, 2.09 Å, 130.7°), intramolecular and intermolecular N−H···O− hydrogen bond (N1−H1B···O3², 1.75 Å, 168.7°; intra N1¹−H1A···O4⁴, 1.72 Å, 167.2°) between ionic NH2 and carboxylic group form ring motif R²(13) (Figure 7). The disorder in the solid-solution co-crystal can be represented at 5 carbons (C29, C30, C31, C32 and C34) (Table IV and V) whereas C29 is the chiral center, and the disordered atoms are C29A and C29B with site occupancy factor 0.641(5) and 0.359 (5) respectively indicating the presence of 64% compound IVb4 and 36% compound IVa4.

It is reported⁵ that chiral enrichment can take place during the formation of co-crystal solid solution and that the chiral enrichment depends on several factors. Individual single crystals of solid solutions can have different chiral compositions.

**Experimental Section**

**Materials and Methods**

All commercially available reagents and solvents were employed without prior purification. Reactions were monitored by thin layer chromatography on silica gel plates (Merck 60 F254) and stained by the use of potassium permanganate solution.

**Analytical Methods**

The enantiomeric excess (ee) was determined by HPLC using a Shimazu LC 2010 system equipped with a chiral column (Chiral Pak IA, 4.6 mm × 250 mm, 5 μm), column oven temperature 40°C and UV visible detector (230 nm). Mobile phase was n-hexane (94) : n-butanol (5) : ethanol (1) : trifluoroacetic acid (0.3 mL) with flow rate 1 mL·min⁻¹, injection volume 20 μL. The diastereomeric excess (de) was determined by HPLC using a Shimadzu LC 2010 system equipped with a chiral column (Chiral Pak IA, 4.6 mm × 250 mm, 5 μm), column oven temperature 40°C and UV visible detector (230 nm). Mobile phase was determined by HPLC using a Shimadzu LC 2010 system equipped with a chiral column (Chiral Pak IA, 4.6 mm × 250 mm, 5 μm), column oven temperature 40°C and UV visible detector (230 nm). Mobile phase was 200 MHz or 400 MHz on Bruker instrument with CDCl₃ as solvent. Chemical shifts (δ) are given in ppm relative to TMS (δ= 0 ppm). IR spectra were recorded on Perkin Elmer Spectrum 100 and absorption bands are given in cm⁻¹. DSC was recorded on Perkin Elmer Diamond DSC at heating rate of 10°C min⁻¹. Solubility measurements were performed on HEL Auto-lab instrument with turbidity probe. Powder X-ray diffraction was recorded on PANalytical BV Netherlands model PN3040/60 X'Pert Pro. Single crystal X-ray data were collected using Oxford Diffraction Ltd. (Version 1.171.33.55) using Cu-Kα radiation (λ = 1.5 Å) at 100 K to ascertain the absolute correctness of the assigned configuration by Flack parameter. Data reduction was performed using CrysAlisPro, Oxford Diffraction Ltd., Version 1.171.33.55. OLEX2-1.0¹ and SHELXTL 97² were used to solve and refine the data. All non-hydrogen atoms were refined anisotropically. C−H hydrogen bond lengths were fixed and N−H and O−H hydrogen bond lengths were located from difference electron density map. Disorder in co-crystal of IVb4: (S)-Binol was modeled by using PART command and s.o.f. (site occupancy factor) was assigned for the two parts using FVAR command. DFIX, SIMU and DELU commands were used to stabilize the disorder.
General process for synthesis of 3-alkyl-4-(1'-phenylethylamino)butanoic acid

5-Hydroxy-4-alkyl-5H-furan-2-one22 (70.5 mmol) was dissolved in i-PrOH (100 mL) and α-methyl benzyl amine (70.5 mmol) was added to it at RT. The mixture was stirred at RT for 1 h and then transferred to a Parr autoclave reactor followed by addition of 50% wet palladium-on-carbon (Pd/C) at 10% catalyst loading. Reactor was purged with hydrogen gas twice and then 3 kg/cm² hydrogen pressure was maintained. Reaction was monitored by TLC [chloroform: methanol (9:1)]. After complete consumption of starting material, the reaction was stopped. In the reaction, diastereomers got separated. After completion of reaction, the reaction mixture was filtered and filtrate was concentrated under vacuum to obtain a semi solid material, which was suspended in cyclohexane (300 mL) and stirred overnight to yield one diastereomer of the desired compound.

Filtered cake contained Pd/C which was suspended in 50 mL methanol and stirred for 20 min to dissolve respective compound and Pd/C was separated by filtration. Filtrate was concentrated under vacuum to obtain the other diastereomer of the desired compound.

**Compound IVa3**: IR: 2960, 1623, 1547 cm⁻¹; ¹H NMR(200 MHz, CDCl₃, Me₂Si): δ 0.84-0.86 (t, 3H), 1.13-1.18 (q, 2H), 1.21-1.26 (q, 2H), 1.69-1.70 (d, 3H), 2.14-2.18 (d, 2H), 2.51-2.58 (t, 2H), 2.75-2.78 (d, 1H), 4.12-4.17 (q, 1H), 7.35-7.42 (m, 3H), 7.47-7.51 (m, 2H); EI-MS: m/z for C₁₂H₁₅NO₂: 207.13; [M+H]⁺: 208.20; DSC T_peak (°C) (@ 10°C/min heating rate): 80; PXRD (Cu-Kα, 40 mA, 45 kV): 20 8.53, 13.5, 15.52, 16.28, 18.16, 19.89, 20.79, 21.56, 27.44, 28.89, 33.88 and 34.90°.

**Compound IVa4**: IR: 2960, 1623, 1547 cm⁻¹; ¹H NMR(200 MHz, CDCl₃, Me₂Si): δ 0.90-0.91 (d, 4H), 1.46-1.48 (d, 1H), 1.69-1.72 (t, 4H), 2.18-2.224 (m, 3H), 2.30-2.36 (m, 3H), 2.74-2.77 (d, 1H), 4.08-4.19 (m, 2H), 7.35-7.42 (m, 3H), 7.47-7.51 (m, 2H); ¹³C NMR (50 MHz, CDCl₃, Me₂Si): δ 20.3, 20.7, 28.2, 46.0, 52.4, 57.6, 127.4, 128.7, 129.1, 138.0, 179.2; EI-MS: m/z for C₁₃H₂₃NO₂: 221; [M+H]⁺: 221.90; DSC T_peak (°C) (@ 10°C/min heating rate): 93; PXRD (Cu-Kα, 40 mA, 45 kV): 20 8.63, 12.88, 15.38, 16.35, 16.93, 18.57, 19.06, 19.84, 20.97, 26.80 and 33.48°.

**Compound IVb3**: IR: 2960, 1623, 1547 cm⁻¹; ¹H NMR(200 MHz, CDCl₃, Me₂Si): δ 0.84-0.86 (t, 3H), 1.13-1.18 (q, 2H), 1.21-1.26 (q, 2H), 1.69-1.70 (d, 3H), 2.14-2.18 (d, 2H), 2.51-2.58 (t, 2H), 2.75-2.78 (d, 1H), 4.12-4.17 (q, 1H), 7.35-7.42 (m, 3H), 7.47-7.51 (m, 2H); EI-MS: m/z for C₁₂H₁₅NO₂: 235.17; [M+H]⁺: 236.05; DSC T_peak (°C) (@ 10°C/min heating rate): 125; PXRD (Cu-Kα, 40 mA, 45 kV): 20 7.63, 12.38, 14.38, 15.35, 16.21, 16.57, 19.98, 21.84, 26.80 and 36.48°.

**Compound IVb4**: IR: 2960, 1623, 1547 cm⁻¹; ¹H NMR(200 MHz, CDCl₃, Me₂Si): δ 0.84-0.86 (t, 3H), 1.13-1.18 (q, 2H), 1.21-1.26 (q, 2H), 1.69-1.70 (d, 3H), 2.14-2.18 (d, 2H), 2.51-2.58 (t, 2H), 2.75-2.78 (d, 1H), 4.12-4.17 (q, 1H), 7.35-7.42 (m, 3H), 7.47-7.51 (m, 2H); ¹³C NMR(50 MHz, CDCl₃, Me₂Si): δ 14.0, 19.8, 21.2, 32.7, 36.5, 44.2, 51.1, 57.4, 127.4, 128.6, 129.2, 138.9, 179.3; EI-MS: m/z for C₁₃H₂₃NO₂: 249.17; [M+H]⁺: 250.20; DSC T_peak (°C) (@ 10°C/min heating rate): 147; PXRD (Cu-Kα, 40 mA, 45 kV): 29 7.66, 10.44, 15.09, 16.55, 19.52, 22.33, 26.93 and 33.74°.

**Compound IVb4**: IR: 2956, 1619, 1549, 1400 cm⁻¹; ¹H NMR(200 MHz, CDCl₃, Me₂Si): δ 0.76-0.79 (t, 3H), 1.14-1.23 (m,4H), 1.66-1.68 (d, 3H), 2.26-2.30 (m, 2H), 2.53-2.59 (t, 2H), 2.77-2.80 (d, 1H), 4.06-4.11 (q, 1H), 7.31-7.57 (m, 5H); ¹³C NMR(50 MHz, CDCl₃, Me₂Si): δ 14.0, 19.7, 20.5, 33.2, 36.2, 43.7, 51.6, 58.5, 127.5, 128.6, 129.2, 137.8, 179.5; EI-MS: m/z for C₁₃H₂₃NO₂: 249.17; [M+H]⁺: 250.05; DSC T_peak (°C) (@ 10°C/min heating rate): 120; PXRD

**Compound IVc4**: IR: 2952, 2925, 2854, 1716, 1599, 1462, 1382, 1257, 1155, 747, 733 cm⁻¹; ¹H NMR(200 MHz, CDCl₃, Me₂Si): δ 0.37-0.88 (t, 2H), 1.15-1.22 (m, 4H), 1.47-1.52 (m, 1H), 1.71-1.76 (m, 2H), 2.18-2.34 (m, 2H), 2.45-2.55 (m, 2H), 2.73-2.79 (d, 1H), 4.36-4.50 (q, 1H), 5.21, 5.48, 7.22, 7.25, 7.40, 9.93. ¹³C NMR(50 MHz, CDCl₃, Me₂Si): δ 19.8, 21.2, 23.6, 25.8, 29.2, 30.8, 36.5, 40.8, 51.1, 57.5, 127.5, 137.4, 137.9, 179.5; EI-MS: m/z for C₆H₅NO₂⁻: 249.17; [M+H⁺]: 250.26; DSC T_peak (°C) (@ 10°C/min heating rate): 121°; PXRD (Cu-Kα, 40 mA, 45 kV): 20 6.62, 7.52, 11.48, 14.97, 17.09, 17.60, 19.69, 22.23, 22.72 and 26.26°.

**Compound IVd4**: IR: 3435, 2955, 1552, 1399, 702 cm⁻¹; ¹H NMR(200 MHz, CDCl₃, Me₂Si): δ 0.81-0.92 (t, 2H), 1.46-1.52 (m, 1H), 1.71-1.77 (m, 2H), 2.12-2.39 (m, 2H), 2.45-2.55 (m, 2H), 2.74-2.80 (d, 1H), 4.11-4.20 (q, 1H), 7.30-7.40 (m, 5H); ¹³C NMR(50 MHz, CDCl₃, Me₂Si): δ 14.0, 19.8, 21.2, 23.6, 25.8, 29.2, 30.8, 36.5, 40.8, 51.1, 57.5, 127.4, 128.6, 129.2, 138.2, 179.2; EI-MS: m/z for C₆H₅NO₂⁻: 249.17; [M+H⁺]: 250.26; DSC T_peak (°C) (@ 10°C/min heating rate): 121°; PXRD (Cu-Kα, 40 mA, 45 kV): 20 6.62, 7.52, 11.48, 14.97, 17.09, 17.60, 19.69, 22.23, 22.72 and 26.26°.

**Resolution of (RS)-Binol via formation of dia stereomeric co-crystals by sequential addition of compound IVa4 and IVb4 and compound IVc4 and IVd4**

(RS)-Binol (19.7 g, 68.88 mmol) was dissolved in methanol (100 mL) and compound IVa4 and IVb4 (8.6 g, 34.5 mmol) was added to it at RT. The mixture was stirred at 60°C for 1 h, during which time solid precipitate came out from the reaction mixture. Reaction mixture was allowed to cool to 15°C and filtered under reduced pressure to obtain 15.1 g (82% yield) of the crude co-crystal, which was further purified by recrystallization from methanol to obtain pure co-crystal (14.5 g).

The co-crystal was suspended in the biphasic mixture of ethyl acetate (100 mL) and 1N hydrochloric acid (50 mL) and stirred for 30 to 45 min to decompose the co-crystal. Aqueous phase was washed with ethyl acetate (2 × 20 mL). Organic phase was mixed together and washed with brine, followed by drying over anhydrous sodium sulfate. Solvent was evaporated under vacuum to obtain optically pure (S)-Binol (7.1 g, 72% isolated yield, 99% ee).

The acid aqueous solution which contained hydrochloride salt of compound IVa4 and IVb4 was neutralized with dilute solution of sodium bicarbonate to recover the compound IVa4 and IVb4 (6.5 g, 76% isolated yield).

Compound IVc4 and IVd4 (8.6 g, 34.5 mmol) was added to the filtrate at RT. The mixture was stirred at 60°C for 1 h, during which time solid precipitate came out from the reaction mixture. Reaction mixture was allowed to cool to 15°C and filtered under reduced pressure to obtain 14.3 g (76% isolated yield) of co-crystal.

The co-crystal was suspended in the biphasic mixture of ethyl acetate (100 mL) and 1N hydrochloric acid (50 mL) and stirred for 30 to 45 min to decompose the co-crystal. Aqueous phase was washed with ethyl acetate (2 × 20 mL). Organic phases were mixed together and washed with brine, followed by drying over anhydrous sodium sulfate. Solvent was evaporated under vacuum to obtain optically pure (R)-Binol (6.7 g, 68% isolated yield, 99% ee).

The acid aqueous solution which contains hydrochloride salt of compound IVc4 and IVd4 was neutralized with dilute solution of sodium bicarbonate to recover the compound IVc4 and IVd4 (6.3 g, 74% isolated yield).

**Large scale resolution of (RS)-Binol via co-crystal formation with diastereomeric mixture of compound IVa4 and IVb4**

Compound IVa4 and IVb4 (870 g, 3.49 mol) was dissolved in methanol (4250 mL) and (RS)-Binol (1000 g, 3.49 mol) was added to it at RT. The mixture was stirred at 50°C for 2 h, during which time solid precipitate came out from the reaction mixture. Reaction mixture was allowed to cool to RT and filtered under reduced pressure to obtain 760 g (82% isolated yield) of co-crystal.

Co-crystal (760 g) was suspended in methanol (1500 mL) and stirred at 50°C for 2 h, after which,
reaction mixture was cooled to RT and filtered under reduced pressure to obtain 620 g of solid co-crystal. Co-crystal (620 g) was suspended in the biphasic mixture of ethyl acetate (2000 mL) and 1N hydrochloric acid (2000 mL) and stirred for 30 to 45 min to decompose the co-crystal. Aqueous phase was washed with 200 mL ethyl acetate. Organic phases were mixed together and washed with brine, followed by drying over anhydrous sodium sulfate. Solvent was evaporated under vacuum to obtain optically pure (S)-Binol (350 g, 70% yield) of 99% ee by chiral HPLC analysis.

Conclusion

An efficient method for the resolution of (RS)-Binol to its optically pure enantiomers has been developed in 75% isolated yield having 99% ee. This method has the advantage that both the optically pure enantiomers are recovered by simple dissociation of the co-crystal in ethyl acetate and aqueous HCl biphasic mixture (10%). The resolving agent is easy to prepare and can be recycled. Single crystal analysis of co-crystal provides the information about the chiral recognition and hydrogen bond interactions.

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