Tetrahedron: *Asymmetry* xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Benzyl isobornyl amines: a simple and practical class of NMR discriminating agents for effective chiral recognition of acids

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ARTICLE INFO

Article history:
Received 18 June 2017
Revised 29 July 2017
Accepted 8 August 2017
Available online xxxx

Dedicated to the memory of Howard Flack

ABSTRACT

The design and synthesis of a few simple *N*-benzyl derivatives of isobornyl amine is presented. The derivatives have been assessed as chiral solvating agents for effective discrimination of the signals of some acids in NMR analysis. The single crystal X-ray analysis of the salts of (*R*)-mandelic acid with two of the title derivatives help to understand the supramolecular interactions and assign the induced chemical shifts in ^{1}H NMR analysis. The title derivative is found to be suitable for quantitative determination of the enantiomeric excess of unknown enantiomeric purity as well as being efficient in resolving racemic mandelic acid.

1. Introduction

The determination of enantiomeric purity of chiral samples is a critical aspect of modern research in asymmetric synthesis. The specific properties of chiral compounds are associated with their optical information and hence establishing the degree of purity as well as their configurations in a quick and reliable manner has acquired much importance. Moreover, the rapid and accurate determination of the enantiomeric purity of the products can help in the optimization of the selective synthesis of chiral molecules. The purity of the chiral material can be established by analyzing the ratio of enantiomers of the sample by different techniques ranging from chromatography,[1] mass spectrometry,[2] IR, UV and fluorescence spectroscopy,[3] CD and electrophoresis.[4] For precise analysis these techniques need certain structural aspects or specific functional groups in the analyte. On the other hand, additional accessories, such as special HPLC or GC stationary chiral columns or additives in the mobile phase are needed for the chromatography.

Nuclear magnetic resonance (NMR) spectroscopy offers another solution for the fast, accurate and reliable determination of the enantiomeric purity of chiral molecules.[5] Nevertheless, the normal NMR analysis of enantiomerically pure molecules in an achiral environment, such as usual NMR solvents, cannot discriminate the signals of the two enantiomers. For a convenient determination of the NMR discrimination, the test sample of enantiomers needed to be derivatized to diastereomers, either by permanent covalent bond formation or temporary non-covalent interactions. The traditional technique of *in situ* preparation of diastereomeric lanthanide chelate complexes is one widely used procedure.[6] This may also be achieved by the use of chiral derivatizing agents[7] for the formation of diastereomeric compounds.[8] The diastereomer formation during the NMR analysis can be done by simply mixing the analyte and the chiral solvating agent during the spectroscopic analysis.[9] The two components, the sample under study and the enantiomerically pure chiral solvating agent interact with each other possibly through non-covalent interactions, primarily hydrogen bonding, halogen bonding, π-stacking, van der Waals interactions etc. The effectiveness of a good chiral solvating agent to distinguish between the two isomers of an analyte should depend on the combination of these supramolecular forces and hence they are often case sensitive and selective in the action. Hence, there is always a constant need to modify the design of new derivatives of chiral solvating agents to effectively serve to analyze a wider range of analytes for NMR analysis. As a part of our studies on chiral compounds and their analysis we have synthesized and assessed several different types of chiral solvating agents, namely aza-macrocycles,[10] amides,[11] amines,[12] aminonaphthols[13] etc. In our previous study,[11a] we described the use of *N*-benzoyl isobornyl amine **I** as an effective chiral solvating agent for the chiral discrimination of various acids (Chart 1).

The compounds of Type I are derivatives of Kagan's amide,[14] which is one of the most effective chiral solvating agents studied

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http://dx.doi.org/10.1016/j.tetasy.2017.08.007
0957-4166/

Chart 1. Types of camphor derived chiral solvating agents.

for the discrimination of signals of many analytes. This is a simple molecule where an amide functional group is present to facilitate the formation of hydrogen-bonding, while the additional π–π interactions with analytes result in the *in situ* formation of a tight diastereomeric complex during the NMR analysis. Due to the neutral nature of **I**, it was necessary to add an external base for its effective use in the NMR analysis. The base enables the abstraction of the proton from the acidic analytes for suitable interactions for molecular recognition. To explore the possibility of overcoming this requirement, we have now designed another set of chiral solvating agents of the Type II, which are secondary amines and are basic in nature. Herein we report their synthesis, characterization and study as chiral solvating agent to perform molecular recognition and discrimination of acidic chiral substrates in NMR analysis.

2. Result and discussion

The molecules of Type II are essentially *N*-benzyl derivatives of isobornyl amine, which can be obtained in enantiomerically pure form from naturally occurring D-(+)-camphor **1**. Enantiomerically pure (−)-**1** was converted into its oxime **2** with hydroxyl amine hydrochloride-NaOH in ethanol–water, and then subjected to catalytic hydrogenation using Pd-C/H_2 at ambient conditions (Fig. 1).[15]

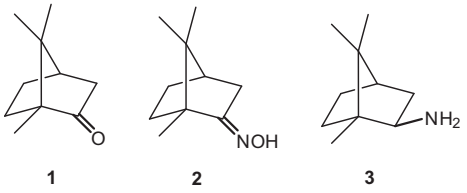
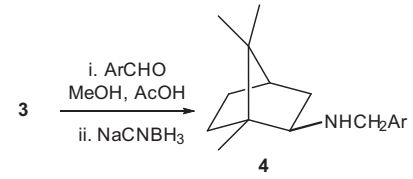


Figure 1. Camphor and its derivatives.

The *N*-benzyl derivatives of **4** were then prepared by converting isobornyl amine **3** into imines by reaction with aldehyde, which were directly reduced with sodium cyanoborohydride (Scheme 1).

A series of derivatives of **4** were synthesized (Chart 2), characterized by spectroscopic and analytical techniques and scanned as chiral solvating agents for the separation of signal of α-H of (±)-mandelic acid in ^{1}H NMR spectroscopy. The efficacy of amine **4** as a chiral solvating agent was studied with racemic mandelic acid as a standard substrate by ^{1}H NMR analysis in $CDCl_3$ at 20 mmol concentration. For all of the screened derivatives of **4**, the signal of α-hydrogen of mandelic acid, which was easily distinguishable from the rest of the signals was studied. Its position shifted considerably from its original value (without chiral solvating agent), where the change was expressed as an induced chemical shift (Δδ), while the separation of the signals due to the two *in situ* formed diastereomers was presented as chemical shift nonequivalence (ΔΔδ) (Table 1).

The considerable up-field shift of the signals (Δδ) suggest abstraction of the acidic hydrogen of mandelic acid by the base **4** and the formation of a salt between the two. The aberration to this



Scheme 1. Synthesis of *N*-benzyl isobornyl amine.

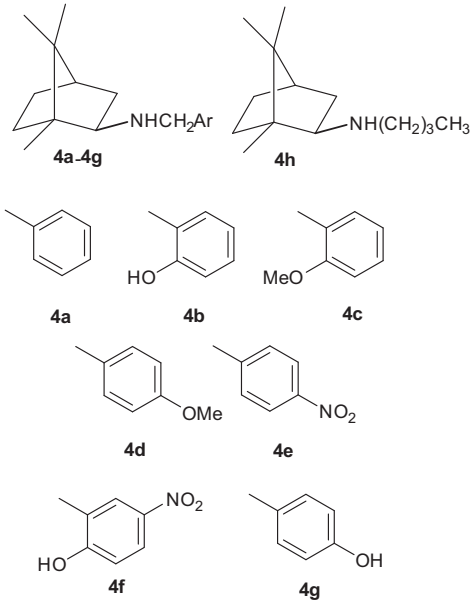


Chart 2. List of the synthesized ligands of Type II.

Table 1
Comparison of chiral solvating agents[a]

No	Amine **4**	Δδ[b]	ΔΔδ[c] (ppm)
1	**4a**	−0.269	0.019
2	**4b**	−0.267	0.013
3	**4c**	−0.399	No Separation
4	**4d**	−0.317	0.023
5	**4e**	−0.058	No Separation
6	**4f**	−0.270	0.005
7	**4g**	−0.156	0.010
8	**4h**	−0.343	0.022

[a] Conditions: mandelic acid:**4** (1:1), 20 mmol, $CDCl_3$, 400 MHz.
[b] Induced chemical shift.
[c] Nonequivalences.

observation was with **4e**, which had a strong electron withdrawing nitro substituent. The benzyl amine **4a** and the other amines with electron releasing substituents were seen to recognize the two enantiomers of the analyte and showed well resolved signals of α-H of mandelic acid on salt formation. The 4-methoxy derivative **4d** showed good resolution of the signals of α-H of mandelic acid, but its isomer, 2-methoxy **4c** failed completely. The substitution at the *ortho*-position showed an interesting effect. The 2-hydroxy derivative **4b** could resolve the signals of the α-H to a considerable extent, but its methyl ether 2-methoxy derivative **2c** could not recognize under identical conditions of analysis. The benzyl amines with nitro substitutions were not very effective in the discrimination of the signals due to poor recognition.

The molecular recognition of the chiral analyte through the two diastereomer pairs with chiral solvating agent involves the combination of supramolecular interactions. The formation of the

carboxylate anion was confirmed when the carbonyl stretch (1716 cm^{-1} for mandelic acid) disappeared in the FT-IR spectra of its mixture with **4a** and **4b**, and the new strong peaks appeared at 1600 and 1616 cm^{-1} respectively (the COO^- stretch).[12b] This may involve π–π interaction between the two aromatic moieties of mandelic acid and the benzyl ligand. However, the aliphatic derivative **4h** also showed a good ability of recognition towards mandelic acid. This may be attributed to the hydrogen bonding and lateral interactions between alkyl chain protons and analyte molecule.

Furthermore, we have extended the scope of amine ligands as chiral solvating agents for other chiral analytes. Ligand **4d**, employed as chiral solvating agent, shows moderate enantiomeric recognition for α-halo-phenylacetic acid derivatives **5a** and **5b**, respectively ($\Delta\Delta\delta$ = 0.008 ppm for both). However, the chiral solvating agent **4d** shows a good baseline separation in the case of 2-chloromandelic acid **6** (0.019 ppm) (Fig. 2), whereas α-halo derivatives of 2-chlorophenylacetic acid **7a** and **7b** show moderate chemical shift non-equivalence (0.008 and 0.009 ppm respectively). Chiral 1,1′-binaphthyl-2,2′-diol (BINOL) **8a** and its derivatives have recently gained significant importance in the field of asymmetric synthesis.[16] Despite its widespread applications, only a few chiral solvating agents are known to enantiodiscriminate BINOL and its derivatives.[17,12b] Herein, we have employed ligand **4d** for the chiral recognition of BINOL. The NMR experiment showed only a marginal shift in proton signal of BINOL without any splitting. The structurally similar 2,2′,7,7′-tetrahydroxy-1,1′-binaphthol (tetrol) **8b** has also been utilized in asymmetric synthesis.[18] Tetrol **8b**, on the contrary, shows better separation (0.020 ppm) with ligand **4d** (Fig. 2). This may be due to the presence of accessible hydroxyl groups, which may exhibit better hydrogen bonding interactions with ligand **4d** as compared to BINOL (Chart 3).

In order to establish the application of ligands as chiral solvating agent for determination of enantiomeric purity of analytes, the enantiomeric purities of various scalemic samples of mandelic acid were determined by integration of proton signals for α-H of mandelic acid in the presence of ligand **4a**. Figure 3b indicates that ligand **4a** maintains resolution for non-racemic samples of mandelic acid. The plot of *ee* values of mandelic acid obtained by ^1H NMR and by gravimetric analysis shows a linear relationship with R^2 = 0.999. The stoichiometry of the diastereomeric complexes formed between chiral solvating agent **4a** and mandelic acid was determined by Job method of continuous variations. The Job's plot

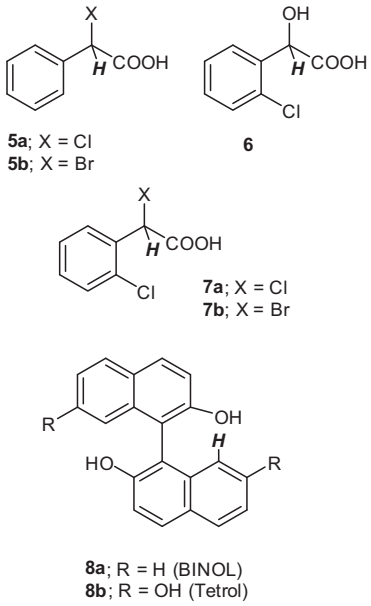


Chart 3. The other acids scanned as analytes.

indicates a maxima at 0.5 which clearly suggests a 1:1 complex under these conditions (Fig. 3c).

Previously our group has been successful in solving the crystal structures of diastereomeric salts of roof shaped amine chiral solvating agent with both the enantiomers of mandelic acid.[12b] In a similar attempt to investigate the interactions responsible for the activity of ligands as chiral solvating agent, the crystal structure for salts of ligand **4a** with (*R*)-mandelic acid and ligand **4b** with (*R*)-mandelic acid were solved. The crystal of salt of ligand **4a** with (*R*)-mandelic acid crystallizes in the orthorhombic chiral space group $P2_12_12_1$ (Fig. 4). The shorter bond length of the (C–O) bond (1.24–1.25 Å) of the carboxylate indicates salt formation via proton transfer from (*R*)-mandelic acid to ligand **4a**. The assembly shows amine ligand **4a** linked with mandelic acid through (NH···O) hydrogen bond (2.538 Å) between amine and (C–O) of carboxylate. The amine ligand shows another hydrogen bond between amine (NH···O) (2.072 Å) and mandelic acid. The acid shows further (CO···H–O) hydrogen bond (1.859 Å) with another molecule of mandelic acid.

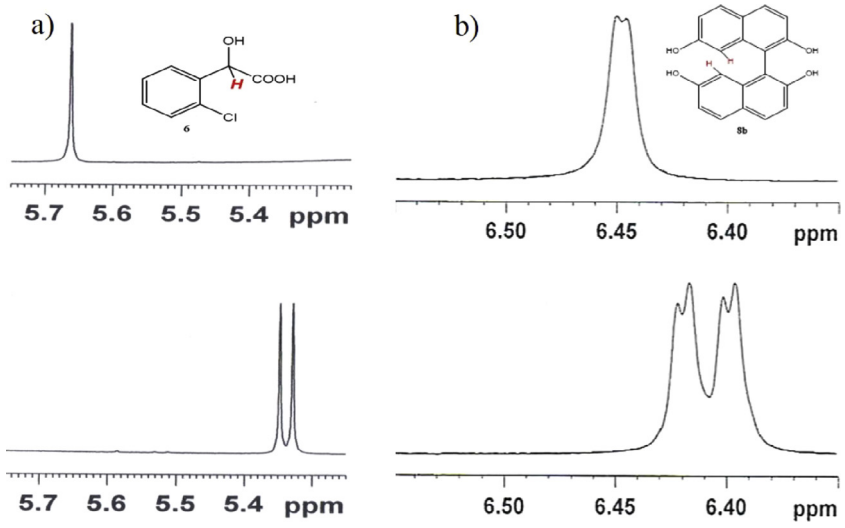


Figure 2. Selected region of ^1H NMR spectra (a) **6** blank (top) and **6** with **4d** (bottom); (b) **8b** blank (top) and **8b** and **4d** (bottom).

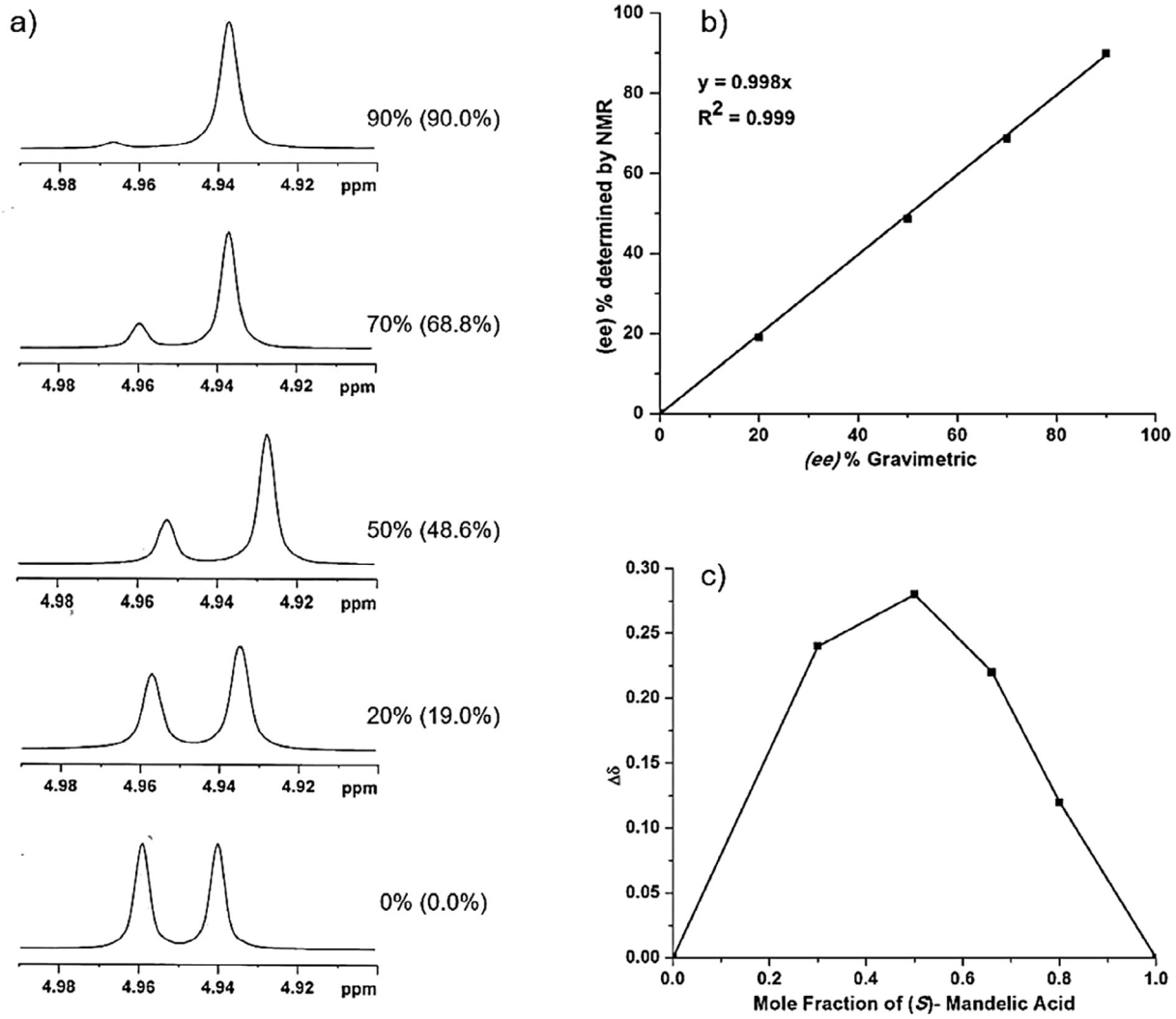


Figure 3. (a) Selected region of ^{1}H NMR spectra of scalemic mixture of mandelic acid in presence of **4a**; (b) correlation between theoretical and observed% *ee* values; (c) Job's plot for determination of stoichiometry of binding of mandelic acid and ligand **4a**.

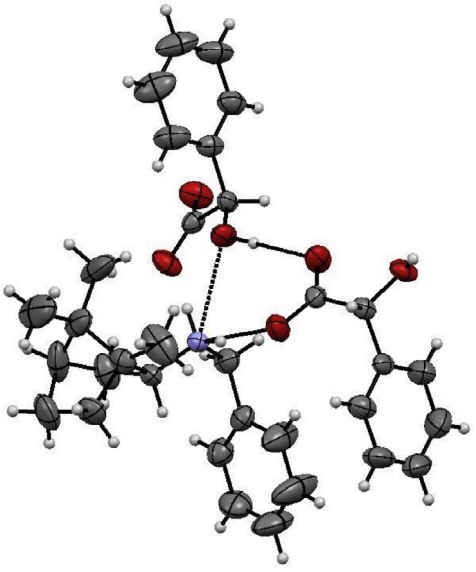


Figure 4. ORTEP diagram of salt between (*R*)-mandelic acid and **4a** (CCDC 1547307).

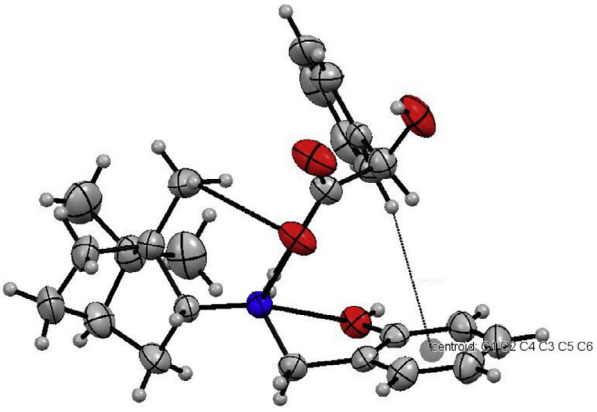
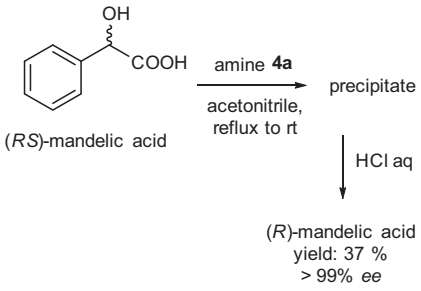


Figure 5. ORTEP diagram of salt between *R*-mandelic acid and **4b** (CCDC 1547308).

The interactions were further studied by growing crystals for the salt of ligand **4b** with (*R*)-mandelic acid. The salt crystalizes in orthorhombic chiral space group $P2_12_12_1$ (Fig. 5). The chiral solvating agent activity of ligand **4b** is moderate. However, the crystal of its salt with (*R*)-mandelic acid show interesting interactions. The



Scheme 2. Resolution of mandelic acid.

(C–O) bond length (1.22–1.25 Å) of carboxylate of mandelic acid is shorter as in case of salt of ligand **4a** with (*R*)-mandelic acid, thus confirming the proton transfer from mandelic acid to ligand **4b**. The assembly in salt shows ligand **4b** linked with two molecules of mandelic acid forming a trimeric assembly via two hydrogen bonds, one CH– π interaction and two CH–O interactions. The two hydrogen bonds are formed between the amine and hydroxyl group of ligand **4b** and mandelic acid. The bond lengths are 1.829 Å (NH···O2) and 1.743 Å (O–H···O3). The ligand also shows an intramolecular hydrogen bond with bond length 2.812 Å (NH···O1). The assembly is further linked by CH–π interaction between CH of phenyl ring of mandelic acid and 2-hydroxy phenyl ring of ligand **4b** with bond length of 3.242 Å. The methyl protons of isobornyl ring form CH–O interaction with O2 of mandelic acid having bond length of 2.671 Å also CH of 2-hydroxy-phenyl ring shows similar CH–O interaction with O3 of mandelic acid having bond length 2.569 Å. The hydrogen attached to chiral carbon of (*R*)-mandelic acid appears to be laying on the top of the aromatic ring of the ligand. The shortest perpendicular distance between the plane passing through this ring and the hydrogen is 3.416 Å. The attempts to grow crystals for salts of ligand **4a** as well as for ligand **4b** with (*S*)-mandelic acid were unsuccessful. Repeated attempts resulted in the formation of poor quality crystals of the salt, and were unsuitable for the diffraction.

The easy availability by simple and practical synthesis of ligand **4a** and its ability to recognize isomers of racemic mandelic acid, encouraged us to attempt its resolution. A solution of racemic mandelic acid was heated with ligand **4a** in acetonitrile and allowed to cool, resulting in the formation crystals of salt of (*R*)-mandelic acid and amine, which was then converted to free (*R*)-mandelic acid (37% Y; >99% ee) (Scheme 2).

3. Conclusion

Herein we have discussed the preparation of a series of *N*-benzyl isobornyl amines and scanned them as chiral solvating agents for the discrimination of signals of chiral acidic compounds in ^{1}H NMR analysis. We were able to study the supramolecular interactions between the chiral solvating agent and the acid moieties by analyzing the crystals of salts. The measurement of the enantiomeric purity of the analyte was accurate enough to be expended as a tool to determine the enantiomeric purity of unknown samples while the amines could be used as an effective resolving agents for separation of isomers of mandelic acid for the practical applications.

4. Experimental

4.1. General

Thin layer chromatography was performed on silica gel plates quoted on aluminum sheets. The spots were visualized under UV light or with iodine vapor. All compounds were purified by column chromatography on silica gel (60–120 mesh). All reactions were carried out under an inert atmosphere (nitrogen) unless other conditions are specified. NMR Spectra were recorded on a 400 MHz spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) with $CDCl_3$ as the solvent and TMS as the internal standard. Single crystal X-ray diffraction data was collected Xcalibur, Eos, Gemini diffractometer. Mass spectra were recorded on GCMS instrument in the direct injection EI-mode. IR Spectra were recorded as KBr pellets and specific optical rotations were measured on JACSO P-2000 polarimeter. Melting points were recorded in Thiele's tube using paraffin oil and are uncorrected.

5. General Procedures for the synthesis of *N*-benzyl amine ligands 4a–4g

In a 25 mL dry RB flask, a solution of (−)-*iso*-bornyl amine (0.250 g, 1.63 mmol) was dissolved in 10 mL anhydrous toluene. To this solution was added the appropriate aldehyde (1.8 mmol) and the reaction mixture was allowed to reflux for nearly 2–3 h until completion on TLC. The reaction mixture was distilled off under vacuum to remove the toluene. The mixture was then charged with methanol (10 mL), cooled to 0 °C and charged with sodium borohydride (3.6 mmol) and stirred for 30–60 min. The reaction mixture was then stirred at rt. The solvent was then evaporated under vacuum and the mixture was extracted from ethyl acetate (3 × 50 mL) and the combined extracts were washed with water (2 × 25 mL). The organic layer was dried over anhydrous sodium sulfate, evaporated under vacuum and then subjected to column chromatography on silica gel (ethyl acetate/hexane) to afford the desired amine.

5.1. (1*R*,2*R*,4*R*)-*N*-Benzyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine 4a[19]

Yield 72%. $[\alpha]_D^{28} = -82.6$ (*c* 1, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.33 (m, 4H), 7.29–7.26 (m, 1H), 3.82 (d, *J* = 13.2 Hz, 1H), 3.65 (d, *J* = 13.6 Hz, 1H), 2.65–2.62 (m, 1H), 1.76–1.50 (m, 5H), 1.33–1.31 (m, 1H), 1.13 (s, 3H), 1.10 (d, *J* = 9.6 Hz, 2H), 0.94 (s, 3H), 0.86 (s, 3H). IR (KBr): cm^{-1} 2983, 2827, 1606, 1492, 1471, 1386, 1371, 1122, 1028, 734, 696. MS (ESI): *m*/*z* 244.4.

5.2. 2-((((1*R*,2*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl)amino)methyl)phenol 4b[20]

Compound **4b** was prepared by same procedure as that of **4a**. Yield 67%. Mp 60 to 62 °C. $[\alpha]_D^{28} = -90.5$ (*c* 1, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (td, *J* = 8.0 Hz & 1.6 Hz, 1H), 7.01 (dd, *J* = 7.6 Hz & 1.6 Hz, 1H), 6.85 (dd, *J* = 8.4 Hz & 1.2 Hz,1 H), 6.79 (td, *J* = 7.6 Hz & 1.2 Hz, 1H), 4.02 (d, *J* = 13.6 Hz, 1H), 3.79 (d, *J* = 13.6 Hz, 1H), 2.63–2.60 (m, 1H), 1.80–1.69 (m, 5H), 1.16–1.10 (m, 2H), 0.99 (s, 3H), 0.97 (s, 3H), 0.86 (s, 3H). IR (KBr): cm^{-1} 3271, 2953, 2877, 2358, 2339, 1591, 1477, 1261, 1097, 748. MS (ESI): *m*/*z* 260.3.

5.3. (1*R*,2*R*,4*R*)-*N*-(2-Methoxybenzyl)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-amine 4c

5.3.1. Compound 4c was prepared by same procedure as that of 4a

Yield 71% $[\alpha]_D^{28} = -108.0$ (*c* 1, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 7.6 Hz, 1H), 7.27–7.23 (m, 1H), 6.96–6.92 (m, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 3.85 (s, 3H), 3.80 (d, *J* = 13.6 Hz, 1H), 3.66 (d, *J* = 14.0 Hz, 1H), 2.58–2.55 (m, 1H), 1.72–1.48 (m, 5H), 1.1 (s, 3H), 1.06 (d, *J* = 8.0 Hz, 2H), 0.91 (s, 3H), 0.84 (s, 3H). IR (KBr): cm^{-1} 2883, 2839, 1602, 1589, 1492, 1462, 1286, 1240, 1120, 1033, 750. MS (ESI): *m*/*z* 274.3.

5.4. (1*R*,2*R*,4*R*)-*N*-(4-Methoxybenzyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine 4d

Compound **4d** was prepared by same procedure as that of **4a**. Yield 76%. $[\alpha]_D^{28} = -85.57$ (*c* 1, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ7.26 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 3.82 (s, 3H), 3.73 (d, *J* = 13.2 Hz, 1H), 3.56 (d, *J* = 12.8 Hz, 1H), 2.61–2.58 (m, 1H), 1.73–1.52 (m, 5H), 1.52–1.50 (m, 5H), 1.49 (s, 3H), 1.28 (s, 3H). IR (KBr): cm^{-1} 2983, 2827, 1612, 1585, 1512, 1471, 1440, 1373, 1246, 1043, 823. MS (ESI): *m*/*z* 274.4.

5.5. (1*R*,2*R*,4*R*)-*N*-(4-Nitrobenzyl)-1,7,7-trimethylbicycle[2.2.1]heptan-2-amine 4e

Compound **4e** was prepared by same procedure as that of **4a**. Yield 81%. Mp. 156 to 159 °C. $[\alpha]_D^{28} = -29.5$ (*c* 1, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.4 Hz, 2H), 4.59 (d, *J* = 14.0 Hz, 1H), 4.36 (d, *J* = 14.0 Hz, 1H), 2.67–2.64 (m, 1H), 2.06–1.45 (m, 5H), 1.04 (s, 3H), 1.03 (s, 3H), 1.0–0.87 (m, 2H), 0.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ149.3, 146.8, 128.6, 123.5, 66.3, 51.9, 48.5, 46.8, 45.2, 38.8, 36.8, 27.3, 20.6, 20.5, 12.2. IR (KBr): cm^{-1} 3415, 2956, 2885, 2374, 1707, 1606, 1570, 1525, 1346, 1190, 1109, 856, 748, 696, 621. MS (ESI) *m*/*z*: 289.3. HRMS (TOF MS ES+): *m*/*z* calculated for $C_{17}H_{25}N_2O_2$ $[M+H]^+$: 289.1916; found; 289.1916.

5.6. 5-Nitro-2-((((1*R*,2*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl)amino)methyl)phenol 4f

Compound **4f** was prepared by same procedure as that of **4a**. Yield 77%. Mp 178 to 180 °C. $[\alpha]_D^{28} = -68.2$ (*c* 1, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (dd, *J* = 9.2 Hz & 2.8 Hz, 1H), 7.96 (d, *J* = 2.8 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 4.12 (d, *J* = 14.4 Hz, 1H), 3.91 (d, *J* = 14.4 Hz, 1H), 2.62–2.58 (m, 1H), 1.82–1.55 (m, 5H), 1.15–1.08 (m, 2H), 0.99 (s, 6H), 0.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ163.3, 139.8, 125.3, 124.4, 122.4, 116.6, 65.9, 50.7, 48.5, 46.9, 44.8, 37.9, 36.9, 26.9, 20.5, 20.4, 12.2. IR (KBr): cm^{-1} 3482, 2954, 2881, 1595, 1562, 1483, 1340, 1303, 1126, 1089, 831, 758. MS (ESI): *m*/*z* 305.4. HRMS (TOF MS ES+): *m*/*z* calculated for $C_{17}H_{25}N_2O_3$ $[M+H]^+$: 305.1865; found; 305.1867.

5.7. 4-((((1*R*,2*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl)amino)methyl)phenol 4g

Compound **4g** was prepared by same procedure as that of **4a**. Yield 72%. $[\alpha]_D^{28} = -75.1$ (*c* 1, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, *J* = 8.4 Hz, 2H), 6.70 (d, 8.4 Hz, 2H), 3.72 (d, *J* = 12.8 Hz, 1H), 3.56 (d, *J* = 12.8 Hz, 1H), 2.64–2.62 (m, 1H), 1.78–1.48 (m, 5H), 1.08 (d, *J* = 8.4 Hz, 2H), 1.06 (s, 3H), 0.90 (s, 3H), 0.83 (s, 3H). IR (KBr): cm^{-1} 3412, 2947, 2872, 2360, 2337, 1612, 1597, 1516, 1381, 1257, 1158, 1049, 985, 889, 819. MS (ESI): *m*/*z* 260.3.

5.8. (1*R*,2*R*,4*R*)-*N*-Butyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine 4h[21]

In a 25 mL dry RB flask containing a solution of (−)-*iso*-bornyl amine (0.250 g, 1.63 mmol) dissolved in anhydrous methanol 10 mL was added a catalytic amount of acetic acid. To this mixture was added butyraldehyde (0.141 g, 1.8 mmol) and the mixture was allowed to cool to 0 °C. The reaction mixture was then charged with sodium cyanoborohydride (0.206 g, 3.26 mmol) portionwise and continued to stir for 3 h at 0 °C. The reaction mixture was then stirred at rt for one hour. The solvent was then removed under vacuum and the residue was washed with sodium bicarbonate and extracted with dichloromethane (3 × 50 mL). The organic layer was dried with anhydrous sodium sulfate and distilled under vacuum. The crude product was column purified on a silica gel column with hexane/ethyl acetate. Yield 68%. $[\alpha]_D^{28} = -7.45$ (*c* 1, Chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.59–2.42 (m, 3H), 1.70–1.66 (m, 2H), 1.58–1.56 (m, 2H), 1.54–1.27 (m, 6H), 1.11–1.04 (m, 2H), 1.02 (s, 3H), 0.91 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 3H), 0.81 (s, 3H). IR (KBr): cm^{-1} 2983, 2827, 1608. MS (ESI): *m*/*z* 210.4.

Acknowledgments

We are grateful to the management of Apicore Pharmaceuticals for providing the access of the infrastructure and research facilities for this work. We thank DST-PURSE for the single crystal X-ray diffraction facility in the Faculty of Science and Council of Scientific and Industrial Research (CSIR), New Delhi for the award of fellowship to ANK and GMU.

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