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L-Menthol as new scaffold for designing chiral phase-transfer catalysts

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Abstract—We herein report, a new class of chiral phase-transfer catalysts derived from L-menthol. The moderately good enantioselectivity exhibited by these catalysts have been explained based on single crystal X-ray data and molecular modelling studies.

1. Introduction

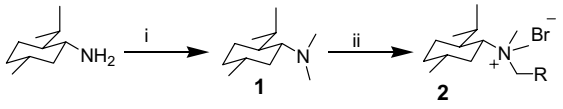
Since, the first successful chiral phase-transfer catalyst (PTC) was reported by Dolling,[1] their applications have increased many fold.[2] Many laboratories across the world are currently engaged in research in this area.[3]

However, most of the research in the development of chiral PTCs from the chirality pool is centered on cinchona alkaloids. Reports on high enantiomeric excess of up to 94% in *C*-alkylation reactions using prolinol derived chiral PTCs[4] had to be retracted on reinvestigation by Dehmlow et al.[5] Camphor based chiral PTCs yielded only 39% enantiomeric excess for similar reaction.[6] Thus, the initial efforts on shifting from cinchona alkaloids to other naturally occurring templates met with limited success. Recently, there have been reports of some successful catalysts based on tartaric acid derivatives.[7]

2. Results and discussion

We report herein, our initial findings in designing new chiral PTCs from naturally occurring L-menthol. Menthol and its derivatives have been widely used as chiral auxiliaries and chiral ligands in the field of asymmetric synthesis.[8] Due to its low cost and ease of availability of both enantiomers, it can be used as a versatile, chiral synthon.

For the preparation of quaternary ammonium salts from L-menthol, it was converted to L-menthylamine.[9] This amine was dimethylated using methyl iodide in 80% yield and was quaternalized with different alkyl halides (viz. benzyl bromide and 2-bromomethylnaphthalene). The quaternization was found to be very sluggish; taking almost 96 h for completion. However, the quaternary ammonium salts **2a** and **2b**, were obtained in good yields (Scheme 1). When the above catalysts were used in the benzylation of benzophenone imine *tert*-butyl glycinate **16**, the product was obtained with very poor enantioselectivites (Scheme 3, Table 1, entries 1–2).



a) R = Ph (80%), b) 2-Naphthyl (65%)

Scheme 1. Reagents and conditions: (i) MeI, KOH, CH_2Cl_2, 2 h, 80%; (ii) RBr, CH_3CN, 96 h.

Attempts at making *N*,*N*-dibenzyl salt **4** from *N*,*N*-dibenzyl menthylamine **3** were not successful (Scheme 2). We then converted this amine to the amide **5** using chloroacetyl chloride in presence of *N*,*N*-dimethylaniline in dichloromethane. Chloride **5** was first aminated using

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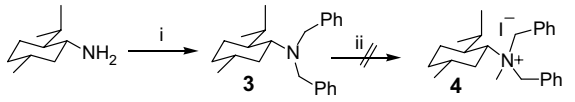
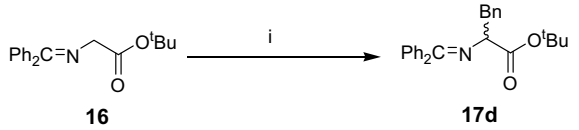
Table 1. Benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester

Entry	Catalyst	Time (h)	Yield[a] (%)	%Selectivity[b] (*R*:*S*)
1	**2a**	36	87	52:48
2	**2c**	32	83	52:48
3	**7**	15	89	62:34
4	**10**	6	87	83:17
5	**11**	2	94	74:26
6	**12**	12	88	74:26
7	**13**	7	80	63:37
8	**14**	8	82	81:19
9	**15**	8	78	81:19

[a] Yields of isolated product.
[b] Based on chiral HPLC using Chiralcel OD-H column.

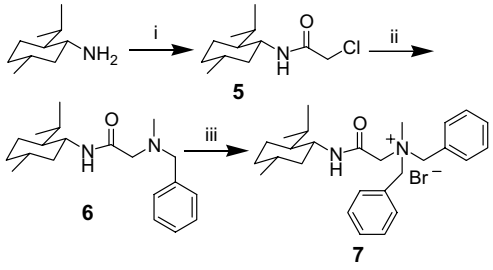


Scheme 2. Reagents and conditions: (i) BnBr, NEt_3, CH_2Cl_2, 4 h, 94%; (ii) MeI, CH_3CN.



Scheme 3. Reagents and conditions: (i) BnBr, cat. (10 mol %), 50% aq KOH, −20 °C.

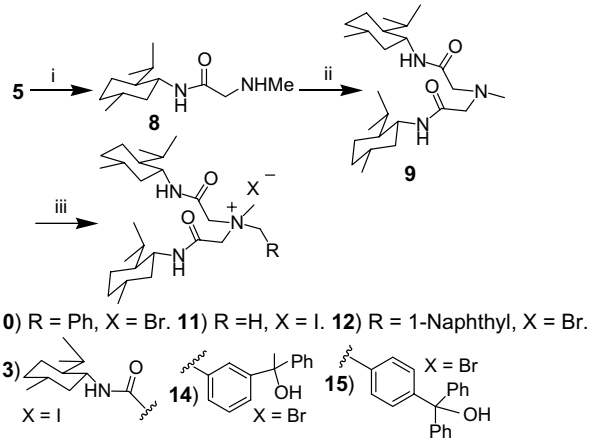
N-methylbenzyl amine to give **6** in 93% yield, which was quaternized with benzyl bromide to afford quaternary ammonium salt **7** in 92% yield (Scheme 4).



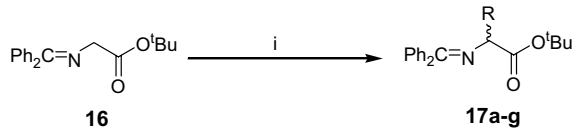
Scheme 4. Reagents and conditions: (i) chloroacetyl chloride, *N*,*N*-dimethylaniline, CH_2Cl_2, 3 h, 80%; (ii) *N*-methyl benzyl amine, K_2CO_3, CH_3CN, 2 h, 93%; (iii) BnBr, CH_3CN, 3 h, 92%.

Using **7** as PTC for the benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester, we obtained the benzylated product in 24% enantiomeric excess with a preference for the (*R*)-isomer (Table 1, entry 3).

Encouraged by the above results, we designed a catalyst having two menthyl units linked by an amide function following Scheme 5. Quaternization of compound **9** with benzyl bromide gave quaternary ammonium salt **10**, which further enhanced the level of enantioselectivity (83%, Table 1, entry 4).



Scheme 5. Reagents and conditions: (i) NH_2Me, 1,3-dioxane, 4 h, 90%; (ii) **5**, K_2CO_3, CH_3CN, 8 h, 93%, (iii) RCH_2X, CH_3CN.



Scheme 6. Reagents and conditions: (i) RBr, **10** (10 mol %), 50% aq KOH, −20 °C.

A systematic study of various quaternary groups on compound **9** was undertaken. Catalyst **11**, having *N*,*N*-dimethyl moieties decreased the enantioselectivity (74:26). Compound **12** with *N*,*N*-methyl(methylnaphthyl) groups showed similar enantiocontrol (74:26). The introduction of another L-menthyl unit linked through the amide bond as in catalyst **13** did not improve the enantioselectivity (Table 1, entry 7). Further, substitution on the phenyl ring as in catalysts **14** and **15** showed almost same level of selectivity (81:19, Table 1, entry 8 and 9). In all the above cases, the absolute stereochemistry of the benzylated product **17d** was found to be *R* as detected by chiral HPLC.[2]

Our endeavors at using L-menthol as a chiral synthon for developing a chiral phase-transfer catalyst has highlighted a few important points. Catalysts **7** and **10**–**15** are novel and though these catalysts are highly flexible, they seem to show significant stereoselectivity in alkylation reactions based on ion-pair mechanism. This suggested that the structure may have obtained some sort of rigidity by internal hydrogen bonding(s).

To understand how the groups are placed around the quaternary nitrogen atom, we decided to obtain X-ray crystal data (Fig. 1). Attempts at crystallizing the best catalyst **10** were unsuccessful; however, the dimethylated analogue **11** was crystallized from acetone. The crystal data of catalyst **11** shows that the two amide groups are far apart and that there is no possibility of internal hydrogen bonding.[10]

However, it is possible that some intermolecular interactions may be playing a part in stabilizing particular orientations of the ion-pair formed between the enolate of

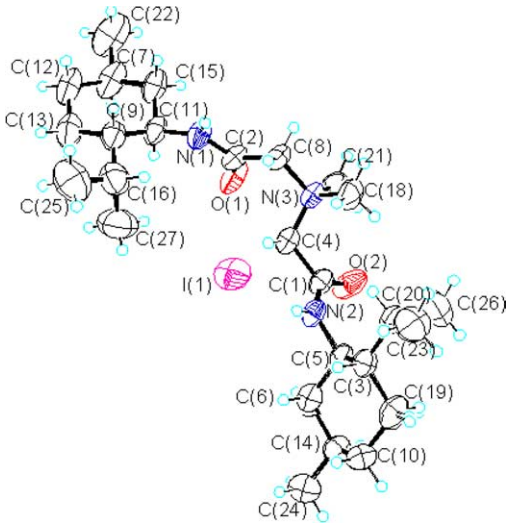


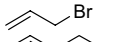
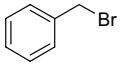
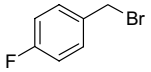
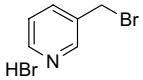
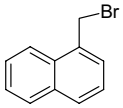
Figure 1. ORTEP diagram of catalyst **11**.

the substrate and the positively charged quaternary nitrogen, during benzylation/alkylation reaction. One can also postulate that the original form of the catalyst may be undergoing conformational changes due to the formation of ammonium ylides (by the abstraction of the α-H of amide by the base). Thus, factors that are responsible for the control of the enantioselectivity are yet to be fully understood.

As expected, catalyst **10**, which has an aromatic group for quaternalization as compared to catalyst **11**, which has alkyl units, have shown better selectivity.[11]

Taking catalyst **10**, phase-transfer alkylation with various alkyl halides was carried out. The results obtained for the asymmetric alkylation of **16** with various alkyl halides, using the similar conditions, and at −20 °C are given in Table 2 (Scheme 6). Good stereoselectivity ranging between 81% and 86% was observed with these alkylating agents (Table 2, entries a–h) for the asymmetric synthesis of α-amino acids.

Table 2. Alkylation of imine **16** using catalyst **10**

Entry	RX[a]	Time (h)	Yield[c] (%)	%Selectivity[d,e] (*R*:*S*)
a	CH_3CH_2I[b]	7	66, **17a**	82:18
b	$CH_3(CH_2)_4CH_2I$[b]	7	78, **17b**	86:14
c		4	92, **17c**	85:14
d		6	87, **17d**	83:17
e		5	91, **17e**	83:17
f		11	84, **17f**	82.5:17.5
g		8	86, **17g**	81:19

[a] The reaction was carried out with RX (2.0 equiv) and aqueous KOH (50%, 12 equiv) in the presence of **10** (10 mol %) in toluene/CH_2Cl_2 (7:3) at −20 °C.
[b] RX (5.0 equiv) was used.
[c] Yields of isolated products.
[d] Based on chiral HPLC using Chiralcel OD-H column.
[e] The absolute configuration was determined by comparision of the HPLC retention time with that of an authentic sample, which was independently checked with the known procedure.[2,3]

3. Conclusion

In conclusion, these are encouraging preliminary studies for helping design better phase-transfer catalysts using L-menthol scaffold.

4. Experimental

4.1. General

Melting points are uncorrected. ^1H and ^{13}C spectra were recorded at 300 and 75 MHz Bruker Advance Spectrometer respectively, with chemical shifts in ppm and tetramethylsilane as the internal standard. Infra-red absorption spectra were recorded on a Nicolet Impact 410 spectrometer, the frequencies in the IR spectra are indicated in cm^{-1}. Mass spectra data were recorded on a Finnigan-MAT LC–MS spectrometer. Elemental analyses were recorded on a Elementa Vario EL. HPLC was performed on a Shimadzu SPD-10A using chiral phase column DIACEL Chiralcel, OD-H). TLC was performed on plates pre-coated (0.25 mm) with silica gel 60, Merck F-254. The plates were visualized by the use of a combination of UV 254 nm) and iodine. Column chromatography was carried out with silica gel Merck 60 (80–230 mesh).

4.2. Synthesis of *N*-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]-*N*,*N*-dimethylamine 1

To a solution of menthylamine (5.0 g, 32.1 mmol) at −10 °C in dichloromethane (25 mL) was added methyl iodide (11.3 g, 79.61 mmol) and 50% aqueous KOH (10.7 mL). After stirring the reaction mixture for 2 h at −5 °C, CH_2Cl_2 (50 mL) was added and the organic phase washed with water (3 × 20 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane–EtOAc, 90:10) to give **1** as oil (4.7 g, 80%). $[\alpha]_D^{25} = -55.8$ (*c* 1.9, $CHCl_3$); IR (film) *ν* 2932, 2563, 1605, 1515, 1462, 1392, 1370, 1170, 1026, 956 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 0.72 (d, *J* = 10.71, 3H), 0.87 (d, *J* = 6.51, 3H), 0.92 (d, *J* = 6.49, 3H), 1.0–1.22 (m, 4H), 1.29 (m, 1H), 1.60–1.79 (m, 4H), 2.20 (s, 6H); MS (APCI): *m*/*z* (%) 184 (M^++1, 100).

4.3. Synthesis of benzyl[(2*S*,1*R*,5*R*)-2-isopropyl-5-methylcyclohexyl]dimethylammonium bromide 2a

To a solution of **1** (0.500 g, 2.72 mmol) in acetonitrile was added benzyl bromide (0.932 g, 5.54 mmol) and the reaction mixture was stirred at 80 °C for 96 h. After removing the solvent in vacuo the residue was crystallized with EtOAc–hexane to afford **2a** as white

crystalline solid (0.695 g, 80%). Mp 158–159 °C. $[\alpha]_D^{25} = -43.4$ (*c* 0.4, $CHCl_3$); IR (KBr) *v* 3019, 2958, 2870, 1467, 1455, 1372, 1346, 1163 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.04 (d, $J = 1.94$, 6H), 1.18 (d, $J = 5.39$, 3H), 1.53–2.24 (m, 9H), 3.04 (s, 3H), 3.15 (s, 3H), 4.38 (m, 1H), 4.91 (d, $J = 12.4$, 1H), 4.84 (d, $J = 12.6$, 1H), 7.43 (d, $J = 7.24$, 3H), 7.76 (d, $J = 7.14$, 2H); ^{13}C NMR ($CDCl_3$): δ 19.9, 22.0, 22.8, 26.3, 27.3, 30.5, 31.7, 40.9, 46.7, 64.3, 74.2, 127.4, 129.0, 130.5, 133.6. MS (APCI): *m*/*z* (%) 274 (M^+−80, 35), 184 (100). Anal. Calcd for $C_{19}H_{32}BrN$: C, 64.40; H, 9.10; N, 3.95. Found: C, 63.97; H, 10.32; N, 3.12.

4.4. Synthesis of (2*S*,1*R*,5*R*)-2-isopropyl-5-methylcyclohexyl(dimethyl)2-naphthylammonium bromide 2b

The procedure described for compound **2a** was followed; **2b** was obtained as a white crystalline solid (0.750 g, 65%) from **1** and 2-(bromomethyl)naphthalene. Mp 182–183 °C; $[\alpha]_D^{25} = -58.1$ (*c* 0.35, $CHCl_3$); IR (KBr) *v* 3010, 2954, 2924, 2866, 1477, 1455, 1370, 1258, 1162 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.04 (s, 6H), 1.21 (s, 3H), 1.58–1.71 (m, 5H), 1.91 (m, 2H), 2.25 (m, 2H), 3.05 (s, 3H), 3.18 (s, 3H), 4.44 (br s, 1H), 5.07 (d, $J =$ 12.2, 1H), 5.01 (d, $J = 12.4$, 1H), 7.53 (t, $J = 7.59$, 2H), 7.77–7.92 (m, 4H), 8.29 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.0, 22.0, 22.1, 22.8, 26.2, 27.3, 30.5, 31.6, 41.1, 46.7, 64.0, 124.4, 126.8, 127.6, 127.6, 128.4, 128.8, 129.5, 132.7, 133.6, 134.2; MS (APCI): *m*/*z* (%) 324 (M^+−80, 100), 185 (35). Anal. Calcd for $C_{22}H_{32}BrN$: C, 67.68; H, 8.26; N, 3.59. Found: C, 66.74; H, 9.32; N, 3.02.

4.5. Synthesis of 2-chloro-*N*-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]acetamide 5

To a cooled (−20 °C) mixture of menthylamine (5.0 g, 32.1 mmol) and *N*,*N*-dimethylaniline (5.07 g, 41.8 mmol) in CH_2Cl_2 (30 mL) was added chloroacetyl chloride (4.36 g, 38.6 mmol) dropwise over a period of 10 min under argon. After stirring the reaction mixture for 3 h, it was diluted with water (15 mL) and the aqueous layer extracted with CH_2Cl_2 (3×50 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, hexane–EtOAc, 95:5) to afford **5** as white solid (6.56 g, 80%). Mp 69–70 °C; $[\alpha]_D^{25} = -52.9$ (*c* 0.65, $CHCl_3$); IR (KBr) *v* 3275, 3089, 2953, 2863, 1651, 1567, 1445, 1365, 1346, 1240, 1161, 1111 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.79 (d, $J = 6.81$, 3H), 0.90 (t, $J = 5.37$, 6H), 1.03–1.19 (m, 4H), 1.48 (br s, 1H), 1.71–1.98 (m, 4H), 3.79 (m, 1H), 4.05 (s, 2H), 6.29 (d, $J = 9.42$, 1H); ^{13}C NMR ($CDCl_3$): δ 16.1, 21.0, 22.0, 23.7, 26.8, 31.7, 34.3, 42.6, 42.7, 47.7, 50.4, 164.8; MS (APCI): *m*/*z* (%) 232 (M^+, 18), 231 (100).

4.6. Synthesis of *N*1-[(2*S*,1*R*,5*R*)-2-isopropyl-5-methylcyclohexyl]-2-benzyl(methyl)aminoacetamide 6

To a suspension of **5** (0.500 g, 2.15 mmol) and K_2CO_3 (0.596 g, 4.31 mmol) in acetonitrile (10 mL) was added *N*-methylbenzylamine (0.260 g, 2.14 mmol). After stirring the reaction mixture for 2 h at 80 °C, the solvent was evaporated, the residue diluted with water (15 mL) and then extracted with CH_2Cl_2 (3×50 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford **6** as oil (0.655 g, 93%). $[\alpha]_D^{25} = -53.0$ (*c* 1, $CHCl_3$); IR (film) *v* 3310, 3018, 2952, 2922, 2863, 1660, 1516, 1454, 1369, 1125, 1027 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.75 (d, $J = 6.84$, 3H), 0.88 (d, $J = 6.80$, 6H), 0.84–0.86 (m, 2H), 1.01–1.16 (m, 2H), 1.47 (br s, 1H), 1.78–1.95 (m, 4H), 2.27 (s, 3H), 2.96 (d, $J = 16.2$, 1H), 3.04 (d, $J = 16.3$, 1H), 3.55 (s, 2H), 3.76 (m, 1H), 6.97 (d, $J = 9.47$, 1H), 7.27–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 15.8, 20.9, 21.9, 23.5, 26.6, 29.45, 31.3, 31.6, 34.8, 42.8, 43.0, 47.7, 46.0, 60.7, 62.0, 127.2, 128.2, 128.5, 137.5, 169.4; MS (APCI): *m*/*z* (%) 318 (M^++2, 20), 317 (100).

4.7. Synthesis of dibenzyl[(2*S*,1*R*,5*R*)-2-isopropyl-5-methylcyclohexylcarbamoylmethyl]methylammonium bromide 7

To a solution of **6** (0.350 g, 1.10 mmol) in toluene (10 mL) was added benzyl bromide (0.378 g, 2.21 mmol). After stirring the reaction mixture for 3 h at 100 °C, toluene was evaporated under vacuum. The residue was diluted with hexane (10 mL), stirred at rt and filtered to afford **7** as an off-white solid (0.506 g, 92%). Mp 98–99 °C. $[\alpha]_D^{25} = -16.0$ (*c* 1.65, $CHCl_3$); IR (KBr) *v* 3421, 3188, 3041, 2954, 2869, 1673, 1556, 1456, 1365, 1288, 1257, 1212, 1111 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.81 (d, $J =$ 6.87, 3H), 0.88 (d, $J = 6.88$, 3H), 0.91 (d, $J = 7.21$, 3H), 1.04–1.28 (m, 3), 1.43 (t, $J = 11.31$, 2H), 1.68 (d, $J = 10.79$, 2H), 1.92–2.04 (m, 2H), 3.07 (s, 3H), 3.86 (m, 1H), 4.17 (d, $J = 14.52$, 1H), 4.56 (d, $J = 14.52$, 1H), 4.67 (d, $J = 12.39$, 1H), 4.75 (d, $J =$ 12.33, 1H), 5.21 (d, $J = 12.33$, 1H), 5.31 (d, $J = 12.39$, 1H), 7.44–7.60 (m, 10H), 8.75 (d, $J = 8.91$, 1H); ^{13}C NMR ($CDCl_3$): δ 15.7, 21.1, 22.0, 23.4, 26.6, 31.9, 34.1, 41.9, 46.2, 47.4, 51.0, 59.3, 65.6, 65.8, 126.6, 129.5, 131.1, 133.2, 162.7; MS (APCI): *m*/*z* (%) 408 (M^+−80, 25), 407 (100), 317 (42). Anal. Calcd for $C_{27}H_{39}BrN_2O$: C, 66.52; H, 8.06; N, 5.75. Found: C, 65.43; H, 8.76; N, 4.98.

4.8. Synthesis of *N*-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]-2-(methyl amino)acetamide 8

To a solution of **5** (5.0 g, 22.0 mmol) in 1,3-dioxane (15 mL) at 0 °C was added a solution of methylamine (10 mL, prepared by bubbling methylamine in 1,3-dioxane for 1 h). After stirring the reaction mixture for 4 h at 0 °C, the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL), washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (MeOH–$CHCl_3$, 5:95) to afford **8** as oil (4.39 g, 90%). $[\alpha]_D^{25} = -91.6$ (*c* 0.24, $CHCl_3$); IR (film) *v* 3293, 2953, 2922, 2870, 1647, 1528, 1451, 1369, 1288, 1115 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.78 (d, $J = 6.94$, 3H), 0.88 (t, $J = 6.01$, 6H), 0.88–1.96 (m, 9H), 2.41 (s, 3H), 3.22 (s, 2H), 3.76 (m, 1H), 6.93 (d, $J = 9.43$, 1H); ^{13}C NMR ($CDCl_3$): δ 16.0, 21.1, 22.1, 3.7, 26.8, 31.8, 34.5, 36.7, 43.1, 47.9, 49.3, 54.6, 170.3; MS (APCI): *m*/*z* (%) 228 (M^++2, 10), 227 (100).

4.9. Synthesis of *N1*-[(2*S*,1*R*,5*R*)-2-isopropyl-5-methylcyclohexyl]-2-[(2*S*,1*R*,5*R*)-2-isopropyl-5-methylcyclohexylcarbamoylmethyl(methyl)amino]acetamide 9

To a suspension of **8** (3.0 g, 13.2 mmol) and K_2CO_3 (1.83 g, 13.2 mmol) in acetonitrile (30 mL) was added **5** (3.4 g, 14.7 mmol). After stirring the reaction mixture for 8 h at 60 °C, the solvent was evaporated, the residue diluted with water (25 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (EtOAc–hexane, 50:50) to afford **9** as an off-white solid (5.19 g, 93%). Mp 123–124 °C; $[\alpha]_D^{25} = -72.1$ (*c* 0.33, $CHCl_3$); IR (KBr) *v* 3352, 3252, 3078, 2953, 2870, 1633, 1531, 1446, 1386, 1305, 1130 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.78 (m, 22H), 1.11 (m, 4H), 149–1.87 (m, 7H), 1.85 (t, 4H), 1.95 (d, J = 12.04, 3H), 2.36 (s, 3H), 3.04 (d, $J = 15.8$, 2H), 3.11 (d, J = 15.8, 2H), 3.81 (m, 2H), 6.33 (d, $J = 9.26$, 2H); ^{13}C NMR ($CDCl_3$): δ 15.9, 21.3, 22.1, 23.6, 27.0, 31.8, 34.4, 43.1, 43.9, 47.9, 49.7, 61.5, 168.6; MS (APCI): *m*/*z* (%) 423 (M^++2, 26), 422 (100).

4.10. Synthesis of benzyl{di[(2*S*,1*R*,5*R*)-2-isopropyl-5-methylcyclohexylcarbamoylmethyl]}methylammonium bromide 10

To a solution of **9** (0.500 g, 1.18 mmol) in acetonitrile (20 mL) was added benzyl bromide (0.608 g, 3.55 mmol). After stirring the reaction mixture for 10 h at 75 °C, acetonitrile was evaporated under reduced pressure. The residue was diluted with hexane (15 mL), stirred at rt and filtered to afford **10** as an off-white solid (0.618 g, 88%). Mp 79–80 °C; $[\alpha]_D^{25} = -43.7$ (*c* 0.37, $CHCl_3$); IR (KBr) *v* 3205, 3055, 2952, 2926, 2856, 1676, 1552, 1455, 1288, 1111 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.79 (d, $J = 5.04$, 6H), 0.88–0.97 (m, 14H), 1.05 (m, 4H), 1.32 (m, 2H), 1.46 (m, 2H), 1.69 (m, 4H), 1.93 (m, 4H), 3.40 (s, 3H), 3.81 (m, 2H), 4.14 (d, $J = 14.25$, 1H), 4.28 (s, 2H), 4.57 (d, $J = 14.27$, 1H), 5.31 (s, 2H), 7.45–7.51 (m, 3H), 7.63 (d, $J = 7.73$, 2H), 8.37 (t, $J = 6.85$, 2H); ^{13}C NMR ($CDCl_3$): δ 15.7, 19.0, 21.0, 21.9, 23.3, 26.6, 29.6, 31.8, 34.0, 41.9, 46.3, 49.6, 50.9, 61.0, 61.2, 65.5, 126.5, 128.7, 129.3, 130.8, 131.0, 133.1, 162.5; MS (APCI): *m*/*z* (%) 513 (M^+−80, 33), 512 (100), 423 (20), 422 (58). Anal. Calcd for $C_{32}H_{54}BrN_3O_2$: C, 64.85; H, 9.18;N, 7.09. Found: C, 64.01; H, 10.02; N, 6.84.

4.11. Synthesis of di[(2*S*,1*R*,5*R*)-2-isopropyl-5-methylcyclohexylcarbamoylmethyl](dimethyl)ammonium iodide 11

To a solution of **9** (0.500 g, 1.18 mmol) in acetonitrile (20 mL) was added methyl iodide (0.502 g, 3.53 mmol). After stirring the reaction mixture for 3 h at rt, acetonitrile was removed under vacuum. The residue was crystallized from acetone to afford **11** as white crystalline solid (0.561 g, 84%). Mp 191–192 °C; $[\alpha]_D^{25} = -57.1$ (*c* 0.26, CH_2Cl_2); IR (KBr) *v* 3212, 2958, 2869, 1678, 1546, 1448, 1380, 1286 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.75 (d, $J = 6.90$, 6H), 0.88–1.05 (m, 16H), 1.34 (t, $J = 11.55$, 2H), 1.46 (m, 2H), 1.70 (d, $J = 10.65$, 4H), 1.90 (d, $J = 9.42$, 4H), 2.09 (s, 2H), 3.58 (s, 6H), 3.80 (m, 2H), 4.61 (d, J = 13.6, 2H), 4.67 (d, $J = 13.6$, 2H), 7.58 (d, $J = 9.09$, 2H); ^{13}C NMR ($CDCl_3$): δ 15.7, 21.0, 21.9, 23.4, 26.7, 31.8, 34.1, 42.1, 46.4, 51.1, 52.7, 64.6, 161.5; MS (APCI): *m*/*z* (%) 436 (M^+−127, 60), 316, 241, 154. Anal. Calcd for $C_{26}H_{50}IN_3O_2$: C, 55.41; H, 8.94; N, 7.46. Found: C, 55.20; H, 8.84; N, 7.35.

4.12. Di[(2*S*,1*R*,5*R*)-2-isopropyl-5-methylcyclohexylcarbamoylmethyl][1-naphthylmethyl](methyl)ammonium bromide 12

The procedure described for compound **10** was followed; **12** was obtained as white solid (0.632 g, 83%) from **7** (0.500 g, 1.18 mmol) and 2-(bromomethyl)-naphthalene (1.305, 1.47 mmol). Mp 94–95 °C; $[\alpha]_D^{25} = -46.4$ (*c* 0.37, $CHCl_3$); IR (KBr: *v* 3207, 3053, 2944, 2922, 2869, 1681, 1557, 1455, 1365, 1288, 1247, 1180 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.80 (t, $J = 7.33$, 6H), 0.92 (d, $J = 6.55$, 12H), 1.09–2.17 (m, 18H) 3.14 (s, 3H), 3.81 (m, 2H), 4.33 (d, $J = 13.86$, 1H), 4.57 (s, 2H), 4.88 (d, $J = 12.93$, 1H), 5.78 (d, $J = 12.4$, 1H), 5.86 (d, J = 12.5, 1H), 6.38 (d, J = 9.39, 2H), 7.57 (q, $J = 7.28$, 1H), 7.71 (t, $J = 7.13$, 1H), 7.94 (d, $J = 7.14$, 1H), 8.03 (d, $J = 7.86$, 1H), 8.16 (d, $J = 8.37$, 1H), 8.23 (d, J = 8.80, 1H), 8.47 (d, $J = 8.47$, 1H); ^{13}C NMR ($CDCl_3$): δ 15.8, 21.1, 21.3, 22.0, 23.5, 26.9, 31.9, 34.1, 41.9, 42.1, 46.5, 48.7, 51.4, 61.8, 62.6, 123.4, 125.2, 126.8, 128.5, 129.4, 132.4, 134.0, 162.2; MS (APCI): *m*/*z* (%) 562 (M^+−80, 45), 422 (100). Anal. Calcd for $C_{36}H_{56}BrN_3O_2$: C, 67.27; H, 8.78; N, 6.54. Found: C, 66.36; H, 9.03; N, 6.42.

4.13. Synthesis of tri[(2*S*,1*R*,5*R*)-2-isopropyl-5-methylcyclohexylcarbamoylmethyl](methyl)ammonium iodide 13

To a solution of **9** (0.150 g, 0.355 mmol) in acetonitrile (15 mL) was added **5** (0.082 g, 0.355 mmol) and sodium iodide (0.053 g, 0.355 mmol) and the reaction mixture stirred at 80 °C for 48 h. Evaporation of the solvent afforded the residue, which was purified by preparative TLC (MeOH–$CHCl_3$, 8:92) to give **13** (0.210 g, 68%) as yellowish solid. Mp 210–211 °C; $[\alpha]_D^{25} = -98.2$ (*c* 0.24, $CHCl_3$); IR (KBr) *v* 3445, 3066, 2956, 2929, 2870, 1668, 1548, 1384, 1180, 1112, 1056, 978 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.75 (d, $J = 6.39$, 9H), 0.89 (m, 18H), 0.98 (m, 6H), 1.25 (m, 3H), 1.45 (m, 3H), 1.68 (m, 6H), 1.86 (m, 6H), 2.12 (m, 3H), 3.61 (s, 3H), 3.76 (m, 3H), 4.71 (dd, $J = 13.53$, 9.78, 6H), 7.03–7.24 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 15.9, 15.8, 21.0, 21.2, 21.9, 22.1, 23.4, 23.6, 26.8, 29.7, 31.9, 34.1, 34.3, 42.2, 42.8, 46.7, 47.3, 50.1, 50.5, 51.2, 60.1, 62.8, 161.7, 169.3; MS (APCI): *m*/*z* (%) 618 (M^+−I, 45), 617 (100), 603 (20). Anal. Calcd for $C_{37}H_{69}BrN_4O_3$: C, 63.68; H, 9.97; N, 8.03. Found: C, 62.86; H, 10.84; N, 7.64.

4.14. Synthesis of 3-(hydroxy-diphenyl-methyl)-benzyl-{di-[(2*S*,1*R*,5*R*)-2-isopropyl-5-methylcyclohexylcarbamoylmethyl]}(methyl) ammonium bromide 14

To a solution of **9** (0.250 g, 0.592 mmol) in acetonitrile (10 mL) was added [3-(bromomethyl)phenyl](diphenyl)-

methanol (0.314 g, 0.88 mmol). After stirring the reaction mixture for 12 h at 75 °C, acetonitrile was evaporated in vacuo and the residue purified by column chromatography ($CHCl_3$–MeOH, 90:10) to afford **14** as off-white solid (0.376 g, 82%). Mp 124–125 °C; $[\alpha]_D^{25} = -42.7$ (*c* 0.25, $CHCl_3$); IR (KBr) *v* 3418, 3213, 3058, 2955, 2929, 2863, 1679, 1551, 1448, 1369, 1288, 1180, 1155, 1111, 1015 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.73 (d, $J = 7.15$, 6H), 0.87 (d, $J = 6.44$, 12H), 0.97–1.08 (m, 4H), 1.25 (m, 2H), 1.42 (m, 2H), 1.67 (d, $J = 11.05$, 4H), 1.87 (m, 6H), 3.33 (s, 3H), 3.74 (m, 2H), 4.04 (d, $J = 13.67$, 2H), 4.30 (d, $J = 13.81$, 1H), 4.40 (d, $J = 14.00$, 1H), 5.10 (q, $J = 11.04$, 2H), 7.26–7.51 (m, 14H), 7.47 (s, 1H), 8.07 (d, $J = 8.85$, 2H); ^{13}C NMR ($CDCl_3$): δ 15.7, 20.9, 22.1, 22.8, 26.5, 29.4, 31.8, 34.0, 41.8, 46.4, 48.5, 51.0, 61.03, 61.30, 65.6, 81.6, 125.3, 127.6, 127.8, 128.2, 128.4, 129.0, 129.2, 132.7 146.1, 150.0, 161.9; MS (APCI): *m*/*z* (%) 695 (M^+−80, 30), 694 (70), 423 (35), 422 (100). Anal. Calcd for $C_{45}H_{64}BrN_3O$: C, 69.75; H, 8.32; N, 5.42. Found: C, 68.83; H, 9.09; N, 4.92.

4.15. Synthesis of 4-(hydroxy-diphenyl-methyl)-benzyl{di[(2*S*,1*R*,5*R*)-2-isopropyl-5-methyl-cyclohexylcarbamoylmethyl]}(methyl)ammonium bromide 15

The procedure described for compound **10** was followed; **15** was obtained as white solid (0.390 g, 85%), from **9** and 4-bromomethylphenyl-diphenylmethanol. Mp 132–133 °C; $[\alpha]_D^{25} = -38.0$ (*c* 0.20, $CHCl_3$); IR (KBr) *v* 3421, 3210, 3047, 2955, 2922, 2863, 1681, 1551, 1450, 1369, 1255 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.76 (dd, $J = 1.2$, 2.5, 6H), 0.87–0.89 (m, 14H), 1.02–1.06 (m, 4H), 1.19–1.32 (m, 4H), 1.44 (br s, 1H), 1.68 (d, $J = 10.64$, 4H), 1.91 (m, 4H), 3.37 (s, 3H), 3.79 (m, 2H), 4.12 (d, $J = 13.93$, 1H), 4.30 (s, 2H), 4.56 (d, $J = 13.89$, 1H), 5.23 (s, 2H), 7.27–7.30 (m, 10H), 7.42 (d, $J = 8.18$, 2H), 7.56 (d, $J = 8.14$, 2H), 8.16 (t, $J = 6.45$, 2H); ^{13}C NMR ($CDCl_3$): δ 15.7, 21.1, 22.0, 23.4, 26.7, 29.6, 31.9, 34.1, 42.0, 46.4, 48.5, 51.1, 61.1, 61.3, 65.6, 81.7, 125.5, 127.6, 127.8, 128.1, 129.03, 132.8, 146.1, 150.1, 162.0; MS (APCI): *m*/*z* (%) 659 (M^+−80, 45), 694 (85), 423 (35), 422 (100). Anal. Calcd for $C_{45}H_{64}BrN_3O$: C, 69.75; H, 8.32;N, 5.42. Found: C, 68.94; H, 9.37; N, 4.98.

4.16. *tert*-Butyl (2*S*)-2-[(diphenylmethylene)amino]-butanoate 17a

Yield 66%; IR (film) *v* 3060, 2926, 2854, 1732, 1662, 1625, 1446, 1367, 1284, 1154 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.87 (t, $J = 7.6$, 3H); 1.44 (s, 9H), 1.87–1.91 (m, 2H), 4.01 (dd, $J = 8.0$, 5.2, 1H), 7.17 (dd, $J = 4.4$, 1.6, 2H), 7.30–7.44 (m, 6H), 7.65 (m, 2H); (MALDI): *m*/*z* 324 (M^++1). R_t HPLC (Chiralcel OD, 95.5:0.5, hexane/2-propanol, $t_S = 11.6$ min, $t_R = 13.3$ min).

4.17. *tert*-Butyl (2*S*)-2-[(diphenylmethylene)amino]-octanoate 17b

Yield 78%; IR (film) *v* 2954, 2929, 2856, 1735, 1627, 1456, 1448, 1391, 1365, 1249, 1153 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.87 (t, $J = 6.8$, 3H), 1.26–1.23 (m, 8H), 1.44 (s, 9H), 1.86 (m, 2H), 3.98 (t, $J = 6.7$, 1H), 7.18 (dd, $J = 5.1$, 2.0, 2H), 7.32–7.43 (m, 5H), 7.64–7.79 (m, 3H); MS (MALDI): *m*/*z* 380 (M^++1). R_t HPLC (Chiralcel OD, 95.5:0.5, hexane/2-propanol, $t_S = 10.5$ min, $t_R = 12.2$ min).

4.18. *tert*-Butyl (2*S*)-2-[(diphenylmethylene)amino]pent-4-enoate 17c

Yield 92%; IR (film) *v* 3061, 2928, 2930, 1734, 1624, 1598, 1576, 1446, 1367, 1277, 1152 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.44 (s, 9H), 2.65 (m, 2H), 4.0 (dd, $J = 7.6$, 5.5, 1H), 4.99–5.09 (m, 2H), 5.72 (m, 1H), 7.17 (m, 2H), 7.47–7.30 (m, 6H), 7.64 (m, 2H); MS (MALDI): 336 [M^++1]. R_t HPLC (Chiralcel OD-H, 99.5:0.5, hexane/*iso*-propanol, $t_S = 10.5$ min, $t_R = 12.0$ min).

4.19. *tert*-Butyl-*N*-(diphenylmethylene)-L-phenylalaninate 17d

Yield 87%; ^1H NMR ($CDCl_3$): δ 1.41 (s, 9H), 3.22–3.09 (m, 2H), 4.08 (dd, $J = 4.98$, 9.08, 1H), 6.53–7.62 (m, 15H); R_t HPLC (Chiralcel OD-H, 254 nm, 0.5 mL, hexane/*iso*-propanol, $t_S = 25.4$ min, $t_R = 17.5$ min).

4.20. *tert*-Butyl (2*S*)-3-(4-fluorophenyl)-2-[(diphenylmethylene)amino]propanoate 17e

Yield 91%; IR (neat) *v* 2977, 2928, 1726, 1626, 1508, 1446, 1369, 1285, 1148 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.45 (s, 9H), 3.15 (dd, $J = 13.4$, 8.6, 1H), 3.22 (dd, $J = 13.4$, 4.8, 1H), 4.06 (dd, $J = 8.6$, 4.8, 1H), 6.69 (d, $J = 7.1$, 2H), 6.85–7.02 (m, 4H), 7.30–7.41 (m, 6H), 7.56–7.58 (m, 2H); R_t HPLC (Chiralcel OD, 99.5:0.5, hexane/*iso*-propanol, $t_S = 8.1$ min, $t_R = 13.5$ min).

4.21. *tert*-Butyl 2-[(diphenylmethylene)amino]-3-pyridin-3-ylpropanoate 17f

Yield: 84%; $[\alpha]_D^{25} = -184.3$ (*c* 1, CH_2Cl_2), IR (neat) *v* 2958, 2869, 1739, 1450, 1425, 1286, 1173 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.44 (s, 9H), 3.25 (dd, $J = 5.3$, 3.3, 2H), 4.95 (dd, $J = 5.9$, 3.3, 1H), 6.87 (d, $J = 6.2$, 2H), 7.23 (dd, $J = 4.9$, 2.8, 1H), 7.39–7.58 (m, 7H), 7.76 (d, $J = 7.0$, 2H), 8.44 (s, 1H), 8.48 (d, $J = 4.7$, 1H) ^{13}C NMR ($CDCl_3$): δ 27.9, 36.6, 67.1, 81.4, 122.9, 127.4, 128.2, 128.4, 128.6, 129.9, 130.3, 132.3, 133.8, 136.1, 137.3, 139.1, 147.6, 170.8; MS (MALDI): *m*/*z* 386 (M^+). R_t HPLC (Chiralcel OD-H, 98:2, hexane/*iso*-propanol, $t_S = 20.4$ min, $t_R = 22.8$ min). Anal. Calcd for $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.25. Found: C, 77.58; H, 6.84; N, 7.18.

4.22. *tert*-Butyl (2*S*)-2-[(diphenylmethylene)amino]-3-(1-naphthyl)propanoate 17g

Yield 86%; IR (film) *v* 3054, 2975, 1730, 1622, 1576, 1446, 1367, 1287, 1150 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.46 (s, 9H), 3.56 (dd, $J = 12.9$, 8.2, 1H), 3.86 (dd, $J = 12.9$, 3.8, 1H), 4.30 (dd, $J = 8.2$, 3.8, 1H), 6.68 (br s, 2H), 6.96 (t, $J = 7.5$, 2H), 7.12–7.34 (m, 8H), 7.39 (ddd, $J = 8.7$, 6.9, 1.2, 1H), 7.50–7.72 (m, 4H); R_t HPLC

(Chiralcel OD, 95.5:0.5, hexane/2-propanol, $t_S = 24.3$ min, $t_R = 21.6$ min).

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