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An efficient chemoenzymatic method to prepare optically active primary–tertiary *trans*-cycloalkane-1,2-diamines

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ABSTRACT

Optically active *trans*-*N*-Boc-cyclopentane- and cyclohexane-1,2-diamines (**7**) were prepared by a chemoenzymatic method from the corresponding (±)-*trans*-*N*,*N*-diallylcycloalkane-1,2-diamine. These mono-carbamates **7** (ee=99%) were used as the starting materials in the syntheses of different vicinal primary–tertiary diamines. Thus, by means of a simple three-step sequence involving a reductive-amination of an aromatic aldehyde with **7**, N-methylation and finally, cleavage of the Boc group, several *trans*-*N*-(arylmethyl)-*N*-methylcyclopentane- and cyclohexane-1,2-diamines were obtained in high yields.

1. Introduction

The vicinal diamino grouping is the structural feature of many natural products and therapeutical agents possessing a wide variety of biological activities.[1] In addition, optically active 1,2-diamines and their derivatives have been extensively used in asymmetric synthesis.[2]

The availability of the enantiopure C_2-symmetric *trans*-cyclohexane-1,2-diamine has motivated its inclusion in a vast number of efficient catalysts and ligands.[3,4] Thus, some *N*,*N*-dialkylcyclohexane-1,2-diamines such as **1** (Fig. 1) and their thiourea derivatives **2** have been used with prominent results in a range of nucleophile–electrophile addition reactions.[5–7] Moreover, we have shown that bis(aminoamides) **3** derived from *N*-benzyl-*N*-methylcyclopentane- and cyclohexane-1,2-diamines have interesting applications in the molecular recognition of carboxylic acids.[8]

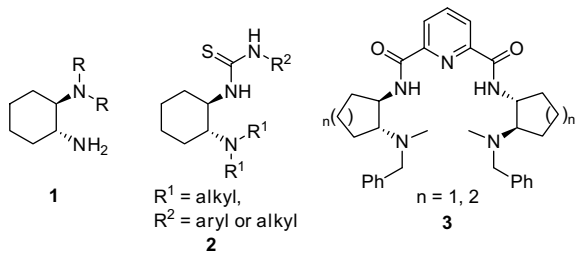
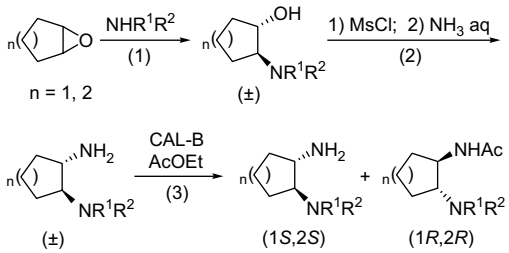


Figure 1. Optically active *trans*-cycloalkane-1,2-diamine derivatives.

The relevance of these optically active cycloalkane-1,2-diamine derivatives has motivated to the organic chemists to continue developing new and efficient methods for their preparation. In this regard, we have recently reported a chemoenzymatic protocol to prepare some enantioenriched *trans*-*N*,*N*-dialkylcyclohexane- and cyclopentane-1,2-diamines.[9,10] The method, summarized in Scheme 1, consists of: (1) opening of the corresponding cycloalkene oxide with the required secondary amine, (2) stereospecific transformation of the racemic *trans*-2-(*N*,*N*-dialkylamino)cycloalkanol into the racemic *trans*-diamine and (3) enzymatic kinetic resolution of the diamine. Although, in general, yields of either the racemic and the optically active compounds were high, the method required the enzymatic resolution of each *N*,*N*-disubstituted diamine, the efficacy of this resolution step strongly depending on the substituents on the nitrogen atom. Moreover, when the diamine bears



Scheme 1. Chemoenzymatic preparation of optically active *trans*-*N*,*N*-dialkylcycloalkane-1,2-diamines.

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a bulky substituent such as 9-antrylmethyl, the yield of the racemic diamine was only moderate.[11]

Continuing with our research about new receptors based on *trans*-cycloalkane-1,2-diamines and analogous to **3** (Fig. 1), we felt the necessity of developing an alternative via to prepare optically active *trans*-*N*-(arylmethyl)-*N*-methylcycloalkane-1,2-diamines, avoiding the enzymatic resolution of each diamine. For this purpose, a common optically active precursor would be desirable. Thus, we envisioned that the mono-Boc-carbamate of the corresponding *trans*-cycloalkane-1,2-diamine would be an interesting precursor of these primary–tertiary diamines. Herein, we wish to report the chemoenzymatic preparation of *trans*-*N*-Boc-cyclohexane-1,2-diamine as well as our results about the new synthetic protocol towards primary–tertiary *trans*-cycloalkane-1,2-diamines.

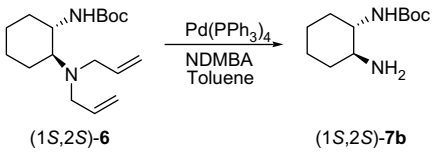
2. Results and discussion

2.1. Chemoenzymatic preparation of optically active *trans*-*N*-Boc-cyclohexane-1,2-diamine

Recently, we have developed an excellent method to obtain both enantiomers of *trans*-cyclopentane-1,2-diamine protected as its mono-Boc-carbamate from optically active *trans*-*N*,*N*-diallylcyclopentane-1,2-diamine, which in turn was prepared such as described in Scheme 1.[12] The high efficacy of this method as well as the high cost of the recently available optically active *trans*-*N*-Boc-cyclohexane-1,2-diamine encouraged us to carry out the synthesis of this derivative following the same strategy as for its cyclopentylic analogue. Thus, racemic *trans*-*N*,*N*-diallylcyclohexane-1,2-diamine (±)-**4** (see Table 1) was obtained with very high yield (90%) from the inexpensive cyclohexene oxide such as described in Scheme 1 [steps (1) and (2)]. Resolution of (±)-**4** was accomplished by enzymatic acetylation catalyzed by the lipase B from *Candida antarctica* (CAL-B). Several combinations of acylating agent and solvent were tested and the results are collected in Table 1. In all cases the enzyme catalyzed the acetylation of the diamine. In order to facilitate the separation of the produced acetamide **5** and the remaining substrate **4**, the reaction crude was treated with *tert*-butyl pyrocarbonate. Thus, the remaining diamine **4** was transformed into the Boc-carbamate and then, the resulting mixture of carbamate **6** and acetamide **5** was easily separated by flash chromatography.

From the reaction using the simplest conditions, that is, ethyl acetate as acyl donor and solvent (Table 1, entry 1), the remaining substrate was isolated with very high ee. However, to obtain the product with the same ee (99%), a more enantioselective reaction is required. Consequently, we tested 1,4-dioxane as solvent and ethyl acetate or 1-phenylethyl acetate[13] as acyl donors (Table 1, entries 2 and 3). In both reactions acetamide **5** was isolated with ee=99%. Nevertheless, in order to prepare higher amounts of (1*R*,2*R*)-**5**, the reaction employing ethyl acetate as the acyl donor (entry 2) should be advisable since the non-reacted ethyl acetate and the produced ethanol are eliminated easier than 1-phenylethyl acetate and 1-phenylethanol, which are present in the reaction mixture of entry 3.

Transformation of (1*S*,2*S*)-**6** into the required optically active *trans*-*N*-Boc-cyclohexane-1,2-diamine [(1*S*,2*S*)-**7b**] was easily accomplished by the selective removing of the allyl groups in the presence of a Pd(0) catalyst and *N*,*N*′-dimethylbarbituric acid (NDMBA) as allyl group scavenger (Scheme 2).[15] Thus, from this process, the mono-Boc derivative (1*S*,2*S*)-**7b** was obtained with 81% yield. Comparison of the sign of the optical rotation of this compound (1*S*,2*S*)-**7b** (see Experimental section) with that of a commercial sample[16] allowed us to assign the configuration of the compounds isolated in the enzymatic reaction, thus corroborating that the lipase preferentially catalyzed the acylation of the (1*R*,2*R*) enantiomer of the diamine. Similarly to the transformation of (1*S*,2*S*)-**6** into (1*S*,2*S*)-**7b**, the mono-Boc-carbamate (1*R*,2*R*)-**7b** could be prepared if acetamide (1*R*,2*R*)-**5** (ee=99%; Table 1, entry 2) is previously transformed into (1*R*,2*R*)-**6** (acidic hydrolysis of the amide function and subsequent *tert*-butoxycarbonylation of the resulting diamine).[12] It is of note the importance of this chemoenzymatic method because it allows easily to access to both enantiomers of compound **7b**, which has proved synthetic interest.[17]

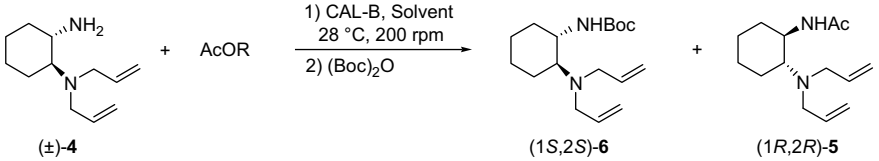


Scheme 2. Pd-catalyzed deallylation of (1*S*,2*S*)-**6**.

2.2. Syntheses of (1*S*,2*S*)-*N*-(arylmethyl)-*N*-methylcycloalkane-1,2-diamines

With both optically active mono-Boc derivatives (1*S*,2*S*)-**7a**,**b** in hands, we attempted the preparation of the *N*-(arylmethyl)-*N*-methylcycloalkane-1,2-diamines (Scheme 3 and Table 2). In this regard, 1- and 2-naphthyl and 9-anthryl were chosen as aryl substituents since these units have been successfully incorporated in the structure of many receptors of anions, amides and biologically

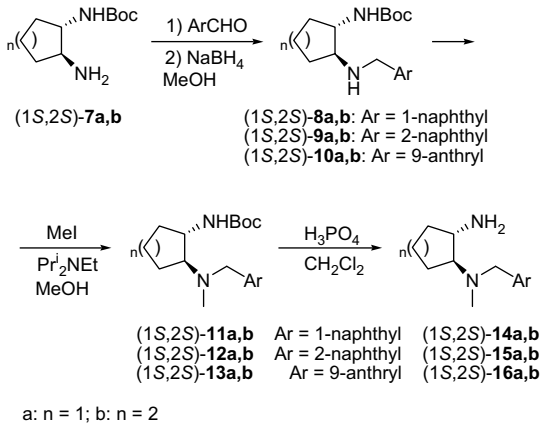
Table 1
CAL-B catalyzed resolution of (±)-**4**



Entry	Acyl donor (AcOR)	Solvent	Time (h)	(1*S*,2*S*)-**6**		(1*R*,2*R*)-**5**		c[b] (%)	E[c]
				Yield[a] (%)	ee$_S$ (%)	Yield[a] (%)	ee$_P$ (%)		
1	AcOEt	AcOEt	71	44	99	49	92	52	125
2	AcOEt[d]	1,4-Dioxane	68	45	95	44	99	49	>200
3	AcOCH(Ph)CH$_3$[e]	1,4-Dioxane	96	n.d.[f]	70	n.d.[f]	99	41	>200

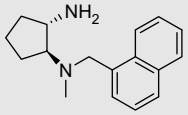
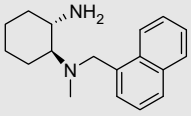
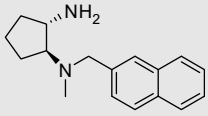
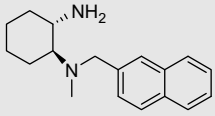
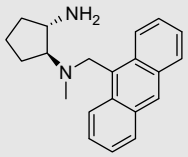
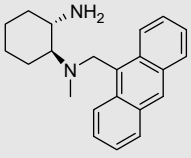
[a] Isolated yields after flash chromatography.
[b] Conversion degree: c=ee$_S$/(ee$_S$+ee$_P$).
[c] Determined from ee$_S$ and ee$_P$ as in Ref. 14.
[d] A molar ratio ester–diamine of 6:1 was used.
[e] A molar ratio ester–diamine of 3:1 was used. Reaction was conducted to a small scale and yields of substrate and product were not determined (n.d.).

important species.[18] Moreover, the anisotropy of these groups has been also exploited to prepare efficient chiral solvating agents.[19] Thus, diamines here prepared could be very useful for our objectives related to the search of new compounds for the efficient and easy determination of the enantiomeric excesses of carboxylic acids.[8]



Scheme 3. Syntheses of (1*S*,2*S*)-*N*-(arylmethyl)-*N*-methylcycloalkane-1,2-diamines.

Table 2
Optically active diamines (1*S*,2*S*)-**14**–**16** produced via Scheme 3

Entry	*n*	Ar		Diamine	Yield[a]
1	1	1-Naphthyl	**14a**		71
2	2	1-Naphthyl	**14b**		75
3	1	2-Naphthyl	**15a**		80
4	2	2-Naphthyl	**15b**		85
5	1	9-Antryl	**16a**		75
6	2	9-Anthryl	**16b**		70

[a] Overall yield of the three steps.

The synthetic sequence consisted of three steps: (1) reductive-amination of an aromatic aldehyde, (2) methylation of a secondary amine and (3) deprotection of the Boc group. At first, reductive-amination step was accomplished by treatment of the desired aromatic aldehyde with the corresponding aminocarbamate **7** in methanol, and in situ reduction of the resulting imine with $NaBH_4$. From these reactions, the *N*-substituted aminocarbamates **8**–**10** were obtained in very high yields (93–99%). N-Methylation of **8**–**10** with methyl iodide was carried out at room temperature in presence of *N*,*N*-diisopropylethylamine. For this process, the choice of methanol as the solvent was critical and justified by the proved slow rate of the undesirable quaternation of the resulting tertiary amine.[20] In these conditions, the corresponding tertiary aminocarbamates **11**–**13** were isolated in 79–95% yields. Finally, the Boc group was easily removed with an 85% aqueous pyrophosphoric solution using dichloromethane as solvent, the yields of this last step being also very high (89–99%). It is worth noting that in this three-step sequence a flash chromatography purification was only required in the second step, compounds in purity states being obtained in the first and last steps.

3. Conclusions

The chemoenzymatic preparation of optically active *trans*-*N*-Boc-cyclohexane-1,2-diamine starting from commercially available and inexpensive reagents has been carried out. This mono-carbamate and its cyclopentylic analogous have been the key compounds in the synthesis of several optically active *trans*-*N*-(arylmethyl)-*N*-methylcyclopentane- and cyclohexane-1,2-diamines. The simplicity and high efficacy of the method will allow its application in the preparation of other primary–tertiary vicinal diamine derivatives.

4. Experimental section

4.1. General

Lipase B from *C. antarctica* (Novozyme 435, available immobilized on polyacrylamide, 7300 PLU/g) was gifted by Novo Nordisk Co. For the enzymatic reactions, ethyl acetate of spectrophotometric grade (stored with 4 Å molecular sieves), anhydrous 1,4-dioxane and (±)-1-phenylethyl acetate were used. Melting points were taken on samples in open capillary tubes and are uncorrected. ^{1}H NMR and proton-decoupled ^{13}C NMR spectra ($CDCl_3$ solutions) were obtained using AC-300 or DPX-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) and AV-400 MHz (^{1}H, 400.13 MHz and ^{13}C, 100.63 MHz) spectrometers using the δ scale (ppm) for chemical shifts; calibration was made on the $CDCl_3$ (^{13}C; 76.95 ppm) or the residual $CHCl_3$ (^{1}H; 7.26 ppm) signals.

In Figure 2 we show the cyclohexylic compounds with the numbering used in the assignation of the ^{1}H NMR signals.

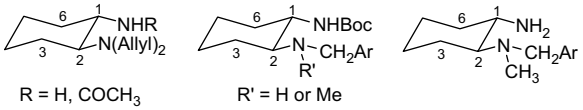


Figure 2. Cyclohexylic compounds.

4.2. Synthesis of racemic *trans*-*N*,*N*-diallylcyclohexane-1,2-diamine (±)-4

Starting from cyclohexene oxide (9.4 mmol) and diallylamine (13.2 mmol), and following the method described in Ref. 12, (±)-**4** was prepared in 90% overall yield. Bp 67 °C (0.1 mmHg). ^{1}H NMR (400 MHz): δ (ppm)=1.11 (m, 4H), 1.62 (m, 1H), 1.74 (m, 2H), 1.98 (m, 1H), 2.14 (br s, 2H, NH_2), 2.25 (td, 1H, $^3J_{1ax,2ax}$=$^3J_{2ax,3ax}$=11.2 Hz, $^3J_{2ax,3eq}$=3.5 Hz, H-2), 2.61 (td, 1H, $^3J_{1ax,2ax}$=$^3J_{1ax,6ax}$=11.2 Hz, $^3J_{1ax,6eq}$=4.2 Hz, H-1), 2.88 (dd, 2H, $|^2J|$=14.2 Hz, ^3J=7.8 Hz, N–C*H*H–CH=CH_2), 3.27 (ddt, 2H, $|^2J|$=14.2 Hz, ^3J=4.6 Hz, ^4J=1.2 Hz, N–CH*H*–CH=CH_2), 5.06 [ddt, 2H, $^3J_{cis}$=10.3 Hz (d), $|^2J|$=2.0 Hz (d), ^4J=1.2 Hz (t), =C*H*H], 5.14 [ddt, 2H, $^3J_{trans}$=17.2 Hz (d), $|^2J|$=2.0 Hz (d), ^4J=1.2 Hz (t), =CH*H*], 5.79 (dddd, 2H, ^3J=17.2, 10.3, 4.6 and 7.8 Hz, HC=); ^{13}C NMR (75.5 MHz): δ (ppm)=22.7 (CH_2), 24.8 (CH_2), 25.5

(CH_2), 34.5 (CH_2), 51.1 (CH), 52.4 (CH_2), 65.0 (CH), 116.0 (CH_2), 137.5 (CH). MS (ESI), *m*/*z* (%)=195 [$(M+H)^+$, 100]. Anal. Calcd for $C_{12}H_{22}N_2$: C, 74.17; H, 11.41; N, 14.42. Found: C, 74.02; H, 11.56; N, 14.21.

4.3. Enzymatic resolution of (±)-4 (Table 1, entry 2)

To a mixture of (±)-**4** (2.5 mmol) and CAL-B (250 mg) under a nitrogen atmosphere, anhydrous 1,4-dioxane (11 mL) and ethyl acetate (15 mmol) were added. The mixture was circularly shaken at 28 °C and 200 rpm for 68 h. After, the enzyme was filtered and washed with Methanol. Once solvents were eliminated, the reaction crude was dissolved in methanol (10 mL) and treated with di-*tert*-butyl pyrocarbonate (1.1 equiv) After 6 h of reaction at room temperature, solvents were eliminated and the crude submitted to flash chromatography (a gradient of hexane–ethyl acetate 10:1 to ethyl acetate was used as eluent) to yield pure acetamide (1*R*,2*R*)-**5** and carbamate (1*S*,2*S*)-**6**.

*4.3.1. (1R,2R)-N-[2-(Diallylamino)cyclohexyl]acetamide [(1R,2R)-**5**].* Yield: 44%; white solid, mp: 103–104 °C. $[\alpha]_D^{20}$ −19.8 (*c* 1.0, $CHCl_3$), ee=99%; ^{1}H NMR (300 MHz): δ (ppm)=1.06 (qd, 1H, $^3J_{ax,ax}$=$|^2J|$=12.3 Hz, $^3J_{ax,eq}$=3.5 Hz, Hax), 1.15 (m, 2H), 1.28 (m, 1H), 1.64 (m, 1H), 1.73 (m, 1H), 1.83 (m, 1H), 1.95 (s, 3H, CH_3), 2.47 (m, 2H, H-2 and Heq), 2.85 (dd, 2H, $|^2J|$=14.3 Hz, ^3J=7.9 Hz, 2×N–C*H*H–CH=CH_2), 3.25 (m, 2H, 2×N–CH*H*–CH=CH_2), 3.51 (m, 1H, H-1), 5.07–5.19 (m, 4H, 2×=CH_2), 5.72 (m, 2H, 2×HC=), 6.04 (br s, 1H, NH); ^{13}C NMR (75.5 MHz): δ (ppm)=23.3 (CH_2), 23.4 (CH_3), 24.5 (CH_2), 25.3 (CH_2), 32.7 (CH_2), 50.8 (CH), 52.0 (CH_2), 61.7 (CH), 116.5 (CH_2), 137.0 (CH), 170.1 (C=O). MS (EI), *m*/*z* (%)=236 ($M^{\bullet+}$, 2), 195 [$(M-CH_2-CH=CH_2)^+$, 100]. Anal. Calcd for $C_{14}H_{24}N_2O$: C, 71.14; H, 10.23; N, 11.85. Found: C, 70.98; H, 10.37; N, 11.95.

*4.3.2. (1S,2S)-tert-Butyl-N-[2-(diallylamino)cyclohexyl]-carbamate [(1S,2S)-**6**].* Yield: 45%; white foam. $[\alpha]_D^{20}$ +16.4 (*c* 1.0, $CHCl_3$), ee=95%; ^{1}H NMR (300 MHz): δ (ppm)=0.93–1.27 (m, 4H), 1.43 (s, 9H, ^{t}Bu), 1.60–1.91 (m, 3H), 2.37 (m, 2H), 2.84 (dd, 2H, $|^2J|$=14.0 Hz, ^3J=7.9 Hz, 2×N–C*H*H–CH=CH_2), 3.25 (m, 3H, H-1 and 2×N–CH*H*–CH=CH_2), 5.00–5.24 (m, 5H, 2×=CH_2 and NH), 5.72 (m, 2H, 2×HC=); ^{13}C NMR (75.5 MHz): δ (ppm)=20.5 (CH_2), 24.6 (CH_2), 25.4 (CH_2), 28.4 (3×CH_3), 33.4 (CH_2), 51.7 (CH), 52.3 (CH_2), 62.0 (CH), 78.7 (C), 116.4 (CH_2), 137.3 (CH), 156.3 (C=O). MS (ESI), *m*/*z* (%)=295 [$(M+H)^+$, 100]. Anal. Calcd for $C_{17}H_{30}N_2O_2$: C, 69.35; H, 10.27; N, 9.51. Found: C, 69.12; H, 10.43; N, 9.30.

*4.3.3. Determination of enantiomeric excesses of **5** and **6**.* Chiral HPLC was used. Conditions: Chiralpak AS column (25 cm×4.6 mm i.d.), hexane–isopropyl alcohol (H/^{i}PA) mixtures, *T*=40 °C. For (±)-**5**: H/^{i}PA 90:10; 0.8 mL/min; t_R=9.6 (*R*,*R*) and 13.9 (*S*,*S*) min; R_S=2.8. For (±)-**6**: H/^{i}PA 98:2; 0.3 mL/min; t_R=11.2 (*R*,*R*) and 12.2 (*S*,*S*) min; R_S=1.0.

4.4. (1*S*,2*S*)-*tert*-Butyl-*N*-(2-aminocyclohexyl)carbamate (1*S*,2*S*)-7b

It was obtained from (1*S*,2*S*)-**6** following the method described in Ref. 12. Yield: 81% (purified by flash chromatography using successively ethyl acetate and ethyl acetate–methanol 10:1 as eluents); cream solid, mp: 118–119 °C. Spectral data are in good agreement with those previously published.[21]

In order to establish the configuration of the compounds isolated in the enzymatic reaction, the sign of the optical rotation of (1*S*,2*S*)-**7b** ($[\alpha]_D^{20}$ +25.8 (*c* 1.0, $CHCl_3$), ee=99%) was compared to that reported in the Aldrich catalogue (see Ref. 16), good correlation being observed between both values. However, when the optical rotation was measured in methanol, the value obtained for our compound differed of that reported in Ref. 21. Thus, for (1*S*,2*S*)-**7b** $[\alpha]_D^{20}$ +30.8 (*c* 1.0, MeOH), ee=99%, the value given in Ref. 21 for this compound being $[\alpha]_D^{23}$ +42.99 (*c* 0.98, MeOH), ee≥99%.

4.5. Reductive-amination of aromatic aldehydes with (1*S*,2*S*)-7a,b. General procedure

The aromatic aldehyde (1.39 mmol) was added under a nitrogen atmosphere to a solution of the corresponding (1*S*,2*S*)-**7** (1.39 mmol) in anhydrous methanol (5 mL). After 5 h stirring at room temperature, sodium borohydride (2.1 mmol) was slowly added in portions. After 12 h, the solvent was evaporated. Except for **8a**, the resulting crude was washed with water and dried under reduced pressure to yield pure the corresponding aminocarbamate. In the case of **8a**, the crude was dissolved in CH_2Cl_2 and the organic solution washed with water. The subsequent elimination of the solvent yielded pure **8a**.

*4.5.1. (1S,2S)-tert-Butyl-N-{2-[(1-naphthylmethyl)amino]cyclopentyl}-carbamate [(1S,2S)-**8a**].* Yield: 98%; white foam, $[\alpha]_D^{20}$ +14.5 (*c* 1.0, $CHCl_3$), ee=99%; ^{1}H NMR (400 MHz): δ (ppm)=1.28–1.57 [m+s, 11H. Singlet corresponds to ^{t}Bu (1.46 ppm)], 1.63 (m, 1H), 1.72 (m, 1H), 1.97 (m, 2H), 2.11 (m, 1H), 2.95 (q, 1H, ^3J=6.4 Hz, H-2), 3.83 (br m, 1H, H-1), AB system (δ_A=4.24, δ_B=4.27 $|^2J_{A,B}|$=13.0 Hz, N–CH_2–Ar), 4.78 (br s, 1H, NH), 7.42–7.54 (m, 4H), 7.75 (d, 1H, ^3J=8.1 Hz), 7.84 (d, 1H, ^3J=8.1 Hz), 8.15 (d, 1H, ^3J=8.1 Hz); ^{13}C NMR (100.6 MHz): δ (ppm)=21.3 (CH_2), 28.2 (3×CH_3), 30.9 (CH_2), 31.2 (CH_2), 49.6 (CH_2), 57.4 (CH), 65.9 (CH), 78.7 (C), 123.5 (CH), 125.1 (CH), 125.2 (CH), 125.7 (CH), 125.8 (CH), 127.3 (CH), 128.3 (CH), 131.5 (C), 133.6 (C), 135.8 (C), 155.5 (C=O). MS (ESI), *m*/*z* (%)=341 [$(M+H)^+$, 100]. Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 74.24; H, 8.47; N, 8.11.

*4.5.2. (1S,2S)-tert-Butyl-N-{2-[(1-naphthylmethyl)amino]cyclohexyl}-carbamate [(1S,2S)-**8b**].* Yield: 99%; white solid, mp: 150–152 °C. $[\alpha]_D^{20}$ +31.4 (*c* 1.0, $CHCl_3$), ee=99%; ^{1}H NMR (300 MHz): δ (ppm)=1.05–1.50 [m+s, 13H. Singlet corresponds to Bu^t (1.40 ppm)], 1.62–1.83 (m, 3H), 2.10 (br d, 1H, $|^2J|$=11.0 Hz), 2.21 (br d, 1H, $|^2J|$=11.0 Hz), 2.34 (br t, 1H, $^3J_{1ax,2ax}$=$^3J_{2ax,3ax}$=9.8 Hz, H-2), 3.35 (br m, 1H, H-1), 4.11 (d, 1H, $|^2J|$=12.9 Hz, N–C*H*H–Ar), 4.35 (d, 1H, $|^2J|$=12.9 Hz, N–CH*H*–Ar), 4.53 (br s, 1H, NH), 7.48 (m, 4H), 7.75 (d, 1H, ^3J=8.1 Hz), 7.84 (d, 1H, ^3J=7.6 Hz), 8.14 (d, 1H, ^3J=8.1 Hz); ^{13}C NMR (75.5 MHz): δ (ppm)=24.5 (CH_2), 24.6 (CH_2), 28.2 (3×CH_3), 31.4 (CH_2), 32.6 (CH_2),,48.14 (CH_2), 54.0 (CH), 60.74 (CH), 78.8 (C), 123.6 (CH), 125.1 (CH), 125.3 (CH), 125.8 (CH), 126.0 (CH), 127.5 (CH), 128.4 (CH), 131.6 (C), 133.6 (C), 136.1 (C), 155.8 (C=O). MS (ESI), *m*/*z* (%)=355 [$(M+H)^+$, 100], 377 [$(M+Na)^+$, 54]. Anal. Calcd for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.31; H, 8.57; N, 7.66.

*4.5.3. (1S,2S)-tert-Butyl-N-{2-[(2-naphthylmethyl)amino]cyclopentyl}-carbamate [(1S,2S)-**9a**].* Yield: 96%; white solid, mp: 112–114 °C. $[\alpha]_D^{20}$ +1.9 (*c* 1.0, $CHCl_3$), ee=99%; ^{1}H NMR (300 MHz): δ (ppm)=1.23–1.50 [m+s, 11H. Singlet corresponds to ^{t}Bu (1.46 ppm)], 1.54–1.82 (m, 2H), 1.95 (m+br s, 2H), 2.12 (m, 1H), 2.85 (q, 1H, ^3J=6.7 Hz, H-2), 3.78 (br m, 1H, H-1), 3.92 (d, 1H, $|^2J|$=12.0 Hz, N–C*H*H–Ar), 4.03 (d, 1H, $|^2J|$=12.0 Hz, N–CH*H*–Ar), 4.51 (br s, 1H, NH), 7.42–7.51 (m, 3H), 7.75 (s, 1H), 7.81 (m, 3H); ^{13}C NMR (75.5 MHz): δ (ppm)=21.5 (CH_2), 28.3 (3×CH_3), 31.1 (CH_2), 31.5 (CH_2), 52.0 (CH_2), 57.6 (CH), 64.9 (CH), 79.1 (C), 125.3 (CH), 125.8 (CH), 126.3 (CH), 126.4 (CH), 127.4 (CH), 127.5 (CH), 127.8 (CH), 132.4 (C), 133.2 (C), 137.8 (C), 155.7 (C=O). MS (ESI), *m*/*z* (%)=341 [$(M+H)^+$, 100], 681 [$(2M+H)^+$, 18]. Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 73.92; H, 8.54; N, 8.01.

*4.5.4. (1S,2S)-tert-Butyl-N-{2-[(2-naphthylmethyl)amino]cyclohexyl}-carbamate [(1S,2S)-**9b**].* Yield: 98%; white solid, mp: 229–231 °C. $[\alpha]_D^{20}$ +80.4 (*c* 1.0, $CHCl_3$), ee=99%; ^{1}H NMR (300 MHz): δ (ppm)=1.10–1.40 (m, 4H), 1.47 (s, 9H), 1.69 (m, 2H), 1.84 (br s, 1H,

NH), 2.02–2.20 (m, 2H), 2.29 (td, 1H, $^3J_{1ax,2ax}=^3J_{2ax,3ax}=10.1$ Hz, $^3J_{2ax,3eq}=3.9$ Hz, H-2), 3.37 (br m, 1H, H-1), 3.86 (d, 1H, $|^2J|=13.4$ Hz, N–C*H*H–Ar), 4.07 (d, 1H, $|^2J|=13.4$ Hz, N–CH*H*–Ar), 4.50 (br s, 1H, NH), 7.46 (m, 3H), 7.76 (s, 1H), 7.80 (m, 3H); ^{13}C NMR (75.5 MHz): δ (ppm)=24.6 (CH_2), 24.8 (CH_2), 28.3 (3×CH_3), 31.6 (CH_2), 32.8 (CH_2), 50.4 (CH_2), 54.2 (CH), 60.4(CH), 79.1 (C), 125.4 (CH), 125.8 (CH), 126.2 (CH), 126.5 (CH), 127.53 (CH), 127.56 (CH), 127.9 (CH), 132.5 (C), 133.3 (C), 138.3 (C), 156.0 (C=O). MS (ESI), *m*/*z* (%)=355 [$(M+H)^+$, 100], 377 [$(M+Na)^+$, 40]. Anal. Calcd for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.37; H, 8.36; N, 8.07.

*4.5.5. (1S,2S)-tert-Butyl-N-{2-[(9-anthrylmethyl)amino]cyclopentyl}-carbamate [(1S,2S)-**10a**].* Yield: 93%; yellow solid, mp: 145–146 °C. $[\alpha]_D^{20}$ +16.4 (*c* 1.0, $CHCl_3$), ee=99%; ^{1}H NMR (300 MHz): δ (ppm)= 1.23–1.55 [m+s, 11H. Singlet corresponds to ^{t}Bu (1.37 ppm)], 1.63–1.95 (m, 3H), 2.14 (m, 2H), 3.13 (q, 1H, ^3J=6.3 Hz, H-2), 3.90 (br m, 1H, H-1), 4.54 (br s, 1H, NH), 4.78 (s, 2H, N–CH_2–Ar), 7.40–7.60 (m, 4H), 8.00 (d, 2H, ^3J=8.3 Hz), 8.32–8.48 (m, 3H); ^{13}C NMR (75.5 MHz): δ (ppm)=21.6 (CH_2), 28.3 (3×CH_3), 31.3 (CH_2), 31.7 (CH_2), 44.2 (CH_2), 57.6 (CH), 66.5 (CH), 79.1 (C), 124.1 (CH), 124.8 (CH), 125.9 (CH), 127.0 (CH), 128.9 (CH), 130.1 (C), 131.4 (C), 155.7 (C=O). MS (ESI), *m*/*z* (%)=391 [$(M+H)^+$, 100]. Anal. Calcd for $C_{25}H_{30}N_2O_2$: C, 76.89; H, 7.74; N, 7.17. Found: C, 76.73; H, 7.95, N, 7.02.

*4.5.6. (1S,2S)-tert-Butyl-N-{2-[(9-anthrylmethyl)amino]cyclohexyl}-carbamate [(1S,2S)-**10b**].* Yield: 98%; yellow solid, mp: 176–177 °C. $[\alpha]_D^{20}$ +36.2 (*c* 1.0, $CHCl_3$), ee=99%; ^{1}H NMR (400 MHz): δ (ppm)=1.15 (m, 1H), 1.27–1.42 [m+s, 11H. Singlet corresponds to ^{t}Bu (1.36 ppm)], 1.49 (m, 1H), 1.60–1.75 (m, 2H, Heq and NH), 1.82 (br d, 1H, $|^2J|=11.7$ Hz, Heq), 2.15 (br d, 1H, $|^2J|=11.7$ Hz, Heq), 2.35 (br d, 1H, $|^2J|=12.7$ Hz, Heq), 2.55 (td, 1H, $^3J_{2ax,1ax}=^3J_{2ax,3ax}=10.5$ Hz, $^3J_{2ax,3ec}=3.9$ Hz, H-2), 3.38 (m, 1H, H-1), 4.58 (br s, 1H, NH), 4.62 (d, 1H, $|^2J|=12.0$ Hz, N–C*H*H–Ar), 4.80 (d, 1H, $|^2J|=12.0$ Hz, N–CH*H*–Ar), 7.42–7.58 (m, 4H), 7.99 (d, 2H, ^3J=8.8 Hz), 8.32 (d, 2H, ^3J=8.8 Hz), 8.39 (s, 1H); ^{13}C NMR (75.5 MHz): δ (ppm)=24.7 (2×CH_2), 28.2 (3×CH_3), 31.6 (CH_2), 32.7 (CH_2), 42.1 (CH_2), 53.7 (CH), 61.0 (CH), 79.0 (C), 124.0 (CH), 124.8 (CH), 126.0 (CH), 127.0 (CH), 129.0 (CH), 130.1 (C), 131.4 (C), 155.8 (C=O). MS (ESI), *m*/*z* (%)=405 [$(M+H)^+$, 100]. Anal. Calcd for $C_{26}H_{32}N_2O_2$: C, 77.19; H, 7.97; N, 6.92. Found: C, 77.38; H, 8.16; N, 6.75.

4.6. General procedure for the N-methylation of (1*S*,2*S*)-8–10

To a solution of the corresponding aminocarbamate **8**–**10** (1.24 mmol) in anhydrous methanol (8 mL), methyl iodide (1.49 mmol) was added. After 12 h stirring at room temperature, *N*,*N*-diisopropylethylamine (1.24 mmol) and methyl iodide (two successive additions of 0.62 mmol) were added under nitrogen atmosphere and the mixture was stirred for another 20 h. Then, the solution was evaporated to dryness, the crude was dissolved in CH_2Cl_2 (15 ml) and washed with aqueous 3 N NaOH (2×15 ml) and brine (10 ml). The organic layer was dried with Na_2SO_4, and evaporated under reduced pressure. The resulting crude was purified by flash chromatography (mixtures of hexane–ethyl acetate).

*4.6.1. (1S,2S)-tert-Butyl-N-{2-[(methyl)(1-naphthylmethyl)amino]-cyclopentyl}carbamate [(1S,2S)-**11a**].* Yield: 81%; white foam. $[\alpha]_D^{20}$ +10.2 (*c* 1.0, $CHCl_3$), ee=99%; ^{1}H NMR (400 MHz): δ (ppm)=1.32–1.75 [m+s, 14H. Singlet corresponds to ^{t}Bu (1.46 ppm)], 2.16 (m, 1H), 2.25 (s, 3H, N–CH_3), 2.81 (m, 1H, H-2), 3.95 (m, 1H, H-1), 3.95 (d, 1H, $|^2J|=13.1$ Hz, N–C*H*H–Ar), 4.11 (d, 1H, $|^2J|=13.1$ Hz, N–CH*H*–Ar), 4.58 (br s, 1H, NH), 7.47 (m, 4H), 7.77 (d, 1H, ^3J=7.8 Hz), 7.85 (d, 1H, ^3J=7.8 Hz), 8.31 (d, 1H, ^3J=7.8 Hz); ^{13}C NMR (100.6 MHz): δ (ppm)=20.6 (CH_2), 22.6 (CH_2), 28.3 (3×CH_3), 31.4 (CH_2), 37.3 (CH_3), 52.3 (CH), 57.7 (CH_2), 70.0 (CH), 78.7 (C), 124.4 (CH), 125.0 (CH), 125.4 (CH), 125.6 (CH), 127.1 (CH), 127.7 (CH), 128.2 (CH), 132.2 (C), 133.7 (C), 134.8 (C), 155.5 (C=O). MS (ESI), *m*/*z* (%)=355 [$(M+H)^+$, 100], 731 [$(2M+Na)^+$, 18]. Anal. Calcd for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.68; H, 8.69; N, 7.75.

*4.6.2. (1S,2S)-tert-Butyl-N-{2-[(methyl)(1-naphthylmethyl)amino]-cyclohexyl}carbamate [(1S,2S2S)-**11b**].* Yield: 85%; white foam. $[\alpha]_D^{20}$ +15.5 (*c* 1.0, $CHCl_3$), ee=99%; ^{1}H NMR (300 MHz): δ (ppm)=0.94 [qd, 1H, $^3J_{ax,ax}=|^2J|=12.8$ Hz (q), $^3J_{ax,eq}=3.6$ Hz (d), Hax], 1.03–1.50 [m+s, 12H. Singlet corresponds to ^{t}Bu (1.41 ppm)], 1.64 (br d, 1H, $|^2J|=10.7$ Hz), 1.81 (m, 1H), 1.99 (br d, 1H, $|^2J|=11.2$ Hz), 2.22 (s, 3H, N–CH_3), 2.29 (td, 1H, $^3J_{1ax,2ax}=^3J_{2ax,3ax}=11.3$ Hz, $^3J_{2ax,3eq}=3.2$ Hz, H-2), 2.39 (br d, 1H, $|^2J|=12.3$ Hz), 3.31 (m, 1H, H-1), 3.94 (d, 1H, $|^2J|=12.9$ Hz, N–C*H*H–Ar), 4.11 (d, 1H, $|^2J|=12.9$ Hz, N–CH*H*–Ar), 5.01 (br s, 1H, NH), 7.35–7.60 (m, 4H), 7.78 (m, 1H), 7.86 (d, 1H, ^3J=7.9 Hz), 8.23 (d, 1H, ^3J=7.9 Hz); ^{13}C NMR (75.5 MHz): δ (ppm)=22.0 (CH_2), 24.5 (CH_2), 25.3 (CH_2), 28.3 (3×CH_3), 33.1 (CH_2), 35.8 (CH_3), 51.6 (CH), 56.6 (CH_2), 64.1 (CH), 78.5 (C), 124.3 (CH), 125.0 (CH), 125.6 (CH), 125.9 (CH), 127.1 (CH), 127.9 (CH), 128.5 (CH), 132.3 (C), 133.8 (C), 134.8 (C), 156.1 (C=O). MS (ESI), *m*/*z* (%)=369 [$(M+H)^+$, 100], 391 [$(M+Na)^+$, 70]. Anal. Calcd for $C_{23}H_{32}N_2O_2$: C, 74.96; H, 8.75; N, 7.60. Found: C, 75.19; H, 8.58; N, 7.35.

*4.6.3. (1S,2S)-tert-Butyl-N-{2-[(methyl)(2-naphthylmethyl)amino]-cyclopentyl}carbamate [(1S,2S)-**12a**].* Yield: 86%; white foam. $[\alpha]_D^{20}$ +8.6 (*c* 1.0, $CHCl_3$), ee=99%; ^{1}H NMR (300 MHz): δ (ppm)=1.30–1.90 [m+s, 14H. Singlet corresponds to ^{t}Bu (1.51 ppm)], 2.13 (m, 1H), 2.27 (s, 3H), 2.77 (br q, 1H, ^3J=6.9 Hz, H-2), 3.69 (d, 1H, $|^2J|=13.2$ Hz, N–C*H*H–Ar), 3.78 (d, 1H, $|^2J|=13.2$ Hz, N–CH*H*–Ar), 3.99 (br m, 1H, H-1), 4.70 (br s, 1H, NH), 7.46 (m, 3H), 7.75 (s, 1H), 7.83 (m, 3H); ^{13}C NMR (75.5 MHz): δ (ppm)=21.0 (CH_2), 24.1 (CH_2), 28.3 (3×CH_3), 31.9 (CH_2), 38.0 (CH_3), 52.6 (CH), 59.0 (CH_2), 70.3 (CH), 78.9 (C), 125.3 (CH), 125.7 (CH), 127.0 (2CH), 127.5 (2CH), 127.7 (CH), 132.5 (C), 133.1 (C), 137.1 (C), 155.4 (C=O). MS (ESI), *m*/*z* (%)=355 [$(M+H)^+$, 100], 709 [$(2M+H)^+$, 23]. Anal. Calcd for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.71; H, 8.72; N, 7.96.

*4.6.4. (1S,2S)-tert-Butyl-N-{2-[(methyl)(2-naphthylmethyl)amino]cyclo-hexyl}carbamate [(1S,2S)-**12b**].* Yield: 95%; white foam. $[\alpha]_D^{20}$ +20.2 (*c* 1.0, $CHCl_3$), ee=99%; ^{1}H NMR (300 MHz): δ (ppm)=1.12–1.42 (m, 4Hax), 1.50 (s, 9H), 1.68 (br d, 1H, $|^2J|=13.9$ Hz, Heq), 1.84 (br d, 1H, $|^2J|=11.7$ Hz, Heq), 1.99 (br d, 1H, $|^2J|=12.6$ Hz, Heq), 2.32 (s, 3H, N–CH_3), 2.41 (m, 2H), 3.39 (m, 1H, H-1), 3.50 (d, 1H, $|^2J|=13.3$ Hz, N–C*H*H–Ar), 3.88 (d, 1H, $|^2J|=13.3$ Hz, N–CH*H*–Ar), 5.30 (br s, 1H, NH), 7.46 (m, 3H), 7.71 (s, 1H), 7.82 (m, 3H); ^{13}C NMR (75.5 MHz): δ (ppm)=22.7 (CH_2), 24.6 (CH_2), 25.4 (CH_2), 28.5 (3×CH_3), 33.4 (CH_2), 37.1 (CH_3), 51.8 (CH), 56.8 (CH_2), 65.9 (CH), 78.8 (C), 125.4. (CH), 125.8 (CH), 127.0 (2CH), 127.5 (2CH), 127.8 (CH), 132.7 (C), 133.3 (C), 137.4 (C), 156.1 (C=O). MS (ESI), *m*/*z* (%)=369 [$(M+H)^+$, 100], 759 [$(2M+Na)^+$, 18]. Anal. Calcd for $C_{23}H_{32}N_2O_2$: C, 74.96; H, 8.75; N, 7.60. Found: C, 75.15; H, 8.49; N, 7.65.

*4.6.5. (1S,2S)-tert-Butyl-N-{2-[(9-anthrylmethyl)-(methyl)amino]cyclo-pentyl}carbamate [(1S,2S)-**13a**].* Yield: 82%; yellow solid, mp: 157–158 °C. $[\alpha]_D^{20}$ +25.3 (*c* 1.0, $CHCl_3$), ee=99%; ^{1}H NMR (300 MHz): δ (ppm)=1.20–1.50 [m+s, 10H. Singlet corresponds to ^{t}Bu (1.45 ppm)], 1.53–1.90 (m, 4H), 2.18–2.30 [m+s, 4H. Singlet corresponds to N–CH_3 (2.26)], 2.83 (m, 1H, H-2), 3.93 (m, 1H, H-1), 4.42–4.67 [m, 3H, AB system corresponding to N–CH_2–Ar ($|^2J|=13.0$ Hz) overlapped with NH], 7.40–7.57 (m, 4H), 8.01 (d, 2H, ^3J=8.2 Hz), 8.41 (s, 1H), 8.49 (d, 2H, ^3J=9.0 Hz); ^{13}C NMR (75.5 MHz): δ (ppm)=20.6 (CH_2), 22.6 (CH_2), 28.6 (3×CH_3), 31.3 (CH_2), 36.6 (CH_3), 51.0 (CH_2), 52.4 (CH), 69.9 (CH), 78.9 (C), 124.75 (CH), 124.79 (CH), 125.6 (CH), 127.3 (CH), 128.9 (CH), 130.3 (C), 131.2 (C), 131.3 (C), 155.7 (C=O). MS (ESI), *m*/*z* (%)=405 [$(M+H)^+$, 100]. Anal. Calcd for $C_{26}H_{32}N_2O_2$: C, 77.19; H, 7.97; N, 6.92. Found: C, 76.95; H, 8.19; N, 6.75.

*4.6.6. (1S,2S)-tert-Butyl-N-{2-[(9-anthrylmethyl)(methyl)amino]cyclo-hexyl}carbamate [(1S,2S)-**13b**].* Yield: 79%; yellow foam. $[\alpha]_D^{20}$ +54.3

(*c* 1.0, $CHCl_3$), ee=99%; ^{1}H NMR (400 MHz): δ (ppm)=0.76 [qd, 1H, $^3J_{ax,ax}$=|^2J|=13.2 Hz (q), $^3J_{ax,eq}$=3.7 Hz (d), Hax], 1.05–1.60 [m+s, 13H. Singlet corresponds to Bu^t (1.37 ppm)], 1.81 (br d, 1H, |^2J|=11.0 Hz, Heq), 2.12–2.25 (m, 2H), 2.28 (s, 3H, N-CH_3), 2.35 (br d, 1H, |^2J|=13.2 Hz, Heq), 3.24 (tt, 1H, $^3J_{1ax,2ax}$=$^3J_{1ax,6ax}$=10.5 Hz, $^3J_{1ax,6eq}$=$^3J_{1ax,NH}$=3.9 Hz, H-1), 4.52 (d, 1H, |^2J|=13.0 Hz, N-C*H*H–Ar), 4.62 (d, 1H, |^2J|=13.0 Hz, N–CH*H*–Ar), 4.87 (br s, 1H, NH), 7.43–7.56 (m, 4H), 8.01 (d, 2H, ^3J=8.6 Hz), 8.41 (m, 3H); ^{13}C NMR (75.5 MHz): δ (ppm)=23.0 (CH_2), 24.4 (CH_2), 25.2 (CH_2), 28.3 (3×CH_3), 32.8 (CH_2), 35.0 (CH_3), 49.7 (CH_2), 51.4 (CH), 63.1 (CH), 78.2 (C), 124.3 (CH), 124.7 (CH), 125.7 (CH), 127.4 (CH), 129.0 (CH), 130.1 (C), 131.0 (C), 131.3 (C), 156.0 (C=O). MS (ESI), *m*/*z* (%)=419 [(M+H)$^+$, 100]. Anal. Calcd for $C_{27}H_{34}N_2O_2$: C, 77.48; H, 8.19; N, 6.69. Found: C, 77.26; H, 8.42; N, 6.51.

4.7. General procedure for the removal of the Boc group of (1*S*,2*S*)-11–13

To a solution of the corresponding aminocarbamate **11**–**13** (1.07 mmol) in CH_2Cl_2 (3 mL), an aqueous solution of H_3PO_4 (85%, 2 mL) was added. After 4 h stirring, water (3 mL) was added to the mixture and the acid aqueous layer washed with CH_2Cl_2 (2×10 mL). Then, the aqueous layer was basified with NaOH pellets and extracted with CH_2Cl_2 (3×15 mL). The combined basic organic layers were washed with brine (10 ml), dried with Na_2SO_4 and evaporated under reduced pressure to yield the corresponding diamine **14**–**16** in state of purity.

*4.7.1. (1S,2S)-N-Methyl-N-(1-naphthylmethyl)cyclopentane-1,2-diamine [(1S,2S)-**14a**].* Yield: 89%; yellow oil. $[\alpha]_D^{20}$ +90.3 (*c* 1.0, $CHCl_3$), ee=99%; ^{1}H NMR (300 MHz): δ (ppm)=1.27 (m, 1H), 1.51 (br s, 2H, NH_2), 1.62–1.79 (m, 4H), 1.91 (m, 1H), 2.20 (s, 3H, N–CH_3), 2.68 (q, 1H, ^3J=8.1 Hz, H-2), 3.17 (q, 1H, ^3J=8.1 Hz, H-1), AB system (δ_A=3.96, δ_B=4.02, |$^2J_{A,B}$|=13.1 Hz, N–C*H*$_2$–Ar), 7.35–7.58 (m, 4H), 7.76 (d, 1H, ^3J=7.7 Hz), 7.84 (dd, 1H, *J*=1.7 and 7.7 Hz), 8.32 (d, 1H, ^3J=8.0 Hz); ^{13}C NMR (75.5 MHz): δ (ppm)=20.4 (CH_2), 21.3 (CH_2), 32.6 (CH_2), 36.8 (CH_3), 53.7 (CH), 58.3 (CH_2), 73.3 (CH), 124.3 (CH), 124.8 (CH), 125.2 (CH), 125.3 (CH), 126.8 (CH), 127.5 (CH), 128.1 (CH), 132.1 (C), 133.6 (C), 135.0 (C). MS (EI), *m*/*z* (%)=254 (M$^{\bullet+}$, 16), 210 (28), 170 (57), 141 (100). HRMS (EI) calcd for $C_{17}H_{22}N_2$ (M$^{\bullet+}$): 254.1783; found: 254.1786.

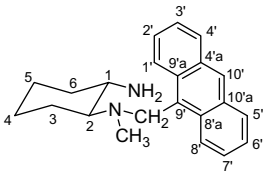
*4.7.2. (1S,2S)-N-Methyl-N-(1-naphthylmethyl)cyclohexane-1,2-diamine [(1S,2S)-**14b**].* Yield: 89%; white solid, mp: 74–76 °C. $[\alpha]_D^{20}$ +55.5 (*c* 1.0, $CHCl_3$), ee=99%; ^{1}H NMR (300 MHz): δ (ppm)=1.08–1.33 (m, 4H), 1.61–1.75 [m+s, 3H. Singlet corresponds to NH_2 (1.72)], 1.85 (m, 1H), 1.95 (m, 2H), 2.16 (s, 3H, N–CH_3), 2.29 (td, 1H, $^3J_{1ax,2ax}$=$^3J_{2ax,3ax}$=10.3 Hz, $^3J_{2ax,3eq}$=3.5 Hz, H-2), 2.67 (td, 1H, $^3J_{1ax,2ax}$=$^3J_{1ax,6ax}$=10.3 Hz, $^3J_{1ax,6eq}$=4.1 Hz, H-1), 4.03 (s, 2H, N–C*H*$_2$–Ar), 7.33–7.62 (m, 4H), 7.77 (dd, 1H, *J*=2.9 and 6.6 Hz), 7.83 (d, 1H, ^3J=7.9 Hz), 8.26 (d, 1H, ^3J=7.5 Hz); ^{13}C NMR (100 MHz): δ (ppm)=21.6 (CH_2), 25.1 (CH_2), 25.7 (CH_2), 35.1 (CH_2), 35.3 (CH_3), 51.4 (CH), 57.4 (CH_2), 68.8 (CH), 124.6 (CH), 125.0 (CH), 125.5 (CH), 125.6 (CH), 127.0 (CH), 127.8 (CH), 128.4 (CH), 132.4 (C), 133.8 (C), 135.4 (C). MS (EI), *m*/*z* (%)=268 (M$^{\bullet+}$, 8), 210 (12), 170 (69), 141 (100). HRMS (EI) calcd for $C_{18}H_{24}N_2$ (M$^{\bullet+}$): 268.1939; found: 268.1938.

*4.7.3. (1S,2S)-N-Methyl-N-(2-naphthylmethyl)cyclopentane-1,2-diamine [(1S,2S)-**15a**].* Yield: 97%; white foam. $[\alpha]_D^{20}$ +61.0 (*c* 1.0, $CHCl_3$), ee=99%; ^{1}H NMR (400 MHz): δ (ppm)=1.27 (m, 1H), 1.58 (s, 2H, NH_2), 1.62 (m, 3H), 1.74 (m, 1H), 1.93 (m, 1H), 2.22 (s, 3H, N-CH_3), 2.64 (q, 1H, ^3J=7.8 Hz, H-2), 3.18 (q, 1H, ^3J=7.8 Hz), 3.65 (d, 1H, |^2J|=13.2 Hz, N–C*H*H–Ar), 3.76 (d, 1H, |^2J|=13.2 Hz, N–CH*H*–Ar), 7.45 (m, 2H), 7.52 (dd, 1H, *J*=1.5 and 8.6 Hz), 7.79 (s, 1H), 7.81 (m, 3H); ^{13}C NMR (100 MHz): δ (ppm)=20.6 (CH_2), 22.6 (CH_2), 33.1 (CH_2), 37.7 (CH_3), 53.9 (CH), 59.2 (CH_2), 73.3 (CH), 125.0 (CH), 125.4 (CH), 126.6 (CH), 126.7 (CH), 127.2 (2CH), 127.4 (CH), 132.3 (C), 133.0 (C), 137.1 (C). MS (EI), *m*/*z* (%)=254 (M$^{\bullet+}$, 12), 210 (17), 170 (59), 141 (100). HRMS (EI) calcd for $C_{17}H_{22}N_2$ (M$^{\bullet+}$): 254.1783; found: 254.1783.

*4.7.4. (1S,2S)-N-Methyl-N-(2-naphthylmethyl)cyclohexane-1,2-diamine [(1S,2S)-**15b**].* Yield: 91%; white solid, mp: 91–93 °C. $[\alpha]_D^{20}$ +26.2 (*c* 1.0, $CHCl_3$), ee=99%; ^{1}H NMR (400 MHz): δ (ppm)=1.08 (m, 1H), 1.19 (m, 3H), 1.65 (m, 1H), 1.72–2.03 [m+s, 5H. Singlet corresponds to NH_2 (1.92)], 2.16 (s, 3H, N–CH_3), 2.21 (m, 1H, H-2), 2.68 (td, 1H, $^3J_{1ax,2ax}$=$^3J_{1ax,6ax}$=10.2 Hz, $^3J_{1ax,6eq}$=4.2 Hz, H-1), 3.58 (d, 1H, |^2J|=13.2 Hz, N–C*H*H–Ar), 3.80 (d, 1H, |^2J|=13.2 Hz, N–CH*H*–Ar), 7.43 (m, 2H), 7.49 (dd, 1H, *J*=1.5 and 8.6 Hz), 7.70 (s, 1H), 7.79 (m, 3H); ^{13}C NMR (100 MHz): δ (ppm)=21.7 (CH_2), 24.8 (CH_2), 25.5 (CH_2), 34.8 (CH_2), 36.1 (CH_3), 51.1 (CH), 58.0 (CH_2), 69.2 (CH), 125.1 (CH), 125.6 (CH), 126.6 (CH), 126.8 (CH), 127.3 (2CH), 127.6 (CH), 132.4 (C), 133.1 (C), 137.6 (C). MS (ESI), *m*/*z* (%)=269 [(M+H)$^+$, 100]. Anal. Calcd for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44. Found: C, 80.32; H, 9.26; N, 10.18.

*4.7.5. (1S,2S)-N-(9-Anthrylmethyl)-N-methylcyclopentane-1,2-diamine [(1S,2S)-**16a**].* Yield: 99%. Spectral data are in good agreement with those previously published.[11]

*4.7.6. (1S,2S)-N-(9-Anthrylmethyl)-N-methylcyclohexane-1,2-diamine [(1S,2S)-**16b**].*



Yield: 90%; yellow foam. $[\alpha]_D^{20}$ +29.9 (*c* 1.0, $CHCl_3$), ee=99%; ^{1}H NMR (400 MHz): δ (ppm)=1.01 [m, 1H, H-6ax], 1.22 (m, 2H, H-4ax and H-5ax), 1.41 (m, 1H, H-3ax), 1.65 (m, 1H, H-5eq), 1.87 (m, 1H, H-4eq), 1.90 (m, 1H, H-6eq), 2.03–2.20 [6H, m (H-3eq)+br s (NH_2)+s (N–CH_3). Singlets are centred to 2.09 and 2.16, respectively], 2.31 (ddd, 1H, $^3J_{2ax,3ax}$=11.6 Hz, $^3J_{2ax,1ax}$=10.2 Hz, $^3J_{2ax,3eq}$=3.2 Hz, H-2), 2.65 (td, $^3J_{1ax,2ax}$=$^3J_{1ax,6ax}$=10.2 Hz, $^3J_{1ax,6eq}$=4.0 Hz, H-1), 4.50 (d, 1H, |^2J|=12.0 Hz, N–C*H*H–Ar), 4.64 (d, 1H, |^2J|=12.0 Hz, N–CH*H*–Ar), 7.44 [m, 2H, H-3′(H-6′)], 7.51 [m, 2H, H-2′(H-7′)], 7.99 [d, 2H, $^3J_{4',3'}$=8.2 Hz, H-4′(H-5′)], 8.40 (s, 1H, H-10′), 8.42 [d, 2H, $^3J_{1',2'}$=8.8 Hz, H-1′(H-8′)]; ^{13}C NMR (100 MHz): δ (ppm)=22.3 (C-3), 25.0 (C-5), 25.6 (C-4), 34.3 (CH_3), 34.6 (C-6), 50.7 (CH_2), 51.1 (C-1), 67.8 (C-2), 124.7 [C-1′(C-8′) and C-3′(C-6′)], 125.5 [C-2′(C-7′)], 127.3 (C-10′), 129.0 [C-4′(C-5′)], 130.9 (C-9′), 131.2 [C-9′a(C-8′a)], 131.3 [C-4′a(C-10′a)]. MS (EI), *m*/*z* (%)=318 (M$^{\bullet+}$, 71), 220 (100), 191 (92), 127 (70). HRMS (EI) calcd for $C_{22}H_{26}N_2$ (M$^{\bullet+}$): 318.2096; found: 318.2098.

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