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A practical and efficient synthesis of chiral *N,N*-disubstituted C_2 symmetric diamines derived from (*R,R*)-1,2-diaminocyclohexane

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Abstract—An improved synthesis of chiral diamine ligands derived from (*R,R*)-1,2-diaminocyclohexane is described, providing *N*-substituted diamines. The synthesis of other new ligands based on this methodology is also reported.

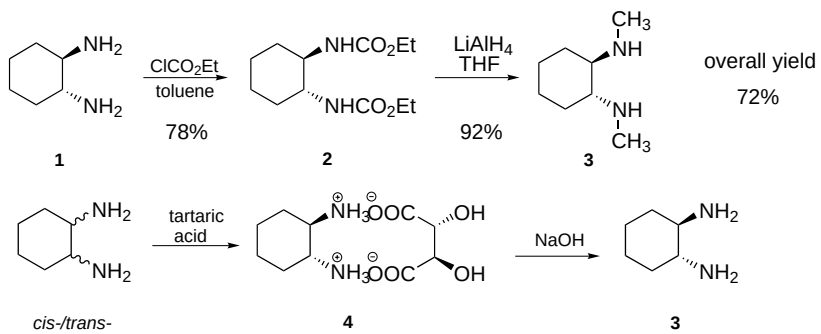
1. Introduction

Chiral diamines possessing C_2 symmetry are particularly attractive auxiliaries in asymmetric synthesis.[1] Among these, compounds derived from (*R,R*)-1,2-diaminocyclohexane are of great interest in our group.[2] In this article, we wish to report a more practical synthesis of these known diamines, and the application of this method in the synthesis of novel diamines.

2. Results and discussion

We have extensively used diastereomerically pure (*R,R*)-1,2-*N,N′*-(dimethyl)diaminocyclohexane **3** for the determination of the enantiomeric purity of chiral alcohols, amines and thiols.[3] This diamine can be readily obtained from commercial enantiopure (*R,R*)-1,2-diaminocyclohexane **1** by a two-step *N*-methylation procedure (Scheme 1).[3,4] However, large-scale processing is severely undermined by the high cost of this starting material. (±)-(*R,R*)-1,2-*N,N′*-(Dimethyl)-diaminocyclohexane **3** could also be synthesised and finally resolved using L-(+)-tartaric acid, starting from the (±)-*trans*-1,2-diaminocyclohexane or even from the very cheap mixture of (±)-*trans*- and *cis*-isomers.

Another possibility involves resolution of (±)-1,2-diaminocyclohexane before *N*-methylation (Scheme 1). This resolution is accomplished with L-(+)-tartaric acid.[5] However the regeneration of enantiopure free 1,2-diaminocyclohexane, under basic conditions, is troublesome due to its high solubility in water (drying has to be carried out with pieces of sodium) and its air sensitivity (it forms carbonates very easily).[5a]



Scheme 1. Synthesis of (*R,R*)-1,2-*N,N′*-(dimethyl)diaminocyclohexane **3**.

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In contrast, the tartrate salt **4** is very stable, can be stored for months at room temperature and is easy to prepare in large amounts according to the recently improved synthesis.[5b] Taking these factors into account, our strategy was to directly use the very stable (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt **4** and to regenerate in situ the free diamine **1** to give the desired *N*-substituted diamine directly.

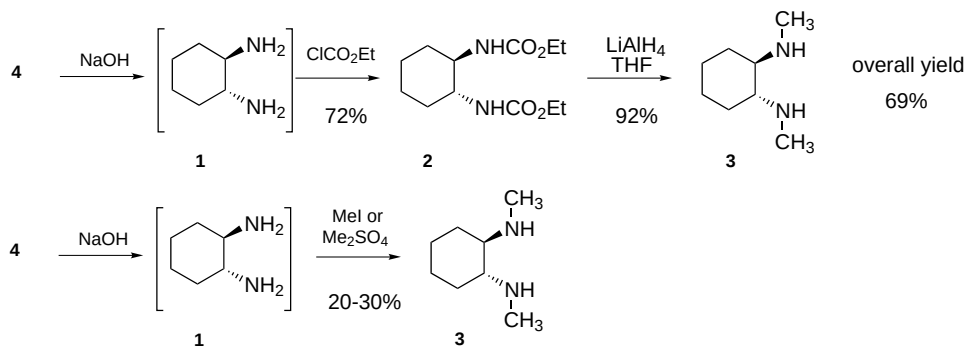
Thus, in situ trapping of the intermediate free diamine **1** with ethyl chloroformate gave directly the bis-carbamate **2** in 72% isolated yield. After LAH reduction, pure (*R*,*R*)-1,2-*N*,*N*′-(dimethyl)diaminocyclohexane **3** could be obtained as shown in Scheme 2.

An even more straightforward approach was conceived, consisting of the direct *N*-methylation of the intermediate free amine with an alkylating agent (Scheme 2). However, all methylation attempts with methyl iodide or methyl sulphate gave the expected (*R*,*R*)-1,2-*N*,*N*′-(dimethyl)diaminocyclohexane **3** in poor yield (20–30%) and contaminated with inseparable *N*-polymethylated side products.

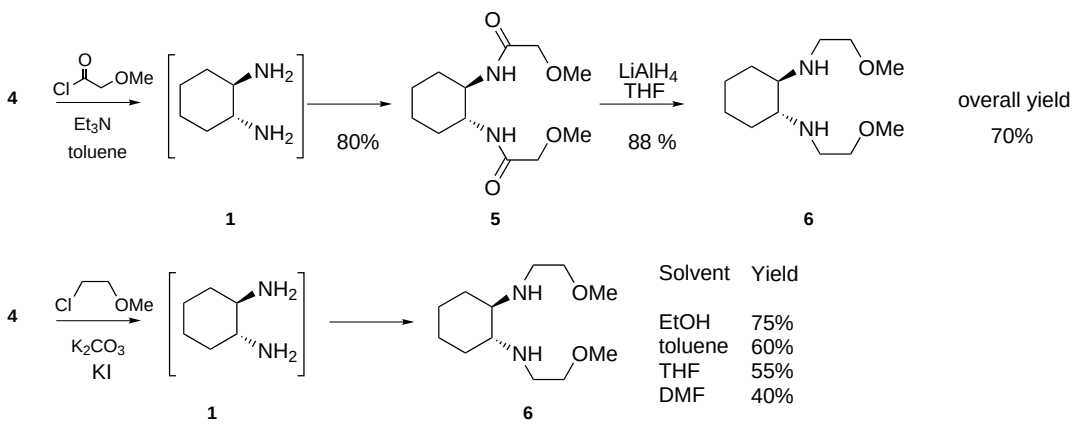
By the same procedure, bis-amide **5** could be obtained in 80% yield, starting from commercially available methoxyacetyl chloride (Scheme 3). Compound **5** has previously been reduced with $LiAlH_4$ to afford (*R*,*R*)-1,2-*N*,*N*′-(2-methoxyethyl)diaminocyclohexane **6** in 88% yield.[6] Diamine **6** has been previously used in the enantioselective *ortho*-lithiation of benzaldehyde chromiumtricarbonyl complex[7] and in the asymmetric desymmetrisation of *meso*-epoxides.[8]

Similarly, direct *N*-alkylation was attempted in order to avoid the additional reduction step. We successfully used this method by refluxing an excess of 1-chloro-2-methoxyethane with the (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt **4** in the presence of potassium carbonate (Scheme 3). The yield was found to be enhanced by the addition of potassium iodide. The best results were obtained in ethanol, as compared to THF, toluene or DMF. After distillation of the crude product, (*R*,*R*)-1,2-*N*,*N*′-(2-methoxyethyl)diaminocyclohexane **6** was obtained in a 75% yield, comparable to that of the two-step procedure (70% overall yield). Elimination of the reduction step provides a facile and convenient one-pot procedure.

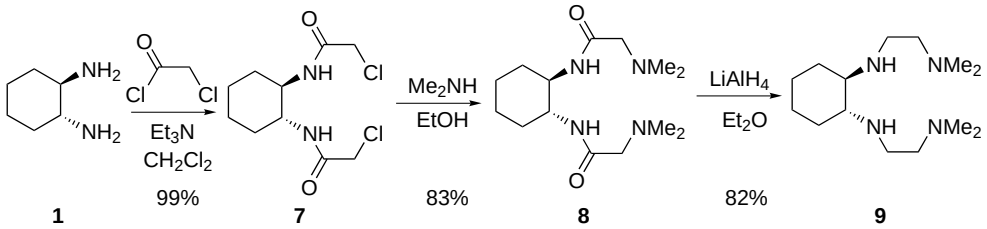
The nitrogen analogue of diamine **6**, compound **9**, was needed for comparative purposes in the laboratory. It has been prepared previously according to Scheme 4.[9] A three-step procedure was necessary: *N*-acylation with chloroacetyl chloride was followed by an *N*-dimethylamino substitution and a final reduction step, giving **9** as an air-sensitive ligand in 67% overall yield. In addition, this approach provides scope for further derivatisation by displacement of the alkyl chloride with other O, N and S nucleophiles.



Scheme 2.



Scheme 3.



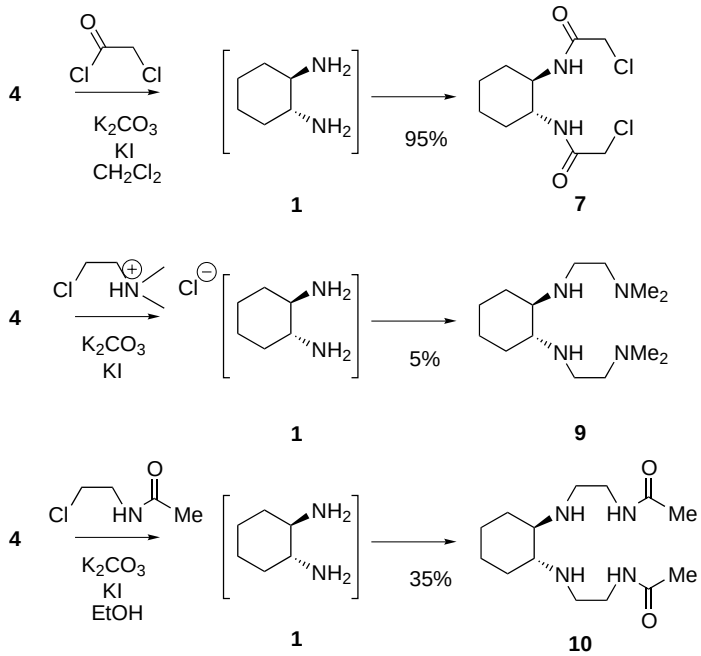
Scheme 4.

Using this methodology, we were able to facilitate the preparation of the first intermediate **7** (yield = 95%) (Scheme 5). By analogy to the above procedure we thought to directly introduce the *N*-dimethylethyl group. Attempts to synthesise tetramine **9** starting from 2-dimethylaminoethyl chloride hydrochloride (Scheme 5) were unsuccessful, irrespective of the solvent or the reaction conditions used: several by-products were obtained and the products were degraded during purification. Better results were achieved with *N*-(2-chloroethyl)acetamide, giving compound **10** with two amine and two amide moieties.

Encouraged by these direct *N*-alkylation results, we tried to extend the methodology to electrophiles possessing other functionalities, for example a trimethylsilyl moiety (Table 1, entry 1). The corresponding diamine **11** has been used for determination of the enantiomeric excess of chiral alcohols.[10] It was successfully prepared in 81% isolated yield by reacting **4** with 3 equiv. of chloromethyltrimethylsilane. Ethanol was found to be the best solvent for the reaction. Selective monosubstitution of the (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt **4** could be achieved if only 1 equiv. of the alkylating agent chloromethyltrimethylsilane was used instead of the three required for disubstitution. An example is given in entry 2 with (*R*,*R*)-*N*-(methyltrimethylsilyl)cyclohexane-1,2-diamine **12**. In this case THF was the preferred solvent for the reaction.

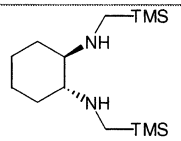
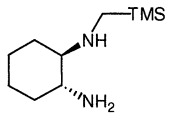
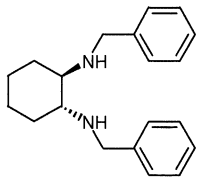
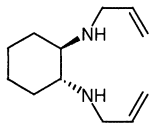
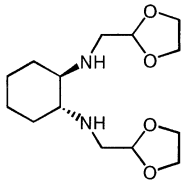
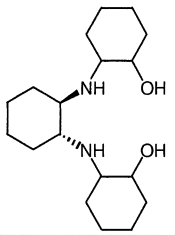
In a similar way, *N*-benzylation was carried out with benzyl bromide (Table 1, entry 3), providing in a single step (*R*,*R*)-*N*,*N*′-dibenzylcyclohexane-1,2-diamine **13**, which is usually synthesised by reduction of the (*N*,*N*)-1,2-bis(benzylidene)diaminocyclohexane.[3,11] *N*-Allylation was more troublesome: potassium iodide had to be added to enhance the rate of the reactions with both allyl chloride or allyl bromide (entry 4). (*N*,*N*)-Diallylcyclohexane-1,2-diamine **14** could be obtained in 55% isolated yield. No reaction was observed in the case of 2-chloromethyl-1,3-dioxolane, which was quantitatively recovered (entry 5) from reactions in all of the reaction conditions studied.

Finally, direct nucleophilic opening of cyclohexene oxide was attempted in analogy to the work of Hancock et al.,[12] giving a much more practical synthesis of *N*,*N*′-bis(2-hydroxycyclohexyl)-*trans*-cyclohexane-1,2-diamine **16** (entry 6).



Scheme 5.

Table 1.

entry	RX		conditions	yield
1		**11**	3 eq $ClCH_2TMS$ refluxing EtOH K_2CO_3, KI 96 h.	81%
2		**12**	1.1 eq $ClCH_2TMS$ refluxing THF K_2CO_3, KI 120 h.	65%
3		**13**	2.1 eq $BrCH_2C_6H_6$ EtOH K_2CO_3, KI RT 140 h.	51%
4		**14**	2.8 eq XCH_2-CH=CH_2 (X = Cl, Br) EtOH, K_2CO_3, KI RT, 140 h.	55%
5		**15**	4 eq chloromethyl-1,3-dioxolane EtOH K_2CO_3, KI RT, 140 h.	0%
6		**16**	4 eq 1-2-epoxycyclohexane EtOH K_2CO_3 RT, 48 h.	63%

3. Conclusion

A novel one-pot procedure has been described for the synthesis of a series of *N*-acylated or *N*-alkylated products derived from (*R*,*R*)-1,2-diaminocyclohexane, these chiral diamines being useful auxiliaries in asymmetric synthesis.[1,2,10] In addition, the use of chloroacetyl chloride as the acylating agent provides the potential for further derivatisation allowing rapid access to highly functionalised chiral diamines. It should also be taken into account that the starting material, (*S*,*S*)-1,2-diammoniumcyclohexane mono-(−)-tartrate salt, can be readily obtained from (−)-tartaric acid providing access to both (*R*,*R*)- or (*S*,*S*)-enantiomeric diamines.

4. Experimental

4.1. General procedures

^{1}H NMR spectra were recorded on Bruker AC-400 (400 MHz) spectrometers in $CDCl_3$. Chemical shifts are quoted in ppm relative to tetramethylsilane ($\delta = 0$ ppm) and referenced to the solvent residual. For convenience, the following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublets, etc. Coupling constants (*J*) are given in Hz. ^{13}C NMR spectra were recorded on a Bruker AC-400 (400 MHz) spectrometer in $CDCl_3$ and with proton decoupling. Chemical shifts are quoted relative to tetramethylsilane ($\delta = 0$ ppm). Microanalyses were carried out by the University of Geneva Microanalytical Department.

Unless otherwise indicated, all materials were obtained from commercial sources and were used without further purification. (*R*,*R*)-1,2-Diammoniumcyclohexane mono-(+)-tartrate salt **4** was synthesised according to the procedure of Jacobsen.[5b]

4.2. (*R*,*R*)-(2-Ethoxycarbonylaminocyclohexyl)carbamic acid ethyl ester 2[4a]

To a solution of (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt **4** (64 g, 0.24 mol) in toluene (300 mL) at 0°C in a 250 mL round-bottomed three-necked flask were added simultaneously ethyl chloroformate

(59.0 g, 2.1 equiv.) and a solution of NaOH (77.6 g, 8 equiv.) in water (80 mL) through two addition funnels. During the addition, the temperature was maintained between 0 and 10°C. When the addition was complete, the mixture was stirred at rt for 5 h and the precipitate was filtered off and rinsed with CH_2Cl_2 (3×150 mL). The filtrate was dried over K_2CO_3 and concentrated in vacuo. The residue was recrystallised from a solution of CH_2Cl_2 containing the minimum amount of cyclohexane, providing **2** as a white solid in 75% yield; mp 166–167°C (lit. 166.5–168.5°C);[3] $[\alpha]_D^{20}=+45.6$ (*c* 1.05, $CHCl_3$) (lit. $[\alpha]_D^{20}=+45.5$ (*c* 1.0, $CHCl_3$)); ^{1}H NMR ($CDCl_3$): δ 1.21 (t, 3H, $J=7$ Hz, -O-CH$_2$-CH$_3$), 1.41–2.23 (m, 8H, -NH-(CH-(CH$_2$)$_4$-CH)-NH-), 3.31 (m, 2H, -N-CH-), 4.17 (q, 4H, $J=7$ Hz, -O-CH$_2$-CH$_3$), 5.04 (m, 2H, -NH-CO); ^{13}C NMR ($CDCl_3$): δ 14.6 (-O-CH$_2$-CH$_3$), 24.89 (-NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 32.91 (-NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 55.40 (-NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 60.7 (CH$_3$-CH$_2$O), 157.1 (-CH$_2$OCO).

4.3. (*R*,*R*)-2-Methoxy-*N*-[(2-(methoxyacetylamino)-cyclohexyl]acetamide 5

To a solution of (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt **4** (6 g, 22 mmol) and triethylamine (15 mL, 107 mmol) in toluene (150 mL) was added at 0°C under nitrogen a solution of CH_3OCH_2COCl (4.9 g, 45 mmol) in toluene (5 mL). The reaction mixture was heated under reflux for 4 h. The salts were removed by filtering through a pad of Celite and the solvent was removed under reduced pressure. The crude diamide **5** was obtained as a pale yellow solid (4.5 g, 80%); mp 92–94°C; $[\alpha]_D^{20}=+34.6$ (*c* 2.6, $CHCl_3$); MS (electrospray) $m/z=259.11$ [(MH)$^+$]; ^{1}H NMR ($CDCl_3$): δ 1.1–1.5 and 1.6–2.1 (m, 8H, -NH-(CH-(CH$_2$)$_4$-CH)-NH), 3.4 (s, 6H, -O-CH$_3$), 3.6–4.0 (m, 4H, -O-CH$_2$), 6.6–6.9 (m, 2H, -NH-CO); ^{13}C NMR ($CDCl_3$): δ 24.7 (-NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 32.3 (-NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 52.7 (-NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 59.2 (CH$_3$O), 71.9 (CH$_2$O), 169.9 (-NHCO).

4.4. (*R*,*R*)-2-Chloro-*N*-[(2-(chloroacetylamino)-cyclohexyl]acetamide 7

To a solution of (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt **4** (11.9 g, 46 mmol) and triethylamine (34 mL, 230 mmol) in dichloromethane (150 mL) at −20°C under nitrogen atmosphere was added a solution of $ClCH_2COCl$ (8.12 mL, 102 mmol) in dichloromethane (50 mL). The reaction mixture was stirred at rt for 30 h and poured into saturated aqueous NH_4Cl. The aqueous layer was extracted with dichloromethane (2×50 mL) and the combined organic phases washed with brine, dried over K_2CO_3, and filtered. The solvents were removed under reduced pressure to afford the crude product **7** as a white solid (11.6 g, 95%); mp 217°C (lit. 215–217°C);[13] $[\alpha]_D^{20}=-22.7$ (*c* 1.1, $CHCl_3$); MS (electrospray) $m/z=266.98$ [(MH)$^+$]; ^{1}H NMR ($CDCl_3$): δ 1.36 (m, 4H, -NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 1.82–2.10 (m, 4H, -NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 3.77 (m, 2H, -NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 4.01 (br s, 4H, -CH$_2$-Cl), 6.82 (br s, 2H, NH-CO); ^{13}C NMR ($CDCl_3$): δ 24.50 (-NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 31.96 (-NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 42.37 (-CH$_2$-Cl), 53.82 (-NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 166.61 (-CH$_2$-CH$_2$-Cl).

4.5. (*R*,*R*)-2-Dimethylamino-*N*-[(2-(dimethylaminoacetyl-amino)cyclohexyl]acetamide 8

To a solution of dimethylamine in ethanol (33 wt%, 430 mL, 2.3 mol) was added the crude product **7** (11.6 g, 43.7 mmol). The reaction mixture was stirred at rt for 2 days. The solvents were removed under reduced pressure and the residue was dissolved in dichloromethane (100 mL). The organic layer was washed with H_2O (3×100 mL), dried over K_2CO_3 and filtered off. The solvents were removed under reduced pressure to afford the crude product **8** as a white solid (10.3 g, 83%). ^{1}H NMR ($CDCl_3$): δ 1.35 (m, 4H, -NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 1.67 (br s, 2H, CO-NH), 1.77–2.05 (m, 4H, NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 2.84 (d, 2H, $^2J=16$ Hz, NH-CO-CH$_2$), 2.93 (d, 2H, $^2J=16$ Hz, NH-CO-CH$_2$), 3.75 (m, 2H, NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-); ^{13}C NMR ($CDCl_3$): δ 14.0 (-NH-(CH$_3$)$_2$), 22.3 and 24.3 (-NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 32.6 and 34.1 (-NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 45.9 (-NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 52.3 and 63.1 (-CH$_2$-CO), 170.6 (NH-CO).

4.6. (*R*,*R*)-*N*,*N*′-Di(2-dimethylaminoethyl)cyclohexane-1,2-diamine 9

$LiAlH_4$ (tablets, 5.4 g, 144 mmol) was added to ether (300 mL). The mixture was heated under reflux for 10 min and then stirred at rt for 14 h. The crude product **8** (10.3 g, 36 mmol) was slowly added and the reaction mixture was heated under reflux for 3 days. Hydrolysis was carried out at 0°C with H_2O (6.5 mL), aqueous sodium hydroxide solution (15%, 6.5 mL) and then with H_2O (13 mL) and ethylenediamine (13 mL). The mixture was stirred for 1 h and then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. After distillation (100°C, 1.3 mbar), the title compound **9** was obtained as a colourless oil (7.5 g, 82%); $[\alpha]_D^{20}=-72.15$ (*c* 1.38, $CHCl_3$); MS (electrospray) $m/z=257.02$ [(MH)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (m, 2H, NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 1.23 (m, 2H, -NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 1.73 (m, 2H, -NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 2.05 (m, 2H, NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 2.16 (m, 2H, -NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 2.23 (s, 12H, -N-(CH$_3$)$_2$), 2.25 (br s, 2H, -NH$_2$), 2.40 (m, 4H, -CH$_2$-N-(CH$_3$)$_2$), 2.53 (dt, $^2J=11.24$ Hz, $^3J=6.5$ Hz, -CH$_2$-CH$_2$-N-(CH$_3$)$_2$), 2.82 (dt, $^2J=11.24$ Hz, $^3J=6.5$ Hz, CH$_2$-CH$_2$-N-(CH$_3$)$_2$); ^{13}C NMR ($CDCl_3$): δ 24.9 (-NH-(CH$_3$)$_2$), 31.4 (NH-CH$_2$), 44.4 (-NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 45.3 (-NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH-), 59.5 and 61.5 (-NH-(CH-CH$_2$-(CH$_2$)$_2$-CH$_2$-CH)-NH- and -NH-CH$_2$-).

4.7. (+)-(*R*,*R*)-*N*,*N*′-Di(methoxyethyl)cyclohexane-1,2-diamine 6

$LiAlH_4$ (tablets, 3 g, 79.2 mmol) was added to THF (150 mL). The mixture was heated under reflux for 10 min and then stirred at rt for 14 h. (*R*,*R*)-2-Methoxy-*N*-[(2-(methoxyacetylamino)cyclohexyl]acetamide **5** (5.1 g, 19.8 mmol) was slowly added and the reaction mixture was heated under reflux for 3 days. The hydrolysis was carried out at 0°C with H_2O (3.5 mL) and aqueous sodium hydroxide solution (15%, 3.5 mL) and then with H_2O (7 mL) and ethylenediamine (7 mL). The reaction mixture was stirred for 1 h and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. After distillation (65°C, 0.35 mbar) the title compound **6** was obtained as a colourless oil (4 g, 88%); $[\alpha]_D^{20}=+109$ (*c* 9.75, $CHCl_3$); MS (electrospray) $m/z=231.15$ [$(MH)^+$]; ^{1}H NMR ($CDCl_3$): δ 0.90–1.35 and 1.6–1.95 (m, 8H, -NH-(CH-(C$\underline{H}_2$)$_4$-CH)-NH), 2.00–2.30 (m, 4H, -N-C$\underline{H}_2$), 2.50–2.80 (m, 2H, NH-(C$\underline{H}$-CH$_2$-(CH$_2$)$_2$-CH$_2$-C$\underline{H}$)-NH-), 2.80–3.10 (m, 2H, -NH-C$\underline{H}$-), 3.35 (s, 6H, -O-CH$_3$), 3.45–3.50 (m, 4H, -O-C$\underline{H}_2$); ^{13}C NMR ($CDCl_3$): δ 25.24 (-NH-(CH-CH$_2$-(C$\underline{H}_2$)$_2$-CH$_2$-CH)-NH-), 31.60 (-NH-(CH-C$\underline{H}_2$-(CH$_2$)$_2$-C$\underline{H}_2$-CH)-NH-), 46.40 (-NH-(C$\underline{H}$-CH$_2$-(CH$_2$)$_2$-CH$_2$-C$\underline{H}$)-NH-), 58.74 (CH$_3$O), 61.61 (-NHC$\underline{H}_2$), 72.40 (C$\underline{H}_2$O-).

Alternatively, **6** could be obtained by *N*-alkylation according to the following procedure.

4.8. Typical procedure for *N*-alkylation

The following typical procedure is systematically applied for *N*-alkylation of the diamines, unless otherwise indicated.

A solution of 1 equiv. of (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt **4** in anhydrous ethanol (200 mL), in a two-necked, round-bottomed flask equipped with a magnetic stirrer, an addition funnel and a water condenser fitted with a nitrogen inlet, was treated with K_2CO_3 (>10 equiv.) and KI (0.1 equiv.). The electrophile (>2 equiv., see Table 1) in solution in ethanol (50 mL) was added via an addition funnel. The mixture was heated under reflux (unless otherwise indicated, see Table 1) then filtered to remove salts. The solvent was evaporated on a rotatory evaporator. The crude product was dissolved in dichloromethane (150 mL) and washed with a saturated aqueous solution of K_2CO_3 (100 mL). This aqueous phase was washed with dichloromethane and then with diethyl ether. The organic layers were dried over K_2CO_3 then the solids were removed by filtration and the solvents evaporated. The pure (*R*,*R*)-*N*,*N*′-dialkylated product was obtained after distillation under reduced pressure, as a colourless or pale yellow oil.

4.9. (+)-(*R*,*R*)-*N*,*N*′-Di(methoxyethyl)cyclohexane-1,2-diamine 6 by *N*-alkylation of the (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt 4 with 2-chloroethylmethyl ether

A mixture of (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt **4** (6 g, 22.7 mmol) in anhydrous ethanol (200 mL), K_2CO_3 (15 g), potassium iodide (0.5 g) and 2-chloroethylmethyl ether (8 mL) was stirred under reflux for 5 days, giving after distillation at reduced pressure (65°C, 0.35 mbar), (+)-(*R*,*R*)-*N*,*N*′-di(methoxyethyl)-cyclohexane-1,2-diamine **6** (4.6 g, 75%).

4.10. (*R*,*R*)-*N*-{2-[2-(2-Acetylaminoethylamino)-cyclohexylamino]ethyl}acetamide 10

A solution of (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt **4** (6 g, 22.7 mmol) in anhydrous ethanol (200 mL) was treated with K_2CO_3 (15 g), potassium iodide (0.5 g) and *N*-(2-chloroethyl)acetamide (6.8 g, 2.5 equiv.). The mixture was stirred under reflux for 3 days, giving, after distillation at reduced pressure (110°C, 0.45 mbar), a colourless oil of **12** that spontaneously solidified on cooling to rt (2.5 g, 35%); $[\alpha]_D^{20}=-17.6$ (*c* 2.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.29 (m, 4H, -NH-(CH-CH$_2$-(C$\underline{H}_2$)$_2$-CH$_2$-CH)-NH-), 1.70 (m, 4H, -NH-(CH-C$\underline{H}_2$-(CH$_2$)$_2$-C$\underline{H}_2$-CH)-NH-), 1.96 (s, CO-CH$_3$), 2.36 (m, 2H, -NH-(C$\underline{H}$-CH$_2$-(CH$_2$)$_2$-CH$_2$-C$\underline{H}$)-NH-), 3.38 (m, 4H, NH-C$\underline{H}_2$-CH$_2$-), 3.42 (m, 4H, NH-CH$_2$-C$\underline{H}_2$-); ^{13}C NMR ($CDCl_3$): 23.47 (CO-C$\underline{H}_3$), 24.97 (NH-(CH-CH$_2$-(C$\underline{H}_2$)$_2$-CH$_2$-CH)-NH-), 32.50 (-NH-(C$\underline{H}$-CH$_2$-(CH$_2$)$_2$-CH$_2$-C$\underline{H}$)-NH-), 35.56 (-NH-CH$_2$-C$\underline{H}_2$-), 54.42 (-NH-C$\underline{H}_2$-CH$_2$-), 56.03 (NH-(C$\underline{H}$-CH$_2$-(CH$_2$)$_2$-CH$_2$-C$\underline{H}$)-NH-), 171.37 (CO-CH$_3$).

4.11. (*R*,*R*)-*N*,*N*′-Di(methyltrimethylsilyl)cyclohexane-1,2-diamine 11

The title compound was synthesised according to the general procedure described above by heating 3 equiv. of chloromethyltrimethylsilane (9.4 g), K_2CO_3 (15 g), potassium iodide (0.5 g) and (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt **4** (6 g, 22.7 mmol) under reflux for 4 days. After distillation (70°C, 0.25 mbar), **11** was obtained as a colourless oil (5.3 g, 81%); $[\alpha]_D^{20}=-102.3$ (*c* 3.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ −0.01 and 1.74 (s, 18H, CH$_2$-Si$\underline{Me}_3$), 2.28 and 1.74 (m, 4H, C$\underline{H}_2$-SiMe$_3$), 1.73 and 1.21 (m, 4H, NH-(CH-C$\underline{H}_2$-(CH$_2$)$_2$-C$\underline{H}_2$-CH)-NH-), 2.16 and 0.95 (m, 4H, NH-(CH-C$\underline{H}_2$-(CH$_2$)$_2$-C$\underline{H}_2$-CH)-NH-), 2.03 (m, 2H, NH-(C$\underline{H}$-CH$_2$-(CH$_2$)$_2$-CH$_2$-C$\underline{H}$)-NH-); ^{13}C NMR ($CDCl_3$): δ −2.65 (CH$_2$-Si$\underline{Me}_3$), 25.18 (NH-(CH-CH$_2$-(C$\underline{H}_2$)$_2$-CH$_2$-CH)-NH-), 36.78 (C$\underline{H}_2$-SiMe$_3$), 30.76 (NH-(CH-C$\underline{H}_2$-(CH$_2$)$_2$-C$\underline{H}_2$-CH)-NH-), 65.40 (NH-(C$\underline{H}$-CH$_2$-(CH$_2$)$_2$-CH$_2$-C$\underline{H}$)-NH-). Anal. calcd for $C_{14}H_{34}N_2Si_2$: C, 58.67; H, 11.96; N, 9.77. Found: C, 58.97; H, 11.99; N, 9.93%.

4.12. (*R*,*R*)-*N*-(Methyltrimethylsilyl)cyclohexane-1,2-diamine 12

A solution of (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt **4** (6 g, 22.7 mmol) in anhydrous THF (200 mL) was treated with K_2CO_3 (15 g) and KI (1 g) followed by a solution of chloromethyltrimethylsilane (1.1 equiv., 3.5 g) in THF (50 mL). The resulting mixture was stirred under reflux for 120 h. The pure (*R*,*R*)-*N*-(methyltrimethylsilyl)cyclohexane-1,2-diamine **12** product was obtained after distillation under reduced pressure (54°C, 0.25 mbar) giving **12** as a pale yellow

oil (3.25 g, 72%); $[\alpha]_D^{20} = -82.7$ (*c* 1.15, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.26 and 1.91 (m, 4H, NH-(CH-$(CH_2)_4$-CH)-NH-), 2.36, 2.08, 1.92, 1.81, 1.24–1.22 (m, 8H, NH-(CH-$(CH_2)_4$-CH)-NH-), 1.80 (m, 2H, CH_2-$SiMe_3$), 0.05 (s, 9H, CH_2-$SiMe_3$); ^{13}C NMR ($CDCl_3$): δ 67.48 (NH_2-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-NH-CH_2-$SiMe_3$), 36.44 and 35.85 (NH_2-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-NH-CH_2-), 25.37 and 25.25 (NH_2-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-NH-CH_2-$SiMe_3$), 54.82 (CH_2-$SiMe_3$), −2.68 (CH_2-$SiMe_3$).

4.13. (*R*,*R*)-*N*,*N*′-Dibenzylcyclohexane-1,2-diamine 13

(*R*,*R*)-*N*,*N*′-Dibenzylcyclohexane-1,2-diamine **13** was synthesised according to the procedure described above with benzyl chloride (5.8 mL, 2.1 equiv.), K_2CO_3 (15 g), potassium iodide (0.5 g) and (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt **4** (6 g, 22.7 mmol). The reaction mixture was stirred at rt for 140 h. After distillation (150°C, 0.4 mbar) a colourless oil was recovered, which solidified upon standing (3.4 g, 51%); mp 37–38°C (lit. 36–37°C);[11] MS (electrospray) m/z = 231.15 $[(MH)^+]$; $[\alpha]_D^{20} = -68$ (*c* 1.3, $CHCl_3$) (lit. $[\alpha]_D^{20} = -67$ (*c* 1.15, $CHCl_3$)); ^1H NMR ($CDCl_3$): δ 1.11, 1.26, 1.75 and 2.19 (m, 8H, -NH-(CH-$(CH_2)_4$-CH)-NH), 2.00–2.30 (m, 4H, -N-CH_2), 2.28 (m, 2H, NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-NH-), 3.91 (d, 2H, CH_2Ph), 7.32–7.36 (m, 10H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 24.98 (-NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-NH-), 31.40 (-NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-NH-), 50.26 (-NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-NH-), 58.74 (CH_3O), 61.61 (-$NHCH_2$), 72.40 (CH_2O), 60.60 (-CH_2Ph), 140.88, 128.28, 127.88, 126.4 (C_{arom}).

4.14. (*R*,*R*)-*N*,*N*′-Diallylcyclohexane-1,2-diamine 14

According to the general procedure, allyl chloride (4 mL, 2.8 equiv.) or allyl bromide (4.35 mL, 2.8 equiv.) were stirred with K_2CO_3 (15 g) and potassium iodide (0.5 g) and (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt **4** (6 g, 22.7 mmol) at rt for 140 h, giving after distillation (52°C, 0.3 mbar), (*R*,*R*)-*N*,*N*′-dibenzylcyclohexane-1,2-diamine **14** (2.4 g, 55%); $[\alpha]_D^{20} = -10.2$ (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.06 (m, 4H, NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-NH-), 1.70 (m, 4H, NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-NH-), 2.97 (m, 2H, NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-NH-), 3.31 (m, 2H, -CH_2-CH=CH_2), 5.11 (dd, 2H, -CH=CH_2), 5.83 (m, 4H, -CH_2=CH_2); ^{13}C NMR ($CDCl_3$): δ 25.91 (NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-NH-), 26.67 (NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-NH-), 52.77 (-CH_2-CH=CH_2), 59.37 (NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-NH-), 115.58 (-CH=CH_2), 138.56 (-CH=CH_2).

4.15. *N*,*N*′-Bis(2-hydroxycyclohexyl)-*trans*-cyclohexane-1,2-diamine 16

This procedure is a modification of that reported by Hancock et al.[12]

To a suspension of (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt **4** (2.3 g, 8.8 mmol) and potassium carbonate (5 g) in anhydrous ethanol was added cyclohexene oxide (3.5 g, 35 mmol). After stirring the solution under reflux for 48 h under a nitrogen atmosphere, the salts were eliminated by filtration and the solvent was evaporated. The crude product was dissolved in ether (150 mL) and washed with a saturated potassium carbonate solution. This aqueous phase was washed with ether and then with dichloromethane. The organic layers were dried over K_2CO_3 and the solids removed by filtration. The filtrate was evaporated. The viscous brown oil contained an alcohol resulting from the opening of the epoxide, which was separated by distillation under reduced pressure (35°C, 0.3 mbar). The resulting solid distillation residue was dissolved in acetone, giving after standing for 24 h in a refrigerator and filtration, a white crystalline solid (1.6 g, 63%); mp 78–80°C; MS (electrospray) m/z = 311.23 $[(MH)^+]$; $[\alpha]_D^{20} = -8.3$ (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.05 (m, 4H, -NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-OH), 1.20 (m, 4H, NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-NH), 1.29 (m, 4H, -NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-OH), 1.66 (m, 4H, -NH-(CH-CH_2-CH_2-CH_2-CH_2-CH)-OH), 1.66 (m, 4H, -NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-OH), 2.02 (m, 4H, -NH-(CH-CH_2-CH_2-CH_2-CH_2-CH)-OH), 2.34 (m, 4H, -NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-NH), 2.48 (m, 4H, NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-OH), 3.45 (m, 2H, CH-OH); ^{13}C NMR ($CDCl_3$): δ 24.33, 25.45, 25.58 (-NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-OH), 30.86, 32.56, 33.19, 35.25 (-NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-OH), 65.43, 65.58 (-NH-(CH-CH_2-$(CH_2)_2$-CH_2-CH)-NH-CH-CH_2-$(CH_2)_2$-CH_2-CH)-OH).

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