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Facile monoprotection of *trans*-1,2-diaminocyclohexane

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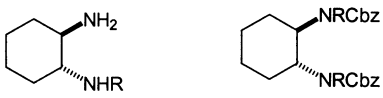
Abstract—A new method of monoprotection of C_2-symmetric *trans*-1,2-diaminocyclohexane as the *N*-phthaloyl, *N*-tetrachlorophthaloyl or *N*-1,8-naphthaloyl derivative is presented. The first two derivatives are obtained with high yields and can be readily transformed into other unsymmetrical derivatives of *trans*-1,2-diaminocyclohexane.

1. Introduction

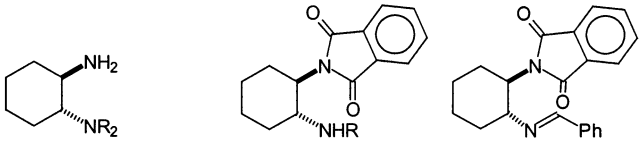
Non-racemic *trans*-1,2-diaminocyklohexane (DACH), **1a**, is readily available in both enantiomeric forms by simple resolution of the crude commercial racemate with tartaric acid.[1] In the past ten years DACH has received much interest as a starting material for making enantiomerically pure reagents, scaffolds and ligands.[2] Examples include the preparation of Jacobsen's salen ligands for asymmetric epoxidation[3] and asymmetric epoxide ring-opening reactions,[4] Trost's ligand for enantioselective allylic alkylations[5] and the synthesis of chiral oligomeric diimines[6] and diimides.[7] Other uses involve controlled formation of hybrid organic–inorganic structures with helical morphology.[8,9]

The majority of reported derivatives of DACH are symmetrically *N*,*N*′-disubstituted. Nevertheless there is a demand for its unsymmetrically substituted derivatives, for example to prepare hybrid ligands. To meet this goal, monoprotection of DACH has been used as the initial synthetic step. Several methods for monoprotection of **1a** have been reported. The versatile mono-*N*-Boc protected derivative **1b** was obtained in three steps, first by diprotection of DACH with the Cbz groups (**2a**), followed by monoprotection with the Boc group (**2b**) and finally by hydrogenolytic removal of both Cbz groups. The overall yield of the three-step sequence was high (89%), in contrast to the failed attempts to directly monoprotect **1a** with 1 equiv. of the acylating reagent which gave the diacylated derivative as the major product. This finding was ascribed to a higher reactivity of the monoacylated derivative, compared to the reactivity of the parent diamine **1a**, as a result of a general base catalysis through intramolecular hydrogen bonding by the acylamino group.[10] Monoprotected derivative **1b** was obtained directly from **1a** (1 equiv.) with the yield 30%, by using 2-(*t*-butoxycarbonyloxyimino)-2-phenylacetonitrile as the acylating agent.[11] Likewise, **1b** was obtained from di-*t*-butyl dicarbonate and **1a** (3 equiv.) with the claimed yield 73%; yield based on **1a** was only 24%.[12]

Since commercial enantiomerically pure **1a** and its enantiomer are expensive, the direct method may not be practical for large-scale applications.

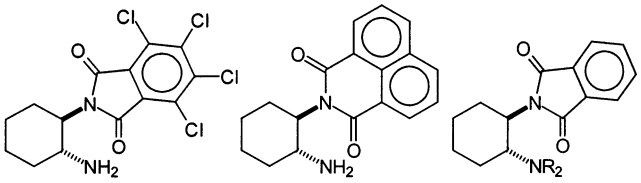


1a, R = H **1d**, R = Ts **2a**, R = H **3**
1b, R = Boc **1e**, R = Ms **2b**, R = Boc
1c, R = Ac **1f**, R = Bn



4a, R = Me
4b, R = Bn

5a, R = H **5d**, R = Ms **6**
5b, R = Bn **5e**, R = Ac
5c, R = Ts



7 **8** **9a**, R = Me
9b, R = Bn

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Monoacetyl derivative **1c** was obtained from DACH with 90% yield by the reaction with the Pinner salt, MeC(OEt)=NH·HCl, followed by hydrolysis of the intermediate imidazoline **3**. Monoprotected **1c** was further converted to the *N*,*N*-dimethyl derivative **4a** by reductive amination, followed by acidic hydrolysis of the acetamide group under rather harsh conditions.[13]

Direct monoderivatization of DACH with 1 equiv. of aryl sulfonyl chloride has been reported to proceed with moderate yield (55–65%).[14] Monotoluenesulfonyl derivative **1d** was alternatively prepared using 3 equiv. of **1a**.[15] More conveniently monosulfonamide derivatives of DACH, free of bis-sulfonamides, can be obtained from the salt of **1a** with tartaric acid, which is a less expensive and more stable commercial source of DACH, but again **1a** had to be used in a three-fold excess (yield of **1d** 31%).[16a] An improved procedure requires 1.5-fold excess **1a** and the yields of monosulfonamide derivatives are around 40%.[16b]

Monourea and monothiourea derivatives were obtained from DACH hydrochloride by the reaction with isocyanates or isothiocyanates at −30°C. The yields were below 50%, based on the used DACH.[17] Monoalkylation of 2 equiv. of DACH with (3-chloropropyl)triethoxysilane was reported to proceed with 70% yield.[18] Similarly, palladium-catalyzed monoarylation of DACH with aryl bromides afforded the products with low to moderate yields.[19]

Finally, we note that monoimine derivatives of DACH were prepared by reacting derivatives of salicylaldehyde with a slight excess of **1a** at 0°C. These intermediates were used for the subsequent preparation of unsymmetrical Schiff bases of **1a** with good to high yields.[20] The ratio of mono- to diimine products apparently depended on the structure of the salicylaldehyde and the solvent used. It was found[21] that the mono-Schiff base derivative of DACH could be separated from the equilibrium mixture by precipitation of its salt with (+)-*O*,*O*′-dibenzoyltartaric acid.

2. Results and discussion

Herein we present a practical method of monoprotection of DACH which was developed in the course of the synthesis of oligoimides of DACH.[7a] The method is based on monophthaloylation of DACH, a process that is simple to carry out and requires only cheap reagents. Monophthaloylation has been achieved by heating in toluene **1a** with 1 equiv. of each phthalic anhydride and *p*-toluenesulfonic acid. The product, the salt **5a**·*p*-TsOH, was directly obtained as a crystalline solid in 92% yield. Free monoprotected diamine **5a** was isolated from the salt by simple carbonate treatment. The success of this monoprotection reaction can be ascribed to the steric effect the phthaloyl group which is exerted on the vicinal amino group, combined with the effect of removal of the product from the reaction medium by the formation of salt with *p*-toluenesulfonic acid. In a similar way, related monoprotected DACH derivatives, **7**·*p*-TsOH and **8**·*p*-TsOH, were obtained with the use of, correspondingly, tetrachlorophthalic anhydride (yield 95%) or 1,8-naphthalic anhydride (yield 67%).

Further substitution reactions of the amino group in **5a** led to products **5b**, **5c**, **5d**, **9a** and **9b**. Orthogonally protected diamine **5b** was obtained by the reaction of **5a** with benzaldehyde, with subsequent reduction of the isolated imine **6** with sodium cyanoborohydride (overall yield 70%). Sulfonylation of **5a** gave products **5c** or **5d** with yields 83–87%. Dialkylated derivatives **9a** and **9b** were obtained correspondingly by the Eschweiler–Clark methylation (yield 86%) or by alkylation with benzyl bromide (yield 72%). The phthaloyl group in **5b**, **5c**, **5d**, **9a** and **9b** was removed by a standard reaction with hydrazine to yield the monoprotected DACH derivatives **1d**, **1e**, **1f**, **4a** and **4b** with yields 90–95%. The products were fully characterized (see Experimental Section).

We have found that DACH derivatives can be conveniently identified by the position of the ^{1}H NMR signals of the protons adjacent to the C–N bonds. These signals appear as doublets of triplets, with two vicinal axial/axial couplings ($J = 10.4$–11.7 Hz) and one axial/equatorial coupling ($J = 3.2$–4.1 Hz), when there is no proton on the adjacent nitrogen atom. The chemical shifts of the signals, relative to those of the parent DACH molecule ($\delta = 2.20$), depend on the nature of substituents on both nitrogen atoms. Remarkable is a large shielding effect of both axial α and β protons due to the protecting imide group. For example, monophthaloylation **5a** brings about a large downfield shift of the C<u>H</u>N(imide) signal ($\Delta\delta = 1.60$), as well as the vicinal C<u>H</u>NH$_2$ signal ($\Delta\delta = 1.20$). Actual positions of the relevant resonance signals of **5a** are 3.80 and 3.41. Bis-1,8-naphthaloylation of DACH shifts the signals of the C<u>H</u>N protons by as much as 4.2 ppm, from $\delta = 2.2$ to $\delta = 6.4$.[22] More detailed data are collected in Table 1.

3. Conclusion

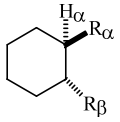
Monoprotection of DACH with either phthalic or tetrachlorophthalic anhydride is a high yield and convenient procedure, opening a way to numerous unsymmetrically substituted and synthetically useful derivatives of DACH.

4. Experimental

4.1. General methods

^{1}H NMR spectra were determined at 298 K in $CDCl_3$, if not stated otherwise; chemical shifts are reported in ppm relative to TMS. IR spectra were measured in KBr pellets. EI mass spectra were taken on an AMD 402 spectrometer. Optical rotations were measured with a Perkin Elmer 243 B polarimeter. Elemental analyses were obtained with a Vario EL III instrument. Melting points are uncorrected.

Table 1. $\Delta\delta$ of R_α and R_β to the chemical shift of H_α in derivatives of *trans*-1,2-diaminocyclohexane



Substituent[a]	NMe_2	NHBn	NBn_2	$NH_3^{\oplus}$	NHTs	NHMs
R_α	–0.1	–0.1	–0.1	0.5	0.4	0.6
R_β	0.3	0.2	0.5	0.4	0.1	0.2

Substituent[a]	N=CHPh[b]	NHBoc[c]	NHAc	NHBz[d]	NHPht[e]	NNph[f]
R_α	1.0	1.0	1.1	1.3	1.6	2.5
R_β	0.2	0.1	0.2	0.3	1.2	1.7

[a] Basal value for H_α in DACH: 2.20 ppm ($CDCl_3$).
[b] Similar values were obtained for *p*-substituted benzylidene derivatives.
[c] Data from Ref. 11.
[d] Data from Ref. 23.
[e] Identical values were obtained for tetrachlorophthalimide substituent.
[f] NNph = 1,8-naphthalenedicarboximide.

4.2. (1*R*,2*R*)-*N*-Phthaloyl-1,2-diaminocyclohexane 5a and (1*R*,2*R*)-*N*-tetrachlorophthaloyl-1,2-diaminocyclohexane 7

A solution of *p*-TsOH·H_2O (1.92 g, 0.01 mol) in xylenes (50 mL) was dehydrated by azeotropic distillation. After cooling to room temperature to the solution was added DACH (**1a**, 1.14 g, 0.01 mol) followed by phthalic anhydride (1.48 g, 0.01 mol) or tetrachlorophthalic anhydride (2.86 g, 0.01 mol). The mixture was heated with stirring until homogeneous solution was obtained and the product begun to crystallize. The product was collected by filtration, washed with xylene–hexane and air-dried.

5a·*p*-TsOH: yield 92%, mp 249–252°C (from dioxane–toluene); $[\alpha]_D^{20}$ −15.8 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.1–2.1 (m, 8H), 3.93 (m, 1H), 4.18 (dt, *J* = 3.8, 11.3 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.4–7.5 (m, 2H), 7.5–7.6 (m, 2H), 7.84 (bs, 3H). IR *v* (cm^{-1}) 3387, 3026, 2949, 2887, 1774, 1707, 1496, 1386, 1214, 816, 684.

7·*p*-TsOH: yield 95%, mp 320–323°C (from ethanol–toluene); $[\alpha]_D^{20}$ −20.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (CD_3OD) δ 1.4–1.6 (m, 3H), 1.85–1.95 (m, 3H), 2.15–2.30 (m, 2H), 2.37 (s, 3H), 3.94 (dt, *J* = 3.8, 11.3 Hz, 1H), 4.18 (dt, *J* = 3.8, 11.3 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.1 Hz, 2H). IR *v* (cm^{-1}) 3083, 3055, 3022, 2960, 2934, 2857, 2835, 2810, 1765, 1707, 1494, 1453, 1390, 1103, 1075, 976, 746, 718, 698.

A solution of either **5a**·*p*-TsOH or **7**·*p*-TsOH (1 mmol) in dichloromethane (25 mL) was stirred overnight with saturated $NaHCO_3$ solution (5 mL). The organic solution was separated, dried over $MgSO_4$ and the solvent removed to give either **5a** or **7**.

5a: yield 83%, mp 123–125°C; $[\alpha]_D^{20}$ −79.3 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.1–1.5 (m, 5H), 1.7–1.9 (m, 3H), 2.0–2.1 (m, 1H), 2.1–2.3 (m, 1H), 3.42 (dt, *J* = 4.0, 11.0 Hz, 1H), 3.81 (dt, *J* = 4.0, 10.6 Hz, 1H), 7.70–7.75 (m, 2H), 7.80–7.85 (m, 2H). IR *v* (cm^{-1}) 3058, 2937, 2862, 1710, 1642, 1556, 1372, 842, 829, 713. Anal. calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.74; H, 6.55; N, 11.49%.

7: yield 92%, mp 132–134°C (from ethanol–diethyl ether); $[\alpha]_D^{20}$ −24.2 (*c* 0.5, MeOH); ^{1}H NMR (CD_3OD) δ 1.2–1.5 (m, 3H), 1.7–1.9 (m, 3H), 2.0–2.2 (m, 2H), 3.40 (dt, *J* = 3.2, 11.5 Hz, 1H), 3.86 (dt, *J* = 3.8, 11.3 Hz, 1H). IR *v* (cm^{-1}) 3268, 3060, 2940, 2860, 1658, 1555, 1406, 1338, 1285, 1020, 914, 742, 659, 649, 618. Anal. calcd for $C_{14}H_{12}Cl_4N_2O_2$: C, 44.01; H, 3.17; N, 7.33. Found: C, 43.93; H, 3.21; N, 7.12%.

4.3. (1*R*,2*R*)-*N*-1′,8′-Naphthaloyl-1,2-diaminocyclohexane 8

To a solution of 1,8-naphthaloyl anhydride (1.98 g, 0.01 mol) in DMF (20 mL), stirred at 90°C, was added **1a** (1.14 g, 0.01 mol) and *p*-TsOH·H_2O (1.92 g, 0.01 mol). Stirring at 120–130°C was continued for 4 h. After cooling to room temperature, water was added to precipitate the unreacted anhydride. The mixture was filtered, the solution evaporated in vacuo and the residue crystallized from methanol–diethyl ether to give **8**·*p*-TsOH: yield 67%, mp 280–282°C; $[\alpha]_D^{20}$ +3.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (CD_3OD) δ 1.4–1.6 (m, 3H), 1.8–2.0 (m, 2H), 2.2–2.3 (m, 1H), 2.37 (s, 3H), 2.5–2.6 (m, 1H), 4.39 (dt, *J* = 3.8, 10.4 Hz, 1H), 5.12 (dt, *J* = 3.8, 10.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.84 (t, *J* = 7.1 Hz, 2H), 8.39 (d, *J* = 7.1 Hz, 2H), 8.60 (m, 2H). IR *v* (cm^{-1}) 3387, 3026, 2949, 2887, 1774, 1707, 1496, 1386, 1214, 816, 684.

The salt was converted to **8** as described for **5a** and **7**. Yield 87%, mp 205–210°C (from benzene–hexane); $[\alpha]_D^{20}$ +2.4 (*c* 0.5, $CHCl_3$); ^1H NMR δ 1.2–1.4 (m, 3H), 1.4–1.6 (m, 2H), 1.7–1.9 (m, 3H), 2.0–2.1 (m, 1H), 2.4–2.6 (m, 1H), 3.78 (dt, $J=3.8$, 10.4 Hz, 1H), 4.79 (dt, $J=3.8$, 10.4 Hz, 1H), 7.76 (t, $J=7.4$ Hz, 2H), 8.20 (d, $J=8.3$ Hz, 2H), 8.60 (bs, 2H). IR ν (cm^{-1}) 3055, 3022, 2935, 2810, 1765, 1707, 1612, 1494, 1310, 746, 718, 699. Anal. calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.53; H, 6.01; N, 9.62%.

4.4. (1*R*,2*R*)-*N*,*N*-Dimethyl-*N*′-phthaloyl-1,2-diaminocyclohexane 9a

A mixture of **5a** (709 mg, 2.9 mmol), 80% formic acid (1.2 mL) and 36% formaldehyde solution (0.5 mL, 6.4 mmol) was stirred under reflux (oil bath 120°C) for 6 h. The solvents were removed in vacuo and the product was extracted with dichloromethane and saturated $NaHCO_3$ solution. The organic solution was dried over $MgSO_4$ and evaporated to give crude product. After crystallization from benzene–hexane **9a** was obtained as colorless crystals, yield 679 mg (86%), mp 117–120°C; $[\alpha]_D^{20}$ −32.5 (*c* 1, $CHCl_3$); ^1H NMR δ 1.1–1.4 (m, 3H), 1.7–2.0 (m, 5H), 2.14 (s, 6H), 3.30 (dt, $J=3.4$, 11.7 Hz, 1H), 4.11 (dt, $J=3.7$, 11.7 Hz, 1H), 7.65–7.70 (m, 2H), 7.80–7.82 (m, 2H). IR ν (cm^{-1}) 3451, 2929, 2861, 1761, 1706, 1468, 1461, 1138, 1078, 1042, 717 cm^{-1}. Anal. calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.41; H, 7.12; N, 10.28%.

4.5. (1*R*,2*R*)-*N*,*N*-Dibenzyl-*N*′-phthaloyl-1,2-diaminocyclohexane 9b

To a solution of **5a** (244 mg, 1 mmol) in acetonitrile (5 mL) was added at room temperature K_2CO_3 (320 mg, 2.3 mmol) and benzyl bromide (0.3 mL, 2.5 mmol). The mixture was refluxed with stirring for 4 h. The solvent was removed in vacuo and the mixture extracted with dichloromethane and saturated $NaHCO_3$ solution. The organic solution was dried over $MgSO_4$ and evaporated. Product **9b** was crystallized from benzene–hexane, yield 72%, mp 123–127°C; $[\alpha]_D^{20}$ −27.3 (*c* 1, $CHCl_3$); ^1H NMR δ 1.2–1.4 (m, 3H), 1.7–1.9 (m, 3H), 2.1–2.3 (m, 2H), 3.30 (m, 1H), 3.33 (d, $J=13.4$ Hz, 2H), 3.75 (d, $J=13.2$ Hz, 2H), 4.31 (dt, $J=3.7$, 11.7 Hz, 1H), 7.0–7.2 (m, 10H), 7.7–7.9 (br m, 4H). IR ν (cm^{-1}) 3456, 3083, 3056, 3022, 2935, 2858, 2810, 1765, 1705, 1612, 1600, 1583, 1494, 1468, 1453, 1389, 1358, 1244, 1104, 1075, 1019, 976, 907, 872, 850, 746, 718, 638. Anal. calcd for $C_{28}H_{28}N_2O_2$: C, 79.22; H, 6.65; N, 6.60. Found: C, 79.25; H, 6.44; N, 6.42%.

4.6. (1*R*,2*R*)-*N*-Benzylidene-*N*′-phthaloyl-1,2-diaminocyclohexane 6

A solution of **5a** (244 mg, 1 mmol) and benzaldehyde (122 μL, 1.2 mmol) in benzene was refluxed with azeotropic removal of water for 6 h. After removal of solvents product **6** was crystallized from benzene–hexane, yield 93%, mp 135–137°C; $[\alpha]_D^{20}$ −24.2 (*c* 1, $CHCl_3$); ^1H NMR δ 1.4–1.6 (m, 2H), 1.7–1.95 (m, 5H), 2.2–2.35 (m, 1H), 4.07 (dt, $J=4.1$, 10.4 Hz, 1H), 4.45 (dt, $J=3.9$, 10.4 Hz, 1H), 7.31 (m, 3H), 7.57 (m, 2H), 7.6–7.7 (m, 2H), 7.7–7.8 (m, 2H), 8.20 (s, 1H). IR ν (cm^{-1}) 3063, 2943, 2862, 2674, 2559, 1769, 1707, 1602, 1583, 1496, 1453, 1424, 1327, 1292, 1128, 1097, 934, 752, 716, 624. Anal. calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06; N, 8.43. Found: C, 75.79; H, 6.17; N, 8.40%.

4.7. (1*R*,2*R*)-*N*-Benzyl-*N*′-phthaloyl-1,2-diaminocyclohexane 5b

To a solution of imine **6** (325 mg, 0.97 mmol) in acetonitrile (7 mL) stirred in an ice bath (0 to −5°C) for 15 min was added $NaBH_3CN$ (126 mg, 2 mmol) followed by a few drops of acetic acid. Stirring was continued for additional 3 h at room temperature. After solvent removal and extractive work-up (dichloromethane–saturated $NaHCO_3$) product **5b** was crystallized from benzene–hexane, yield 75%, mp 92–94°C; $[\alpha]_D^{20}$ −53.7 (*c* 1, $CHCl_3$); ^1H NMR δ 1.05–1.2 (m, 1H), 1.3–1.45 (m, 3H), 1.7–1.9 (m, 3H), 2.2–2.3 (m, 2H), 3.25 (dt, $J=3.8$, 11.0 Hz, 1H), 3.60 (d, $J=13.7$ Hz, 1H), 3.81 (d, $J=13.2$ Hz, 1H), 3.96 (dt, $J=3.8$, 11.0 Hz, 1H), 7.0–7.1 (m, 5H), 7.65–7.75 (m, 2H), 7.8–7.9 (m, 2H). IR ν (cm^{-1}) 3450, 3334, 3087, 3063, 3030, 2938, 2855, 1766, 1699, 1465, 1371, 1072, 717. Anal. calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.44; H, 6.53; N, 8.32%.

4.8. (1*R*,2*R*)-*N*-*p*-Toluenesulfonyl-*N*′-phthaloyl-1,2-diaminocyclohexane 5c and (1*R*,2*R*)-*N*-methanesulfonyl-*N*′-phthaloyl-1,2-diaminocyclohexane 5d

To a solution of **5a** (244 mg, 1 mmol) and diisopropylethylamine (0.26 mL, 1.5 mmol) at 0°C was added appropriate sulfonyl chloride (1 mmol) and the mixture was stirred at room temperature for 6 h. Extraction with dichloromethane–1N HCl followed by washing with brine and drying over $MgSO_4$ afforded products **5c** or **5d**.

5c: crystallized from benzene–hexane, yield 89%, mp 198–202°C; $[\alpha]_D^{20}$ −19.9 (*c* 1, $CHCl_3$); ^1H NMR δ 1.1–1.6 (m, 4H), 1.7–1.9 (m, 3H), 2.13 (s, 3H), 2.3–2.45 (m, 1H), 3.83 (m, 2H), 4.44 (d, $J=9.3$ Hz, 1H), 6.88 (d, $J=8.0$ Hz, 2H), 7.48 (d, $J=8.2$ Hz, 2H), 7.7 (bs, 4H). IR ν (cm^{-1}) 3449, 3223, 2953, 2921, 2856, 1760, 1695, 1447, 1391, 1326, 1153, 1087, 921, 723, 661 cm^{-1}. Anal. calcd for $C_{21}H_{22}N_2O_4S$: C, 63.29; H, 5.56; N, 7.03; S, 8.05. Found: C, 63.19; H, 5.63; N, 7.06; S 8.11%.

5d: oil, yield 83%, $[\alpha]_D^{20}$ −48.9 (*c* 0.5, $CHCl_3$), ^1H NMR δ 1.3–1.5 (m, 3H), 1.8–1.9 (m, 3H), 2.2–2.5 (m, 2H), 2.75 (s, 3H), 3.95 (m, 2H), 4.50 (d, $J=9.1$ Hz, 1H), 7.7–7.75 (m, 2H), 7.8–7.9 (m, 2H). IR (film) ν (cm^{-1}) 3406, 3228, 3076, 2933, 2860, 1581, 1447, 1325, 1447, 1325, 1152, 1072, 980, 817 cm^{-1}. Anal. calcd for $C_{15}H_{18}N_2O_4S$: C, 55.88; H, 5.63; N, 8.69; S 9.95. Found: C, 55.47; H, 5.28; N, 8.72, S 9.67%.

4.9. (1*R*,2*R*)-*N*-Acetyl-*N*′-phthaloyl-1,2-diaminocyclohexane 5e

A sample of **5a** (50 mg) was refluxed with acetic anhydride (0.2 mL) until all substrate reacted. The anhydride was removed in vacuo and the residue crystallized from toluene–hexane, mp 180–182°C, $[\alpha]_D^{20}$ −37.2 (*c* 0.5, $CHCl_3$), ^1H NMR δ 1.2–1.6 (m, 3H), 1.7–1.9 (m, 3H), 1.74 (s, 3H), 2.1–2.2 (m, 1H), 2.5–2.65 (m, 1H), 3.92 (dt, $J=3.9$, 11.0 Hz, 1H), 4.51 (ddd, $J=4.4$, 8.8, 11.0 Hz, 1H), 5.30 (d, $J=8.8$ Hz, 1H), 7.7–7.75 (m, 2H), 7.8–7.9 (m, 2H). IR ν (cm^{-1}) 3416, 3323, 2925, 2862, 1777, 1706, 1655, 1547, 1373, 719. Anal. calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.13; H, 6.28; N, 9.72%.

4.10. Removal of the phthaloyl protecting group

A sample of **5b**, **5c**, **5d**, **9a** or **9b** (1 mmol) was refluxed with hydrazine hydrate (0.12 mL) in ethanol (2 mL) for 2 h. After cooling the solution was diluted with diethyl ether to precipitate phthaloyl hydrazide. The mixture was filtered and the filtrate evaporated to dryness. The products were purified either by extraction into the dilute HCl, followed by neutralization with saturated $NaHCO_3$ solution and back extraction with dichloromethane, or by crystallization. Yields were in the range 85–95%.

Products **1d**,[16a] **1e**,[16b] and **4a**[13,24] were previously reported. We note, however, that **1e** is a crystalline solid, mp 112–113°C (from benzene–hexane).

4.10.1. (1*R*,2*R*)-*N*-Benzyl-1,2-diaminocyclohexane 1f. Oil, $[\alpha]_D^{20}$ −87.4 (*c* 1, $CHCl_3$); ^1H NMR δ 0.9–1.4 (m, 4H), 1.6–1.9 (m, 6H), 2.05–2.2 (m, 2H), 2.41 (m, 1H), 3.68 (d, $J=13.2$ Hz, 2H), 3.94 (d, $J=13.4$ Hz, 2H), 7.2–7.4 (m, 5H). IR (film) ν (cm^{-1}) 3271, 3060, 2932, 2857, 1495, 1451, 1089, 972, 697 cm^{-1}. HRMS found 204.16104 $C_{13}H_{20}N_2$ requires 204.16264.

4.10.2. (1*R*,2*R*)-*N*,*N*-Dibenzyl-1,2-diaminocyclohexane 4b. Oil, $[\alpha]_D^{20}$ −42.5 (*c* 0.36, $CHCl_3$); ^1H NMR δ 0.8–1.0 (m, 1H), 1.05–1.3 (m, 3H), 1.6–1.7 (m, 3H), 1.7–1.85 (m, 1H), 1.9–2.05 (m, 2H), 2.13 (m, 1H), 2.68 (dt, $J=3.8$, 10.4 Hz, 1H), 3.38 (d, $J=13.5$ Hz, 2H), 3.82 (d, $J=13.4$ Hz, 2H), 7.2–7.4 (m, 10H). IR (film) ν (cm^{-1}) 3060, 3026, 2928, 2855, 1494, 1452, 748, 698. HRMS found 294.20959 $C_{20}H_{26}N_2$ requires 294.20892.

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