General Route to a New Class of Homochiral Azetidine-Derived 1,2-Diamines

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A short access to novel azetidine-derived *anti*-1,2-diamines starting from easily accessible 2-cyanoazetidines has been developed. A one-pot sequence, including a nucleophilic addition and reduction of the resulting imine, allows for a diastereoselective synthesis of variously substituted diamines.

Introduction

Vicinal diamines are commonly found in biologically active compounds[1] that display a wide range of useful biological activities, and they have recently been shown to have excellent properties in asymmetric synthesis as chiral lithium or magnesium amides[2] and in transition-metal-assisted[3] or metal-free[4] asymmetric catalysis. Although these applications have stimulated the synthesis of a large variety of vicinal diamines, there is a steady demand for new enantiopure 1,2-diamines. In addition to having novel structural features, these diamines must be easily accessible and available in both enantiomeric forms, and their synthesis should allow for an easy modification of both steric and electronic effects in order to finely tune the targeted properties. Among the 1,2-diamines reported to date, diamines of general structure **1**, in which one of the nitrogen atoms is included in a ring, have attracted recent attention (Figure 1).

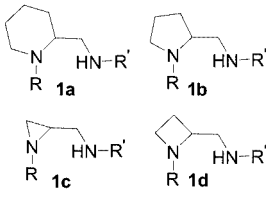

Figure 1. Vicinal diamines **1**

Several studies have established the role of this class of compounds **1** as chiral ligands, valuable synthetic intermediates and biologically active chemicals. For example, (2-aminomethyl)piperidines **1a** are key synthetic intermediates in the preparation of 3-aminoazepanes, obtained through a ring-enlargement procedure.[5] Nonracemic (2-aminomethyl)pyrrolidines **1b** have recently been used as constrained chiral ligands in Rh-based catalytic hydrogenation[6] and Zn-mediated asymmetric reactions.[7] Enantiopure (2-aminomethyl)aziridines **1c**, synthesized from α-chloro ketimines,[8] have been shown to be prone to undergo a regio- and stereoselective ring-opening, yielding various diaminoalkanols.[9] While (2-aminomethyl)azetidines **1d**, prepared as racemates, have been described as G-protein receptor ligands[10a] and antimicrobial agents,[10b] the synthesis of chiral nonracemic (2-aminomethyl)azetidines remains, to the best of our knowledge, unreported. This is certainly due to the lack of general and efficient methods for the synthesis of enantiopure azetidines. Driven by our continuing interest in the synthesis and reactivity of these heterocycles,[11] we envisioned the preparation of enantiopure azetidine-derived vicinal diamines using a sequence of nucleophilic addition and reduction, starting from enantiopure 2-cyanoazetidine, which is summarized in Figure 2.

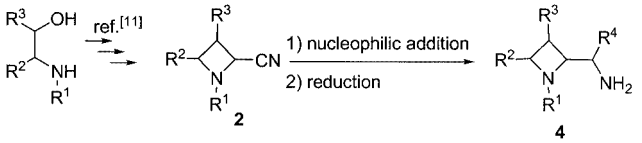

Figure 2. Synthesis of azetidine-based diamines from commercially available β-amino alcohols

In this paper, we report the first general preparation of azetidine-derived vicinal diamines **4** from 2-cyanoazetidines that are easily accessible in a few steps from the chiral pool.[11]

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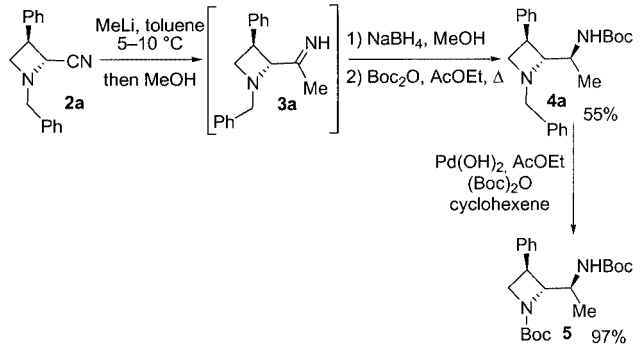
Results and Discussion

In a preliminary study, 2-cyanoazetidine **2a** was allowed to react with MeLi in toluene at 5−10 °C to give the corresponding imine **3a**. In a one-pot, two-step process, in situ reduction of this imine using $NaBH_4$ in methanol at 0 °C afforded the expected diamine as a single diastereoisomer which was converted, for easier isolation and purification, to its *N*-Boc derivative **4a** (Boc_2O, EtOAc, reflux) in good overall yield (55%) (Scheme 1).[12]



Scheme 1. Synthesis of vicinal diamines **4a** and **5**

In order to elucidate the configuration of the stereocenter created in this process, diamine **4a** was converted, in high yield, into its crystalline di-*N*-Boc derivative **5** by reaction with $Pd(OH)_2$, cyclohexene as an H_2 source, and $(Boc)_2O$ in ethyl acetate. X-ray crystallographic analysis[13] of compound **5** clearly demonstrates that the reaction sequence from 2-cyanoazetidines **2** leads to *anti*-1,2-diamines **4**, as can be seen from the ORTEP view in Figure 3.

Since the addition of organometallic reagents onto an α-aminonitrile **A** usually results in the displacement of the cyanide (Bruylants reaction[14]), leading to the formation of **B** instead of the imine **C** (Figure 4), the stereoselectivity of the reduction of **C** has been studied in very few cases.[15] In the present work, the formation of **B** is highly disfavored by the presence of the azetidine ring, since this reaction would induce the formation of a strained four-membered azetidinium ion.

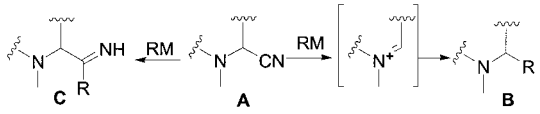


Figure 4. Addition of an organometallic reagent to 2-cyanoazetidine

The relative stereochemistry in **5** results from a hydride attack on the *Re* face of the imine moiety. The diastereoselectivity could be explained by using the models depicted in Figure 3. In these models, which are analogous to the well-established Cram chelate model in carbonyl chemistry, chelation could result either from an intramolecular hydrogen bond between the tertiary amine and imino moieties (Figure 3, top case) or from the formation of a five-membered lithio chelate (Figure 3, bottom case). The proposed chelate model and the observed *anti* selectivity are in good agreement with the chelation-controlled products obtained by addition of organometallic reagents to aziridinyl aldimines[16] and α-silyloxy imines.[17] It is worth noting that the hydride addition proceeds with no detectable epimerization at the C-2 stereocenter.

We next studied the synthesis of other diamines, starting from various 2-cyanoazetidines. Treatment of *trans*-2,3-cyanoazetidine **2a** with various organometallic reagents (arylLi, alkylLi, allylMgBr), followed by hydride addition and *N*-protection, gave diastereomerically pure diamines **4a**−**4e** (Table 1, Entries 1−5) with yields ranging from 53 to 72%, regardless of the nature and bulkiness of the introduced R^4 group. At this stage, we were interested in determining whether the substitution pattern on the azetidine ring and its relative configuration could affect the stereoselectivity of this reaction. Thus, the addition/reduction/protection sequence was next examined on five different azetidines **2b**−**2f**. Starting from *cis*-2,3-cyanoazetidine **2b**, diamines **4f**

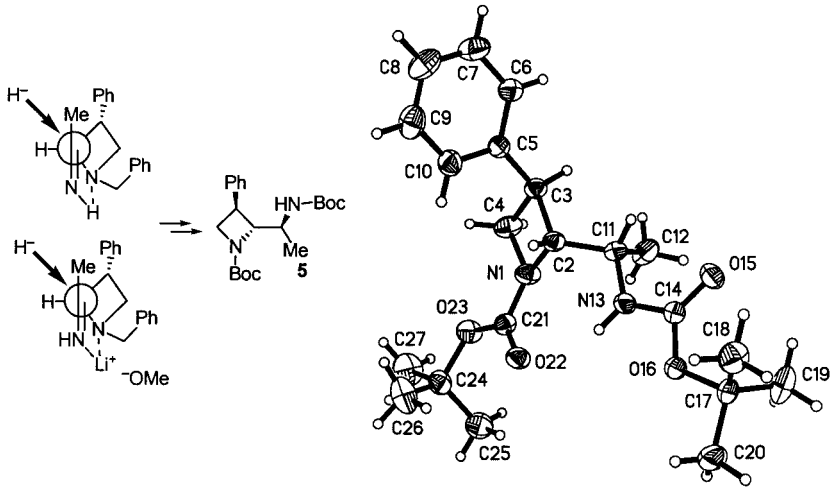
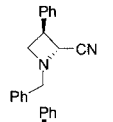
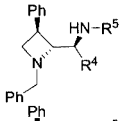
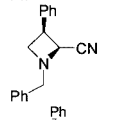
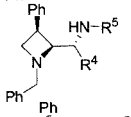
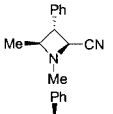
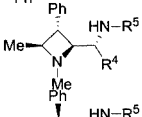
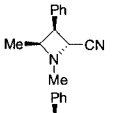
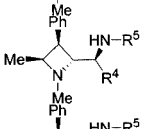
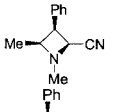
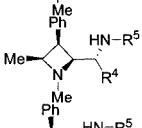
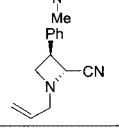
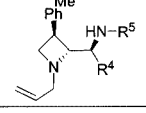


Figure 3. Stereochemistry of hydride addition and X-ray structure of diamine **5**

Table 1. Synthesis of azetidine-based vicinal diamines **4**

Entry	Starting cyanoazetidine **2**	Diamine **4**	R^4	R^5	Yield (%)[a]	dr[b]
1		 **4a**	Me	Boc	55	> 95:5
2		**4b**	Ph	Boc	53	> 95:5
3	**2a**	**4c**	*n*Bu	Boc	72	> 95:5
4		**4d**	*t*Bu	Boc	60	> 95:5
5		**4e**	allyl	Boc	61	> 95:5
6	 **2b**	 **4f**	Ph	H	68	> 95:5
7		**4g**	Me	Boc	42	> 95:5
8	 **2c**	 **4h**	Ph	H	74	> 95:5
9	 **2d**	 **4i**	Me	H	76	> 95:5
10	 **2e**	 **4j**	Ph	H	62	> 95:5
11	 **2f**	 **4k**	Ph	Boc	41	> 95:5
12		**4l**	allyl	Boc	82	> 95:5

[a] Yields of isolated, analytically pure materials. [b] Determined by ^{1}H NMR spectroscopic analysis of crude reaction mixtures.

and **4g** were readily obtained as single diastereomers in 68 and 42% yields respectively (Table 1, Entries 6 and 7).

Subsequently, *N*-methyl- or *N*-allyl-protected azetidines **2c**−**2f** were subjected to the addition/reduction sequence (Entries 8−12). In all cases, diastereomerically pure diamines **4h**−**4l** were successfully obtained in good yields. Isolation and purification of diamines **4h**−**4j** did not require protection of the polar newly formed amino group. Application of the proposed chelate model shown in Figure 3 to the imines derived from substrates **2b**−**e**, with different substitution patterns on the azetidine ring, is depicted in Figure 5. For clarity, the absolute configurations of the C-2 stereocenter in **2b**−**e** have been fixed as in **2a**. Construction of these rigid chelated structures with molecular models shows that there is no severe steric interaction between the R group of the imine and the substituents on the azetidine ring (Ph on C-3 in **2b**,**e** or Me on C-4 in **2c**,**e**). In fact, the shielding of the *Si* face by these substituents should be a positive parameter to enhance the stereoselectivity towards *Re*-face attack, particularly for the imines generated from **2b**,**c**,**e**. The relative *anti* stereochemistry was therefore rationalized on the basis of the chelate model depicted above.

Further functionalization of the diamine skeleton **4** proved to be particularly flexible. As exemplified in Figure 6, we were able to introduce additional substituents at the extracyclic nitrogen atom in compound **4h**. For instance, **4h** can be converted into its *N*-tosyl derivative **6** (TsCl, Et_3N, CH_2Cl_2, room temp.) or *N*-benzyl derivative **7** (PhCHO, $MgSO_4$, CH_2Cl_2, room temp. then $NaBH_4$, MeOH) in 71% and 82% yields, respectively. In addition, reduction of 2-cyanoazetidine **2a** with $LiAlH_4$ afforded the primary diamine **8** in 68% yield.

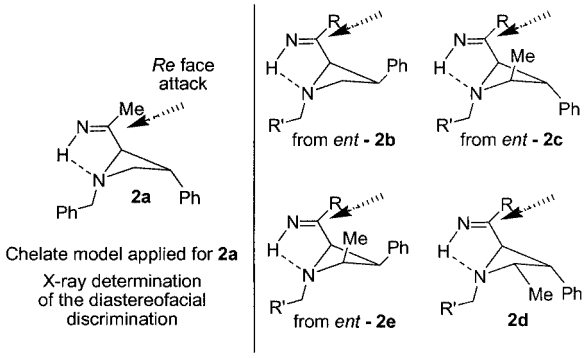


Figure 5. Postulated chelation-controlled hydride addition

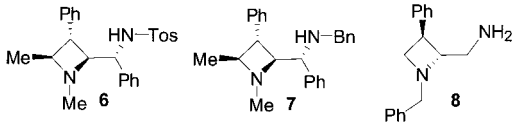


Figure 6. Azetidine-based vicinal diamines

Conclusion

In conclusion, we have developed the first diastereoselective synthesis of azetidine-derived 1,2-diamines. This methodology conveniently gives access to novel *anti*-1,2-diamines by a short reaction sequence using starting materials taken from the chiral pool. Additionally, there is scope for the flexible introduction of additional substituents.

Experimental Section

General Remarks: Melting points were determined with a Reichert apparatus and are uncorrected. NMR spectra were recorded with a Bruker AC spectrometer at 200 or 300 (^{1}H) and 75 (^{13}C) MHz, using $CDCl_3$ as the solvent. Optical rotations were determined with a Perkin−Elmer 141 instrument. THF and toluene were distilled from sodium/benzophenone ketyl.

General Procedure for the Addition/Reduction/Protection Sequence: The appropriate organolithium reagent (2 mmol) was added to a solution of 2-cyanoazetidine **2** (1 mmol) in dry THF (10 mL) at 0 °C under argon. After stirring for 20 min, MeOH (10 mL) and $NaBH_4$ (1.2 mmol) were successively added. After a further 1 h, the reaction was quenched with saturated aqueous NH_4Cl solution (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried with magnesium sulfate and concentrated under reduced pressure. Amines **4f** and **4h**−**j** were purified by silica gel column chromatography at this stage. $(Boc)_2O$ (1.2 mmol) was added to a solution of crude amines **4a**−**e**, **4g** and **4k**−**l** in EtOAc (10 mL).The reaction mixture was heated at reflux for 2 h. The solvent was then removed to give a crude product which was purified by silica gel column chromatography.

Diamine 4a: Yield 201 mg, 55%, m.p. 82 °C. $[\alpha]_D^{20} = -6.1$ (c = 4.3, $CHCl_3$). R_f (C_6H_{12}/Et_2O, 2:1) = 0.46. ^{1}H NMR (200 MHz): δ = 1.08 (d, J = 6.6 Hz, 3 H), 1.44 (s, 9 H), 2.95 (dd, J = 4.0, 6.6 Hz, 1 H), 3.32 (dd, J = 5.5, 6.7 Hz, 1 H), 3.50 (q, J = 8.1 Hz, 1 H),

3.70 (m, 2 H), 3.85 (d, J = 13.1 Hz, 1 H), 4.69 (d, J = 6.6 Hz, 1 H), 7.22−7.41 (m, 10 H) ppm. ^{13}C NMR (75 MHz): δ = 26.9, 28.5, 39.1, 49.2, 58.3, 62.6, 76.32, 78.9, 126.5, 127.2, 127.6, 128.4, 128.8, 138.1, 141.6, 155.7 ppm. $C_{23}H_{30}N_2O_2$ (366.23): calcd. C 75.37, H 8.25, N 7.64; found C 74.99, H 8.42, N 8.12.

Diamine 4b: Yield 227 mg, 53%, m.p. 182 °C. $[\alpha]_D^{20}$ = +42.8 (c = 4.9, $CHCl_3$). R_f (C_6H_{12}/Et_2O, 1:1) = 0.62. ^{1}H NMR (200 MHz): δ = 1.46 (s, 9 H), 3.01 (dd, J = 6.1, 7.5 Hz, 1 H), 3.39 (s, 2 H), 3.70 (m, 3 H), 4.77 (br. s, 1 H), 5.27 (d, J = 6.1 Hz, 1 H), 7.08 (d, J = 7.6 Hz, 2 H), 7.22−7.35 (m, 13 H) ppm. ^{13}C NMR (75 MHz): δ = 26.9, 28.3, 39.9, 57.8, 61.8, 76.2, 79.2, 125.8, 126.3, 126.9, 127.2, 127.4, 127.5, 127.6, 128.2, 128.3, 128.4, 128.5, 128.8, 155.3 ppm. $C_{28}H_{32}N_2O_2$ (428.25): calcd. C 78.47, H 7.53, N 6.54; found C 78.57, H 7.46, N 6.22.

Diamine 4c: Yield 293 mg, 72%, m.p. 106 °C. $[\alpha]_D^{20}$ = +15.5 (c = 6.0, $CHCl_3$). R_f (C_6H_{12}/Et_2O, 2:1) = 0.27. ^{1}H NMR (200 MHz): δ = 0.85 (t, J = 6.0 Hz, 3 H), 1.16−1.53 (m, 6 H), 1.49 (s, 9 H), 2.96 (t, J = 8.1 Hz, 1 H), 3.35 (t, J = 6.4 Hz, 1 H), 3.50 (m, 1 H), 3.61 (d, J = 12.7 Hz, 1 H), 3.70 (t, J = 7.4 Hz, 1 H), 3.95 (d, J = 13.0 Hz, 1 H), 4.54 (d, J = 8.3 Hz, 1 H), 7.23−7.40 (m, 10 H) ppm. ^{13}C NMR (75 MHz): δ = 14.0, 22.6, 27.9, 28.5, 31.0, 39.7, 54.2, 58.2, 62.8, 75.7, 78.8, 126.5, 127.2, 127.7, 128.4, 128.8, 138.3, 141.7, 156.0 ppm. $C_{26}H_{36}N_2O_2$ (408.28): calcd. C 76.43, H 8.88, N 6.86; found C 76.35, H 8.94, N 6.85.

Diamine 4d: Yield 245 mg, 60%, m.p. 145 °C. $[\alpha]_D^{20}$ = +25.0 (c = 2.62, $CHCl_3$). R_f (petroleum ether/Et_2O, 4:1): 0.39. ^{1}H NMR (200 MHz): δ = 0.78 (s, 3 H), 1.52 (s, 9 H), 2.80 (dd, J = 6.6, 8.3 Hz, 1 H), 3.30 (m, 1 H), 3.43 (d, J = 12.5 Hz, 1 H), 3.60 (t, J = 7.4 Hz, 1 H), 3.70 (m, 1 H), 4.08 (d, J = 12.9 Hz, 1 H), 4.71 (d, J = 10.8 Hz, 1 H), 7.20−7.38 (m, 10 H) ppm. ^{13}C NMR (75 MHz): δ = 22.1, 27.2, 28.5, 34.1, 39.8, 59.4, 60.5, 60.8, 71.9, 126.7, 126.8, 128.1, 128.3, 128.4, 128.9, 138.3, 141.3, 156.6 ppm. $C_{26}H_{36}N_2O_2$ (408.28): calcd. C 76.43, H 8.88, N 6.86; found C 76.51, H 8.92, N 6.65.

Diamine 4e: Yield 239 mg, 61%. $[\alpha]_D^{20}$ = +52.6 (c = 3.95, $CHCl_3$). R_f (C_6H_{12}/Et_2O, 4:1) = 0.62. ^{1}H NMR (200 MHz): δ = 1.42 (s, 9 H), 2.25 (t, J = 6.8 Hz, 2 H), 2.94 (dd, J = 6.6, 8.2 Hz, 1 H), 3.40 (m, 3 H), 3.60 (d, J = 12.8 Hz, 1 H), 3.68 (t, J = 7.5 Hz, 1 H), 3.90 (d, J = 12.8 Hz, 1 H), 4.57 (d, J = 7.6 Hz, 1 H), 4.89 (m, 2 H), 5.68 (m, 1 H), 7.20−7.38 (m, 10 H) ppm. ^{13}C NMR (75 MHz): δ = 28.4, 35.4, 39.5, 53.1, 58.2, 62.5, 74.7, 77.3, 79.0, 117.6, 126.6, 127.2, 127.7, 128.4, 128.8, 134.3, 138.2, 141.4, 155.9 ppm. $C_{25}H_{32}N_2O_2$ (392.25): calcd. C 76.49, H 8.22, N 7.14; found C 76.56, H 8.11, N 7.18.

Diamine 4f: Yield 223 mg, 68%. $[\alpha]_D^{20}$= +218.2 (c = 2.25, $CHCl_3$). R_f (C_6H_{12}/Et_2O, 1:1) = 0.19. ^{1}H NMR (200 MHz): δ = 1.21 (br. s, 2 H), 2.81 (m, 2 H), 3.14 (t, J = 4.9 Hz, 1 H), 3.34 (d, J = 5.2 Hz, 1 H), 3.50 (t, J = 5.6 Hz, 1 H), 3.70 (dt, J = 1.5, 5.4 Hz, 1 H), 3.80 (d, J = 6.2 Hz, 1 H), 7.14−7.34 (m, 13 H), 7.64 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 28.2, 39.2, 56.8, 61.7, 71.9, 79.1, 126.7, 126.8, 127.2, 127.3, 128.1, 128.2, 128.3, 128.5, 129.1, 138.3, 139.6, 140.8, 156.1 ppm. $C_{28}H_{32}N_2O_2$ (328.19): calcd. C 78.47, H 7.53, N 6.54; found C 78.31, H 7.69, N 6.47.

Diamine 4g: Yield 153 mg, 42%, m.p. 179 °C. $[\alpha]_D^{20}$ = +134.2 (c = 1.55, $CHCl_3$). R_f (C_6H_{12}/Et_2O, 6:4) = 0.42. ^{1}H NMR (200 MHz): δ = 1.30 (d, J = 6.4 Hz, 3 H), 1.34 (s, 9 H), 3.16 (t, J = 7.7 Hz, 1 H), 3.40 (d, J = 13.2 Hz, 1 H), 3.44−3.57 (m, 3 H), 3.86 (br. s, 1 H), 4.06 (d, J = 12.8 Hz, 1 H), 7.24−7.40 (m, 10 H), 7.48 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 17.7, 28.4, 38.8, 47.3, 56.9, 62.8, 72.2, 78.6, 126.6, 126.9, 128.2, 128.4, 129.0, 138.5, 140.1, 154.8 ppm. $C_{23}H_{30}N_2O_2$ (366.23): calcd. C 75.37, H 8.25, N 7.64; found C 75.26, H 8.37, N 7.59.

Diamine 4h: Yield 165 mg, 62%. $[\alpha]_D^{20}$ = +149.1 (c = 4.4, $CHCl_3$). R_f (C_6H_{12}/Et_2O, 1:1) = 0.34. ^{1}H NMR (200 MHz): δ = 1.27 (d, J = 6.6 Hz, 3 H), 1.64 (br. s, 2 H), 2.12 (s, 3 H), 2.83 (m, 1 H), 3.17 (m, 2 H), 4.12 (d, J = 5.4 Hz, 1 H), 7.10−7.41 (m, 10 H) ppm. ^{13}C NMR (75 MHz): δ = 20.2, 42.7, 48.0, 59.2, 67.9, 76.9, 126.2, 127.1, 127.6, 128.2, 141.2 ppm. $C_{18}H_{22}N_2$ (266.18): calcd. C 81.16, H 8.32, N 10.52; found C 80.93, H 8.51, N 10.47.

Diamine 4i: Yield 202 mg, 76%. $[\alpha]_D^{20}$ = −20.3 (c = 2.85, $CHCl_3$). R_f (Et_2O) = 0.50. ^{1}H NMR (200 MHz): δ = 0.99 (d, J = 6.8 Hz, 3 H), 1.33 (d, J = 5.4 Hz, 3 H), 2.38 (s, 3 H), 2.79 (q, J = 6.8 Hz, 1 H), 3.19 (m, 2 H), 3.19 (dq, J = 2.6, 6.8 Hz, 1 H), 7.03−7.45 (m, 10 H) ppm. ^{13}C NMR (75 MHz): δ = 11.0, 35.6, 42.9, 59.7, 59.8, 73.7, 125.9, 127.3, 127.9, 128.3, 138.2, 143.1 ppm. $C_{18}H_{22}N_2$ (266.18): calcd. C 81.16, H 8.32, N 10.52; found C 80.98, H 8.37, N 10.55.

Diamine 4k: Yield 155 mg, 41%, m.p. 141 °C. $[\alpha]_D^{20}$ = +43.4 (c = 3.8, $CHCl_3$). R_f (Et_2O) = 0.50. ^{1}H NMR (200 MHz): δ = 1.37 (s, 9 H), 2.79 (d, J = 6.6 Hz, 2 H), 2.89 (dd, J = 6.6, 8.3 Hz, 1 H), 3.38 (t, J = 7.5 Hz, 1 H), 3.57 (q, J = 7.9 Hz, 1 H), 3.73 (t, J = 6.6 Hz, 1 H), 4.78 (br. s, 1 H), 5.05−5.21 (m,3 H), 5.75 (m, 3 H), 5.75 (m, 1 H), 7.05 (d, J = 7.8 Hz, 2 H), 7.15−7.22 (m, 8 H) ppm. ^{13}C NMR (75 MHz): δ = 28.3, 40.1, 57.5, 59.1, 60.5, 76.2, 79.4, 117.5, 126.4, 126.9, 127.5, 128.2, 128.4, 134.3, 141.2, 155.5 ppm. $C_{24}H_{30}N_2O_2$ (378.23): calcd. C 76.16, H 7.99, N 7.40; found C 76.15, H 8.08, N 7.31.

Diamine 4l: Yield 280 mg, 82%. $[\alpha]_D^{20}$ = +125.8 (c = 1.2, $CHCl_3$). R_f (C_6H_{12}/Et_2O, 1:1) = 0.17. ^{1}H NMR (200 MHz): δ = 1.40 (s, 9 H), 2.24 (t, J = 7.0 Hz, 2 H), 2.89 (dd, J = 7.0, 8.6 Hz, 1 H), 3.05 (dd, J = 12.0, 6.8 Hz, 1 H), 3.23 (t, J = 7.0 Hz, 1 H), 3.43 (m, 2 H), 3.73 (d, J = 7.2 Hz, 1 H), 3.82 (m, 1 H), 4.57 (br. s, 1 H), 5.12 (m, 4 H), 5.74 (m, 2 H), 7.24−7.39 (m, 5 H) ppm. ^{13}C NMR (75 MHz): δ = 28.4, 35.6, 39.8, 56.4, 57.9, 61.4, 74.7, 79.1, 117.5, 117.7, 126.6, 127.7, 128.3, 134.1, 134.5, 141.4, 155.8 ppm. $C_{21}H_{30}N_2O_2$ (342.23): calcd. C 72.69, H 8.86, N 8.07; found C 72.81, H 9.09, N 7.88.

Diamine 5: $Pd(OH)_2$ (87.5 mg) was added to a solution of compound **4a** (179 mg, 0.49 mmol), $(Boc)_2O$ (133 mg, 0.61 mmol) and cyclohexene (2.3 mL) in ethanol (4 mL). The mixture was refluxed for 3 h and then filtered through a short pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc) to give **5** as a solid (183 mg, 97%). M.p. 136 °C. $[\alpha]_D^{20}$ = −44.0 (c = 5.8, $CHCl_3$). R_f (EtOAc) = 0.64. ^{1}H NMR (200 MHz): δ = 1. 27 (d, J = 6.6 Hz, 3 H), 1.41 (s, 9 H), 1.49 (s, 9 H), 3.35−3.45 (m, 1 H), 3.88−3.95 (t, J = 6.6 Hz, 2 H), 4.13 (t, J = 8.6 Hz, 1 H), 4.25 (m, 1 H), 7.22−7.35 (m, 5 H) ppm. ^{13}C NMR (75 MHz): δ = 15.3, 27.4, 28.4, 37.3, 48.9, 53.7, 73.9, 79.1, 80.4, 126.8, 127.1, 128.7, 140.9, 146.7, 155.3 ppm. $C_{21}H_{32}N_2O_4$ (376.24): calcd. C 66.99, H 8.57, N 7.44; found C 66.92, H 8.64, N 7.40.

Diamine 6: *p*-Toluenesulfonyl chloride (232 mg, 1.25 mmol) was added to a solution of compound **4h** (250 mg, 0.94 mmol) and Et_3N (135 mg, 1.35 mmol) in CH_2Cl_2 (20 mL). After 16 h at room temperature, saturated aqueous NH_4Cl solution (5 mL) and CH_2Cl_2 (20 mL) were added. The organic extract was washed with brine, dried with magnesium sulfate, concentrated under reduced pressure and purified by silica gel column chromatography (CH_2Cl_2/Et_2O, 3:1) to give **6** as a solid (280 mg, 71%). M.p. 62 °C. $[\alpha]_D^{20}$ = −20.8 (c = 3.65, $CHCl_3$). R_f (CH_2Cl_2/Et_2O, 3:1) = 0.31. ^{1}H NMR

(200 MHz): δ = 1.23 (d, *J* = 6.6 Hz, 3 H), 1.45 (s, 3 H), 2.32 (s, 3 H), 3.21 (dd, *J* = 2.6, 7.9 Hz, 1 H), 3.64 (t, *J* = 8.1 Hz, 1 H), 3.73 (dd, *J* = 2.4, 6.6 Hz, 1 H), 3.99 (d, *J* = 9.0 Hz, 1 H), 5.13 (br. s, 1 H), 6.95 (d, *J* = 7.9 Hz, 2 H), 7.15 (m, 3 H), 7.35 (m, 7 H), 7.51 (m, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 14.4, 21.3, 35.8, 47.4, 58.5, 62.1, 71.3, 126.9, 127.3, 127.8, 127.9, 128.4, 128.9, 129.1, 136.8, 137.7, 138.9, 142.3 ppm. $C_{25}H_{28}N_2O_2S$ (420.19): calcd. C 71.40, H 6.71, N 6.66; found C 71.12, H 6.09, N 7.01.

Diamine 7: $MgSO_4$ (1 g) was added to a solution of compound **4h** (340 mg, 1.3 mmol) and benzaldehyde (139 mg, 1.3 mmol) in CH_2Cl_2 (3 mL). After 3 h at room temperature, the mixture was filtered and the filtrate concentrated under reduced pressure. The residue was dissolved in EtOH (5 mL), and $NaBH_4$ (60 mg, 1.6 mmol) was added at 0 °C. After 1 h, the reaction was quenched by addition of a saturated aqueous NH_4Cl solution (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried with magnesium sulfate, concentrated under reduced pressure and purified by silica gel column chromatography (C_6H_{12}/Et_2O, 2:1) to give **7** as an oil (378 mg, 82%). $[\alpha]_D^{20}$ = −20.5 (*c* = 4.45, $CHCl_3$). R_f (C_6H_{12}/Et_2O, 2:1) = 0.38. ^{1}H NMR (200 MHz): δ = 1.28 (d, *J* = 6.6 Hz, 3 H), 1.54 (s, 3 H), 2.78 (d, *J* = 12.6 Hz, 1 H), 3.24 (m, 2 H), 3.47 (d, *J* = 9.8 Hz, 1 H), 3.67 (m, 1 H), 3.80 (m, 1 H), 6.75 (m, 2 H), 7.16 (m, 3 H), 7.27−7.44 (m, 8 H), 7.61 (m, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 14.8, 36.3, 47.9, 50.9, 62.1, 63.7, 73.1, 126.1, 126.9, 127.3, 128.1, 128.2, 128.3, 128.5, 128.6, 129., 139.9, 140.1, 141.3 ppm. $C_{25}H_{28}N_2$ (356.23): calcd. C 84.23, H 7.92, N 7.86; found C 84.09, H 8.13, N 8.01.

Diamine 8: A solution of cyanoazetidine **2a** (400 mg, 1.6 mmol) in dry THF (4 mL) was added to a suspension of $LiAlH_4$ (72 mg, 1.8 mmol) in dry THF (5 mL). After 1 h at room temperature, the reaction was quenched by addition of a saturated aqueous NH_4Cl solution (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried with magnesium sulfate and concentrated under reduced pressure. Compound **8** was purified by silica gel column chromatography (EtOAc then EtOAc/MeOH, 8:2) to give **8** as an oil (274 mg, 68%). $[\alpha]_D^{20}$ = +4.7 (*c* = 4.65, $CHCl_3$). R_f (EtOAc) = 0.18. ^{1}H NMR (200 MHz): δ = 1.45 (br. s, 2 H), 2.72 (d, *J* = 4.4 Hz, 2 H), 3.05 (dd, *J* = 8.6, 6.6 Hz, 1 H), 3.35 (m, 1 H), 3.56 (m, 1 H), 3.75 (d, *J* = 12.5 Hz, 1 H), 3.73−3.83 (m, 2 H), 7.28−7.37 (m, 10 H) ppm. ^{13}C NMR (75 MHz): δ = 38.6, 44.6, 58.4, 62.9, 75.1, 126.5, 127.2, 127.3, 128.4, 128.5, 128.8, 138.3, 141.5 ppm. $C_{17}H_{20}N_2$ (256.16): calcd. C 80.91, H 7.91, N 11.10; found C 80.72, H 8.12, N 11.01.

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[12] Alternatively, the *N*-Boc protected diamine **4a** could also be obtained in two steps. Indeed, the intermediate imine **3** proved to be stable enough to be isolated, and could then be reduced and protected under similar conditions to afford **4a**.

[13] X-ray crystallographic data of **5**: $C_{21}H_{32}N_2O_4$, orthorhombic, space group *P*2(1)2(1)2(1), *a* = 9.4465(4) Å, *b* = 11.5992(5) Å, *c* = 19.9718(9) Å, *V* = 2188.35(16) Å^3, $D_{calcd.}$ = 1.143 g cm^{-3}, *Z* = 4, μ(Mo-K_α) = 0.079 mm^{-1}, total reflections collected: 15280, independent reflections: 5647 (3421 $I > 2\sigma(I)$], number of variables: 252, R_1 = 0.0462, wR_2= 0.1090 (all data). X-ray data for **5** were collected with a three-circle diffractometer equipped with a 2-dimensional CCD detector. CCDC-230430 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

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