Synthesis of New Chiral Mixed *cis*-Tetraheterodecalines by Highly Selective Cyclization of *N*,*N*′-Bisalkyl 2,3-Diaminobutanediols

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Abstract: Chiral secondary *vic*-diamines of diaminobutanediols have been efficiently prepared from L-tartaric acid. Their selective cyclization led to *cis*-tetraheterodecalines having a (1*S*,6*S*)-2,7-diaza-4,9-dioxa[4.4.0]decane core system.

Key words: amino alcohols, fused-ring systems, heterocycles, ring closure

Enantiomerically pure vicinal diamines occur commonly in nature, with many of them having biological properties. Some of them and several synthetic *vic*-diamines are used as medicinal agents.[1] In the laboratory *vic*-diamines have found widespread use as chiral ligands in asymmetric reactions, especially C_2-symmetric *vic*-diamines with their symmetry element added.[2] Moreover, with the degree of conformational freedom of chiral complexes with a transition metal being reduced in cyclic derivatives, only a few such chiral *vic*-diamines have been designed. For example bipyrrolidines **1** were used in the asymmetric dihydroxylation of alkenes[3] and the ligand activity of bioxazoles **2**, where the two oxazoline rings are directly bonded, has been reported in Cu, Rh, Ir catalyzed asymmetric hydrosilylation of ketones,[4] cyclopropanation of olefins,[5] and transfer hydrogenation of ketones (Figure 1).[6]

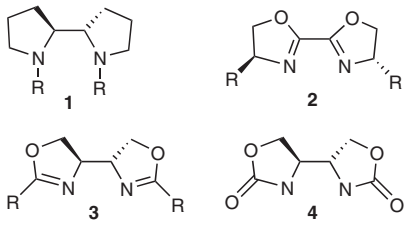

Figure 1 Chiral *vic*-diamines **1**–**4**

Several reports show the biological importance of diaminobutanediols. Indeed, drugs based on 1,2,3,4-diaminobutanediols and derivatives showed anticancer properties, and complexes of *threo*-2,3-diaminobutane-1,4-diol derived from mannitol were used as antitumor agents.[7] These compounds are also the precursors of bioxazoles **3**[8] and bioxazolidinones **4**,[9] useful for asymmetric hydrosilylation and allylic substitution.[10]

Our continuing interest in utilizing tartaric acid as a chiral source for the synthesis of optically active products[11] led us to investigate an efficient construction of polyfunctionalized, N-substituted compounds **5** and of the corresponding *N*,*O*-formacetals **6** (Figure 2). These C_2-symmetric *cis*-tetraheterodecalines have two chelating oxygen atoms, plus two nitrogen atoms that can be substituted.[12] These compounds bearing chirality on their backbone could be related to (–)-sparteine (**7**), a natural polycyclic diamine used in asymmetric synthesis, for instance in the deprotonation of carbamates.[13] The cavity defined by the concave shape of the *cis*-decaline configuration could be useful for metal binding.[14] The basic acyclic diaminobutanediol skeleton has been prepared by various groups and the cyclic heterodecalines have been obtained recently by Fuchs and co-workers.[15] Probably due to synthetic drawbacks no *N*,*N*′-bisalkyl derivative has been reported yet, except a formally parent 2,3-substituted DABCO derivative.[16]

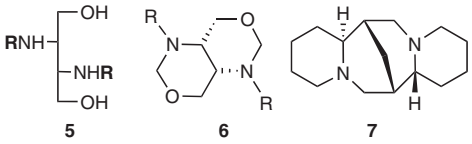

Figure 2 Optically active N-substituted compounds **5**–**7**

Therefore, we report here an efficient and selective synthesis of *N*,*N*′-bisalkyl-2,3-diaminodiols **5** and *N*,*N*′-substituted (1*S*,6*S*)-2,7-diaza-4,9-dioxabicyclo[4.4.0]decanes **6**, starting from L-tartaric acid. The enantiomeric tetraheterodecalines could be similarly obtained starting from D-tartaric acid.

The synthesis of chiral diaminodiols **5** was achieved from tartaric acid as the free (R = H) or carbamate protected primary amine, via a 1,4-protected threitol. Preparing *N*-alkyl *vic*-diamines was a critical step. The secondary amino groups could not be introduced by direct Mitsunobu amination of diol **8** to form secondary amines **11**. Moreover, S_N2 displacement of the corresponding sulfonyl ester by a primary amine mostly led to olefin **10** after β-elimination (Scheme 1).

However vicinal primary amine **11a** was easily synthesized in seven steps,[17] and could become a convenient

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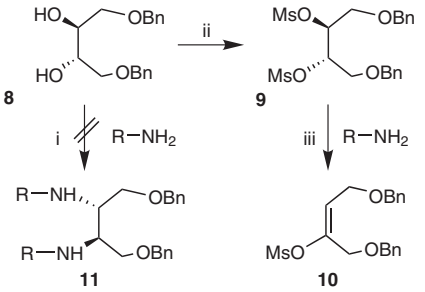
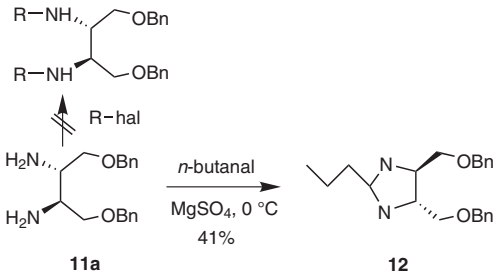


Scheme 1 *Reagents and conditions*: i) DEAD, Ph_3P, THF, r.t.; ii) MsCl, Et_3N, CH_2Cl_2; iii) R = Bn or *t*-Bu, base: Na_2CO_3, K_2CO_3 or Cs_2CO_3, with/without 18-CE-6, MeCN, reflux.

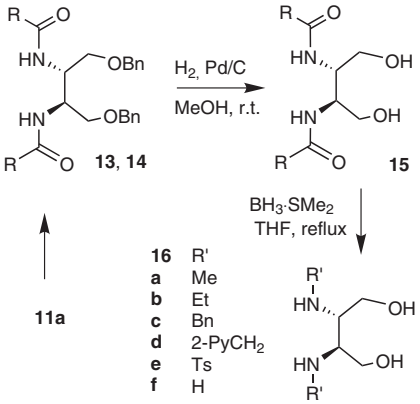
building block. The synthesis of **11a** was performed in 55% overall yield, without purification of the intermediates. Crude diamine **11a** was purified via the corresponding dihydrochloride. Williamson-type alkylation of **11a** could not be controlled and hence was of no practical use. Condensation of *n*-butanal to give the diimine led only to imidazolidine **12**, formed by intramolecular condensation from the intermediate monoimine (Scheme 2).



Scheme 2

Pure vicinal diamine **11a** was efficiently converted into diacylated derivatives **13** under experimental conditions specific to each case, followed by a standard work-up and chromatographic purification (Scheme 3). Bistosylamine **14** was obtained using TsCl (Table 1).

Debenzylation of **13** and **14** was efficiently accomplished under an atmospheric pressure of H_2 using Pd/C in methanol at room temperature, to provide **15b**, **15c** and **16e**. However, alcohol **15d** was obtained in only 39% yield under these standard conditions, the pyridyl moiety probably poisoning the catalyst. Pearlman's catalyst was found to



Scheme 3

be clearly superior in that case. Refluxing dibenzyl ether derivative **13d** with cyclohexene in ethyl acetate–methanol (1:1) in the presence of $Pd(OH)_2/C$ for 16 hours afforded **15d** in 72% yield. Compound **16a** could not be cleanly obtained because of solubility problems with **15a** (R = H).

The amides were conveniently reduced by borane/dimethyl sulfide complex in refluxing THF, a better reagent than lithium aluminum hydride in this case, to give the corresponding new secondary alkylamines **16**. These *vic*-diamines should behave differently because of their nitrogen atoms being more nucleophilic than the known compound **16f** (R′ = H).

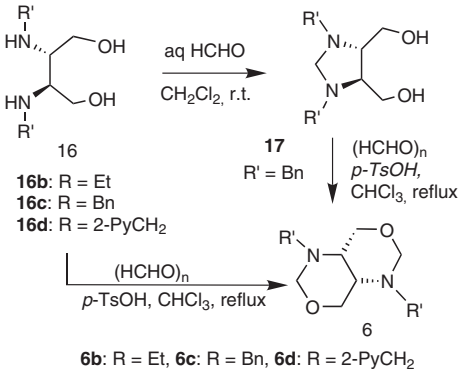
The cyclization of amines **16** to heterodecalines **6** with their 6 member rings was another critical step, most cyclizations in this area leading to five-membered rings. Cyclization under basic conditions of diaminobutanediol **16f** having the amino groups protected as carbamates or by an acyl group like in **15c** and **15d**, led to bioxazoles **3**[11] and bisoxazolidinones **4**,[10] i.e. compounds having only five-membered rings. Cyclization of **16f** with aqueous formaldehyde under required strong acidic conditions gave a moderate yield of **6a**, as a 1:2 mixture with the five-membered oxazolidine rings.[18] DL-2,3-Dianilinobutane-1,4-diol as well reacted with aqueous formaldehyde forming a dioxazolidine.[19]

Eventually, reaction of **16c** with aqueous formaldehyde at room temperature gave a kinetic product in 43% yield, identified as the imidazoline **17**. In this reaction catalysis

Table 1 Acylation and Sulfonation of Primary Amine **11a**

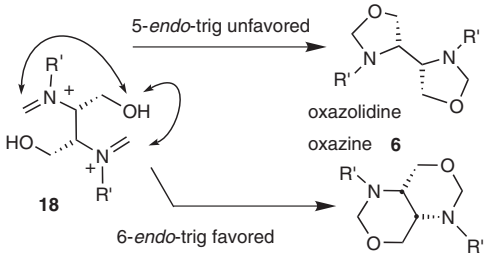
R	Product	Reagent	Reaction conditions	Yield (%)
H	**13a**	HCO_2H/Ac_2O	THF, r.t.	60
Me	**13b**	Ac_2O/Et_3N/DMAP	CH_2Cl_2, 0 °C	ca. 100
Ph	**13c**	PhCOCl	CH_2Cl_2, 0 °C	90
2-Py	**13d**	2-$PyCO_2H$/DCC/DMAP	CH_2Cl_2, 0 °C/r.t.	ca. 100
RCO = Ts	**14**	TsCl	CH_2Cl_2, 0 °C	88

by TsOH was not necessary. The desired tetraheterodecaline **6c** was isolated in 71% yield using paraformaldehyde as the source of methylene, under acidic conditions and refluxing dichloromethane for 4 days. At higher temperature, such as refluxing chloroform, **6c** was obtained in 16 hours only and in 86% yield. The tetraheterodecaline appeared thus to be the thermodynamic product. This was confirmed by the conversion of imidazoline **17** to decaline **6c** in 60% yield and under the same conditions (Scheme 4). The bis(2-pyridinylmethyl)- and bis(ethyl)tetraheterodecalines **6d** and **6b** were also synthesized under the same conditions in 34% and 70% yields from **16d** and **16b**, respectively.



Scheme 4

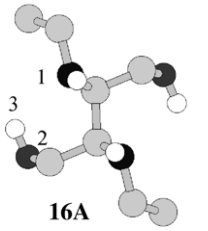
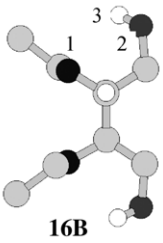
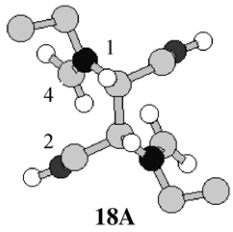
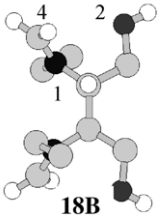
The ring closure occurred via the intramolecular addition of the hydroxyl group onto the iminium ion, easily formed by reaction of the nucleophilic secondary amine on formaldehyde and stabilized by the donor effect of R′ group. In this process, in compliance with Baldwin's rules the 6-*endo*-trig type ring closure seemed to be favored over the 5-*endo*-trig type (Scheme 5).[20]



Scheme 5 Ring closure according to Baldwin rules

MM2 calculations on the diaminobutanediols **16**, illustrated by **16b** (R′ = Et), indicated that the conformation of lowest energy was a pseudo *cis*-fused bicyclic structure **16bA** precursor of the oxazine (Table 2). This conformation is favored by a N---HO hydrogen bond, stronger within a six-membered ring than within the five-membered ring **16bB** that would give the oxazolidine: albeit the N1–O2 atoms are closer to each other in **16bB**, atoms N1 and H3 are closer in **16bA**. In the corresponding iminium ions **18**, O2 is closer to the Csp^2 C4 in **18A** than in **18B**.

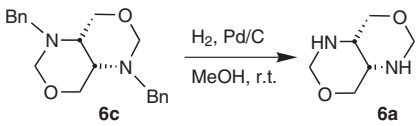
Table 2 MM2 Calculated Conformations of Amino Alcohol **16b** and Iminium Ions **18** Leading to the Oxazine (**A**) and Oxazoline (**B**) Isomers[a]

Parameters	 **16A**	 **16B**
En (kcal)	9.48	10.64
N(1)–OH (Å)	2.77	2.72
N(1)–HO (Å)	2.31	2.41
	 **18A**	 **18B**
N^+CH_2–OH (Å)	2.95	3.01

[a] Some hydrogen atoms are omitted.

The pre-organized conformation **16A** was confirmed by NMR spectroscopy. The diaminobutanediols gave more splitting than the corresponding amides. The methylene protons in the OCH_2CHN fragment resonated as two well separated ABX signals in **16b** (J_{AB} = 11.3) and AB signals in **16c** (J_{AB} = 9.3). The methine proton gave only a broadened singlet. These data were consistent with a pre-organized chair conformation of a pseudo six-membered ring.

Debenzylation of **6c** using Pd/C in methanol under an atmospheric pressure of hydrogen gave the unsubstituted tetraheterodecaline **6a** in 94% yield. This indirect approach to **6a** was more efficient than the direct cyclization of primary amine **16f** (Scheme 6).



Scheme 6

Tetraheterodecalines **6** were fully and unambiguously characterized by usual spectroscopic methods. The *N*,*O*-methylene acetal protons resonated as an AB pattern typical of six-membered rings. The coupling constant (J = 10.6 to 11.3 Hz) indicated that there is no nitrogen inversion, but rather an axial configuration for the NR and NH substituents.[21]

In conclusion, we have reported the efficient synthesis of enantiomerically pure new C_2-symmetric vicinal second-

ary amines in diaminobutanediols, that cyclized to mixed tetraheterodecalines having a (1*S*,6*S*)-2,7-diaza-4,9-dioxabicyclo[4.4.0]decane core. The different chemical behavior of the secondary diamines when compared to diaminobutanediols having primary or deactivated amino groups, should result in different bio and chemical properties for their derivatives.

Studies on the potential of this kind of ligands for metal-catalyzed asymmetric reactions are in progress.

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer IR FT-1605 spectrophotometer. The ^{1}H NMR spectra and the ^{13}C NMR spectra were recorded on an AC 200 Bruker instrument, in $CDCl_3$ as internal reference for chemical shifts at 7.24 ppm and 77.1 ppm, respectively, and are expressed as δ values in ppm. Coupling constants are in Hz. Optical rotations were measured on a Perkin-Elmer 341 polarimeter at the sodium D line, at the designated concentration in g per mL. Chromatography was carried out on columns packed with Merck silica gel 60 (70–230 mesh).

All reactions were performed under argon. THF was distilled from sodium benzophenone ketyl under argon, and CH_2Cl_2 and $CHCl_3$ were distilled from P_2O_5. DMF was distilled from BaO and MeOH from CaH_2. Petroleum ether used refers to the fraction boiling at 40–65 °C. Reagents were used as received or were purified by standard methods.[22]

Methanesulfonic Acid (*E*)-3-Benzyloxy-1-benzyloxymethylpropenyl Ester (10)

To a solution of dimesylate **9** (114 mg, 0.249 mmol) in MeCN (2.5 mL) were added Na_2CO_3 or K_2CO_3 or Cs_2CO_3 (0.6 mmol), benzyl- or *tert*-butylamine (0.6 mmol). The mixture was stirred at various temperatures until total conversion of **9**. The solvent was evaporated under vacuum and the residue was filtered through Celite with the help of CH_2Cl_2, then chromatographed on silica gel to give **10** (65 mg, 72%) as a colorless oil.

IR (film): 3030, 2920, 2870, 1360, 1180, 1100, 1060 cm^{-1}.

^{1}H NMR: δ = 7.33 (m, 10 H), 5.72 (t, *J* = 6.1 Hz, 1 H), 4.51 (d, *J* = 3.4 Hz, 4 H), 4.25 (d, *J* = 6.1 Hz, 2 H), 4.12 (s, 2 H), 3.11 (s, 3 H).

^{13}C NMR: δ = 145.1, 137.8, 137.2, 127.8–128.5 (10 C), 121.6, 72.8, 72.1, 69.4, 64.3, 38.9.

(4*S*,5*S*)-4,5-Bis(benzyloxymethyl)-2-propylimidazolidine (12)

To a solution of diamine **11a** (150 mg, 0.5 mmol) in THF (2 mL) cooled to 0 °C were added $MgSO_4$ (30 mg, 0.25 mmol) and *n*-butanal (112.5 μL, 1.25 mmol). After total conversion of **11**, the mixture was filtered through silica gel with the help of Et_2O containing Et_3N (1%). Chromatography on silica gel afforded **12** (72 mg, 41%) as a colorless oil.

IR (film): 3300, 3050, 3020, 2980, 1450, 1200, 1090 cm^{-1}.

^{1}H NMR: δ = 7.35–7.28 (m, 10 H), 4.50 (s, 4 H), 3.85 (t, *J* = 5.5 Hz, 1 H), 3.69–3.33 (m, 4 H), 3.10 (m, 2 H), 1.95 (br s, 2 H), 1.63–1.36 (m, 4 H), 0.90 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 138.2, 127.6–128.4 (10 C), 74.8, 73.8 (2 C), 72.4 (2 C), 59.1 (2 C), 37.6, 19.7, 14.8.

(2*S*,3*S*)-1,4-Dibenzyloxy-2,3-bis(formylamino)butane (13a)

Ac_2O (159 μL, 1.56 mmol) and formic acid (72 μL, 1.92 mmol) were heated at 60 °C for 2 h. The mixture was cooled to 0 °C and diluted with THF (1 mL) before the addition of diamine **11a** (100 mg, 0.3 mmol) in THF (1 mL). The mixture was stirred for 3 h at r.t. The solvent was evaporated and the residue was chromatographed on silica gel to give **13a** (65 mg, 60%) as a solid; mp 145–146 °C.

IR ($CHCl_3$): 3010, 2990, 1680, 1210, 1060 cm^{-1}.

^{1}H NMR: δ = 8.10 (s, 2 H), 7.37–7.21 (m, 10 H), 6.35 (br s, 2 H), 4.45 (d, *J* = 12 Hz, 2 H), 4.35 (d, *J* = 12 Hz, 2 H), 3.46 (m, 4 H), 4.40 (m, 2 H).

^{13}C NMR: δ = 161.6, 137.4, 128.4, 127.9, 127.6, 73.4, 68.6, 49.0.

(2*S*,3*S*)-1,4-Dibenzyloxy-2,3-bis(acetamino)butane (13b)

Ac_2O (660 μL, 6.99 mmol) was added to a solution of diamine **11a** (1 g, 3.33 mmol), Et_3N (965 μL, 6.99 mol) and *N*,*N*-dimethylaminopyridine (8 mg, 0.06 mmol) in CH_2Cl_2 (13 mL) at 0 °C. The reaction was instantaneous. The mixture was quenched by addition of H_2O (20 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried ($MgSO_4$). Chromatography on silica gel with 0.5% and 1% MeOH in CH_2Cl_2 as eluent afforded diacetamide **13b** as a white solid (1.27 g, 99%); mp 134–136 °C.

IR ($CHCl_3$): 3420, 2990, 2900, 2880, 1640, 1530, 1460, 1100, 1050 cm^{-1}.

^{1}H NMR: δ = 7.34–7.21 (m, 10 H), 6.27 (m, 2 H), 4.44 (d, *J* = 12 Hz, 2 H), 4.35 (d, *J* = 12 Hz, 2 H), 4.25 (m, 2 H), 3.43 (m, 4 H), 1.89 (s, 6 H).

^{13}C NMR: δ = 170.5, 137.5, 128.3, 127.7, 127.3, 73.1, 68.7, 50.4, 23.1.

(2*S*,3*S*)-1,4-Dibenzyloxy-2,3-bis(benzoylamino)butane (13c)

Benzoyl chloride (810 μL, 6.99 mmol) was added to a solution of diamine **11a** (1 g, 3.33 mmol), Et_3N (965 μL, 6.99 mmol) in CH_2Cl_2 (13 mL) at 0 °C. The reaction was instantaneous. The mixture was quenched by addition of H_2O (20 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried ($MgSO_4$). Chromatography on silica gel with 0.5% and 1% MeOH in CH_2Cl_2 as eluent afforded dibenzoylamide **13c** as a white solid (1.52 g, 90%); mp 113–114 °C.

IR ($CHCl_3$): 3460, 3020, 2990, 1660, 1530, 1220, 1090 cm^{-1}.

^{1}H NMR: δ = 7.63–7.46 (m, 4 H), 7.43–7.26 (m, 16 H), 4.64 (m, 2 H), 4.48 (br s, 4 H), 3.68 (m, 4 H), 1.61 (br s, 2 H).

^{13}C NMR: δ = 167.5, 137.4, 133.9, 131.4, 128.5, 128.42, 128.4, 128.0, 126.9, 73.5, 68.9, 50.9.

(2*S*,3*S*)-1,4-Dibenzyloxy-2,3-bis(2-pyridinoylamino)butane (13d)

Piconilic acid (775 mg, 6.3 mmol) was added to a solution of diamine **11a** (900 mg, 3 mmol), dicyclohexylcarbodiimide (1.32 g, 6.3 moles) and *N*,*N*-dimethylaminopyridine (36 mg, 0.3 mmol) in CH_2Cl_2 (12 mL) at 0 °C. The reaction was monitored by TLC. Et_2O (10 mL) was added and the crystalline urea was filtered off over silica gel using Et_2O as eluent. Concentration gave **13d** as a white solid (1.53 g, 99%); mp 86–88 °C.

IR ($CHCl_3$): 3020, 2960, 1680, 1560, 1280, 1260, 1110, 1050 cm^{-1}.

^{1}H NMR: δ = 8.71 (m, 2 H), 8.45 (m, 2 H), 8.08 (m, 2 H), 7.74 (m, 2 H), 7.37–7.23 (m, 12 H), 4.71 (m, 2 H), 4.51 (s, 4 H), 3.69 (m, 4 H).

^{13}C NMR: δ = 164.5, 149.7, 148.2, 137.8, 137.0, 128.3, 127.8, 127.7, 126.0, 122.1 73.4, 69.4, 50.3.

(2*S*,3*S*)-1,4-Dibenzyloxy-2,3-bis(*O*-tosylamino)butane (14)

To a solution of diamine **11a** (103 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added tosyl chloride (458 mg, 1.2 mmol); Et_3N (166 μL, 1.2 mmol) and DMAP (1.2 mg, 0.01 mmol). After 30 min, the mixture was acidified with 5% HCl (5 mL). The organic layer was washed with aq $NaHCO_3$ (5 mL) and distilled H_2O (5 mL), and

dried ($MgSO_4$). Chromatography on silica gel afforded **14** as a white solid (226 mg, 88%); mp 121–123 °C; $[\alpha]_D^{20}$ –34.2 (*c* 25×10^{-3}, $CHCl_3$).

IR ($CHCl_3$): 3390, 3050, 3000, 2900, 1530, 1460, 1350, 1180, 1100, 1020 cm^{-1}.

^1H NMR: δ = 7.64 (d, *J* = 8.2 Hz, 4 H), 7.33–7.10 (m, 10 H), 7.30 (d, *J* = 8.2 Hz, 4 H), 5.08 (d, *J* = 6.1 Hz, 2 H), 4.23 (s, 4 H), 3.52 (br s, 2 H), 3.38–3.22 (m, 4 H), 2.38 (s, 6 H).

^{13}C NMR: δ = 143.2, 137.5, 137.0, 129.5–127.6 (18 C), 72.8, 68.4, 53.5, 21.4.

(2*S*,3*S*)-2,3-Bis(acetamino)butane-1,4-diol (15b)
To a solution of dibenzyl ether **13b** (1.273 g, 3.31 mmol) in anhyd MeOH (33 mL) was added 10% Pd/C (382 mg). The mixture was vigorously stirred under an atmospheric pressure of H_2 and was monitored by TLC. The catalyst was removed by filtration over Celite with MeOH–CH_2Cl_2 (1:1) as eluent. Concentration gave **15b** (662 mg, 98%) as a white solid; mp 160–162 °C.

IR ($CHCl_3$): 3440, 3040, 2990, 2900, 1660, 1050 cm^{-1}.

^1H NMR (CD_3OD): δ = 4.09 (m, 2 H), 3.54 (m, 4 H), 1.97 (s, 6 H).

^{13}C NMR (CD_3OD): δ = 173.8, 62.3, 52.9, 22.7.

(2*S*,3*S*)-2,3-Bis(benzoylamino)butane-1,4-diol (15c)
To a solution of dibenzyl ether **13c** (1.52 g, 2.99 mmol) in anhyd MeOH (30 mL) was added 10% Pd/C (380 mg). The mixture was vigorously stirred under an atmospheric pressure of H_2 and was monitored by TLC. The catalyst was removed by filtration over Celite with MeOH in CH_2Cl_2 (1:1) as eluent. Concentration gave **15c** (947 mg, 97%) as a white solid; mp 174–176 °C.

IR (CCl_4): 3420, 3010, 2980, 1490, 1220, 1090 cm^{-1}.

^1H NMR (CD_3OD): δ = 7.84–7.78 (m, 4 H), 7.56–7.38 (m, 6 H), 4.49 (m, 2 H), 3.82 (m, 4 H).

^{13}C NMR (CD_3OD): δ = 170.9, 135.5, 132.7, 129.5, 128.4, 62.4, 54.0.

(2*S*,3*S*)-2,3-Bis(2-pyridinoylamino)butane-1,4-diol (15d)
To a solution of dibenzyl ether **13d** (255 mg, 0.5 mmol) in anhyd MeOH (1.5 mL) was added 20% $Pd(OH)_2/C$ (80 mg) and cyclohexene (1.3 mL, 13 mmol). The mixture was vigorously stirred under reflux for 16 h. The catalyst was removed by filtration over Celite with EtOAc as eluent. Concentration and chromatography on silica gel using 1% Et_3N in 5% MeOH–CH_2Cl_2 as starting eluent, then MeOH–CH_2Cl_2 (1:1) gave **15d** (120 mg, 72%) as a white solid; mp 144–145 °C.

IR ($CHCl_3$): 3380, 3040, 2910, 1680, 1530, 1440, 1060 cm^{-1}.

^1H NMR: δ = 8.51 (m, 2 H), 8.24 (m, 2 H), 8.16 (m, 2 H), 7.89–7.40 (m, 2 H), 7.46–7.23 (m, 2 H), 4.53 (d, *J* = 7.9 Hz, 2 H), 4.04 (m, 2 H), 3.87 (dd, *J* = 11.6, 4.1 Hz, 2 H), 3.66 (dd, *J* = 11.6, 4.1 Hz, 2 H).

^{13}C NMR: δ = 165.9, 148.8, 148.3, 137.5, 126.7, 122.6, 62.0, 51.6.

(2*S*,3*S*)-2,3-Diethylaminobutane-1,4-diol (16b)
To a solution of diacetamide **15b** (676 mg, 3.31 mmol) in THF (165 mL) was added borane dimethyl sulfide complex (1.88 mL, 19.88 mmol) at 0 °C. The mixture was refluxed for 2 d, then quenched with H_2O (20 mL) at 0 °C. The aqueous layer was washed with CH_2Cl_2, acidified with 35% HCl (6 mL) and refluxed for 16 h. The pH of the mixture was adjusted to 9 by addition of solid NaOH at 0 °C. The mixture was extracted with CH_2Cl_2, the organic extracts were dried (Na_2SO_4) and the solvent was evaporated to give crude **16b** (553 mg, 95%) as a colorless liquid.

IR (film): 3300, 2980, 2920, 1260, 1050 cm^{-1}.

^1H NMR: δ = 3.85 (dd, *J* = 11.3, 3.1 Hz, 2 H), 3.76 (dd, *J* = 11.3, 3.1 Hz, 2 H), 3.65 (m, 4 H), 2.85 (dq, *J* = 11.3, 7.2 Hz, 2 H), 2.66 (br s, 2 H), 1.09 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 63.4, 61.3, 41.9, 15.5.

(2*S*,3*S*)-2,3-Dibenzylaminobutane-1,4-diol (16c)
To a solution of dibenzylamide **15c** (950 mg, 2.89 mmol) in THF (86 mL) was added borane dimethyl sulfide complex (1.21 mL, 12.72 mmol) at 0 °C. The mixture was refluxed for 16 h, then 6 N HCl (965 μL, 5.78 mmol) was added at 0 °C. The mixture was refluxed for 1 h, then basified by addition of 6 N NaOH (1.447 mL, 8.67 mmol) at 0 °C, then distilled H_2O (20 mL) was added. The mixture was extracted with CH_2Cl_2, the organic extracts were dried (Na_2SO_4) and the solvent was evaporated to give crude **16c** (870 mg, 99%) as a white solid; mp 82–84 °C.

IR ($CHCl_3$): 3320, 3040, 2940, 2880, 1460, 1100, 1070 cm^{-1}.

^1H NMR: δ = 7.29 (m, 10 H), 3.91 (d, *J* = 12.6 Hz, 2 H), 3.89 (d, *J* = 9.4 Hz, 2 H), 3.68 (d, *J* = 12.6 Hz, 2 H), 3.66 (d, *J* = 9.4 Hz, 2 H), 2.73 (br s, 2 H).

^{13}C NMR: δ = 139, 128.6, 128.4, 127.4, 62.5, 60.4, 51.5.

(2*S*,3*S*)-2,3-Bis(2-pyridinylamino)butane-1,4-diol (16d)
Prepared from **15d** (157 mg, 0.476 mmol) following the procedure used for **16c**. Crude product without purification (74 mg, 51%).

^1H NMR: complex unresolved multiplets.

^{13}C NMR: δ = 149.1, 148.3, 136.9, 122.5, 122.3, 60.7, 52.6.

(2*S*,3*S*)-2,3-Bis(tosylamino)butane-1,4-diol (16e)
Prepared from **14** (561 mg, 1.09 mmol) following the procedure used for **15b** and **15c**; yield: 341 mg (93%); white solid; mp 171–173 °C; $[\alpha]_D^{20}$ –42.6 (*c* 21×10^{-3}, $CHCl_3$).

IR ($CHCl_3$): 3400, 3040, 2990, 1530, 1480, 1430, 1060 cm^{-1}.

^1H NMR (CD_3OD): δ = 7.78 (d, *J* = 6.5 Hz, 4 H), 7.39 (d, *J* = 6.5 Hz, 4 H), 3.38–3.22 (m, 4 H), 3.29–3.18 (m, 2 H), 2.47 (s, 6 H).

(1*S*,6*S*)-2,7-Di(*N*-benzyl)aza-4,9-dioxabicyclo[4.4.0]decane (6c)
To a solution of **16c** (300 mg, 1 mmol) in $CHCl_3$ (6 mL) were added anhyd paraformaldehyde (120 mg, 4 mmol) and *p*-TsOH (9 mg, 0.05 mmol). The mixture was refluxed for 16 h, then cooled to r.t. before addition of H_2O (5 mL) and K_2CO_3. After extraction with CH_2Cl_2, the organic layer was dried (Na_2SO_4) and concentrated. Chromatography on silica gel with Et_2O in petroleum ether (3:7 to 1:1) as eluent afforded tetraheterodecalin **6c** as a white solid (279 mg, 86%); mp 54–55 °C; $[\alpha]_D^{20}$ +61.6 (*c* 24×10^{-3}, $CHCl_3$).

IR ($CHCl_3$): 3000, 2960, 2900, 1480, 1220, 1110, 1060, 1010 cm^{-1}.

^1H NMR: δ = 7.35–7.25 (m, 10 H), 4.41 (d, *J* = 11.3 Hz, 2 H), 4.17 (d, *J* = 11.3 Hz, 2 H), 3.95 (dd, *J* = 11.3, 11.0 Hz, 2 H), 3.91 (br s, 4 H), 3.80 (dd, *J* = 11.3, 5.6 Hz, 2 H), 3.26 (m, 2 H).

^{13}C NMR: δ = 138.9, 128.7, 128.6, 127.4, 80.1, 64.9, 57.4, 46.8.

Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.63. Found: C, 74.03; H, 7.45; N, 8.59.

(1*S*,6*S*)-2,7-Di(*N*-ethyl)aza-4,9-dioxabicyclo[4.4.0]decane (6b)
Prepared from **16b** in a similar manner to **6c**; yield: 70%; colorless liquid; $[\alpha]_D^{20}$ +1.8 (*c* 60×10^{-3}, $CHCl_3$).

IR ($CHCl_3$): 2990, 2960, 2900, 1480, 1400, 1230, 1100, 1050 cm^{-1}.

^1H NMR: δ = 4.32 (d, *J* = 11.3 Hz, 2 H), 4.21 (d, *J* = 11.3 Hz, 2 H), 3.89 (dd, *J* = 11.3, 10.9 Hz, 2 H), 3.80 (dd, *J* = 11.3, 6.3 Hz, 2 H), 3.25 (m, 2 H), 2.90 (dq, *J* = 12.7, 7.2 Hz, 2 H), 2.80 (dq, *J* = 12.7, 7.2 Hz, 2 H), 2.07 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR: δ = 79.2, 64.7, 48.1, 47.5, 14.1.

Anal. Calcd for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.07; N, 13.99. Found: C, 59.89; H, 10.10; N, 13.90.

(1*S*,6*S*)-2,7-Bis[*N*-(2-pyridinylmethyl)]-4,9-dioxabicyclo[4.4.0]decane (6d)

Prepared from **16d** in a similar manner to **6c**. The crude product was purified by chromatography on silica gel using 1% Et_3N in 1 to 5% MeOH–CH_2Cl_2 to give **6d**; yield: 34%; white solid.; mp 97–99 °C; $[\alpha]_D^{20}$ +47.7 (*c* 13 × 10^{-3}, $CHCl_3$).

IR ($CHCl_3$): 3000, 2950, 2920, 1470, 1220, 1100, 1040 cm^{-1}.

^1H NMR: δ = 8.52 (d, *J* = 4.8 Hz, 2 H), 7.63 (d, *J* = 7.8 Hz, 2 H), 7.34 (d, *J* = 7.8 Hz, 2 H), 7.18–6.96 (m, 2 H), 4.45 (d, *J* = 11.3 Hz, 2 H), 4.20 (d, *J* = 11.3 Hz, 2 H), 4.11–3.92 (m, 2 H), 4.07 (d, *J* = 4.1 Hz, 2 H), 3.29 (m, 2 H).

^{13}C NMR: δ = 159.1, 149.5, 136.7, 122.4, 122.3, 80.6, 64.9, 59.6, 47.9.

Anal. Calcd for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.16. Found: C, 66.22; H, 6.79; N, 17.10.

(1*S*,6*S*)-2,7-Diaza-4,9-dioxabicyclo[4.4.0]decane (6a)

To a solution of tetraheterodecalin **6c** (279 mg, 0.86 mmol) in MeOH (10 mL) was added 10% Pd/C (139 mg). The mixture was vigorously stirred under an atmospheric pressure of H_2 and the reaction was monitored by TLC. The catalyst was removed by filtration over Celite with MeOH in CH_2Cl_2 (1:1) as eluent. Concentration gave **6a** (117 mg, 94%) as a white solid; mp 108–110 °C; $[\alpha]_D^{20}$ +15.0 (*c* 20 × 10^{-3}, MeOH).

IR (CCl_4): 3400, 3040, 2980, 2900, 1460, 1240, 1050 cm^{-1}.

^1H NMR: δ = 4.59 (d, *J* = 10.6 Hz, 2 H), 4.24 (d, *J* = 10.6 Hz, 2 H), 3.95 (d, *J* = 12 Hz, 2 H), 3.80 (d, *J* = 12 Hz, 2 H), 2.74 (br s, 2 H).

^{13}C NMR: δ = 78.9, 70.7, 49.5.

Anal. Calcd for $C_6H_{12}N_2O_2$: C, 49.99; H, 8.39; N, 19.43. Found: C, 49.91; H, 8.41; N, 19.36.

(4*S*,5*S*)-4,5-Dihydroxymethyl-1,2-di(*N*-benzyl)imidazolidine (17)

To a solution of dialkylaminodiol **16c** (59 mg, 0.196 mmol) in CH_2Cl_2 (1.8 mL) was added 30% aq formaldehyde (42 μL, 0.413 mmol) or paraformaldehyde (12.5 mg, 0.413 mmol). The mixture was stirred for 1.5 h, then distilled H_2O (5 mL) was added. The mixture was extracted with CH_2Cl_2 and the organic layer was dried (Na_2SO_4) and concentrated. Chromatography on silica gel with 1 to 3% MeOH–CH_2Cl_2 as eluent afforded imidazolidine **17** (27 mg, 43%) as a white solid; mp 70–72 °C; $[\alpha]_D^{20}$ –24.59 (*c* 22 × 10^{-3}, $CHCl_3$).

IR (film): 3380, 2920, 2820, 1420, 1050 cm^{-1}.

^1H NMR: δ = 7.26 (m, 10 H), 3.86 (d, *J* = 13 Hz, 2 H), 3.55 (d, *J* = 13 Hz, 2 H), 3.54 (s, 2 H), 3.43 (m, 4 H), 2.87 (br s, 2 H), 2.54 (br s, 2 H).

^{13}C NMR: δ = 138.8, 128.5, 127.4, 75.9, 67.3, 60.6, 58.3.

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