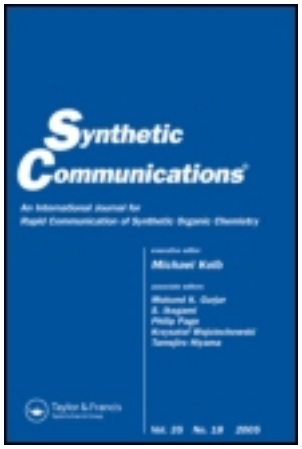

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SYNTHESIS OF 5,5′-DISUBSTITUTED BIMORPHOLINES

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A general method for the synthesis of 5,5′-disubstituted bimorpholines is proposed. According to the method, methyl-substituted and benzyl-substituted compounds were synthesized, starting from tartaric ester acetal. Target compounds were obtained in good yield and high enantiomeric purity.

Keywords: Asymmetric synthesis; bimorpholine; cyclic diamines

INTRODUCTION

Enantiomerically pure nitrogen-containing heterocycles are of great importance in organic chemistry. Their use as chiral auxiliaries, chiral reagents, and chiral ligands in many organic reactions is well known.[1] Additionally, such heterocycles are important building blocks for bioactive compounds.[2] Many pharmaceutical agents contain morpholine derivatives as part of their structure. The C-substituted morpholines have revealed antidepressant, appetite suppressant, antioxidative, and antitumor biological activity.[3]

At the same time, the expanding scope of asymmetric aminocatalysis[4] has led to the synthesis and wide use of a variety of diamines. These compounds are efficient organocatalysts in many C−C− and C-heteroatom bond-forming reactions.[5] C_2-symmetric bridged compounds that have a C−C bond between two heterocyclic rings and possess both H donor and acceptor sites and a secondary amino group are potential bifunctional catalysts (bimorpholines **1** and **2**, Fig. 1). Substitution in the morpholine rings makes them also attractive synthetic building blocks for bioactive molecules.

In connection with our ongoing project of organocatalysis with diamines, we have previously reported on the synthesis of (2*S*,2′*S*)-bimorpholine **1** and (3*R*,3′*R*)-bimorpholine **2**.[6] Derivatives of these bimorpholines have been used as organocatalysts in several reactions.[7] The main idea of their preparation is to

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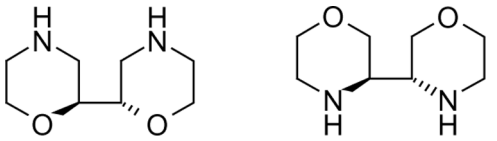


1 **2**

Figure 1. 2,2′-Bimorpholine **1** and 3,3′-bimorpholine **2**.

introduce the chiral structure of a readily available and cheap tartaric acid ester to a backbone of a cyclic derivative. The key steps of the synthesis are the introduction of nitrogen-containing functionality into tartaric acid derivatives and the intramolecular cyclization.

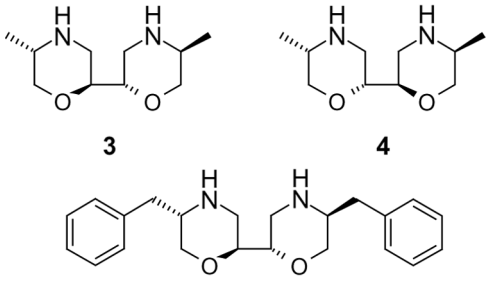
Recently, we have reported on the synthesis of unsubstituted bimorpholine **1** via amidation of tartaric ester with 2-aminoethanol, followed by cyclization.[8] This significant improvement of the preparation scheme increased the yield of the target compound after the six-step sequence to 35%.

In the present work, we describe the synthesis of new 5,5′-disubstituted bimorpholines as a general objective to functionalize the α-position of the nitrogen atom in bimorpholines. The proposed scheme allows introduction of various substituents and is based on the abovementioned route through amide formation. Thus, it is an efficient synthesis of enantiomerically pure 5,5′-dimethyl-2,2′-bimorpholines **3** and **4** together with 5,5′-dibenzyl derivative **5** (Fig. 2).

RESULTS AND DISCUSSION

Stereogenic centers in target compounds at bridgehead carbons were transformed from tartaric ester and methyl or benzyl-substituted carbons from (*S*)-aminoalcohol **7**. Derivatives **3** and **5** were obtained from (*R,R*)-tartaric ester acetal **6**, whereas its diastereoisomeric **4** was obtained from (*S,S*)-tartaric ester acetal.

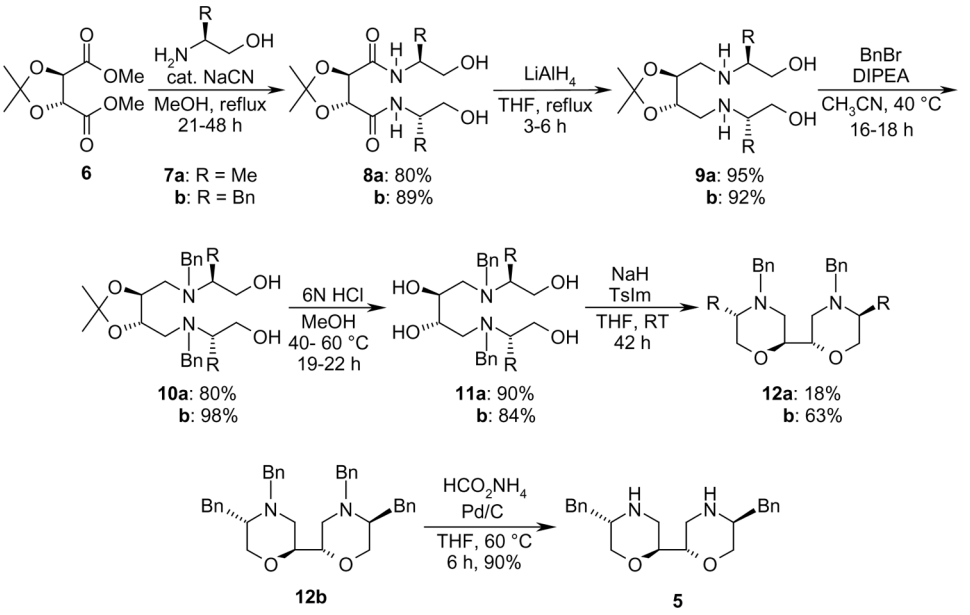
The synthesis started with the cyanide-catalyzed amidation[9] of tartaric ester acetal **6** with aminoalcohols **7** (**a** or **b**), which afforded amides **8** (**a** or **b**, respectively) in more than 80% yield (Scheme 1). In a single step, the skeleton of the target



3 **4**

5

Figure 2. 5,5′-Disubstituted bimorpholines.

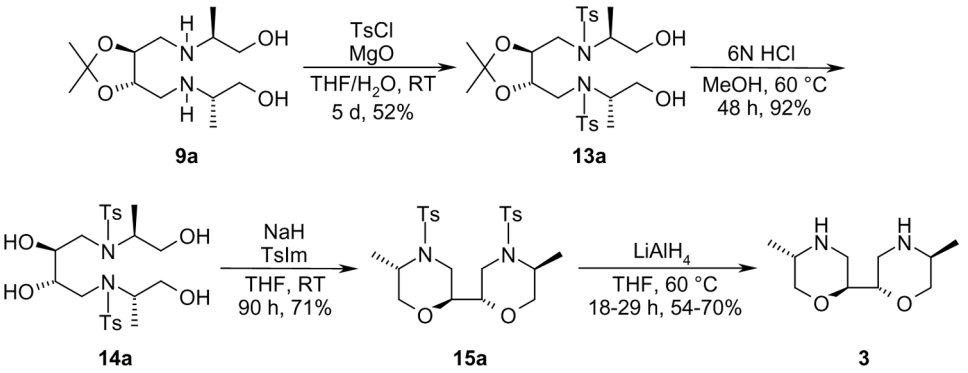


Scheme 1. Synthesis of bimorpholine **5**.

bimorpholine was formed. Reduction of amides with $LiAlH_4$ gave rise to amines **9a, b** in good yield. The synthesis of bimorpholines **3** and **5** was completed analogously to our previous preparation of unsubstituted bimorpholines (described by us before).[8] Thus, secondary amino groups of compounds **9a, b** were protected with benzyl bromide in the presence of diisopropylethyl amine (DIPEA) in 80–98% yield.

When K_2CO_3 was used instead of DIPEA, the reaction was not complete in 2 days, and a mixture of starting material and monobenzylated and dibenzylated products was detected. The acetal groups in compounds **10a, b** were removed under acidic conditions, which gave the desired tetraols **11a, b** for the cyclization. So far, all reactions were high-yielding. The final step of the sequence was intramolecular cyclization. Tetraols **11a, b** were cyclized in a one-step procedure with NaH and 1-(p-toluenesulfonyl)imidazole,[10] affording bimorpholines **12**. Benzyl derivative **12b** was obtained with a moderate yield (63%) and deprotection of it by ammonium formate afforded the desired bimorpholine **5** in 90% yield.

Methyl substituted bimorpholine **12a** was obtained via cyclization in an unexpectedly poor yield—only 18%. A similar phenomenon was observed in the synthesis of *trans*-2,5-disubstituted morpholines by Lanman and Myers[10]—*N*-benzyl-protected α-methyl substituted synthon gave a mixture of products in the cyclization. The intermediate aziridinium ion was reversibly formed in the course of the reaction. Nonregioselective opening of it led to several products, lowering the yield of the target compound. Lanman and Myers showed that the use of *p*-toluenesulfonamide protective group is critical to increase the yield of the target compound. Therefore, we used the tosyl group instead of the benzyl group to protect amine **9a** (Scheme 2). The choice of the base played a crucial role in the



Scheme 2. Synthesis of bimorpholine **3**.

reaction. The selective *N*-protection in the presence of primary hydroxyl groups was achieved by using MgO as the base[11] (Table 1). Although the selective *N*-protection in the presence of Et_3N is described in the literature,[12] in our case the reaction with compound **9a** resulted in a mixture of undetermined products (entry 1). The use of sterically more hindered base (DIPEA) resulted in 24% yield (entry 2). When NaH was added to the reaction, only the starting material was recovered (entry 3). The best results were obtained by using MgO in THF/H_2O (entries 4–6)—40% of the yield was achieved within 24 h. Increasing the reaction time to 5 days increased the isolated yield of the product to 52%. When the reaction was performed in the microwave reactor during 1 h at 40–60°C, it resulted in 22% yield together with a considerable amount of by-products (entry 7). When dimethylformamide (DMF) was used as the solvent in the microwave-assisted reaction, no reaction occurred (entry 8).

The synthesis with *N*-tosylated intermediate was similar to the method used in the previous route. Thus, acetal **13a** was deprotected under acidic conditions in 97% yield. Using the present approach, the cyclization of tetraol **14a** was efficient and afforded bimorpholine **15a** in 71% yield. It is likely that the formation of aziridinium intermediate in the present case is retarded because of sulfoxonium ion character of

Table 1. Tosylation of amine **9a**

Entry	Base	Solvent	Temp. (°C)	Reaction time	**13a** yield (%)
1	Et_3N	CH_2Cl_2	RT	48 h	n.d.[a]
2	DIPEA	CH_2Cl_2	0	19 h	24
3	NaH	DMF	0	5 h	n.r.[b]
4	MgO	THF/H_2O	RT	24 h	40
5	MgO	THF/H_2O	RT	3 d	48
6	MgO	THF/H_2O	RT	5 d	52
7	MgO	THF/H_2O	MW[c] 40–60	1 h	22
8	MgO	DMF	MW 100	30 min	n.r.

[a]Not determined.
[b]No reaction.
[c]Microwave reactor CEM Discover-S.

tosylamide. The target compound **3** was obtained by the reduction of tosyl amide **15** by $LiAlH_4$ in 70% yield (Scheme 2).

The diastereoisomer **4** of bimorpholine **3** was synthesized according to the same synthetic route as depicted in Scheme 2, starting from (*S,S*)-tartaric acid ester acetal (see the experimental section for details). All the corresponding intermediates are marked with the letter **c**. We have previously shown that this synthetic route led to unsubstituted bimorpholines with high enantiomeric purity (ee 99%).[8] Now, the NMR analysis of diastereomeric bimorpholines **3** and **4** revealed that no epimerization takes place in the course of the reactions. Diastereomeric purities of the synthesized compounds were high (>98%), and the same can be concluded for enantiomeric purity.

CONCLUSIONS

In summary, we have developed a general strategy for the synthesis of 5,5′-disubstituted bimorpholines. The substituents and the absolute configuration of those positions are determined by the configuration and structure of the chosen amino alcohol. Bimorpholines **3, 4**, and **5** were all synthesized in good yield and high enantiomeric purity over six steps. The investigation of catalytic properties of these new compounds is currently under study.

EXPERIMENTAL

General

Chemicals were purchased from Aldrich Chemical Co. and were used as received. Tetrahydrofuran (THF) was distilled over $LiAlH_4$. Precoated silica-gel 60 F_{254} plates from Merck were used for thin-layer chromatography (TLC), whereas for column chromatography silica gel KSK40–100 μm was used. Full assignment of ^1H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra measured on a Bruker AMX500, Avance III 400 and Avance III 800 instruments. Solvent peaks ($CHCl_3$ $\delta = 7.27$, CHD_2OD $\delta = 3.30$, $CDCl_3$ $\delta = 77.00$, CD_3OD $\delta = 49.00$) were used as chemical shift references. Infrared (IR) spectra were measured on a Perkin-Elmer Spectrum BX Fourier transform (FT)–IR spectrometer. Mass spectra (MS) were recorded on a Shimadzu GCMS-QP2010 spectrometer using EI (70 eV). High-resolution mass spectra (HRMS) were recorded on a Hitachi M80B spectrometer using EI (70 eV) or on LTQ Orbitrap (Thermo Electron). Elemental analyses were performed on a Perkin-Elmer C,H,N,S–Analyzer 2400. Optical rotations were obtained using a Krüss Optronic GmbH Polarimeter P 3002. All reactions sensitive to moisture or oxygen were carried out under Ar atmosphere in oven-dried glassware.

(4*R*,5*R*)-*N*,*N*′-Bis[(1*S*)-2-hydroxy-1-methylethyl]-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxamide, 8a

(*S*)-Alaninol **7a** (2.58 mL, 33.16 mmol) and sodium cyanide (81 mg, 1.66 mmol) were added to a solution of (*R,R*)-tartaric acid ester acetal **6** (3.618 g, 16.58 mmol) in MeOH (55 mL). The reaction mixture was refluxed for 48 h. MeOH was evaporated,

and the crude mixture was purified by column chromatography on silica gel (7% MeOH in CH_2Cl_2), affording amide **8a** as a yellow oil (yield 4.029 g, 80%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.16 (br d, $J = 7.8$, 2H, NH), 4.54 (s, 2H, H-4,5), 4.08 (m, 2H, NHC**H**), 3.67 (dd, $J = 3.8$, 11.2, 2H, CH_2O), 3.51 (dd, $J = 6.3$, 11.2, 2H, CH_2O), 3.39 (br s, 2H, OH), 1.49 (6H, s, 2-CH_3), 1.19 (d, $J = 6.9$, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 170.05 (CO), 112.51 (C-2), 77.46 (C-4,5), 66.25 (CH_2OH), 47.59 (NHCH), 26.03 (2-CH_3), 16.80 (**C**H_3CH). IR: ν=3409, 3088, 2981, 2939, 2880, 1668, 1538, 1456, 1386, 1215, 1090, 1056 cm^{-1}. $[\alpha]_D^{23} = -27.5$ (c 1.45, MeOH). MS m/z: 305 ($M^+ + 1$), 273, 255, 144, 114. HRMS calcd. for $C_{12}H_{21}N_2O_5$ ($M^+ - CH_3OH$) 273.1449. Found 273.1440.

(4*R*,5*R*)-*N*,*N*′-Bis[(1*S*)-1-benzyl-2-hydroxyethyl]-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxamide, 8b

(*S*)-phenylalaninol **7b** (7.287 g, 48.20 mmol) and sodium cyanide (118 mg, 2.41 mmol) were added to a solution of (*R,R*)-tartaric acid ester acetal **6** (5.258 g, 24.10 mmol) in MeOH (80 mL). The reaction mixture was refluxed for 24 h. MeOH was evaporated, and the crude mixture was purified by column chromatography on silica gel (7% MeOH in CH_2Cl_2), affording amide **8b** as a yellow solid (yield 9.777 g, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36–7.25 (m, 10H, Bn), 7.22 (d, $J = 8.3$, 2H, NH), 4.35 (s, 2H, CHO), 4.32–4.23 (m, 2H, NCH), 3.75 (dd, $J = 3.7$, 11.1, 2H, C**H**$_2$OH), 3.64 (dd, $J = 5.5$, 11.1, 2H, C**H**$_2$OH), 3.14 (br s, 2H, OH), 2.95 (m, 4H, Bn CH_2), 1.42 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.08 (C=O), 137.40 (*s*-Bn), 129.21 (*o*-Bn), 128.52 (*m*-Bn), 126.64 (*p*-Bn), 112.43 (**C**$(CH_3)_3$), 77.26 (CHO), 63.82 (CH_2OH), 52.72 (NCH), 36.96 (Bn CH_2), 25.81 (CH_3). IR: $\nu = 3408$, 3062, 2989, 2937, 1677, 1530, 1454, 1385, 1213, 1091, 1040, 746, 701 cm^{-1}. $[\alpha]_D^{24} = -82.4$ (c 1.18, MeOH). MS m/z: 456 (M^+), 365, 347, 134, 120, 91. Anal. calcd. for $C_{25}H_{32}N_2O_6$ (456.54): C, 65.77; H, 7.07; N, 6.14. Found: C, 65.50; H, 7.04; N, 6.10.

(2*S*,2′*S*)-2,2′-[[(4*S*,5*S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]bis(methyleneimino)]dipropan-1-ol, 9a

Amide **8a** (2.589 g, 8.51 mol) in THF (60 mL) was added to a suspension of $LiAlH_4$ (1.937 g, 51.04 mol) in THF (50 mL) at 0°C. After refluxing for 6 h, water (1.9 mL), 15% NaOH solution (1.9 mL), and water (5.7 mL) were added at 0°C. The mixture was filtered and washed with EtOAc. The filtrate was dried over Na_2SO_4. Solvents were evaporated, and the residue was purified by crystallization (petroleum ether/EtOAc), affording amine **9a** as white crystals (yield 2.225 g, 95%, mp 47–49°C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.94 (m, 2H, H-4,5), 3.57 (dd, $J = 3.7$, 10.8, 2H, CH_2O), 3.29 (dd, $J = 7.0$, 10.8, 2H, CH_2O), 2.90 (dm, $J = 12.3$, 2H, NHC**H$_2$**), H-4,5), 2.79 (m, 2H, NHC**H**), 2.75 (dm, $J = 12.3$, 2H, NHC**H$_2$**), 2.6 (br s, 4H, NH+OH), 1.39 (6H, s, 2-CH_3), 1.04 (d, $J = 6.5$, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 108.63 (C-2), 78.81 (C-4,5), 65.71 (CH_2OH), 54.59 (NHCH), 48.62 (CH_2NH), 27.16 (2-CH_3), 16.96 (**C**H_3CH). IR: $\nu = 3293$, 3119, 2989, 2968, 2934, 2852, 1443, 1379, 1230, 1082, 1056 cm^{-1}. $[\alpha]_D^{24} = +4.9$ (c 5.13, MeOH). MS m/z: 277 ($M^+ + 1$), 245, 187, 130, 88. HRMS calcd. for $C_{12}H_{25}N_2O_3$ ($M^+ - CH_3OH$) 245.1863. Found 245.1869.

(2*S*,2′*S*)-2,2′-[[(4*S*,5*S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]-bis(methyleneimino)]bis(3-phenylpropan-1-ol), 9b

Amide **8b** (9.746 g, 21.34 mmol) in THF (60 mL) was added to a suspension of $LiAlH_4$ (4.861 g, 128.09 mmol) in THF (150 mL) at 0°C. After refluxing for 3 h, water (4.8 mL), 15% NaOH solution (4.8 mL), and water (14.6 mL) were added at 0°C. The mixture was filtered and washed with EtOAc. The filtrate was dried over Na_2SO_4. Solvents were evaporated, and the residue was purified by crystallization (EtOAc/petroleum ether). The mother liquid was purified by column chromatography on silica gel (3% $MeOH/NH_3$ in CH_2Cl_2), affording amine **9b** as white crystals (yield 8.372 g, 92%, mp 71–77°C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.29–7.14 (m, 10H, Bn), 3.85 (s, 2H, CHO), 3.60 (dd, $J = 3.6$, 11.1, 2H, C**H**$_2$OH), 3.34 (dd, $J = 5.6$, 11.1, 2H, C**H**$_2$OH), 2.87 (m, 2H, NCH), 2.81–2.75 (m, 4H, NCH_2), 2.74–2.69 (m, 4H, Bn CH_2), 1.29 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.40 (*s*-Bn), 129.16 (*o*-Bn), 128.54 (*m*-Bn), 126.40 (*p*-Bn), 108.49 [**C**$(CH_3)_2$], 78.43 (CHO), 62.76 (CH_2OH), 60.68 (NCH), 48.25 ($NHCH_2$), 37.86 (Bn CH_2), 27.05 (CH_3). IR: $\nu = 3421$, 3290, 3027, 2964, 2860, 1945, 1455, 1380, 1231, 1101, 1065, 743, 700 cm^{-1}. $[\alpha]_D^{23} = -31.6$ (c 1.18, MeOH). MS m/z: 429 ($M^+ + 1$), 413, 397, 337, 206, 91. Anal. calcd. for $C_{25}H_{36}N_2O_4$ (428.58): C, 70.06; H, 8.47; N, 6.54. Found: C, 69.74; H, 8.50; N, 6.50.

(2*S*,2′*S*)-2,2′-{[(4*S*,5*S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]-bis[methylene(benzylimino)]}dipropan-1-ol, 10a

To a solution of amine **9a** (1.96 g, 7.09 mmol) in CH_3CN (24 mL), DIPEA (3.71 mL, 21.28 mmol) and benzyl bromide (2.53 mL, 21.28 mmol) were added. The reaction mixture was stirred at 40°C for 18 h. CH_3CN was evaporated, water (30 mL) was added, and the mixture was extracted with EtOAc (3×20 mL). The organic phase was dried (Na_2SO_4), and solvent was evaporated. The residue was purified by crystallization (petroleum ether/EtOAc), affording benzylated amine **10a** as white crystals (yield 2.595 g, 80%, mp 91–92°C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.30 (m, 4H, *m*-Bn), 7.26 (m, 4H, *o*-Bn), 7.25 (m, 2H, *p*-Bn), 3.85 and 3.39 (2d, $J = 13.7$, 4H, Bn CH_2), 3.59 (m, 2H, H-4,5), 3.33 and 3.30 (2 m, 4H, CH_2O), 3.23 (br s, 2H, OH), 3.04 (m, 2H, NC**H**), 2.59 and 2.51 (dm, 4H, $J = 14.0$, NCH_2), 1.36 (6H, s, 2-CH_3), 0.88 (d, $J = 6.7$, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 139.29 (*s*-Bn), 128.92 (*o*-Bn), 128.41 (*m*-Bn), 127.11 (*p*-Bn), 109.10 (C-2), 80.41 (C-4,5), 63.18 (CH_2OH), 56.28 (NCH), 54.32 (Bn), 51.41 (CH_2N), 27.25 (2-CH_3), 9.11 (**C**H_3CH). IR: $\nu = 3463$, 3028, 2964, 2935, 2877, 1946, 1495, 1374, 1223, 1105, 1061, 736, 698 cm^{-1}. $[\alpha]_D^{23} = +42.9$ (c 1.18, MeOH). MS m/z: 456 (M^+), 425, 232, 220, 178, 148, 91. Anal. calcd. for $C_{27}H_{40}N_2O_4$ (456.63): C, 71.02; H, 8.83; N, 6.13. Found: C, 70.92; H, 8.87; N, 6.11.

(2*S*,2′*S*)-2,2′-{[(4*S*,5*S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]-bis[methylene(benzylimino)]}bis(3-phenylpropan-1-ol), 10b

To a solution of amine **9b** (1.000 g, 2.33 mmol) in MeOH (8 mL), DIPEA (1.22 mL, 7.00 mmol) and benzyl bromide (0.83 mL, 7.00 mmol) were added. The

reaction mixture was stirred at 40°C for 16 h. MeOH was evaporated, water (30 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 25 mL). The organic phase was dried (Na_2SO_4), and solvent was evaporated. The residue was purified by column chromatography on silica gel (33% EtOAc in petroleum ether), affording benzylated amine **10b** as a white solid (yield 1.392 g, 98%, mp 101–103°C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.43–7.16 (m, 20H, Ar), 4.04 (d, $J = 13.6$, 2H, N-Bn CH_2), 3.70–3.61 (m, 2H, CHO), 3.52 (d, $J = 13.6$, 2H, N-Bn CH_2), 3.40 (d, $J = 7.4$, 4H, C**H**$_2$OH), 3.28 (m, 2H, NCH), 3.20 (br s, 2H, OH), 3.04 (dd, $J = 4.0$, 13.3, 2H, Bn CH_2), 2.79–2.65 (m, 4H, NCH_2), 2.39 (dd, $J = 9.9$, 13.3, 2H, Bn CH_2), 1.47 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 139.12 and 139.10 (*s*-Bn), 128.99, 128.92, 128.53 and 128.47 (*o*-Bn, *m*-Bn), 127.29 and 126.17 (*p*-Bn), 109.36 [**C**$(CH_3)_2$], 80.51 (CHO), 63.12 (NCH), 60.80 (CH_2OH), 54.48 (N-Bn CH_2), 52.05 (NCH_2), 31.74 (Bn CH_2), 27.30 (CH_3). IR: $\nu = 3454$, 3027, 2984, 2933, 2856, 1496, 1455, 1371, 1215, 1030, 735, 699 cm^{-1}. $[\alpha]_D^{23} = -18.0$ (c 1.05, MeOH). MS m/z: 608 (M^+), 577, 517, 254, 91. Anal. calcd. for $C_{39}H_{48}N_2O_4$ (608.83): C, 76.94; H, 7.95; N, 4.60. Found: C, 76.87; H, 8.00; N, 4.57.

(2*S*,3*S*)-1,4-Bis{benzyl[(1*S*)-2-hydroxy-1-methylethyl]amino}-butane-2,3-diol, 11a

HCl solution (6 N) (2 mL) was added to a solution of *N*-benzyl amine **10a** (103 mg, 0.23 mmol) in MeOH (3 mL), and the mixture was heated at 40°C for 22 h. Then 10 N NaOH solution was added in an ice-water bath until pH 8–9. After the addition of brine (5 mL), MeOH was evaporated, and the mixture was extracted with CH_2Cl_2 (4 × 10 mL). The organic phase was dried (Na_2SO_4), and solvent was evaporated. The residue was purified by column chromatography on silica gel (5% MeOH/NH_3 in CH_2Cl_2), affording tetraol **11a** as a white solid (yield 85 mg, 90%, mp 88–89°C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33–7.22 (m, 10H, Bn), 3.75 (d, $J = 13.6$, 2H, Bn CH_2), 3.59 (t, $J = 6.3$, 2H, C**H**OH), 3.52–3.38 (m, 6H, Bn CH_2, C**H**$_2$OH), 2.99–2.89 (m, 2H, C**H**CH_3), 2.70 (dd, $J = 6.8$, 13.4, 2H, NCH_2), 2.57 (dd, $J = 6.3$, 13.4, 2H, NCH_2), 0.93 (d, $J = 6.7$, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 139.44 (*s*-Bn), 128.77 (*o*-Bn), 128.50 (*m*-Bn), 127.19 (*p*-Bn), 69.26 (CHOH), 64.00 (CH_2OH), 57.18 (**C**HCH_3), 55.39 (Bn), 52.25 (NCH_2), 9.71 (CH_3). IR: ν =3339, 3024, 2964, 2930, 2831, 1494, 1451, 1369, 1164, 1113, 1062, 726, 696 cm^{-1}. $[\alpha]_D^{23} = +65.8$ (c 1.71, MeOH). MS m/z: 417 ($M^+ + 1$), 385, 238, 220, 178, 148, 130, 91. Anal. calcd. for $C_{24}H_{36}N_2O_4$ (416.57): C, 69.20; H, 8.71; N, 6.72. Found: C, 69.12; H, 8.72; N, 6.71.

(2*S*,3*S*)-1,4-Bis{benzyl[(1*S*)-1-benzyl-2-hydroxyethyl]amino}-butane-2,3-diol, 11b

HCl solution (6 N) (10 mL) was added to a solution of *N*-benzyl amine **10b** (1.392 g, 2.29 mmol) in MeOH (15 mL) and the mixture was heated at 60°C for 19 h. Then 10 N NaOH solution was added in an ice-water bath until pH 8–9. After evaporation of MeOH, brine (30 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 25 mL). The organic phase was dried (Na_2SO_4) and solvent was evaporated. The residue was purified by column chromatography on silica gel

(50% EtOAc in petroleum ether), affording tetraol **11b** as a white solid (yield 1.095 g, 84%, mp 44–49°C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.37–7.12 (m, 20H, Ar), 3.89 (d, $J = 13.7$, 2H, N-Bn CH_2), 3.69 (m, 4H, N-Bn CH_2, C**H**OH), 3.60 (m, 2H, C**H**$_2$OH), 3.55–3.48 (m, 2H, C**H**$_2$OH), 3.21 (br s, 4H, OH), 3.10–3.01 (m, 2H, NCH), 2.97 (dd, $J = 5.2$, 13.4, 2H, Bn CH_2), 2.89 (dd, $J = 6.7$, 13.3, 2H, NC**H**$_2$), 2.79 (dd, $J = 6.9$, 13.3, 2H, NC**H**$_2$), 2.62 (dd, $J = 9.2$, 13.4, 2H, Bn CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 139.38 and 139.26 (*s*-Bn), 129.02, 128.72, 128.53 and 128.50 (*o*-Bn, *m*-Bn), 127.25 and 126.15 (*p*-Bn), 69.00 (CHOH), 63.80 (NCH), 62.10 (CH_2OH), 55.98 (N-Bn CH_2), 52.88 (NCH_2), 32.33 (Bn CH_2). IR: $\nu = 3368$, 3026, 2933, 2838, 1495, 1454, 1118, 1075, 1029, 738, 699 cm^{-1}. MS m/z: 567 (M^+-1), 537, 477, 314, 296, 284, 254, 224, 264, 91. Anal. calcd. for $C_{36}H_{44}N_2O_4$ (568.76): C, 76.02; H, 7.80; N, 4.93. Found: C, 75.73; H, 7.81; N, 4.88.

(2*S*,2′*S*,5*S*,5′*S*)-4,4′-Dibenzyl-5,5′-dimethyl-2,2′-bimorpholine, 12a

Tetraol **11a** (85 mg, 0.20 mmol) in THF (20 mL) was added to NaH (41 mg, 1.02 mmol) at 0°C under an Ar atmosphere. The mixture was stirred at 0°C for 5 min and at rt for 1 h. The reaction mixture was cooled to 0°C, and 1-(p-toluenesulfonyl)imidazole (91 mg, 0.40 mmol) was added. After stirring for 15 min at 0°C, the reaction mixture was allowed to warm to rt and stirred for 42 h. The suspension was cooled to 0°C, and the reaction was quenched by dropwise addition of sat. NH_4Cl solution (5 mL). THF was evaporated, brine was added, and the mixture was extracted with EtOAc (4×20 mL). The organic phase was dried (Na_2SO_4) and solvent was evaporated. The residue was purified by column chromatography on silica gel (2% MeOH/NH_3 in CH_2Cl_2), affording dibenzyl bimorpholine **12a** as a yellow oil (yield 14 mg, 18%). ^{1}H NMR ($CDCl_3$, 400 MHz,) δ: 7.35–7.25 (m, 10H, Bn), 4.12 (d, $J = 13.3$, 2H, Bn CH_2), 3.80 (dd, $J = 3.3$, 11.2, 2H, OCH_2), 3.42–3.36 (m, 2H, OCH), 3.29–3.22 (m, 2H, OCH_2), 3.05 (d, $J = 13.3$, 2H, Bn CH_2), 2.43 (m, 4H, NCH_2, NCH), 2.12 (dd, $J = 10.4$, 11.6, 2H, NCH_2), 1.05 (d, $J = 6.2$, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.56 (*s*-Bn), 129.00 (*o*-Bn), 128.16 (*m*-Bn), 126.83 (*p*-Bn), 73.16 (OCH_2), 58.04 (Bn), 55.34 (NCH), 53.15 (NCH_2), 15.32 (CH_3). IR: ν =3028, 2963, 2892, 2841, 1494, 1453, 1377, 1106, 734, 699 cm^{-1}. $[\alpha]_D^{23} = +128.1$ (c 2.50, MeOH). MS m/z: 380 (M^+), 289, 217, 202, 188, 178, 91. Anal. calcd. for $C_{24}H_{32}N_2O_2$ (380.53): C, 75.75; H, 8.48; N, 7.36. Found: C, 75.57; H, 8.45; N, 7.33.

(2*S*,2′*S*,5*S*,5′*S*)-4,4′,5,5′-Tetrabenzyl-2,2′-bimorpholine, 12b

Tetraol **11b** (486 mg, 0.85 mmol) in THF (45 mL) was added to a suspension of NaH (171 mg, 4.27 mmol) in THF (40 mL) at 0°C under an Ar atmosphere. The mixture was stirred at 0°C for 5 min and at rt for 1 h. The reaction mixture was cooled to 0°C, and 1-(p-toluenesulfonyl)imidazole (380 mg, 1.71 mmol) was added. After stirring for 15 min at 0°C, the reaction mixture was allowed to warm to rt and stirred for 43 h. The suspension was cooled to 0°C, and the reaction was quenched by dropwise addition of sat. NH_4Cl solution (10 mL). THF was evaporated, brine was added, and the mixture was extracted with EtOAc (2×20 mL). The organic phase was dried (Na_2SO_4), and solvent was evaporated. The residue

was purified by column chromatography on silica gel (30% EtOAc in petroleum ether), affording dibenzyl bimorpholine **12b** as a white solid (yield 287 mg, 63%, mp 47–55°C). ^{1}H NMR ($CDCl_3$, 800 MHz) δ: 7.31 (m, 8H, *m, o*- 4,4′Bn), 7.26 (m, 2H, *p*-4,4′Bn), 7.23 (t, $J = 7.5$ Hz, 4H, *m*-5,5′Bn), 7.18 (t, $J = 7.5$ Hz, 2H, *p*-5,5′Bn), 7.14 (d, $J = 7.5$ Hz, 4H, *o*-5,5′Bn), 4.30 and 3.10 (2d, $J = 13.3$ Hz, 4H, 4,4′Bn CH_2), 3.67 (dd, $J = 3.0$ and 11.7 Hz, 2H, H-6,6′e), 3.33 (d, $J = 10.5$ Hz, 2H, H-2,2′a), 3.24 (dd, $J = 10.1$ and 11.7 Hz, 2H, H-6,6′a), 3.17 (dd, $J = 4.2$ and 14.2 Hz, 2H, 5,5′Bn), 2.64 (m, 2H, H-5,5′a), 2.48 (d, $J = 12.0$ Hz, 2H, H-3,3′e), 2.44 (dd, $J = 8.8$ and 14.2 Hz, 2H, 5,5′Bn), 2.20 (dd, $J = 10.5$ and 12.0 Hz, H-3,3′a). ^{13}C NMR ($CDCl_3$, 201 MHz) δ: 138.79 (*s*-4,4′Bn), 138.59 (*s*-5,5′Bn), 129.23 (*o*-5,5′Bn), 129.11 (*o*-4,4′Bn), 128.53 (*m*-5,5′Bn), 128.47 (*m*-4,4′Bn), 127.14 (*p*-4,4′Bn), 126.44 (*p*-5,5′Bn), 76.35 (C-2,2′), 71.51 (C-6,6′), 61.29 (C-5,5′), 58.45 (4,4′Bn), 53.70 (C-3,3′), 36.51 (5,5′Bn). IR: $\nu = 3026$, 2952, 2890, 2826, 1494, 1453, 1119, 740, 697 cm^{-1}. $[\alpha]_D^{23} = +146.7$ (c 1.05, EtOAc). MS m/z: 532 (M^+), 441, 292, 266, 254, 91. Anal. calcd. for $C_{36}H_{40}N_2O_2$ (532.73): C, 81.17; H, 7.57; N, 5.26. Found: C, 80.95; H, 7.61; N, 5.23.

(2*S*,2′*S*,5*S*,5′*S*)-5,5′-Dibenzyl-2,2′-bimorpholine, 5

To a solution of *N*-benzyl-bimorpholine **12b** (250 mg, 0.47 mmol) in THF (5 mL), 10% Pd/C (375 mg) and ammonium formate (148 mg, 2.35 mmol) were added under an Ar atmosphere. After heating the reaction mixture at 60°C for 6 h, the mixture was filtrated and washed with MeOH. MeOH was evaporated, and the crude mixture was purified by column chromatography (5% MeOH/NH_3 in CH_2Cl_2), affording bimorpholine **5** as a yellow oil (yield 149 mg, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.31–7.25 (m, 4H, *m*-Bn), 7.24–7.18 (m, 2H, *p*-Bn), 7.18–7.14 (m, 4H, *o*-Bn), 3.92 (dd, $J = 3.0$, 11.1, 2H, CH_2O), 3.44–3.38 (m, 2H, CHO), 3.31–3.25 (m, 2H, CH_2O), 3.02–2.94 (m, 2H, NHC**H**), 2.76–2.68 (m, 4H, NHC**H**$_2$), 2.64 (dd, $J = 4.6$, 13.4, 2H, Bn CH_2), 2.40 (dd, $J = 9.2$, 13.4, 2H, Bn CH_2), 1.71 (br s, 2H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz,) δ: 137.67 (*s*-Bn), 129.09 (*o*-Bn), 128.58 (*m*-Bn), 126.53 (*p*-Bn), 76.68 (CHO), 72.66 (CH_2O), 55.55 (NHCH), 47.38 ($NHCH_2$), 38.56 (Bn CH_2). IR: ν =3285, 3028, 2907, 2851, 1496, 1454, 1339, 1105, 746, 701 cm^{-1}. $[\alpha]_D^{24} = -8.5$ (c 2.24, MeOH). MS m/z: 353 ($M^+ + 1$), 261, 204, 178, 128, 117, 91. Anal. calcd. for $C_{22}H_{28}N_2O_2$ (352.48): C, 74.97; H, 8.01; N, 7.95. Found: C, 74.71; H, 8.07; N, 7.89.

N,N-[[(4*S*,5*S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]di(methylene)]bis{*N*-[(1*S*)-2-hydroxy-1-methylethyl]-4-methylbenzenesulfonamide}, 13a

MgO (654 mg, 16.23 mmol) was added to a solution of amine **9a** (897 mg, 3.25 mmol) in THF (10 mL) and H_2O (2.5 mL) and the mixture was stirred at rt for 30 min. TsCl (1.238 g, 6.49 mmol) was added, and the mixture was stirred for 5 d. The mixture was filtered through celite, and the filtrate was washed with EtOAc. After the evaporation of solvents, the precipitate was dissolved in EtOAc (30 mL) and washed with H_2O (2×20 mL). The organic phase was dried (Na_2SO_4), and solvent was evaporated. The residue was purified by column chromatography on silica gel (50% EtOAc in petroleum ether), affording tosylamide **13a** as an

amorphous white solid (yield 980 g, 52%). ^{1}H NMR (MeOD, 400 MHz) δ: 7.82–7.78 (m, 4H, *o*-Ts), 7.35 (dd, $J = 0.6$, 8.6, 4H, *m*-Ts), 3.97–3.88 (m, 4H, CHO, C**H**CH$_3$), 3.69 (d, $J = 14.9$, 2H, NCH$_2$), 3.54 (dd, $J = 7.1$, 11.5, 2H, C**H**$_2$OH), 3.45 (dd, $J = 6.2$, 11.5, 2H, C**H**$_2$OH), 3.34–3.27 (m, 2H, NCH$_2$), 2.41 (s, 6H, *para*-CH$_3$), 1.35 (s, 6H, CCH$_3$), 1.17 (d, $J = 6.9$, 6H, CHC**H**$_3$). ^{13}C NMR (MeOD, 100 MHz) δ: 144.81 (*p*-Ts), 139.13 (*s*-Ts), 130.70 (*m*-Ts), 128.48 (*o*-Ts), 110.97 [**C**(CH$_3$)$_2$], 81.55 (CHO), 64.38 (CH$_2$OH), 57.03 (**C**HCH$_3$), 47.40 (NCH$_2$), 27.33 [C(**C**H$_3$)$_2$], 21.45 (*p*-CH$_3$), 16.75 (CH**C**H$_3$). IR: $\nu = 3522$, 2984, 2936, 1599, 1375, 1329, 1244, 1156, 817 cm^{-1}. $[\alpha]_D^{23} = -108.6$ (c 0.66, MeOH). MS m/z: 585 ($M^+ + 1$), 569, 553, 509, 495, 284, 242, 212, 155, 91. Anal. calcd. for $C_{27}H_{40}N_2O_8S_2$ (584.76): C, 55.46; H, 6.89; N, 4.79; Found: C, 55.15; H, 6.92; N, 4.76.

N,N′-[(2*S*,3*S*)-2,3-Dihydroxybutane-1,4-diyl]bis{*N*-[(1*S*)-2-hydroxy-1-methylethyl]-4-methylbenzenesulfonamide}, 14a

To a solution of tosylamide **13a** (980 mg, 1.68 mmol) in MeOH (8 mL), 6 N HCl solution (5 mL) was added, and the mixture was heated at 55°C for 48 h. In an ice-water bath, 10 N NaOH solution was added until pH 8–9. After addition of brine (10 mL), MeOH was evaporated, and the mixture was extracted with CH_2Cl_2 (4×25 mL). The organic phase was dried (Na_2SO_4), and solvent was evaporated. The residue was purified by column chromatography on silica gel (3% MeOH in CH_2Cl_2), affording tetraol **14a** as a white solid (yield 838 mg, 92%, mp 56–61°C). ^{1}H NMR (MeOD, 400 MHz) δ: 7.77 (d, $J = 8.0$, 4H, *o*-Ts), 7.39 (d, $J = 8.0$, 4H, *m*-Ts), 4.00 (t, $J = 6.3$, 2H, C**H**OH), 3.90 (dt, $J = 6.9$, 13.6, 2H, C**H**CH$_3$), 3.58 (dd, $J = 6.9$, 11.4, 2H, C**H**$_2$OH), 3.48 (dd, $J = 6.1$, 11.4, 2H, C**H**$_2$OH), 3.34–3.19 (m, 4H, NCH$_2$), 2.42 (s, 6H, *p*-CH$_3$), 0.96 (d, $J = 6.9$, 6H, CHC**H**$_3$). ^{13}C NMR (MeOD, 100 MHz) δ: 145.04 (*p*-Ts), 138.53 (*s*-Ts), 130.85 (*m*-Ts), 128.58 (*o*-Ts), 71.11 (CHOH), 65.55 (CH$_2$OH), 57.54 (NCH), 48.00 (NCH$_2$), 21.47 (*p*-CH$_3$), 14.75 (CH**C**H$_3$). IR: $\nu = 3430$, 2978, 2938, 1598, 1330, 1155, 817 cm^{-1}. $[\alpha]_D^{23} = +37.5$ (c 0.66, MeOH). MS m/z: 513 ($M^+ - CH_2OH$), 469, 242, 155, 91. Anal. calcd. for $C_{24}H_{36}N_2O_8S_2$ (544.69): C, 52.92; H, 6.66; N, 5.14. Found: C, 52.63; H, 6.69; N, 5.10.

(2*S*,2′*S*,5*S*,5′*S*)-5,5′-Dimethyl-4,4′-bis[(4-methylphenyl)sulfonyl]-2,2′-bimorpholine, 15a

Tetraol **14a** (1.304 g, 2.39 mmol) in THF (60 mL) was added to a suspension of NaH (479 mg, 11.97 mmol) in THF (180 mL) at 0°C under an Ar atmosphere. The mixture was stirred at 0°C for 5 min and at rt for 1 h. The reaction mixture was cooled to 0°C, and 1-(p-toluenesulfonyl)imidazole (1.064 g, 4.79 mmol) was added. After stirring for 15 min at 0°C, the reaction mixture was allowed to warm to rt and stirred for 90 h. The suspension was cooled to 0°C, and the reaction was quenched by dropwise addition of sat. NH_4Cl solution (15 mL). THF was evaporated, brine was added, and the mixture was extracted with EtOAc (3×30 mL). The organic phase was dried (Na_2SO_4), and solvent was evaporated. The residue was purified by column chromatography on silica gel (40% EtOAc in petroleum ether), affording ditozyl bimorpholine **15a** as a white solid (yield 862 mg, 71%, mp 62–68°C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.68 (d, $J = 8.0$, 4H, *o*-Ts), 7.35

(d, $J = 8.0$, 4H, *m*-Ts), 3.83–3.73 (m, 4H, CHO, CH_2O), 3.64 (dd, $J = 2.1$, 12.3, 2H, NCH_2), 3.30 (dd, $J = 7.5$, 11.7, 2H, CH_2O), 3.09–3.00 (m, 2H, NCH), 2.85 (dd, $J = 7.3$, 12.3, 2H, NCH_2), 2.45 (s, 6H, *p*-CH_3), 1.23 (d, $J = 6.5$, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.82 (*p*-Ts), 134.47 (*s*-Ts), 129.84 (*m*-Ts), 127.48 (*o*-Ts), 72.99 (CHO), 70.64 (CH_2O), 51.53 (NCH), 45.89 (NCH_2), 21.53 (*para*-CH_3), 15.52 (CH_3). IR: $\nu = 2977$, 2926, 2870, 1598, 1349, 1166, 1112, 817 cm^{-1}. $[\alpha]_D^{24} = +22.2$ (c 1.58, MeOH). MS m/z: 509 ($M^+ + 1$), 353, 254, 240, 198, 155, 139, 100, 91.

(2*S*,2′*S*,5*S*,5′*S*)-5,5′-Dimethyl-2,2′-bimorpholine, 3

Tosylamide **15a** (777 mg, 1.53 mmol) in THF (30 mL) was added to a suspension of $LiAlH_4$ (464 mg, 12.22 mmol) in THF (20 mL) at 0°C. After refluxing for 29 h, water (464 μL), 15% NaOH solution (464 μL), and water (1.4 mL) were added at 0°C. The mixture was filtered and washed with EtOAc. The filtrate was dried over Na_2SO_4. After filtration, solvents were evaporated, and the residue was purified by column chromatography on silica gel (7% MeOH/NH_3 in CH_2Cl_2), affording bimorpholine **3** as a white solid (yield 164 mg, 54%, mp 81–86°C). ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.86 (dd, $J = 3.1$, 11.1, 2H, CH_2O), 3.39–3.33 (m, 2H, CHO), 3.15–3.08 (m, 2H, CH_2O), 2.93–2.78 (m, 6H, C**H**$_2$NH, C**H**NH), 1.67 (br s, 2H, NH), 0.94 (d, $J = 6.4$, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 76.92 (CHO), 74.09 (CH_2O), 49.85 (CHNH), 47.34 (CH_2NH), 17.51 (CH_3). IR: ν =3308, 3272, 2970, 2898, 2860, 1444, 1377, 1105 cm^{-1}. $[\alpha]_D^{23} = +11.3$ (c 2.76, MeOH). MS m/z: 200 (M^+), 169, 141, 128, 113, 102, 97, 70, 56. HRMS calcd. for $C_{10}H_{20}N_2O_2$ (M^++H) 201.15975; found 201.15991.

(4*S*,5*S*)-*N*,*N*′-Bis[(1*S*)-2-hydroxy-1-methylethyl]-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxamide, 8c

(*S*)-Alaninol **7a** (1.98 mL, 25.42 mmol) and sodium cyanide (62 mg, 1.27 mmol) were added to a solution of (*S,S*)-tartaric acid ester acetal **6c** (2.773 g, 12.71 mmol) in MeOH (42 mL). The reaction mixture was refluxed for 21 h. MeOH was evaporated, and the crude mixture was purified by column chromatography on silica gel (7% MeOH in CH_2Cl_2), affording amide **8c** as an amorphous white solid (yield 3.169 g, 82%). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.07 (d, $J = 8.2$, 2H, NH), 4.58 (s, 2H, CHO), 4.13–4.01 (m, 2H, NHC**H**), 3.81 (t, $J = 5.5$, 2H, OH), 3.66 (m, 2H, C**H**$_2$OH), 3.47 (m, 2H, C**H**$_2$OH), 1.46 (s, 6H, CCH_3), 1.17 (d, $J = 6.8$, 6H, CHC**H**$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.34 (C=O), 112.76 (**C**$(CH_3)_2$), 77.67 (CHO), 65.96 (CH_2OH), 47.65 (NHCH), 26.28 (C**C**H_3), 17.01 (CH**C**H_3). IR: ν =3408, 3086, 2980, 2938, 2878, 1667, 1535, 1457, 1385, 1219, 1090, 1054 cm^{-1}. $[\alpha]_D^{24} = +16.5$ (c 3.68, MeOH). MS m/z: 305 ($M^+ + 1$), 273, 255, 144, 114, 154. Anal. calcd. for $C_{13}H_{24}N_2O_6$ (304.35): C, 51.31; H, 7.95; N, 9.20. Found: C, 50.93; H, 7.97; N, 9.16.

(2*S*,2′*S*)-2,2′-[[(4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]-bis(methyleneimino)]bis(3-phenylpropan-1-ol), 9c

Amide **8c** (3.057 g, 10.04 mol) was added in THF (60 mL) to a suspension of $LiAlH_4$ (2.287 g, 60.27 mol) in THF (40 mL) at 0°C. After refluxing for 4 h, water

(2.3 mL), 15% NaOH solution (2.3 mL), and water (6.9 mL) were added at 0°C. The mixture was filtered and washed with EtOAc. The filtrate was dried over Na_2SO_4. After filtration, solvents were evaporated, and the residue was purified by column chromatography on silica gel (10–20% MeOH/NH_3 in CH_2Cl_2), affording amine **9c** as an amorphous yellow solid (yield 1.909 g, 69%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.88–3.81 (m, 2H, CHO), 3.57 (dd, $J = 3.9$, 10.8, 2H, C**H**$_2$OH), 3.28 (dd, $J = 7.0$, 10.8, 2H, C**H**$_2$OH), 2.93 (ddd, $J = 1.9$, 4.6, 11.9, 2H, NHC**H**$_2$), 2.76 (pd, $J = 3.9$, 6.5, 2H, NHC**H**), 2.67 (dd, $J = 4.1$, 11.9, 2H, NHC**H**$_2$), 1.39 (s, 6H, CCH_3), 1.05 (d, $J = 6.5$, 6H, CHC**H**$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 108.84 [**C**$(CH_3)_2$], 79.58 (CHO), 65.53 (CH_2OH), 54.85 (NHCH), 49.73 (NHC**H**$_2$), 27.14 (C**C**H_3), 17.01 (CH**C**H_3). IR: $\nu = 3307$, 2933, 1459, 1380, 1250, 1057 cm^{-1}. $[\alpha]_D^{23} = +56.8$ (c 3.55, MeOH). MS m/z: 277 ($M^+ + 1$), 261, 245, 187, 158, 144, 130, 100, 88. HRMS calcd. for $C_{12}H_{25}N_2O_3$ ($M^+ - CH_3OH$) 245.1863; found 245.1860.

N,N′-[[(4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]di(methylene)]bis{*N*-[(1*S*)-2-hydroxy-1-methylethyl]-4-methylbenzenesulfonamide}, 13c

MgO (1.094 g, 27.14 mmol) was added to a solution of amine **9c** (1.500 g, 5.43 mmol) in THF (18 mL) and water (4.5 mL) and the mixture was stirred at rt for 30 min. TsCl (2.069 g, 10.85 mmol) was added, and the mixture was stirred for 4 d. The mixture was filtered through celite, and the filtrate was washed with EtOAc. After the evaporation of solvents, the precipitate was dissolved in EtOAc (30 mL) and washed with water (3 × 30 mL). The organic phase was dried (Na_2SO_4), and solvent was evaporated. The residue was purified by column chromatography on silica gel (50% EtOAc in petroleum ether), affording tosylamide **13c** as an amorphous white solid (yield 2.005 g, 63%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.78 (d, $J = 8.1$, 4H, *o*-Ts), 7.34 (d, $J = 8.1$, 4H, *m*-Ts), 4.32–4.24 (m, 2H, CHO), 4.02–3.91 (m, 2H, C**H**CH_3), 3.71 (d, $J = 15.6$, 2H NCH_2), 3.59–3.42 (m, 4H, C**H**$_2$OH), 3.38 (dd, $J = 5.5$, 9.2, 2H, OH), 3.08–2.97 (m, 2H, NCH_2), 2.44 (s, 6H, *para*-CH_3), 1.43 (s, 6H, CCH_3), 0.78 (d, $J = 6.8$, 6H, CHC**H**$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.79 (*p*-Ts), 136.88 (*s*-Ts), 129.84 (*m*-Ts), 127.25 (*o*-Ts), 110.63 [**C**$(CH_3)_2$], 80.27 (CHO), 64.49 (CH_2OH), 55.49 (**C**HCH_3), 44.88 (NCH_2), 26.82 [C(**C**$H_3)_2$], 21.53 (*p*-CH_3), 12.84 (CH**C**H_3). IR: ν =3510, 2981, 2938, 1598, 1384, 1325, 1246, 1156, 815 cm^{-1}. $[\alpha]_D^{23} = +125.3$ (c 2.37, MeOH). MS m/z: 553 ($M^+ - CH_2OH$), 509, 495, 284, 242, 212, 155, 91. Anal. calcd. for $C_{27}H_{40}N_2O_8S_2$ (584.76): C, 55.46; H, 6.89; N, 4.79; Found: C, 55.47; H, 6.93; N, 4.74.

N,N′-[(2*R*,3*R*)-2,3-Dihydroxybutane-1,4-diyl]bis{*N*-[(1*S*)-2-hydroxy-1-methylethyl]-4-methylbenzene-sulfonamide}, 14c

To a solution of tosylamide **13c** (2.085 g, 3.57 mmol) in MeOH (15 mL), 6 N HCl solution (10 mL) was added, and the mixture was heated at 60°C for 22 h. In an ice-water bath, 10 N NaOH solution was added until pH 8–9. After addition of sat. NaCl solution (20 mL), MeOH was evaporated, and the mixture was extracted with CH_2Cl_2 (5 × 25 mL). The organic phase was dried (Na_2SO_4), and solvent was evaporated. The residue was purified by column chromatography on silica gel

(3% MeOH in CH_2Cl_2), affording tetraol **14c** as an amorphous white solid (yield 1.942 g, 100%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.76 (d, $J = 8.1$, 4H, *o*-Ts), 7.33 (d, $J = 8.1$, 4H, *m*-Ts), 4.22–4.14 [m, 2H, C**H**OH)], 4.03–3.93 (m, 2H, C**H**CH_3), 3.63–3.44 (m, 4H, C$\mathbf{H}_2$OH), 3.40 (dd, $J = 3.6$, 15.3, 2H, NCH_2), 3.12 (dd, $J = 9.1$, 15.3, 2H, NCH_2), 2.43 (s, 6H, *p*-CH_3), 0.83 (d, $J = 6.8$, 6H, CHC$\mathbf{H}_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.76 (*p*-Ts), 136.79 (*s*-Ts), 129.88 (*m*-Ts), 127.21 (*o*-Ts), 71.08 (CHOH), 64.41 (CH_2OH), 55.48 (NCH), 45.94 (NCH_2), 21.54 (*p*-CH_3), 13.11 (CH**C**H_3). IR: $\nu = 3421$, 2978, 2930, 1598, 1333, 1155, 816 cm^{-1}. $[\alpha]_D^{24} = +73.4$ (c 1.97, MeOH). MS m/z: 513 ($M^+ - CH_2OH$), 495, 469, 242, 155, 91. Anal. calcd. for $C_{24}H_{36}N_2O_8S_2$ (544.69): C, 52.92; H, 6.66; N, 5.14. Found: C, 52.52; H, 6.63; N, 5.07.

(2*R*,2′*R*,5*S*,5′*S*)-5,5′-Dimethyl-4,4′-bis[(4-methylphenyl)sulfonyl]-2,2′-bimorpholine, 15c

Tetraol **14c** (1.916 g, 3.52 mmol) in THF (80 mL) was added to NaH (704 mg, 17.59 mmol) in THF (270 mL) at 0°C under Ar atmosphere. The mixture was stirred at 0°C for 5 min and at rt for 1 h. The reaction mixture was cooled to 0°C, and 1-(p-toluenesulfonyl)imidazole (1.564 g, 7.04 mmol) was added. After stirring for 15 min at 0°C, the reaction mixture was allowed to warm to rt and stirred for 22 h. The suspension was cooled to 0°C, and the reaction was quenched by dropwise addition of sat. NH_4Cl solution (50 mL). THF was evaporated, brine was added, and the mixture was extracted with EtOAc (3×30 mL). The organic phase was dried (Na_2SO_4). After filtration, solvents were evaporated, and the residue was purified by crystallization (in boiling MeOH). The mother liquid was purified by column chromatography on silica gel (50% EtOAc in petroleum ether), affording ditozyl bimorpholine **15c** as white crystals (yield 1.510 g, 84%, mp 174–177°C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.69 (d, $J = 8.0$, 4H, *o*-Ts), 7.32 (d, $J = 8.0$, 4H, *m*-Ts), 4.01–3.93 (m, 2H, NCH), 3.61 (m, 4H, CH_2O), 3.50 (dd, $J = 1.8$, 12.7, 2H, NCH_2), 3.44–3.38 (m, 2H, CHO), 3.09 (dd, $J = 10.6$, 12.7, 2H, NCH_2), 2.44 (s, 6H, *p*-CH_3), 1.07 (d, $J = 6.8$, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.54 (*p*-Ts), 137.30 (*s*-Ts), 129.87 (*m*-Ts), 127.05 (*o*-Ts), 75.51 (CHO), 71.41 (CH_2O), 48.37 (NCH), 40.29 (NCH_2), 21.52 (*para*-CH_3), 13.65 (CH_3). IR: ν =2982, 2932, 2874, 1600, 1341, 1157, 1123, 809 cm^{-1}. $[\alpha]_D^{24} = +94.9$ (c 2.37, $CHCl_3$). MS m/z: 353 (M^+- Ts), 254, 198, 155, 100, 91. Anal. calcd. for $C_{24}H_{32}N_2O_6S_2$ (508.66): C, 56.67; H, 6.34; N, 5.51. Found: C, 56.67; H, 6.31; N, 5.49.

(2*R*,2′*R*,5*S*,5′*S*)-5,5′-Dimethyl-2,2′-bimorpholine, 4

Tosylamide **15c** (432 mg, 0.85 mmol) in THF (10 mL) was added to a suspension of $LiAlH_4$ (258 mg, 6.79 mmol) in THF (18 mL) at 0°C. After refluxing for 10 h, water (260 μL), 15% NaOH solution (260 μL), and water (780 μL) were added at 0°C. The mixture was filtered and washed with EtOAc. The filtrate was dried over Na_2SO_4. After filtration, solvents were evaporated, and the residue was purified by column chromatography on silica gel (3–10% MeOH/NH_3 in CH_2Cl_2), affording bimorpholine **4** as a yellow oil, which solidifies in the freezer (yield 133 mg, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.73–3.61 (m, 6H, CHO, CH_2O), 3.02–2.90 (m,

4H, CHNH, CH_2NH), 2.80 (dd, $J = 2.7$, 12.6, 2H, CH_2NH), 2.14 (br s, 2H, NH), 1.18 (d, $J = 6.7$, 6H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 74.46 (CHO), 70.47 (CH_2O), 47.99 (CHNH), 42.71 (CH_2NH), 16.88 (CH_3). IR: $\nu = 3304$, 3235, 2955, 2897, 2852, 1456, 1382, 1097 cm^{-1}. $[\alpha]_D^{22} = -2.2$ (c 8.82, MeOH). MS m/z: 200, 141, 128, 114, 102, 97, 70.

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