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Convenient preparation of optically active *N*,*N*-bis(4-substituted-4-aminobutyl)amines

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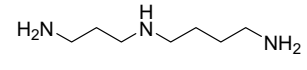
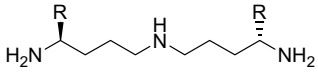
Abstract—An efficient and convenient method for the synthesis of chiral triamines with two substituents at the α position to the terminal amino group (spermidine analogues) is described. These chiral *N*,*N*-bis(4-substituted-4-aminobutyl)amines may have anticancer activities.

1. Introduction

Natural polyamines, for example, spermidine and spermine which are derived from arginine and methionine through biosynthesis, are important constituents of cell components. These polyamines play important roles, such as in cell proliferation, cell differentiation and stabilization of DNA and RNA.[1] Therefore, polyamine analogues and their conjugates with other biomolecules have been widely investigated as potential anticancer drugs, gene delivery agents, and so on.[2] Several efficient methods have been reported for the synthesis of optically active diamines and triamines, based on the reduction of amide or azide derivatives derived from amino acids or natural amino products,[3] and ring opening of an aziridinium ion with amines.[4] However, to the best of our knowledge, there are no reported methods for the synthesis of chiral triamines with two alkyl substituents at the α and α′ positions of a terminal amino group.[5] We report here a convenient and practical method for the preparation of optically active *N*,*N*-bis(4-substituted-4-aminobutyl)amines **1a**–**c**.



spermidine



(*S*,*S*)-**1a**; R = Me
(*R*,*R*)-**1b**; R = *i*-Pr
(*R*,*R*)-**1c**; R = CH_2Ph

2. Results and discussion

Our concept for the synthesis of optically active **1** was as follows: (1) both enantiomers could be synthesized, (2) a variety of substituents could be introduced into the triamine skeleton, and (3) simple handling (UV detection and low solubility in water). Therefore, we chose benzyloxycarbonyl Z-protected amino acid methyl esters (*S*)-**2a**–**c** as starting materials. Our synthetic routes for optically active triamines **1a**–**c** are shown in Scheme 1.

Z-protected amino acid methyl esters (*S*)-**2a**–**c** were treated with 1.6 equiv of DIBAL in toluene at −78 °C to give aldehydes **3** in excellent yields. Horner–Wadsworth–Emmons olefination of aldehydes **3a**–**c** with triethyl phosphonoacetate proceeded smoothly to afford **4** in good yields. However, some degree of epimerization took place during two steps, especially in the case of alanine derivative **2a** (88% ee). Next, based on a previously reported method,[6,7] the reaction of **4a**–**c** and DIBAL in the presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 provided the

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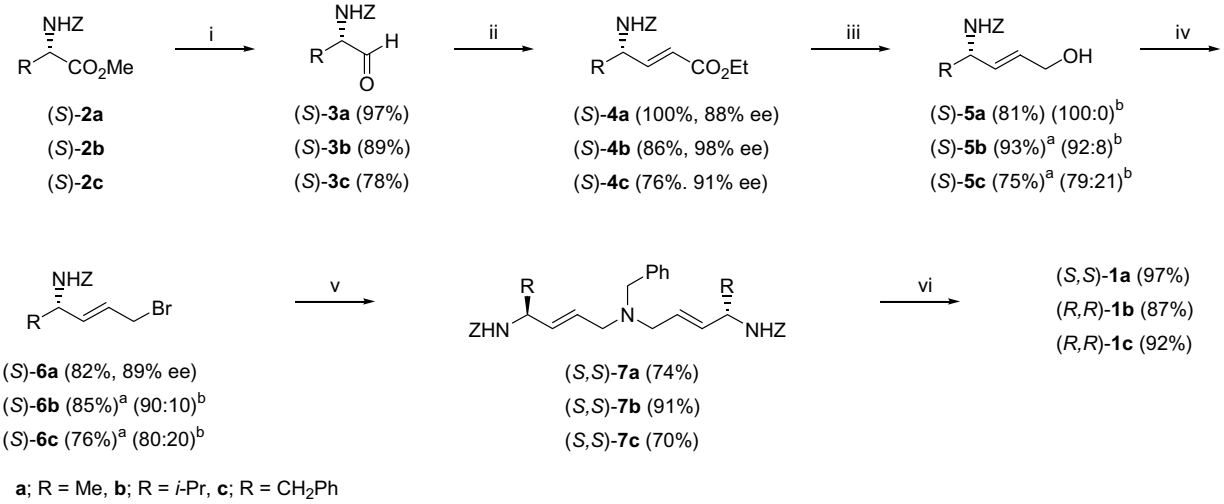

Scheme 1. Reagents and conditions: (i) DIBAL; (ii) triethyl phosphonoacetate; (iii) DIBAL, $BF_3{\cdot}OEt_2$; (iv) PPh_3, CBr_4; (v) benzylamine; (vi) $Pd(OH)_2$, H_2. (a) combined yield, (b) ratio of double/single bonds.

desired allylic alcohols **5a**–**c** as well as some over-reduced saturated alcohols in combined yields of 75–93%. Since these two products could not be separated by column chromatography, the mixture was brominated with CBr_4–PPh_3 to give the corresponding allylbromides **6a**–**c**, along with the corresponding saturated bromides, in combined yields of 76–85%. These disturbances in chirality and the over-reduction of double bonds were cleaned up in the subsequent double-allylation step. Double allylation of benzylamine with **6a**–**c** furnished the corresponding bis-adducts **7a**–**c** in 70–91% yields. Under these reaction conditions, only allylbromides reacted smoothly with benzylamine and the saturated bromides remained. In addition, minor products (*R*)-**6a**–**c**, which arose from epimerization of starting (*S*)-**2** to (*S*)-**4**, led to the *meso*-forms. The ratios of (*R*,*R*):(*meso*):(*S*,*S*) were as follows: for **7a**, 0.0:10.5:89.5, for **7b**, 0.6:0.0:99.4, and for **7c**, 0.0:7.4:92.6, respectively. While the *meso*- and *dl*-forms were almost inseparable by column chromatography, *meso*-**7a**–**c** could be easily removed by trituration with *n*-hexane/ether or recrystallization from *iso*-propyl ether/ethyl acetate to afford (*S*,*S*)-**7a**–**c** with >99% de and >99% ee. Deprotection of the two Z-groups on the terminal amino groups and one benzyl group on an inner amino group, as well as reduction of the two double bonds of (*S*,*S*)-**7a**–**c**, proceeded under $Pd(OH)_2$/hydrogen balloon conditions to give the desired **1a**–**c** in excellent yield. Based on the results of 200 MHz ^{1}H NMR analysis, the optical purities of **1a**–**c** were 95% ee and above, since the corresponding diastereomers were not detected at all.

DIBAL–$BF_3{\cdot}OEt_2$ reduction of **4c** in *toluene* gives almost a 1:1 mixture of desired **5c** and saturated alcohols. Our synthetic procedure could be applied to the crude **5c** to obtain enantiomerically pure **7c** as follows: starting **4c** (91% ee), **5c** (63% combined yield, double bond/single bond = 48:52), **6c** (83% combined yield, 54:46 mixture), and **7c** (49% isolated yield, (*R*,*R*):(*meso*):(*S*,*S*) = 0.0:7.4:92.6, after recrystallization >99% de, >99% ee).

3. Conclusion

In summary, we have developed a method for the synthesis of chiral triamines with two substituents at the α position to the terminal amino group. This method is quite convenient and practical, and is suitable for the synthesis of chiral triamine derivatives, and might be useful in the field of biochemistry for the production of polyamine analogues.

4. Experimental section

4.1. Ethyl (2*E*,4*S*)-4-{[(benzyloxy)carbonyl]amino}pent-2-enoate (*S*)-4a

Triethyl phosphonoacetate (4.41 g, 3.90 mL, 19.6 mmol) was added dropwise to a suspension of sodium hydride (0.65 g, 16.3 mmol, 60% oil dispersion in mineral oil) in THF (100 mL) at 0 °C under a nitrogen atmosphere, and the mixture was stirred for 1 h. (*S*)-**3a** (3.4 g, 16.3 mmol) in THF (60 mL) was added dropwise to this suspension at 0 °C and the reaction mixture was stirred for 1 h. The solvent was evaporated off, and ethyl acetate and water were added to the residue and separated. The organic layer was washed successively with water (twice) and brine. After being dried over sodium sulfate, the solvent was evaporated in vacuo to give a residue as a pale yellow oil. The residue was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate = 4/1–2/1) to give (*S*)-**4a** (4.51 g, 100% yield). $[\alpha]_D^{20} = -13.4$ (*c* 0.95, $CHCl_3$, for 88% ee); IR (KBr) 3308, 2979, 1718, 1530 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.2 Hz, 3H), 1.30 (d, *J* = 7.0 Hz, 3H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.30–4.60 (m, 1H), 4.70–4.90 (m, 1H, N*H*), 5.11 (s, 2H) 5.91 (dd, *J* = 15.6 Hz, *J* = 1.6 Hz, 1H), 6.88 (dd, *J* = 15.6 Hz, *J* = 4.8 Hz, 1H), 7.20–7.45 (m, 5H); HRMS Calcd for $C_{15}H_{19}NO_4$: 277.1315. Found: 277.1324; Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.66; H, 6.87; N, 5.07.

HPLC conditions; CHIRALCEL OD, *iso*-PrOH/*n*-hexane = 5/95, 0.5 mL/min, t_R 33.9 min (*R*)-**4a**, t_R 41.1 min (*S*)-**4a**.

(*S*)-4**b**; colorless oil; $[\alpha]_D^{20} = +0.5$ (*c* 0.91, $CHCl_3$, for 98% ee); IR (neat) 3341, 2962, 1714, 1530 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, $J = 5.6$ Hz, 3H), 0.95 (d, $J = 5.6$ Hz, 3H), 1.29 (t, $J = 7.2$ Hz, 3H), 1.80–2.00 (m, 1H), 4.19 (q, $J = 7.2$ Hz, 2H), 4.10–4.40 (m, 1H), 4.70–4.90 (m, 1H, N*H*), 5.11 (s, 2H), 5.93 (d, $J = 15.6$ Hz, 1H), 6.86 (dd, $J = 15.6$ Hz, $J = 5.6$ Hz, 1H), 7.30–7.45 (m, 5H); HRMS Calcd for $C_{17}H_{23}NO_4$: 305.1627. Found: 305.1628; Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.81; H, 7.60; N, 4.70. HPLC conditions; CHIRALCEL OD, *iso*-PrOH/*n*-hexane = 5/95, 0.5 mL/min, t_R 23.7 min (*R*)-**4b**, t_R 25.7 min (*S*)-**4b**.

(*S*)-**4c**; pale yellow oil; $[\alpha]_D^{20} = +2.2$ (*c* 1.12, $CHCl_3$, for 91% ee); IR (neat) 3325, 2980, 1714, 1531 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, $J = 7.0$ Hz, 3H), 2.80–3.00 (m, 2H), 4.18 (q, $J = 7.0$ Hz, 2H), 4.50–4.90 (m, 2H), 5.06 (s, 2H), 5.86 (dd, $J = 15.6$ Hz, $J = 1.4$ Hz, 1H), 6.91 (dd, $J = 15.6$ Hz, $J = 5.0$ Hz, 1H), 7.15–7.20 (m, 2H), 7.25–7.40 (m, 8H); HRMS Calcd for $C_{21}H_{23}NO_4$: 353.1627. Found: 353.1626; Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.20; H, 6.62; N, 3.98. HPLC conditions; CHIRALCEL OD, *iso*-PrOH/*n*-hexane = 5/95, 0.5 mL/min, t_R 48.8 min (*R*)-**4c**, t_R 68.6 min (*S*)-**4c**.

4.2. Benzyl (1*S*,2*E*)-4-hydroxy-1-methylbut-2-enylcarbamate (*S*)-5a

To a solution of (*S*)-**4a** (4.50 g, 16.2 mmol) in dichloromethane (160 mL), boron trifluoride diethyl etherate (2.06 mL, 16.2 mmol) was added at −78 °C under nitrogen atmosphere and stirred for 30 min. Diisobutylaluminum hydride (0.94 M solution in hexane 69.0 mL, 64.9 mmol) was added dropwise to the solution and stirred at −78 °C for 1.5 h. The reaction mixture was poured into the mixed solvent of ethyl acetate and 1 N aqueous hydrochloric acid. The organic layer was separated, washed successively with water (twice) and brine. After dried over sodium sulfate, the solvent was evaporated in vacuo. The residue was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate = 1/1) to give (*S*)-**5a** as colorless solid (3.08 g, 81% yield). Mp = 43.1–44.8 °C; $[\alpha]_D^{21} = -9.4$ (*c* 1.11, $CHCl_3$, 88% ee); IR (KBr) 3349, 1710, 1537, 1454 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.23 (d, $J = 6.8$ Hz, 3H), 2.00 (br s, 1H, O*H*), 4.11 (d, $J = 3.5$ Hz, 2H), 4.20–4.50 (m, 1H), 4.60–4.90 (m, 1H, N*H*), 5.09 (s, 2H), 5.60–5.90 (m, 2H), 7.20–7.40 (m, 5H); HRMS Calcd for $C_{13}H_{17}NO_3$: 235.1208. Found: 235.1212; Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.06; H, 7.38; N, 5.89.

(*S*)-**5b**; (93% combined yield, 86% calculated yield). A small amount of (*S*)-**5b** was subjected to purification by PTLC to give analytical sample as white powder. Mp = 55.5–56.1 °C; $[\alpha]_D^{20} = +7.6$ (*c* 0.76, $CHCl_3$, for 98% ee); IR (KBr) 3308, 2955, 1686, 1543 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, $J = 7.0$ Hz, 3H), 0.91 (d, $J = 6.6$ Hz, 3H), 1.60–1.90 (m, 2H), 4.00–4.10 (m, 1H), 4.14 (d, $J = 4.6$ Hz, 2H), 4.70–4.90 (m, 1H, N*H*), 5.10 (s, 2H), 5.60 (dd, $J = 15.6$ Hz, $J = 5.8$ Hz, 1H), 5.77 (dt, $J = 15.6$ Hz, $J = 4.6$ Hz, 1H), 7.25–7.45 (m, 5H); HRMS Calcd for $C_{15}H_{21}NO_3$: 263.1522. Found: 263.1527; Anal. Calcd for $C_{15}H_{21}NO_3 \cdot 0.25H_2O$: C, 67.27; H, 8.09; N, 5.23. Found: C, 67.28; H, 8.30; N, 5.31.

(*S*)-**5c**; (75% combined yield, 59% calculated yield). A small amount of (*S*)-**5c** was subjected to purification by PTLC to give analytical sample as white powder. Mp = 70.4–71.0 °C; $[\alpha]_D^{20} = +11.5$ (*c* 0.77, $CHCl_3$, for 91% ee); IR (KBr) 3330, 2942, 1690, 1541 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.51 (br s, 1H, O*H*), 2.85 (d, $J = 6.8$ Hz, 2H), 4.05–4.15 (m, 2H), 4.40–4.60 (m, 1H), 4.60–4.90 (m, 1H, N*H*), 5.06 (s, 2H), 5.60–5.80 (m, 2H), 7.10–7.40 (m, 10H); HRMS Calcd for $C_{19}H_{21}NO_3$: 311.1522. Found: 311.1529; Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.07; H, 7.10; N, 4.48.

4.3. Benzyl (1*S*,2*E*)-4-bromo-1-methylbut-2-enylcarbamate (*S*)-6a

To a stirred solution of (*S*)-**5a** (3.10 g, 13.1 mmol) and carbon tetrabromide (6.5 g, 19.6 mmol) in dichloromethane (130 mL) was added portionwise triphenylphosphine (4.1 g, 15.7 mmol) 0 °C under nitrogen atmosphere. The solution was stirred for 5 h at room temperature. The reaction mixture was poured into the mixed solvent of ethyl acetate and water. The organic layer was separated, washed successively with water and brine, and evaporated under reduced pressure. Diethyl ether was added to the residue and triphenylphosphineoxide was filtered off. The filtrate was evaporated under reduced pressure and diethyl ether was again added to the residue and triphenylphosphineoxide was filtered off. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel with *n*-hexane/ethyl acetate = 3/1 as an eluent to afford (*S*)-**6a** (3.19 g, 82%). Mp = 52.8–53.5 °C; $[\alpha]_D^{20} = -25.0$ (*c* 1.08, $CHCl_3$, 88% ee); IR (KBr) 3309, 1692, 1535, 1453 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.25 (d, $J = 6.8$ Hz, 3H), 3.93 (d, $J = 6.3$ Hz, 2H), 4.20–4.40 (m, 1H), 4.60–4.80 (m, 1H, N*H*), 5.10 (s, 2H), 5.65–5.90 (m, 2H), 7.30–7.50 (m, 5H); HRMS Calcd for $C_{13}H_{16}{}^{81}BrNO_2$: 299.0344. Found: 299.0353; Anal. Calcd for $C_{13}H_{16}BrNO_2$: C, 52.37; H, 5.41; N, 4.70. Found: C, 52.14; H, 5.47; N, 4.74. HPLC conditions; CHIRALCEL OB-H, *iso*-PrOH/*n*-hexane = 5/95, 0.5 mL/min, t_R 85.5 min (*S*)-**6a**, t_R 121.1 min (*R*)-**6a**.

(*S*)-**6b**; (85% combined yield, 77% calculated yield). A small amount of (*S*)-**5b** was subjected to purification by PTLC to give analytical sample as white powder. Mp = 67.8–69.0 °C; $[\alpha]_D^{20} = -5.8$ (*c* 0.82, $CHCl_3$); IR (KBr) 3297, 2961, 1683, 1547 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 6.8$ Hz, 3H), 1.60–1.95 (m, 1H), 3.95 (d,

J = 7.2 Hz, 2H), 4.00–4.20 (m, 1H), 4.70–4.85 (m, 1H, N*H*), 5.11 (s, 2H), 5.67 (dd, J = 15.0 Hz, J = 5.8 Hz, 1H), 5.75–5.95 (m, 1H), 7.30–7.40 (m, 5H); HRMS Calcd for $C_{15}H_{20}{}^{79}BrNO_2$: 325.0677. Found: 325.0672, Calcd for $C_{15}H_{20}{}^{81}BrNO_2$: 327.0657. Found: 327.0669; Anal. Calcd for $C_{15}H_{20}BrNO_3$: C, 55.23; H, 6.18; N, 4.29. Found: C, 54.93; H, 6.29; N, 4.40.

(*S*)-**6c**; (76% combined yield, 61% calculated yield). A small amount of (*S*)-**5c** was subjected to purification by PTLC to give analytical sample as white powder. Mp = 70.5–72.0 °C; $[\alpha]_D^{20} = +2.7$ (*c* 0.73, $CHCl_3$, for 92% ee); IR (KBr) 3317, 3028, 1694, 1504 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.86 (d, J = 6.4 Hz, 2H), 3.95 (d, J = 6.0 Hz, 2H), 4.40–4.60 (m, 1H), 4.65–4.80 (m, 1H), 5.06 (s, 2H), 5.60–5.80 (m, 2H), 7.00–7.45 (m, 10H); HRMS Calcd for $C_{19}H_{20}{}^{79}BrNO_2$: 373.0677. Found: 373.0662, Calcd for $C_{19}H_{20}{}^{81}BrNO_2$: 375.0657. Found: 375.0658.

4.4. Dibenzyl {(benzylimino)bis[(2*E*,4*S*)pent-2-ene-1,4-diyl]}biscarbamate (*S*,*S*)-7a

A suspension of (*S*)-**6a** (ca. 88% ee, 3.20 g, 10.7 mmol), benzylamine (584 μL, 5.3 mmol) and potassium carbonate (3.0 g, 21.4 mmol) in DMF (110 mL) was stirred for 13 h at room temperature under nitrogen atmosphere. The reaction mixture was poured into the mixed solvent of ethyl acetate and water. The organic layer was separated, washed successively with water and brine (three times). After dried over sodium sulfate, the solvent was evaporated in vacuo to give the residue as white powder ((*R*,*R*)-**7a**:(*meso*)-**7a**:(*S*,*S*)-**7a** = 0.0:10.5:89.5 determined by HPLC, CHIRALCEL OD, *i*-PrOH/*n*-hexane = 10/90, 1.0 mL/min, λ = 254 nm; t_R 19.5 min (*R*,*R*)-**7a**, t_R 26.1 min (*meso*)-**7a** and t_R 30.7 min (*S*,*S*)-**7a**). The white powder was recrystallized with *iso*-propyl ether to afford (*S*,*S*)-**7a** as colorless solid (2.57 g, 74% yield, >99% de, >99% ee). Mp = 99.6–100.7 °C (from *iso*-propyl ether); $[\alpha]_D^{20} = -23.0$ (*c* 1.02, $CHCl_3$); IR (KBr) 3320, 2797, 1699, 1544 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.21 (d, J = 6.6 Hz, 6H), 3.02 (d, J = 4.6 Hz, 4H), 3.51 (s, 2H), 4.15–4.40 (m, 2H), 4.60–4.80 (m, 2H, N*H*), 5.09 (s, 4H), 5.45–5.75 (m, 4H), 7.10–7.50 (m, 15H); HRMS Calcd for $C_{33}H_{39}N_3O_4$: 541.2941. Found: 541.2943; Anal. Calcd for $C_{33}H_{39}N_3O_4$: C, 73.17; H, 7.26; N, 7.76. Found: C, 72.91; H, 7.25; N, 7.73.

(*S*,*S*)-**7b**; (91% yield). Mp = 119.5–120.5 °C (from *iso*-propyl ether); $[\alpha]_D^{20} = -3.8$ (*c* 0.74, $CHCl_3$); IR (KBr) 3319, 2959, 1687, 1539 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (d, J = 6.8 Hz, 6H), 0.88 (d, J = 6.8 Hz, 6H), 1.60–1.90 (m, 2H), 3.05 (d, J = 6.0 Hz, 4H), 3.53 (s, 2H), 3.90–4.10 (m, 2H), 4.70–4.90 (m, 2H), 5.09 (s, 4H), 5.40–5.70 (m, 4H), 7.10–7.40 (m, 15H); HRMS Calcd for $C_{37}H_{47}N_3O_4$: 597.3567. Found: 597.3549; Anal. Calcd for $C_{37}H_{47}N_3O_4{\cdot}0.45H_2O$: C, 73.35; H, 7.97; N, 6.94. Found: C, 73.18; H, 7.76; N, 6.94. HPLC conditions; CHIRALCEL OD-H, *iso*-PrOH/*n*-hexane = 5/95, 0.5 mL/min, t_R 43.6 min (*R*,*R*)-**7b**, t_R 55.1 min (*meso*)-**7b** and t_R 62.3 min (*S*,*S*)-**7b**.

(*S*,*S*)-**7c**; (70% yield). Mp = 83.8–85.1 °C (from *iso*-propyl ether); $[\alpha]_D^{20} = +8.8$ (*c* 0.73, $CHCl_3$); IR (KBr) 3325, 1687, 1525 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.60–3.00 (m, 8H), 3.35 (s, 2H), 4.35–4.60 (m, 2H), 4.65–4.85 (m, 2H), 5.06 (s, 4H), 5.40–5.60 (m, 4H), 7.00–7.40 (m, 25H); HRMS Calcd for $C_{45}H_{47}N_3O_4$: 693.3566. Found: 693.3578; Anal. Calcd for $C_{45}H_{47}N_3O_4{\cdot}0.85H_2O$: C, 76.21; H, 6.92; N, 5.93. Found: C, 75.88; H, 6.57; N, 5.93. HPLC conditions; CHIRALCEL OD, *iso*-PrOH/*n*-hexane = 10/90, 1.0 mL/min, t_R 33.2 min (*R*,*R*)-**7c**, t_R 49.9 min (*meso*)-**7c** and t_R 70.1 min (*S*,*S*)-**7c**.

4.5. *N*,*N*-Bis[(4*S*)-4-aminopentyl]amine (*S*,*S*)-1a

A suspension of (*S*,*S*)-**7a** (100 mg, 0.18 mmol) and palladium hydroxide (10% on carbon 10 mg) in methanol (2 mL) was stirred for 17 h at room temperature under hydrogen atmosphere. The reaction mixture was poured into the mixed solvent of ethyl acetate and water. The catalyst was filtered off and the filtrate was evaporated under reduced pressure and the residue was purified by PTLC with chloroform/methanol/*iso*-propylamine = 10/1/1 as an eluent to afford (*S*,*S*)-**1a** as an oil (33.6 mg, 97%). $[\alpha]_D^{21} = +4.0$ (*c* 1.10, MeOH); IR (film) 3341, 2932, 1586, 1470 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 1.03 (d, J = 6.4 Hz, 6H), 1.20–1.60 (m, 8H), 2.45–2.65 (m, 4H), 2.70–2.90 (m, 2H); HRMS Calcd for $C_{10}H_{25}N_3$: 187.2049. Found: 187.2039.

(*R*,*R*)-**1b**; colorless oil; (87%). $[\alpha]_D^{21} = +17.6$ (*c* 0.44, MeOH); IR (film) 2923, 1560, 1459 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 0.85–0.95 (m, 12H), 1.20–1.80 (m, 10H), 2.50–2.75 (m, 6H); HRMS Calcd for $C_{14}H_{33}N_3$: 243.2675. Found: 243.2687.

(*R*,*R*)-**1c**; colorless oil; (92%). $[\alpha]_D^{20} = -5.4$ (*c* 0.52, MeOH); IR (film) 3350, 3027, 2924, 1454 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 1.20–1.70 (m, 8H), 2.50–2.85 (m, 8H), 2.90–3.05 (m, 2H), 7.15–7.35 (m, 10H); HRMS Calcd for $C_{22}H_{34}N_3$: 340.2753. Found: 340.2741.

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