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One-pot synthesis of C_2-symmetric N,N'-diaryl bis(oxazolidin-2-ones) as precursors for N,N'-diaryl 2,3-diamino-1,4-butanediols

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Abstract

A new and general one-pot synthetic method for C_2-symmetric N,N'-aryl-disubstituted bis(oxazolidin-2-ones) has been developed. Highly regioselective intramolecular cyclization reactions of 2,3-di(methanesulfonyloxy)-1,4-dihydroxybutane with arylisocyanates in the presence of sodium hydride afforded the corresponding C_2-symmetric N,N'-aryl-disubstituted bis(oxazolidin-2-ones) in 82–92% yields. Hydrolytic ring opening of the bis(oxazolidin-2-ones) provided a convenient synthetic route for optically pure C_2-symmetric N,N'-aryl-disubstituted 2,3-diamino-1,4-butanediols (58–86% yields).

1. Introduction

Chiral oxazolidin-2-ones have been utilized as chiral auxiliaries for a wide range of asymmetric reactions such as diastereoselective alkylations, aldol reactions, Michael additions and Diels–Alder reactions.[1] Moreover, chiral oxazolidinones gained much interest in their own right as antibacterial agents[2] and precursors for optically active 1,2-aminoalcohols.[3] A number of chiral 1,2-aminoalcohols have been synthesized by hydrolytic ring opening of chiral oxazolidin-2-ones which derived from the reaction of 2,3-epoxy alcohols with isocyanates.[3] During our study on the development of C_2-symmetric chiral ligands,[4] we were interested in vicinal diamines bearing two neighboring stereogenic centers such as (2*S*,3*S*)-2,3-diamino-1,4-butanediol[4a,5] as a starting material for C_2-symmetric chiral ligands. Many N,N'-disubstituted ethylenediamine derivatives with C_2-symmetry have been synthesized and widely used as chiral tools in several reactions.[6–8] The most common approach was by reductive coupling of the corresponding imine, isomerization of the *meso* compound into the *dl* one, and subsequent resolution of the

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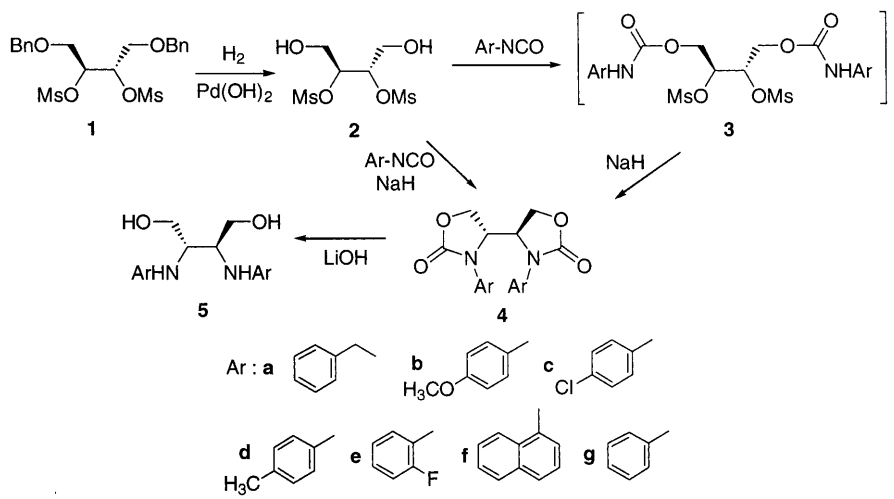
racemate.[8] Nevertheless, synthetic methods of chiral *N*,*N*′-diarylated ethylenediamines have been scarcely developed.[7–9]

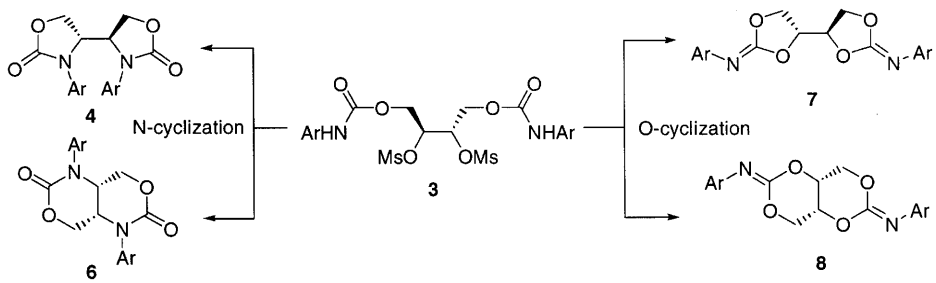
It can be expected that the hydrolytic ring opening of enantiopure C_2-symmetric *N*,*N*′-diaryl bis(oxazolidin-2-ones) **4** may become a convenient synthetic route for *N*,*N*′-diaryl vicinal diamines. However, as far as we know, no such bis(oxazolidin-2-ones) **4** have been reported. In a previous communication,[10] we reported the double intramolecular cyclization of bis(carbamate) **3a** to furnish **4a** which transformed to (5*S*,5′*S*)-5,5′-bis(oxazolidin-2-one), water-soluble C_2-symmetric bifunctional chiral auxiliary.[11] In this paper, we wish to report detailed experiments of the intramolecular cyclization of bis(carbamate) **3a** and a general one-pot synthesis of C_2-symmetric *N*,*N*′-diaryl bis(oxazolidin-2-ones) **4** from diol **2**, and their conversion to *N*,*N*′-diaryl-2,3-diamino-1,4-butanediols **5** (Scheme 1).



Scheme 1.

2. Results and discussion

Regiocontrolled intramolecular cyclization of hydroxyl ureas are often used in the syntheses of imidazolidinones and oxazolines.[12] The selectivity for *N*-cyclization versus *O*-cyclization during the intramolecular cyclization of carbamates derived from 2,3-epoxy alcohol and isocyanates depend on the reaction conditions and, thus, afforded oxazolidinones and/or carbonates.[3a,e] Under basic conditions, *N*-cyclized oxazolidinones were formed in preference to *O*-cyclized carbonates. However, the intramolecular cyclization of bis(carbamates) **3** is expected to be more complicated. Four isomers, namely, two that are *N*-cyclized, bis(oxazolidinone) **4** and fused-bicyclic oxazidinone **6**, and two *O*-cyclized imino carbonates **7** and **8** could be formed. To investigate the cyclization route shown in Scheme 2, the L-tartaric acid-derived (2*S*,3*S*)-2,3-di(methanesulfonyloxy)-1,4-dibenzyloxybutane **1** was debenzylated to give **2** which converted to the bis(carbamate) **3a** by reaction with benzylisocyanate in 90% yield.



Scheme 2.

Initially, sodium hydride (NaH) was added portionwise to a solution of bis(carbamate) **3a** in THF at 0°C, then the reaction mixture was refluxed for 6 h. One major compound **4a** was detected in TLC (*n*-hexane:EtOAc = 1:2) and isolated in 90% yield. However, when the same reaction was carried out overnight at room temperature, a mixture of *N*-cyclized products **4a** and **6a** was formed in 90% yield in a ratio of 9:1, determined by ^{1}H NMR spectrum analysis. In ^{1}H NMR, the diastereotopic benzyl protons of relatively less polar **4a** were resonated as two sets of doublets at δ 4.38 and 4.19, whereas at δ 4.96 and 4.32 for more polar **6a**. There was no sign of *O*-cyclized products **7a** and **8a**. After chromatographic separation of **4a** and **6a**, their structures were unambiguously determined by X-ray crystallographic analyses (Fig. 1). Employing *t*-BuOK or *t*-BuONa as base under the same reaction conditions exhibited almost the same selectivity with that of the value obtained with sodium hydride. However, other bases such as triethylamine, diisopropylethylamine, potassium carbonate and cesium carbonate gave only a trace amount of **4a**, even at elevated reaction temperatures, and most of the starting bis(carbamate) **3a** was recovered.

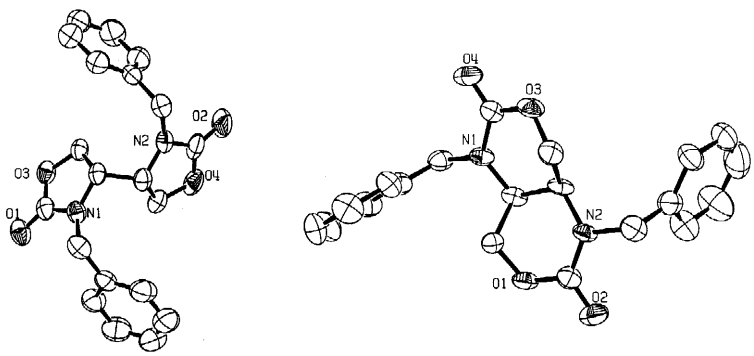


Figure 1. ORTEP diagram of compounds **4a** and **6a**

To avoid the inconvenience of the separation of carbamate **3a**, we turned to a one-pot reaction. Thus, to a solution of mesylate **2** in THF was successively added benzylisocyanate (2.2 equiv.) and NaH (6 equiv.) at 0°C, and the mixture was stirred at room temperature for 10 h to give **4a** (82%) and **6a** (8%). We expected to apply this reaction condition to a general synthesis of *N*,*N*′-aryl disubstituted C_2-symmetric bis(oxazolidinones) **4b–4g**. On the basis of the above reaction conditions, various arylisocyanates were reacted with **2**, and the yields were

summarized in Table 1. In contrast with benzylisocyanate, all of the arylisocyanates examined afforded only **4b–4g** with high selectivity. No other compounds including **6b–6g** could be isolated. The X-ray crystal structure of **4e** clearly supported that the isolated compounds were bis(oxazolidinones) **4b–4g**.[13]

Table 1
C_2-Symmetric *N*,*N*′-aryl-disubstituted bis(oxazolidin-2-ones) **4** and *N*,*N*′-aryl-disubstituted 2,3-diamino-1,4-butanediols **5**

Entry	**4**	Yield (%)	**5**	Yield (%)
1	**a**	82	**a**	81
2	**b**	91	**b**	76
3	**c**	92	**c**	86
4	**d**	84	**d**	76
5	**e**	89	**e**	62
6	**f**	90	**f**	58
7	**g**	87	**g**	72

Once C_2-symmetric *N*,*N*′-diaryl bis(oxazolidinones) **4a–4g** were in hand, the *N*,*N*′-aryl-disubstituted (2*S*,3*S*)-2,3-diamino-1,4-butanediols **5a–5g** could be synthesized by simple hydrolytic ring opening of the corresponding **4a–4g**.[3,14] Upon treatment with lithium hydroxide, the oxazolidinone rings of **4a–4g** were opened to furnish **5a–5g** in moderate to good yields. The yields after chromatographic purification (*n*-hexane:EtOAc = 2:1) on silica are summarized in Table 1. Interestingly, the relative polarities on TLC of the diaminodiols **5a–5g** are lower than the corresponding bis(oxazolidinones) **4a–4g**.

In conclusion, we have described in detail the regioselective intramolecular cyclization of bis(carbamate) **3a** and the development of a general one-pot method for the synthesis of C_2-symmetric *N*,*N*′-diaryl bis(oxazolidin-2-ones) **4** from dihydroxydimesylate **2** and arylisocyanates in the presence of NaH. Hydrolytic ring opening of **4** provided a convenient synthetic route for enantiomerically pure *N*,*N*′-diaryl-(2*S*,3*S*)-2,3-diamino-1,4-butanediols **5**. Studies on the synthesis of C_2-symmetric chiral ligands using vicinal diamines **5** are underway.

3. Experimental

3.1. General methods

NMR spectra were recorded at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR with TMS as internal reference. Chemical analyses were carried out by the Advanced Analysis Center at Korea Institute of Science and Technology. The Mass Spectrometry Analysis Group at Korea Basic Science Institute carried out HRMS (FAB) analysis. All solvents were distilled prior to use. (2*S*,3*S*)-2,3-Di(methanesulfonyloxy)-1,4-dibenzyloxybutane **1** has been prepared from L-tartaric acid according to our previously published procedures.[4]

3.2. Synthesis of (2S,3S)-2,3-di(methanesulfonyloxy)-1,4-butanediol **2**

A solution of **1** (16 g, 53 mmol) in MeOH/EtOAc (1:1, v/v) was stirred in the presence of $Pd(OH)_2$ (1 g) under an atmosphere of hydrogen at room temperature for 12 h. The catalyst was removed by filtration through Celite 545. After evaporation of the solvent under reduced pressure, the oily residue was purified by column chromatography on silica gel (2:1, EtOAc/*n*-hexane) to give **2** as colorless oil (10.9 g, 96%) which solidified after prolonged storage in a refrigerator. Mp 69–70°C; $[\alpha]_D^{25}$ −2.9 (*c* 0.42, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6) δ 5.32 (t, $J=5.3$ Hz, 2H), 4.74 (dt, $J=6.9$, 3.5 Hz, 2H), 3.86 (m, 4H), 3.22 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 81.3, 60.6, 39.0. Anal. calcd for $C_6H_{14}O_8S_2$: C, 25.89; H, 5.07. Found: C, 25.90; H, 5.08.

3.3. Synthesis of (2S,3S)-2,3-di(methanesulfonyloxy)-1,4-di(N,N′-dibenzylaminocarbonyloxy)-butane **3a**

To a solution of **2** (9.2 g, 43 mmol) in THF was added benzylisocyanate (12 g, 94.4 mmol) at 0°C. The reaction mixture was stirred overnight at room temperature and diluted with methylene chloride, washed with 2% aqueous HCl solution, water and brine. The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to give benzyl bis(carbamate) **3a** (21 g, 90%) which was recrystallized in ether. Mp 118–120°C; $[\alpha]_D^{25}$ −101.1 (*c* 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 10H), 5.42 (m, 2H), 5.06 (m, 2H), 4.53 (d, $J=11.8$ Hz, 2H), 4.35 (m, 6H), 3.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 138.3, 129.1, 128.1, 127.9, 127.5, 77.9, 63.0, 45.6, 39.3. Anal. calcd for $C_{22}H_{28}N_2O_{10}S_2$: C, 48.52; H, 5.18; N, 5.14. Found: C, 47.80; H, 5.36; N, 4.81. IR (KBr) ν 1698 cm^{-1} (C=O).

3.4. Intramolecular cyclization of **3a**

To a solution of bis(carbamate) **3a** (0.54 g, 0.1 mmol) in THF was added 95% NaH (0.1 g, 4.2 mmol) at 0°C, and the reaction mixture was stirred for 10 h at room temperature. The reaction mixture was quenched carefully with water and extracted with methylene chloride. Evaporation of the solvent afforded a mixture of **4a** and **6a**. After chromatographic separation (1:2, *n*-hexane/EtOAc, **4a**: $R_f=0.4$ and **6a**: $R_f=0.3$) on silica, each of **4a** and **6a** was recrystallized from methanol to give single crystals suitable for X-ray crystallographic analysis.

3.4.1. (5S,5′S)-N,N′-Dibenzyl-5,5′-bis(oxazolidin-2-one) **4a**

Mp 158–160°C; $[\alpha]_D^{25}$ −20.3 (*c* 0.99, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.36 (m, 6H), 7.08–7.12 (m, 4H), 4.38 (d, $J=15.0$ Hz, 2H), 4.19 (d, $J=15.0$ Hz, 2H), 4.09 (dd, $J=9.7$, 4.9, 2H), 3.87 (dd, $J=9.7$, 9.8 Hz, 2H), 3.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 135.7, 129.6, 129.0, 128.6, 62.4, 54.2, 48.0. The X-ray data were collected on an Enraf–Nonius CAD-4 automatic diffractometer with graphite-monochromated Mo Kα ($\lambda=0.71073$ Å) at 293 K. The structure was solved by the Patterson method (SHELXS-86) and refined by full-matrix least-squares technique. $C_{20}H_{20}N_2O_4$, $M=352.38$. Monoclinic, $a=11.889(3)$, $b=6.3358(11)$, $c=12.214(3)$ Å, $\alpha=90.00(2)°$, $\beta=108.14(2)°$, $\gamma=90.00(2)°$, space group = $P2_1/a$ (no. 14), $V=874.4(4)$ Å^3, $Z=2$, $D_c=1.338$ g/cm^3, crystal size = 0.2×0.2×0.3 mm, $F(000)=372$, a total of 1049 reflections in the range of $1.75° \leq \theta \leq 24.96°$ were measured, the $\Delta\rho_{max}$ and $\Delta\rho_{min}$ are 0.110 and −0.109 e Å^{-3}, goodness-of-fit = 1.113, $I/\sigma(I) \geq 2.0$, $R=0.0377$.

3.4.2. (1S,6S)-2,7-Diaza-2,7-dibenzyl-4,9-dioxabicyclo[4,4,0^{1,6}]decane-3,8-dione ***6a***

Mp 210–211°C; $[\alpha]_D^{25}$ −4.42 (*c* 1.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.36 (m, 6H), 7.25–7.28 (m, 4H), 4.96 (d, $J=15.4$ Hz, 2H), 4.32 (d, $J=15.4$ Hz, 2H), 4.16–4.28 (m, 6H), 3.72–3.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 135.6, 129.1, 128.3, 127.9, 63.5, 50.6, 49.4. The X-ray data were collected on an Enraf–Nonius CAD-4 automatic diffractometer with graphite-monochromated Mo Kα ($\lambda=0.71073$ Å) at 293 K. The structure was solved by the Patterson method (SHELXS-86) and refined by full-matrix least-squares technique. There are two independent molecules in the asymmetric region of the monoclinic unit cell and the features of the two molecules are within error of being identical. $C_{40}H_{40}N_4O_8$, $M=704.76$. Monoclinic, $a=6.149(2)$, $b=26.555(2)$, $c=10.484(1)$ Å, $\alpha=90.00(2)°$, $\beta=90.35(2)°$, $\gamma=90.00(1)°$, space group $=P2_1/a$ (no. 14), $V=1711.9(6)$ Å^3, $Z=2$, $D_c=1.367$ g/cm^3, crystal size $=0.2\times0.2\times0.3$ mm, $F(000)=744$, a total of 1936 reflections in the range of $1.75°\leq\theta\leq24.96°$ measured, the $\Delta\rho_{max}$ and $\Delta\rho_{min}$ are 0.242 and −0.212 e Å^{-3}, goodness-of-fit $=1.132$, $I/\sigma(I)\geq2.0$, $R=0.0531$.

3.5. One-pot synthesis of (5S,5′S)-N,N′-dibenzyl-5,5′-bis(oxazolidin-2-ones) ***4***

To a solution of diol **2** (1.42 g, 6.6 mmol) in THF was successively added arylisocyanate (14.6 mmol) and 95% NaH (1 g, 39.6 mmol) at 0°C. The reaction mixture was stirred overnight at room temperature. After workup as above, the residue was purified by column chromatography on silica (1:2, *n*-hexane/EtOAc) to give the bis(oxazolidin-2-ones) **4**. For elemental analyses, compounds **4b**–**4g** were recrystallized in ethanol.

3.5.1. (5S,5′S)-N,N′-Di(p-methoxyphenyl)-5,5′-bis(oxazolidin-2-one) ***4b***

Mp 131–133°C; $[\alpha]_D^{25}$ −81.0 (*c* 0.91, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, $J=9.0$ Hz, 4H), 6.93 (d, $J=9.0$ Hz, 4H), 4.58–4.60 (m, 2H), 4.41–4.44 (m, 4H), 3.82 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 155.7, 127.9, 124.3, 115.0, 61.8, 55.5, 55.2. Anal. calcd for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29. Found: C, 62.40; H, 5.30; N, 7.16. IR (KBr) ν 1742 cm^{-1} (C=O).

3.5.2. (5S,5′S)-N,N′-Di(p-chlorophenyl)-5,5′-bis(oxazolidin-2-one) ***4c***

Mp 240–241°C; $[\alpha]_D^{25}$ −119.7 (*c* 1.70, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, $J=8.9$ Hz, 4H), 7.29 (d, $J=8.9$ Hz, 4H), 4.69 (t, $J=5.3$ Hz, 2H), 4.42–4.44 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 133.9, 132.0, 130.0, 122.9, 61.9, 54.5. Anal. calcd for $C_{18}H_{14}Cl_2N_2O_4$: C, 54.98; H, 3.59; N, 7.12. Found: C, 54.90; H, 3.69; N, 7.15. HRMS (FAB$^+$) calcd for $C_{18}H_{15}Cl_2N_2O_4$ [(M+H)$^+$]: 393.0331. Found: 393.0404. IR (KBr) 1752 cm^{-1} (C=O).

3.5.3. (5S,5′S)-N,N′-Di(p-tolyl)-5,5′-bis(oxazolidin-2-one) ***4d***

Mp 168–170°C; $[\alpha]_D^{25}$ −92.9 (*c* 0.93, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.26 (m, 8H), 4.68–4.72 (m, 2H), 4.38–4.50 (m, 4H), 2.37 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 136.4, 132.7, 130.3, 122.0, 61.7, 54.6, 20.8. Anal. calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.20; H, 5.76; N, 7.92. IR (KBr) 1750 cm^{-1} (C=O).

3.5.4. (5S,5′S)-N,N′-Di(o-fluorophenyl)-5,5′-bis(oxazolidin-2-one) ***4e***

Mp 171–172°C; $[\alpha]_D^{25}$ +0.6 (*c* 0.98, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.40 (m, 4H), 7.16–7.26 (m, 4H), 4.54–4.57 (m, 4H), 4.80–4.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6 (d, $J_{C-F}=248.9$ Hz), 155.7, 130.0 (d, $J_{C-F}=8.2$ Hz), 128.5, 125.4 (d, $J_{C-F}=3.8$ Hz), 122.8, 117.1

(d, $J_{C-F}=19.7$ Hz), 62.8, 56.3. Anal. calcd for $C_{18}H_{14}F_2N_2O_4$: C, 60.00; H, 3.92; N, 7.77. Found: C, 60.10; H, 3.92; N, 7.76. HRMS (FAB$^+$) calcd for $C_{18}H_{15}F_2N_2O_4$ [(M+H)$^+$]: 361.0922. Found: 361.1002. IR (KBr) 1752 cm^{-1} (C=O). The X-ray data were collected on an Enraf–Nonius CAD-4 automatic diffractometer with graphite-monochromated Mo Kα ($\lambda=0.71073$ Å) at 293 K. The structure was solved by the Patterson method (SHELXS-86) and refined by full-matrix least-squares technique. $C_{18}H_{14}F_2N_2O_4$, $M=360.31$. Orthorhombic, $a=11.784(2)$, $b=19.064(2)$, $c=7.316(3)$ Å, space group $=P2_12_12_1$ (no. 19), $V=1643.5(7)$ Å^3, $Z=4$, $D_c=1.456$ g/cm^3, crystal size $=0.3\times0.35\times0.5$ mm, $F(000)=744$, a total of 2536 reflections in the range of $2.03°\leq\theta\leq 24.97°$ were measured, the $\Delta\rho_{max}$ and $\Delta\rho_{min}$ are 0.275 and −0.224 e Å^{-3}, goodness-of-fit $=1.132$, $I/\sigma(I)\geq 2.0$, $R=0.045$.

3.5.5. (5S,5′S)-N,N′-Di(1-naphthyl)-5,5′-bis(oxazolidin-2-one) ***4f***

Mp 246–249°C; $[\alpha]_D^{25}$ −141.1 (*c* 1.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85–7.92 (m, 4H), 7.40–7.63 (m, 8H), 7.18–7.21 (m, 2H), 4.84–4.89 (m, 2H), 4.75 (m, 2H), 4.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 134.7, 131.2, 129.6, 128.9, 127.6, 126.9, 125.4, 121.5, 62.9, 57.7. Anal. calcd for $C_{26}H_{20}N_2O_4$: C, 73.30; H, 4.75; N, 6.59. Found: C, 73.57; H, 4.76; N, 6.60. HRMS (FAB$^+$) calcd for $C_{26}H_{21}N_2O_4$ [(M+H)$^+$]: 425.1423. Found: 425.1491. IR (KBr) *v* 1764 cm^{-1} (C=O).

3.5.6. (5S,5′S)-N,N′-Diphenyl-5,5′-bis(oxazolidin-2-one) ***4g***

Mp 179–180°C; $[\alpha]_D^{25}$ −58.9 (*c* 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.49 (m, 10H), 4.76–4.80 (m, 2H), 4.42–4.48 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 135.8, 130.3, 126.9, 122.2, 62.2, 54.8. Anal. calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.49; H, 4.99; N, 8.56. IR (KBr) *v* 1746 cm^{-1} (C=O).

3.6. Synthesis of N,N′*-diaryl (2*S,*3*S*)-2,3-diamino-1,4-butanediols* ***5***

To a solution of bis(oxazolidinone) **4** (0.26 mmol) in 30% aqueous ethanol solution was added $LiOH\cdot H_2O$ (5.2 mmol) at room temperature. After 48 h reflux, the reaction temperature was allowed to cool to room temperature and diluted with ethyl acetate. The organic layer was washed with water, brine and dried with $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on silica using *n*-hexane:EtOAc = 1:2 as eluent to give *N*,*N*′-diaryl (2*S*,3*S*)-2,3-diamino-1,4-butanediols **5**.

*3.6.1. (2*S,*3*S*)-N,N′-Dibenzyl-2,3-diamino-1,4-butanediol* ***5a***

Oil; $[\alpha]_D^{25}$ −22.2 (*c* 0.88, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.38 (m, 10H), 4.02 (dd, $J=9.1$, 5.3 Hz, 2H), 3.79 (s, 4H), 3.62 (dd, $J=9.1$, 3.9 Hz, 2H), 3.23 (pseudo pentet, $J=3.8$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.5, 128.2, 127.3, 72.7, 64.1, 52.3. HRMS (FAB$^+$) calcd for $C_{18}H_{25}N_2O_2$ [(M+H)$^+$]: 301.1838. Found: 301.1840.

*3.6.2. (2*S,*3*S*)-N,N′-Di(*p*-methoxyphenyl)-2,3-diamino-1,4-butanediol* ***5b***

Mp 124–126°C; $[\alpha]_D^{25}$ +28.6 (*c* 0.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (bs, 2H), 6.75 (s, 8H), 4.15 (dd, $J=9.9$, 5.4 Hz, 2H), 3.92 (m, 2H), 3.79 (m, 1H), 3.75 (m, 1H+s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 135.5, 118.5, 115.0, 71.4, 61.9, 55.6. Anal. calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 65.02; H, 7.31; N, 8.40.

*3.6.3. (2*S*,3*S*)-*N*,*N*′-Di(*p*-chlorophenyl)-2,3-diamino-1,4-butanediol* ***5c***

Mp 126–128°C; $[\alpha]_D^{25}$ +29.1 (*c* 0.65, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6) δ 7.08 (d, $J=8.3$ Hz, 4H), 6.67 (d, $J=8.3$ Hz, 4H), 5.35 (d, $J=9.1$ Hz, 2H), 4.80 (m, 2H), 3.65–3.70 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 148.0, 128.7, 118.7, 113.8, 60.4, 54.4. Anal. calcd for $C_{16}H_{18}Cl_2N_2O_2$: C, 56.32; H, 5.32; N, 8.21. Found: C, 56.30; H, 5.29; N, 8.25. HRMS (FAB$^+$) calcd for $C_{16}H_{19}Cl_2N_2O_2$ [(M+H)$^+$]: 341.0824. Found: 341.0811.

*3.6.4. (2*S*,3*S*)-*N*,*N*′-Di(*p*-tolyl)-2,3-diamino-1,4-butanediol* ***5d***

Oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, $J=8.2$ Hz, 4H), 6.67 (d, $J=8.2$ Hz, 4H), 4.17 (m, 2H), 3.89 (m, 2H), 3.72 (m, 2H), 2.28 (s, 6H), 1.68 (bs, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 130.0, 128.0, 114.4, 61.5, 55.8, 20.4. HRMS (FAB$^+$) calcd for $C_{18}H_{25}N_2O_4$ [(M+H)$^+$]: 301.1916. Found: 301.1914.

*3.6.5. (2*S*,3*S*)-*N*,*N*′-Di(*o*-fluorophenyl)-2,3-diamino-1,4-butanediol* ***5e***

Oil; $[\alpha]_D^{25}$ −31.6 (*c* 0.98, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.96–7.03 (m, 4H), 6.80 (td, $J=8.6$, 1.4 Hz, 2H), 6.64–6.71 (m, 2H), 4.50 (bs, 2H), 3.92 (d, $J=10.4$ Hz, 2H), 3.70–3.77 (m, 4H), 3.28 (bs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9 (d, $J_{C-F}=239.1$ Hz), 135.2 (d, $J_{C-F}=11.6$ Hz), 124.7 (d, $J_{C-F}=3.5$ Hz), 117.8 (d, $J_{C-F}=7.0$ Hz), 115.0 (d, $J_{C-F}=18.8$ Hz), 113.1, 60.6, 54.3. HRMS (FAB$^+$) calcd for $C_{16}H_{19}F_2N_2O_2$ [(M+H)$^+$]: 309.1336. Found: 309.1404.

*3.6.6. (2*S*,3*S*)-*N*,*N*′-Di(1-naphthyl)-2,3-diamino-1,4-butanediol* ***5f***

Oil; $[\alpha]_D^{25}$ −121.2 (*c* 0.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.79–7.85 (m, 4H), 7.24–7.48 (m, 8H), 6.82 (d, $J=7.4$ Hz, 2H), 5.10 (bs, 2H), 4.05–4.12 (m, 4H), 3.86–3.90 (m, 2H), 3.24 (bs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 134.6, 128.8, 126.5, 125.9, 125.1, 123.8, 119.8, 118.2, 105.5, 60.8, 54.4. HRMS (FAB$^+$) calcd for $C_{24}H_{25}N_2O_2$ [(M+H)$^+$]: 373.1838. Found: 373.1908.

*3.6.7. (2*S*,3*S*)-*N*,*N*′-Diphenyl-2,3-diamino-1,4-butanediol* ***5g***

Oil; $[\alpha]_D^{25}$ −28.2 (*c* 1.08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.22–7.27 (m, 4H), 6.81 (t, $J=7.1$ Hz, 2H), 6.73 (d, $J=7.1$ Hz, 4H), 3.88 (m, 6H) 3.70–3.78 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 129.5, 118.3, 113.8, 60.9, 54.7. HRMS (FAB$^+$) calcd for $C_{16}H_{21}N_2O_2$ [(M+H)$^+$]: 273.1525. Found: 273.1611.

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