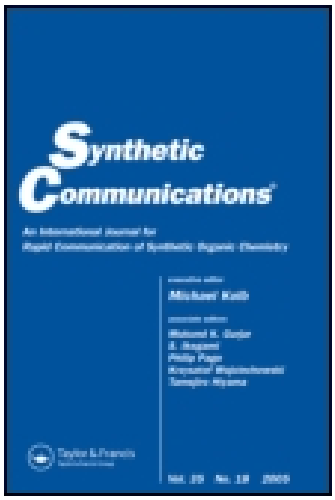

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of Novel Chiral C_2-Symmetric Bisoxazoline Ligands Containing 2,5-Di(*m*-substituted)phenyl-1,3,4-oxadiazole

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Published online: 20 Aug 2006.

To cite this article: Dong-Cheng Xu, Da-Ming Du, Nan Ji, Zhan-Yue Wang & Wen-Ting Hua (2003) Synthesis of Novel Chiral C_2-Symmetric Bisoxazoline Ligands Containing 2,5-Di(*m*-substituted)phenyl-1,3,4-oxadiazole, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:14, 2563-2574, DOI: 10.1081/SCC-120021848

To link to this article: http://dx.doi.org/10.1081/SCC-120021848

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SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 14, pp. 2563–2574, 2003

Synthesis of Novel Chiral C_2-Symmetric Bisoxazoline Ligands Containing 2,5-Di(*m*-substituted)phenyl-1,3,4-oxadiazole

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ABSTRACT

Seven novel chiral C_2-symmetric substituted bisoxazoline ligands containing 2,5-di(*m*-substituted)phenyl-1,3,4-oxadiazole have been synthesized from 2,5-di-(*m*-carboxylphenyl)-1,3,4-oxadiazole and aminoalcohol by NaOH or Et_3N cyclization method via halogenated amide intermediate.

Key Words: Bisoxazoline; Oxadiazole; Synthesis.

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DOI: 10.1081/SCC-120021848 0039-7911 (Print); 1532-2432 (Online)

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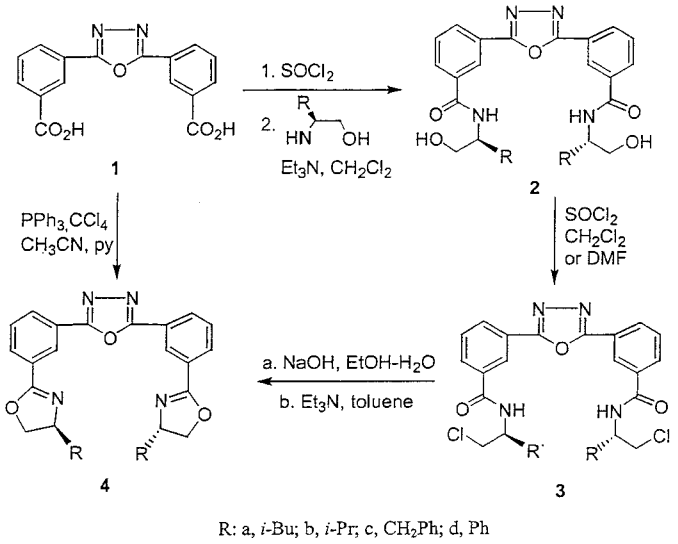
INTRODUCTION

The 2,5-diaryl-oxadiazole is one class of very rigid and almost planar molecule possessing many π-conjugated system.[1–3] Recently, much attention has been focused on the use of aromatic 1,3,4-oxadiazole unit in development of new photoelectric materials, such as conductor and electroluminescent owing to their special structure unit and properties.[4–6] Moreover, the structural factors may be advantageous to the molecular stereo-recognition in the host-guest inclusion when they were involved in this system. For this reason, a series of chiral macrocycles containing 2,5-diphenyl-1,3,4-oxadiazole have been synthesized as host, which showed remarkable chiral recognition to D- or L-amino acids, peptides, and some activity molecules in our previous report.[7]

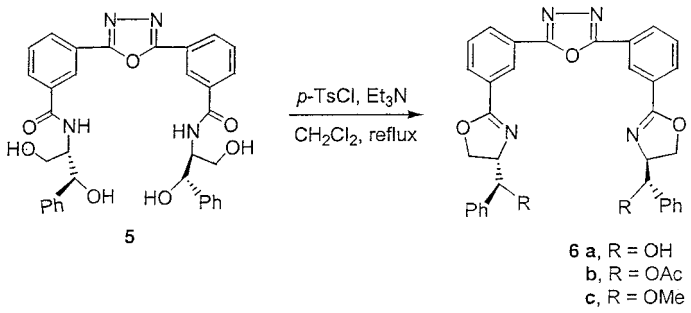
In recent years, the bisoxazoline ligands and their metal complexes have been used extensively in varied asymmetric catalytic reaction as C_2-symmetric chiral catalysts.[8–14] It is a new idea that make up a novel chiral catalyst system employing the two special structural units. In this article, we designed and synthesized the new chiral C_2-symmetric ligands containing both a rigid 2,5-di(*m*-substituted)phenyl-1,3,4-oxadiazole and two 4-substituted chiral oxazoline rings. Here, we reported the synthesis of these novel chiral bisoxazoline ligands containing 2,5-di(*m*-substituted)phenyl-1,3,4-oxadiazole units.

Results and Discussion

The ligands **4a–d** were synthesized from 2,5-di-(*m*-carboxylphenyl)-1,3,4-oxadiazole **1** with corresponding β-amino alcohols by two methods respectively as shown in Sch. 1. The β-amino alcohols have been prepared from corresponding chiral amino acids by reduction with $LiAlH_4$ or $NaBH_4$ according to the reported methods.[15] First is multistep method. The 2,5-di-(*m*-carboxylphenyl)-1,3,4-oxadiazoles **1** were reacted with $SOCl_2$, condensation of the resulting diacyl dichloride intermediates with β-amino alcohols afforded the corresponding dihydroxy diamide intermediates **2a–d** in 84.7–81.5% yield. The following is replacement of **2a–d** with $SOCl_2$ in dichloromethane (**2a–c**) or DMF (**2d**) and furnished the **3a–d** in 64.5–79% yield. Owing to the low solubility of **2d** in dichloromethane, very low yield was obtained. When DMF was used alternatively for **2d**, good yield for **3d** was obtained (64.5%). Finally, the chiral bisoxazoline ligands **4a–c** were obtained via intramolecular cyclization of **3a–c** in the presence of NaOH (method a). **4d** cannot use this method for cyclization. Fortunately, **4d** was obtained in 72.8% yield



Scheme 1. Preparation of chiral ligands **4a–d**.



Scheme 2. Preparation of chiral ligands **6a–c**.

via cyclization with Et_3N in refluxing toluene and DMF (method b). It is advantageous in this three step method that the higher yields and more pure products could be obtained in the every steps, except for reaction process is longer.

Diamide **5** was synthesized according to the same procedure of dihydroxy diamides **2a–d** from 2,5-di-(*m*-carboxylphenyl)-1,3,4-oxadiazole **1** and (1*R*,2*S*)-(-)-2-amino-1-phenyl-1,3-propanediol, but with longer reaction time for fluxing 36 h. However, diamide **5** cannot be treated with

$SOCl_2$ and subsequent with NaOH for cyclization to obtain the corresponding bisoxazoline **6a**, owing to it has two hydroxy groups. Fortunately, treatment of diamide **5** with *p*-TsCl and triethylamine in refluxing dichloromethane,[16] activation of the primary OH group by formation of the tosylate can give the desired bisoxazoline **6a** in 59% yield. The bisoxazoline **6a** can be further converted to acetate **6b** and methyl ether **6c** in 78.3% and 58.3% yield respectively. The structures of these new ligands were identified by ^{1}H NMR, MS, IR, and elemental analysis.

Second is one pot method, which was developed by Vorbrüggen.[17] This method is applicable for synthesis of varied ligands containing mono oxazoline and bisoxazolines from corresponding aromatic acid or heterocyclic acid.[17,18] But, there is also trouble in the one pot method that the large triphenyl phosphine oxide was produced at the same time as by product, this add to the difficulties in purification of product. The 2,5-di-(*m*-carboxylphenyl)-1,3,4-oxadiazole **1** can also were transformed into ligands **4** directly in one step with corresponding β-amino alcohols in the presence of triphenyl phosphine. This method is simple and convenient, however the yield is lower. In this article, we have used crystallizeable method in steps in preliminary separation of the large triphenyl phosphine oxide, the crude product was further purified via column chromatography on silica gel.

In conclusion, we have found efficent synthetic procedure for synthesis of a new series of chiral diphenyl oxdiazole bisoxazoline ligands. These novel diphenyloxadiazole bisoxazolines may have potential as chiral ligands for catalytic asymmetric reaction. Further application of this series new chiral ligands in catalytic enantioselective reaction are under research in our laboratory.

EXPERIMENTAL SECTION

Melting points were uncorrected. ^{1}H NMR spectra were recorded on a Bruker ARX 400 MHz spectrometer, tetramethylsilane (TMS) serving as internal standard. Infrared spectra were obtained on a Bruker Vector 22 spectrometer. Mass spectra were obtained on a VG-ZAB-HS mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 MC spectrometer. Elemental analyses were carried out on an Elementar Vario EL instrument. Solvents used were purified and dried by standard procedures. All reactions were carried out under an atmosphere of nitrogen. 2,5-di(*m*-carboxyphenyl)-1,3,4-oxadizole was synthesized according to literature produre.[19]

2,5-*bis*[*m*-[*N*-(1′S)-(1′-isobutyl-2′-hydroxyethyl)amido]phenyl]-1,3,4-oxadiazole 2a. General Procedure I. A solution of 2,5-di-(*m*-carboxyphenyl)-1,3,4-oxadiazole **1** (1.17 g, 3.76 mmol) and $SOCl_2$ (20 mL) was refluxed for 10 h. The excess $SOCl_2$ was removed under reduced pressure, benzene (20 mL) was added and the solvent was removed again to dryness to afford the diacyl dichloride. The above diacyl dichloride in CH_2Cl_2 (50 mL) was added dropwise to a solution of *S*-leucinol (0.88 g, 7.52 mmol) and Et_3N (2.82 mL) in CH_2Cl_2 (30 mL) at 0°C and stirring at room temperature for 24 h. The precipitate was filtered and washed with diethyl ether to afford the colorless solid powder **2a** 1.51 g (79.2% yield). M.p. 163–169°C. IR (KBr): 3470, 3320, 2920, 2840, 1640, 1570 cm^{-1}. EI MS: 508 (M^+). ^1H NMR (DMSO): δ 0.90 (6H, d, $J = 5.2$ Hz, CH_3), 0.92 (6H, d, $J = 5.2$ Hz, CH_3), 1.37–1.54 (4H, m, CH_2), 1.62–1.67 (2H, m, CH), 3.33–3.50 (4H, m, CH_2), 4.09–4.15 (2H, m, CH), 4.75 (2H, t, $J = 5.8$Hz, OH), 7.74 (2H, t, $J = 7.8$ Hz, ArH), 8.12 8.15 (2H, m, ArH), 8.28–8.31 (2H, m, ArH), 8.37 (2H, d, $J = 8.6$ Hz, NH), 8.63 (2H, t, $J = 1.4$ Hz, ArH). Anal. calcd. $C_{28}H_{36}N_4O_5$: C, 66.14; H, 7.08; N, 11.02. Found: C, 66.12; H, 7.13; N, 10.93.

2,5-*bis*[*m*-[*N*-(1′S)-(1′-isopropyl-2′-hydroxyethyl)amido]phenyl]-1,3,4-oxadiazole 2b. Following general procedure I, from 2,5-di-(*m*-carboxyphenyl)-1,3,4-oxadiazole **1** (1.68 g, 5.3 mmol) , $SOCl_2$ (30 mL), *S*-valinol (1.09 g, 10.5 mmol) and Et_3N (4.0 mL) to provide colorless solid **2b** in 74.7% yield (1.9g). M.p. 240–242°C. IR (KBr): 3400, 2950, 1650, 1530 cm^{-1}. EI MS: 480 (M^+). ^1H NMR (DMSO): δ 0.92 (6H, d, $J = 6.8$ Hz, CH_3), 0.94 (6H, d, $J = 6.8$ Hz, CH_3), 1.92–2.00 (2H, m, CH), 3.53–3.59 (4H, m, CH_2), 3.83–3.90 (2H, m, CH), 4.63 (2H, t, $J = 5.6$, OH), 7.74 (2H, t, $J = 7.8$ Hz, ArH), 8.15 (2H, d, $J = 7.8$ Hz, ArH), 8.28–8.31 (2H, m, ArH), 8.32 (2H, d, $J = 8.8$ Hz, NH), 8.62 (2H, s, ArH). Anal. calcd. $C_{26}H_{32}N_4O_5$: C, 64.98; H, 6.71; N, 11.67. Found: C, 64.85; H, 6.71; N, 11.52.

2,5-*bis*[*m*-[*N*-(1′S)-(1′-benzyl-2′-hydroxyethyl)amido]phenyl]-1,3,4-oxadiazole 2c. Following general procedure I, from 2,5-di-(*m*-carboxyzphenyl)-1,3,4-oxadiazole **1** (0.82 g, 2.65 mmol), $SOCl_2$(20 mL), *S*-phenylalaninol (0.8 g, 5.3 mmol) and Et_3N (2.0 mL) to give a colorless solid **2c** in 80.8% yield (1.24 g). M.p. 240–242°C. IR (KBr): 3400, 3350, 1620, 1550 cm^{-1}. FAB-MS: 577 (M + 1). ^1H NMR (DMSO): δ 2.82 (2H, dd, $J = 8.8$, 13.0 Hz, CH_2), 2.97 (2H, dd, $J = 5.2$, 13.4 Hz, CH_2), 3.23–3.40 (2H, m, CH_2), 3.43–3.56 (2H, m, CH_2), 4.15–4.28 (2H, m, NCH), 4.89 (2H, t, $J = 5.6$ Hz, OH), 7.10–7.34 (10H, m, ArH), 7.72 (2H, t, $J = 7.4$ Hz, ArH), 8.05 (2H, dd, $J = 1.2$, 7.4 Hz, ArH), 8.27 (2H, dd, $J = 1.2$, 7.4 Hz, ArH), 8.52 (2H, d, $J = 8.0$ Hz, NH), 8.55 (2H, s, ArH). Anal. calcd. $C_{34}H_{32}N_4O_5$: C, 70.82; H, 5.59; N, 9.72. Found: C, 70.97; H, 5.59; N, 9.50.

2,5-*bis*[*m*-[*N*-(1′S)-(1′-phenyl-2′-hydroxyethyl)amido]phenyl]-1,3,4-oxadiazole 2d. Following general procedure I, from 2,5-di-(*m*-carboxyphenyl)-1,3,4-oxadiazole **1** (1.9 g, 6.1 mmol), $SOCl_2$ (34 mL), *R*-phenylglycinol (1.65 g, 12.0 mmol) and Et_3N (6.9 mL) to give a colorless solid **2d** in 81.5% yield (2.68 g). M.p. 278–280°C. ^{1}H NMR (DMSO): δ 3.67–3.82 (4H, m, OCH_2), 5.09 (4H, $J = 6.0$ Hz, CH and OH), 7.19–7.46 (10H, m, ArH), 7.45 (2H, t, $J = 8.0$ Hz, ArH), 8.21 (2H, d, $J = 7.8$ Hz, ArH), 8.33 (2H, d, $J = 7.8$ Hz, ArH), 8.81 (2H, s, ArH), 9.20 (2H, d, $J = 7.8$ Hz, NH). IR (KBr): 3311, 1640, 1543, 1320 cm^{-1}. FAB MS: 549 (M + 1,7), 475 (24). Anal. calcd. $C_{32}H_{28}N_4O_5$: C, 70.06; H, 5.14; N, 10.20. Found: C, 69.90; H, 5.25; N, 10.32.

2,5-*bis*[*m*-[*N*-(1′S)-(1′-isobutyl-2′-chloroethyl)amido]phenyl]-1,3,4-oxadiazole 3a. General Procedure II. To the suspension of compound **2a** (508 mg, 1 mmol) in the CH_2Cl_2 (10 mL) was added $SOCl_2$ (4 mL) and the mixture refluxing for 5 h. The reaction mixture was cooled and poured into the ice-water, the organic phase (CH_2Cl_2) was separated from mixtures. The aqueous layer was extracted with CH_2Cl_2 (5×5 mL). The extracts were combined and washed to neutral with 5% $NaHCO_3$ and brine respectively, dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to afford the product **3a** in 79% yield (430 mg). M.p. 125–128°C. IR (KBr): 3350, 2990, 1640, 1520 cm^{-1}. MS (FAB): 545 (M + 1), δ 1.00 (12H, m, $4CH_3$), 1.42–1.48 (1H, m, CH_2), 1.55–1.62 (1H, m, CH_2), 1.65–1.88 (4H, m, CH_2, CH), 3.70–3.74 (1H, m, CH_2Cl), 3.86–3.91 (1H, m, CH_2Cl), 4.05–4.10 (1H, m, CH_2Cl), 4.35–4.45 (1H, m, CH_2Cl), 4.56–4.62 (2H, m, NCH), 6.40 (2H, d, $J = 8.6$ Hz, NH), 7.55–7.66 (2H, m, ArH), 8.01 (1H, t, $J = 8.2$ Hz, ArH), 8.15 (1H, dd, $J = 1.2$, 7.8 Hz, ArH), 8.28–8.32 (2H, m, ArH), 8.52 (1H, d, $J = 1.4$ Hz, ArH), 8.68 (1H, s, ArH). Anal. calcd. $C_{28}H_{34}Cl_2N_4O_3$: C, 61.65; H, 6.28; N, 10.27. Found: C, 61.54; H, 6.12; N, 10.23.

2,5-*bis*[*m*-[*N*-(1′S)-(1′-isopropyl-2′-chloroethyl)amido]phenyl]-1,3,4-oxadiazole 3b. Following general procedure II, from compound **2b** (480 mg, 1 mmol), $SOCl_2$ (4 mL) to afford the product **3b** in 76% yield (393 mg). M.p. 138–143°C. IR (KBr): 3400, 3350, 1680, 1550 cm^{-1}. MS (FAB): 517 (M + 1). ^{1}H NMR ($CDCl_3$): δ 1.08 (12H, d, $J = 6.7$ Hz, $4CH_3$), 1.88–1.96 (1H, m, CH), 2.04–2.16 (1H, m, CH), 3.82–3.90 (3H, m, CH_2), 4.15–4.28 (3H, m, CH_2, CH), 4.52 (1H, s, NH), 6.48 (2H, d, $J = 9.0$ Hz, NH), 7.59–7.67 (2H, m, ArH), 8.07 (1H, t, $J = 8.2$ Hz, ArH), 8.17 (1H, d, $J = 7.8$ Hz, ArH), 8.31 (2H, t, $J = 7.6$ Hz, ArH), 8.53 (1H, s, ArH), 8.56 (1H, s, ArH). Anal. calcd. $C_{26}H_{30}Cl_2N_4O_3$: C, 60.35; H, 5.84; N, 10.83. Found: C, 60.58; H, 5.86; N, 11.04.

2,5-*bis*[*m*-[*N*-(1′S)-(1′-benzyl-2′-chloroethyl)amido]phenyl]-1,3,4-oxadiazole 3c. Following general procedure II, from compound **2c** (576 mg,

1 mmol), $SOCl_2$ (5 mL) to afford the product **3c** in 69% yield (417 mg). M.p. 197–200°C. IR (KBr): 3360, 1650, 1530 cm^{-1}. MS (FAB): 613 (M + 1). ^1H NMR ($CDCl_3$): δ 3.10 (4H, dd, $J = 4.2$, 8.4 Hz, CH_2), 3.65 (2H, dd, $J = 3.4$, 11.2 Hz, CH_2Cl), 3.82 (2H, dd, $J = 4.0$, 11.2 Hz, CH_2Cl), 4.63–4.78 (2H, m, NCH), 6.49 (2H, d, $J = 8.4$ Hz, NH), 7.20–7.39 (10H, m, ArH), 7.65 (2H, t, $J = 7.8$ Hz, ArH), 7.95 (2H, d, $J = 7.6$ Hz, ArH), 8.30 (2H, d, $J = 7.6$ Hz, ArH). Anal. calcd. $C_{34}H_{30}Cl_2N_4O_3$: C, 66.56; H, 4.93; N, 9.13. Found: C, 66.63; H, 4.81; N, 8.91.

2,5-*bis*[*m*-[*N*-(1′R)-(1′-phenyl-2′-chloroethyl)amido]phenyl]-1,3,4-oxadiazole 3d. To the solution of dihydroxy diamide **2d** (1.49 g, 2.71 mmol) in the DMF (25 mL) was added dropwise a solution of thionyl chloride (1.5 mL, 20 mmol) in DMF (5 mL) via syringe. The mixture was kept stirring at room temperature for 24 h. The reaction mixture was poured into the ice-water (100 mL), the precipitate was filtered and dried to give 1.32 g (83.3% yield) of the crude product. The crude product was recrystallized from methanol to afford colorless solid 1.03 g (64.5%). M.p. 188–190°C. ^1H NMR ($CDCl_3$): δ 4.00 (4H, d, $J = 7.6$ Hz, CH_2Cl), 5.30–5.42 (2H, m, NCH), 7.30–7.53 (10H, m, ArH), 7.78 (2H, t, $J = 7.6$ Hz, ArH), 8.16 (2H, d, $J = 7.8$ Hz, ArH), 8.33 (2H, d, $J = 7.8$ Hz, ArH), 8.66 (2H, s, ArH), 9.37 (2H, d, $J = 8.2$ Hz, NH). IR (KBr): 3430, 3280, 1643, 1537, 1312 cm^{-1}. MS (FAB): 585 (M + 1, 14). Anal. calcd. $C_{32}H_{26}Cl_2N_4O_3$: C, 65.64; H, 4.48; N, 9.57. Found: C, 65.69; H, 4.47; N, 9.71.

2,5-*bis*[*m*-[(4′S)-4′-isobutyloxazolin-2′-yl]phenyl-1,3,4-oxadiazole 4a. General procedure III. To a solution of compounds **3a** (625 mg, 1.14 mmol) in MeOH (20 mL) was added the solution of NaOH (2.5 g) in water (10 mL) and stirring for 72 h at room temperature. The mixture was extracted with ethyl acetate (5 × 10 mL). The extracts were combined and washed with brine, dried over anhydrous $NaSO_4$ and filtered. The filtrate was concentrated in vacuo and the residue was separated by column chromatography on silica gel elution with CH_2Cl_2-MeOH (9:1) to afford crude product, which was recrystallized from ethyl acetate and hexane to give colorless solid **4a** 341 mg (63%). M.p. 138–140°C. $[\alpha]_D^{20} = -43.8^\circ$ (c = 1, MeOH). IR (KBr): 1680 cm^{-1}. MS (EI): 472 (M^+). ^1H NMR ($CDCl_3$): δ 0.95–0.98 (12H, t, $J = 7.0$ Hz, CH_3), 1.35–1.40 (2H, m, CH), 1.65–1.72 (2H, m, CH_2), 1.78–1.83 (2H, m, CH_2), 3.95–3.99 (2H, t, $J = 8.0$ Hz, CH_2), 4.29–4.33 (2H, $J = 7.8$ Hz, CH), 4.47–4.51 (2H, t, $J = 8.6$ Hz, CH_2), 7.44–7.48 (2H, t, $J = 7.7$ Hz, ArH), 7.99–8.00 (2H, d, $J = 7.6$ Hz, ArH), 8.06–8.08 (2H, d, $J = 7.6$ Hz, ArH), 8.44 (2H, s, ArH). Anal. calcd. $C_{28}H_{32}N_4O_3$: C, 71.16; H, 6.82; N, 11.86. Found: C, 71.31; H, 6.99; N, 11.63.

2,5-*bis*[*m*-[(4′S)-4′-isopropyloxazolin-2′-yl]phenyl] -1,3,4-oxadiazole 4b. Compound **4b** was synthesized according to the general precedure III

employing the **3b** (400 mg, 0.77 mmol) and NaOH (2 g) to give the colorless solid 243 mg (71%), M.p. 143–145°C. $[\alpha]_D^{20} = -57.2^\circ$ ($c = 1$, MeOH). IR (KBr): 1680 cm^{-1}; MS (EI): 444 (M^+). ^1H NMR ($CDCl_3$): δ 0.97 (6H, d, $J = 6.8$ Hz, CH_3), 1.07 (6H, d, $J = 6.6$ Hz, CH_3), 1.82–1.98 (2H, m, CH), 4.10–4.25 (4H, m, CH_2), 4.43–4.55 (2H, m, NCH), 7.60 (2H, t, $J = 7.8$ Hz, ArH), 8.16 (2H, dd, $J = 1.4$, 7.8 Hz, ArH), 8.31 (2H, dd, $J = 1.4$, 7.8 Hz, ArH), 8.69 (2H, s, ArH). Anal. calcd. $C_{26}H_{28}N_4O_3$: C, 70.25; H, 6.35; N, 12.60. Found: C, 70.20. H, 6.30; N, 12.40.

2,5-*bis*[*m*-[(4′S)-4′-benzyloxazolin-2′-yl]phenyl]-1,3,4-oxadiazole 4c. Compound **4c** was synthesized according to the general procedure III employing the **3c** (600 mg, 0.98 mmol) and NaOH (2 g) to afford the colorless solid in 67% yield (355 mg). M.p. 178–178.5°C. $[\alpha]_D^{20} = 53.6^\circ$ ($c = 1$, MeOH). IR (KBr): 1680 cm^{-1}; EIMS: 540 (M^+). ^1H NMR ($CDCl_3$): δ 2.76–2.82 (2H, dd, $J = 8.8$, 13.8 Hz, CH_2), 3.26–3.31 (2H, dd, $J = 5.1$, 13.8 Hz, CH_2), 4.20–4.24 (2H, dd, $J = 7.6$, 8.2 Hz, CH_2), 4.40–4.45 (2H, t, $J = 8.7$ Hz, CH_2), 4.61–4.69 (2H, m, CH), 7.22–7.34 (10H, m, ArH), 7.59–7.63 (2H, t, $J = 7.8$ Hz, ArH), 8.15–8.17 (2H, t, $J = 7.8$ Hz, ArH), 8.32–8.34 (2H, t, $J = 6.4$ Hz, ArH), 8.68–8.69 (2H, t, $J = 1.6$ Hz, ArH). Anal. calcd. $C_{34}H_{28}N_4O_3$: C, 75.54; H, 5.22; N, 10.36. Found: C, 75.34; H, 5.23; N, 10.26.

2,5-*bis*[*m*-[(4′R)-4′-phenyloxazolin-2′-yl]phenyl]-1,3,4-oxadiazole 4d. A round 100 mL round-bottom flask with a magnetic stir bar was charged with compound **3d** (0.8 g, 1.36 mmol), DMF (10 mL) and toluene (30 mL). Et_3N (1.9 mL, 13.6 mmol) was added to the reaction mixture. The solution was stirred under reflux for 12 h. After cooling to room temperature, ethyl acetate (50 mL) was added and the resulting mixture was washed saturated $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic layers was washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure. Purification of the residue by column chromatography on silica gel (ethyl acetate–petroleum ether1:3) to afford the pure colorless solid **4d** 0.51 g (72.8%). M.p. 121–122°C; $[\alpha]_D^{20} = +16.3^\circ$. ^1H NMR ($CDCl_3$): δ 4.35(2H, t, $J = 8.4$ Hz, CH), 4.87 (2H, dd, $J = 8.4$, 9.8 Hz, CH_2), 5.45 (2H, dd, $J = 8.2$, 9.8 Hz, CH_2), 7.30–7.42(10H, m, ArH), 7.63 (2H, t, $J = 7.8$ Hz, ArH), 8.25 (2H, d, $J = 7.8$ Hz, ArH), 8.35 (2H, d, $J = 7.8$ Hz, ArH), 8.78 (2H, s, ArH). IR (KBr): 3029, 2996, 2876, 1644, 1602, 15441475, 1451, 1363, 1315, 1260, 1070 cm^{-1}. FAB MS: 513 (M + 1, 100), 394 (49), 367 (**7**). Anal. calcd. $C_{32}H_{24}N_4O_3$: C, 74.98; H, 4.72; N, 10.93. Found: C, 74.99; H, 4.76; N, 10.96.

2,5-*bis*[*m*-[*N*-(2′S,3′R)-(1′,3′-dihydroxy-3′-phenylpropyl)amido]phenyl]-1,3,4-oxadiazole 5. A solution of 2,5-di-(*m*-carboxyphenyl)-1,3,4-oxadiazole **1** (3.1 g, 10.0 mmol) and $SOCl_2$ (40 mL) was refluxed for 12 h. The excess $SOCl_2$ was removed under reduced pressure, benzene (20 mL) was added and the solvent was removed again to dryness to afford the diacyl dichloride. A solution of the above diacyl dichloride in CH_2Cl_2 (100 mL) was added dropwise to the suspension of (1*R*, 2*S*)-(-)-2-amino-1-phenyl-1,3-propanediol (3.26 g, 19.5 mmol) and Et_3N (7.5 mL) in CH_2Cl_2 (100 mL) at 0°C and then stirring at room temperature for 36 h. The precipitate was filtered and washed with dichloromethane and diethyl ether to afford the colorless solid 3.89 g (65.6% yield). The mother solution was washed with water, dried over Na_2SO_4 and concentrated to give 0.32 g of the starting material amino alcohol. Based on recovered starting material, the total yield of was 69%. m.p. 240–242°C. $[\alpha]_D^{20} = +110.9^\circ$ ($c = 0.1$, MeOH). ^{1}H NMR (DMSO): δ 3.38–3.46 (2H, m, OH), 3.58–3.69 (2H, m, OH), 4.23 (2H, m, CHN), 4.77 (2H, t, $J = 5.4$ Hz, $HOCH_ACH_B$), 4.94 (2H, t, $J = 4.8$ Hz, $HOCH_ACH_B$), 5.51 (2H, d, $J = 5.2$ Hz, CHPh), 7.16–7.40 (10H, m, ArH), 7.71 (2H, t, $J = 8.0$ Hz, ArH), 8.04 (2H, d, $J = 8.2$ Hz, ArH), 8.20 (2H, d, $J = 9.0$ Hz, NH), 8.26 (2H, d, $J = 7.8$ Hz, ArH), 8.51 (2H, s, ArH). IR (KBr): ν 3333, 3062, 3032, 1624, 1606, 1550, 1490, 1042 cm^{-1}. FAB MS: m/z 609(M + 1, 6), 181 (100). Anal. calcd. $C_{34}H_{32}N_4O_7$: C, 67.09; H, 5.30; N, 9.21. Found: C, 66.94; H, 5.13; N, 9.01.

2,5-*bis*[*m*-[(4′S)-4′-((1R)-1-phenyl-1-hydroxymethyl)oxazolin-2′-yl]phenyl]-1,3,4-oxadiazole 6a. To a solution of diamide **5** (3.09 g, 5.08 mmol) and dry Et_3N (9.8 mL, 70.7 mmol) in $CHCl_2$ (70 mL) was added *p*-methyl benzenesulfonyl chloride *p*-TsCl (2.94 g, 15.4 mmol) at room temperature under nitrogen. The reaction mixture was kept at reflux for 12 h. After addition of 4 mL of water the solution was heated to reflux for 1 h. The cold reaction mixture was then extracted with water (3 × 30 mL). The organic layer was dried over anhydrous $NaSO_4$, and filtered. The filtrate was concentrated in vacuo to afford the crude product 2.64 g (90.8%). The crude product was purified by column chromatography on silica gel (chloroform–ethyl acetate 1:1) to afford colorless solid 1.72 g (59.2%). M.p. 189–189.5°C. $[\alpha]_D^{20} = +113.0^\circ$ ($c = 0.1$, MeOH). ^{1}H NMR ($CDCl_3$): δ 3.59 (2H, s, OH), 4.16–4.37 (4H, m, CH_2O), 4.55–4.65 (4H, m, CHN + HPh), 7.31–7.47 (10H, m, ArH), 7.59 (2H, t, $J = 7.8$ Hz, ArH), 8.15 (2H, d, $J = 8.0$ Hz, ArH), 8.29 (2H, d, $J = 7.8$ Hz, ArH), 8.68 (2H, s, ArH). IR (KBr): ν 3250, 3088, 3027, 1640, 1602, 1543, 1479, 1381, 1081, 967 cm^{-1}. FAB MS: m/z 573 (M + 1, 43), 217 (10), 91 (100). Anal. calcd. $C_{34}H_{28}N_4O_5$: C, 71.31; H, 4.93; N, 9.78. Found: C, 71.22; H, 4.86; N, 9.57.

2,5-*bis*[*m*-[(4′S)-4′-((1R)-1-methylcarboxy-1-phenylmethyl)oxazolin-2′-yl]-phenyl]-1,3,4-oxadiazole 6b. To a suspension of bisoxazoline **6a** (202.5 mg, 0.43 mmol), triethylamine (0.28 mL, 1.5 mmol) and 4-dimethylaminopyridine (2 mg) in dichloromethane (15 mL) was added dropwise acetic anhydride (143 μL, 1.5 mmol) at 0°C. The mixture was stirred for 3 h at 0°C. After warming to room temperature, water (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers was washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure. Purification of the residue by recrystallization from ethyl acetate-petroleum ether to afford the pure colorless needles 220 mg (78.3%). M.p. 175–177°C. $[\alpha]_D^{20} = +26.3^\circ$ ($c = 0.3$, $CHCl_3$); ^{1}H NMR($CDCl_3$): δ 2.16 (6H, s, CH_3), 4.18–4.41 (4H, m, CH_2O), 4.80–4.85 (2H, m, CHN), 5.90 (2H, d, $J = 6.6$ Hz, CHPh), 7.31–7.45 (10H, m, ArH), 7.60 (2H, t, $J = 7.8$ Hz, ArH), 8.14 (2H, d, $J = 8.2$ Hz, ArH), 8.31 (2H, d, $J = 8.2$ Hz, ArH), 8.65 (2H, s, ArH). IR (KBr): ν 3070, 3025, 2912, 1728, 1655, 1605, 1546, 1475, 1375, 1235, 1056, 1029, 913, 705 cm^{-1}. FAB MS: m/z 657(M + 1). Anal. calcd. $C_{38}H_{32}N_4O_7$: C, 69.50; H, 4.91; N, 8.53. Found: C, 69.31; H, 4.99; N, 8.31.

2,5-*bis*[*m*-[(4′S)-4′-((1R)-1-methoxy-1-phenylmethyl)oxazolin-2′-yl]phenyl]-1,3,4-oxadiazole 6c. To a suspension of NaH (46 mg, 52% in mineral oil, 1 mmol) in THF (15 mL) was added bisoxazoline **6a** (202.5 mg, 0.43 mmol) in portions. The resulting mixture was heated at 36°C for 2 h. After cooling to room temperature, methyl iodide (80 μL, 1.29 mmol) was added dropwise to the above reaction mixture. The mixture was further stirred overnight. Then the solvent was removed under reduced pressure and dichloromethane was added (30 mL) to the residue. The solution was washed with 1 N HCl (10 mL), 5% $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure to give the crude product. Purification of the crude product by recrystallization cfrom ethyl acetate-petroleum ether to afford the pure colorless solid 150 mg (58.3%). M.p. 153–154°C. $[\alpha]_D^{20} = +42.5^\circ$ ($c = 0.3$, MeOH). ^{1}H NMR ($CDCl_3$): δ 3.34 (6H, s, CH_3), 4.16–4.28 (4H, m, CH_2O), 4.35 (2H, d, $J = 6.8$ Hz, CHPh), 4.68–4.75 (2H, m, CHN), 7.32–7.36 (10H, m, ArH), 7.58 (2H, t, $J = 7.8$ Hz, ArH), 8.15 (2H, d, $J = 7.8$ Hz, ArH), 8.30 (2H, d, $J = 7.8$ Hz, ArH), 8.64 (2H, s, ArH). IR (KBr): ν 3070, 2898, 2827, 1653, 1548, 1482, 1365, 1109, 1070, 978, 708 cm^{-1}. FAB MS: m/z 601(M + 1, 100), 480 (12), 437 (5). Anal. calcd. $C_{36}H_{32}N_4O_5$: C, 71.98; H, 5.37; N, 9.42. Found: C, 71.83; H, 5.46; N, 9.38.

Synthesis of 2,5-*bis*[*m*-[(4′S)-4′-isobutyloxazolin-2′-yl]phenyl]-1,3,4-oxadiazole 4a via 'one pot' method. To a solution of 2,5-di-(*m*-carboxylphenyl)-1,3,4-oxadiazole **1** (310 mg, 1 mmol) in CH_3CN (50 mL) and DMF (30 mL) was added the *S*-leucinol (234 mg, 2 mmol), Ph_3P (1 g), CCl_4 (2 mL), Et_3N (2 mL), and pyridine (15 mL) respectively and stirring for 12 h at room temperature. The reaction mixture was concentrated in vacuo progressively and filter out triphenyl phosphine oxide step by step. The filtrate was separated further by column chromatography on silica gel eluted with CH_2Cl_2–MeOH (10:1) to give crude product, which was recrystallized from ethyl acetate and hexane to afford colorless solid **4a** in 38% yield (179 mg). Compounds **4b–d** were also obtained employed 'one pot' method according to the same procedure.

ACKNOWLEDGMENT

This work was supported by the National Natural Science Foundation of China (Grant No. 20172001).

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Received in the Netherlands November 14, 2002