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

The Synthesis of Chiral Macrocyclic Ligands Containing A 2,5-Bisphenyl-1,3,4-Oxadiazole Unit

Hongwu Zhao [a] & Wenting Hua [a]
[a] Department of Chemistry , Peking University , Beijing, 100871, P.R., China
Published online: 04 Dec 2007.

To cite this article: Hongwu Zhao & Wenting Hua (2000) The Synthesis of Chiral Macrocyclic Ligands Containing A 2,5-Bisphenyl-1,3,4-Oxadiazole Unit, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 30:16, 2923-2931, DOI: 10.1080/00397910008087442

To link to this article: http://dx.doi.org/10.1080/00397910008087442

SYNTHETIC COMMUNICATIONS, 30(16), 2923–2931 (2000)

THE SYNTHESIS OF CHIRAL MACROCYCLIC LIGANDS CONTAINING A 2,5-BISPHENYL-1,3,4-OXADIAZOLE UNIT

Hongwu Zhao and Wenting Hua*

Department of Chemistry, Peking University, Beijing 100871, P. R. China

Abstract Six new chiral 2,5-bisphenyl-1,3,4-oxadiazole-containing macrocylic ligands, which can be used to recognize the enantiomers of D- and L-amino acid methyl ester hydrochloride, have been synthesized and characterized.

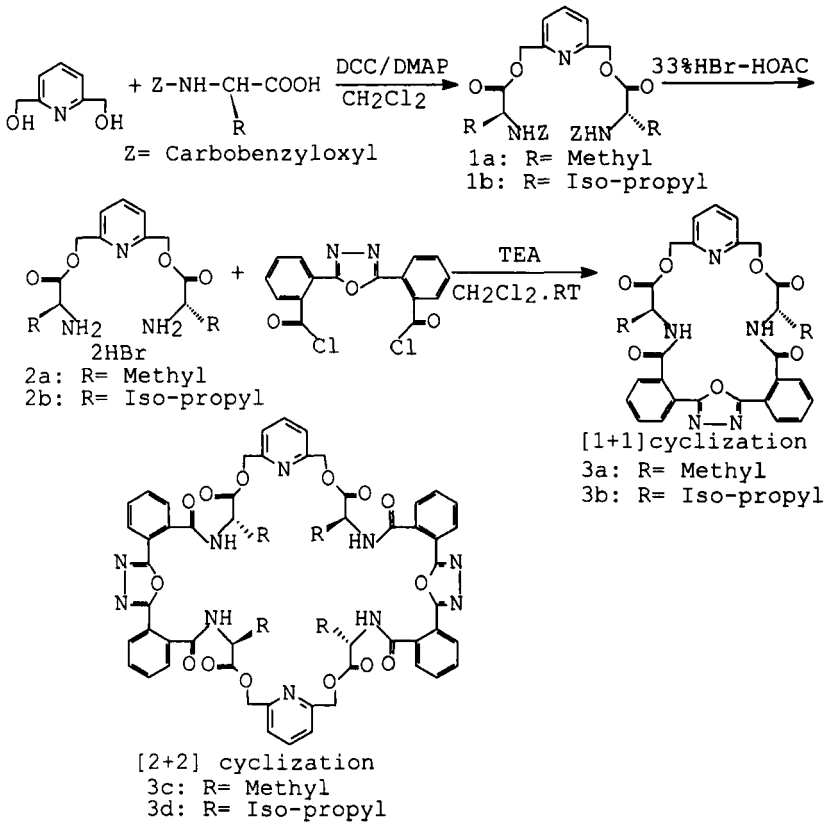
Chiral recognition of single enantiomers of amino acids, sugars, and other bio-relevant substrates such as peptides and nucleotides, by biological macromolecules occurs in many biochemical processes. It is a fundamental property of biological systems. Since Cram and his coworkers[1-3] first used chiral crown ethers to recognize enantiomers of chiral organic ammonium salts, many different artificial chiral macrocyclic ligands which are capable of recognizing other chiral species have been successfully used in enantiomeric separation,[4-5] asymmetric catalysis,[6-7] enzymatic mimics,[8-9] and other areas involving chiral recognition interactions. It has been demonstrated that in-built configurational

*To whom correspondence should be addressed.

rigidity of chiral macrocyclic ligands and hydrogen bonding interaction between host and guest play a key role in chiral recognition,[10-12] and some of these chiral macrocyclic ligands contain various subcyclic units such as pyridine, triazole and macrocycles incorporating twisted aromatic moieties.

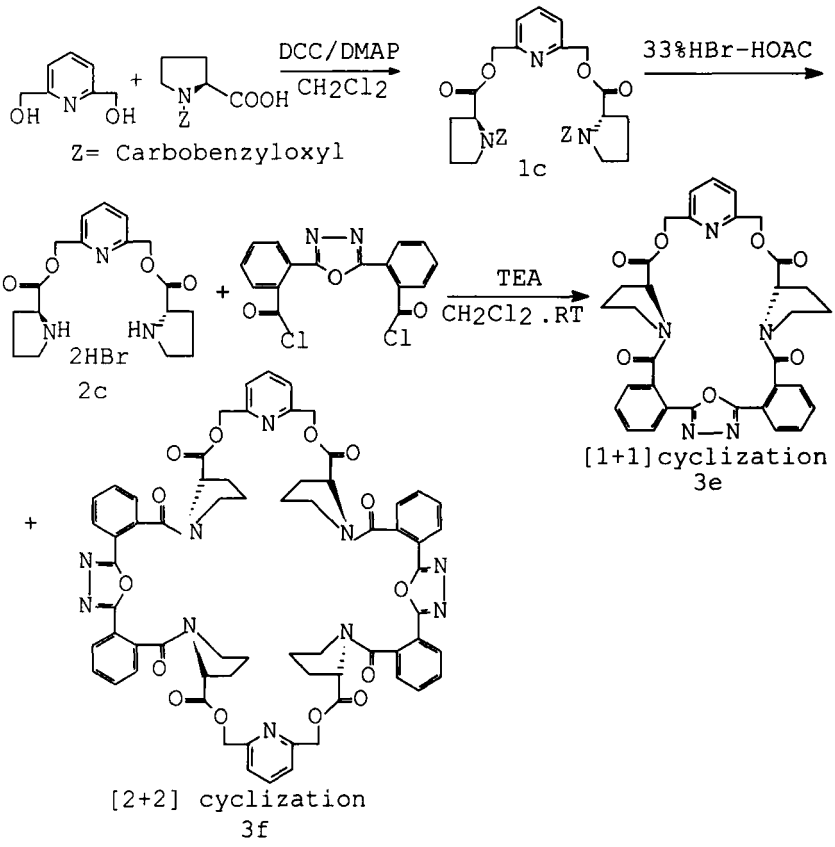
In this paper, we report the design and synthesis of a series of novel chiral polyamide-polyester macrocyclic ligands containing 2,5-bisphenyl-1,3,4-oxadiazole and pyridine subcyclic units which make the configuration of the synthetic

Schemel. The preparation of chiral ligands 3a, 3b, 3c and 3d



macrocyclic receptors rather rigid. In addition, amide, ester and pyridine groups present in the periphery of these chiral macrocyclic ligands can possibly serve as hydrogen-bond donors and acceptors. Studies on the enantiomeric recognition of D- and L-amino acid methyl ester hydrochlorides by these synthetic chiral macrocycles are underway. The synthetic route and structures are shown in schemes I and II.

SchemeII. The preparation of chiral ligands 3e and 3f



The chiral intermediates 1a, 1b and 1c, needed for the preparation of the chiral macrocycles, were obtained from the condensation of corresponding Z-N-amino acids and 2,6-bis-hydroxymethyl pyridine in the presence of DCC and DMAP. The cyclization conditions significantly affect the yield of product. High dilution and dropwise addition of the 2,5-bis(o-chloroformyl phenyl)-1,3,4-oxadiazole at 0°C are necessary for obtaining the desired products.

Experimental Section

Infrared spectra were obtained on Bruker VECTOR22. ^{1}HNMR spectra were recorded on a Bruker ARX 400 spectrometer. Chemical shifts are indicated in δ values (ppm) downfield from internal TMS. Multiplicities were recorded as s (singlet), d (doublet), t (triplet) and m (multiplet). FAB-mass spectra were obtained on a VG-ZAB-HS mass spectrometer. Elemental analysis was carried out on Carlo-Erba-106 or Elementar Vario EL instruments. Melting points were taken on a XT-4 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Commercial grade solvents were used without further purification unless specified. CH_2Cl_2 was distilled from calcium hydride. Starting materials were purchased from the Acros chemical company unless otherwise noted. The 2,6-pyridinedimethanol and 2,5-bis(o-chloroformylphenyl)-1,3,4-oxadiazole were prepared as reported[13,14].

Preparation of N-carbobenzyloxyl-L-alanine diester 1a

In dry CH_2Cl_2 (75ml) were dissolved 2.6- pyridinedimethanol(500mg, 3.6mmol), N-carbobenzyloxyl-L-alanine, (1.8g,8mmol), 4-dimethylaminopyridine (DMAP)

(200mg, 1.62 mmol) and 1.3-dicyclohexylcarbodiimide (DCC) (1.7g,8.16mmol). After the reaction was stirred overnight at room temperature,the resulting white suspension was filtered. The filtrate was evaporated. The residue was chromatographed on silica gel using petroleum/ethyl acetate (1/1) as eluent to give a colorless oil(1.5g); yield: 75.8%.$[\alpha]_D^{25}$= -15.5 (c=1, CH_2Cl_2).^{1}HNMR: δ 7.8(m,3H), 7.3 (m, 10H), 5.2(m, 4H), 5.0(s, 4H), 4.2(t, 2H), 1.3(d,6H). IR(KBr) : 3349, 1746, 1688, 1532, 1456, 1261, 1076cm^{-1}. MS(FAB$^+$): M/Z=550(M+H)$^+$. Anal. $C_{29}H_{31}N_3O_8$ (549): Calcd: C63.38, H5.69, N7.65, O23.28. found:C63.08, H5.89, N7.78, O23.25.

Preparation of N-carbobenzyloxyl-valine diester 1b

1b was prepared as described above, colorless oil. yield: 92%.$[\alpha]_D^{25}$= -12.6 (c=1, CH_2Cl_2) ^{1}HNMR: δ 7.8(m, 3H), 7.3(m, 10H), 5.2 (m, 4H),5.0(m, 4H), 4.0(m, 2H), 2.11(m, 2H), 0.9(d, 12H). IR(KBr) : 3371, 2966, 1712, 1592, 1526, 1459, 1227, 1192, 1044cm^{-1}. MS(FAB)$^+$: M/Z=606(M+H). Anal. $C_{33}H_{39}N_3O_8$(605): Calcd: C65.44, H6.49, N6.94, O21.13. Found: C65.29, H6.54, N 6.90, O21.27.

Preparation of N-carbobenzyloxyl-L-proline diesters 1c

1c was prepared as described above. colorless oil; yield: 92.4%. $[\alpha]_D^{25}$=-81.0 (c=1, CH_2Cl_2). ^{1}H NMR δ 7.26-7.56(m, 13H), 5.27(d,2H), 5.11(m,6H), 4.51(m,2H), 3.64(m,4H), 2.26(wd, 2H), 2.11(ws,2H), 1.95(m,4H). IR (KBr) 3328, 2943, 1751, 1705, 1416, 1352, 1169cm^{-1}. MS(FAB$^+$)=602(M+H)$^+$. Anal. $C_{33}H_{35}N_3O_8$(601):CalcC65.88, H5.86, N6.98, O21.28. found:C66.18, H5.89, N7.22, O20.98.

Preparation of L-alanine diester diamine dihydrobromide 2a

In 10ml 33% HBr-HOAc was dissolved N-carbobenzyloxyl-L-alanine diester (1g,

1.8mmol), the mixture was stirred at room temperature for two hours, and the solution was concentrated to dryness. After that, 10ml anhydrous ethyl ether was added to the residue, then the mixture was stirred for another one hour, and filtered to give a light yellow powder 0.80g(100%). yield: ca 100%. MS(FAB^+): M/Z = 282$(M+H)^+$. ^{1}HNMR: δ8.43(brs,6H), 7.93(t,1H), 7.46(d,2H), 5.31(m,4H), 4.27 (t,2H), 1.49(d,6H).IR(KBr):3416, 2931, 2560, 1764, 1628, 1512, 1235, 1186, 1117cm^{-1}.

Preparation of L-valine diester diamine dihydrobromide 2b

2b was prepared as described above. Light yellow solid. Yield: ca 100%.MS (FAB^+):M/Z=338$(M+H)^+$. ^{1}HNMR: δ8.43(brs,6H), 7.93(t,1H), 7.52(m,2H), 5.36(m,4H), 4.06(brs,2H), 2.23(m,2H), 1.06(m,12H). IR(KBr): 3426, 2968, 1748, 1629, 1510, 1465, 1289, 1215, 1162, 1041cm^{-1}.

Preparation of L-proline diester diamine dihydrobromide 2c

2c was prepared as described above. Light yellow solid. yield: ca 100%. MS(FAB^+): M/Z=334$(M+H)^+$. ^{1}HNMR: δ 9.61(brs, 2H), 8,99(brs, 2H), 7.93(t, 1H), 7.49(d, 2H), 5.34(m, 4H), 4.55(m, 2H), 3.25(m, 4H), 2.31(m, 2H), 2.10(m,2H), 1.96(m, 4H). IR(KBr) : 3416, 2925, 2548, 1889, 1753, 1649, 1626, 1569, 1390, 1241, 1196, 1063cm^{-1}.

Preparation of chiral macrocyclic ligands 3a.3c.

A solution of freshly prepared 2,5-bis(o-chloroformylphenyl)-1,3,4-oxadiazole 0.316g (0.9 mmol) in dry dichloromethane(10ml) was added dropwise to well-stirred solution of diester diamine dihydrobromide 2a 0.4g(0.9mmol) and triethylamine(TEA) 0.6ml(3.7mmol) in dry CH_2Cl_2 (120ml) at 0^0C over half an

hour. The reaction mixture was stirred for additional 12hrs at room temperature. The resulting white suspension was filtered. The filtrated was evaporated. The residue was chromatographed on silica gel using dichlormethane/ethyl acetate/petroleum ether/methanol (2/1/0.1/0.2) as eluent to give a white solid 3a 0.1g(19.8%), and white solid 3c 20mg (1.98%) simultaneously.3a: $[\alpha]_D^{25}$=+14.05 (c=1,CH_2Cl_2). m.p.208-210°C. ^{1}HNMR: δ8.81(d,2H), 7.86(m,2H), 7.71(m,7H), 7.28(d,2H), 5.10(d,2H), 4.79(d,2H), 4.50(t,2H), 1.37(d,6H) IR(KBr):3478, 3066, 1744, 1651, 1540, 1455, 1345, 1250, 1203, 1168, 1059cm^{-1}. MS(FAB$^+$): M/Z =556(M+H)$^+$. Anal. $C_{29}H_{25}N_5O_7 \cdot 0.5H_2O$(564). Calcd: C61.70, H4.60, N12.41, O21.29. Found: C61.96, H4.61, N12.39, O21.31.

3c: $[\alpha]_D^{25}$=+11.6(c=1,CH_2Cl_2). m.p.196-198°C. ^{1}HNMR: δ 9.0(d,4H), 7.89(m,4H), 7.63(m,14H), 7.27(d, 4H), 5.11(s, 8H), 4.59(t, 4H), 1.37(d, 12H). IR(KBr):3423, 3067, 2934, 1744, 1652, 1598, 1536, 1457, 1169cm^{-1}. MS(FAB$^+$): M/Z=1111(M+H)$^+$. Anal. $C_{58}H_{50}N_{10}O_{14}H_2O$(1128). Calcd: C61.70, H4.60, N12.41, O21.29. Found: C61.55, H4.39, N12.38, O21.60.

Preparation of chiral macrocyclic ligands 3b, 3d.

3b, 3d were prepared as described above.

3b: white solid. Yield:10.8%. $[\alpha]_D^{25}$= +36.72(c=1, CH_2Cl_2). m.p 130-132^{0}C. ^{1}HNMR: δ 8.54(d,2H), 7.82(t,2H), 7.68(m,7H), 7.24(d,2H), 5.11(d,2H), 4.75(d,2H), 4.36(t, 2H), 2.19(m, 2H), 1.0(m,12H). IR(KBr): 3446, 3065, 2965, 1743, 1653, 1540, 1466, 1317,1252,1188,1159cm^{-1}. MS(FAB$^+$):M/Z=612(M+H)$^+$. Anal.$C_{33}H_{33}N_5O_7 \cdot 0.5H_2O$ (620). Calcd: C63.87, H5.48, N11.29, O19.35. Found: C64.00, H5.58, N11.00, O19.42.

3d: white solid. Yield:4.54%. $[\alpha]_D^{25}$=-48(c=1, CH_2Cl_2). m.p 206-208°C. ^{1}HNMR: δ 8.68(d,4H), 7.8(m,6H), 7.62(m,12H), 7.54(m,4H), 5.16(m,8H), 4.45(m,4H), 2.17(m,4H), 1.22 (m,24H). IR(KBr):3422, 2964, 2927, 1741, 1645, 1534, 1468, 1189cm^{-1}. MS(FAB$^+$): M/Z=1223(M+H)$^+$. Anal.$C_{66}H_{33}N_{10}O_{14}\cdot 1.5H_2O$(1249). Calcd: C63.41, H5.52, N11.20, O19.87. Found: C63.51, H5.55, N11.27, O19.67.

Preparation of chiral macrocycle ligands 3e, 3f

3e, 3f were prepared as described above.

3e:white solid. yield:20.3%. $[\alpha]_D^{25}$=-75(c=1, CH_2Cl_2). m.p178-180°C. ^{1}HNMR δ 7.99(d,1H), 7.73(m,5H), 7.50(m,4H), 7.36(d,1H), 5.30(d,1H), 4.91(d,1H), 4.8(m,2H), 4.42(m,1H), 4.03(m,1H), 3.64(m,4H) 1.98(m,8H). IR(KBr): 3446, 2953, 2881, 1747, 1638, 1449, 1420, 1175, 1091, 1037 cm^{-1}. MS(FAB$^+$): M/Z=608(M+H)$^+$. Anal. $C_{33}H_{29}N_5O_7\cdot 0.5H_2O$(616): Calcd: C64.28, H4.87, N11.36, O19.48. Found: C64.58, H4.96, N11.14, O19.32.

3f: white solid. yield:2.0%. $[\alpha]_D^{25}$=-46.7(c=1,CH_2Cl_2). m.p 258-260°C. ^{1}HNMR δ 8.05(d,4H),7.71(m,14H),7.33(m,4H),5.13(m,8H),4.59(t,4H),3.19(t,8H),1.85(m,16 H). IR(KBr): 3446, 2953, 2881, 1747, 1638, 1449, 1420, 1175, 1091, 1037. MS(FAB$^+$): M/Z=1215(M+H)$^+$. Anal. $C_{66}H_{58}N_{10}O_{14}\cdot H_2O$(1232): Calcd: C64.28, H4.87, N11.36, O19.48. Found: C64.43, H4.88, N11.26, O19.43.

References

1. Cram, D. J. *Science*, **1988,** *240, 760.*
2. Gokel,G. W.; Timko, J. M. and Cram, D. J. *J. Chem. Soc., Chem. Commun.*, **1975,** *394*
3. Artz, S. P.; deGrandpre, M. P. and Cram, D. J. *J. Org. Chem.*, **1985,** *50, 1486*
4. Helgson, R. C.; Koga, K.; Timko, J. M. and Cram, D. J. *J. Am. Chem. Soc.*, **1973,** *95, 3021*

5. Gasparrini, F.; Misiti, D.; Borchardt, A.; Burger, M.T. and Still, W. C. *J. Org. Chem.*, **1995,** *60, 4314*
6. O'Malley, S. and Kodadek, T. *Tetrahedron Lett.*, **1991,** *32, 2445*
7. Groves, J. T. and Myers, R. S. *J. Am. Chem.Soc.*, **1983,** *105, 5791*
8. Breslow, R.; Hammond, M. and Lauer, M. *J. Am. Chem. Soc.*, **1980,** *102, 421*
9. De Vries, J. G. and Kellogg, R. M. *J. Am. Chem. Soc.*, **1979,** *101, 2759*
10. Goswami, S.; Ghosh, K. and Dasgupta, S. *Tetrahedron,* **1996,** *52, 12223*
11. Lehn, J. M. *Angew. Chem. Int. Ed. Engl.*, **1990,** *29, 1304*
12. Perreault, D. M.; Chen, X. and Anslyn, E. V. *Tetrahedron,* **1995,** *51, 353*
13. Wllson Baker; Buggle, K.M.; Mcomie, J. E. W. and Watkins, D. A. M. *J. Chem.Soc.*, **1958,** *3594*
14. Preston, J. *Journal of Heterocyclic Chemistry,* **1965,** *2(4), 441*

Received in the UK 8/6/99