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A CONVENIENT SYNTHESIS OF CHIRAL SULFUR-CONTAINING MACROCYCLIC LIGANDS

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Abstract Eight new chiral sulfur-containing macrocyclic ligands, which can be used in chiral recognition and modificated furtherly for various uses, have been synthesized and characterized.

Chiral macrocylic ligands, which are capable of recognition other chiral species selectively and can be used potentially in seperations of enantiomers, catalysis asymmetric reactions, are greatly interesting to researchers. Since Cram and his coworkers published their pioneering studies on the use of chiral macrocylic ligands in enantiomeric recognition[1~3], many chiral macrocycles have been synthesized and used in recogniting chiral moleculers[4~5].

We have investigated sulfur-containing α-amino acids and their derivatives in the use of enantioselective reduction of aromatic ketones with borane[7,8], and our interest in macrocycles is to study chiral sulfur-containing macrocyclic ligands, which can form complex with transition metal cation and have potential application in asymmetric synthesis and chiral recognition. This paper describes the synthesis of eight new sulfur-containing chiral macrocyclic ligands starting from

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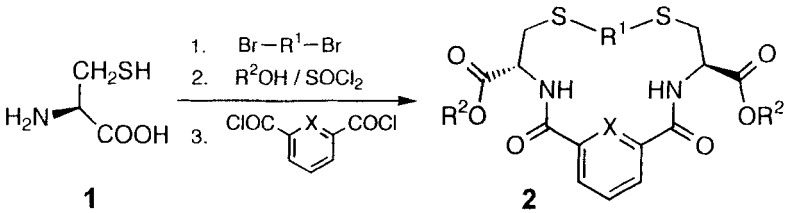
L-cysteine. Four of them contain pyridine units that can be used in chiral recognition for the enantiomers of various organic guests[5]. All of them can be reducted to β-aminoalcohols which are useful in asymmetric synthesis[9] and modificated furtherly for various uses. The synthetic route and structures are shown in scheme 1.

Scheme 1 The synthetic route and structure of the chiral macrocyclic ligands



1 2

Compound **2**	—R^1—	R^2	X
a	—CH_2CH_2—	Et	CH
b	—$CH_2CH_2CH_2$—	Et	CH
c	—$CH_2CH_2CH_2CH_2$—	Et	CH
d	—CH_2—C$_6$H$_4$—CH_2—	Me	CH
e	—CH_2CH_2—	Et	N
f	—$CH_2CH_2CH_2$—	Et	N
g	—$CH_2CH_2CH_2CH_2$—	Me	N
h	—CH_2—C$_6$H$_4$—CH_2—	Me	N

L-cysteine is a cheaply commercial material, and its mercapto can selectively reacts with bromoalkanes in very mild conditions. In the presence of $NaHCO_3$, it reacts with 1, 2-dibromoethane, 1, 3-dibromopropane, 1, 4-dibromobutane and p-xylylene bromide to form bridged bis-amino acids respectively. Because of

its difficulty and complexity to react with bis-acid chloride, it is better to trams-form these bis-amino acids to the forms of their ester.

The reaction condition significantly affects the yield of product. It should be pointed out that the highly diluted method and dropwise addition of the dibromides are necessary for getting desired products. These chiral macrocyclic ligands are easily soluble in methylene dichloried, trichloromethane, tetrahydrofuran, ethanol and sparingly soluble in water. Their structures are confirmed by MS, ^{1}HNMR, IR and elemental analysis (Table 1), The physical properties are listed in the Table 2.

Table 1. Preparation of macrocyclic ligands 2a～h

Compound	yield(%)	m. p. (℃)	$[\alpha]_D^{25}$ (0.5,CH_2Cl_2)
2a	73.9	165～168	+51.70
2b	77.8	170～173	+61.34
2c	57.9	230～232	+49.82
2d	72.8	242～244	−69.82
2e	72.0	189～191	+18.60
2f	77.0	160～163	+52.98
2g	60.8	61～64	+59.71
2h	76.8	191～193	−31.37

Experimental Section

Melting points were taken on a micro-melting apparatus and are uncorrected. Infrared (IR) spectras were obtained on Nicolet 170 sx spectrometers. MS and ^{1}HNMR spectra were recorded on a Finnigan 4510 and a JEOL FX-90 Q respec-

Table 2. MS, ^{1}HNMR, IR and Elemental Analysis of 2a～h

Compound	MS m/z(%)	^{1}HNMR($CDCl_3$,TMS)	IR(cm^{-1}) (KBr disk)	Elementary Analysis(%) C H N Found(Calculated)
2a	455(M^++1,62) 246(100)	1.25 (tr, 6H, $2CH_3$), 2.6～3.6 (br, 8H, CH_2CH_2, $2CH_2$), 4.2 (m, 4H, $2OCH_2$), 5.0 (m, 2H, 2CH), 7.4 (m, 4H, HAr), 7.8 (d, 2H, 2NH)	3255, 3062, 2991, 2880, 1742, 1650, 1605, 1584, 1211	52.66 5.80 6.63 (52.84)(5.77)(6.16)
2b	470(M^++2,100) 246(100)	1.30 (tr, 6H, $2CH_3$), 2.0 (m, 2H, CH_2), 2.5～3.5 (br, 8H, $4CH_2$), 4.25 (m, 4H, $2OCH_2$), 5.0 (m, 2H, 2CH), 7.45 (m, 4H, HAr), 7.9 (d, 2H, 2NH)	3262, 3053, 2977, 2922, 1758, 1645, 1600, 1581, 1211	53.56 6.00 5.88 (53.83)(6.02)(5.98)
2c	483(M^++1,100)	1.90 (m, 4H, CH_2CH_2), 3.1～3.7 (br, 8H, $4CH_2$), 3.85 (S, 6H, $2CH_3$), 4.1 (m, 4H, $2OCH_2$), 5.0 (m, 2H, 2CH), 7.1 (m, 4H, HAr), 8.0 (d, 2H, 2NH)	3257, 3063, 2988, 2927, 1758, 1655, 1600, 1581, 1180	55.10 6.30 5.76 (54.75)(6.27)(5.81)

2d	503(M^+,5) 104(100)	3.1～3.2(m,4H,$2CH_2$),3.70～3.73(s,4H,$2CH_2$),3.72～3.81(s,6H,$2CH_3$),4.29～4.45(m,2H,2CH), 7.20～7.50(m,8H,HAr),8.25～8.35(d,2H,2NH)	3312, 2944, 3050, 3010, 1750, 1750, 1647, 1600, 1581, 1225	53.74 5.30 5.50 (53.75)(5.21)(5.58)
2e	456(M^++1,15) 78(100)	1.27(tr,6H, $2CH_3$),3.0(m,4H, CH_2CH_2), 3.35～3.65(br, 4H,$2CH_2$),4.25(m,4H, $2OCH_2$),5.0(m,2H, 2CH), 8.0～8.4(br, 3H, HPy), 8.5(d, 2H, 2NH)	3403, 3305, 3100, 2882, 2828, 1745, 1684,1520,1186	50.33 5.65 9.09 (50.09) (5.53) (9.23)
2f	471(M^++2,27) 218(100)	1.3(tr, 6H, $2CH_3$), 1.95(m,2H, CH_2), 2.7～3.1(br, 4H, $2CH_2$),3.35～3.65(br, 4H, $2CH_2$),4.25(m,4H,$2OCH_2$), 5.0(m, 2H,2CH), 7.9～8.05(br,3H, HPy),8.87 (d, 2H,2NH)	3377, 3303, 3074, 2960, 2990, 1745, 1682, 1513,1185	51.45 5.87 8.78 (51.15)(5.80)(8.95)
2g	457(M^++2,100)	1.75,(m,4HCH_2CH_2), 3.0～3.5(m, H, $4CH_2$),3.80(s, 6H, $2OCH_3$),5.0(m,2H, 2CH), 8.0～8.5(br, 3H, HPy), 8.7(d, 2H,2NH)	3335, 3001, 2951, 2927, 1746, 1681, 1521,1175	50.31 5.65 9.05 (50.09)(5.53)(9.23)
2h	504(M^+,57) 104(100)	3.05～3.15(m,4H,$2CH_2$),3.67～3.70(s, 4H, $2CH_2$),3.70～3.80(s, 6H, $2OCH_3$), 4.30～4.50(m,2H,2CH), 7.1～7.3(m, 4H,HAr),7.7～8.1(m,3H,HPy),8.3～8.4(d, 2H,2NH).	3355, 3276, 3050, 2850, 2825, 1755, 1655,1521,1255	54.72 5.04 8.30 (54.85)(5.00)(8.35)

tively. Elemental analysis were performed with a Carlo-Erba-1106 instruments. Optical rotations were taken on a WZZ-1 polarimeter. L-cysteine hydrogen chloride were purchased from Sino-American Biotechnology Company for use without purifed further. The p-xylylene bromide, benzene-1, 3-biscarbonyl chloride and pyridine-2, 6-biscarbonyl were prepared according the routine methods. Methylene dichloride, trichloromethane were purified according standard methods. All other chemicals and reagents were obtained commercially and used without further purification.

General procedure for preparation of chiral macrocyclic ligands 2a～h:

The preparation of bis-amino acids: 20 mmol(3.2 g) L-cysteine hydrochloride was dissolved in a solution of 160 mL water and 20 mL ethanol, and 40 mmol (3.3 g) $NaHCO_3$ was added slowly in stirring. A solution of 10 mmol dibromides in 20 mL ethanol was dropwise within 30 min and stirring continued for 6 ～12 hours at room temperature or at 70～90℃ for one hour. The mixture was cooled in ice bath and the precipitate filtered off and washed with water, ethanol, ether and dried to gain bridged ammino acids.

The preparation of the esters of bis-aminoacies: The bridged amino acids were suspended in 50 mL ethanol or methanol and cooled to the temperature of 0℃ in ice bath, 2 mmol (2.38g) $SOCl_2$ was added dropwise in stirring. The mixture was stirred at the same temperature for one hour and then at 80℃ for another 3 ～6 hours. The solvent was evaporated under vacuum to give the ester of bridged amino acids hydrochloride.

The preparation of macrocyclic ligands 2a～h: 2 mmol ester was added to a solution of 250 mL dry CH_2Cl_2($CHCl_3$) and 4 mmol (0.43g) Na_2CO_3, and the mix-

ture was stirred for 3～5 hours. Benzene 1, 3-bisdicarbonyl chloride (or pyridine 2. 6-bisdicarbonyl chloried) 1 mmol in 25 mL CH_2Cl_2 was dropwised. When the reaction was completed as monitored by TLC, water 10 mL was added and organic layers were seperated and the aqueous phase was extracted twice with 25 mL methylene dichloride, the combined organic phase were washed with brine and dried over anhydrous magnesium sulfate. The filtered solution was evaporated under reduced pressure and the raw products was chromatographed on silica gel using ethyl acetate/petroleum ether 2/1 (v/v) as eluants to gain products.

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