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Synthesis of Novel C_2-Symmetric Chiral Polyamide Macrocycles Containing Pyridyl Side-arm

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Abstract: Three novel C_2-symmetric macrocycles containing pyridyl units have been prepared by the cyclic condensation of chiral diamide intermediates with 2,6-pyridinedicarbonyl dichloride in highly diluted solution at room temperature.

Keywords: Synthesis, macrocycles, chiral, pyridine.

The design and synthesis of different kinds of synthetic macrocycles and studies on molecular recognition, stereoselective catalysis and specific photoelectric property have been one focus in the fields of life science and material science[1-3]. Among them, optical active macrocycles as receptors for enantioselective recognition have particularly attracted much attention[4].

Here, we describe the synthesis of three chiral macrocycles **4**-**6**, which have C_2-symmetry axis and their chirality comes from *L*-amino acids derivatives. Pyridine units as building blocks are incorporated into the ring structure and side-arm, not only providing proton acceptor at the pyridyl nitrogen but also bringing rigidity into the ring. All the structural characteristics make macrocycles offer a chiral environment for selectively binding guest organic compounds.

The synthesis of macrocycles **4**-**6** was shown in **Scheme 1.** The tosylamine was transformed into sodium salt, then reacted with 2,6-bis(bromomethyl)pyridine to give compound **1**. Followed detosylation in concentrated H_2SO_4, the desired 2, 6-bis(N -picolylaminomethyl)pyridine **2** was condensed with Z-valine in the presence of DCC to give compound **3**. It should be noticeable that Z-valine must be mixed with DCC for 0.5 h to form symmetric anhydride before the addition of compound **2** to the mixture. Subsequently, compound **3** was deprotected in 33% HBr-HAc, and then the obtained diamine dihydrobromide was condensed with 2, 6-pyridinedicarbonyl dichloride in highly diluted solution (10^{-3} mol/L) at room temperature for 12 h under the existence of Et_3N. After separation by silica gel column chromatography with the eluent ($CHCl_3$: MeOH = 30:1), three new chiral macrocycles **4**, **5**, **6** were obtained in yields of 15.6%, 5.1% and 3.7%, which were the products of [1+1], [2+2] and [3+3] cyclization

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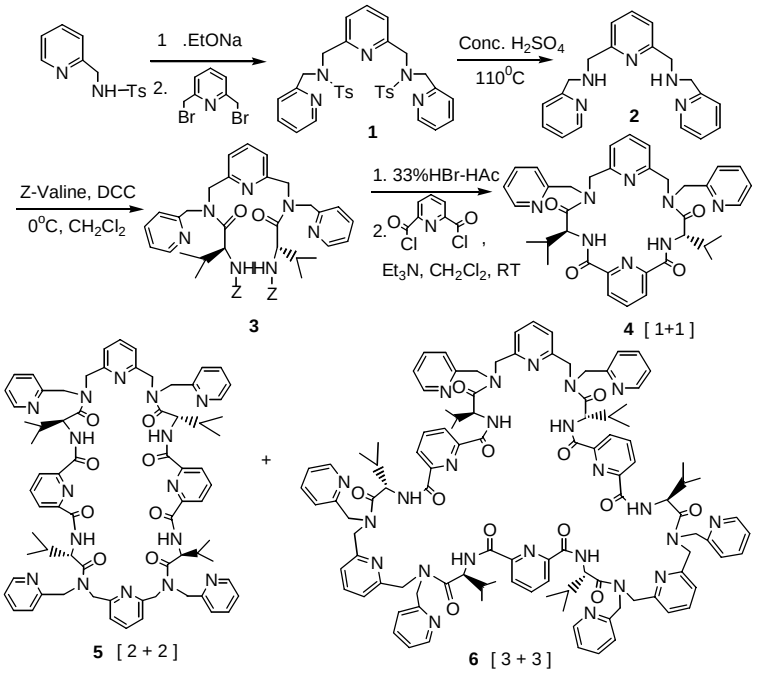
respectively. To our knowledge, the product **6** as a 54-membered macrocycle was seldom reported previously. The structures of the new chiral macrocycles were confirmed by a combination of ^{1}HNMR, MS, IR and elemental analysis[5].

Scheme 1 Synthetic route of macrocycles



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5. Spectral data for compounds **4-6**: **4**: m.p.150-151^{0}C, $[\alpha]_D^{20}$ = -104.32 (c 1.1, $CHCl_3$); FABMS: *m*/*z* = 649 $(M+H)^+$; IR (KBr, ν, cm^{-1}): 3452, 2926, 1669, 1593, 1437, 1323, 1220; ^{1}HNMR ($CDCl_3$): δ 8.16 (d, 2H, *J* = 0.011), 8.05(d, 2H, *J* = 0.019), 7.90 (t, 1H, *J* = 0.019), 7.67 (t, 2H, *J* = 0.019), 7.36 (m, 2H), 7.19 (m, 2H), 6.56 (m, 3H), 5.71 (d, 2H, *J* = 0.038), 4.92-4.09 (m, 8H), 2.57 (m, 2H), 0.98 (d, 12H, *J* = 0.017); Anal. Calcd.(%) for $C_{36}H_{40}N_8O_4$: C, 66.65; H, 6.21; N, 17.27, Found: C, 66.47; H, 6.23; N, 17.13. **5**: m.p.136-138^{0}C, $[\alpha]_D^{20}$ = +7.87 (c 2.7, $CHCl_3$); FABMS: *m*/*z* = 1297 $(M+H)^+$; IR (KBr, ν, cm^{-1}): 3455, 2966, 2352, 1645, 1523, 1434, 1330, 1173; ^{1}HNMR ($CDCl_3$): δ 8.53-7.00 (m, 28H), 5.29-4.03 (m, 20H), 2.37 (m, 4H), 1.01 (m, 24H); Anal. Calcd.(%) for $C_{72}H_{80}N_{16}O_8 \cdot H_2O$: C, 65.73; H, 6.28; N, 17.04, Found: C, 65.59; H, 6.31; N, 17.02. **6**: m.p.134-136^{0}C, $[\alpha]_D^{20}$ = +23.9 (c 1.1, $CHCl_3$); MS(MALDI-TOF): *m*/*z* = 1945 $(M+H)^+$; IR (KBr, ν, cm^{-1}): 3470, 2966, 1641, 1525, 1432, 1330, 1212, 1170; ^{1}H NMR ($CDCl_3$): δ 8.52-7.09 (m, 42H), 5.13-4.10 (m, 30H), 2.27 (m, 6H), 0.95 (m, 36H); Anal. Calcd.(%) for $C_{108}H_{120}N_{24}O_{12} \cdot 1.5H_2O$: C, 65.74; H, 6.28; N, 17.04, Found: C, 65.67; H, 6.26; N, 16.98.

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