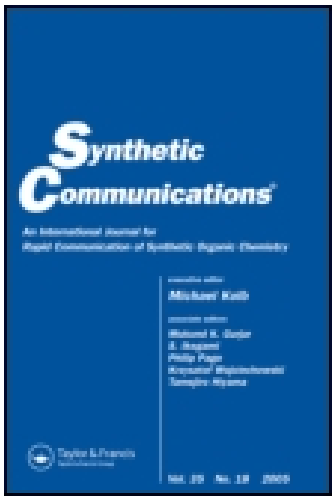

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The Synthesis of New Chiral Dioxocyclens

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The Synthesis of New Chiral Dioxocyclens

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ABSTRACT

This article reports a short and efficient synthesis of chiral dioxocyclens starting from natural amino acids. Four new chiral dioxocyclens that contain different substituents at the chiral center were obtained. These dioxocyclens could not only be used for chiral recognition, but provide a feasible way for the synthesis of chiral cyclens.

Key Words: Chiral dioxocyclens; Synthesis; Amino acids.

One of the most interesting and challenging topics is chiral recognition in the field of molecular recognition because enantiomeric recognition is a fundamental property of biological molecules. A better

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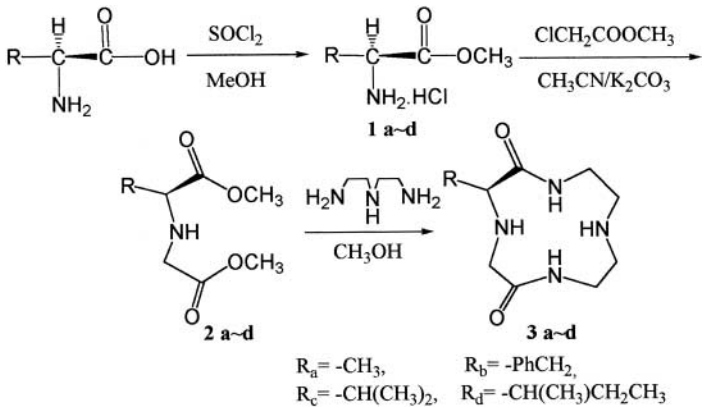
understanding of the interactions occurring in chiral recognition may help developing new methods for asymmetric synthesis and chromatographic resolution of enantiomers.[1]

Many kinds of host molecules, such as natural amino acids, cyclodextrins and their derivatives, proteins, carbohydrates and synthetic chiral macrocycles have been used for enantiomeric recognition and separation. The synthetic chiral macrocyclic compounds have been recognized as successful and promising chiral selectors mainly because of their complexation ability and inherent reduced flexibility comparing to their acyclic counterparts.[2] However, the preparation of these molecules is often fraught with difficult procedures, low yields and laborious purifications. Only a few reports about the synthesis and application for chiral perazamacrocycles appeared.[3]

We have previously reported the synthesis of chiral macrocyclic dioxopolyamine derived from L-proline.[4] NMR experiments were undertaken to assess the chiral recognition property of these compounds.[5] The results revealed that these chiral macrocyclic dioxopolyamines have different enantiomeric discrimination abilities to the mandelic acid and its derivatives. It suggested that this type of dioxocyclens might be promising hosts for enantiomeric recognition, especially for neutral molecules that contain carboxylic group.[6] Here, we report the synthesis of four new dioxocyclens derived from other amino acids. The synthetic route to compound **1–3** is shown in Sch. 1.

The use of amino acids as building blocks not only allows a convenient introduction of chiral unit into macrocyclic ring, which is



Scheme 1.

expected to gain more steric rigidity at chiral carbon that may be helpful in chiral recognition, but different substituents at the chiral center will help to know more about chiral recognition mechanism. Furthermore, amino acids could provide charged and polar functionalities, which improves water-solubility and provides sites for hydrogen-bonding or π–π interaction.

This synthetic approach has some advantages as that all products were synthesized without *N*-protection. Mild conditions were chosen to synthesize the intermediates **2** and only mono-substituted products were obtained.

EXPERIMENTAL

General Methods

Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on Varian Mercury VX300 FT-NMR spectrometer (Varian, USA) operating at 298K. Chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane (TMS). ^{13}C NMR spectra were recorded at 75 MHz on the same instrument in $CDCl_3$. Mass spectra were recorded on ZAB 3F-HF spectrometer. Optical rotations were measured with a Perkin–Elmer Model 341LC polarimeter using the sodium D line at 589 nm.

L-Amino acids were purchased from Shanghai Chemical Reagents Company, China National Medicines Group.

N-Methoxycarbonylmethyl-L-alanine Methyl Ester (**2a**)

L-Alanine (4.45 g, 0.050 mol) was converted to L-alanine methyl ester hydrochloric salt (**1a**) as described in literature.[7] Then methyl chloroacetate (5.43 g, 0.050 mol) and the L-alanine methyl ester were added to a suspension of anhydrous K_2CO_3 (10 g) in CH_3CN (75 mL), stirred at 50°C for 2 days in the atmosphere of nitrogen. The precipitate was filtered off and the filtrate was concentrated under reduced pressure, a colorless oil *N*-methoxyl carbonylmethyl-L-alanine methyl ester **2a** was obtained by distillation in vacuo, 5.10 g (yield 58%), ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.17$–4.30 (q, 1H, HNC*H*CO), 3.70 (s, 6H, 2OCH_3), 3.36–3.52 (q, 2H, HNCH_2CO), 2.69 (br, 1H, N*H*), 1.33–1.39 (d, 3H, CH_3). **2b–2d** were prepared by the same method as that described for **2a**.

***N*-Methoxycarbonylmethyl-L-phenylalanine methyl ester (2b): 2b** was given as a yellow oil, 9.51 g (yield 66%), ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.17$–7.31 (m, 5H, Ph), 3.66–3.67 (2s, 6H, $2OCH_3$), 3.57–3.60 (t, 1H, HNC*H*CO), 3.30–3.46 (q, 2H, HNCH_2CO), 2.96–3.03 (m, 2H, PhCH_2).

***N*-Methoxycarbonylmethyl-L-valine methyl ester (2c): 2c** was given as a colorless oil, 8.50 g (yield 84%), ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 3.74–3.75 (2s, 6H, $2OCH_3$), 3.38–3.68 (q, 2H, HNCH_2CO), 3.08–3.10 (d, 1H, HNC*H*CO), 1.95–2.1 (m, 1H, C$H(CH_3)_2$), 0.96–0.98 (d, 6H, $2CH_3$).

***N*-Methoxycarbonylmethyl-L-ilenine methyl ester (2d): 2d** was given as a pale yellow oil, 5.72 g (yield 53%), ^{1}H NMR (300 MHz, $CDCl_3$); $\delta = 3.72$ (s, 6H, $2OCH_3$), 3.31–3.46 (q, 2H, HNCH_2CO), 3.14–3.16 (d, 1H, HNC*H*CO), 1.91 (br, 1H, N*H*), 1.69–1.74 (m, 1H, CH_2CHCH_3), 1.17–1.59 (m, 2H, $CHCH_2CH_3$), 0.90–0.93 (d, 6H, $2CH_3$).

3-Methyl-(3*S*)-1,4,7,10-tetraazacyclododecane-2,6-dione (3a): 2a (8.75 g, 0.050 mol) was dissolved in absolute MeOH (100 mL) and then added to a solution of diethylenetriamine (5.15 g, 0.05 mol) in 300 mL absolute MeOH, stirred at 40°C in nitrogen atmosphere for 5 days, then the solvent was evaporated, and the white macrocycle **3a** was afforded as white powder by recrystallization from CH_3CN. 1.04 g (yield 10%). M.p. 181–183°C, $[\alpha]_D^{20} = +23.71$ ($c = 0.8$, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.55$ (br, 1H, CON*H*), 7.38 (br, 1H, CON*H*), 3.17–3.24 (q, $^3J = 6.9$ Hz, 1H, NHC*H*CO), 3.38–3.68 (m, 4H, 2CONHCH*H*, NCH_2CO), 2.58–3.11 (m, 6H, 2CONHCH*H*, 2NHCH_2), 1.83 (br, 2H, 2N*H*), 1.34–1.36 (d, $^3J = 6.6$ Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.0$, 172.0, 62.3, 53.9, 45.3, 45.1, 38.3, 37.6, 20.6; IR (KBr, cm^{-1}): $\nu = 3424$, 3312, 3288, 3088, 2930, 1652, 1559, 1437, 1379, 1150; MS (FAB): 215 $[M+1]^+$, Anal. calcd. for $C_9H_{18}N_4O_2$: C, 50.5; H, 8.5; N, 26.2; Found: C, 50.6; H, 8.1; N, 25.4.

Compound **3b–3d** were prepared by the same method as that described for **3a**.

3-Benzyl-(3*S*)-1,4,7,10-tetraazacyclododecane-2,6-dione (3b): The crude product was recrystallization from CH_3CN to give **3b** as a white powder, 1.82 g (yield 16%). M.p. 192–194°C, $[\alpha]_D^{20} = +40.34$ ($c = 1.0$, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.54$ (br, 1H, CON*H*), 7.49 (br, 1H, CON*H*), 7.26–7.42 (m, 5H, Ph), 3.27–3.64 (m, 5H, 2CONHCH*H*, NHCH_2CO, 1H, NHC*H*CO), 3.03–3.22 (m, 2H, 2CONHC*H*H), 2.64–3.01 (m, 6H, 2NHCH_2, PhCH_2), 1.94 (br, 2H, 2N*H*); ^{13}C NMR (75 MHz, $CDCl_3$); $\delta = 173.7$, 172.0, 137.3, 129.3(2C), 127.5, 67.5, 57.3, 45.3, 45.0, 39.9, 38.4, 37.6; IR (KBr, cm^{-1}): $\nu = 3449$, 3321, 3287, 3082, 2918, 1651, 1559, 1379, 1372, 1298, 1150; MS (FAB): 291 $[M+1]^+$, Anal. calcd. for $C_{15}H_{22}N_4O_2$: C, 62.1; H, 7.6; N, 19.3; Found: C, 61.6; H, 7.3; N, 19.3.

3-Isopropyl-(3*S*)-1,4,7,10-tetraazacyclododecane-2,6-dione (3c). The crude product was recrystallization from CH_3CN to give **3c** as a white powder, 1.50 g (yield 12%). M.p. 201–203°C, $[\alpha]_D^{20} = +39.11$ ($c = 1.0$, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.69$ (br, 1H, CON*H*), 7.30 (br, 1H, CON*H*), 3.04–3.77 (m, 6H, NHCH_2CO, 2CONHCH_2), 2.67–2.99 (m, 5H, NHC*H*CO, 2NHCH_2), 1.86 (br, 2H, 2N*H*), 1.61–2.12 (m, 1H, CH_3CHCH_3), 0.97–1.05 (m, 6H, 2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.9$, 171.9, 72.5, 54.7, 45.7, 45.3, 38.1, 31.7, 19.7, 18.5; IR (KBr, cm^{-1}): $\nu = 3441$, 2926, 1654, 1562, 1384, MS (FAB): 243 $[M+1]^+$, Anal. calcd. for $C_{11}H_{22}N_4O_2$: C, 54.5; H, 9.2; N, 23.1; Found: C, 53.8; H, 9.2; N, 23.3.

3-*sec*-Butyl-(3*S*)-1,4,7,10-tetraazacyclododecane-2,6-dione (3d). The crude product was recrystallization from CH_3CN to give **3d** as a white powder, 1.47 g (yield 11%). M.p. 213–215°C, $[\alpha]_D^{20} = +22.32$ ($c = 1.0$, MeOH), ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.63$ (br, 1H, CON*H*), 7.26 (br, 1H, CON*H*), 2.98–3.71 (m, 6H, NCH_2CO, 2CONHCH_2), 2.60–2.97 (m, 5H, 2NHCH_2, NHC*H*CO), 1.72–1.78 (m, 3H, 2N*H*, CH_2CHCH_3) 1.08–1.60 (m, 2H, $CHCH_2CH_3$), 0.89–0.97 (m, 6H, 2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.1$, 172.1, 71.4, 54.7, 45.5, 45.1, 38.4, 37.9, 37.9, 25.3, 15.9, 11.6; IR (KBr, cm^{-1}): $\nu = 3443$, 3319, 3283, 2965, 1650, 1558, 1457, 1381, 1141; MS (FAB): 257 $[M+1]^+$, Anal. calcd. for $C_{12}H_{24}N_4O_2$: C, 56.2; H, 9.4; N, 21.9; Found: C, 56.0; H, 9.1; N, 21.4.

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