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Preparation of a new type of homochiral L-proline derived cyclam and their nickel(II) complexes

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Abstract

A convenient and efficient synthesis of a novel class of chiral ligands able to form stable complexes with transition metal ions is presented. Nickel(II) complexes with three ligands of this type are characterized.

Keywords: macrocycles; lactams; chiral complexes; nickel and compounds.

Polyazamacrocycles are effective for complexing most of the transition metal elements.[1] They are the subjects of wide interest owing to their application in transition metal coordination processes, such as ion sequestration,[2] biomimetic catalysis,[3] biomedical uses,[4] etc. Among the polyazamacrocycles, the 14-membered ring system, cyclam (1,4,8,11-tetraazacyclotetradecane) and its dioxoderivatives are important because of their ability to form kinetically and thermodynamically stable complexes with Co^{II}, Ni^{II}, Pt^{II}, and Cu^{II} ions, and to stabilize their high oxidation states.[2,5] Moreover, certain complexes of Ni^{II} with cyclam and its derivatives have been shown to act as catalysts for some oxidations of alkenes.[3,6] Keeping in mind that alkene oxidation processes, such as epoxidation, *syn*-dihydroxylation etc. are associated with the formation of new stereogenic centres, the use of optically active catalysts is, in this respect, of high interest. In exploiting the concept that the incorporation of functionalized side chains into a cyclam framework may modify its coordination properties, Burrows et al. have synthesized an optically pure cyclam derivative using (*S*)-2,4-diaminobutyric acid,[7] and several 5,7-dioxocyclams, starting from L-phenylalanine,[6a] L-valine and L-leucine[6c] (enantiomerically pure cyclam derivatives could also be obtained by resolution of respective racemates,[8] or via multicentre template condensation of chiral amines with appropriate ketones[9]). The above-mentioned chiral ligands have been used for the preparation of Ni^{II} complexes, but unfortunately, in these particular cases they were not effective catalysts for asymmetric epoxidation.[3b]

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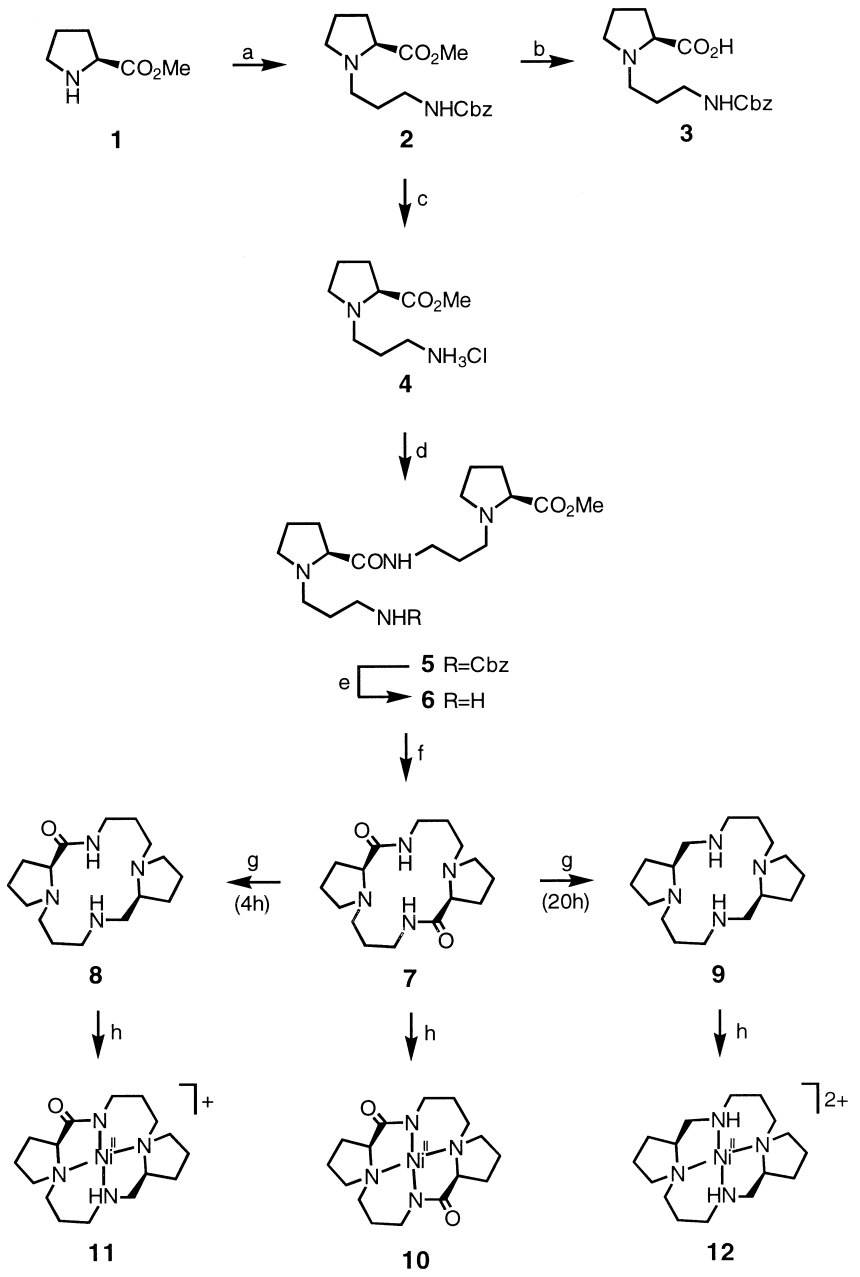
In this communication we would like to show a synthetic approach to a new class of enantiomerically pure tetra-azamacrocyclic ligands, represented by cyclam derivatives **7**–**9**, able to form complexes with various transition metal ions. The synthesis of macrocycles **7**–**9** is summarized in Scheme 1, and is based upon an original step-by-step functionalization of L-proline ester **1**.



Scheme 1. (a) *N*-Cbz-*O*-Ms-3-amino-1-propanol, Et_3N, MeCN, rt, 2 days, 72%; (b) H_2O, reflux; 4 h; (c) H_2, 5% Pd/C, HCl/MeOH, rt, 1 h; (d) **3**, *i*BuOCOCl, Et_3N, CH_2Cl_2, –20°C rt, 90%; (e) H_2, 5% Pd/C, MeOH, rt, 1 h; (f) MeONa, MeOH, rt, 28 days, 82%; (g) BH_3Me_2S, THF, reflux, 4 h (20 h) 57% (75%); (h) $Ni(OAc)_2 4H_2O$, MeOH

N-Alkylation of L-proline ester **1** with *N*-Cbz-*O*-Ms-3-amino-1-propanol, readily available from the corresponding aminoalcohol,[10] afforded aminoester **2** in a good yield. After deprotection of **2**, the resulting aminoester hydrochloride **4** was condensed with acid **3**, previously obtained by hydrolysis of **2**, to furnish compound **5**. After deprotection, the resulting derivative **6** was transformed into 2,9-dioxocyclam **7**, using MeONa in MeOH as a cyclization reagent. Careful reduction of **7** with BH_3Me_2S complex[6c] over 4 h afforded 2-oxocyclam **8** as a major product, whereas exhaustive reduction (20 h) of **7** with the same reagent gave chiral cyclam **9**. Final treatment of **7**, **8**, and **9** with $Ni(OAc)_2{\cdot}4H_2O$ in MeOH afforded crystalline complexes **10**,[11] **11**,[12] and **12**,[13] respectively. Their crystal structures were determined by X-ray analysis.[14]

A synthetic pathway has been developed in which enantiomerically pure dioxo-, monooxo-, as well as saturated cyclams derived from L-proline were prepared. The cyclams served as chiral ligands for the formation of Ni^{II} complexes, potentially useful as chiral catalysts. Further investigations, including the preparation of complexes with other transition metals and their use in asymmetric catalysis, are in progress.

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11. Selected analytical and spectral data for complex **10**: dark red crystals; m.p. 247°C; $[\alpha]_D^{20} = -294$ ($c = 0.0468$ in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C, TMS): $\delta = 4.79$–4.73 (m, 2H), 3.30–3.23 (m, 4H), 2.99 (dt, 2H, $J_1 = 14.1$ Hz, $J_2 = 4.0$ Hz), 2.78–2.70 (m, 2H), 2.28–2.21 (m, 2H), 2.19–2.21 (m, 2H), 2.07–1.95 (m, 4H), 1.93–1.82 (m, 4H), 1.64–1.57 (m, 2H), 1.49–1.39 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 30°C, TMS): $\delta = 178.6$, 74.4, 57.3, 55.7, 40.4, 26.5, 24.8, 21.2.
12. Selected analytical and spectral data for complex **11**: red crystals; m.p. 263°C; $[\alpha]_D^{20} = -510$ ($c = 0.238$ in MeOH); ^{1}H NMR (500 MHz, CD_3OD, 30°C): $\delta = 4.17$ (dd, 1H, $J_1 = 4.4$ Hz, $J_2 = 7.3$ Hz, $J_3 = 11.7$ Hz), 4.09–4.02 (m, 1H),

3.69 (dt, 1H, $J_1 = 2.3$ Hz, $J_2 = 12.8$ Hz), 3.21–2.94 (m, 6H), 2.85–2.77 (m, 2H), 2.75–2.66 (m, 2H), 2.64–2.54 (m, 2H), 2.39 (dt, 1H, $J_1 = 5.4$ Hz, $J_2 = 11.3$ Hz), 2.33–2.04 (m, 7H), 1.99–1.87 (m, 2H), 1.83–1.71 (m, 3H); ^{13}C NMR (125 MHz, CD_3OD, 30°C): $\delta = 75.0$, 70.1, 65.4, 60.0, 58.7, 58.2, 55.3, 49.4, 38.0, 29.4, 26.9, 25.8, 24.6, 24.4, 24.2.

13. Selected analytical and spectral data for complex **12**: blue crystals; m.p. 246°C (decomp.); $[\alpha]_D^{20} = -117$ ($c = 0.216$ in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$, 30°C, TMS): $\delta = 7.60$–7.10 (m, 2H), 3.33 (br. t, 2H, $J = 7.2$ Hz), 2.97–2.91 (m, 2H), 2.84 (dt, 2H, $J_1 = 2.54$ Hz, $J_2 = 12.6$ Hz), 2.71–2.64 (m, 4H), 2.54 (dt, 2H, $J_1 = 1.6$ Hz, $J_2 = 10.9$ Hz), 2.49–2.44 (m, 2H), 2.37 (dt, 2H, $J_1 = 2.6$ Hz, $J_2 = 12.1$ Hz), 2.06–1.58 (m, 14H), 1.26 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 30°C, TMS): $\delta = 64.1$, 56.4, 54.3, 52.4, 51.8, 29.7, 27.6, 27.2, 24.1.
14. Crystal structure analysis was performed for ligand **7** and complexes **10**–**12**. Complete results are soon to be published in a full paper.