Synthesis of an Optically Active C-Functionalized Cyclam: (*S*)-5-(Hydroxymethyl)-1,4,8,11-tetra-azacyclotetradecane and its Nickel(II) Complex

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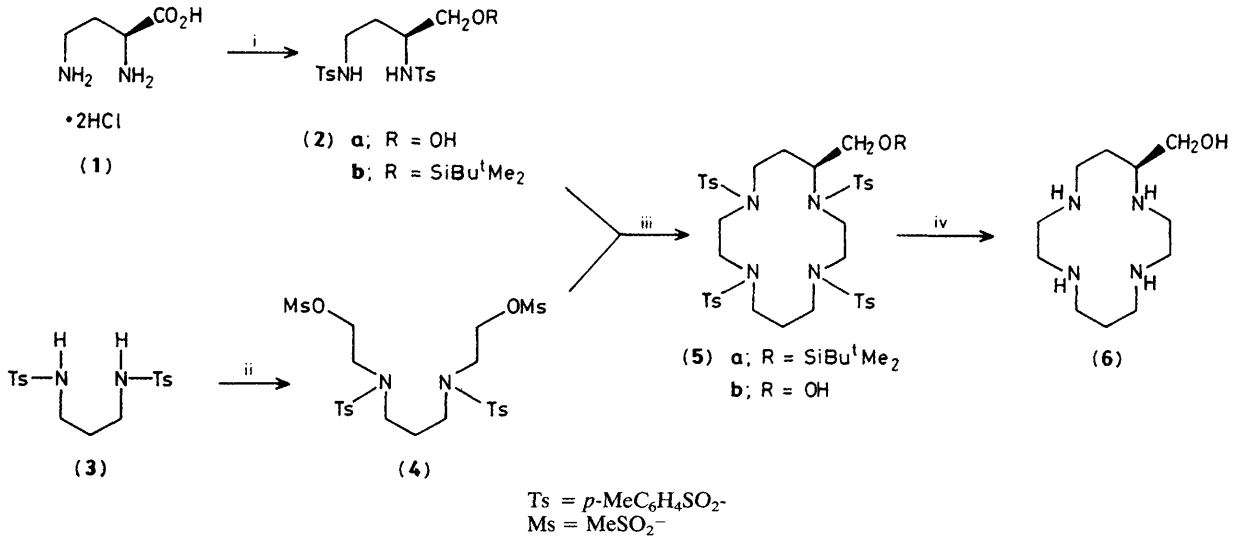
An optically active cyclam ligand bearing a functionalized side chain appended to a ring carbon and its nickel(II) complex are readily prepared from a diamino acid precursor.

Among the wealth of macrocyclic polyamine ligands the cyclam† family has enjoyed particular favour for its ability to impart kinetic and thermodynamic stability to various oxidation states of ligated transition metals.[1,2] Recently, cyclam derivatives bearing functionalized side chains have been investigated wherein the pendant group may provide either an additional ligating site or a point of further synthetic elabora-

† Cyclam = 1,4,8,11-tetra-azacyclotetradecane.



Scheme 1. *Reagents:* i, 2.2 equiv. TsCl, aq. NaOH; BH_3–THF, 0—20 °C, 16 h; Bu^tMe_2SiCl, imidazole, dimethylformamide (DMF), 20 °C, 2 h; ii, 10 equiv. ethylene carbonate, K_2CO_3, DMF, 60 °C, 24 h; 2.2 equiv. MsCl, NEt_3, CH_2Cl_2, 2 h; iii, Cs_2CO_3, DMF, 70 °C, 24 h; $Bu^n_4N^+F^-$, THF; iv, Li, NH_3–MeOH–THF.

tion in order to develop metal-promoted reactions and biomimetic systems.[3—5] The present communication describes the first optically active C-functionalized cyclam bearing, in this case, a hydroxymethyl substituent.

The synthesis of the title compound, (**6**), from (*S*)-2,4-diaminobutyric acid is summarized in Scheme 1. In order to minimize both intramolecular cyclization (to a γ-lactam) and racemization, (**1**) was first converted into the *N*,*N*′-ditosylamide and then reduced with BH_3–tetrahydrofuran(THF) to the corresponding alcohol, (**2a**), obtained in 80% yield as a white solid crystallized from methylene chloride (m.p. 118—120 °C). The optical purity of (**2a**) was determined by the method of Feringa[6] to be >90%. Conversion into the t-butyldimethylsilyl ether provided the top portion of the macrocycle, (**2b**).

The remaining portion of the macrocycle was constructed by *N*-alkylation of (**3**) with ethylene carbonate and conversion of the resultant diol to the dimethanesulphonate (**4**) in 90% overall yield. Macrocyclization of (**2b**) with (**4**) followed the Kellogg[7] modification of the Richman–Atkins[8] procedure utilizing Cs_2CO_3 and produced compound (**5a**) in 80% yield after flash column chromatography (1:1 ether–hexane). However, the yield of macrocyclization was only 10% if the unprotected alcohol (**2a**) was used. Since silylation and subsequent deprotection proceed in high yields (>90% each), these extra steps present minimal loss of material. Accordingly, desilylation of (**5a**) with $Bu^n_4N^+F^-$ gave the macrocyclic alcohol (**5b**), an intermediate suitable for further derivatization of the side chain. In this work, (**5b**) was carried directly on to the desired ligand *via* reductive cleavage of the tosyl groups with Li–NH_3 and precipitation of the tetrahydrochloride salt of (**6**) from 90% aqueous ethanol (m.p. 275—6 °C, decomp.). The free amine was prepared by extraction into chloroform from an aqueous NaOH solution.

Characterization of ligand (**6**) provided spectral and analytical data consistent with the proposed structure, including $[\alpha]_D^{20}$ = 11.4° (*c* 1.4, $CHCl_3$) and ^1H n.m.r. resonances ($CDCl_3$) at δ 3.41 (dd, *J* 2, 10.5 Hz, 1H) and 3.65 (dd, *J* 4.5, 10.5 Hz, 1H) for the hydroxymethylene group. The $NiCl_2$·(**6**) complex was prepared in methanol and recrystallized from 3:1 MeOH–EtOAc to yield lavender crystals. The stoicheiometry of the complex was confirmed by microanalysis. Unlike the parent $NiCl_2$·cyclam[9] the hydroxymethylcyclam complex remains violet in MeOH solution [λ(ε): 346(20), 526(10), 670(<3) nm] suggesting participation of the sidearm hydroxy in metal co-ordination, perhaps in a similar way to related Co^{III} and Ni^{II} complexes.[4,10]

In summary, a stereogenic centre may be incorporated into the cyclam macrocycle by the use of an optically active diamino acid. Chiral Ni^{II} and Co^{III} complexes find applications as resolving agents[11] and may be of use in asymmetric oxidations[12] and carbon–carbon bond forming reactions.[13]

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