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Synthesis of a Chiral Dioxo-Cyclam Derived from L-Phenylalanine and its Application to Olefin Oxidation Chemistry

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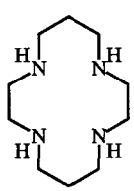
Abstract. *An optically active dioxo-cyclam macrocycle bearing two benzyl side chains derived from phenylalanine has been synthesized; its Ni(II) complex catalyzes the oxidation of olefins using hypochlorite under phase transfer conditions.*

Polyaza-macrocycles are the subject of growing interest due to their utilization in transition metal coordination chemistry related to metal ion sequestration,[1] biomimetic catalysis,[2] and biomedical applications.[3] The 14-membered ring systems cyclam (**1**) and dioxo-cyclam (**2**) have received particular attention because of their ability to form strong complexes with Co(II), Ni(II), Pt(II), and Cu(II) ions and to stabilize high oxidation states of some of these ions.[4,5] The addition of functionalized side chains to cyclam[5-7] and dioxo-cyclam[8] gives rise to modulation of the conformational and redox properties of the metal complex. Here, we report on two new facets of these molecules, the synthesis of an optically active *anti*-disubstituted dioxo-cyclam (**3**) derived from L-phenylalanine and oxidation chemistry catalyzed by its Ni(II) complex. The synthetic approach insures that the two side chains of the macrocycle will be oriented in an *anti* fashion (assuming no epimerization of the stereocenters occurs) such that both faces of the macrocycle are equivalent. Asymmetric metal complexes of C_2 symmetry are of interest in applications to catalysis.[9]



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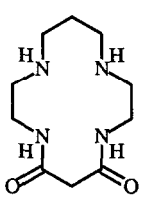

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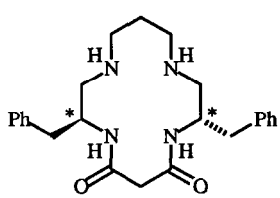
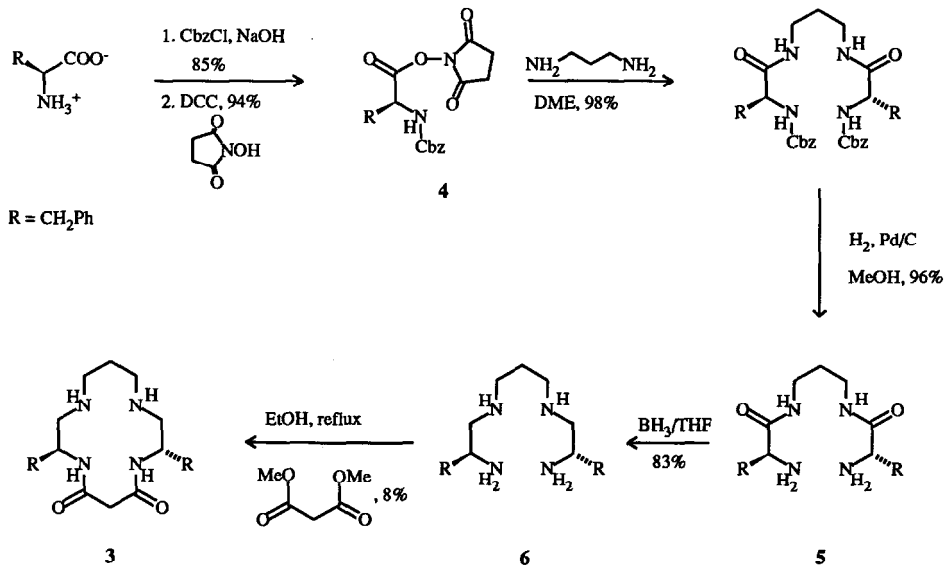


3

The synthesis of macrocycle **3** is summarized in Scheme I and is based in part upon the macrocyclization reported by Tabushi et al. for the synthesis of the parent compound **2**.[10] In our case, L-phenylalanine was first N-protected with the carbobenzyloxy group according to a known procedure,[11,12] followed by activation of the

Scheme I



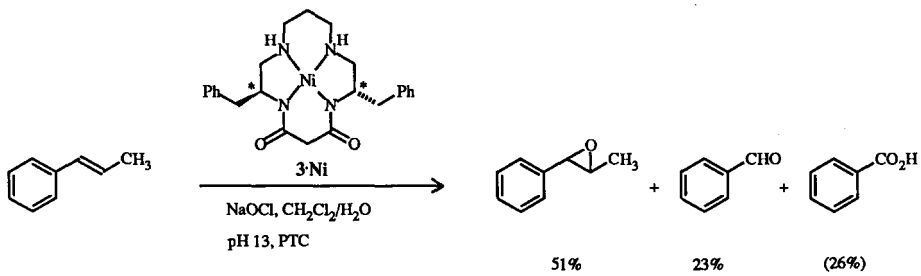
carboxyl group by conversion to the corresponding N-hydroxysuccinimide (NHS) ester (**4**) by treatment with equimolar amounts of NHS and dicyclohexylcarbodiimide in DMF for 5 h. at 0° (94% yield). Choice of the NHS ester was based upon its crystallinity and likelihood of non-racemization of the stereogenic carbon. Two equivalents of **4** were then allowed to react with one equivalent of 1,3-diaminopropane in dry dimethoxyethane (98% yield). Catalytic hydrogenolysis (40 psi H_2, 5% Pd on C, MeOH) afforded the deprotected diamine **5** in 96% yield. Compound **5** was then reduced with borane/THF (5 equiv., 0° to reflux, 18 h.) leading to the tetraamine **6** in 83% yield after work-up with 6N HCl and neutralization. Up to this point, each reaction step produced crystallizable solids in very high yields. The final macrocyclization to yield **3** was accomplished by reaction of equimolar amounts of dimethylmalonate and tetraamine **6** in refluxing EtOH for 5 days followed by concentration to a yellow oil. TLC (silica, 20% MeOH in $CHCl_3$, trace NH_3) of the crude material and subsequent analysis showed that there were only two non-polar products. The major product (R_f=0.30) appeared to be the uncyclized intermediate in which only one amide bond had formed while the minor product (R_f=0.25) was the desired macrocycle **3**.[13] In this particular case, addition of diethyl ether dissolved many impurities and a white precipitate was collected. Further purification of the precipitate by chromatography on neutral alumina (5% MeOH in $CHCl_3$) led to **3** as an off-white solid in 8% yield. Attempts were made to improve upon the macrocyclization yield. Unfortunately, both the use of high pressure (8-9 kbar, 50°, 24 h) and the replacement of dimethylmalonate with malonyl dichloride had little effect on the reaction.

Compound **3** was characterized by ^{1}H and ^{13}C-NMR, IR and elemental analysis. In particular, the ^{13}C-NMR clearly showed only 6 aliphatic carbons indicating that no other diastereomers were present.[14] It is reasonable to assume that all reactions have occurred with retention of the 3S,9S-stereocenters. In other work, dioxo-cyclams have been reduced to their corresponding cyclam ligands by treatment with BH_3/THF.[8,10] Thus, the general route described above should also be applicable to the synthesis of C-functionalized cyclams derived from amino acids.

The Ni(II) complex of ligand **3** was readily obtained by refluxing it with one equiv. $Ni(OAc)_2$ in EtOH for 30

min. and precipitation with diethyl ether to yield a yellow-orange solid. The diamagnetic complex (λ_{max} 450 nm) was characterized by ^{1}H-NMR, IR, elemental analysis and FAB mass spectroscopy. All were consistent with double deprotonation of the ligand. Notably, the carbonyl stretching frequency of **3** shifts from 1640 to 1560 cm^{-1} upon Ni(II) complexation.

Recently, square-planar Ni(II) complexes have been of interest as catalysts for the epoxidation of alkenes using either iodosylbenzene[2,15,16] or hypochlorite[17] as terminal oxidant. Since **3**·Ni displayed low solubility in CH_3CN, we were unable to test this new Ni(II) complex under reaction conditions identical to those we had previously studied with PhIO.[2,16] However, Koola and Kochi have reported Ni(II)-catalyzed epoxidation in CH_2Cl_2 with this oxidant.[15] Accordingly, we attempted the oxidation of *trans*-β-methylstyrene (0.52 mmol) with PhIO (0.067 mmol) in the presence of 0.032 mmol of **3**·Ni in 1.5 mL CH_2Cl_2. After 18 h, no oxidation products of the alkene were observable by GC, and only a trace of PhIO had been reduced to PhI. On the other hand, *rapid olefin oxidation occurred using hypochlorite as the terminal oxidant under phase transfer conditions.* In this experiment, 1.7 mmol *trans*-β-methylstyrene, 0.02 mmol **3**·Ni catalyst and 0.08 mmol $PhCH_2NMe_3^+Br^-$ (phase transfer catalyst) dissolved in 5.0 mL CH_2Cl_2 were stirred vigorously with 10 mL 0.77M aqueous NaOCl (pH 12-13). After 6.5 h, all of the alkene had disappeared producing a 51% yield of *trans*-β-methylstyrene oxide. The remainder of the alkene had been subjected to C=C bond cleavage to yield PhCHO and (in the presence of OCl^-) benzoic acid. Analysis of the epoxide produced in the reaction by ^{1}H-NMR spectroscopy in the presence of a chiral shift reagent ($Eu(hfc)_3$) indicated that there had been no appreciable asymmetric induction in the epoxidation reaction. This result is perhaps not surprising in light of the small steric size of the benzyl group and the positioning of only one such group per face of the nickel complex.



The role of the nickel complex in catalysis of alkene oxidation is unclear at this point but may parallel the mechanism suggested for nickel-salen catalyzed oxidation with OCl^-.[17] It is important to note that only diamagnetic square-planar nickel complexes with an accessible Ni(III) oxidation state have displayed catalytic activity. The combination of two amino and two amido nitrogen donors in macrocycle **3** and the fact that it acts as a doubly anionic ligand suggest that **3** may more resemble a porphyrin in terms of its strong coordinating ability and stabilization of high oxidation states. As a 14-membered ring, **3** more closely fits the hole size required for Ni(II) or Ni(III) coordination. It is interesting that (tetraphenylporphyrinato)nickel(II),[18] a 16-membered chelate ring, is inactive as a catalyst under all conditions studied to date,[16,17] although MnTPPCl is an efficient catalyst with OCl^-.[19] In addition, the Ni(II) complex of the parent macrocycle **2** yielded only 5% *trans*-β-methylstyrene oxide and 2% PhCHO under reaction conditions identical with those described above. The balance was unreacted alkene. The lack of catalysis by **2**·Ni can be attributed to its more favorable solubility in the aqueous rather than the organic layer. We conclude that the best nickel catalysts for alkene oxidation will combine strong square-planar donor ligands with appropriate hole size to generate a diamagnetic

complex. In the present work, addition of two benzylic side chains has altered the solubility and hence the catalytic properties of the complex. Furthermore, it serves as a model for other modifications of substituents and catalytic behavior.

In summary, a general synthetic route has been developed which incorporates two amino acid units into a tetraaza-macrocyclic ring. The resulting dioxo-macrocycle readily coordinates Ni^{2+} with concomitant double deprotonation of the ligand yielding a metal complex capable of catalysis of olefin epoxidation. Extension of this work to other amino acids and their derivatives and an exploration of the alkene oxidation chemistry is in progress.

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12. All yields are for crystallized products.
13. Systematic name: (3S,9S)-3,9-dibenzyl-1,4,8,11-tetraazacyclotetradecane-5,7-dione.
14. ^{1}H-NMR of **3** (300 MHz, $CDCl_3$, ppm δ): 1.6, 2H, m; 2.04, 2H, br s; 2.4-2.6, 4H, m; 2.63-2.8, 8H, m; 3.18, 2H, s; 4.4, 2H, m; 7.1, 2H, d; 7.2-7.4, 10H, m. ^{13}C-NMR of **3** (75.5 MHz, ^{1}H decoupled, $CDCl_3$): 28.9, 39.6, 46.1, 49.7, 50.1, 53.7, 126.5, 128.5, 129.1, 137.8, 167.6 ppm δ.
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