in THF (40 mL) was introduced glyoxal gas, generated by heating glyoxal polymer (10.2 g) in the presence of phosphorus pentoxide (14 g).[11] The mixture was stirred at 40 °C for 2 h to produce **10** (1.53 g, 22%), together with recovered 2-naphthol (2.28 g, 46%) and a trace amount of **1**.

An improved procedure for preparing **10** is as follows. A mixture of **2** (0.53 g, 0.0029 mol), methanol (50 mL), and aqueous NaOH (0.5 N, 10 mL) was refluxed for 3 h. After cooling, the mixture was acidified with aqueous HCl to pH 2 and extracted with ether. Evaporation of the ether gave **10** (0.55 g, 93%).

10: mp 150 °C (from $CHCl_3$, lit.[12] mp 147 °C); IR (KBr, cm^{-1}) 3350 (strong and broad), 1705 (s), 1210 (s), 815 (w), 740 (m); ^1H NMR (DMSO-d_6) δ 3.97 (s, 2 H, $ArCH_2COOH$), 7.1–7.8 (m, 7 H, ArH + ArOH), 9.74 (s, broad, COOH); ^{13}C NMR (DMSO-d_6) δ 30.7 (t, $ArCH_2COOH$), 113.3 (s), 118.1 (d), 122.4 (d), 122.8 (d), 126.4 (d), 128.2 (strong signal with a shoulder; this may be composed of two doublets and one singlet), 133.7 (s), 152.9 (s), 173.0 (s, $ArCH_2COOH$); MS *m/e* 202 (M^+, 11), 184 (65), 156 (56), 128 (base peak, 100). Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 70.99; H, 5.09.

Bis(2-hydroxy-1-naphthyl)methane (11). To a stirred THF solution (100 mL) of 2-naphthol (5.12 g, 0.0356 mol) at −10 °C was introduced glyoxal gas generated as described above, followed by a dropwise addition of concd sulfuric acid (3 mL) in THF (5 mL). The resulting mixture was stirred at 40 °C for 70 min. Aqueous NaOH (2%, 200 mL) was added and the precipitate (crude **4**) was filtered off (1.50 g, 27%). The filtrate was acidified with aqueous HCl to afford **11** (2.24 g, 42%) as a precipitate. The filtrate contained unreacted 2-naphthol (1.28 g, 25%) with a small amount of **2** (<1%).

The yield of **11** was 18% (0.96 g) when the same reaction was carried out at 20 °C.

11: mp 207 °C (from toluene, lit.[12] mp 200 °C); ^1H NMR (acetone-d_6) δ 4.90 (s, 2 H, $ArCH_2Ar$), 7.1–7.8 (m, 12 H, ArH), 8.3–8.4 (m, 2 H, ArOH); ^{13}C NMR (acetone-d_6) δ 22.2 (t, $ArCH_2Ar$), 119.2 (d), 120.7 (s), 123.7 (d), 125.3 (d), 127.0 (d), 129.2 (d), 129.6 (d), 130.7 (s), 135.5 (s), 153.1 (s); MS *m/e* 300 (M^+, base peak, 100), 157 (71), 145 (64), 144 (96). Anal. Calcd for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37. Found: C, 84.04; H, 5.42.

The IR spectrum was identical with that of an authentic sample.[13]

Supplementary Material Available: ^{13}C NMR and MS spectra for compounds 1–4 (8 pages). Ordering information is given on any current masthead page.

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Synthesis and Structure of Macrocyclic Amides Containing a 2,2′-Dipyridylmethane Unit. A New Class of Chiral Macrocyclic Ligands

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Received June 19, 1990

A novel class of 13-membered tetraaza rings containing dipyridylmethaneamide units was obtained by condensation of 1,2-diamines with 1,1-bis[6-(chloroformyl)-2-pyridyl]-1-methoxypropane. By use of *trans*-1,2-diaminocyclohexane, a chiral macrocyclic amide was obtained, while the cis isomer afforded two diastereomeric pseudochiral compounds. The chiral ligand yielded a square-planar complex with Ni(II) by loss of the amide protons, with the chirality close to the metal center. The structures of the two macrocyclic dipyridylmethane amides derived from (*R*,*R*)- and (*R*,*S*)-diaminocyclohexane (**5a** and **6a**, respectively), and that of 1,1-bis(6-carboxy-2-pyridyl)-1-methoxypropane (**1**) were studied by X-ray diffraction. In the crystal of **1**-monohydrate, the dipyridylmethane moiety adopts an anti conformation with the two aromatic rings nearly perpendicular to one another. The crystal of **5a** and that of **6a** contain two and three crystallographically independent molecules, respectively. These five macrocycles are very similar in their overall bowllike shape but exhibit minor conformational differences. ^1H NMR studies demonstrate that similar conformations are maintained in solution.

Introduction

Synthetic macrocyclic ligands have attracted considerable attention due to their widespread chemical and biochemical applications.[1] Of particular importance are dissymmetric ligands capable of chiral recognition for use in asymmetric synthesis and chiral separations.[2]

Pyridine and bipyridine have commonly been incorporated into macrocyclic frameworks, affording ligands which readily complex transition-metal ions.[3] An extensively used method for the construction of macrocyclic ligands with these heterocycles as subunits involves condensation of heterocyclic biscarboxylic acid derivatives with diamines, affording macrocyclic pyridine[4] or bipyridine diamides.[5] Chiral amide derivatives have been obtained analogously by incorporation of amino acid derivatives in the macrocycles.[6] Amides are able to form both strong complexes with metal ions by substitution of the amide hydrogen for a metal ion and weaker complexes where the metal ion

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interacts either with the carbonyl oxygen or the neutral nitrogen atom.[7] Amide derivatives have also commonly been reduced to amines, affording aza-crown ethers, prior to complexation.[8]

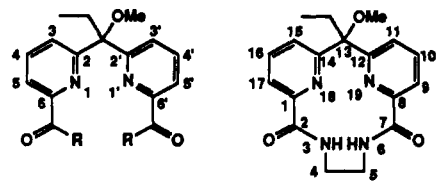
In this paper we present the preparation and crystal structures of macrocyclic compounds containing a dipyridylmethane unit,[9] as well as the crystal structure of 1,1-bis(6-carboxy-2-pyridyl)-1-methoxypropane (1). In analogy with dipyridylmethanes, which are known to complex various metal ions affording six-membered chelates,[10] the present macrocyclic compounds readily afford metal complexes. The ligands and their complexes have several attractive features compared to the bipyridine analogues. The presence of the sp^3 carbon connecting the two pyridine nuclei results in greater flexibility of the system. In addition, different alkyl and alkoxy groups can be introduced in this position, allowing for extensive structural modifications.[11,12] In the few macrocyclic compounds of this type reported so far, the sp^3 carbon is readily rehybridized since these compounds contain either a ketal group, which readily undergoes hydrolysis, or a secondary alcohol, which is sensitive to oxidation.[13]

Results and Discussion

Preparation of Ligands. Various 1,2-diamines were condensed with 1,1-bis[6-(chloroformyl)-2-pyridyl]-1-methoxypropane (2) under high dilution in toluene or methylene chloride in the presence of triethylamine. The acid chloride was obtained from 1,1-bis(6-carboxy-2-pyridyl)-1-methoxypropane (1), which in turn was prepared according to a previously described procedure.[11d] Thus, condensation of 2 with 1,2-diaminoethane or 1,2-diaminobenzene yielded macrocyclic amides 3 and 4, respectively. The compounds were obtained in crude yields of 72 and 78%, respectively. Chromatography using silica gel proved inconvenient, since large amounts of the compounds were retained by the column. Recrystallization of the diaminobenzene derivative (ethanol) yielded the pure compound in 61% yield, whereas recrystallization of the diaminoethane derivative (acetonitrile) afforded merely 19%.

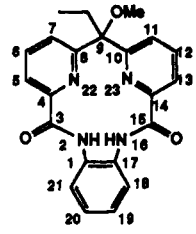
By employing this method, chiral derivatives, using chiral 1,2-diamines, are easily accessible. Racemic amide 5 was obtained from 2 and *trans*-1,2-diaminocyclohexane (crude yield 73%, after recrystallization from ethanol 56%). The *R,R* enantiomer **5a**, with an optical rotation of −27°, was obtained analogously from (−)-(*R,R*)-diaminocyclohexane.

While the trans compound 5 contains two asymmetric centers of the same configuration at C-1 and C-17 and a prochiral center at C-9, the corresponding cis-fused macrocycles have asymmetric centers of different absolute



1: R=OH
2: R=Cl

3



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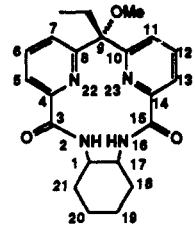
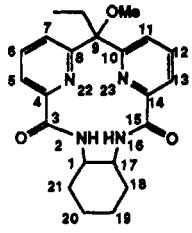
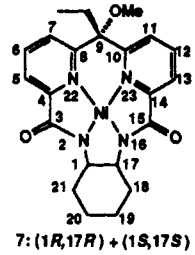


5 : (1*R*,17*R*) + (1*S*,17*S*)
5a: (1*R*,17*R*)



6a: (1*R*,9*r*,17*S*)
6b: (1*R*,9*s*,17*S*)



7: (1*R*,17*R*) + (1*S*,17*S*)

configuration and thus a pseudochiral center at C-9.[14] From *cis*-diaminocyclohexane, two diastereomeric optically inactive meso forms are therefore expected. Both isomers (**6a** and **6b**) were formed, and according to ^1H NMR obtained in a ratio of 5:1. The major isomer was shown by X-ray crystallography (see below) to have the 1*R*,9*r*,17*S* configuration.

NMR Spectroscopy. The ^1H NMR spectra of ligands 3 and 4 in chloroform-*d* show the expected pattern of two doublet of doublets and one triplet for the heterocyclic aromatic protons, broad singlets for the amide protons, and patterns characteristic of the methoxy and ethyl groups. Ligand 3 shows a further broad singlet for the two methylene groups and ligand 4 and AA'XX' pattern for the aromatic group. The spectrum of the chiral ligand 5 is more complicated since, in the absence of a mirror plane, all protons are chemically nonequivalent. The aliphatic protons of the cyclohexane ring have coupling constants typical for a chair conformation. Large downfield shifts, caused by the anisotropy of the carbonyl groups, are observed for one cyclohexane bridgehead proton, the equatorial proton of the vicinal methylene group, and the axial proton of the methylene group adjacent to the second ring junction. These shifts indicate that the molecule is nonplanar, adopting a bowl-shaped conformation. Assuming that this preferred conformation is similar to the solid-state structure (see below), with the ethyl group rather than the methoxy group pointing out of the cavity, the shifted protons are identified as H-18a, H-21e, and H-1, due to their proximity to the carbonyl functions. The asymmetry of the ligand is demonstrated in separate signals for the amide protons, their chemical shifts differing by 0.75 ppm. What is interesting is that the diastereotopic methylene protons of the ethyl group appear as separate signals, their

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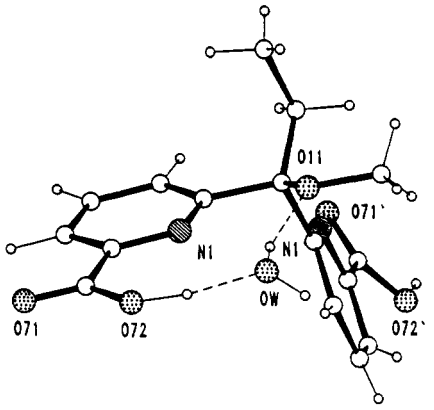

Figure 1. Perspective view of 1,1-bis(6-carboxy-2-pyridyl)-1-methoxypropane monohydrate (1·monohydrate). Solid and dashed lines represent covalent and hydrogen bonds, respectively. O atoms are dotted and N atoms are hatched.

chemical shifts differing by as much as 0.26 ppm, despite their position eight bonds from the chiral center.[15] The aromatic protons overlap considerably, preventing their complete assignments. In toluene-d_8, however, the signals are well separated. The low-field doublets of doublets (δ 7.50 and 7.70) were assigned as H-7 and H-11 due to NOE effects of 10 and 8%, respectively, upon irratiation of the methoxy group. The two remaining doublets of doublets (δ 7.20 and 7.35) were thus assigned as H-5 and H-13, and the two triplets (δ 6.95 and 7.05) as H-6 and H-12. The pyridine protons of other macrocycles were assigned accordingly.

The temperature dependence of the ^{1}H NMR spectrum of ligand **5** in toluene-d_8 was investigated. The chemical shifts for the protons in the 5-positions (H-5 and H-13) and for one of the protons in the 3-position (H-7 or H-11) of the aromatic rings remained essentially constant in the temperature range from −50 to 85 °C, whereas the second 3-pyridyl and the 4-pyridyl protons (H-6 and H-12) shifted 0.15, 0.40, and 0.40 ppm, respectively, to lower field on increasing the temperature from −50 to 85 °C. These shift differences of the different protons are thought to reflect the exposure of the different protons to the aromatic solvent. A temperature dependence was also shown for H-17, H-18e, and H-21e (0.17 ppm to lower field for the former and 0.10 ppm to higher field for the latter two, i.e. a decrease in the chemical shift difference) upon increasing the temperature from 25 to 85 °C, suggesting a flattening of the bowl with increased temperature. At the same time, one of the methylene protons of the ethyl group moved 0.12 ppm to higher field (from δ 2.66 to 2.54), while the second remained constant (at δ 2.32), thus decreasing the chemical shift difference between the diastereotopic protons.

In the ^{1}H NMR spectrum of isomer **6a**, one proton at C-18 and one proton at C-21 are shifted 0.4 ppm to lower field compared to the remaining two protons on these carbons. This downfield shift may also originate from the anisotropy of the carbonyl group, assuming a bowl-shaped structure with the ethyl group pointing out of the cavity. The cis isomer is flexible at room temperature, interconverting between two chair conformations. From variable-temperature ^{1}H NMR studies, the barrier to ring flipping was calculated to 44 kJ/mol[16] (T_c −48 °C for coalescence of H-2 and H-16). At −60 °C, the spectrum was further split, with, for example, one of the amide protons appearing as two signals.

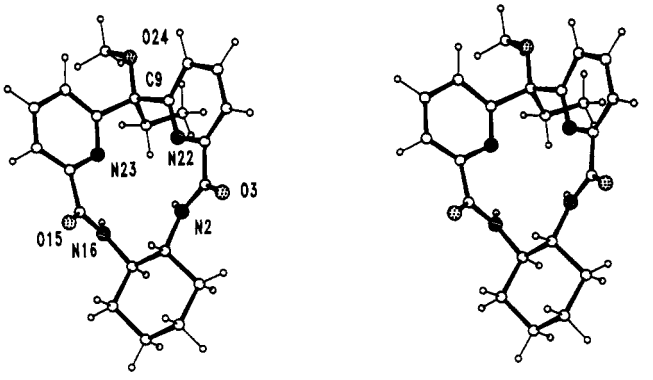

Figure 2. Stereoview of one of the two solid-state conformers of **5a**. O atoms are dotted and N atoms are hatched.

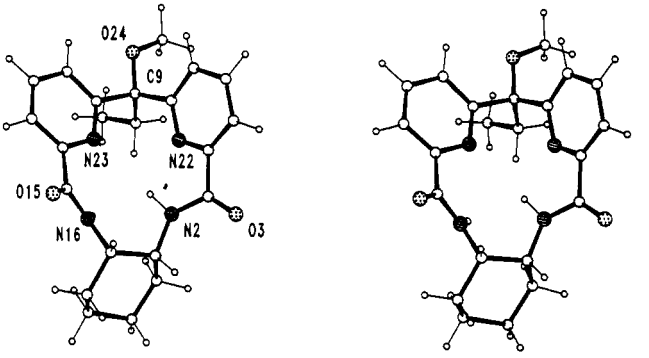

Figure 3. Stereoview of one of the three solid-state conformers of **6a**. O atoms are dotted and N atoms are hatched.

Crystallographic Description of the Structures of 1, 5a, and 6a.[17] A perspective view of compound **1** is depicted in Figure 1, and stereoviews of one conformer each of compounds **5a** and **6a** are shown in Figures 2 and 3, respectively.

Compound **1** crystallizes from aqueous acetonitrile as the monohydrate. The water molecule takes part in at least two intramolecular hydrogen bonds: one to the methoxy O(11) and one from O(72) (Figure 1). The dipyridylmethane moiety adopts an anti conformation (cf. Figure 1) with the two pyridine rings nearly perpendicular to one another.

Compounds **5a** and **6a** were crystallized from aqueous ethanol. The crystal of monochiral **5a** contains two crystallographically independent molecules in the asymmetric unit ($P2_1$, $Z = 4$), while that of **6a** contains three molecules ($P\bar{1}$, $Z = 6$). The crystallographic investigation proved the configuration of the major meso isomer derived from *cis*-diaminocyclohexane (**6a**) to be 1*R*,9*r*,17*S*.

The five crystallographically independent macrocycles show very similar overall shape, (as shown for two conformers in Figures 2 and 3) but also small conformational variations. The two pyridine rings of all the crystallographically independent macrocycles are nearly perpendicular to each other. The cyclohexane ring adopts a more or less distorted chair conformation in all five molecules. It is interesting to note that the methoxy C(9)–O(24) bond is approximately coplanar with the nearest C–C and C–N bonds of the pyridine rings in all five molecules, thus giving rise to a bowllike form for these macrocycles. In both **5a** and **6a**, the N–C–C(9)–O(24) and the C–C–C(9)–O(24)

(15) In a recent publication,[12] AB spectra for the corresponding methylene protons in optically active [2,2′-(6,6′-alkoxydipyridyl)]-methanes are reported.

(16) Dalling, D. K.; Grant, D. M.; Johnson, L. F. *J. Am. Chem. Soc.* 1971, *93*, 3678.

(17) Details of the crystallographic investigation will be published elsewhere.

torsional angles are approximately 180 and 0°, respectively, which is similar to the values previously observed for corresponding angles in related macrocyclic compounds.[13a] If it is assumed that the conformation observed in the crystallographic investigation, with the C(9)–O(24) bond nearly coplanar with the pyridine ring, is attained in **1** prior to cyclization, the preference for formation of **6a** over **6b** from *cis*-1,2-diaminocyclohexane can be explained, since the sterically more favorable approach of the *cis*-diamine to the reacting conformation of the carboxylic acid derivative results in the 1*R*,9*r*,17*S* isomer, obtained in larger amount.

In the crystal structure of **5a**, hydrogen bonds involving only three of the four amide groups of the crystallographic asymmetric unit, linking the molecules into endless chains, were found. One of the carbonyl oxygens is a proton acceptor in two weak bonds. Thus, from the crystallographic determination it can be concluded that three N(H) groups but only two carbonyl oxygens are involved in hydrogen bonding.

In the structure of **6a**, containing the cis-1,2-disubstituted cyclohexane moiety, the hydrogen bonds between the molecules form closed loops, in which only one amide group of each conformer is involved.

Infrared Spectroscopy.[18] The IR spectrum of compound **5** in KBr shows two peaks in the carbonyl stretching region (1686 and 1659 cm^{-1}) with approximately the same strength and width, and a strong, narrow peak (3302 cm^{-1}) with a small shoulder (3345 cm^{-1}) in the N–H stretching region. The high frequency carbonyl band can be assigned to a free unstrained large ring lactam.[19] Most likely, the second carbonyl band is at lower frequency due to intermolecular hydrogen bonding rather than to conjugation with the aromatic ring, as indicated by the results of the X-ray crystallographic determination. The two N–H stretching frequencies indicate two hydrogen bonded amides of different strengths with s-trans configuration.[19] The absence of the expected band from a free N–H is astonishing in relation to the results from X-ray crystallography, which indicated the presence of a free N–H group (see above).

In $CHCl_3$ (0.05 and 0.005 M), only one carbonyl stretching peak appears (1682 cm^{-1}), slightly wider than those observed in the KBr matrix, suggesting the absence of hydrogen bonding. A drastic decrease in intensity of one of the N–H bands (3302 cm^{-1}) is observed in $CHCl_3$ compared to that in KBr, resulting in two peaks of equal intensity (3302 and 3346 cm^{-1}), their position being explained by hydrogen bonding to the solvent.

In CCl_4 (0.05 M), **5** shows a broad carbonyl stretching peak (1670 cm^{-1}) of low intensity with a shoulder (1690 cm^{-1}) and a broad N–H stretching peak at 3280–3400 cm^{-1}, whereas in toluene (0.05 M), two distinct carbonyl bands (1676 and 1697 cm^{-1}, respectively) and a broad N–H stretch (3280–3420 cm^{-1}) of low intensity appear. These data suggest that in nonpolar aprotic solvents, as in the solid state, **5** is involved in intermolecular hydrogen bonding since there is no competition from the solvent.

In a KBr matrix, the IR spectra of macrocyclic ligands **3**, **4**, and **6** have similar patterns consisting of one broad carbonyl stretch in the region 1660–1700 cm^{-1} and two N–H stretches around 3300 cm^{-1}.

Complexation with Nickel(II). When ligand **5** as an ethanol solution was treated with an aqueous solution of nickel acetate, immediate formation of a yellow complex took place. In the IR spectrum of the complex, bands assigned to N–H stretching vibrations were absent, suggesting that the complex is formed by deprotonation of the two amide groups. A low spin, diamagnetic square-planar structure (**7**) is suggested by ^1H NMR, although the expected d-d transition (at around 18000–25000 cm^{-1}, or 400–555 nm, with ϵ = 50–500)[20] is obscured by a strong charge transfer transitions most probably due to π-bonding[21] between the aromatic system and Ni. A flattening of the bowl-shaped structure of the free ligand upon complexation was suggested by the small chemical shift differences between H-18a and H-21a as well as between H-18e and H-21e, and a decrease in the chemical shift difference of the diastereotopic methylene protons in the ethyl group from 0.26 ppm in the free ligand to 0.05 ppm in the complex. Complex **7** is thus similar in structure to previously reported open chain analogues,[22] with the difference that complexes protonated at the amide nitrogen were not observed in the present investigation.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were recorded in either $CDCl_3$ with Me_4Si as internal standard or in toluene-d_8 with the methyl protons in toluene-d_8 (δ 2.03 ppm) as internal standard. DEPT (distortionless enhancement by polarization transfer) was employed to assign carbon multiplicities (s, C; d, CH; t, CH_2; q, CH_3) in some cases. NOE experiments were performed in degassed toluene-d_8. Electronic spectra (UV/vis) were recorded in DMSO. Melting points were corrected with the use of standard substances. For slow additions, a Sage Instrument Model 355 syringe pump was used. Flash chromatography was performed according to the method described by Stille, Kahn, and Mitra[23] using silica gel (Merck 230–400 mesh). The purity of all title compounds was judged to be ≥90% by ^1H NMR.

Materials. 1,1-Bis(6-carboxy-2-pyridyl)-1-methoxypropane (**1**) was synthesized from dipyridyl ketone according to a previously described procedure,[11d] except for the desilylation of 1,1-bis(6-cyano-2-pyridyl)-1-[(trimethylsilyl)oxy]propane, which was carried out using *p*-toluenesulfonic acid (0.1 equiv) in MeOH (0.11 M in silyl ether, 2 h, ambient temperature) instead of HCl/MeOH. CH_2Cl_2 was distilled from P_2O_5 and stored over molecular sieves (4 Å). Triethylamine was dried over KOH. Petroleum ether (bp 30–50 °C) and ethyl acetate were distilled before use. Oxalyl chloride (98%), 1,2-diaminoethane (99%), 1,2-diaminobenzene (98%), (±)-*trans*-1,2-diaminocyclohexane (99%), and *cis*-1,2-diaminocyclohexane (99%) were obtained from Aldrich and used without further purification. (–)-(1*R*,2*R*)-Diaminocyclohexane was purchased from Alfa.

1,1-Bis[6-(chloroformyl)-2-pyridyl]-1-methoxypropane (2). To a solution of **1** (420 mg, 1.33 mmol) in dry CH_2Cl_2 (10 mL) were added oxalyl chloride (150 μL, 1.75 mmol) and 2 drops of dry DMF at ambient temperature under N_2. When the gas evolution had ceased, an additional amount of oxalyl chloride (150 μL, 1.75 mmol) was added. After the first addition, a solid formed which disappeared during the reaction. After 5 h, the solvent and the excess of oxalyl chloride were removed. A yellow oil (469 mg, 100%) was recovered: ^1H NMR (200 MHz, $CDCl_3$) δ 0.75 (t, 3 H, J = 7.5 Hz, CH_3), 2.86 (q, 2 H, J = 7.5 Hz, CH_2), 3.28 (s, 3 H, OCH_3), and 7.75–7.95 (m, 6 H, H-3, H-3′, H-4, H-4′, H-5 and H-5′); IR (KBr) 1752 cm^{-1} (C=O).

General Procedure for the Synthesis of the Macrocyclic Ligands 3–6. To a predried flask equipped with a septum and a nitrogen inlet, dry CH_2Cl_2 (140 mL/mmol of diamine) and triethylamine (2 equiv) were added. To this mixture, **2** (1 equiv)

(18) Caution must be exercised due to the possibility of overtones, combination bands and Fermi resonance.
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in dry CH_2Cl_2 (37.5 mL/mmol of diamine) and an equivalent amount of the appropriate diamine in an equal volume of dry CH_2Cl_2 were added simultaneously via two separate syringes over 5–7 h while stirring at ambient temperature, using a syringe pump. After additional stirring for 30 min, half of the amount of solvent was evaporated and the remaining solution was washed with 3 × (30–50) mL of H_2O and dried ($MgSO_4$). Evaporation of the solvent gave essentially pure compounds according to ^1H NMR spectroscopy.

2,7-Dioxo-1,8,9,10,11,12,14,15,16,17,18,19-dodecadehydro-13-ethyl-13-methoxy-3,6,18,19-tetraazatetracyclo[12.3.1.1^{8,12}]nonadecane (3). Diamine: 1,2-diaminoethane (34 μL, 0.51 mmol). Light yellow oil/crystal mixture (120 mg, 72%). The product (120 mg) was purified by recrystallization from CH_3CN, yielding white crystals (23 mg): mp 186–186.5 °C dec; R_f = 0.20 (EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 0.73 (t, J = 7.4 Hz, 3 H, CH_3), 2.46 (q, J = 7.4 Hz, 2 H, CH_2CH_3), 3.45 (s, 3 H, OCH_3), 3.52–3.60 (m, 2 H, H-4 and H-5), 3.73–3.81 (m, 2 H, H-4 and H-5), 7.75 (dd, J = 7.8 and 1 Hz, 2 H, H-11 and H-15), 7.86 (t, J = 7.7 Hz, 2 H, H-10 and H-16), 7.95 (dd, J = 7.6 and 1 Hz, 2 H, H-9 and H-17), and 8.82 (bs, 2 H, H-3 and H-6); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 7.79, 32.80, 37.69, 52.63, 86.33, 119.85, 123.56, 138.13, 149.14, 159.26, and 165.76; IR (KBr) 1662–1683 (C=O), 3264, and 3300 cm^{-1} (NH).

3,15-Dioxo-9-ethyl-9-methoxy-1,4,5,6,7,8,10,11,12,13,14,-17,18,19,20,21,22,23-octadecadehydro-2,16,22,23-tetraazatetracyclo[15.4.0.1^{4,8}.1^{10,14}]tricosane (4). Diamine: 1,2-diaminobenzene (142 mg, 1.25 mmol). Light yellow crystals (380 mg, 78%). The product (16 mg) was purified by recrystallization from EtOH, yielding a white powder (10 mg): mp 222–226 °C dec; R_f = 0.45 (EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 0.69 (t, J = 7.4 Hz, 3 H, CH_3), 2.59 (q, J = 7.4 Hz, 2 H, CH_2), 3.60 (s, 3 H, OCH_3), 7.28 (AA′ part of AA′XX′, 2 H, H-19 and H-20), 7.83 (dd, J = 8 and 1.5 Hz, 2 H, H-7 and H-11), 7.91 (t, J = 8 Hz, 2 H, H-6 and H-12), 8.04 (dd, J = 8 and 1.5 Hz, 2 H, H-5 and H-13), 8.09 (XX′ part of AA′XX′, 2 H, H-18 and H-21), 10.85 (s, 2 H, H-2 and H-16); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 7.61 (q), 31.48 (t) 52.21 (q), 86.12 (s), 120.21 (d), 122.79 (d), 123.51 (d), 125.52 (d), 129.37 (s), 138.48 (d), 149.31 (s), 159.76 (s), and 163.00 (s); IR (KBr) 1699 (C=O), 3260, and 3340 cm^{-1} (NH).

(±)-*trans*-3,15-Dioxo-4,5,6,7,8,10,11,12,13,14,22,23-dodecadehydro-9-ethyl-9-methoxy-2,16,22,23-tetraazatetracyclo[15.4.0.1^{4,8}.1^{10,14}]tricosane (5). Diamine: (±)-*trans*-1,2-diaminocyclohexane (168 μL, 1.40 mmol). Light yellow crystals (384 mg, 73%). The product (16 mg) was purified by recrystallization from EtOH, yielding white crystals (9 mg): mp 277–278.5 °C dec; R_f = 0.40 (EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 0.72 (t, J = 7.4 Hz, 3 H, CH_3), 1.36–1.61 (m, 3 H, H-19a, H-20a and H-21a), 1.81 (br d, J = 13 Hz, 1 H, H-19e), 1.89 (br d, J = 13 Hz, 1 H, H-20e), 2.18 (br q, J = 13 Hz, 1 H, H-18a), 2.48 (dq, J = 14.7 and 7.4 Hz, 1 H, CH_2CH_3), 2.60 (br d, J = 13 Hz, 1 H, H-18e), 2.75 (dq partly hidden, J = 15 and 7.5 Hz, 1 H, CH_2CH_3), 2.81 (br d partly hidden, J = 13 Hz, 1 H, H-21e), 3.43 (tt, J = 11.3 and 3.8 Hz, 1 H, H-17), 3.54–3.66 (m partly hidden, 1 H, H-1), 3.58 (s, 3 H, OCH_3), 7.60–7.64 (m, 1 H, py), 7.71–7.79 (m, 4 H, py), 7.82–7.86 (m, 1 H, py), 8.14 (br s, 1 H, H-16), 8.89 (br s, 1 H, H-2); ^1H NMR (400 MHz, toluene-d_8) δ 0.60 (t, J = 7.4 Hz, 3 H, CH_3), 1.12–1.30 (m, 3 H, H-19a, H-20a and H-21a), 1.45 (br d, J = 13 Hz, 1 H, H-19e or H-20e), 1.52 (br d, J = 13 Hz, 1 H, H-20e or H-19e), 2.10–2.17 (m partly hidden, 1 H, H-18a), 2.31 (dq, J = 14.8 and 7.4 Hz, 1 H, CH_2CH_3), 2.49 (br d, J = 13 Hz, 1 H, H-18e), 2.66 (dq, J = 14.8 and J = 7.4 Hz, 1 H, CH_2CH_3), 2.80 (tt, J = 11.2 and 3.5 Hz, 1 H, H-17), 2.93 (br d, J = 13 Hz, H-21e), 3.12 (s, 3 H, OCH_3), 3.58 (tt, J = 11 and 3 Hz, 1 H, H-1), 6.95 (t distorted, J = 7.7 Hz, 1 H, H-6 or H-12), 7.03 (t distorted, J = 7.7 Hz, 1 H, H-12 or H-6), 7.21 (dd distorted, J = 7.8 and 1 Hz, 1 H, H-7 or H-11), 7.37 (dd distorted, J = 7.9 and 0.9 Hz, 1 H, H-11 or H-7), 7.51 (dd, J = 7.7 and 0.9 Hz, 1 H, H-5 or H-13), 7.63 (br s, 1 H, H-16), 7.73 (dd distorted, J = 7.7 and 1 Hz, 1 H, H-13 or H-5), 8.75 (br s, 1 H, H-2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 7.61 (q), 24.55 (t), 25.60 (t), 29.72 (t), 31.62 (t), 32.62 (t), 51.92 (q), 56.11 (d), 58.72 (d), 86.47 (s), 119.33 (d), 119.56 (d), 122.38 (d), 122.55 (d), 137.75 (d), 137.89 (d), 149.46 (s), 151.50 (s), 159.51 (s), 160.05 (s), 166.35 (s), and 168.54 (s); IR (KBr) 1659, 1686 (C=O), 3302, and 3345 cm^{-1} (NH); IR ($CHCl_3$, 0.05 M) 1682 (C=O), 3302, and 3346 cm^{-1} (NH); IR (CCl_4, 0.05 M) 1670, 1690 (C=O), and 3280–3400 cm^{-1} (NH); IR (toluene, 0.05 M) 1676, 1697 (C=O), and 3280–3400 cm^{-1} (NH); UV λ_{max} = 268 nm (ε = 5840). Anal. Calcd for $C_{22}H_{28}N_4O_3$: C, 66.99; H, 6.64; N, 14.20. Found: C, 66.75; H, 6.58; N, 14.04.

(1*R*,17*R*)-3,15-Dioxo-4,5,6,7,8,10,11,12,13,14,22,23-dodecadehydro-9-ethyl-9-methoxy-2,16,22,23-tetraazatetracyclo[15.4.0.1^{4,8}.1^{10,14}]tricosane (5a). Diamine: (−)-(1*R*,2*R*)-diaminocyclohexane (62.5 mg, 0.547 mmol). White crystals (130 mg, 63%). The product (130 mg) was purified by recrystallization from EtOH/H_2O, yielding white crystals (42 mg): mp 271–273.5 °C dec; $[\alpha]^{21}_D$ −27.0° (*c* 0.69, $CHCl_3$). Anal. Calcd for $C_{22}H_{26}N_4O_3$: C, 66.99; H, 6.64; N, 14.20. Found: C, 66.85; H, 6.71; N, 14.10.

(1*R*,9*r*,17*S*)- and (1*R*,9*s*,17*S*)-3,15-Dioxo-4,5,6,7,8,10,11,12,13,14,22,23-dodecadehydro-9-ethyl-9-methoxy-2,16,22,23-tetraazatetracyclo[15.4.0.1^{4,8}.1^{10,14}]tricosane (6a and 6b). Diamine: *cis*-1,2-diaminocyclohexane (168 μL, 1.40 mmol). Light yellow crystals (343 mg, 65%). Two isomers in a ratio of 5:1 were identified by ^1H NMR. Flash chromatography on two consecutive silica gel columns (1.5 × 3 cm, elution with EtOAc and 1 × 14 cm, elution with EtOAc/petroleum ether, 70:30; 80:20; 90:10; 100:0, 25 mL of each, respectively) afforded **6a** (37.8 mg, 7%) and a mixture of **6a**/**6b**. **6a** was recrystallized from EtOH/H_2O: mp 209–210 °C; R_f = 0.40 (EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, J = 7.4 Hz, 3 H, CH_3), 1.52–1.56 (m, 2 H, H-19 and H-20), 1.69–1.73 (m, 2 H, H-19 and H-20), 1.81–1.86 (m, 2 H, H-18 and H-21), 2.17–2.29 (m, 2 H, H-18 and H-21), 2.74 (q, J = 7.4 Hz, 2 H, CH_2CH_3), 3.66 (s, 3 H, OCH_3), 4.04–4.10 (m, 2 H, H-1 and H-17), 7.64 (dd, J = 7.8 and 1.0 Hz, 2 H, H-7 and H-11 or H-5 and H-13), 7.74 (t, J = 7.7 Hz, 2 H, H-6 and H-12), 7.82 (dd, J = 7.6 and 1.0 Hz, 2 H, H-5 and H-13 or H-7 and H-11), 8.72 (br s, 2 H, H-2 and H-16); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 7.66, 22.25, 28.22, 28.88, 50.95, 51.75, 86.73, 119.65, 122.28, 138.00, 149.98, 159.70, 165.91; IR (KBr) 1685 (C=O), 3290, and 3340 cm^{-1} (NH). **6b**: R_f = 0.30 (EtOAc); ^1H NMR (200 MHz, $CDCl_3$, selected peaks from a mixture of **6a**/**6b**) δ 0.72 (t, 3 H, CH_3), 2.32 (q, 2 H, CH_2CH_3), 3.33 (s, 3 H, OCH_3), pyridine and cyclohexane region similar to **6a**.

[(±)-*trans*-3,15-Dioxo-9-ethyl-9-methoxy-2,16,22,23-tetraaza-4,5,6,7,8,10,11,12,13,14,22,23-dodecadehydrotetracyclo[15.4.0.1^{4,8}.1^{10,14}]tricosanato(2−)]nickel(II) (7). To Ni(OAc)$_2$·4H_2O (20 mg, 0.081 mmol) in H_2O (0.25 mL) was added **5** (32 mg, 0.081 mmol) in boiling EtOH (2 mL), causing an immediate formation of a yellow solution. The reaction mixture was refluxed for 10 min, and then the solvent was evaporated. The yellow solid was dissolved in CH_2Cl_2 (5 mL); the organic phase washed twice with 2 mL of saturated Na_2CO_3 and dried ($MgSO_4$). The solvent was evaporated to give **7** as a yellow powder (32 mg, 87%): ^1H NMR (400 MHz, $CDCl_3$) δ 0.72 (t, J = 7.5 Hz, 3 H, CH_3), 1.25–1.42 (m, 2 H, H-19a and H-20a), 1.49 (br dq, J = 12 and 4 Hz, 1 H, H-18a or H-21a), 1.59 (br dq, J = 12 and 4 Hz, 1 H, H-21a or H-18a), 1.66–1.74 (m, 2 H, H-19e and H-20e), 1.98 (A part of AB split into two q, J_{AB} = 15.4 and J = 7.5 Hz, 1 H, CH_2CH_3), 2.03 (B part of AB split into two q, J_{AB} = 15.4 and J = 7.5 Hz, 1 H, CH_2CH_3), 3.04 (br d, J = 12 Hz, 1 H, H-18e or H-21e), 3.13 (br d partly hidden, J = 12 Hz, 1 H, H-21e or H-18e), 3.15 (s, 3 H, OCH_3), 3.41 (dt, J = 11.0 and 3.0 Hz, 1 H, H-1 or H-17), 3.48 (dt, J = 11.0 and 3.0 Hz, 1 H, H-17 or H-1), 7.71–7.78 (two AB parts of two ABX, 4 H, H-5, H-7, H-11 and H-13), 8.07 (t, J = 7.9 Hz, 1 H, H-6 or H-12), 8.08 (t, J = 7.9 Hz, 1 H, H-12 or H-6); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 8.11 (q, 1 C), 25.38 (t, 1 C), 25.54 (t, 1 C), 32.19 (t, 1 C), 32.39 (t, 1 C), 42.51 (t, 1 C), 54.02 (q, 1 C), 70.76 (d, 1 C), 70.91 (d, 1 C), 89.20 (s, 1 C), 122.70 (d, 1 C), 122.72 (d, 1 C), 124.76 (d, 1 C), 124.95 (d, 1 C), 140.20 (d, 2 C), 155.69 (s, 1 C), 155.93 (s, 1 C), 158.33 (s, 1 C), 158.86 (s, 1 C), 166.42 (s, 1 C), 167.58 (s, 1 C); IR (KBr) 1595 and 1635 cm^{-1}; UV λ_{max} = 237 (ε = 2630), 316 (ε = 2960), 400 (ε = 2990), and 430 nm (ε = 2990).

Crystallography. The crystal structures of 1·monohydrate, **5a**, and **6a** have been solved by direct methods and refined by full-matrix least-squares technique based on three-dimensional diffractometer data. Crystal data: 1·monohydrate: monoclinic, $P2_1/c$, a = 8.2341 (5) Å, b = 9.7275 (5) Å, c = 20.8316 (12) Å, β = 92.74 (5)°, Z = 4, R = 0.047 for 2020 reflections. **5a**: monoclinic, $P2_1$, a = 10.2585 (3) Å, b = 19.7992 (7) Å, c = 9.9408 (4) Å, β = 92.009 (4)°, Z = 4, R = 0.056 for 1935 observations. **6a**: triclinic, $P\bar{1}$, a = 10.336 (1), b = 18.478 (2), c = 19.048 (2) Å, α = 115.906 (1)°, β = 101.773 (5)°, γ = 98.575 (4)°, Z = 6, R = 0.058 for 4412

reflections. Details of the data collection and processing as well as of the structure analysis and refinement calculations are given elsewhere.

Acknowledgment. Financial support from the Swedish Natural Science Research Council and the Swedish Board for Technical Development is gratefully acknowledged. We thank Prof. Margaret C. Etter (University of Minnesota) for valuable discussions concerning hydrogen bonding. I.C. and A. E. are also indebted to Prof. Peder Kierkegaard (Stockholm University) for his continuous interest and encouragement.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for compounds 3-7 (10 pages). Ordering information is given on any current masthead page.

Development of a Triply Convergent Aldol Approach to Prostanoids†

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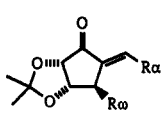
Received September 14, 1990

Various organocopper-mediated methods for the conjugate addition of alkyl and alkenyl groups to enone 1 to provide cyclopentanones 4 were studied. A variety of aldol-based procedures for the production of ketones 3 was evaluated, including a two-pot procedure involving generation of lithium enolates from 4, one-pot conjugate additions/aldol condensations methods, and methods involving the intermediate production of silyl enol ethers. The most promising procedure was found to be that involving trapping of the initial enolates from 1 as enol acetates and regeneration of enolates with methyllithium followed by aldol and dehydration reactions.

A triply convergent approach to PGE_2 has been developed in this laboratory based on enone (+)-1.[1] Conjugate addition followed by in situ electrophilic allylation afforded the desired ketone 2, which was converted to PGE_2 methyl ester, by hydrofluoric acid desilylation and aluminum amalgam deoxygenation (Scheme I). Variations on this approach, particularly involving the use of aldehydes as the electrophilic components,[2] provide the main theme of the present article.

We anticipated that cuprate additions followed by aldol condensations would result in enones 3, which would serve as intermediates to various types of prostanoids. The presence of the acetonide protecting group on 1 offers three advantages in this approach: (1) It should suppress enolate equilibration, which is the major obstacle in conjugate addition approachs to prostanoids. (2) It should allow regiospecific generation of the enolate from the corresponding ketone 4. (3) It offers a 10α-hydroxy (PG numbering) group for further manipulation.



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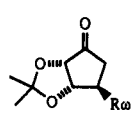

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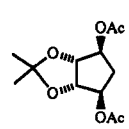

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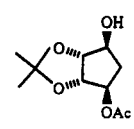
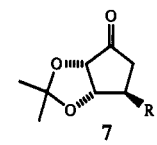


6

An efficient route to optically active (+)-1 has been developed in our laboratory by use of an enzymatic hydrolysis of diacetate 5 to furnish optically active monoacetate 6.[1,3] Oxidation of 6 provided enone (+)-1 with high optical purity (98% ee). The developmental chemistry described in the present paper was done with racemic 1.

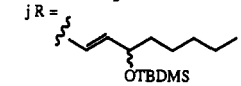
Results and Discussion

Cuprate Addition Reactions. Addition of lithium dibutylcuprate to enone 1 proceeded cleanly at −78 °C in THF to give a 92% yield of conjugate addition product



7

a R = *n*-Bu
b R = Me
c R = *n*-Oct
d R = *i*-Pr
e R = *t*-Bu
f R = $(CH_2)_7OTHP$
g R = $(CH_2)_7OTBDMS$
h R = $(CH_2)_6CH{=}CH_2$
i R = $CH{=}CH_2$
j R =



7a; the addition of lithium dimethylcuprate was equally successful in the production of ketone **7b** (90%). Cuprous bromide–dimethyl sulfide complex catalyzed addition of octylmagnesium bromide to enone 1 also results exclusively in conjugate addition to give ketone 7c in 87% yield. Recently, trimethylsilyl chloride has been noted to enhance the rate of additions of cuprates to enones.[4] Hexamethylphosphoric triamide (HMPA) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in conjunction with TMSCl facilitate the addition of organocopper reagents to enones according to a report of Kuwajima and coworkers.[5] Utilization of tetramethylethylenediamine (TMEDA) as a promoter has been developed in this laboratory.[6] Indeed, 5% cuprous iodide in conjunction with TMSCl-promoted octylmagnesium bromide addition in conjugate fashion to enone 1 to give a mixture of ketone

† This paper is dedicated to Prof. Norman A. LeBel on the occasion of his 60th birthday.

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