Synthesis of Chiral Azamacrocycles Using the Bis(α-chloroacetamide)s Derived From Chiral 1,2-Diphenylethylenediamine

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Optically active diphenyl-substituted tetraaza-12-crown-4 diamide (**10**), tetraaza-15-crown-5 diamide (**12**), tetraaza-18-crown-6 diamide (**11**), and hexaaza-18-crown-6 diamide (**9**) ligands were prepared by treating the appropriate secondary diamines with the (*R,R*)- and (*S,S*)- forms of 1,2-bis(*N*-methyl-α-chloracetamido)-1,2-diphenylethane (**20**). Macrocyclic diamides **9** and **10** were reduced to form the optically active diphenyl-substituted hexaaza-18-crown-6 (**13**) and tetraaza-12-crown-4 (**14**), respectively. Reduction of macrocyclic diamide ligands **11** and **12** gave a complex mixture of products from which the desired tetraaza-15-crown-5 and 18-crown-6 compounds could not be isolated. Dichloride **20** was prepared by treating the chiral forms of 1,2- diphenylethylenediamine with chloroacetic anhydride or chloroacetyl chloride. The crystal structures for the (*R,R*)-form of dichloride **20** and the (*S,S*)-forms of macrocycles **10** and **11** are reported.

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Introduction.

Chiral macrocyclic polyethers and their analogues are of particular interest as ligands in asymmetric synthesis, differentiating reagents in chiral separations, and as enzyme models. A large number of chiral crown ethers have been synthesized for various purposes [1]. Azamacrocyclic compounds have a much stronger association with transition metal ions than the all-oxygen macrocyclic ligands and they are indispensable starting materials for the synthesis of cryptands [2]. Although a high percentage of all synthetic macrocycles have at least one nitrogen atom in the ring, only a few chiral azamacrocyclic compounds have been reported.

Amino acids are widely used to prepare chiral azamacrocycles [3]. The amino acid is either reduced to a chiral amine and incorporated into the chiral macrocyclic ring or incorporated into the macrocyclic ring and the resulting amidomacrocycle is reduced to the azamacrocycle. Joly and Schroder [4] have reported the synthesis of a new C2-symmetric diazacrown ether (**1**, Figure 1) from L-threonine. Neumann and coworkers reported a general method for the asymmetric synthesis of highly functionalized chiral perazamacrocycles via reduction of cyclic peptide precursors (**2**, for example) [5].

Chiral *trans*-1,2-cyclohexanediamine is a very important chiral building block in asymmetric synthesis because of its C2 symmetry and bulky structure [6]. Commercially available enantiomers of 1,2-cyclohexanediamine are very expensive. Recently, an efficient procedure has been developed to resolve the inexpensive racemic mixture [7]. Several chiral macrocyclic ligands have been prepared from *trans*-1,2-cyclohexanediamine [8-10]. Neumann and coworkers prepared pentaazamacrocycles with the *trans*-1,2-cyclohexanediamine subunit via pseudopeptide intermediates **3** [8]. Reduction of the cyclic pseudopeptides gave pentaazamacrocycles **4** without racemizing the stereogenic centers. Pentaazamacrocles with two *trans*-1,2-cyclohexanediamine subunits have also been prepared by this process [9]. *Trans*-1,2- cyclohexanediamine also condensed with a bis-(chloroformyl-substituted pyridine) to form **5** or **6**. These latter macrocycles formed complexes with Ni(II) by deprotonation of the two amide groups [10].

Bradshaw and coworkers demonstrated that bis(α-chloroacetamide)s of vicinal diamines can be cyclized with triamines to give aza-15-crown-5 macrocycles with

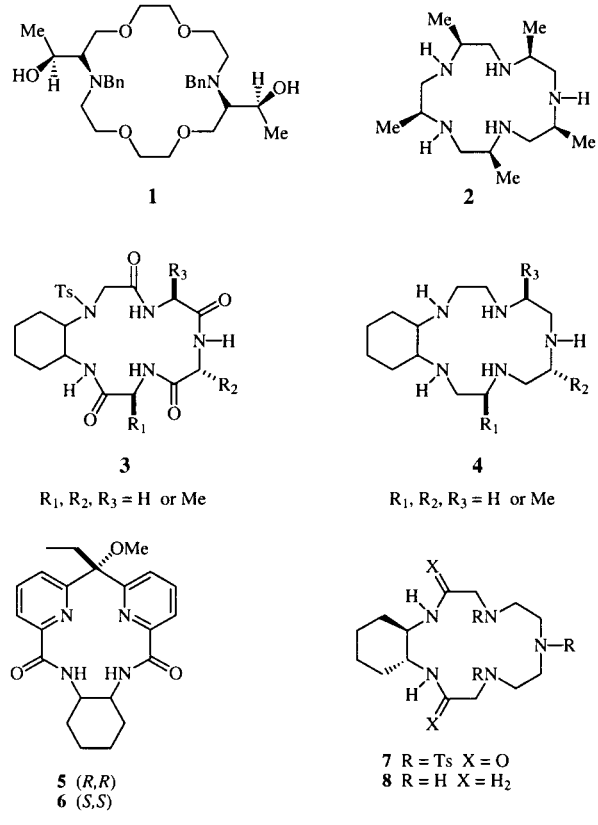


Figure 1. Chiral Polyazamacrocycles.

some [11] or all [12] of the macroring nitrogen atoms becoming tertiary amines in the reduced macrocyclic products. Lennon *et al.* [13] applied the "bis(α-chloroacetamide)" technique for the synthesis of chiral azamacrocycles. A bis(α-chloroacetamide) derived from *trans*-1,2-cyclohexanediamine was cyclized with tritosylated diethylenetriamine to give macrocyclic diamide **7** in a 38% yield. Reduction and detosylation of **7** was accomplished by treatment with lithium aluminum hydride to give chiral pentaazamacrocycle **8**.

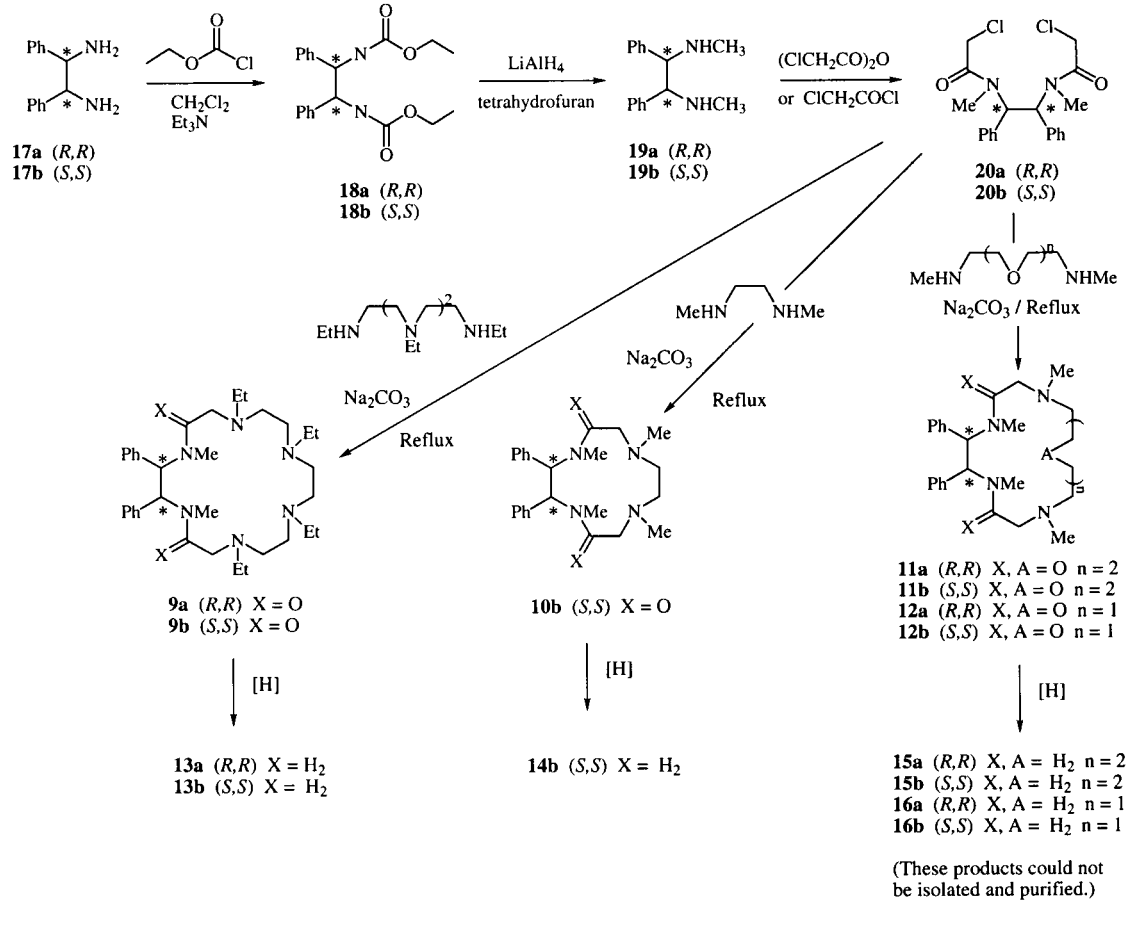
This paper describes the synthesis of a series of chiral polyazamocrocycles derived from chiral 1,2-diphenylethylenediamine. The diamine was converted to a bis(α-chloroacetamide) which was reacted with a number of polyamines to from the macrocyclic polyaminodiamides (Scheme 1). These latter compounds were reduced to form chiral macrocyclic polyamines.

Results and Discussion.

Since optically pure 1,2-diphenylethylenediamine (**17**) is very expensive, it was prepared and resolved to its (*R,R*)- and (*S,S*)-forms according to the Pikul and Corey procedure [14]. Conversion of primary diamines **17** to *N,N'*-dimethyl-substituted secondary diamines was accomplished by treatment of **17** with ethyl chloroformate [15] followed by reduction to form **19** (Scheme 1). Preparation of **19** was reported using McMurry-type coupling of *N*-methylbenzylimine [16]. This latter method gave a mixture of meso and racemic diamines plus various other by-products. The synthesis of **19** shown in Scheme 1 gave only the desired diamine. Bis(α-chloroacetamide)s **20** were obtained by treating secondary diamines **19** either with chloroacetyl chloride in the presence of a base or with chloroacetic anhydride. The yield is relatively low (50-60%) for this type of transformation. Under the same conditions, 3-oxa-1,5-diaminopentane was converted to its bis(α-chloroacetamide) derivative in a 98% yield [17]. The benzylic amines of **19** would be more reactive than an alkyl amine and could react with the formed bis(α-chloroacetamide) to produce polymeric by-products.

Macrocyclic diamides **9-12** were prepared in excellent yields by treating **20** with the appropriate α,ω-diamines in the presence of a weak base (Scheme 1). Reduction of perazaheteromacrocycles **9a,b** and **10b** with lithium aluminum

Scheme 1. Preparation of Chiral Diphenyl-substituted Polyazamacrocycles



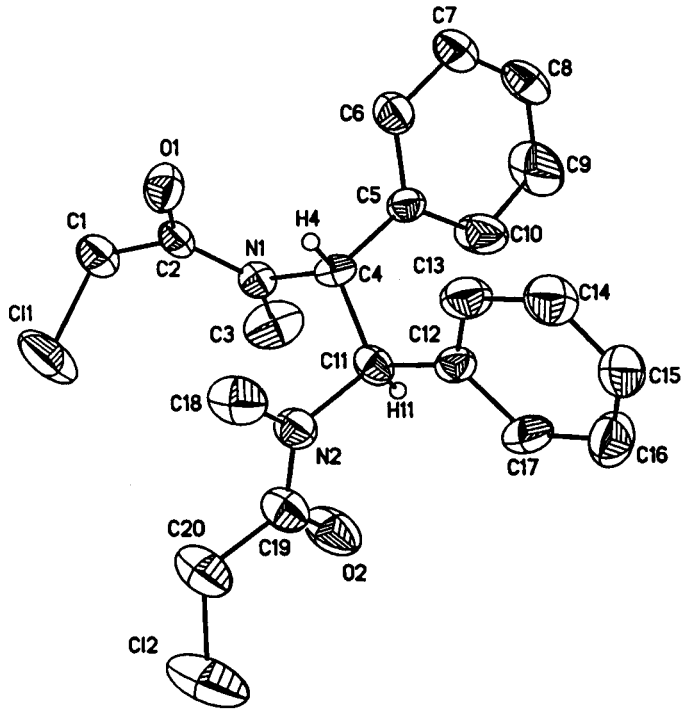


Figure 2. The crystal structure of **20a** (*R,R*- isomer) with the thermal ellipsoids drawn at the 30% probability level. Hydrogen atoms were omitted for clarity except those bonded to the chiral carbon atoms.

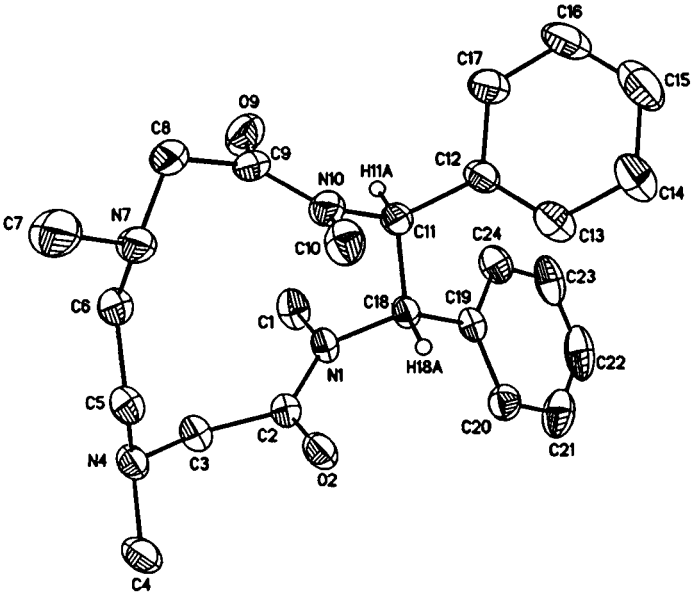


Figure 3. The crystal structure of **10b** (*S,S*- isomer) with the thermal ellipsoids drawn at the 30% probability level. Hydrogen atoms were omitted for clarity except those bonded to the chiral carbon atoms.

hydride gave **13a,b** and **14b** in good yields. However, reductions of oxygen-containing macrocycles **11** and **12** with lithium aluminum hydride were not as successful. The reductions were not complete in refluxing tetrahydrofuran after three days and gave a mixture of products. The expected products in these cases are cyclic β-amino ethers, which are excellent ligands for aluminum ions. Aluminum ions can complex with either half-reduced intermediates or the fully reduced azacrown ethers. The complexes of aluminum ion with the half-reduced intermediates are expected to be insoluble in tetrahydrofuran and reduction stalls at the half-reduced level. This explains the dark color of the reacting mixture and the appearance of peaks corresponding to the half-reduced intermediates in the ms spectra. A similar case was reported where reduction with lithium aluminum hydride did not give the desired azacrown ether [18]. Difficulties with lithium aluminum hydride reduction are also encountered when the required reduced products are open-chained amino alcohols. Amino alcohols can function as bidentate or multidentate ligands and, thus, are hard to isolate by conventional work-up procedures [19]. Diborane reductions of **11** and **12** were also tried. No reduction products could be isolated. Conversion of the macrocyclic diamides to macrocyclic dithionoamides by Lawerson's Reagent followed by Raney nickel desulfurization [20] was also tried. In each case, as mentioned above for the lithium aluminum hydride reductions, desired products **15** and **16** could be observed in the ms spectra but could not be isolated. The products may not be stable under these reduction conditions.

The solid state structures of **20a**, **10b** and **11b** which are shown in Figures 2, 3 and 4, respectively, were determined by X-ray diffraction in order to verify their formula and also to determine the conformations of the two macrocycles. The positional and thermal parameters of all atoms of

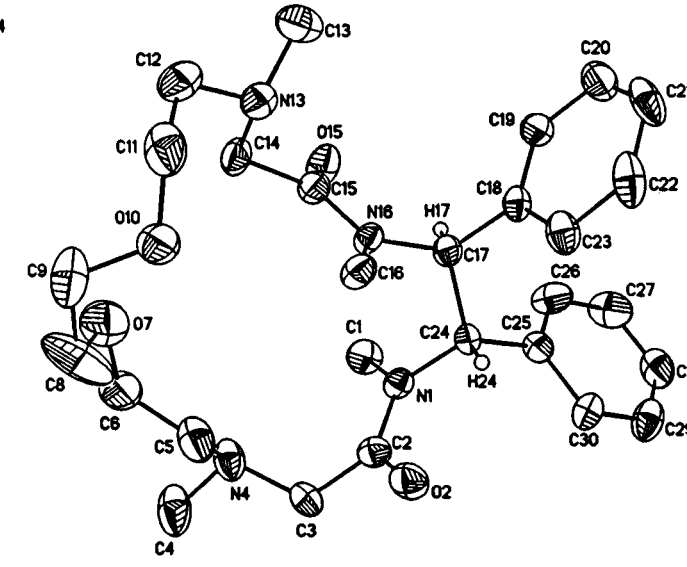


Figure 4. The crystal structure of **11b** (*S,S*- isomer) with the thermal ellipsoids drawn at the 25% probability level. Hydrogen atoms were omitted for clarity except those bonded to the chiral carbon atoms.

Table 1

Atomic Coordinates [x10^4] and Equivalent Isotropic (isotropic for hydrogen atoms) Displacement Parameters [Å^2 x 10^3] for **20a**. Ueq is defined as one-third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Cl1	1970(4)	7228(6)	5995(3)	139(2)
Cl2	3055(4)	1597(7)	7409(4)	167(2)
O1	3016(7)	7732(7)	3335(6)	72(2)
O2	1814(9)	1987(12)	4758(7)	106(3)
N1	1599(6)	5825(8)	3121(6)	49(2)
N2	3290(7)	3552(9)	4277(7)	61(2)
Cl	1369(11)	7961(14)	4485(8)	74(3)
C2	2046(9)	7155(12)	3583(7)	53(2)
C3	356(9)	5211(16)	3260(13)	98(4)
C4	2356(8)	5008(10)	2356(7)	46(2)
C5	1685(8)	5044(10)	954(8)	52(2)
C6	1895(9)	6230(12)	274(8)	64(3)
C7	1323(11)	6331(15)	-1029(9)	81(3)
C8	533(11)	5249(17)	-1609(9)	85(4)
C9	311(15)	4102(20)	-952(12)	129(6)
C10	920(12)	3912(15)	344(10)	98(4)
C11	2670(8)	3470(11)	2888(7)	56(2)
C12	3549(9)	2596(10)	2221(8)	51(2)
C13	4497(11)	3204(13)	1695(10)	75(3)
C14	5258(11)	2333(15)	1106(10)	80(3)
C15	5120(13)	895(15)	1054(11)	82(3)
C16	4202(12)	210(15)	1546(11)	87(4)
C17	3408(10)	1068(11)	2146(10)	72(3)
C18	4510(8)	4400(15)	4657(10)	83(3)
Cl9	2779(11)	2744(14)	5080(9)	75(3)
C20	3518(13)	2902(18)	6448(10)	105(4)
HIA	1558(11)	9004(14)	4485(8)	89
HIB	431(11)	7827(14)	4230(8)	89
H3A	233(9)	4263(16)	2865(13)	146
H3B	359(9)	5114(16)	4139(13)	146
H3C	-342(9)	5852(16)	2865(13)	146
H4	3191(8)	5522(10)	2444(7)	56
H6	2422(9)	6992(12)	670(8)	77
H7	1491(11)	7140(15)	-1489(9)	98
H8	148(11)	5314(17)	-2464(9)	102
H9	-266(15)	3385(20)	-1352(12)	155
H10	809(12)	3051(15)	768(10)	118
H11	1845(8)	2934(11)	2790(7)	67
H13	4628(11)	4215(13)	1733(10)	90
H14	5882(11)	2769(15)	738(10)	96
H15	5665(13)	337(15)	674(11)	99
H16	4099(12)	-804(15)	1486(11)	104
H17	2779(10)	616(11)	2497(10)	86
H18A	4688(8)	4889(15)	3932(10)	124
H18B	4416(8)	5115(15)	5278(10)	124
H18C	5219(8)	3750(15)	5005(10)	124
H20A	4447(13)	2815(18)	6493(10)	126
H20B	3357(13)	3870(18)	6753(10)	126

Table 2

Atomic Coordinates [x10^4] and Equivalent Isotropic (isotropic for hydrogen atoms) Displacement Parameters [Å^2 x 10^3] for **10b**. U(eq) is defined as one-third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Nl	4832(4)	10847(3)	2694(3)	42(1)
Cl	4729(6)	12244(4)	2787(4)	59(1)
C2	5593(4)	10258(4)	2067(3)	43(1)
O2	5795(3)	9089(3)	2115(3)	59(1)
C3	6150(5)	11101(4)	1241(3)	50(1)
N4	6078(4)	10481(3)	117(3)	49(1)
C4	7303(5)	9617(5)	236(4)	64(1)
C5	4680(4)	9849(4)	-494(3)	50(1)
C6	3356(5)	10710(5)	-670(4)	56(1)
N7	2015(4)	9932(4)	-965(3)	62(1)
C7	1454(6)	9556(8)	-2228(4)	100(2)
C8	875(5)	10523(6)	-596(3)	73(2)
C9	1334(5)	10837(6)	745(4)	59(1)
O9	1178(4)	11946(4)	1048(3)	79(1)
N10	1895(4)	9883(4)	1538(3)	51(1)
C10	1944(5)	8533(5)	1205(4)	63(1)
C11	2416(4)	10187(4)	2829(3)	46(1)
C12	1582(4)	9422(5)	3477(3)	51(1)
C13	2110(5)	8310(5)	4111(4)	66(1)
C14	1285(6)	7625(6)	4672(5)	81(2)
C15	-90(7)	8049(8)	4578(5)	98(2)
C16	-630(6)	9168(9)	3950(5)	111(3)
C17	193(5)	9839(7)	3402(4)	81(2)
C18	4095(4)	10044(4)	3359(3)	41(1)
Cl9	4728(4)	10330(4)	4701(3)	42(1)
C20	6082(4)	9811(5)	5334(4)	55(1)
C21	6709(6)	10064(5)	6545(4)	77(2)
C22	6009(8)	10821(6)	7129(4)	83(2)
C23	4677(7)	11350(5)	6510(4)	75(2)
C24	4036(5)	11113(4)	5291(4)	59(1)
H1A	5624(21)	12627(38)	2764(29)	89
H1B	4568(36)	12486(41)	3517(17)	89
H1C	3924(23)	12541(39)	2116(20)	89
H3A	5574(5)	11888(4)	1062(3)	60
H3B	7161(5)	11341(4)	1664(3)	60
H4A	7296(44)	9246(32)	-509(19)	96
H4B	7307(44)	8939(25)	791(23)	96
H4C	8164(28)	10140(32)	559(28)	96
H5A	4591(4)	9097(4)	-35(3)	60
H5B	4681(4)	9551(4)	-1270(3)	60
H6A	3478(5)	11197(5)	55(4)	68
H6B	3275(5)	11317(5)	-1313(4)	68
H7A	624(36)	8986(37)	-2415(56)	150
H7B	2197(43)	9180(43)	-2499(50)	150
H7C	1155(55)	10370(28)	-2620(51)	150
H8A	36(5)	9947(6)	-801(3)	88
H8B	564(5)	11315(6)	-1046(3)	88
H10A	1300(32)	8361(41)	407(13)	95
H10B	1622(37)	8055(39)	1767(26)	95
H10C	2925(17)	8278(42)	1276(32)	95
H11A	2192(4)	11099(4)	2904(3)	55
H13A	3039(5)	8011(5)	4165(4)	79
H14A	1664(6)	6884(6)	5107(S)	97
H15A	-660(7)	7586(8)	4935(5)	117
H16A	-1557(6)	9467(9)	3900(5)	133
H17A	-187(5)	10585(7)	2975(4)	97
H18A	4326(4)	9142(4)	3248(3)	49
H20A	6571(4)	9293(5)	4946(4)	66
H21A	7621(6)	9713(5)	6966(4)	92
H22A	6436(8)	10977(6)	7944(4)	99
H23A	4199(7)	11870(5)	6905(4)	90
H24A	3135(5)	11484(4)	4872(4)	71

the three structures are listed in Tables 1, 2, and 3. The results of the three structural studies established that the desired compounds were synthesized.

The conformations of the macrocycles are important because they suggest whether or not the macrocycles can complex cations. In both **10b** and **11b** the methyl groups bonded to nitrogen atoms next to the chiral carbon atoms point into the ring. In order to form complexes involving

Table 3

Atomic Coordinates [x10^4] and Equivalent Isotropic (isotropic for hydrogen atoms) Displacement Parameters [Å^2 x 10^3] for **11b**. U(eq) is defined as one-third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
N1	-1315(7)	-994(4)	5004(3)	51(2)
C1	-2503(9)	-893(6)	5483(4)	71(3)
C2	-676(10)	-1779(6)	4876(4)	57(2)
O2	253(7)	-1864(4)	4441(3)	77(2)
C3	-1172(10)	-2595(5)	5260(4)	65(2)
N4	-857(9)	-2573(5)	5967(4)	76(2)
C4	-1384(12)	-3391(7)	6268(5)	118(5)
C5	621(12)	-2464(7)	6121(5)	92(3)
C6	996(14)	-2340(7)	6826(6)	117(5)
O7	2076(11)	-1740(5)	7033(4)	125(3)
C8	3435(14)	-2135(7)	6874(9)	149(7)
C9	4564(14)	-1414(8)	7027(5)	112(4)
O10	4408(9)	-747(5)	6558(4)	79(2)
O10'	4076(25)	-538(9)	7081(14)	94(9)
C11	4977(11)	86(6)	6738(6)	99(4)
C12	4021(11)	785(7)	7034(5)	81(3)
N13	2797(8)	1005(5)	6601(3)	61(2)
C13	2403(12)	1927(6)	6648(5)	93(3)
C14	1553(10)	445(6)	6747(4)	66(3)
C15	364(10)	541(5)	6215(4)	57(2)
O15	-812(7)	853(4)	6379(3)	79(2)
N16	654(7)	280(4)	5583(3)	50(2)
C16	2038(8)	-115(6)	5383(4)	59(2)
C17	-350(8)	552(5)	5047(4)	52(2)
C18	259(9)	1303(6)	4645(4)	53(2)
C19	-123(11)	2149(6)	4798(4)	72(3)
C20	460(14)	2847(7)	4460(5)	90(3)
C21	1492(13)	2738(8)	3971(6)	98(4)
C22	1890(11)	1897(8)	3810(5)	89(3)
C23	1274(9)	1167(7)	4134(5)	71(3)
C24	-859(9)	-222(5)	4607(4)	51(2)
C25	-2041(8)	62(5)	4113(4)	54(2)
C26	-3088(10)	676(6)	4256(5)	86(3)
C27	-4142(11)	890(7)	3792(7)	100(4)
C28	-4194(13)	497(7)	3182(6)	90(3)
C29	-3156(11)	-122(7)	3030(5)	83(3)
C30	-2107(10)	-346(6)	3491(4)	66(2)
H1A	-2692(9)	-1438(6)	5710(4)	80
H1B	-2242(9)	-452(6)	5805(4)	80
H1C	-3359(9)	-711(6)	5246(4)	80
H3A	-687(10)	-3098(5)	5074(4)	80
H3B	-2198(10)	-2673(5)	5194(4)	80
H4A	-1213(12)	-3398(7)	6742(5)	80
H4B	-2408(12)	-3443(7)	6183(5)	80
H4C	-883(12)	-3874(7)	6063(5)	80
H5A	1000(12)	-1969(7)	5878(5)	80
H5B	1121(12)	-2982(7)	5971(5)	80
H6A	1215(14)	-2901(7)	7024(6)	80
H6B	115(14)	-2129(7)	7027(6)	80
H8A	3574(14)	-2421(7)	6450(9)	80
H8B	3592(14)	-2561(7)	7222(9)	80
H9A	5536(14)	-1632(8)	6971(5)	80
H9B	4487(14)	-1169(8)	7468(5)	80
H11A	5387(11)	324(6)	6334(6)	80
H11B	5767(11)	-19(6)	7042(6)	80
H12A	4570(11)	1300(7)	7150(5)	80
H12B	3623(11)	545(7)	7439(5)	80
H13A	3223(12)	2298(6)	6555(5)	80
H13B	1648(12)	2040(6)	6327(5)	80
H13C	2048(12)	2048(6)	7090(5)	80
H14A	1160(10)	565(6)	7183(4)	80
H14B	1903(10)	-150(6)	6744(4)	80
H16A	2588(8)	-257(6)	5778(4)	80
H16B	1861(8)	-642(6)	5131(4)	80
H16C	2577(8)	293(6)	5114(4)	80
H17	-1210(8)	772(5)	5262(4)	80
H19	-844(11)	2239(6)	5139(4)	80
H20	140(14)	3435(7)	4554(5)	80
H21	1969(13)	3231(8)	3767(6)	80
H22	2575(11)	1799(8)	3455(5)	80
H23	1525(9)	578(7)	4003(5)	80
H24	-21(9)	-396(5)	4353(4)	80
H26	-3040(10)	978(6)	4677(5)	80
H27	-4916(11)	1276(7)	3925(7)	80
H28	-4884(13)	698(7)	2855(6)	80
H29	-3212(11)	-412(7)	2604(5)	80
H30	-1405(10)	-794(6)	3390(4)	80

all the donor atoms of the macrocycles, the conformations of both molecules would have to change significantly. Such a change seems unlikely for the smaller macrocycle, **10b**. The 12 atom ring has substituents bonded to 8 of the ring atoms. The substituents include two phenyl groups and two carbonyl oxygens each bonded to a carbon atom and four methyl groups, one bonded to each nitrogen atom (see Figure 3). The N4-C5-C6-N7 torsion angle of **10b** has a value of -164°, which differs significantly from a gauche conformation, approximately ± 60° which is usually found in macrocylic complexes for D-C-C-D (D = oxygen or nitrogen donor atom) torsion angles.

In the larger macrocycle **11b**, there are 18 atoms in the ring. This allows the ring of the molecule to have a greater flexibility which allows a greater opportunity for the complexation of a cation. The disorder of the ring in the region of O10 is evidence of that flexibility. Some of the D-C-C-D torsion angles involving atoms in the N4 to N13 portion of the macrocyclic have values which are more typical of complexes. For example the torsion angles O7-C8-C9-O10 and O10-C11-C12-N13 are -69.1° and -57.4° respectively. Figure 4 shows that O7 and O10 point into the cavity and that N4 and N13 point below and above the cavity. This is in contrast to the situation in **10b** in which N4 points out of the cavity of the macrocycle (Figure 3).

EXPERIMENTAL

The ^{1}H and ^{13}C nmr spectra were obtained on Varian Gemini 200 MHz or Varian 300 MHz spectrometers using deuterated chloroform unless stated otherwise. Mass spectra were obtained on a Finnegan 8430 high resolution mass spectrometer using electronic ionization (ei), chemical ionization (ci), and fast atom bombardment (fab) methods. Optical rotation was measured with a Perkin-Elmer 241 polarimeter. *N,N',N'',N'''*-Tetraethyltriethylenetetraamine was prepared from triethylenetetraamine by acetylation with acetic

Table 4

Crystal Data and Experimental Details for **20a**, **10b** and **11b**

	20a	**10b**	**11b**
Formula	$C_{20}H_{22}Cl_2N_2O_2$	$C_{24}H_{32}N_4O_2$	$C_{28}H_{40}N_4O_4$
Formula weight	393.30	408.54	496.64
F(000)	412	440	1072
Crystal size, mm	0.50x0.36x0.20	0.5x0.4x0.1	0.55x0.40x0.40
μ, mm^{-1}	0.336	0.079	0.080
Crystal system	Monoclinic	Monoclinic	Orthorhombic
Space group	$P2_1$	$P2_1$	$P2_12_12_1$
a, Å	10.496(3)	9.655(2)	9.197(5)
b, Å	9.108(4)	10.357(3)	15.205(5)
c, Å	10.877(2)	11.8400(13)	19.974(12)
β, deg.	102.92(2)	109.344(9)	90
Volume, $Å^3$	1013.5	1117.1	2793
Z	2	2	4
ρ calc., Mg/m^3	1.289	1.215	1.181
2θ max. deg.	50	53	52
Independent data	1917	2089	3122
Data/restraints/parameters	1912/0/236	2088/1/284	3121/4/330
Goodness-of-fit on F^2	1.028	1.095	1.022
Final R indices (I>2σ(I))	$R_1 = 0.0784$ $wR^2 = 0.1896$	$R_1 = 0.0467$ $wR^2 = 0.0952$	$R_1 = 0.0780$ $wR^2 = 0.1563$
Largest peak, Δ map $eÅ^{-3}$	0.445	0.150	0.307
Largest hole, Δ map $eÅ^{-3}$	-0.246	-0.125	-0.260

anhydride followed by reduction with lithium aluminum hydride [21]. Other starting materials were used as purchased.

General Procedure A. Cyclization of Bis(α-chloroacetamide)s **20** With Various Diamines (Scheme 1).

(*R,R*) or (*S,S*)-1,2-Bis(*N*-methyl-α-chloroacetamido)-1,2-diphenylethane **20** was mixed with 1 equivalent of various α,ω-diamines in the presence of sodium carbonate in acetonitrile. The mixture was refluxed under nitrogen and the reaction was followed by tlc. When the reaction was completed, the sodium carbonate was filtered. Evaporation of the acetonitrile and purification by flash chromatography gave cyclized products **9-12.**

General Procedure B. Lithium Aluminum Hydride Reduction.

The cyclic diamide was dissolved in dry tetrahydrofuran and the solution was cooled in an ice bath. Lithium aluminum hydride was carefully added to the solution and the mixture was refluxed. The reaction was followed by tlc. When the reaction was completed, the mixture was cooled in an ice bath and water, 15% aqueous sodium hydroxide, and more water were added in succession. The white precipitate was filtered and the solid was washed with ether. The combined organic solutions were evaporated to give the crude reduced product which was purified by flash chromatography on silica gel (1:1:25/triethlyamine: methanol: ethyl acetate). The product was dissolved in methylene chloride, the solution was filtered through a glass filter paper and evaporated to give the desired product.

(*R,R*) and (*S,S*)-1,2-Bis(ethoxyamido)-1,2-diphenylethane (**18**) (Scheme 1).

Enantiopure 1,2-diphenylethylenediamine (**17**) [14] (5.0 g, 23 mmoles) and ethyl chloroformate (5.5 g, 50 mmoles) were added to a solution of pyridine (8 ml, 100 mmoles) in 60 ml of benzene. After stirring for 2 hours, the organic solvent was evaporated. The solid residue was washed with water (2 x 100 ml) and dried in an oven to give 6.6 g (80%) of the crude product. A small portion of the crude product was further purified by recrystallization in ethanol; mp 182-183°; ^1H nmr (perdeuterated dimethyl sulfoxide): δ 7.69 (d, J = 7.2 Hz, 2H), 7.25-7.18 (m, 10H), 4.93 (d, J = 7.2 Hz, 2H), 3.84 (q, J = 7.0 Hz, 4H), 1.05 (t, J = 7.0 Hz, 6H); ^{13}C nmr (perdeuterated dimethyl sulfoxide): δ 155.9, 141.1, 128.4, 128.0, 127.0, 126.9, 59.8, 59.0, 14.5; ms (ci) m/z 357 (MH^+).

Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79. Found: C, 67.24; H, 6.72.

(R,R) and (S,S)-*N,N'*-Dimethyl-1,2-diphenylethylenediamine (**19**) (Scheme 1).

To the suspension of lithium aluminim hydride (4.43 g, 116 mmoles) in 100 ml of tetrahydrofuran, **18** (5.2 g, 15 mmoles) was slowly added at 0°. The mixture was warmed and refluxed overnight. The reaction was worked up by general procedure B. Compounds **19a** and **19b** were obtained as white solids (2.9 g, 80%), mp = 44-45° (literature value 45° [16]) $[\alpha]_D^{20} = +32°$ (c = 2.0, methylene chloride) for **19a**; $[\alpha]_D^{20} = -33.4°$ (c = 2.0, methylene chloride) for **19b**; ^1H nmr: δ 7.17-7.10 (m, 6H), 7.05-7.00 (m, 4H), 3.53 (s, 2H), 2.25 (s, 6H), 1.95 (br s, 2H); ^{13}C nmr: δ 141.2, 128.1, 128.1, 127.0, 71.3, 34.7; ms: (ci) m/z 241 (MH^+).

Anal. Calcd. for $C_{16}H_{20}N_2$ (**19b**): C, 79.96; H, 8.39. Found: C, 80.08; H, 8.41.

(*S,S*)-1,2-Bis(*N*-methyl-α-chloroacetamido)-1,2-diphenylethane (**20b**) (Scheme 1).

Chloroacetyl chloride (4.5 ml, 56.1 mmoles) was added dropwise to a solution of (*S,S*)- **19b** (4.5 g, 18.7 mmoles) and triethylamine (13 ml, 90 mmoles) in 200 ml of methylene chloride at 5°. After stirring at room temperature for 15 hours, the resulting white precipitate was filtered. The dark filtrate was washed successively with 200 ml of water, 100 ml of 1 *N* aqueous hydrochloric acid, and 200 ml of water. The mixture was filtered and the solid was purified twice by flash chromatography. Compound **20b** was obtained as a white solid (5.6 g, 76%), mp 175-176°; $[\alpha]_D^{20} = +460°$ (c = 1.0, methylene chloride); ^1H nmr: δ 7.27-7.22 (m, 10 H), 6.70 (s, 2H),

4.10 (d, J = 2.4 Hz, 4H), 2.80 (s, 6H); ^{13}C nmr: δ 167.5, 135.9, 129.3, 128.8, 128.2, 53.8, 41.9, 30.9; ms: (ci) m/z 394 (MH^+).

Anal. Calcd. for $C_{20}H_{22}Cl_2N_2O_2$: C, 61.08; H, 5.64. Found: C, 60.81; H, 5.45.

(*R,R*)-1,2-Bis(*N*-methyl-α-chloroacetamido)-1,2-diphenylethane (**20a**) (Scheme 1).

Chloroacetic anhydride (2.42 g, 13.7 mmoles) was added dropwise to a solution of (*R,R*)-**19a** (1.5 g, 6.2 mmoles) in 20 ml of methylene chloride. After stirring for 30 minutes at room temperature, the solution was washed with a saturated sodium bicarbonate solution (50 ml) and brine (20 ml). The organic solvent was evaporated and the solid was purified by flash chromatography and recrystallized in ethanol to give **20a** as a white crystal (0.9 g, 37%), mp 175-176°; $[\alpha]_D^{20}$ = - 458° (c = 1.08, methylene chloride); ^{1}H, ^{13}C nmr, and ms spectra were the same as those of **20b**.

Anal. Calcd. for $C_{20}H_{22}Cl_2N_2O_2$: C, 61.08; H, 5.64. Found: C, 61.22; H, 5.74.

(*S,S*)-8,11,14,17-Tetraethyl-2,5-dimethyl-3,4-diphenyl-2,5,8,11,14,17-hexaazacyclooctadecane-1,6-dione (**9b**) (Scheme 1).

Compound **9b** (0.94 g, 54%) was prepared by general procedure A from **20b** (1.18 g, 3.0 mmoles), *N,N',N'',N'''*-tetraethyltriethylenetetraamine (0.78 g, 3.0 mmoles), and 10 g of sodium carbonate in 1 liter of acetonitrile as a yellow oil; $[\alpha]_D^{20}$ = + 284° (c = 1.2, methylene chloride); ^{1}H nmr: δ 7.30-7.26 (m, 4H), 7.21-7.15 (m, 6H), 6.77 (s, 2H), 3.39 (s, 4H), 2.83 (s, 6H), 2.69-2.61 (m, 12H), 2.49 (t, J = 7.2 Hz, 8H), 0.99 (q, J = 7.2 Hz, 12H); ^{13}C nmr: δ 171.4, 137.2, 129.3, 128.5, 127.6, 57.0, 53.0, 52.0, 51.7, 49.0, 48.5, 30.0, 12.1, 11.4; ms: (fab) m/z 579 (MH^+), 601 (MNa^+); hrms: (fab) m/z Calcd. for $C_{34}H_{55}N_6O_2$ (MH^+): 579.4387; Found: 579.4395. A satisfactory elemental analysis was obtained for **9a**, the enantiomer of **9b**.

(*R,R*)-8,11,14,17-Tetraethyl-2,5-dimethyl-3,4-diphenyl-2,5,8,11,14,17-hexaazacyclooctadecane-1,6-dione (**9a**) (Scheme 1).

Compound **9a** (1.02 g, 62%) was prepared by general procedure A from **20a** (1.18 g, 3.0 mmoles), *N,N',N'',N'''*-tetraethyltriethylenetetraamine (0.78 g, 3.0 mmoles), and 10 g of sodium carbonate in 1 liter of acetonitrile as a yellow oil; $[\alpha]_D^{20}$ = - 279° (c = 1.2, methylene chloride); ^{1}H, ^{13}C nmr, and ms spectra were the same as those of **9b**.

Anal. Calcd. for $C_{34}H_{54}N_6O_2$: C, 70.55; H, 9.40. Found: C, 70.36; H, 9.30.

(*S,S*)-2,5,8,11-Tetramethyl-3,4-diphenyl-2,5,8,11-tetraazacyclododecane-1,6-dione (**10b**) (Scheme 1).

Compound **10b** (0.29 g, 65%) was prepared by general procedure A from **20b** (424 mg, 1.08 mmoles), *N,N'*-dimethylethylenediamine (95 mg, 1.08 mmoles), and 3 g of sodium carbonate in 1 liter of acetonitrile as a white solid. Further purification by recrystallization in hexanes and ethanol gave **10b** as white needles, mp 166-168°; $[\alpha]_D^{20}$ = + 455° (c = 1.2, methylene chloride); ^{1}H nmr: δ 7.30-7.25 (m, 4H), 7.21-7.15 (m, 6H), 6.76 (s, 2H), 3.45 (d, J = 13.5 Hz, 2H), 3.03 (d, J = 13.5 Hz, 2H), 2.87 (s, 6H), 2.76-2.60 (m, 2H), 2.58-2.50 (m, 2H), 2.40 (s, 6H); ^{13}C nmr: δ 171.1, 136.8, 129.5, 128.3, 127.4, 61.1, 55.0, 53.0, 45.1, 30.8; ms: (fab) m/z 409 (MH^+), 431 (MNa^+); hrms: (fab) m/z Calcd. for $C_{24}H_{33}N_4O_2$ (MH^+): 409.2603; Found: 409.2599.

Anal. Calcd. for $C_{24}H_{32}N_4O_2$: C, 70.56; H, 7.89. Found: C, 70.64; H, 7.87.

(*S,S*)-2,5,8,17-Tetramethyl-3,4-diphenyl-2,5,8,17-tetraaza-11,14-dioxacyclooctadecane-1,6-dione (**11b**) (Scheme 1).

Compound **11b** (0.94 g, 63%) was prepared by general procedure A from **20b** (1.18 g, 3.0 mmoles) and 1,8-bis(methylamino)-3,6-dioxaoctane (0.54 g, 3.0 mmoles) as a white solid, mp: 135-136°; $[\alpha]_D^{20}$ = + 322° (c = 1.2, methylene chloride); ^{1}H nmr: δ 7.35-7.31 (m, 4H), 7.24-7.18 (m, 6H), 6.82 (s, 2H), 3.65-3.59 (m, 8H), 3.55 (d, J = 15 Hz, 2H), 3.29 (d, J = 15 Hz, 2H), 2.90-2.81 (m, 2H), 2.79 (s, 6H), 2.71-2.62 (m, 2H), 2.41 (s, 6H); ^{13}C nmr: δ 171.1, 137.2, 129.1, 128.6, 127.7, 70.9, 70.7, 59.7, 56.5, 53.0, 44.0, 29.9; ms: (fab) m/z 497 (MH^+).

Anal. Calcd. for $C_{28}H_{40}N_4O_4$: C, 67.72; H, 8.12. Found: C, 67.89; H, 8.17.

(*R,R*)-2,5,8,17-Tetramethyl-3,4-diphenyl-2,5,8,17-tetraaza-11,14-dioxacyclooctadecane-1,6-dione (**11a**) (Scheme 1).

Compound **11a** (0.42 g, 67%) was prepared by general procedure A from **20a** (0.50 g, 1.27 mmoles) and 1,8-bis(methylamino)-3,6-dioxaoctane (0.22 g, 1.27 mmoles) as a white solid, mp 134-135°; $[\alpha]_D^{20}$ = - 317° (c = 1.2, methylene chloride); ^{1}H, ^{13}C nmr and ms spectra were the same as those of **11b**.

Anal. Calcd. for $C_{28}H_{40}N_4O_4$: C, 67.72; H, 8.12; Found: C, 67.69; H, 7.96.

(*S,S*)-2,5,8,14-Tetramethyl-3,4-diphenyl-2,5,8,14-tetraaza-11-oxacyclopentadecane-1,6-dione (**12b**) (Scheme 1).

Compound **12b** (0.95 g, 75%) was prepared by general procedure A from **20b** (1.18 g, 3.0 mmoles) and 1,5-bis(methylamino)-3-oxapentane (0.40 g, 3.0 mmoles) as a white solid, mp 156-157°; $[\alpha]_D^{20}$ = + 402° (c = 1.1, methylene chloride); ^{1}H nmr: δ 7.32-7.24 (m, 4H), 7.20-7.14 (m, 6H), 6.78 (s, 2H), 3.90 (d, J = 12 Hz, 2H), 3.64-3.46 (m, 4H), 3.40-3.24 (m, 2H), 3.04 (d, J = 12 Hz, 2H), 2.76 (s, 6H), 2.50-2.40 (m, 2H), 2.54 (s, 6H); ^{13}C nmr: δ 171.1, 137.4, 129.3, 128.5, 127.6, 70.4, 58.0, 54.3, 52.6, 43.8, 29.7; ms: (fab) m/z 453 (MH^+).

Anal. Calcd. for $C_{26}H_{36}N_4O_3$: C, 69.00; H, 8.02; Found: C, 68.82; H, 7.86.

(*R,R*)-2,5,8,14-Tetramethyl-3,4-diphenyl-2,5,8,14-tetraaza-11-oxacyclopentadecane-1,6-dione (**12a**) (Scheme 1).

Compound **12a** (150 mg, 59%) was prepared by general procedure A from **20a** (0.22 g, 0.56 mmole) and 1,5-bis(methylamino)-3-oxapentane (74 mg, 0.56 mmole) as a white solid, mp 155-156°; $[\alpha]_D^{20}$ = - 412° (c = 1.1, methylene chloride); 1H, ^{13}C nmr and ms spectra were the same as those of **12b**. A satisfactory elemental analysis was obtained for **12b**, the enantiomer of **12a**.

(*S,S*)-7,10,13,16-Tetraethyl-1,4-dimethyl-2,3-diphenyl-1,4,7,10,13,16-hexaazacyclooctadecane (**13b**) (Scheme 1).

Lithium aluminum hydride (0.20 g, 5.27 mmoles) was added slowly to a solution of **9b** (510 mg, 0.88 mmole) in 20 ml of dry tetrahydrofuran at 0°. The resulting mixture was refluxing for 3 hours and worked up as general procedure B. Azamacrocycle **13b** (435 mg, 90%) was obtained as an oil which absorb carbon dioxide readily; $[\alpha]_D^{20}$ = + 8.3° (c = 1.2, methylene chloride); ^{1}H nmr: δ 7.14-7.02 (m, 10H), 4.25 (s, 2H), 2.71-2.49 (m, 24H), 2.42-2.36 (m, 4H), 2.27 (s, 6H), 1.10-0.95 (m, 12H); ^{13}C nmr: δ 136.6, 129.7, 127.7, 126.7, 68.9, 53.4, 52.8, 52.1, 52.0, 51.6, 49.6, 48.7, 38.5, 12.1, 12.0; ms: (FAB) m/z 551(MH^+); hrms: (fab) m/z Calcd. for $C_{34}H_{59}N_6$ (MH^+): 551.4801; Found: 551.4797. A satisfactory elemental anlysis was obtained for **13a**, the enantiomer of **13b**.

(*R*,*R*)-7,10,13,16-Tetraethyl-1,4-dimethyl-2,3-diphenyl-1,4,7,10,13,16-hexaazacyclooctadecane (**13a**) (Scheme 1).

Azamacrocycle **13a** (290 mg, 96%) was prepared from **9a** (316 mg, 0.55 mmmole) and lithium aluminum hydride (100 mg, 2.64 mmoles) in the same manner as **13b**; $[\alpha]_D^{20}$ = - 8.2° (c = 1.2, methylene chloride); 1H, ^{13}C nmr and ms spectra are the same as those of **30b**; hrms: (fab) m/z Calcd. for $C_{34}H_{59}N_6$ (MH^+): 551.4801; Found: 551.4795.

Anal. Calcd. for $C_{34}H_{58}N_6$: C, 74.13; H, 10.61. Found: C, 73.98; H, 10.51.

(*S*,*S*)-2,5,8,11-Tetramethyl-3,4-diphenyl-2,5,8,11-tetraazacyclododecane (**14b**) (Scheme 1).

Macrocycle **10b** (270 mg, 0.71 mmole) and lithium aluminum hydride (100 mg, 2.64 mmoles) were added to 20 ml of dry tetrahydrofuran at room temperature and the mixture was refluxed for 1 hour. The reaction was worked up as general procedure B. Macrocycle **14b** (147 mg, 54%) was isolated as an oil in its hydrate form; ^1H nmr: δ 7.28-7.24 (m, 2H), 7.17-7.02 (m, 8H), 5.40-5.20 (broad s, 2H), 4.01-3.93 (m, 2H), 3.74-3.60 (m, 2H), 2.78-2.63 (m, 2H), 2.62-2.44 (m, 4H), 2.43-2.19 (m, 4H), 2.35 (s, 3H), 2.31 (s, 3H), 2.27 (s, 6H); ^{13}C nmr: δ 134.7, 129.7, 129.2, 128.2, 127.7, 127.3, 127.2, 73.3, 65.6, 60.2, 59.4, 56.6, 55.8, 55.4, 50.2, 43.5, 43.2, 38.8, 33.7; ms: (fab) m/z 399 ($MH^+ \bullet H_2O$), 421($MNa^+ \bullet H_2O$); hrms: (fab) m/z Calcd. for $C_{24}H_{39}N_4O$ ($MH^+ \bullet H_2O$): 399.3124; Found: 399.3138.

(*S*,*S*)-2,5,8,17-Tetramethyl-3,4-diphenyl-2,5,8,17-tetraaza-11,14-dioxacyclooctadecane (**15b**) (Scheme 1).

Lithium aluminum hydride (240 mg, 6.32 mmmoles) was added to a solution of azamacrocycle **11b** (200 mg, 0.4 mmole) in 50 ml of dry tetrahydrofuran at 0°. The resulting mixture was refluxed for 24 hours. The reaction was worked up as general procedure B. Flash chromatography of the crude oil gave very impure macrocycle **15b** (45 mg, 24%); ^1H nmr: δ 7.30-7.00 (m, 10H), 4.30 (s, 2H), 3.68-3.46 (m, 8H), 2.80-2.40 (m, 10H), 2.79 (s, 6H), 2.41 (s, 6H); ^{13}C nmr: δ 135.9, 129.7, 127.5, 126.7, 70.7, 68.9, 68.7, 57.7, 55.7, 51.2, 43.1, 38.0; ms: (fab) m/z 469 (MH^+), 491 (MNa^+). This mixture could not be further purified. Reduction products **15a**, **16a**, and **16b** likewise could not be purified.

X-ray Crystal Structural Analysis.

Crystals of **20**a, **10**b, and **11**b suitable for X-ray structure studies were prepared. Crystal data and intensity data were collected using an automated diffractometer which utilized MoKα radiation (λ = 0.71073Å). Crystal data and information concerning the structure determinations are listed in Table 4.

The three structures were solved using direct methods. There was disorder in **11** in the region of O10. The disorder of O10 was resolved with O10 having a population parameter of 0.75 while O10' had a population parameter of 0.25. The large thermal motion of neighboring atoms suggested that these atoms were also disordered but this disorder could not be resolved. All non-hydrogen atoms of the three compounds were refined anisotropically with the exception of O10'. Positions for all hydrogen atoms were calculated and these atoms were allowed to ride on their neighboring heavy atoms during the refinement. The isotropic thermal parameter of each hydrogen atom of **20a** and **10b** were assigned based on the value of the equivalent isotropic thermal parameter of its neighboring heavy atom while those in **11b** were all given the same value. The structures were refined using a full-matrix least-squares procedure based on F^2. The absolute configuration of each compound was established by its synthesis. All programs used in the refinement and display of the structures were part of a program package supplied by Bruker Analytical X-ray [22]. The program used to solve **20** and **10** was also included in that program package. The program used to solve **11** is included in SHELTX-PLUS™ [23].

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