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Synthesis of Dibenzo-Monoazacrown Ethers

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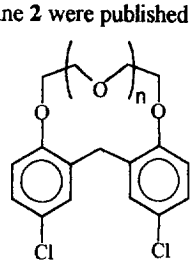
Abstract: Novel dibenzo-monoaza-12-crown-3, -15-crown-4, -18-crown-5 and -21-crown-6 derivatives (**7a-d**) were synthesized. Two independent methods were developed for the heterocyclization and the better one was optimized. The structure of crowns **7a,b,c** was confirmed by single-crystal X-ray diffraction. Copyright © 1996 Elsevier Science Ltd

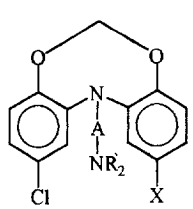
INTRODUCTION

Enormous number of macroheterocyclic compounds (crown ethers, coronands, cryptands etc.) of great variety have been synthesized in the past decades, the majority of them have been studied and used in artificial systems as ionophores, complexing- and transport mediating agents. Relatively few reports have been published, however, on the biological investigations. Russian authors reported on the antihypoxic and anticonvulsant data[1] of hundred known crown ethers and on the antimicrobial effects[2] of novel heterocyclic dibenzo-18-crown-6 derivatives. On the other hand, Vögtle[3] introduced pharmacophore groups into crown matrices to investigate how the pharmacological behavior was influenced by the crown subunite which was expected to facilitate the membrane transport.

Dibenzo-crown derivatives **1** were patented by Squibb researchers and claimed to exhibit remarkable analgesic and coccidiostatic activity[4]. In the meantime some derivatives of a new heterocyclic system, dibenzo-dioxazocine **2** were published to show interesting CNS activity[5].

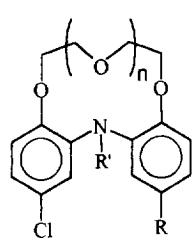


1



2

A: alkyl
X: H,Cl



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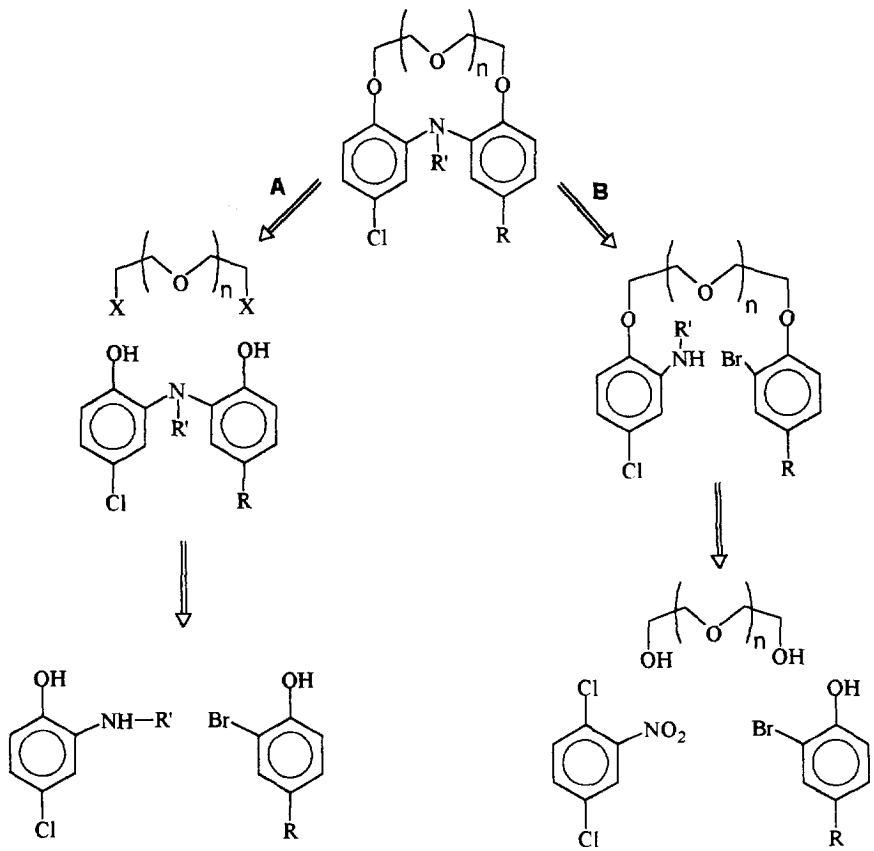
In spite of the different therapeutic effects exhibited by compounds **1** and **2**, our attention was drawn by some important structural similarities: two phenoxy units are separated by one (C or N) sp^3 atom and linked with a chain of various length.

It seemed to be reasonable for us to combine these elements in one molecule and investigate how the pharmacological properties will change. We aimed at keeping the diphenylamine moiety and linking the aromatic rings with a polyoxyethylene chain to synthesize **7** which, on the other hand, can be further derivatized on the nitrogen atom. Compounds of type **7**, at the same time, represent new dibenzo-azacrown ethers hitherto not described in the literature.

In this paper we report on the synthesis of crowns **7** trying two approaches and on the optimation of the better method.

RESULTS AND DISCUSSION

The retrosynthetic approaches for the target macrocycle are illustrated in Scheme 1.

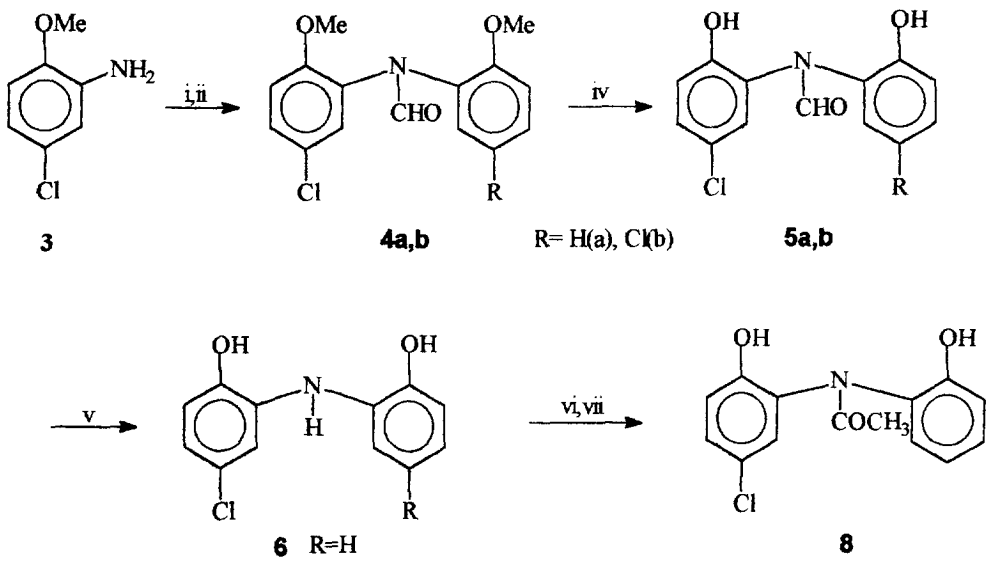


Scheme 1

In most cases route **A** was used since the starting 2,2'-dihydroxydiphenylamine could be prepared in large scale from cheap sources, moreover this method provided higher yields. Route **B** is a unique example of the formation of azacrown ring via intramolecular Ullmann reaction.

Route A

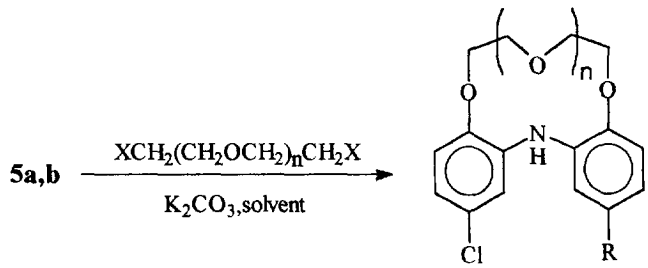
Three step reaction was developed by Rózsa et. al.[5a] for the preparation of the bis-phenole precursor **5** according to Scheme 2.



Reagents: i: HCOOH,Δ; ii: 2-Br-4(R=H,Cl)anisole,Na_2CO_3,CuBr,Dowtherm,220°C; iv: $AlCl_3$,chlorobenzene; v: HCl/EtOH or NaOH; vi: Ac_2O,Δ; vii: MeOH,aq.K_2CO_3,rt

Scheme 2.

The amino group of 2-amino-4-chloroanisole(**3**) had to be formylated prior to Ullmann arylation to improve the yields of **4** . The O-methyl protecting groups were removed by $AlCl_3$ under standard conditions. This optimized procedure was used for the preparation of the starting **5a,b** which were cyclized with various bis-alkylating agents derived from olygoethylene glycols. Usually bis-chloroethers were applied but in one case the appropriate bromide and tosylate were also tried. (Scheme 3)



7	a	b	c	d	e
R	H	H	H	Cl	H
n	1	2	3	3	4

7

Scheme 3.

The reaction conditions of ring closure resulting in **7c** were optimized with **5a** and 1,11-dichloro-3,6,9-trioxaundecane varying the reagent ratios, solvent, temperature and time. The results are summarized in Table 1.

Table 1. Optimation of the ring closure[a] in the preparation of **7c** starting from **5a**(**8, 6**)

Solvent	temp. [°C]	**5a**	**8**	**6**
		Yields [%]		
DMF-Me,Et keton 10:1	80	7.4		
DMF-Me,i-Bu keton 10:1	120	19.0		
Me,i-Bu keton	120	0		
DMF	120	8.5		
	120	24[b]		
BuOH	110	43.4		12
AmOH	130	33.3		
Cyclohexanone	120	42.2[c] (31.8)[d]	27	24
	120	51[e] (46)[d]		
	120	10.4[f]		
	120	8.2[g]		
	140	23		

a: standard conditions: **5a** (0.02mol), bis-alkylating agent (0.02mol), K_2CO_3 (0.1mol), solvent (120ml) in 18h reaction. Yields refer to isolated **7c**.

b: cyclization with the appropriate ditosylate

c: further 3.4% of **7c** can be isolated by chromatography from the tarry residue (total yield: 45.6%)

d: after 5 hour (36.8% /8 hour)

e: cyclization with 1,11-dibromo-3,6,9-trioxaundecane without KI

f: 1mol K_2CO_3/mol **5a**

g: 1mol excess of 1,11-dichloro-3,6,9-trioxaundecane

The highest yields were achieved in cyclohexanone or n-BuOH solvents using eqvimolar reagent ratio, excess of solid K_2CO_3 base (5mol/mol **5a,b**), catalytic amount of KI (10mol%) at 120°C for 17-20h. Cyclohexanone solvent was found to be superior to n-BuOH because the product obtained by heptane extraction of the residue was not required further purification. 1,11-Dibromo-3,6,9-trioxaundecane resulted in somewhat higher yield (51%) even in the absence of KI but it is much more expensive than the dichloride. The corresponding ditosylate, however, was inferior to the previous alkylating agents (24% yield).

The optimized procedure was applied for the other cyclizations affording monoaza-12-crown-3 (**7a**), -15-crown-4 (**7b**), -18-crown-5 (**7d**) and -21-crown-6 (**7e**) derivatives in fair yields. It is worth noting that the yield of **7a** could significantly be improved from 8% to 30% by adding LiBr templating salt (Table 2).

Table 2. Yields of **7a,b,d,e** using the optimized procedure of **7c**

Product		**7a**	**7b**	**7d**	**7e**
solvent [°C]	time [hour]	Yields [%]			
Cyclohexanone (120)	3		15		7
	5		23.9		
	17	30.5 (8)[a]	39.5	31.5	24.3[b]
BuOH (110)	17	14	17.2		10

a, without LiBr

b, after 25 hours

It should be emphasized that during the cyclization of **5a,b** the N-formyl group cleaved resulting in the free macrocycles **7** with secondary amino function in each case. The presence of this protective group, however, proved to be necessary at least in the first stage of the bis-alkylation process to avoid the formation of N-alkylated products. Actually, when starting from **6** the yield of **7c** dramatically decreased to 12% (n-BuOH) and 24% (cyclohexanone), respectively. Similar phenomenon (N-acetyl cleavage) was observed if N-acetyl protective group (**8**) was used instead of formyl but the cyclization gave lower yield (27%, Table 1). We have unambiguously proved that the N-acyl cleavage should occur prior to formation of the macrocycle. In separate experiments **7c** was acylated with HCOOH and Ac_2O respectively[6], and treated with K_2CO_3 in cyclohexanone at 120°C (20h) but neither the formyl nor the acetyl group could be removed under these conditions.

The N-deacylation reaction can be supposed to proceed after the alkylation of one of the phenolic OH groups meanwhile the K^+ counter ion of the other phenolate (or Li^+ in case of **7a**) is complexed by the ether oxygen atoms of the forming pseudocycle with the participation of the carbonyl oxygen (Fig.1.). As a result a more reactive carbonyl carbon was formed being prone to nucleophilic attack by the weak nucleophile CO_3^{2-} ions. The assistance of the neighbouring phenoxide group and a subsequent quick deformylation of the phenolester formed can also be taken into consideration.

Structure determination.

Only one characteristic feature is worth mentioning in the ^1H NMR and IR spectra of azacrowns **7**. The NH signals in $CDCl_3$ appear at higher chemical shifts than that of diphenylamine by 1.4 - 2.4 ppm in the order of **7a** > **7b** ≈ **7d** > **7c** ≈ **7e**. Similar tendency can be observed with νNH in solid state (Table 3).

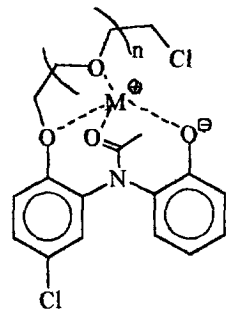


Figure 1. The possible structure of complex formed in the first alkylation step.

Table 3. NH, OH signals and frequencies of compounds 7

7	^{1}H NMR (ppm)	IR (KBr, cm^{-1})	
	NH	NH	OH
a	7.95	3300	-----
b	7.35	3300	-----
c	6.90	3150	3450
d	7.25	3200	----
e	6.87	3200	3480

From these date we can conclude that two kinds of NH hydrogen bonding should exist in compounds **7**. The NH signals of higher values (**7a,b,d**) can be attributed to an intramolecular hydrogen bonding with one of the neighbouring ArO oxygen atoms. The appearance of νOH bands in the IR spectra of **7c,e** indicate that these compounds can bind water probably with the participation of NH group.

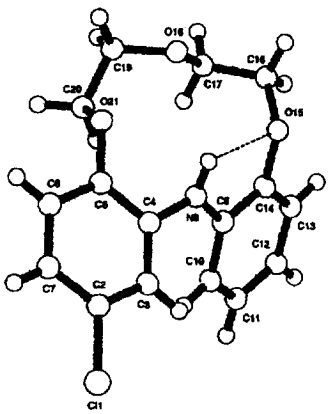
The questions were answered by single crystal X-ray determination[7]. The results of the X-ray diffraction experiments for crowns **7a**, **7b** and **7c** are shown in Figure 2.

The propeller-like conformational behaviour of the two phenyl rings leads to the presence of two chiral conformers in the unit cell of the crystals. Additionally, due to the conformationally non-equivalent role of the two phenyl rings, the chlorine substition leads to two further species, resulting in four different conformers in each crystal structure. In the case of **7a** there are two crystallographically independent molecules with similar crown conformations differing only in the location of the Cl atom (only one of them is shown in Fig.2). These two chiral molecules assume chiral shape and a centre of symmetry transforms them into their counterparts. For **7b** and **7c** the two chirally unrelated species (differing only in the location of the Cl atom attached to either one or the other phenyl group) occupy the same position in an alternative manner.

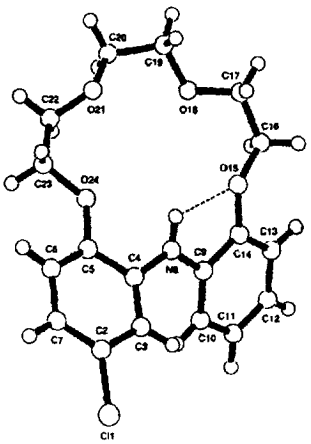
Compound **7c**, as expected, binds one molecule of water inside the crown ring involving the NH group in the hydrogen bonding system. Thus, it behaves as a tridentate ligand providing optimal environment (hydrogen-bonding donor and acceptor sites) for the encapsulation of water molecule. The intermolecular distances (the

length of H bonds) are as follows: N8...H8...O28: 1.95Å, O28...H28A...O24: 2.07Å, O28...H28B...O18: 1.89Å indicate fairly high complex stability.

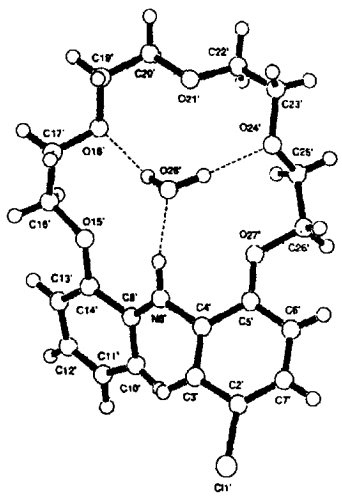
The two phenyl rings of all three compounds become distinguishable since the NH group prefers to be coplanar with one of the rings and not with the other. The lone pair on the nitrogen atom will become delocalized with the phenyl rings, resulting in a shortening of the corresponding C-N bonds and a C-N-C bond angle characteristic of sp^2 atoms[7].



7a



7b

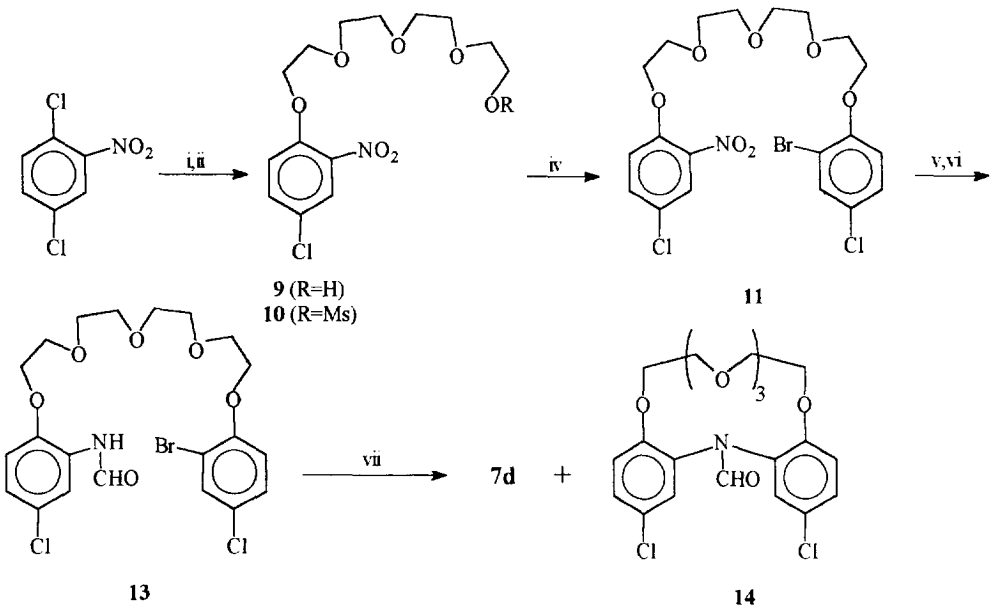


7c

Figure 2. ORTEP drawings showing the hydrogen-bonding pattern of **7a,b,c** with the water molecule in the cavity of **7c**

Route B

In one entry intramolecular Ullmann N-arylation was attempted to construct the azacrown ring after introducing the polyether chain (Scheme 4.).



Reagents i: tetraethylene glycol,Na; ii: MsCl,pyridine; iv: 2-bromo-4-chlorophenol, NaOH/BuOH; v: Fe,HCl (**12**); vi: HCOOH,Δ (**13**); vii: K_2CO_3, CuBr,Dowtherm,220°C

Scheme 4.

The unusual cyclization took place giving rise the mixture of the free crown **7d** and its N-formyl derivative **14** in 1:2 ratio with 34% total yield comparable to that achieved in route **A** (32% for **7d**). The predominant formation of N-formyl compound **14** also substantiates the assistance of the free phenoxide neighbouring group in the intermediate assumed for the deacylation process observed in route **A**. The minor **7d** could be formed prior to cyclization by the direct hydrolysis of the formamide **13**.

In the synthesis of dibenzo-azacrowns containing diphenylamine substructure the Ullmann cyclization (**B**) can be of not only theoretical value. In our work, however, owing to preparative difficulties arising in the synthesis of some intermediates, the O,O-ring closure (**A**) was preferred.

Functionalization of the N-atom in macrocycles **7** and the result of pharmacological investigations thereof will be reported elsewhere.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ at 100MHz on a JEOL FX100 spectrometer. All δ values are reported in ppm, TMS was used as internal standard. Precoated silica gel plates

(Merck 60 F_{254}) were used for analytical TLC. All chemicals were reagent grade and used without further purification. Compounds **5a,b** were prepared as described in the literature[5a].

*General procedure for the cyclization of **4a,b** with oligo(ethylene glycol)dichlorides (Route A)*

Bis-phenol **5a,b** (0.1 mol),alkylating agent (0.1mol), dry K_2CO_3 (82.8g, 0.6mol) and KI (1.7g, 0.01mol) were mixed in cyclohexanone (600ml) and stirred at 120°C for 17-20 h. The inorganic solid was filtered off, the solvent was removed under reduced pressure. The residue was extracted with hot heptane (3x100ml) then the extract was evaporated to dryness. Compounds **7b,c,d** obtained as white solids were sufficiently pure for analysis whereas **7a** and **7e** were subjected to column chromatography (silica gel, EtOAc).

2-Chloro-6,7,9,10-tetrahydro-16H-dibenzo[b,k][1,4,7,10]-monoaza-trioxacyclododecin (**7a**)

5a: 26.3g (0.1mol), 1,5-dichloro-3-oxapentane: 14.3g (0.1mol), LiBr templating salt: 5g (0.057mol). Yield: 19.32g (30%), mp: 99°C. ^{1}H NMR δ: 7.95 (s,1H,NH), 7.7-6.5 (m,7H,ArH), 4.4-3.5 (m,8H,OCH_2), Anal. calcd. for $C_{16}H_{16}ClNO_3$ (305.76) N 3.94, Cl 9.97, found: N 4.00, Cl 9.99
MS, *m/z* (%): 305(61.2), 290(10.3), 277(15.2), 261(17.4), 246(23.5), 235(9.8), 217(16.2), 199(13.1), 183(11.3), 170(15.4), 154(9.6), 142(10.8), 120(7.9), 99(8.5), 91(14.1), 77(37.2), 65(13.5), 51(11.3), 45(100)

2-Chloro-6,7,9,10,12,13-hexahydro-19H-dibenzo[b,n][1,4,7,10,13]-monoaza-tetraoxacyclopentadecin (**7b**)

5a: 26.3g (0.1mol), 1,8-dichloro-3,6-dioxaoctane: 18.7g (0.1mol), Yield: 13.8g (39.5%), mp: 102°C. ^{1}H NMR δ: 7.35 (s,1H,NH), 7.3-6.6 (m,7H,ArH), 4.3-3.7 (m,12H,OCH_2), Anal. calcd. for $C_{18}H_{20}ClNO_4$ (349.81), N 4.00, Cl 10.14, found: N 3.99, Cl 9.95.
MS, *m/z* (%): 349(57.9), 334(9.4), 321(10,8), 290(11.4), 261(18.2), 246(25.6), 235(8.7), 217(14.3), 199(10.8), 183(12.4), 170(12.9), 154(10.2), 142(8.7), 120(9.5), 99(7.2), 91(10.3), 77(28.5), 65(12.5), 51(9.4), 45(100).

2-Chloro-6,7,9,10,12,13,15,16-octahydro-22H-dibenzo[b,q][1,4,7,10,13,16]-monoaza-pentaoxa-cyclo-octadecin (**7c**)

5a: 26.3g (0.1mol), 1,11-dichloro-3,6,9-trioxaundecane:23.1g (0.1mol), Yield: 16.6g (42%), mp: 112°C ^{1}H NMR δ: 6.9 (s,1H,NH), 7.5-6.6 (m,7H,ArH), 4.3-3.7 (m,16H,OCH_2), Anal. calcd. for $C_{20}H_{24}ClNO_5$ (393.86), N 3.56, Cl 9.00, found: N 3.52, Cl 8.90
MS, *m/z* (%): 393(100), 378(11.3), 364(18.2), 334(10.7), 290(10.9), 261(14.3), 246(23.8), 235(11.6), 217(14.7), 199(11.2), 183(12.6), 170(11.7), 154(10.7), 120(7.7), 89(6.5), 71(8.2), 59(9.5), 51(9.2), 45(47.7)

2,20-Dichloro-6,7,9,10,12,13,15,16-octahydro-22H-dibenzo[b,q][1,4,7,10,13,16]-monoaza-pentaoxacyclo-octadecin (**7d**)

5b: 29.7g (0.1mol), 1,11-dichloro-3,6,9-trioxaundecane:23.1g (0.1mol), Yield: 13.5g (31.5%), mp: 137°C. ^{1}H NMR δ: 7.31 (d,2H,J_m=2Hz,ArH), 7.25 (s,1H,NH), 7.08 (dd,2H,J_o=8Hz,J_m=2Hz,ArH), 6.78 (d,2H,Jo=8Hz,ArH), 4.30-4.00 (m,4H,$ArOC\underline{H}_2$), 4.00-3.80 (m,4H,$ArCH_2C\underline{H}_2O$), 3.72 (bs,8H,CH_2O),Anal. calcd. for $C_{20}H_{23}Cl_2NO_5$ (428.30),N 3.27, Cl 16.56, found N 3.37, Cl 16.45

MS, *m/z* (%): 427(57.1)M-1$^+$, 400(13), 368(15.1), 324(14.2), 295(13.2), 280(25.0), 233(20.0), 204(22.3), 45(100)

2-Chloro-6,7,9,10,12,13,15,16,18,19-decahydro-25H-dibenzo[b,t][1,4,7,10,13,16,19]-monoaza-hexaoxacycloheneicosin (**7e**)

5a: 26.3g (0.1mol), 1,11-dichloro-3,6,9,12-tetraoxatetradecane:27.5g (0.1mol),Yield: 10.7g (24%), mp: 76°C. ^{1}H NMR δ: 6.87 (s,1H,NH), 7.4-6.5 (m,7H,ArH), 4.3-3.65 (m,20H,OCH_2), Anal. calcd. for $C_{22}H_{28}ClNO_6$ (437.90) N 3.20, Cl 8.10, found N 3.29, Cl 8.12
MS, *m/z* (%): 437(64.5), 422(18.2), 407(15.6), 378(10.9), 349(12.4), 334(11.3), 290(12.1), 261(10.8), 246(25.7), 235(13.4), 217(18.2), 199(13.9), 183(9,7), 170(10.5), 154(11.3), 120(9.1), 89(7.1), 71(6.5), 59(10.2), 51(12.3), 45(100).

N-(2-hydroxyphenyl)-N-(2-hydroxy-5-chlorophenyl)acetamide (**8**)

Formamide **5a** (13.2g , 0.05mol) was boiled in a mixture of EtOH (120ml) and aqueous HCl (18% w/w, 40ml) for 3h. The solution was concentrated in vacuo, the residue was dissolved in $CHCl_3$ (100ml), washed with aq.NaOH solution (5%), dried (Na_2SO_4) and evaporated to give 11g (96%) **6**

Compound **6** (11g, 0.046mol) was refluxed with Ac_2O (100ml) for 6h, the reaction mixture was then evaporated to dryness , dissolved in MeOH (100ml) and stirred with aqueous K_2CO_3 solution (10% w/w, 100ml) at room temperature for 4h. After standard work-up 12.5g (98%) **8** as a thick oil was obtained. Rf: 0.75 (EtOAc), IR (neat): 1710cm^{-1} (νCO), 3300cm^{-1} (νOH). Anal. calcd. for $C_{14}H_{12}ClNO_3$ (277.71), N 5.04, Cl 12.77, found: N 4.85, Cl 12.70

1-Hydroxy-11-(4-chloro-2-nitro)phenoxy-3,6,9-trioxaundecane (**9**)

Sodium (2.3g, 0.1mol) was dissolved in tetraethylene glycol (78g, 0.4mol) at 70-80°C under argon then 2,5-dichloro-1-nitrobenzene (19.2g, 0.1mol) was added and reacted at 110°C for 3h. The mixture was cooled, taken up in $CHCl_3$ (150ml) and washed with water (3x100ml), dried ($MgSO_4$) to give 29.7g (85%) yellow oil. Rf: 0.26 (EtOAc), ^{1}H NMR δ: 7.8 (d,1H,J_m=2.4Hz,ArH), 7.46 (dd,1H,J_o=9.6Hz,J_m=2.4Hz,ArH), 7.08 (d,1H,J_o=9.6Hz,ArH), 4.36-4.05 (m,2H,CH_2OAr), 4.0-3.45 (m,14H,OCH_2), 2.25 (s,1H,OH).

1-Methansulfonyloxy-11-(4-chloro-2-nitro)phenoxy-3,6,9-trioxaundecane (**10**)

Compound **9** (29.7g, 0.08mol), pyridine (7.25g, 0.09mol) was dissolved in $CHCl_3$ (100ml) then MsCl (13.3g, 0.12mol) was added at room temperature and stirred for 3h. The mixture was poured into ice-water, stirred 1h to hydrolize the excess of MsCl whereupon the phases were separated. The organic phase was washed with saturated aqueous Na_2CO_3 and water, subsequently, dried ($MgSO_4$) evaporated to yield 33.1g (97%) red oil. Rf: 0.55 (EtOAc), ^{1}H NMR δ: 7.78 (d,1H,J_m=2.4Hz,ArH), 7.47 (dd,1H,J_o=9.6Hz, J_m=2.4Hz,ArH), 7.09 (d,1H,J_o=9.6Hz,ArH), 4.50-4.13 (m,4H,CH_2OAr,$MsOCH_2$), 4.00-3.60 (m,12H,CH_2O), 3.03 (s,3H,CH_3SO_2O).

1-(4-Chloro-2-nitro)phenoxy-11-(2-bromo-4-chloro)phenoxy-3,6,9-trioxaundecane (**11**)

Compound **10** (5.5g, 0.013mol), 2-bromo-4-chlorophenol (2.93g, 0.014mol) and aqueous NaOH (50% w/w, 1.2ml) were refluxed in n-BuOH (40ml) for 3h. The solvent was removed under reduced pressure,the residue was dissolved in CH_2Cl_2 (50ml) washed with aqueous NaOH (5%,w/w)and water, subsequently. The organic phase was dried (Na_2SO_4) concentrated to give 5.6g (80%) **11** as an orange oil Rf: 0.4 (EtOAc), ^{1}H NMR δ: 7.8-6.7 (m,6H,ArH), 4.30-3.5 (m,16H,OCH_2)

*1-(4-Chloro-2-formamido)phenoxy-11-(2-bromo-4-chloro)phenoxy-3,6,9-trioxaundecane (***13***)*

Nitro compound **11** (35.4g, 0.066mol) and Fe powder (56g, 1mol) were suspended in EtOH (95%, 200ml) and HCl (37%, 5.7ml) was dropped at 60°C under vigorous stirring. The reaction mixture was then refluxed 1h, filtered while hot and evaporated to dryness. The residue was stirred in MeOH (150ml), clarified with charcoal, filtered while hot and after evaporating the solvent 16.3g oily material (**12**) was obtained. It was boiled with HCOOH (85%, 60ml) for 3h, concentrated and washed with water to remove acid then purified by column cromatography (silica gel, EtOAc) to give 9.9g (28%) oil, Rf: 0.33 (EtOAc)

Ullmann cyclization of **13** *(Route B)*

Compound **13** (4.1g, 0.008mol), K_2CO_3 (2.2g, 0.016mol) and CuBr (0.8g) were stirred in Dowtherm (30ml) at 220°C for 2h under argon. The reaction mixture was cooled to 80°C, filtered and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (EtOAc-$CHCl_3$= 1:3) to give two fractions: **7d** (0.4g, 11.6%) and **14** (0.8g, 22%)

N-Formyl-2,20-dichloro-6,7,9,10,12,13,15,16-octahydro-22H-dibenzo[b,q][1,4,7,10,13,16]-monoaza-pentaoxacyclo-octadecin (**14**)

Mp: 130-132°C ^{1}H NMR δ: 8.42 and 8.39 (s,1H,CHO,rotamer ratio: 2/1), 7.32 (d,2H,J_m=2Hz,ArH), 7.08 (dd,2H,J_o=7.9Hz,J_m=2Hz,ArH), 6.79 (d,2H,J_o=7.9Hz,ArH), 4.30-4.05 (m,4H,CH_2O), 4.00-3.80 (m,4H,CH_2O), 3.73 (bs,8H,CH_2O), Anal. calcd. for $C_{21}H_{23}Cl_2NO_6$ (456.31), N 3.07, Cl 15.54, found: N 3.18, Cl 15.48

When **7d** was subjected to formylation (HCOOH, 110°C, 8h, mp. 132°C) the same compound was obtained which was identical with **14** in every respect.

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6. Compound **7c** (0.01mol) was boiled in HCOOH(10ml, 8h) or Ac_2O (20ml, 24h), concentrated in vacuo and crystallized to give N-formyl-**7c** (60%), m.p. 128°C (ether), IR (KBr): 1730cm^{-1} (ν CO), ^{1}H NMR δ: 8.50 (s,1H,CHO), 7.23-6.90 (m,7H,ArH), 4.25-3.60 (m,16H,OCH_2) and N-acetyl-**7c** (76%) m.p. 134°C (i-PrOH), IR (KBr): 1671 cm^{-1} (ν CO), ^{1}H NMR δ: 7.35-7.05 (m,4H,ArH), 7.00-6.85 (m,3H,ArH), 4.20-3.40 (m,16H,CH_2O), 2.08 and 2.04 (s each,3H,rotamer ratio=2:1,CH_3CO)
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