Synthesis of functionalised macrocyclic compounds as Na^+ and K^+ receptors: a mild and high yielding nitration in water of mono and bis 2-methoxyaniline functionalised crown ethers

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The syntheses of the bis-aromatic 15-crown-5 and 18-crown-6-ether derivatives **1** and **2**, for the selective recognition of intra- and extracellular concentrations of Na^+ and K^+, from *o*-anisidine are described. These compounds were made with the aim of incorporating them into luminescent sensors. To facilitate their incorporation into such sensors, the compounds were nitrated. Whereas the use of conventional nitration reagents such as HNO_3, HNO_3–H_2SO_4 or NO_2BF_4 only gave low yields of the desired products, both mono- and bis-nitration products were formed in good yield by one-pot synthesis using $NaNO_2$ in a mixture of water and acetic acid (10 : 1). The use of X-ray crystallography proved the presence of the nitro-substituted products. An investigation into this mild nitration method revealed that the substitution pattern on the aromatic ring governed the ability of the compounds to undergo nitration.

Introduction

The recognition and targeting of ions and neutral molecules are at the heart of supramolecular chemistry.[1] Over the past years there has been great interest in the development of fluorescent and luminescent sensors and reagents for cations, anions and neutral molecules under physiological conditions.[1,2] In such systems the ion or molecular recognition can modulate the various photophysical properties of the luminescent centre, *e.g.* the wavelength, luminescence quantum yield (Φ_F) and/or lifetime.[2,3] Furthermore, those which display '*off–on*' or '*on–off*' (changes in Φ_F) switching of luminescence are particularly interesting since they can be designed in such a way that the switching action is governed by more than one ion or molecular receptor.[4] Such a design can give rise to switching actions that mimic the behaviour of logic gate operations in silicon-based computing.[5–7]

Designing such ion-selective receptors can be a challenging task from a synthetic point of view.[8] For an efficient sensor system the recognition event has to be reversible, selective and sensitive towards the desired species. Over the years many elegant examples of macrocyclic syntheses have been reported for the development of ion-selective receptors, and this field has been extensively reviewed.[9] However, very often such macrocyclic systems are designed for use in non-aqueous solutions which often renders them useless in the physiological environment. This is an important issue when dealing with ions under physiological conditions such as sodium and potassium. Nearly all animal cells maintain a large concentration difference in their intra- *vs.* extra-cellular concentrations of these ions.[10] For instance, for blood or serum analysis of Na^+, the ion concentration range has an upper limit of 145 mM and a lower limit of 133 mM, whereas the corresponding upper and lower limits for K^+ are much lower at 3.5–4.8 mM.[11] In contrast, the intracellular concentration range of K^+ is much higher than that of Na^+, being *ca.* 135 mM compared to that of 5 mM for Na^+. We have been interested in designing simple hosts for ion and molecular recognition that show good selectivity and sensitivity for physiologically important cations.[11] We have used these for the incorporation into both fluorescent and colorimetric (chromogenic) chemosensors for detecting Na^+, Mg^{2+}, Ca^{2+} and Zn^{2+}.[12,13] Herein we describe the design and the synthesis of several new macrocyclic receptors from aromatic crown ethers made in high yield from *o*-anisidine. Of these the macrocyclic receptors **1** and **2** were designed for incorporation into luminescent sensors for the detection of intracellular concentrations of Na^+ and K^+, respectively.[14,15]

With the aim of facilitating their incorporation into chemosensors we undertook the nitration of **1** and **2** to give **3** and **4** respectively, which were then reduced to the corresponding amines. Similarly, **12** and **17**, the mono aromatic crown ether analogues of **1** and **2** were also chosen for such modifications and incorporation into luminescent chemosensors. Use of the most common nitration reagents, such as HNO_3, HNO_3–H_2SO_4 or NO_2BF_4, gave very low yields in all cases. To investigate this further we decided to synthesise the corresponding nitroso compounds by using $NaNO_2$ in a mixture of (*ca.* 10 : 1) H_2O–AcOH. However, this method gave in each case the corresponding *nitro* compound in high or moderately good yield, but not the nitroso compounds. This was confirmed by NMR, HRMS (high resolution MS) and IR, and by X-ray crystal structural analysis. Accordingly we set out to investigate this mild nitration method further, which is highly specific, gives high yields of the desired products, is easily scaled up, as well as being extremely environmentally friendly since it is carried out in aqueous solution.

Results and discussion

Synthesis and crystallographic investigation of 1 and 2 and their complexes

The two receptors **1** and **2** were synthesised according to Scheme 1. Both receptors are flanked by the methoxy groups that function as lariat ethers that will affect both the selectivity

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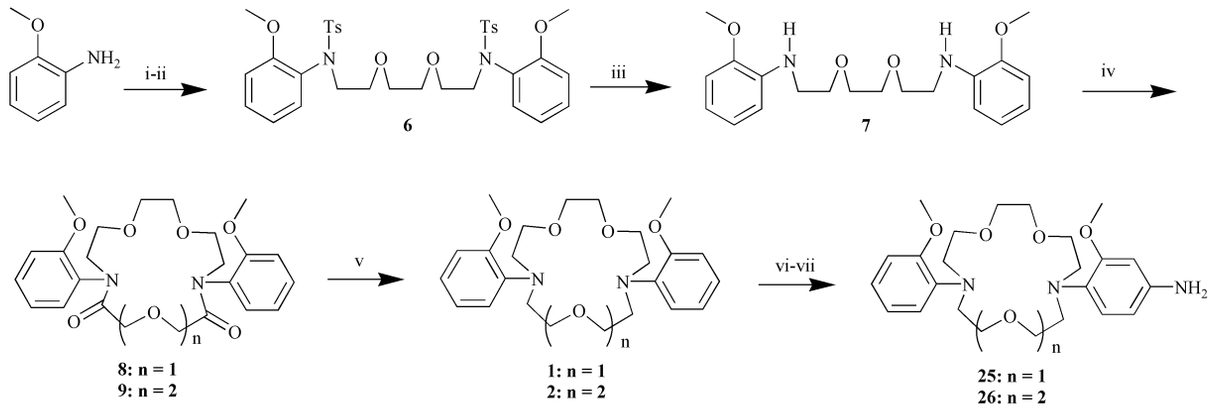


Scheme 1 The synthesis of **1** and **2**. *Reagents and conditions*: i) *o*-anisidine, pyridine, toluene-*p*-sulfonyl chloride (TsCl), reflux, giving **5** after aqueous work-up and crystallisation from ethanol. ii) **5**, DMF, KI, K_2CO_3, $(ClCH_2CH_2OCH_2)_2$, 70 °C, 3 days. iii) (3 : 2) AcOH–H_2SO_4 (98% pure), 60 °C, 24 hours. iv) For **8**: $O(CH_2COCl)_2$, pyridine, benzene, high dilution at 75 °C, 36 hours; for **9** $(ClCOCH_2OCH_2)_2$. v) B_2H_6, THF. vi) Nitration (see text). vii) **3** or **4**, H_2 (atm) 10% Pd/C.

and the sensitivity of the recognition process by providing extra binding sites and a steric effect.[16] Our attempt to make **1** and **2** in a single step from 2-fluoro-1-methoxybenzene was unsuccessful and because of this the longer synthetic route shown in Scheme 1 was chosen.

The starting material, *o*-anisidine, was treated in refluxing pyridine with toluene-*p*-sulfonyl chloride to give the corresponded tosylamide **5**, which was poured into ice–water, giving an off-white powder that was recrystallised from EtOH in 87% yield. These were allowed to react in a 2 : 1 ratio with 1,2-bis(2-chloroethoxy)ethane in the presence of two equivalents of KI and K_2CO_3 in dry DMF at 70 °C for 72 hours. The resulting solution was treated with a mixture of water and EtOAc giving **6** as an oily resin that was triturated with EtOH to give **6** in 91% yield as a solid. The podand **6** had three characteristic singlets in its ^{1}H NMR at δ 3.38 and 3.40 for the methyl ether and the two sets of methylene groups adjacent to the central oxygen of the diethyl ether respectively and at δ 2.40 for the methyl groups of the two tosyl groups.

The detosylation of **6** was achieved by stirring in a 3 : 2 mixture of glacial AcOH and H_2SO_4 (98% pure) at *exactly* 60 °C for 24 hours. The resulting mixture was neutralised with KOH and extracted several times with diethyl ether to give the detosylated product **7** in 32% yield. This reaction was extremely sensitive to temperature changes and the quality and ratio of acid used. For example, temperature changes of ±2–3 °C led on many occasions to the isolation of mixtures of products, or no product at all. Similar results were observed upon changing the quality of the sulfuric acid. For instance, using 95% pure H_2SO_4 reduced the overall yield of **7** to less than 20%. Analysis of the remaining residues indicated that the mono-tosylated product was the main product formed, but changing the reaction time did not result in the conversion of this product into **7**.

The diamide 15-crown-5 and the 18-crown-6 derivatives **8** and **9** were formed using classical macrocyclic high dilution synthesis,[17] by reacting **7** in an equimolar amount with either oxydiacetyl dichloride, or 2-(chlorocarbonylmethoxyethoxy)-acetyl chloride, to give **8** and **9** respectively in dry benzene and in the presence of dry pyridine at 75 °C. The two acid chlorides were made by a published procedure from the corresponding acids.[17] The resulting macrocycles **8** and **9** were isolated as oils, that were further purified by trituration with EtOH and diethyl ether for **8** and **9** respectively to give off-white solids in 66 and 73% yields respectively. These were finally treated with B_2H_6 (formed *in situ* from $NaBH_4$ and BF_3–Et_2O in dry THF) to yield **1** and **2** as oils after aqueous work-up in *ca.* 90% yield.

The sodium receptor **1** produced low melting crystals upon prolonged standing, whereas the potassium receptor **2** gave a crystalline solid upon trituration with diethyl ether. All the synthetic steps were easily scaled up without any changes to the synthetic procedures. The two macrocycles were characterised by conventional methods (see Experimental section). For instance, the ^{1}H NMR of **2** (in $CDCl_3$) indicated that the structure had high symmetry in solution, showing two triplets and two doublets for the aromatic protons, and two triplets at δ 3.61 and 3.55 ppm respectively and a singlet at δ 3.57 for the 24-crown ether protons. A characteristic singlet at 3.85 ppm was also observed for the two sets of the aromatic methoxy groups. We were able to grow crystals of **2** by crystallisation from CH_2Cl_2 suitable for X-ray crystallographic investigation. The structure of **2** is shown in Fig. 1, demonstrating that in the

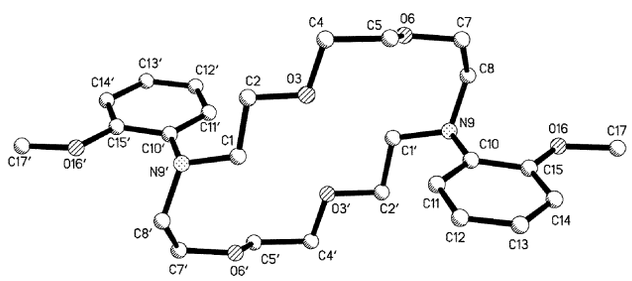


Fig. 1 Diagram of **2** showing the relative orientation of the aromatic methoxy units relative to the crown ether. Hydrogen atoms have been omitted for clarity.

solid state the molecule adopts C_{2v} symmetry where the two aromatic methoxy groups are on opposite sides of a plane cutting through the centre of the crown ether.[18,19] The dihedral angle between the methoxy group and the aromatic amine C1′–N9–C10–C11 is −16.8°. The dihedral angle for the C8′–N9′–C1′–C2′ was measured to be 154.5°. The crown ether, possessing the four oxygen and the two amino moieties, has a cavity with an N9 ··· N9′ distance of 6.75 Å, whereas the distances between O6 ··· O6′ and O3 ··· 03′ are 7.03 and 4.43 Å respectively. We were also able to obtain crystals of the sodium receptor **1**. We have previously reported these results.[9] The $K^+(PF_6^-)$ complex of **2**, **2**–**K** was also obtained by slow evaporation from 95 : 5 CH_2Cl_2–MeOH solution. The unit cell of **2**–**K** contains two unique K^+ complexes A and B, located about inversion centres. Of these two complexes, A is shown in Fig. 2, where the K^+ is coordinating to the four oxygens and the two nitrogen moieties of the crown ether. Both of the complexes A and B showed disorder within the crown ether backbone adjacent to the nitrogens of the ring. In both compounds the aromatic methoxy groups participate in the K^+ binding, with the MeO ··· K distances between 2.5 and 2.8 Å (for A the methoxy group is also disordered), giving an overall coordination geometry of eight. The bond lengths for N9 ··· K1 were measured to be 2.95 and 2.93 Å for A and B

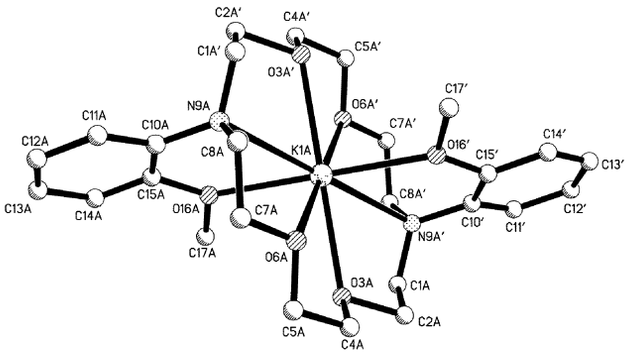


Fig. 2 Diagram of the K^+ complex of **2**, showing the eight coordination geometry of complex A. Hydrogen atoms and disorder have been omitted for clarity.

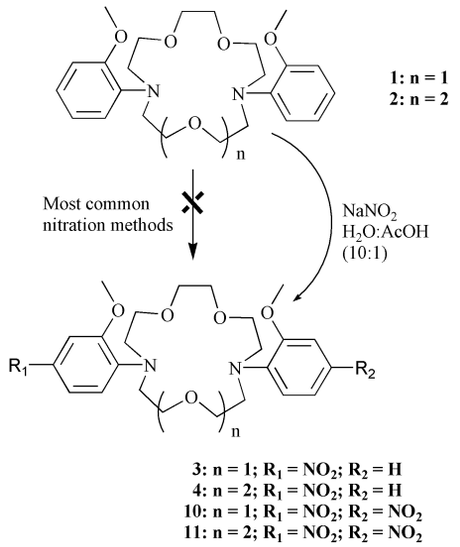
respectively, whereas the O3A ··· K1 distances were found to be 2.66 and 2.65 Å for A and B respectively. These values indicate that the ion is sitting almost in the centre of the crown cavity. The interaction of the methoxy group with the metal ion has a dramatic effect upon the overall structure; the dihedral angles C8–N9–C10–C11 are now 50.3 and 77.6° for complexes A and B respectively, indicating that the lone pair of the nitrogen has been deconjugated to a great extent from the aromatic ring. This is an important observation for the future incorporation of these receptors into luminescent sensors since the oxidation potential of the receptor is greatly increased upon K^+ complexation. This in turn could be used to modulate the rate of energy or electron transfer from the receptor, upon ion recognition, to the emitting moiety of such a sensor. Similar results were observed for the Na^+ complex of **1** (giving **1**–**Na**).[13]

The formation of **1**–**Na** and **2**–**K** was also observed by ^{1}H NMR and ESMS. For **2**–**K** the ^{1}H NMR ($CDCl_3$) showed that both the aromatic and the crown ether protons were substantially affected upon K^+ complexation. The largest effect was seen in the resonances of the crown ether protons and for the aromatic methoxy groups that participate directly in the complexation (as seen in the crystal structure above). In the ESMS, the addition of K^+ to **2** in CH_3CN gave exclusively the mass for the **2**–**K** mass peak.

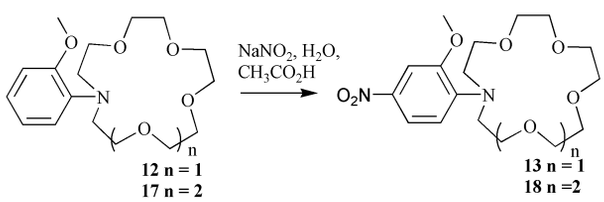
Synthesis of nitro compounds

With the aim of preparing the two receptors **1** and **2** for possible incorporation into luminescent chemosensors the two compounds were nitrated, followed by reduction to the corresponding aromatic amines. We have previously shown that **1** undergoes Vilsmeier–Haack formylation to give the mono aldehyde derivative of **1**.[13] However, we were unsuccessful in making the bis-formylated product. From this experience we anticipated that we could possibly mono-nitrate the two receptors. With this in mind the attempted nitration of **1** and **2** was undertaken using conventional nitration reagents such as HNO_3, HNO_3–H_2SO_4, HNO_3–AcOH or NO_2BF_4. For all of these, a mixture of the mono- and the bis-nitration products was observed, but in *ca.* 5–10% overall yield. Other combinations and reaction conditions, such as changing the solvent, acid ratio, temperature and reaction times, did not significantly increase the yield of these products.

To enable the scale up of the synthesis of **1** and **2** an alternative way of nitrating **1** and **2** was chosen (Scheme 2). Our original idea was to react **1** and **2** with $NaNO_2$ under acidic aqueous conditions to form the corresponding nitroso compounds, which could be converted to **3** and **4** (or **10** and **11**) using HNO_3 (Scheme 2), or the corresponding amines (**25** and **26** from **3** and **4** respectively). To investigate these reactions we initially carried out nitrosation on **12** (Scheme 3), the mono-substituted 2′-methoxyaniline derived 15-crown-5 receptor which we have previously used for incorporation into colorimetric and fluorescent chemosensors for blood and serum



Scheme 2 Synthesis of **3**, **4**, **10** and **11** by the use of $NaNO_2$ in a mixture of (10 : 1) H_2O–AcOH.



Scheme 3 The one-pot nitration method of **12** and **17** to give **13** and **18**.

analysis of Na^+.[9] The first step involved the nitroso formation in water using glacial acetic acid (HOAc) at room temperature. However, the only product obtained was the mono-nitrated derivative **13**, in over 80% yield after work-up and column chromatographic purification using aluminium oxide. Though it is known that the nitro compound can be formed under such experimental conditions, it is usually formed as a minor product. We noticed that the addition of $NaNO_2$ (in water) to a solution of **12** in aerated water and glacial acidic acid solution immediately gave an orange-coloured solution, which suggested that the nitro derivative was formed instantly and the colour change was due to the formation of an ICT (internal charge transfer) excited state in these compounds, where the aniline and the nitro moieties act as electron donor and receptors respectively. To ensure that the reaction was complete the resulting orange solution was stirred at room temperature overnight, followed by extraction using CH_2Cl_2. On all occasions an equimolar amount of the crown ether and $NaNO_2$ was used. Furthermore, the reaction did not proceed below 0 °C. The reaction times for these reactions were also short, and we were able to obtain high yields of products after only 10 minutes.

All characterisation techniques indicated that the nitro compound was the sole product, for instance the IR spectra of **13** showed only the nitro group at 1500 and 1350 cm^{-1} for the asymmetric and symmetric stretches, and ESMS showed two peaks for **13** at 371.8 for the molecular ion (M + 1) and at 392.7 for the Na^+ complex (M + Na). Examination of the crude product by ESMS did not show the presence of the nitroso compound. This reaction was also repeated in the absence of oxygen. The solution of **12** was stirred and purged with argon before addition of the $NaNO_2$ solution. A deeply orange-coloured solution was formed, indicating the formation of the nitro compound **13**. We were able to grow crystals from CH_2Cl_2, which were suitable for crystallographic investigation. Indeed, as shown in Fig. 3, the product obtained was **13**, with the nitro group *para* to the amino moiety.

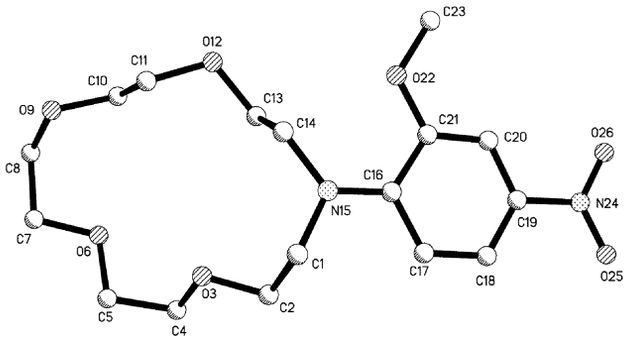


Fig. 3 Diagram of the structure of **13** showing the nitro group in the *para* position to the crown amino moiety. Hydrogen atoms have been omitted for clarity.

When the reactions were carried out using **1** and **2**, a mixture of mono- and bis-substituted nitro products, **3** and **4**, and **10** and **11** respectively, were isolated in over 80% overall yield. On both occasions the mono-nitrated product was easily isolated from the bis product by trituration or by chromatography. We were able to increase the yield of the mono-nitrated product substantially by carrying out the reaction in larger volumes. For instance, when the reaction was carried out on a 4.5 g scale of **1**, in 500 ml of water with the addition of $NaNO_2$ in 80 ml of HOAc over four hours, **4** was formed in over 70% yield.

As for **13**, the presence of the nitro groups in **11** was established by X-ray crystallography, as shown in Fig. 4. As

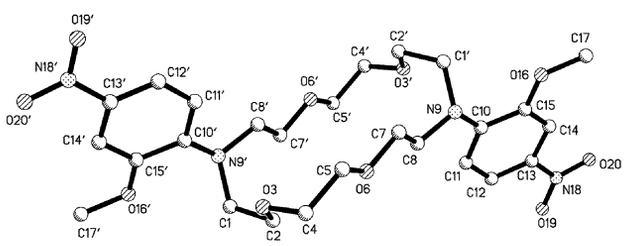
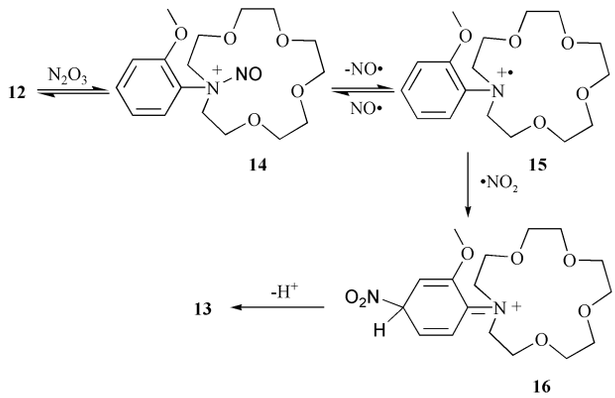


Fig. 4 Diagram of the structure of **11** showing the two nitro groups in the *para* position to the crown amino moiety. Hydrogen atoms have been omitted for clarity.

before, the crystal structure showed C_{2v} symmetry. The ^1H NMR also indicated the presence of C_2 symmetry.

The use of $NaNO_2$ in a mixture of H_2O and AcOH is a very mild method for obtaining nitro-based compounds, and is extremely attractive since it is carried out in a large excess of water and as such is environmentally friendly. To the best of our knowledge only a few examples of such a nitration method have been reported previously, and many of these used stronger acids such as HCl, H_2SO_4 or HNO_3 in the presence of $NaNO_2$.[20] Loeppky *et al.* have recently investigated in detail the mechanism behind the nitrosamine formation of *N*,*N*-dialkyl aromatic amines.[21] In the synthesis of these nitrosamines the authors used $NaNO_2$ (in a 3–15-fold excess) in either HOAc or 60% HOAc–H_2O solution buffered to pH 3.8 with NaOAc. The authors observed that in most cases the nitrosamines were formed in high yields (up to 86%). However, on several occasions a minor product was identified as the nitro-substituted *N*,*N*-dimethylaniline derivatives. The authors also reported that on occasion the ratio between the two products could be dramatically altered, in favour of the nitro product, by slight changes in the reactions conditions. The authors proposed that the mechanism for these reactions involved the formation of a nitrosammonium ion which could undergo reversible homolysis to generate NO and a radical cation or, alternatively, lose NOH to give the nitrosamine. In both cases the source of NO is N_2O_3.[22] The proposed analogous mechanism for the nitration of **12** to give **13** is shown in Scheme 4. Here the first intermediate is the nitrosammonium ion **14**,



Scheme 4 The proposed mechanism for the nitration of **14**. The same mechanism is expected in the nitration of **1** and **2**.

which breaks down to give the radical cation **15**. This reactive intermediate reacts with $NO_2^{\bullet}$ in an irreversible manner to give the nitro adduct **16**, which gives the desired product **13**, upon aromatisation. Other researchers have proposed similar mechanisms involving radical cations for the nitration of *N*,*N*-substituted anilines.[23] Nitration of **17**, the potassium receptor analogue of **12**, was also achieved under the same experimental conditions, giving **18** in 67% yield (Scheme 3).

The interesting difference between our work and that of Loeppky *et al.*[21] is the fact that in all of our reactions the nitrated products are formed exclusively, and the nitroso products are not observed at all by us either in the crude mixture or after work-up. We also carried out the nitration of **12** in the presence of a 10-fold excess of $NaNO_2$. However, the nitro product **13** was the only product isolated. The ESMS showed only two peaks for the crude reaction mixture after 12 hours: for the (M + 1) and the (M + Na) ions respectively.

To investigate this mild nitration method further we carried out a more detailed examination. For instance, we chose to nitrate several intermediates from Scheme 1, *e.g.* **5**, **6**, **7**, and several other aniline based compounds. Some of these results are summarised in Fig. 5. It can been seen that when the amino

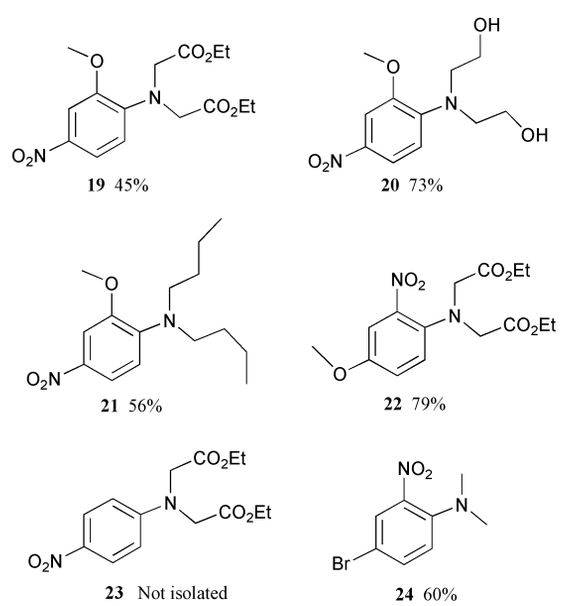


Fig. 5 The observed products and yields using $NaNO_2$ in AcOH and H_2O (1 : 10 v/v). All products were isolated after 12 hours.

moiety is tertiary, with the methoxy group in the *ortho* position, an acceptable yield of the corresponding nitro compound is obtained, *e.g.* examples **19**–**21**. When the group is in the *para* position, good yields were also obtained, as for **22**. However, this method failed to produce the desired nitro compounds

Table 1 Data collection and structure refinement details for **2**, **2–K**, **11** and **13**

Empirical formula	$C_{26}H_{38}N_2O_6$	$C_{26}H_{38}N_2O_6KPF_6$	$C_{26}H_{36}N_4O_{10}$	$C_{17}H_{26}N_2O_6$
Compound	**2**	**2–K**	**11**	**13**
M	474.58	658.65	564.59	370.40
Crystal size/mm	0.65 × 0.54 × 0.16	0.28 × 0.18 × 01.6	0.66 × 0.60 × 0.42	0.52 × 0.30 × 0.12
Crystal system	Monoclinic	Triclinic	Triclinic	Triclinic
Space group (Z)	$P2_1/c$ (2)	$P\bar{1}$ (2)	$P\bar{1}$ (1)	$P\bar{1}$ (2)
a/Å	7.218(2)	11.908(3)	7.4201(17)	8.696(3)
b/Å	7.852(2)	12.219(3)	8.1588(19)	8.943(4)
c/Å	21.449(6)	12.268(3)	11.055(3)	12.098(5)
α/°	90	86.206(3)	99.130(3)	83.932(6)
β/°	93.011(4)	70.910(3)	100.381(3)	71.217(6)
γ/°	90	64.190(3)	93.595(3)	76.937(6)
U/Å^3	1213.9(6)	1512.5(6)	647.1(3)	876.1(6)
D_c/g cm^{-3}	1.298	1.446	1.449	1.419
F(000)	512	688	300	396
μ(Mo-Kα)/mm^{-1}	0.092	0.308	0.112	0.110
ω scans; 2θ range/°	3.5–57	3–58	3.5–57	3.5–58
Unique reflections	2810	6681	2884	3838
$wR2$ ($R1$)	0.1052 (0.0483)	0.1924 (0.0593)	0.1317 (0.0460)	0.1939 (0.0640)

when the amino unit was secondary, such as in the attempted nitration of **7**, or in the case of **23**, which lacks the methoxy functionality. Furthermore, the tosylamide derivatives **5** and **6** gave no nitrated products, but the solubility of these starting materials is poor in aqueous solution. Nitration of benzo-15-crown-5 and benzo-18-crown-6, which lack the amino moieties, was also unsuccessful, whereas nitration of *N*,*N*-dimethyl-4-bromoaniline gave the corresponding nitro compound **24**.[24] On all occasions an equimolar amount of $NaNO_2$ was used. The effect of the solvent and choice of acid on the nitration product was also investigated using **21**. Using a mixture of water and glacial acetic acid and HCl or H_2SO_4 gave on all occasions the desired product under either aerated or degassed conditions. However, no nitration occurred if MeOH was used instead of water. It is apparent from these results that the substitution pattern of the starting material is very important and that the reaction only yields the nitro compounds when the amino moiety is tertiary. This is in agreement with the observations of Loeppky *et al.*[21] However, whenever the desired nitro compounds were formed, they were formed in good yield and the procedure could be scaled up.

Of these nitrated products, **3**, **4**, **13** and **18** were all reduced to the corresponding aromatic amines **25**, **26**, **27** and **28** in good yields using 10% Pd on carbon and an atmospheric pressure of H_2. Even though these products were found to be stable to oxidation in air over a long period of time (weeks) they were nevertheless stored under argon. We did not think it necessary to protect them in any other way. We are currently incorporating these aromatic amines as recognition sites in luminescent chemosensors.

Conclusion

The synthesis of the two receptors **1** and **2** was achieved in good yield in a few steps and can be easily scaled up. These compounds can be both formylated and nitrated in good yield to facilitate their incorporation into chemosensors. Although conventional nitration reagents failed to give the desired nitro products, a very mild nitration method, involving $NaNO_2$ in a mixture of water and mild acid, gave the desired products in good yields. This is a particularly attractive nitration method since it is carried out in aqueous solution, and as such it might be of great relevance to industry. This method is specific, and works well if the aromatic amino moiety is tertiary and the benzene ring is electron-rich. Of the nitrated products synthesised several were reacted further to give the corresponding amines. We are currently using these compounds for incorporation into new types of luminescent chemosensors.

Experimental

Melting points were determined using GallenKamp melting point apparatus. Infrared spectra were recorded on a Mattson Genesis II FTIR spectrophotometer equipped with a Gateway 2000 4DX2-66 workstation. Oils were analysed using NaCl plates, solid samples were dispersed in KBr and recorded as clear pressed discs. ^{1}H NMR spectra were recorded at 400 MHz using a Bruker Spectrospin DPX-400 instrument. Tetramethylsilane (TMS) was used as an internal reference standard, with chemical shifts expressed in parts per million (ppm or δ) downfield from the standard. ^{13}C NMR were recorded at 100 MHz using a Bruker Spectrospin DPX-400 instrument. Mass spectra were determined by detection using Electrospray on a Micromass LCT spectrometer, using a Waters HPLC. The whole system was controlled by MassLynx 3.5 on a Compaq Deskpro workstation.

Crystal data were collected using a Bruker SMART diffractometer with graphite monochromated Mo-Kα radiation at *ca.* 150 K in a dinitrogen stream (Table 1). Crystal stabilities were checked and there were no significant variations (< ±1%). $\omega\phi$ scans were employed for data collection and Lorentz and polarisation corrections were applied. The structures were solved by direct methods and the non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen-atom positions were added at idealised positions; a riding model with fixed thermal parameters [U_{ij} = 1.2U_{eq} for the atom to which they are bonded (1.5 for Me)] was used for subsequent refinements. The function minimised was $\Sigma[\omega(|F_o|^2 - |F_c|^2)]$ with reflection weights $\omega^{-1} = [\sigma^2|F_o|^2 + (g_1P)^2 + (g_2P)]$ where $P = [\max|F_o|^2 + 2|F_c|^2]/3$. The SAINT-NT[19] and SHELXTL[20] program packages were used for data reduction and structure solution and refinement.

CCDC reference numbers 186701–186704. See http://www.rsc.org/suppdata/p1/b2/b205299g/ for crystallographic files in .cif or other electronic format.

N-(2-Methoxyphenyl)-4-methylbenzenesulfonamide (5)

In a 250 ml round-bottom flask, 2-methoxyaniline (30.00 g, 248.5 mmol) and toluene-4-sulfonyl chloride (47.37 g, 248.5 mmol) in pyridine (120 ml) were refluxed for 45 minutes. The solution was left to cool to room temperature, then poured into 100 ml of ice–water and stirred for one hour. The grey precipitate was filtered and washed with cold water (3 × 50 ml) and then recrystallised from ethanol and dried under vacuum to give **5** (59 g, 87.23% yield) as white crystals, mp 146–147 °C. Calculated for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05, found: C, 60.60; H, 5.40; N, 5.05%; calculated for $C_{14}H_{16}NO_3S$: [M + H peak] m/z = 278.0851, found: 278.0867; δ_H($CDCl_3$, 400 MHz) 7.65 (d, J = 8.0 Hz, 2H, Ar-*H*), 7.52 (d, J = 8.0 Hz, 1H, Ar-*H*), 7.18 (d, J = 8.0 Hz, 2H, Ar-*H*), 7.05 (s, 1H, N*H*), 7.02 (t, J = 8.0

Hz, 1H, Ar-*H*), 6.89 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 6.74 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 3.64 (s, 3H, Ar-O-C*H*$_3$), 2.35 (s, 3H, Ar-C*H*$_3$); δ_C($CDCl_3$, 100 MHz) 149.46, 143.51, 136.29, 129.24, 127.15, 125.98, 125.21, 120.99, 120.96, 110.58, 55.54, 21.35; MS (MeCN, ES+) *m*/*z* expected: 277.3, found: 278.2 (M^+), 300.2 (M + Na), 316.1 (M + K); IR ν_{max}/cm^{-1} 3332, 3010, 1594, 1500, 1467, 1446, 1399, 1334, 1309, 1286, 1257, 1208, 1159, 1114, 1089, 1050, 1025, 932, 916, 823, 781, 754, 707, 661, 626, 582, 556, 536.

1,10-Bis(2-methoxyphenyl)-1,10-bis(4-methylphenylsulfonyl)-4,7-dioxa-1,10-diazadecane (6)

N-(2-Methoxyphenyl)-4-methylbenzenesulfonamide (20.00 g, 72 mmol) was placed into a 250 ml round-bottom flask containing K_2CO_3 (20.00 g, 144 mmol) and KI (4.00 g, 24 mmol) in DMF (120 ml). To this solution 1,2-bis(2-chloroethoxy)ethane (6.77 g, 5.616 ml, 36.05 mmol) was added and the mixture stirred under dry conditions for 72 hours at 70 °C. The mixture was cooled and poured into a mixture of 1 : 1 water–ethyl acetate (200 ml each) and the solution was shaken vigorously. The two layers were separated and the aqueous layer was washed 3 times with ether. The combined organic layers were dried over $MgSO_4$ and then the solvent was removed under reduced pressure to give a yellow oil that was triturated from ethanol to produce **6** (21.57 g, 90.76% yield) as a white solid, mp 142–143 °C; calculated for $C_{34}H_{40}N_2O_8S_2$: C, 61.06; H, 6.03; N, 4.19, found: C, 61.39; H, 5.80; N, 4.42%; calculated for $C_{34}H_{41}N_2O_8S_2$: [M + H peak] *m*/*z* = 669.2304, found: 669.2305; δ_H($CDCl_3$, 400 MHz) 7.56 (d, *J* = 8.04 Hz, 4H, Ar-*H*), 7.26 (m, 4H, Ar-*H*), 7.22 (d, *J* = 8.0 Hz, 4H, Ar-*H*), 6.90 (t, *J* = 7.52 Hz, 2H, Ar-*H*), 6.77 (d, 2H, *J* = 8.0 Hz, Ar-*H*), 3.73 (s, 4H, C*H*$_2$), 3.51 (t, *J* = 6.52 Hz, 4H, C*H*$_2$), 3.41 (s, 4H, C*H*$_2$), 3.38 (s, 6H, Ar-O-C*H*$_3$), 2.41 (s, 6H, Ar-C*H*$_3$); δ_C($CDCl_3$, 100 MHz) 156.37, 142.62, 137.51, 133.19, 129.68, 128.87, 127.57, 127.04, 120.49, 111.53, 70.10, 69.42, 54.79, 49.12, 21.39; MS (MeCN, ES+) *m*/*z* expected: 668.2, found: 669.7 (M^+), 691.7 (M + Na), 707.6 (M + K); IR ν_{max}/cm^{-1} 3463, 2960, 2904, 2867, 1596, 1498, 1459, 1436, 1322, 1284, 1263, 1221, 1160, 1135, 1116, 1091, 1074, 1043, 1024, 960, 914, 860, 811, 782, 757, 709, 657, 586, 553, 528, 511, 489.

1,10-Bis(2-methoxyphenyl)-4,7-dioxa-1,10-diazadecane (7)

To a 3 : 2 mixture of glacial acetic acid and sulfuric acid (70 ml : 46.6 ml) at 60 °C (exactly), 1,10-bis(2-methoxyphenyl)-1,10-bis(4-methylphenylsulfonyl)-4,7-dioxa-1,10-diazadecane (5.00 g, 7.24 mmol) was added and the suspension stirred for 24 hours. The mixture was then poured hot into 400 ml of H_2O and the pH brought up to 7, by adding KOH pellets. The aqueous solution was extracted three times with ether, and the combined ether layers were washed twice with K_2CO_3 (0.1 M) solution and twice with H_2O. The salt was also washed with ether and combined with the organic layer. The organic layers were then dried over $MgSO_4$ and the solvent removed under reduced pressure, to give a thick brown oil (1.85 g) which was purified by flash column chromatography using 25 : 75, ethyl acetate–hexane to yield **7** (0.85 g, 31.6% yield) as a pale yellow oil that was triturated and later recrystallised from ethanol, mp 216–217 °C; calculated for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77, found: C, 66.09; H, 7.78; N, 7.68%; calculated for $C_{20}H_{29}N_2O_4$: [M + H peak] *m*/*z* = 361.2127, found: 361.2126; δ_H($CDCl_3$, 400 MHz) 6.89 (t, *J* = 7.52 Hz, 2H, Ar-*H*), 6.79 (d, *J* = 7.52 Hz, 2H, Ar-*H*), 6.70 (t, *J* = 7.56 Hz, 2H, Ar-*H*), 6.65 (d, *J* = 7.52 Hz, 2H, Ar-*H*), 4.62 (br s, 2H, N-H), 3.85 (s, 6H, C*H*$_2$), 3.77 (t, *J* = 5.00 Hz, 4H, C*H*$_2$), 3.70 (s, 4H, C*H*$_2$), 3.37 (t, *J* = 5.00 Hz, 4H, C*H*$_2$); δ_C($CDCl_3$, 100 MHz) 147.07, 138.15, 121.16, 116.56, 109.91, 109.49, 70.31, 69.80, 55.32, 43.24; MS (MeCN, ES+) *m*/*z* expected: 360.2, found: 361.2 (M^+), 383.2 (M + Na), 399.2 (M + K); IR ν_{max}/cm^{-1} 3413, 3064, 3002, 2937, 2896, 2685, 1602, 1513, 1456, 1430, 1346, 1222, 1178, 1139, 1027, 935, 904, 738.

7,13-Bis(2-methoxyphenyl)-1,4,10-trioxa-7,13-diazacyclopentadecane-8,12-dione (8)

1,10-Bis(2-methoxyphenyl)-4,7-dioxa-1,10-diazadecane (7.0 g, 19.43 mmol) and oxydiacetyl dichloride (95% purity, 3.48 g, 19.4 mmol), each dissolved in dry benzene (300 ml), were placed into two pressure equalising dropping funnels, and over a period of 12 hours were simultaneously dripped into a stirred mixture of dry benzene (800 ml) and dry pyridine (16 ml) placed in a 2 l, three-neck, round-bottom flask under an inert atmosphere. The solution was stirred for a further 12 hours at 75 °C after addition had been completed. The solvent was removed under vacuum, and the residues were dissolved in CH_2Cl_2. The organic solution was washed twice with HCl (1 M) and twice with H_2O, dried over $MgSO_4$ and removed under reduced pressure to give an off-yellow residue (8.183 g, 17.85 mmol). The product was recrystallised from ethanol to form a white solid (5.92 g, 12.91 mmol) in 67% yield, mp 152–153 °C; calculated for $C_{24}H_{30}N_2O_7$: C, 62.85; H, 6.60; N, 6.11, found: C, 62.35; H, 6.66; N, 5.93%; calculated for $C_{24}H_{31}N_2O_7$: [MH^+ peak] *m*/*z* = 459.2131, found: 459.2132; δ_H($CDCl_3$, 400 MHz) 7.3 (m, 8H, Ar-*H*), 3.77 (m, 22H, Ar-O-C*H*$_3$, crown-H); δ_C($CDCl_3$, 125.8 MHz) 170, 169, 155, 154, 132, 130, 129, 128, 127, 121, 120, 119, 112, 111, 76, 70, 69, 68, 66, 55, 47, 45; MS (MeCN, ES+) *m*/*z* expected: 458.20, found: 459.2 (M^+), 481.1 (M + Na), 497.2 (M + K), 916.76 (M_2^+), 938.65 (M_2Na^+); IR ν_{max}/cm^{-1} 3449, 2986, 2939, 2346, 1672, 1596, 1500, 1458, 1440, 1414, 1359, 1341, 1290, 1278, 1246, 1219, 1190, 1149, 1120, 1096, 1058, 1044, 1019, 990, 968, 926, 898, 867, 780, 763, 670, 578, 500.

7,16-Bis(2-methoxyphenyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-6,17-dione (9)

The synthesis of compound **9** is identical to that for compound **8** using 1,10-bis(2-methoxyphenyl)-4,7-dioxa-1,10-diazadecane (7.00 g, 19.43 mmol) and (2-chlorocarbonylmethoxyethoxy)-acetyl chloride (4.176 g, 19.42 mmol). After reaction, the organic layer was dried over $MgSO_4$ and removed under reduced pressure to give a yellow–white residue (7.09 g, 14.10 mmol) of a mixture of the *cis* and *trans* forms of **9**, which solidified on standing to give a white solid in 72.64% yield. Calculated for $C_{26}H_{35}N_2O_8$: [M + H peak] *m*/*z* = 503.2393, found: 503.2383; δ_H($CDCl_3$, 400 MHz) 7.58 (d, 2H, *J* = 8.04 Hz, Ar-*H*), 7.32 (t, 2H, *J* = 8.30 Hz, Ar-*H*), 7.06 (t, 2H, *J* = 8.04 Hz, Ar-*H*), 6.90 (d, 2H, *J* = 8.04 Hz, Ar-*H*), 4.03 (s, 1H, C*H*$_2$), 3.99 (s, 1H, C*H*$_2$), 3.89 (s, 1H, C*H*$_2$), 3.86 (s, 1H, C*H*$_2$), 3.87 (s, 6H, Ar-O-C*H*$_3$), 3.61–3.56 (m, 8H, C*H*$_2$), 3.42–3.37 (m, 6H, C*H*$_2$), 2.98 (t, 1H, *J* = 4.52 Hz, C*H*$_2$), 2.95 (t, 1H, *J* = 4.52 Hz, C*H*$_2$); δ_C($CDCl_3$, 100 MHz) 169.85, 154.92, 132.26, 129.72, 127.75, 121.28, 111.21, 71.05, 70.50, 69.91, 67.63, 55.26, 45.72; MS (MeCN, ES+) *m*/*z* expected: 502.56, found: 503.37 (M^+), 525.42 (M + Na), 549.48 (M + K); IR ν_{max}/cm^{-1} 3434, 2928, 2876, 1648, 1596, 1500, 1459, 1438, 1399, 1347, 1290, 1260, 1159, 1098, 1022, 769, 584.

7,13-Bis(2-methoxyphenyl)-1,4,10-trioxa-7,13-diazacyclopentadecane (1)

7,13-Bis(2-methoxyphenyl)-1,4,10-trioxa-7,13-diazacyclopentadecane-8,12-dione (4.905 g, 10.7 mmol) was added to a stirred solution of dry THF (60 ml). To this stirred solution, at room temperature, a six-fold equivalent of $NaBH_4$ (2.524 g, 66.7 mmol) was added, and then over a period of two hours, an eight-fold equivalent of boron trifluoride–diethyl ether (12.519 g, 88.2 mmol) in dry THF (60 ml) was added.

After addition the suspension was refluxed for 4 hours and then poured into 30 ml of H_2O and the pH brought to 7 using KOH. The aqueous solution was extracted twice with CH_2Cl_2. The organic layer washed several times with H_2O, and then dried over $MgSO_4$. The solvent was removed under reduced pressure to give a colourless oil, which crystallised upon standing to give a 97.67% yield (4.502 g, 10.4 mmol) of **1**. Calculated for $C_{24}H_{34}N_2O_5$: C, 66.94; H, 7.96; N, 6.51, found: C, 66.08; H, 7.96; N, 6.35%; calculated for $C_{24}H_{35}N_2O_5$: [M + H peak] *m*/*z* = 431.2546, found: 431.2538; δ_H($CDCl_3$, 400 MHz) 7.05 (d, 2H, *J* = 7.56 Hz, Ar-*H*), 6.95 (t, 2H, *J* = 6.04 Hz, Ar-*H*), 6.87 (m, 4H, Ar-*H*), 3.84 (s, 6H, Ar-O-CH_3), 3.72 (t, 4H, *J* = 5.52 Hz, CH_2), 3.66 (m, 8H, CH_2), 3.51–3.44 (m, 8H, CH_2); δ_C($CDCl_3$, 100 MHz) 152.96, 140.55, 122.21, 121.01, 120.75, 111.90, 71.20, 70.78, 69.80, 53.38, 53.21, 52.51; MS (MeCN, ES+) *m*/*z* expected: 430.2, found: 431.3 (M^+), 453.3 (M + Na), 861.6 (M_2 + H), 883.7 (M_2 + Na); IR ν_{max}/cm^{-1} 3059, 2927, 2856, 1725, 1593, 1499, 1461, 1353, 1238, 1180, 1108, 1028, 795, 744.

7,16-Bis(2-methoxyphenyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (2)

The synthesis of compound **2** is identical to that for **1** using 7,16-bis(2-methoxyphenyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane-6,17-dione (6.077 g, 12.1 mmol), which was added to a stirred solution of dry THF (60 ml). To this stirred solution, at room temperature, a six-fold equivalent of $NaBH_4$ (2.852 g, 75.3 mmol) was added, and then over a period of two hours, an eight-fold equivalent of boron trifluoride–diethyl ether (14.142 g, 99.6 mmol) in dry THF (60 ml) was added. After work-up, a colourless oil was isolated that crystallised upon standing to give a 91.59% yield (5.256 g, 11.07 mmol) of **2**. A small sample of this material was crystallised by slow evaporation from DCM. Mp 206–208 °C; calculated for $C_{26}H_{38}N_2O_6{\cdot}CH_2Cl_2$: C, 57.96; H, 7.21; N, 5.01, found: C, 57.89; H, 6.91; N, 5.04%; calculated for $C_{26}H_{39}N_2O_6$: [M + H peak] *m*/*z* = 475.2808, found: 475.2798; δ_H($CDCl_3$, 400 MHz) 7.18 (d, 2H, *J* = 7.52 Hz, Ar-*H*), 6.98 (t, 2H, *J* = 7.56 Hz, Ar-*H*), 6.91 (t, 2H, *J* = 7.56 Hz, Ar-*H*), 6.87 (d, 2H, *J* = 8.04 Hz, Ar-*H*), 3.85 (s, 6H, Ar-O-CH_3), 3.61 (t, 8H, *J* = 5.52 Hz, CH_2), 3.56 (s, 8H, CH_2), 3.49 (t, 8H, *J* = 6.04 Hz, CH_2); δ_C($CDCl_3$, 100 MHz) 153.07, 139.28, 122.45, 121.45, 120.72, 111.78, 70.54, 69.90, 55.37, 52.65; MS (MeCN, ES+) *m*/*z* expected: 474.2, found: 475.3 (M^+), 497.3 (M + Na), 513.3 (M + K); IR ν_{max}/cm^{-1} 3446, 3069, 3002, 2889, 2859, 1579, 1499, 1458, 1436, 1368, 1336, 1285, 1266, 1243, 1209, 1187, 1170, 1129, 1103, 1088, 1050, 1022, 994, 915, 880, 824, 799, 744, 718, 612, 584, 542, 479, 410.

General procedure for the nitration

To a 250 ml single-necked round-bottom flask 13-(2-methoxyphenyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (0.585 g, 1.89 mmol) was added along with 60 ml of distilled water and 6 ml of glacial acetic acid (100%). The solution was stirred at room temperature. Over a ten minute period 10 ml of deionised water containing $NaNO_2$ (0.144 g, 2.09 mmol, 97%) was added. The solution turned bright orange during this addition. The solution was then left to stir overnight. The orange solution was washed with DCM (4 × 50 ml). The organic phases were combined and dried over K_2CO_3, and the resulting solution was reduced to a yellow oil. This was purified by column chromatography through alumina using 99 : 1 diethyl ether–MeOH, or by trituration.

7-(2-Methoxy-4-nitrophenyl)-13-(2-methoxyphenyl)-1,4,10-trioxa-7,13-diazacyclopentadecane (3)

Isolated in 48% yield as a yellow oil. Calculated for $C_{24}H_{34}N_3O_7$: [M + H peak] *m*/*z* = 476.2397, found: 476.2420; δ_H($CDCl_3$, 400 MHz) 7.81 (dd, 1H, J_1 = 6.52, J_2 = 2.48 Hz Ar-*H*), 7.67 (d, 1H, *J* = 2.52 Hz, Ar-*H*), 6.99 (d, 1H, *J* = 8.04 Hz, Ar-*H*), 6.94 (d, 1H, *J* = 7.52 Hz, Ar-H), 6.93–6.83 (m, 3H, Ar-H), 3.87 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.77 (t, 2H, *J* = 5.0 Hz, OCH_2CH_2), 3.71–3.61 (m, 14H, OCH_2CH_2), 3.46 (t, 2H, *J* = 5.48 Hz, OCH_2CH_2), 3.38 (t, 2H, *J* = 4.52 Hz, OCH_2CH_2); δ_C($CDCl_3$, 100 MHz) 153.19, 149.56, 146.30, 140.43, 139.46, 122.53, 121.42, 120.70, 118.34, 115.54, 111.92, 107.32, 71.44, 70.85, 70.75, 69.73, 69.38, 55.82, 55.33, 53.68, 55.35, 53.14, 52.24; MS (MeCN, ES+) *m*/*z* expected: 475.23, found: 476.1 (M + H); IR ν_{max}/cm^{-1} 3431 (H_2O), 2922, 2857, 1585, 1509, 1458, 1322, 1276, 1240, 1183, 1096, 1025, 862, 798, 745.

7,13-Bis(2-methoxy-4-nitrophenyl)-1,4,10-trioxa-7,13-diazacyclopentadecane (10)

Isolated in 17% yield as a yellow solid. Mp 130–131 °C. Calculated for $C_{24}H_{32}N_4O_9$: C, 55.38; H, 6.20; N, 10.76, found: C, 55.63; H, 6.20; N, 10.46%; calculated for $C_{24}H_{33}N_4O_9$: [M + H peak] *m*/*z* = 521.2248, found: 521.2260; δ_H($CDCl_3$, 400 MHz) 7.81 (dd, 2H, J_1 = 9.00, J_2 = 2.52 Hz, Ar-*H*), 7.68 (d, 2H, *J* = 2.52 Hz, Ar-*H*), 6.86 (d, 2H, *J* = 9.04 Hz, Ar-*H*), 3.87 (s, 6H, OCH_3), 3.73 (t, 4H, *J* = 5.0 Hz, OCH_2CH_2), 3.68 (m, 8H, OCH_2CH_2), 3.62 (s, 8H, OCH_2CH_2); δ_C($CDCl_3$, 100 MHz) 149.76, 146.32, 139.79, 118.28, 115.72, 107.37, 71.35, 70.90, 69.50, 55.88, 53.67, 52.68; MS (MeCN, ES+) *m*/*z* expected: 520.5, found: 521.2 (M + H); IR ν_{max}/cm^{-1} 2927, 2885, 2862, 1584, 1491, 1319, 1278, 1242, 1095, 1062, 1025, 967, 872, 798, 746, 721, 643, 593, 556.

7-(2-Methoxy-4-nitrophenyl)-16-(2-methoxyphenyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (4)

Isolated in 43% yield as a yellow oil. Calculated for $C_{26}H_{37}N_3O_8$: C, 60.10; H, 7.18; N, 8.09, found: C, 60.49; H, 7.41; N, 7.58%; calculated for $C_{26}H_{38}N_3O_8$: [M + H peak] *m*/*z* = 520.2659, found: 520.2676; δ_H($CDCl_3$, 400 MHz) 7.82 (dd, 1H, J_1 = 6.52, J_2 = 2.52 Hz, Ar-*H*), 7.68 (d, 1H, *J* = 2.0 Hz, Ar-*H*), 7.11 (d, 1H, *J* = 6.04 Hz, Ar-*H*), 6.97–6.84 (m, 4H, Ar-H), 3.89 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.73–3.71 (m, 8H, OCH_2CH_2), 3.62–3.57 (m, 12H, OCH_2CH_2), 3.53–3.48 (m, 4H, OCH_2CH_2); δ_C($CDCl_3$, 100 MHz) 153.12, 149.76, 146.16, 139.77, 139.94, 122.58, 121.41, 120.66, 118.19, 116.05, 111.84, 107.27, 70.73, 70.57, 70.08, 69.82, 55.82, 55.34, 52.70, 52.67; MS (MeCN, ES+) *m*/*z* expected: 519.6, found: 520.7 (M + H); IR ν_{max}/cm^{-1} 3434 (H_2O), 2921, 2863, 1579, 1508, 1457, 1321, 1275, 1242, 1181, 1095, 800, 746, 669.

7,16-Bis(2-methoxy-4-nitrophenyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (11)

Isolated in 36% yield) as a yellow solid. Mp 147–149 °C. Calculated for $C_{26}H_{36}N_4O_{10}$: C, 55.31; H, 6.43; N, 9.92, found: C, 55.37; H, 6.45; N, 9.61%; calculated for $C_{26}H_{37}N_4O_{10}$: [M + H peak] *m*/*z* = 565.2510, found: 565.2507; δ_H($CDCl_3$, 400 MHz) 7.82 (dd, 2H, J_1 = 6.52, J_2 = 2.52 Hz Ar-*H*), 7.68 (d, 2H, *J* = 2.48 Hz, Ar-*H*), 6.91 (d, 2H, *J* = 9.04 Hz, Ar-*H*), 3.89 (s, 6H, OCH_3), 3.70 (s, 12H, OCH_2CH_2), 3.60 (s, 12H, OCH_2CH_2); δ_C($CDCl_3$, 100 MHz) 149.84, 146.11, 139.94, 118.19, 115.97, 107.34, 70.80, 70.07, 55.88, 52.76; MS (MeCN, ES+) *m*/*z* expected: 564.2, Found: 565.2 (M + H), 586.7 (M + Na), 602.7 (M + K); IR ν_{max}/cm^{-1} 3434 (H_2O), 2922, 2886, 2856, 1582, 1509, 1484, 1453, 1328, 1280, 1249, 1127, 1094, 1026, 991, 910, 873, 801, 728, 528, 554, 483, 431.

13-(2-Methoxy-4-nitrophenyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (13)

Isolated as yellow oil that solidified upon standing for a few days in 89% yield. Mp 75–76 °C. Calculated for $C_{17}H_{26}N_2O_7$: C, 55.13; H, 7.08; N, 7.56, found: C, 55.35; H, 7.09; N, 7.26%;

calculated for $C_{17}H_{27}N_2O_7$: [M + H peak] *m/z* = 371.1818, found: 371.1817; δ_H($CDCl_3$, 400 MHz) 7.77 (dd, 1H, J_1 = 9.04, J_2 = 2.52 Hz, Ar-*H*), 7.63 (d, 1H, *J* = 2.52 Hz, Ar-*H*), 6.86 (d, 1H, J_1 = 9.04 Hz, Ar-*H*), 3.83 (s, 3H, OCH_3), 3.70 (t, 4H, *J* = 5.52 Hz, OCH_2CH_2), 3.64–3.59 (m, 16H, OCH_2CH_2); δ_C($CDCl_3$, 100 MHz) 149.36, 145.96, 139.25, 118.24, 115.37, 107.21, 70.97, 70.30, 70.17, 69.72, 55.72, 53.64; MS (MeCN, ES+) *m/z* expected: 370.4, found: 371.8 (M + H), 392.7 (M + Na); IR ν_{max}/cm^{-1} 2940, 2885, 2856, 1585, 1512, 1497, 1319, 1292, 1269, 1239, 1223, 1120, 1096, 1051, 1025, 992, 940, 891, 857, 800, 742, 669, 615.

16-(2-Methoxy-4-nitrophenyl)-1,4,7,10,13-pentaoxa-16-aza-cyclooctadecane (18)

Isolated in 68% yield as a yellow oil. Calculated for $C_{19}H_{30}N_2O_8$: C, 55.06; H, 7.30; N, 6.76, found: C, 54.57; H, 7.20; N, 6.42; calculated for $C_{19}H_{31}N_2O_8$: [M + H peak] *m/z* = 415.2080, found: 415.2066; δ_H($CDCl_3$, 400 MHz) 7.81 (dd, 1H, J_1 = 9.36, J_2 = 2.32 Hz, Ar-*H*), 7.66 (d, 1H, *J* = 2.92 Hz, Ar-*H*), 6.93 (d, 1H, J_1 = 9.32 Hz, Ar-*H*), 3.88 (s, 3H, OCH_3), 3.70–3.66 (m, 16H, OCH_2CH_2), 3.65–3.63 (m, 4H, OCH_2CH_2), 3.61–3.60 (m, 4H, OCH_2CH_2); δ_C($CDCl_3$, 100 MHz) 149.85, 146.20, 139.81, 118.20, 116.36, 107.26, 70.77, 70.68, 70.53, 69.76, 55.85, 52.81; MS (MeCN, ES+) *m/z* expected: 414.4, found: 415.2 (M + H), 437.2 (M + Na), 453.2 (M + K); IR ν_{max}/cm^{-1} 2914, 2870, 1584, 1509, 1458, 1321, 1275, 1243, 1176, 1096, 1024, 923, 800, 748.

[Ethoxycarbonylmethyl(2-methoxy-4-nitrophenyl)amino]acetic acid ethyl ester (19)

Isolated in 44% yield as a yellow oil. Calculated for $C_{13}H_{17}N_2O_7$: [M + H peak] *m/z* = 313.1036, found: 313.1038; δ_H($CDCl_3$, 400 MHz) 7.80 (dd, 1H, J_1 = 9.04, J_2 = 2.52 Hz, Ar-*H*), 7.69 (d, 1H, *J* = 2.48 Hz, Ar-*H*), 6.67 (d, 1H, *J* = 9.0 Hz, Ar-*H*), 4.20 (s, 4H, CH_2), 3.85 (s, 3H, OCH_3), 3.78 (s, 6H, $COOCH_3$); δ_C($CDCl_3$, 100 MHz) 170.90, 149.55, 144.97, 141.21, 118.06, 115.77, 107.50, 56.11, 54.17, 52.07; MS (MeCN, ES+) *m/z* expected: 312.3, found: 313.2 (M + H), 335.2 (M + Na); IR ν_{max}/cm^{-1} 3448, 3000, 2953, 2852, 1750, 1685, 1588, 1515, 1458, 1329, 1289, 1249, 1207, 1176, 1101, 1011, 946, 863, 804, 745, 721, 627, 560.

2-[(2-Hydroxyethyl)(2-methoxy-4-nitrophenyl)amino]ethanol (20)

Isolated in 59% yield as a yellow oil. Calculated for $C_{11}H_{17}N_2O_5$: [M + H peak] *m/z* = 257.1137, found: 257.1137; δ_H($CDCl_3$, 400 MHz) 7.82 (dd, 1H, J_1 = 9.04, J_2 = 2.52 Hz, Ar-*H*), 7.71 (d, 1H, *J* = 2.52 Hz, Ar-*H*), 7.0 (d, 1H, *J* = 8.52 Hz, Ar-*H*), 3.93 (s, 3H, OCH_3), 3.77 (t, 4H, *J* = 5.04 Hz, CH_2), 3.56 (t, 4H, *J* = 5.0 Hz, CH_2), 2.96 (br s, 2H, OH); δ_C($CDCl_3$, 100 MHz) 150.84, 145.42, 141.07, 117.98, 117.82, 107.39, 60.43, 55.94, 55.15; MS (MeCN, ES+) *m/z* expected: 256.2, found: 257.1 (M + H); IR ν_{max}/cm^{-1} 3387, 2957, 2928, 2873, 1584, 1509, 1321, 1274, 1241, 1093, 1068, 1024, 799, 745.

Dibutyl(2-methoxy-4-nitrophenyl)amine (21)

Isolated in 55% yield as a yellow oil. Calculated for $C_{15}H_{25}N_2O_3$: [M + H peak] *m/z* = 281.1865, found: 281.1879; δ_H($CDCl_3$, 400 MHz) 7.82 (dd, 1H, J_1 = 9.04, J_2 = 2.0 Hz, Ar-*H*), 7.68 (d, 1H, *J* = 2.52 Hz, Ar-*H*), 6.72 (d, 1H, *J* = 9.04 Hz, Ar-*H*), 3.89 (s, 3H, OCH_3), 3.32 (t, 4H, *J* = 7.52 Hz, CH_2), 1.54 (m, 4H, CH_2), 1.30 (quartet, 4H, *J* = 7.04 Hz, CH_2), 0.92 (t, 6H, *J* = 7.52 Hz, CH_3); δ_C($CDCl_3$, 100 MHz) 149.93, 146.51, 139.31, 118.31, 115.72, 107.37, 55.81, 55.24, 29.86, 20.28, 13.88; MS (MeCN, ES+) *m/z* expected: 280.3, found: 281.3 (M + H); IR ν_{max}/cm^{-1} 2958, 2930, 2871, 1585, 1509, 1465, 1323, 1285, 1241, 1099, 1029, 932, 864, 801, 746.

[Ethoxycarbonylmethyl(4-methoxy-2-nitrophenyl)amino]acetic acid ethyl ester (22)

Isolated in 79% as a yellow oil. Calculated for $C_{13}H_{17}N_2O_7$: [M + H peak] *m/z* = 313.1036, found: 313.1038; δ_H($CDCl_3$, 400 MHz) 7.46 (d, 1H, *J* = 8.76 Hz, Ar-*H*), 7.23 (d, 1H, *J* = 2.92 Hz, Ar-*H*), 7.03 (dd, 1H, J_1 = 9.36, J_2 = 2.92 Hz, Ar-*H*), 4.06 (s, 4H, CH_2), 3.81 (s, 3H, OCH_3), 3.68 (s, 6H, $COOCH_3$); δ_C($CDCl_3$, 100 MHz) 171.00, 156.16, 147.10, 136.34, 127.88, 119.59, 109.21, 55.83, 55.40, 51.74; MS (MeCN, ES+) *m/z* expected: 312.3, found: 313.2 (M + H), 335.2 (M + Na); IR ν_{max}/cm^{-1} 3432, 3006, 2955, 2847, 1751, 1530, 1438, 1355, 1292, 1203, 1174, 1029, 849, 808, 624, 562.

3-Methoxy-4-[13-(2-methoxyphenyl)-1,4,10-trioxa-7,13-diaza-cyclopentadecan-7-yl]phenylamine (25)

Compound **3** (0.7643 g, 1.61 mmol) was placed in a 250 ml round-bottom flask. To this was added 10% Pd–C (0.10 g) and ethanol (100 ml). The solution was stirred under a H_2 atmosphere until no more H_2 was consumed. The resulting solution was passed through a Celite filter, and the resulting solution reduced under vacuum to produce a colourless resin, which slowly turned light purple over time. The resin was purified by acid/base extraction to yield **25** (0.4228 g, 59.0%). Calculated for $C_{24}H_{36}N_3O_5$: [M + H peak] *m/z* = 446.2655, found: 446.2655; δ_H($CDCl_3$, 400 MHz) 7.04 (d, 1H, *J* = 7.52 Hz, Ar-*H*), 6.92 (m, 2H, Ar-*H*), 6.87 (d, 1H, *J* = 7.52 Hz, Ar-*H*), 6.82 (d, 1H, *J* = 8.04 Hz, Ar-*H*), 6.19 (m, 2H, Ar-*H*), 3.80 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.70 (t, 2H, *J* = 5.52 Hz, OCH_2CH_2O), 3.62 (m, 8H, OCH_2CH_2O), 3.54 (t, 2H, *J* = 6.0 Hz, OCH_2CH_2O), 3.46 (m, 4H, OCH_2CH_2O), 3.41 (m, 4H, OCH_2CH_2O); δ_C($CDCl_3$, 100 MHz) 155.15, 152.70, 143.20, 140.36, 131.52, 125.10, 121.93, 120.72, 120.56, 111.73, 106.49, 100.50, 70.83, 70.78, 70.52, 69.66, 69.54, 55.20, 55.03, 53.91, 53.39, 53.27, 52.96, 52.49; MS (MeCN, ES+) *m/z* expected: 445.56, found: 446.23 (M + H), 468.28 (M + Na); IR ν_{max}/cm^{-1} 3426, 2927, 2858, 1617, 1509, 1458, 1353, 1239, 1212, 1171, 1110, 1028, 950, 830, 748, 568.

3-Methoxy-4-[16-(2-methoxyphenyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl]phenylamine (26)

Same procedure as for compound **25**: from compound **4** (0.7643 g, 1.61 mmol), giving **26** in 74.47% yield (0.487 g). Calculated for $C_{26}H_{40}N_3O_6$: [M + H peak] *m/z* = 490.2917, found: 490.2912; δ_H($CDCl_3$, 400 MHz) 7.10 (dd. 1H, J_1 = 7.52, J_2 = 1.52 Hz, Ar-*H*), 6.96 (d, 1H, *J* = 8.04 Hz, Ar-*H*), 6.91 (t, 1H, *J* = 7.52 Hz, Ar-*H*), 6.85 (t, 1H, *J* = 7.54 Hz, Ar-*H*), 6.80 (d, 1H, *J* = 7.54 Hz, Ar-*H*), 6.20 (m, 2H, Ar-*H*), 3.96 (br s 2H, N-H), 3.77 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.54 (t, 4H, *J* = 5.04 Hz, OCH_2CH_2O), 3.50 (m, 16H, OCH_2CH_2O), 3.35 (t, 4H, *J* = 6.04 Hz, OCH_2CH_2O); δ_C($CDCl_3$, 100 MHz); 154.82, 152.89, 143.03, 139.06, 130.08, 124.40, 122.27, 121.32, 120.49, 111.63, 106.56, 99.98, 70.27, 70.23, 69.71, 69.26, 55.15, 55.04, 53.28, 52.47; MS (MeCN, ES+) *m/z* expected: 489.61, found: 490.16 (M + H); IR ν_{max}/cm^{-1} 3463, 3341, 3208, 2932, 2870, 1620, 1509, 1463, 1349, 1249, 1213, 1174, 1139, 1116, 1032, 992, 927, 874, 819, 751, 635, 613, 548, 477.

13-(2-Methoxy-4-aminophenyl)-1,4,7,10-tetraoxa-13-azacyclo-pentadecane (28)

Same procedure as for **25**, using **18** (3.052 g, 7.36 mmol). Isolated as a coloured oil that was purified by column chromatography through alumina using DCM to yield **28** (1.923 g, 67.85%) as a purple resin. Calculated for $C_{19}H_{33}N_2O_6$: [M + H peak] *m/z* = 385.2339, found: 385.2349; δ_H($CDCl_3$, 400 MHz) 7.28 (s, 2H, N-H), 6.73 (d, 1H, *J* = 8.52 Hz, Ar-*H*), 6.33 (s, 1H, Ar-*H*), 6.19 (d, 1H, *J* = 8.04 Hz, Ar-*H*), 3.56 (s, 3H, OCH_3), 3.41 (s, 8H, OCH_2CH_2), 3.36 (br s, 4H, OCH_2CH_2), 3.21 (br s, 4H, OCH_2CH_2), 3.10 (br s, 4H, OCH_2CH_2), 2.92 (br s, 4H,

OCH_2CH_2); δ_C($CDCl_3$, 100 MHz) 155.25, 127.50, 125.40, 124.02, 108.67, 99.84, 69.23, 69.06, 69.02, 68.74, 66.76, 55.14, 55.02; MS (MeCN, ES+) *m*/*z* expected: 384.8, found: 385.12 (M + H), 407.1 (M + Na); IR ν_{max}/cm^{-1} 3427, 2897, 1610, 1513, 1468, 1350, 1285, 1258, 1215, 1106, 1029, 956, 834, 602.

16-(2-Methoxy-4-aminophenyl)-1,4,7,10,13-pentaoxa-16-aza-cyclooctadecane (27)

Same procedure as for **25**, using **13** (0.464 g, 1.25 mmol). The resulting oil was purified by column chromatography through alumina using DCM to give **27** in 98% yield (0.419 g). Calculated for $C_{17}H_{29}N_2O_5$: [M + H peak] *m*/*z* = 341.2076, found: 341.2070; δ_H($CDCl_3$, 400 MHz) 7.00 (d, 1H, *J* = 6.80 Hz, Ar-*H*), 6.30 (s, 1H, Ar-*H*), 6.22 (d, 1H, *J* = 8.28 Hz, Ar-*H*), 5.46 (br s 2H, N-H), 3.78 (s, 3H, OCH_3), 3.70 (s, 4H, OCH_2CH_2), 3.64 (t, 4H, *J* = 3.28 Hz, OCH_2CH_2), 3.53 (t, 4H, *J* = 4.52 Hz, OCH_2CH_2), 3.42 (s, 4H, OCH_2CH_2), 3.26 (s, 4H, OCH_2CH_2); δ_C($CDCl_3$, 100 MHz) 173.35, 154.78, 145.96, 125.05, 106.85, 98.65, 68.88, 68.80, 68.83, 67.01, 54.95, 54.89; MS (MeCN, ES+) *m*/*z* expected: 340.4, found: 340.9 (M + H), 362.9 (M + Na); IR ν_{max}/cm^{-1} 3433, 3208, 2917, 2874, 1610, 1513, 1458, 1352, 1294, 1258, 1214, 1122, 1027, 941, 829, 631.

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