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Synthesis of New Macrocyclic Bispidinone Ionophores

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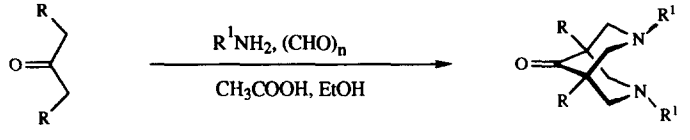
Abstract: A linear synthesis, a convergent synthesis and cyclic Mannich reactions were used to prepare the macrocyclic bispidinone ionophores (6-7), (14) and (12-13). The convergent synthesis required successful alkylation of the *N*-unsubstituted bispidinone (9).

Macrocyclic crown ethers and other ionophores can bind cations,[1] anions and small neutral organic molecules.[2] The initial design of macrocycles focused on simple ether and amine donors that were essential for efficient substrate binding. Progress has led to the incorporation of different structural moieties such as thiophene,[3] pyridine,[4] bipyridine,[5] and tetrapyridine[6] which has allowed a greater selectivity in substrate binding. The 3,7-diazabicyclo[3.3.1]nonan-9-one (1) ring system (bispidinone) contains two nitrogen donor atoms enclosed as a 1,3-diaminopropane fragment within a novel backbone of two fused cyclohexylamine rings. This provides structural constraints and a unique molecular platform capable of substituent versatility and modification. We were interested in preparing ionophores with new conformational sites and chose to investigate the synthesis of macrocycles containing the bispidinone ring system.

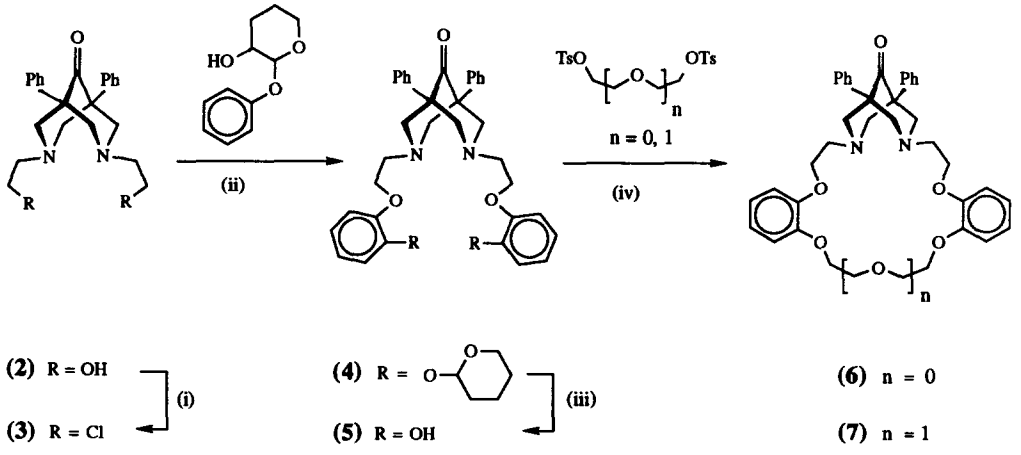


(1)

Symmetrically *N*-substituted bispidinones can be readily prepared by Mannich condensations between a propanone, formaldehyde and primary amine.[7] The substituents on the bispidinone can be controlled by varying the amine or propanone employed in the Mannich reaction and functional group transformations allow further elaboration within this system.

Initially, macrocyclisation reactions on the dicatechol bispidinone (5) were explored. The preparation[8] of (5) was undertaken by a linear Williamson like synthesis from the dihydroxy ethyl bispidinone (2). (Scheme 1). Catechol protected as the tetrahydropyranyl ether[9] was condensed with the dichloroethyl bispidinone (3) to give the protected bispidinone (4). Hydrolysis of (4) gave the hydrochloride of (5) quantitatively. The dichloro ethyl bispidinone (3) was obtained by facile treatment of the dihydroxy ethyl bispidinone (2) with thionyl chloride.

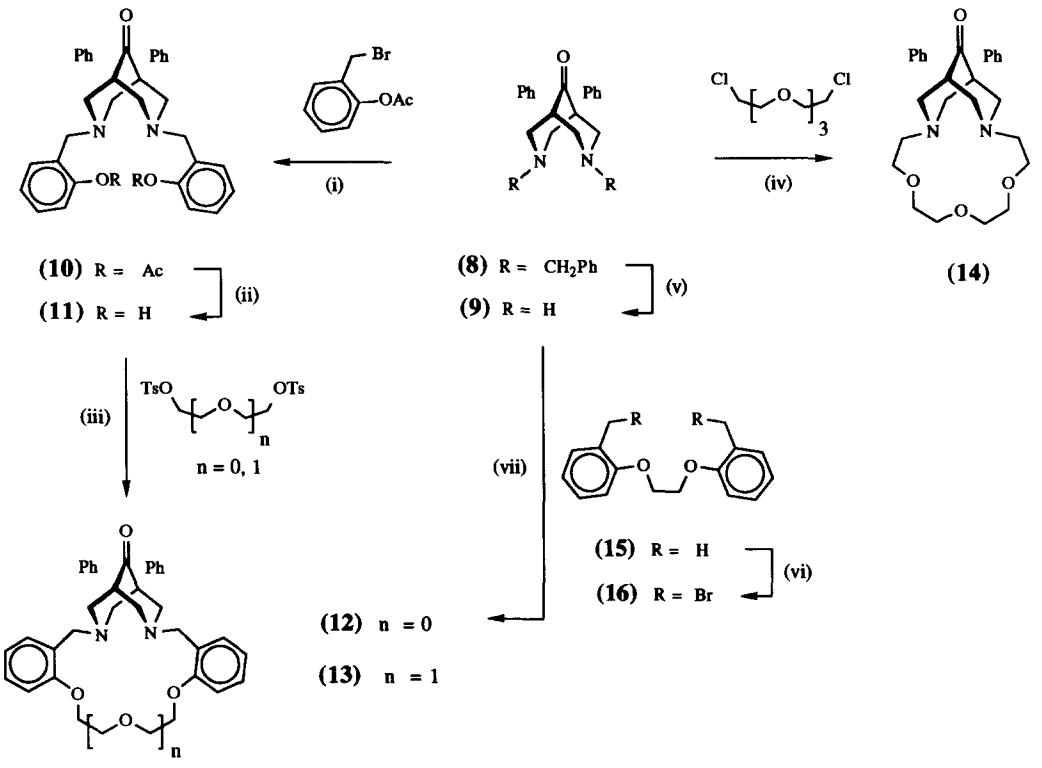
Macrocycles containing phenoxyether linkages have been prepared[10] following the condensation of biscatechol ethers with divalent halogenated substrates. Surprisingly, attempts to induce the cyclisation of (5) with 1,2-dibromoethane under analogous conditions were unsuccessful. Alternatively the condensation of bispidinone (5) with bistosylate esters,[11] using potassium hydroxide as a base, allowed the effective synthesis of the macrocycles (6) and (7) in 91% and 72% yield respectively.



Scheme 1. Reaction conditions: (i) $SOCl_2$. (ii) NaOH, DMF. (iii) 1. HCl; 2. NH_4OH. (iv) KOH, THF, H_2O.

A more general and convergent synthetic route for the preparation of macrocyclic bispidinones was investigated next. This methodology relied upon dialkylation of the *N*-unsubstituted bispidinone (9) (Scheme 2).

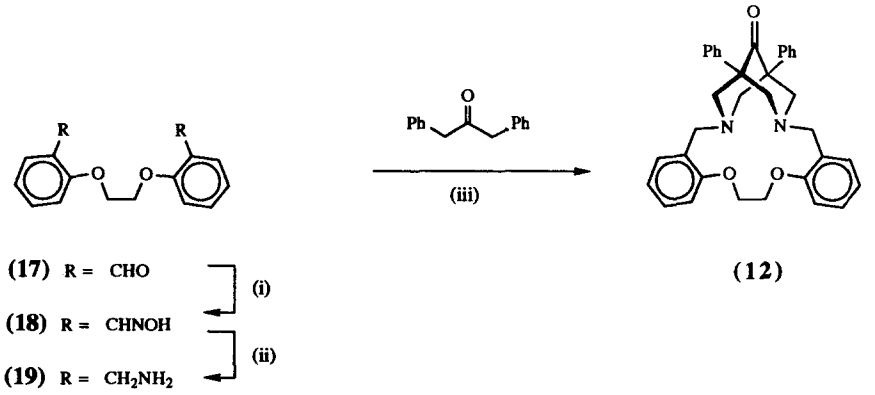
The bispidinone (9) was generated after the hydrogenolysis of the dibenzyl bispidinone (8). The original account[12] of this preparation had claimed the use of alcohol with palladium/carbon; however this reduction was found to be extremely slow due to the almost complete insolubility of (8). Previously we have demonstrated[8] that addition of a catalytic amount of perchloric acid to the alcoholic reaction mixture increased the hydrogenation rate and now we report that the change of solvent system to hot ethyl acetate results in the ready dissolution of (8) and provides the most efficient environment for this reduction.



Scheme 2. Reaction conditions: (i) K_2CO_3, MeCN. (ii) KOH, EtOH, H_2O. (iii) KOH, THF, H_2O. (iv) NaI, Na_2CO_3, MeCN. (v) H_2-Pd/C, EtOAc. (vi) *N*-bromosuccinimide, dibenzoylperoxide, CCl_4. (vii) KOH, DMSO, H_2O.

N-Alkylation of the bispidinone (9) directly provided macrocycles (14), (12) or the macrocyclic precursor (10). The synthesis of macrocycle (14) required the *in situ* preparation of diiodo diethylene glycol from the homologous dichloride.[11] Alkylation of (9) with the diiodide using sodium carbonate as a base in acetonitrile produced (14) in a 72% yield. In an analogous reaction (9) was dialkylated with 2-bromomethylphenylacetate,[13] using potassium carbonate as a base, to give the bispidinone (10) in 75% yield. Comparatively the macrocycle (12) was prepared in a highly polar and nucleophilic reaction environment. Dialkylation of (9) with the dibromobenzyl ether (16) was completed in dimethyl sulfoxide with potassium hydroxide as a base to give (12) in a 54% yield. The dibromobenzyl ether (16) was prepared in 56% yield by the benzylic bromination of the toluic ether (15)[14] with *N*-bromosuccinimide and dibenzoylperoxide.

The macrocyclic precursor (10) was deprotected by alkaline hydrolysis to give the diphenoxy bispidinone (11). Condensation of the bispidinone (11) with bistosylate esters, using potassium hydroxide as a base, allowed the effective synthesis of the macrocycles (12) and (13) in 46% and 75% yield respectively.



Scheme 3. Reaction conditions: (i) $NH_2OH{\bullet}HCl$, CH_3COONa, EtOH. (ii) $LiAlH_4$, THF. (iii) CH_3COOH, $(CHO)_n$, EtOH.

Finally, macrocyclic ring formation with a Mannich reaction on a suitable diamine template was explored (Scheme 3). The diamine (19), precursor to the macrocycle (12), was prepared in a 25% yield by the reduction of the bisoxime (18) with lithium aluminium hydride. The oxime (18) was obtained quantitatively after treating the bisaldehyde (17)[15] with hydroxylamine. A Mannich reaction between the diamine (19), dibenzyl ketone and formaldehyde gave the macrocycle (12) in 48% yield.

The bispidinone skeleton was clearly characterised by ^1H nmr, ^{13}C nmr and infrared spectroscopy (see Table). ^1H nmr spectroscopy identified the protons of the 1,5-disubstituted bispidinone ring system as an AB quartet. This pattern derives from the geminal couplings between the isolated axial and equatorial protons and can be interpreted by two methods. One interpretation is that in which these protons are fixed in a symmetrical configuration, the other suggests an average representation of the axial and equatorial protons of the bispidinone in different conformations that are in a rapid equilibrium on the nmr time scale.

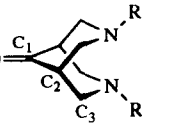
A double chair conformation was anticipated for the macrocyclic bispidinones although bispidinones with 1,5 phenyl substituents,[16] or containing sp^3 nitrogen atoms are reported[12] to adopt two degenerate chair-boat conformations. A crystal structure of the macrocycle (14) revealed the degenerate chair-boat conformation and a variable temperature nmr study demonstrated that in solution this configuration was in a rapid equilibrium.[17] Accordingly it is likely that the majority of bispidinones and macrocycles described here would behave in a similar manner.

Axial protons are more strongly shielded than equatorial protons and the lower field doublet of the AB pattern has been assigned accordingly. The chemical shifts, in deuterated chloroform, of the axial protons range between 2.96-3.45 ppm and the equatorial protons range between 3.48-3.94 ppm. Coupling constants for the axial and equatorial protons range between 10.66-11.73 Hz.

In the ^{13}C nmr spectra of symmetrically substituted bispidinones individual signals were observed for the equivalent methylene and the bridgehead carbon atoms. The chemical shifts of these carbons ranged between 53-67 ppm. Generally it was observed that the carbonyl groups of bispidinones behaved as ketones.

Their ^{13}C resonances ranged between 208-212 ppm, and the infrared absorbances were observed in the region between 1720-1740 cm^{-1}.

Table . The ^{1}H n.m.r. chemical shifts (δ)[a,d] of axial and equatorial protons, with their coupling constants (J)[b], the ^{13}C n.m.r. chemical shifts (δ)[a,d] of ring carbons, and the carbonyl absorptions (υ)[c] in some symmetrical and macrocyclic bispidinones.



Bispidinone	δ ax	δ eq	J ax eq	δC_1	δC_2	δC_3	υ (carbonyl)
(5)	3.21	3.78	11.30	209.9	54.2	65.4	1733
(6)	3.22	3.87	11.04	211.5	54.8	65.4	1732
(7)	3.45	3.80	10.78	211.3	54.7	66.4	1724
(10)	3.10	3.51	10.86	210.7	56.0	65.1	1734, 1764
(11)	3.17	3.66	11.73	208.9	53.6	65.1	1735
(12)	2.96	3.58	11.00	211.5	54.8	65.0	1729
(13)	3.08	3.48	10.66	211.9	54.4	64.7	1732
(14)	3.12	3.94	10.87	211.8	55.4	64.6	1727

[a]In ppm. [b]In Hz. [c]In cm^{-1}. [d]Spectrum recorded in deuterated chloroform.

In summary, the preparation of novel macrocyclic bispidinone ionophores by a linear synthesis, a convergent synthesis, and a cyclic Mannich reaction has been demonstrated. The convergent synthesis was general requiring dialkylation of a unique *N*-unsubstituted bispidinone.

EXPERIMENTAL

General Information

^{1}H n.m.r. spectra were recorded at 300 MHz with a Bruker CXP-300 or at 500 MHz with a Bruker AM-500 spectrometer, and refer to deuterochloroform solutions with chloroform (7.26 ppm) as an internal standard. Signals due to exchangeable protons (NH) were identified by exchange with deuterium oxide. The usual notational conventions are used. ^{13}C n.m.r. spectra were recorded at 125.77 MHz with a Brucker AM-500 spectrometer, and refer to deuterochloroform solutions with chloroform (77.0 ppm) as an internal standards. Low resolution mass spectra were obtained on an A.E.I. MS12 spectrometer at 70eV and 8000V accelerating potential at 210 °C ion source temperature. Infrared spectra were recorded with a Perkin Elmer 580B and refer to paraffin mulls or KBr disks of solids. Microanalyses were performed by Dr. H.P. Pham of the UNSW Microanalytical Unit.

3,7-Bis-(2-hydroxyphenoxyethyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one **(5)**

A suspension of 3,7-bis-(2-hydroxyphenoxyethyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one hydrochloride[8] (25.0 g) in acetone was treated with a solution of concentrated ammonium hydroxide. The

mixture was heated gently until the salt had dissolved. After evaporation, the residue was suspended in a concentrated ammonium hydroxide solution and extracted with dichloromethane. The organic extracts were washed with a saturated sodium chloride solution, dried ($MgSO_4$), and concentrated to give an oil which crystallized upon addition of ethanol. Recrystallization from ethanol gave the free base of the bispidinone (5) (15.7g) as a white solid m.p. 141 °C (Found: C, 74.8; H, 6.7; N, 5.0. $C_{35}H_{36}N_2O_5$ requires C, 74.5; H, 6.4; N, 5.0%). υ_{max} 1733, 1381, cm^{-1}. ^1H n.m.r. δ 2.86, t, 4H, J 5.46 Hz, NCH_2; 3.21, d, 4H, J_{axeq} 11.30 Hz, Hax; 3.78, d, 4H, J_{axeq} 11.30 Hz, Heq; 4.26, t, 4H, J 5.46 Hz, OCH_2; 6.79-7.36, m, 18H, aryl. ^{13}C n.m.r. δ 54.2 CPh; 55.8, NCH_2; 65.4 ring CH_2; 68.0, OCH_2; 115.8, 116.4, 120.1, 123.4, 127.2, 128.1, aryl CH; 139.6, 145.4, 148.3, aryl C; 209.9, CO. *m/z* 387 (18%), 91 (100).

18,21-Diphenyldibenzo[e, k]4,7,10,13-tetraoxa-1,16-diazatricyclo[14.3.3.1^{18,21}]tricosan-23-one (6)

A mixture of 3,7-bis-(2-hydroxyphenoxyethyl)-1,5-diphenyl-3, 7-diazabicyclo[3.3.1]nonan-9-one (6) (4.00 g, 7.10 mmol), potassium hydroxide (2.40 g, 36.4 mmol), ethyleneglycol ditosylate[11] (3.05 g, 8.24 mmol) in tetrahydrofuran (200 ml) with water (4 ml) was heated under reflux for 48 h and concentrated. The residue was triturated with dichloromethane and chromatographed on a short column of alumina. The fraction eluted with dichloromethane (ca. 400 ml) was concentrated and recrystallized from dichloromethane/ethanol to give the macrocycle (6) (3.8 g, 91%) as colourless crystals, m.p. 216-217 °C (Found: C, 75.3; H, 6.7; N, 4.6. $C_{37}H_{38}N_2O_5$ requires C, 75.2; H, 6.5; N, 4.7%). υ_{max} 1732, 1598, 1507, 1475, 1258, 1218, 1131, 747, 702 cm^{-1}. ^1H n.m.r. δ 3.06, t, 4H, J 4.81 Hz, NCH_2; 3.22, d, 4H, J_{axeq} 11.04 Hz, Hax; 3.87, d, 4H, J_{axeq} 11.04 Hz, Heq; 4.25, t, 4H, J 4.81 Hz, OCH_2; 4.30, s, 4H, OCH_2CH_2O; 6.87-7.28, m, 18H, aryl. ^{13}C n.m.r. δ 54.8 CPh; 56.2, NCH_2; 65.4 ring CH_2; 67.4, 68.6, OCH_2; 114.0, 115.7, 121.5, 121.9, 126.5, 127.0, 127.8, aryl CH; 142.7, 148.8, 149.2, aryl C; 211.5, CO. *m/z* 590 (M, 4%), 103 (100).

21,24-Diphenyldibenzo[e, n]4,7,10,13,16-pentaoxa-1,19-diazatricyclo[17.3.3.1^{21,24}]hexacosan-26-one (7)

This was prepared as described for the macrocycle (6), from 3,7-bis-(2-hydroxyphenoxyethyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (5) (1.00 g, 71.8 mmol), potassium hydroxide (600 mg, 7.13 mmol), diethyleneglycol ditosylate[11] (800 mg, 1.88 mmol) in tetrahydrofuran (49 ml) with water (1 ml). Recrystallization from dichloromethane/isopropanol gave the macrocycle (7) (810 mg, 72%) as colourless crystals, m.p. 83-85 °C (Found: C, 75.3; H, 6.9; N, 4.4. $C_{39}H_{42}N_2O_6$ requires C, 73.8; H, 6.7; N, 4.4%). υ_{max} 1724, 1501, 1456, 1252, 1126 cm^{-1}. ^1H n.m.r. δ 2.98, t, 4H, J 4.65 Hz, NCH_2; 3.45, d, 4H, J_{axeq} 10.78 Hz, Hax; 3.53, t, 4H, J 5.16 Hz, OCH_2; 3.80, d, 4H, J_{axeq} 10.78 Hz, Heq; 3.94, t, 4H, J 5.16 Hz, OCH_2; 4.23, t, 4H, CH_2O; 6.80-6.94, m, 18H, aryl. ^{13}C n.m.r. δ 54.7 CPh; 56.2, NCH_2; 66.4 ring CH_2; 66.8, 69.3, 70.2, OCH_2; 113.7, 114.0, 121.3, 121.4, 126.5, 127.2, 127.8, aryl CH; 143.0, 148.9, 149.0, aryl C; 211.3, CO. *m/z* 634 (M, 2%), 103 (100).

***1,5-Diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one* (9)**

A solution of 1,5-diphenyl-3,7-dibenzyldiazabicyclo[3.3.1]nonan-9-one[8] (8) (20.0 g, 42.4 mmol) in ethyl acetate (500 ml) was treated with palladium/charcoal (10%, 2.0 g). This mixture was stirred under a hydrogen atmosphere, at 70 °C and ambient pressure, until uptake of this gas ceased (ca. 6h). The reaction mixture was concentrated, suspended in chloroform and filtered. Evaporation and recrystallization from ethanol gave the bispidinone (9) (9.5 g, 77%) as colourless crystals, m.p. 204-205 °C (lit[18] 205-206 °C), this was spectroscopically identical to an authentic sample prieviously reported by us[8].

***15,18-Diphenyl-4,7,10-trioxa-1,13-diazatricyclo[11.3.3.1^{15,18}]eicosan-20-one* (14)**

Under a nitrogen atmosphere a mixture of diethylene glycol bis(2-bromoethyl)ether[11] (1.20 g, 3.75 mmol), sodium iodide (1.60 g, 10.7 mmol) and anhydrous sodium carbonate (3.50 g, 33.0 mmol), in acetonitrile (150 ml), was heated under reflux for 24h. 1,5-Diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (9) (1.00 g, 3.42 mmol) was introduced and the reaction mixture was maintaind under reflux for 4h. After cooling, the mixture was filtered and any remaining solid was washed with dichloromethane. The filtrates were combined, concentrated and the residue was chromatographed on a short column of alumina. After eluting with dichloromethane (ca. 400 ml) and then dichloromethane/methanol (46:1), the fraction was concentrated and recrystallized from ethanol to give the macrocycle (14) (1.11 g, 72%) as colourless crystals, m.p. 139-140 °C (Found: C, 71.7; H, 7.8; N, 6.3. $C_{27}H_{34}N_2O_5$ requires C, 72.0; H, 7.6; N, 6.2%). υ_{max} 2862, 1727, 1357, 1132, 700 cm^{-1}. ^{1}H n.m.r. δ 2.98, m, 4H, NCH_2; 3.12, d, 4H, J_{axeq} 10.87 Hz, Hax; 3.65-3.71, m, 12H, OCH_2; 3.94, d, 4H, J_{axeq} 10.87 Hz, Heq; 7.15-7.32, m, 10H, aryl. ^{13}C n.m.r. δ 55.4, CPh; 56.6, NCH_2; 64.6 ring CH_2; 67.7, 70.14, 70.42, OCH_2; 126.5, 127.0, 127.8, aryl CH; 141.3, aryl C; 211.8, CO. *m/z* 450 (M, 70%), 380 (100).

***3,7-Bis(2-acetoxybenzyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one* (10)**

Under a nitrogen atmosphere 1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (9) (1.00 g, 3.42 mmol) was dissolved in hot acetonitrile (40 ml). 2-Bromomethylphenyl acetate[13] (1.75 g, 7.65 mmol) and anhydrous potassium carbonate were introduced and the resulting mixture was heated under reflux for 1h. After cooling, the reaction mixture was filtered and concentrated. Crystallization of the residue from ether gave the bispidinone (10) (1.5 g, 75%) as colourless crystals, m.p. 174-175 °C (Found: C, 75.5; H, 6.4; N, 4.9. $C_{37}H_{36}N_2O_5$ requires C, 75.5; H, 6.2; N, 4.8%). υ_{max} 1764, 1734, 1371, 1214, 1177 cm^{-1}. ^{1}H n.m.r. δ 2.36, s, 6H, CH_3; 3.10, d, 4H, J_{axeq} 10.86 Hz, Hax; 3.51, d, 4H, J_{axeq} 10.86 Hz, Heq; 3.64, s, 4H, NCH_2; 7.08, dd, 2H, J 7.84 Hz, J 1.52 Hz, aryl; 7.15-7.36, m, 14H, aryl; 7.56, dd, 2H, J 7.43 Hz, J 1.93 Hz, aryl. ^{13}C n.m.r. δ 21.1, CH_3; 54.3, CPh; 56.0, NCH_2; 65.1 ring CH_2; 122.6, 126.1, 126.7, 126.9, 127.9, 128.7, aryl CH; 129.9, aryl C; 131.0, aryl CH; 142.5, 149.5, aryl C; 169.2, $COCH_3$; 210.7, CO. *m/z* 588 (M, 3%), 107 (100).

***3,7-Bis(2-hydroxybenzyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one* (11)**

A mixture of 3,7-bis(2-acetoxybenzyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (10) (6.00 g, 10.2 mmol) and potassium hydroxide (0.6 g), in ethanol (40 ml) with water (1 ml) was heated under reflux for 1h. After cooling the precipitate was collected, washed with ethanol and dried to give the bispidinone (11) (4.7 g, 91%) as a white solid. Recrystallization from methanol/dichloromethane gave colourless crystals, m.p. 197-199 °C (Found: C, 78.9; H, 6.7; N, 5.6. $C_{33}H_{32}N_2O_5$ requires C, 78.6; H, 6.4; N, 5.6%). υ_{max} 1735, 1381, cm^{-1}. ^{1}H n.m.r. δ 3.17, d, 4H, J_{axeq} 11.73 Hz, Hax; 3.66, d, 4H, J_{axeq} 11.73 Hz, Heq; 3.81, s, 4H, NCH_2; 6.86, dt, 2H, J 7.40 Hz, J 0.92 Hz, aryl; 6.99, dd, 2H, J 8.0 Hz, aryl; 7.07, dd, 2H, J 7.8 Hz, J 1.1 Hz, aryl; 7.19-7.35, m, 12H, aryl; 10.12, bs, 2H, OH. ^{13}C n.m.r. δ 53.6, CPh; 60.0, NCH_2; 65.1 ring CH_2; 117.4, 120.2, aryl CH; 121.5, aryl C; 127.1, 127.5, 128.2, 129.6, 130.0, aryl CH; 138.6, 156.3, aryl C; 208.9, CO. *m/z* 504 (M, 2%), 103 (100).

***1,2-Bis(2-bromomethylphenoxy)ethane* (16)**

Under a nitrogen atmosphere a mixture of 1,2-bis(2-methylphenoxy)ethane (15)[14] (10 g, 42 mmol), *N*-bromosuccinimide (16 g, 90 mmol) and dibenzoylperoxide (300 mg) in carbon tetrachloride (150 ml) was heated under reflux for 1h. After cooling, the reaction mixture was filtered, concentrated and triturated with ethyl acetate to give the dibromide (16) (9.3 g, 56%) as a white solid, m.p. 122-125 °C (Found: C, 48.1; H,

4.1. $C_{16}H_{16}Br_2O_2$ requires C, 48.0; H, 4.0%). υ_{max} 1601, 1499, 1457, 1293, 1255, 1221, 1056, 752 cm^{-1}. ^1H n.m.r. δ 4.48, s, 4H, OCH_2; 4.56, s, 4H, CH_2Br; 6.93-7.00, m, 4H, aryl; 7.28-7.36, m, 4H, aryl. ^{13}C n.m.r. δ 29.1, CH_2Br; 67.1, OCH_2; 112.3, 121.3, aryl CH; 126.7 aryl C; 130.2, 131.1, aryl CH; 156.6 aryl C. *m/z* 402 (Br^{81}) (M, 3%), 400 (Br^{81}, Br^{79}) (M, 5), 398 (Br^{79}) (M, 3), 239 (100).

***Ethyleneglycol-O,O'-bis(2-benzaldoxime)* (18)**

A mixture of diethyleneglycol-O,O'-bis(2-benzaldehyde) (17)[15] (15 g, 56 mmol), hydroxylamine hydrochloride (8.50 g, 122 mmol) and anhydrous sodium acetate (10.0 g, 122 mmol) in ethanol (250 ml) was heated under reflux for 2h. The solvent was removed and the residue was taken up in ether/water. The organic phase was collected, washed with a saturated sodium chloride solution, dried ($MgSO_4$), concentrated and recrystallized from ethanol to give the oxime (18) (15.9 g, 96%) as colourless crystals, m.p. 171 °C (Found: C, 64.0; H, 5.6; N, 9.2. $C_{16}H_{16}N_2O_4$ requires C, 64.0; H, 5.4; N, 9.3%). υ_{max} 1500, 1480, 1455, 1318, 1243, 1165, 1113, 1055, 1031, 968, 756 cm^{-1}. ^1H n.m.r. δ 4.49, s, 4H, OCH_2; 6.96, m, 2H, aryl; 7.14, m, 2H, aryl; 7.36, m, 2H, aryl; 7.75, m, 2H, aryl; 8.46, s, 2H, CHN; 10.26, s, 2H, OH. ^{13}C n.m.r. δ 68.5, OCH2; 113.9, 122.2, aryl CH; 123.1, aryl C; 127.0, 131.9, aryl CH; 145.2, CNOH; 157.8, aryl C. *m/z* 300 (M, 11%), 119 (100).

***Ethyleneglycol-O,O'-bis(2-benzylamine)* (19)**

Under a nitrogen atmosphere a suspension of lithium aluminium hydride (10.3 g, 0.27 mol) in dry tetrahydrofuran (100 ml) was heated under gentle reflux. A solution of ethyleneglycol-O,O'-bis(2-benzaldoxime) (18) (12.5 g, 420 mmol) in dry tetrahydrofuran (200 ml) was slowly introduced, and the resulting mixture was maintained under reflux for 20h. After cooling, water (10 ml) and a 20% sodium hydroxide solution (10 ml) were cautiously added. The precipitate was filtered and washed well with ethanol. The combined filtrates were concentrated, and the residue partitioned between ether/20% sodium hydroxide solution. The organic phase was collected, concentrated, and triturated with ether to give the amine (19) (2.9 g, 25%) as a white solid, m.p. 71-73 °C. υ_{max} 1460, 1235, 753 cm^{-1}. ^1H n.m.r. δ 1.72, bs, 4H, NH_2; 3.83, bs, 4H, CH_2N; 4.39, s, 4H, OCH_2; 6.94, m, 4H, aryl; 7.25, m, 4H, aryl. ^{13}C n.m.r. δ 42.5, CH_2N; 66.6, OCH_2; 111.35, 121.2, 128.1, 128.8, aryl CH; 156.4, aryl C. *m/z* 272 (M, 4%), 121 (100).

***14,17-Diphenyldibenzo[c,i]5,8 -dioxa-1,12-diazatricyclo[10.3.3.1^{14,17}]nonadecan-19-one* (12)**

Method A. This was prepared as described for the macrocycle (6), from 3,7-bis(2-hydroxybenzyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (11) (1.00 g, 1.98 mmol), potassium hydroxide (0.65 g, 9.87 mmol), ethyleneglycol ditosylate[11] (0.80 g, 2.16 mmol) in tetrahydrofuran (49 ml) with water (1 ml). The fraction eluted with 10% methanol in dichloromethane and recrystallization from ethanol/dichloromethane gave the macrocycle (12) (480 mg, 46%) as colourless crystals, m.p. 244-247 °C (Found: C, 78.9; H, 6.7; N, 5.1. $C_{35}H_{34}N_2O_3$ requires C, 79.2; H, 6.5; N, 5.3%). υ_{max} 1729, 1606, 1499, 1455, 1246, 1126, 757, 701 cm^{-1}. ^1H n.m.r. δ 2.96, d, 4H, J_{axeq} 11.00 Hz, Hax; 3.58, d, 4H, J_{axeq} 11.00 Hz, Heq; 3.81, s, 4H, NCH_2; 4.42, s, 4H, OCH_2; 6.91, m, 4H, aryl; 7.18-7.28, m, 14H, aryl. ^{13}C n.m.r. δ 54.8, CPh; 57.8, NCH_2; 65.0 ring CH_2; 65.9, OCH_2; 110.9, 120.6, 126.5, aryl CH; 126.9, aryl C; 127.3, 127.7, 129.1, 132.4, aryl CH; 141.9, 157.4, aryl C; 211.5, CO. *m/z* 531 (M, 17%), 353 (100).

Method B. A mixture of 1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (9) (500 mg, 1.17 mmol), and potassium hydroxide (800 mg, 14.3 mmol) in dimethyl sulfoxide (30 ml) was stirred for 10 min. 1,2-Bis(2-bromomethyl phenoxy)ethane (16) (750 mg, 1.88 mmol) was introduced and the resulting mixture was stirred for a further 30 min. The reaction mixture was diluted with water (150 ml) and extracted with ethyl acetate.

The organic extracts were washed with water, a saturated sodium chloride solution, dried ($MgSO_4$) and concentrated to give a solid. Successive trituration from hot ether and ethanol gave the macrocycle (12) (485 mg, 54%) as colourless crystals which were spectroscopically identical to those produced by method A.

Method C. An ice cold solution of ethyleneglycol-O,O'-bis(2-benzylamine) (19) (680 mg, 2.50 mmol) in ethanol (20 ml) was neutralised by the slow addition of glacial acetic acid (0.3 ml). Paraformaldehyde (300 mg, 100 mmol), dibenzylketone (500 mg, 2.4 mmol) and ethanol (10 ml) were introduced and the resulting suspension was heated gently under reflux for 4h. The reaction mixture was cooled to ambient temperature and made basic by the addition of concentrated ammonium hydroxide. The solvent was evaporated and the residue was taken up in dichloromethane/concentrated ammonium hydroxide. The organic phase was collected, washed with water followed by a saturated sodium chloride solution, dried ($MgSO_4$) and concentrated. The residue was triturated with ethanol and chromatographed on a short column of alumina. The fraction eluted with 10% methanol in dichloromethane and trituration with hot ether gave the macrocycle (12) (630 mg, 48%) as colourless crystals which were spectroscopically identical to those produced by method A.

***17,20-Diphenyldibenzo[c,l]5,8,11-trioxa-1,15-diazatricyclo[13.3.3.1^{17,20}]docosan-22-one* (13)**

This was prepared as described for the macrocycle (6), from 3,7-bis(2-hydroxybenzyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (11) (1.00 g, 1.98 mmol), potassium hydroxide (0.65 g, 9.87 mmol), diethyleneglycol ditosylate[11] (906 mg, 2.19 mmol) in tetrahydrofuran (49 ml) with water (1 ml). Recrystallization from ethanol/dichloromethane gave the macrocycle (13) (854 mg, 75%) as colourless crystals, m.p. 235-238 °C (Found: C, 77.0; H, 6.8; N, 4.8. $C_{37}H_{38}N_2O_4$ requires C, 77.3; H, 6.7; N, 4.9%). υ_{max} 1732, 1607, 1499, 1455, 1252, 1137, 1124, 758, 702 cm^{-1}. ^1H n.m.r. δ 3.08, d, 4H, J_{axeq} 10.66 Hz, Hax; 3.48, d, 4H, J_{axeq} 10.66 Hz, Heq; 3.68, s, 4H, NCH_2; 3.98, m, 4H, OCH_2; 4.21, m, 4H, OCH_2; 6.92, dd, 2H, J 8.20 Hz J 0.92 Hz, aryl; 7.00, dt, 2H, J 7.40 Hz J 1.10 Hz, aryl; 7.13-7.28, m, 12H, aryl; 7.39, dd, 2H, J 7.40 Hz J 1.82 Hz, aryl. ^{13}C n.m.r. δ 54.4, CPh; 55.5, NCH_2; 64.7 ring CH_2; 68.4, 69.7, OCH_2; 112.6, 120.9, 126.3, 127.0, aryl CH; 127.3, aryl C; 127.7, 128.7, 131.7, aryl CH; 143.2, 157.4, aryl C; 211.9, CO. *m/z* 574 (M, 28%), 91 (100).

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