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New Macrocyclic Ligands. XV.* Isomeric, Benzylated and Xylyl-Linked Macrocyclic Ligands Derived from Selectively Protected N_3O_2-Donor Rings

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Direct alkylation of the N_3O_2-macrocycle 1,12,15-triaza-3,4 : 9,10-dibenzo-5,8-dioxacycloheptadecane (1) with benzyl bromide in the presence of sodium hydrogen carbonate (in the respective molar ratios 1.0 : 2.0 : 1.3) led to a mixture of the mono-, bis-, and tris-*N*-benzylated derivatives (2)–(6) which were separated using their differential solubilities in warm acetone, fractional crystallization, coupled with column chromatography on silica gel. The X-ray structure of the symmetrical dibenzylated product (4) (as its HNO_3 salt) is described. In a parallel study, *N*-protection of (1) using 1.7 molar equivalents of di-*tert*-butyl dicarbonate $(Boc)_2O$ yielded a mixture from which the symmetrical and unsymmetrical di-protected isomers (8) and (9) were separated by chromatography. Reaction of the symmetrically protected derivative (8) with benzyl chloride in the presence of excess sodium carbonate, followed by removal of the Boc groups, provided an alternative route to the corresponding (symmetrical) mono-*N*-benzylated macrocycle (2). A similar strategy, involving the use of α,α′-dibromo-*p*-xylene as a dialkylating agent, was employed to bridge a pair of *N*-diprotected macrocycles of type (8) or (9) to yield isomeric linked products (12) and (14), respectively. Deprotection of the resulting bis-macrocyclic products gave the 'central' and 'side' linked ligands (13) and (15), respectively.

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Introduction

In previous studies we have been interested in the effect of *N*-benzylation of mixed-donor macrocyclic ligands on the latters' metal ion recognition behaviour.[1] In particular, it has been demonstrated that it is sometimes possible to 'detune' the affinity of a given macrocyclic species of the above type towards a number of divalent transition and post-transition ions by *N*-benzylation while the affinity for silver(I) remains much less affected. As a consequence, enhanced discrimination for silver occurs.[2]

In recent years a considerable number of linked polyamine bis-macrocyclic ligands capable of complexing two metal ions in close proximity have been reported.[3,4] There is continuing interest in such systems since they tend to yield metal complexes exhibiting unusual electronic, catalytic, and/or redox properties that, for example, may act as models for the electron transport behaviour found in particular metal-containing biochemical systems. An additional attraction of the incorporation of macrocyclic rings is that their cyclic nature imposes an element of preorganization for metal ion binding, usually resulting in enhanced kinetic and thermodynamic stabilities of the products.[5]

Recently, *tert*-butyloxycarbonyl (Boc) has been used for the selective protection of secondary amines in macrocycles that include both all-nitrogen donor systems [such as 1,4,8,11-tetraazacyclotetradecane (cyclam)][6,7] as well as mixed donor systems.[8] Using a related strategy, we now report the synthesis of the single ring, selectively benzylated macrocycle (2) and the related bis-ring (isomeric) *N*,*N*-linked macrocycles (13) and (15) in which the position of the *p*-xylyl linkage between the macrocyclic units is varied.

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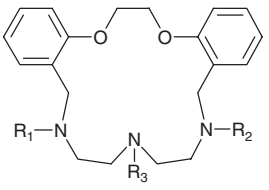
Results and Discussion

In an initial experiment, direct alkylation of (1) using two molar equivalents of benzyl bromide in acetonitrile in the presence of 1.3 molar equivalents excess of sodium hydrogen carbonate yielded a mixture of the *N*-benzylated derivatives (2)–(6) as their HBr salts (Diagram 1). This mixture of partially and fully benzylated derivatives was successfully separated using a combination of solubility difference, recrystallization, and conventional column chromatography on silica gel. Thus solubility differences in warm acetone allowed separation of the original mixture into two parts – a less soluble solid component, largely a mixture of (4) and (6) [with some (3)], and a more soluble component, largely a mixture of (3) and (5) [with some (2)]. Fractional crystallization of the solid from methanol yielded a mixture of (4) and (6). From this mixture (4) was isolated following chromatography (5 : 95, methanol/dichloromethane as eluent) on silica gel. The acetone solution containing the soluble fraction was taken to dryness and the residue was chromatographed (10 : 90, methanol/dichloromethane as eluent) to afford (3). After (3) was isolated, crude (5) was obtained from the initial portion of the eluent by removal of the solvent; it was purified by chromatography on silica gel (using 60 : 40, ethyl acetate/hexane as eluent). All products isolated as their HBr salts were neutralized with aqueous NaOH followed by normal workup procedures. On HBr removal, the chemical shifts of the methylene protons closest to the nitrogen heteroatoms typically shifted upfield by ca. 0.2–0.4 ppm.

Under the synthetic conditions employed, only a trace of the mono-substituted derivative (2) was formed. Due to this extremely low yield, and subsequent difficulties with chromatographic separation, (2) was synthesized using an alternative procedure that employed the corresponding di-Boc precursor. All new derivatives were characterized from their ^{1}H and ^{13}C NMR and HRMS data. In all cases the results were in accordance with the structures assigned. An X-ray analysis (see later) of the symmetrical dibenzylated derivative (4) (as its HNO_3 salt) provided confirmation of its structure (Fig. 1).

Two alternative general routes to the synthesis of *p*-xylyl linked polyamine macrocyclic species such as (13) and (15) appeared feasible. The first involved the incorporation of the *p*-xylyl linking group in a difunctional precursor prior to carrying out a (bis-) macrocyclization reaction. The second involved the linking via an α,α′-dihalo-*p*-xylene of two appropriately protected macrocyclic precursors, each incorporating a single unprotected amine site. Deprotection of the amine groups would then result in the required bis-ring system.



(1) $R_1 = R_2 = R_3 = H$
(2) $R_1 = R_2 = H$, $R_3 = Bz$
(3) $R_1 = R_3 = H$, $R_2 = Bz$
(4) $R_1 = R_2 = Bz$, $R_3 = H$
(5) $R_1 = R_3 = Bz$, $R_2 = H$
(6) $R_1 = R_2 = R_3 = Bz$

Diagram 1

The latter is a common strategy applied previously for the synthesis of a range of linked two-ring systems that includes linked cyclam derivatives.[3,4] In the present study, we also used this approach and carried out the condensation of α,α′-dibromo-*p*-xylene with two equivalents of the selectively diprotected precursors (8) and (9) followed by deprotection to yield (13) or (15), respectively (see Schemes 1 and 2).

The reaction of di-*tert*-butyl dicarbonate (Boc_2O) with the parent O_2N_3-macrocycle (1) was carried out in one step (Scheme 1). A $(Boc)_2O$/macrocycle molar ratio of 1.7 was found to be optimum for maximizing the yields of the desired di-Boc protected species precursors (8) and (9). However, this ratio also resulted in the formation of some tri-protected derivative (7) as well as, in lesser yields, the mono-protected species (10) and (11). Some unreacted starting material (1), also remained. Separation of the desired di-Boc protected precursors (8) and (9), was achieved by column chromatography on silica gel using gradient elution (20% ethyl acetate/hexane to 100% ethyl acetate). The latter procedure was found to be superior for the present systems compared with the methanol/dichloromethane mixture employed previously for related separations involving all-nitrogen heteroatom systems.[7]

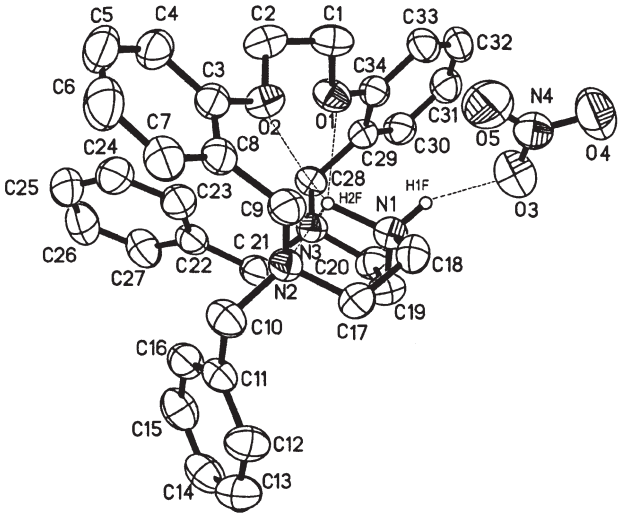
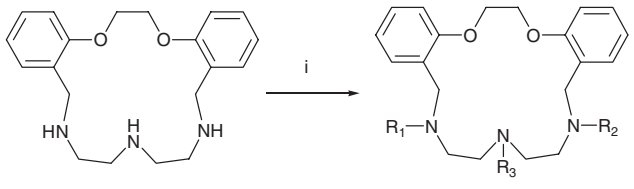


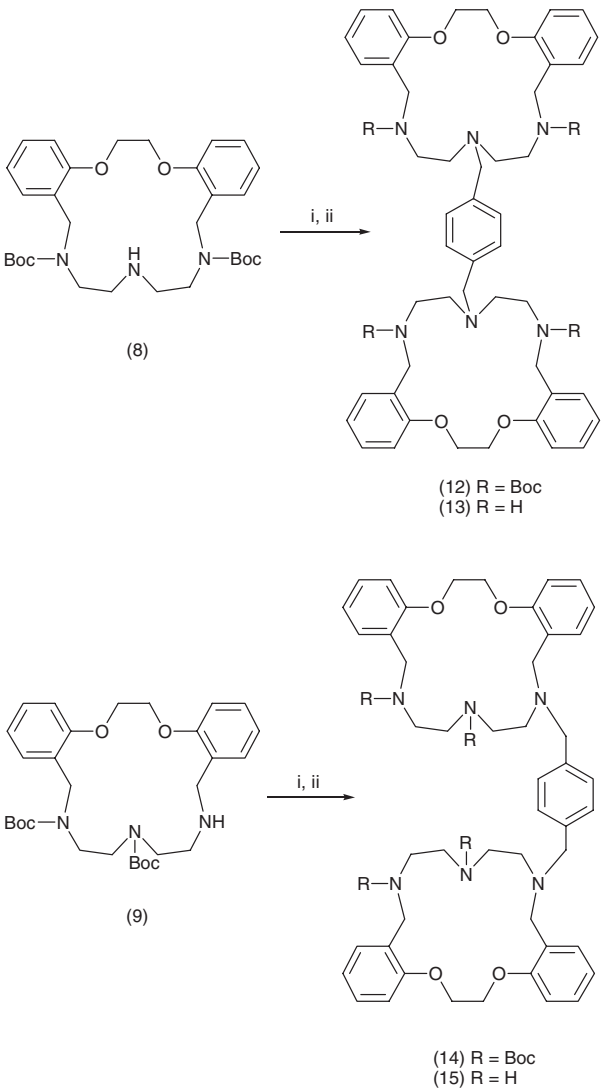
Fig. 1. X-Ray structure of the nitric acid salt of the *N*-dibenzylated O_2N_3 macrocycle, (4).HNO_3.



(1)

(7) $R_1 = R_2 = R_3 = Boc$
(8) $R_1 = R_2 = Boc$, $R_3 = H$
(9) $R_1 = R_3 = Boc$, $R_2 = H$
(10) $R_1 = R_2 = H$, $R_3 = Boc$
(11) $R_1 = Boc$, $R_2 = R_3 = H$

Scheme 1. Boc = *tert*-butyloxycarbonyl. Reagents and conditions: (i) Boc_2O, dichloromethane.



Scheme 2. Boc = *tert*-butyloxycarbonyl. Reagents and conditions: (i) α,α′-dibromo-*p*-xylene, Na_2CO_3, acetonitrile; (ii) trifluoroacetic acid.

The ^1H and ^{13}C NMR spectra of (8) and (9) clearly show the success of the (isomeric) di-protecting manipulations and subsequent workup procedures. The ^1H spectra of the purified products are readily assignable, despite the presence of somewhat broad resonances caused by a combination of the slow rotation of the 'amide rotamers' and the restricted (and hence slower) ring flexing engendered by the presence of the bulky protecting groups. The ^1H NMR spectrum of (8) resembles that of (1), except for the chemical shift of the benzylic methylene resonance (see below), while the spectrum of (9) exhibits the expected increase in signal complexity arising from its asymmetrical nature. On Boc protection, the proton resonance of the benzylic methylene shifts from 3.80 ppm in (1) to 4.64 ppm in (8). The *tert*-butyl components of the Boc-protecting groups show a strong singlet resonance at 1.43 ppm for symmetric (8), while asymmetric (9) exhibits two singlets at 1.48 and 1.39 ppm.

Reaction of the symmetrically protected derivative (8) with benzyl chloride in the presence of sodium carbonate, followed by removal of the Boc groups, provided the alternative route to the mono-*N*-benzylated macrocycle (2) mentioned previously. The Boc-protecting groups were readily removed by treating the protected species with trifluoroacetic acid.

Having successfully obtained the di-protected species (8) and (9), we proceeded to the synthesis of the xylyl-linked dimers (Scheme 2). Exclusive mono-*N*-alkylation of the available secondary amines on two molecules of (8) or (9) with α,α′-dibromo-*p*-xylene in acetonitrile in the presence of sodium carbonate gave the dimeric intermediates (12) and (14), in reasonable yields. These two compounds were isolated and purified by recrystallization from ethyl acetate/hexane. Their ^1H and ^{13}C NMR spectra exhibited characteristic singlets at 3.48 (12), 3.76 (14) ppm and 59.6 (12), 58.7 (14) ppm, respectively, arising from the xylyl methylene groups. The Boc groups of (12) and (14) were readily removed by treatment with trifluoroacetic acid, the desired linked-macrocycle products (13) and (15), respectively, being isolated and recrystallized from acetone in almost quantitative yield.

Finally, it may be noted that the alternative approach to the preparation of (13), via the [1 + 2] bicyclization of 1,4-bis(bis(2-aminoethyl)aminomethyl)benzene[9] with two equivalents of the appropriate dialdehyde[10] followed by reduction of the corresponding tetraimine derivative, was also accomplished during the present study. However, in our hands this procedure was less efficient than that described above, resulting in a lower yield and requiring a more time-consuming workup procedure.

X-Ray Structure of (4).HNO$_3$

The molecular structure of the salt is shown in Figure 1 together with the atomic labelling. Selected bond dimensions defining the macrocycle skeleton are given in Table 1. These structural features may be compared with those of the tribenzylated derivative (6), which has been described previously.[1]

Table 1. Selected bond lengths (Å) and angles (deg) for (4).HNO$_3$

Bond	Length	Bond	Angle
O(1)–C(34)	1.3701(18)	C(34)–O(1)–C(1)	117.68(11)
O(2)–C(3)	1.3729(18)	C(19)–N(1)–C(18)	114.13(12)
N(1)–C(19)	1.4884(19)	C(20)–N(3)–C(28)	113.53(12)
N(2)–C(17)	1.4622(18)	O(2)–C(2)–C(1)	109.90(13)
N(3)–C(20)	1.4593(19)	C(3)–C(8)–C(9)	121.09(13)
C(1)–C(2)	1.484(2)	N(2)–C(17)–C(18)	112.51(12)
C(8)–C(9)	1.498(2)	N(1)–C(19)–C(20)	110.35(12)
C(19)–C(20)	1.510(2)	N(3)–C(28)–C(29)	115.12(12)
C(29)–C(34)	1.395(2)	O(1)–C(34)–C(29)	115.95(12)
O(1)–C(1)	1.4328(17)	C(3)–O(2)–C(2)	116.37(11)
O(2)–C(2)	1.4312(18)	C(17)–N(2)–C(9)	108.48(11)
N(1)–C(18)	1.494(2)	O(1)–C(1)–C(2)	109.10(13)
N(2)–C(9)	1.4715(18)	O(2)–C(3)–C(8)	115.98(12)
N(3)–C(21)	1.4626(19)	N(2)–C(9)–C(8)	116.62(12)
C(3)–C(8)	1.400(2)	N(1)–C(18)–C(17)	112.47(12)
C(17)–C(18)	1.507(2)	N(3)–C(20)–C(19)	111.01(13)
C(28)–C(29)	1.504(2)	C(34)–C(29)–C(28)	122.18(13)

The molecular structure displays no unusual features, but it does confirm the structure assignment based on the other physical measurements. The central amine group is involved in H-bonding to one oxygen atom (O3) of the nitrate group (N1–H1F, 0.95; N1···O3, 2.786; H1F···O3, 1.89 Å), and electrostatic interactions with the other four heteroatoms of the macrocyclic ring are indicated. The latter is evidenced by the equidistant positioning of proton H2F relative to those four atoms (N1–H2F, 1.36; H2F···O1, 2.56; H2F···O2, 2.57; H2F···N2, 2.54, H2F···N3, 2.49 Å). These intramolecular interactions cause an obvious increase in puckering of the macrocycle compared with the tribenzylated structure (6).[1] Like the structure of (6), the absence of pseudo-symmetry in the molecule and the shortened C–C bond between the ether oxygens (1.484(2) Å) are again noted.

Experimental Section

General

Where available, all reagents were analytical grade. The parent N_3O_2-donor macrocycle, 1,12,15-triaza-3,4 : 9,10-dibenzo-5,8-dioxacycloheptadecane (1) was synthesized as described previously.[10] ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 NMR spectrometer with tetramethylsilane (TMS) as internal standard. High-resolution mass spectra were obtained on a Bruker BioApex 47e ICR mass spectrometer while low-resolution spectra (ESIMS) were obtained on a Finnigan Mat LCQ spectrometer (using dimethyl sulfoxide/methanol solutions).

Direct Benzylation of (1) and Separation of (3)–(6)

To a stirred solution of (1) (5.71 g, 16.73 mmol) and sodium hydrogen carbonate (1.89 g, 22.47 mmol) in acetonitrile (500 cm^3) two mole equivalents of benzyl bromide (5.72 g, 33.46 mmol) in acetonitrile (100 cm^3) was added over 40 min. The mixture was then stirred at room temperature for 17 h. The solvent was removed under reduced pressure and acetone (50 cm^3) was added to the residue with stirring. The resulting mixture was filtered to separate the acetone-soluble and insoluble components. The solution was later shown to contain a mixture of (3) (major) and (5) (minor) together with a trace amount of (2). The insoluble component proved to be a mixture of (3) (small amount), (4), and (6) (by means of combined thin-layer chromatography (TLC) and NMR analysis). The separation of these mixtures is described below.

1,12-Dibenzyl-1,12,15-triaza-3,4 : 9,10-dibenzo-5,8-dioxacycloheptadecane (4)

The acetone-insoluble component was recrystallized from methanol to give a mixture of (4) and (6) as their colourless crystalline HBr salts. This mixture was separated by flash chromatography on silica gel, eluting with 5% methanol/dichloromethane. The HBr salt of (4) was collected and isolated (1.19 g), m.p. 235–236 °C. δ_H ($CDCl_3$; 500 MHz) 2.78, m, 8H, NC**H**$_2$C**H**$_2$NH; 3.50, s, 4H, NC**H**$_2$Ar; 3.68, s, 4H, ArC**H**$_2$NCH$_2$Ar; 4.56, s, 4H, OC**H**$_2$C**H**$_2$O; 6.95–7.45, m, 18H, Ar**H.** δ_c ($CDCl_3$; 500 MHz) 45.2, 48.5, 55.5, 59.4, 67.5, 112.2, 121.1, 125.45, 127.4, 128.4, 129.1, 129.7, 132.7, 137.9, 157.2. In order to obtain (4) in free form, the salt was redissolved in dichloromethane and the solution was shaken three times with aqueous 2 M NaOH. The dichloromethane phase was then washed three times with distilled water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was dried under high vacuum to yield (4) as a colourless glassy solid (0.40 g, 5%), m.p. 135–136 ºC (Found: M + H$^+$, 521.3049. $C_{34}H_{40}N_3O_2$ requires 521.3042). δ_H ($CDCl_3$; 500 MHz) 2.51, m, 8H, NC**H**$_2$C**H**$_2$NH; 3.52, s, 4H, NC**H**$_2$Ar; 3.62, s, 4H, ArC**H**$_2$NCH$_2$Ar; 4.41, s, 4H, OC**H**$_2$C**H**$_2$O; 6.88–7.33, m, 18H, Ar**H.** δ_C ($CDCl_3$; 125 MHz) 46.3, 53.0, 55.1, 59.6, 67.2, 111.3, 120.3, 126.5, 127.2, 127.9, 128.6, 128.9, 132.7, 140.0, 157.8.

A crystal of (4).HNO_3 was obtained for X-ray analysis. A sample of (4) was dissolved in warm methanol (2 cm^3) to which dilute nitric acid (1 cm^3) was added; colourless crystals separated on allowing the solution to stand.

1-Benzyl-1,12,15-triaza-3,4 : 9,10-dibenzo-5,8-dioxacycloheptadecane (3)

The solvent was removed from the original acetone-soluble component and the residue, primarily a HBr salt mixture of (3) and (5), was separated on silica gel by eluting with 10% methanol/dichloromethane. The major product was the HBr salt of (3) (0.72 g), m.p. 198–200 ºC. δ_H ($CDCl_3$; 200 MHz) 2.65, m, 6H, HNCH$_2$C**H**$_2$NHC**H**$_2$C**H**$_2$NCH$_2$Ar; 2.83, m, 2H, HNC**H**$_2$CH$_2$NH; 3.58, s, 2H, NC**H**$_2$Ar; 3.60, s, 2H, ArC**H**$_2$NCH$_2$Ar; 3.85, s, 2H, ArC**H**$_2$NH; 4.34, d, 2H, OCH$_2$C**H**$_2$O; 4.38, d, 2H, OC**H**$_2$CH$_2$O; 6.93–7.29, m, 13H, Ar**H**. The free form of (3) was obtained as a colourless glassy solid (0.22 g, 3%) in a similar manner to that described above, m.p. 90–91 ºC (Found: M + H$^+$, 431.2565. $C_{27}H_{34}N_3O_2$ requires 431.2573). δ_H ($CDCl_3$; 500 MHz) 2.60, m, 6H, HNCH2C**H**2NHC**H**$_2$C**H**$_2$–NCH$_2$Ar; 2.75, m, 2H, HNC**H**$_2$CH$_2$NH; 3.56, s, 2H, NC**H**$_2$Ar; 3.58, s, 2H, ArC**H**$_2$N CH$_2$Ar; 3.81, s, 2H, ArC**H**$_2$NH; 4.32, d, 2H, OCH$_2$C**H**$_2$O; 4.38, d, 2H, OC**H**$_2$CH$_2$O; 6.90–7.31, m, 13H, Ar**H**. δ_C ($CDCl_3$; 125 MHz) 46.6, 48.7, 48.8, 51.0, 51.8, 55.6, 59.5, 66.6, 67.1, 110.8, 111.5, 120.4, 120.9, 126.6, 127.1, 128.0, 128.5, 128.7, 128.8, 131.0, 132.5, 139.6, 157.2, 157.6.

1,15-Dibenzyl-1,12,15-triaza-3,4 : 9,10-dibenzo-5,8-dioxacycloheptadecane (5)

After the HBr salt of (3) was obtained using the chromatographic procedure described above, the initial fraction of the eluent [before the appearance of (3)] was taken to dryness to yield crude (5) as its HBr salt. This product was purified by chromatography on silica gel (eluting with 60% ethyl acetate/hexane). Yield 0.66 g, m.p. 114–115 ºC. δ_H ($CDCl_3$; 200 MHz) 2.43, t, 2H, NCH$_2$C**H**$_2$NCH$_2$Ar; 2.53, t, 2H, NC**H**$_2$CH$_2$NCH$_2$Ar; 2.66, m, 4H, HNC**H**$_2$C**H**$_2$N; 3.24, s, 2H, CH$_2$CH$_2$NC**H**$_2$Ar; 3.33, s, 2H, ArCH$_2$NC**H**$_2$Ar; 3.81, s, 2H, ArC**H**$_2$NCH$_2$Ar; 3.86, s, 2H, ArC**H**$_2$NHCH$_2$CH$_2$N; 4.41, m, 4H, OC**H**$_2$C**H**$_2$O; 6.85–7.33, m, 18H, Ar**H.** δ_C ($CDCl_3$; 50 MHz) 45.7, 48.8, 51.0, 51.8, 53.2, 57.7, 58.9, 66.4, 66.7, 111.0, 120.8, 126.6, 126.9, 127.7, 128.0, 128.2, 128.7, 129.3, 130.3, 131.5, 138.4, 139.5, 156.5, 156.8. The free form of (5) was obtained as a colourless glassy solid (0.32 g, 4%) in a similar manner to that described above, m.p. 62–64 ºC (Found: M + H$^+$, 521.3036. $C_{34}H_{40}N_3O_2$ requires M + H$^+$, 521.3042). δ_H ($CDCl_3$; 500 MHz) 2.41, t, 2H, NCH$_2$C**H**$_2$NCH$_2$Ar; 2.52, t, 2H, NC**H**$_2$CH$_2$NCH$_2$Ar; 2.66, m, 4H, HNC**H**$_2$C**H**$_2$N; 3.25, s, 2H, CH$_2$CH$_2$NC**H**$_2$Ar; 3.35, s, 2H, ArCH$_2$NC**H**$_2$Ar; 3.80, s, 2H, ArC**H**$_2$NCH$_2$Ar; 3.85, s, 2H, ArC**H**$_2$NHCH$_2$CH$_2$N; 4.41, m, 4H, OC**H**$_2$C**H**$_2$O; 6.87–7.29, m, 18H, Ar**H**. δ_C ($CDCl_3$; 500 MHz) 48.1, 51.5, 52.7, 53.5, 54.7, 55.9, 59.2, 60.9, 68.4, 68.5, 112.7, 112.8, 122.4, 122.6, 128.4, 128.5, 129.1, 129.8, 129.9, 130.2, 130.3, 130.5, 130.8, 131.0, 131.2, 131.5, 132.7, 141.1, 141.9, 158.4, 158.7.

1,12,15-Tribenzyl-1,12,15-triaza-3,4 : 9,10-dibenzo-5,8-dioxacycloheptadecane (6)

Product (6) was obtained by the direct benzylation method described previously.[1]

*1,12-Bis(*tert*-butoxycarbonyl)-1,12,15-triaza-3,4 : 9,10-dibenzo-5,8-dioxacycloheptadecane (8)*

To a stirred solution of (1) (5.00 g, 14.64 mmol) in dichloromethane (500 cm^3) was added 1.7 equiv. of di-*tert*-butyl dicarbonate (5.43 g, 24.89 mmol) in dichloromethane (150 cm^3) over 1.5 h and the mixture stirred at room temperature for a further 2 h. The solvent was then removed under reduced pressure. Chromatography on silica gel using 20% ethyl acetate/hexane then 100% ethyl acetate as the eluent led to the isolation of (8) (3.00 g, 45%) as a white powder (Found: C, 66.4; H, 7.7; N, 7.5%. Calc. for $C_{30}H_{43}N_3O_6$: C, 66.5; H, 8.0; N, 7.8%. Found: M + H$^+$, 542.3213. $C_{30}H_{43}N_3O_6$ requires 542.3224). δ_H ($CDCl_3$; 200

MHz) 1.42, s, 18H, $(CH_3)_3$; 2.81, s, 4H, Boc–NCH_2CH_2NH; 3.28, s, 4H, Boc–NCH_2CH_2NH; 4.32, s, 4H, OCH_2CH_2O; 4.64, s, 4H, $ArCH_2N$; 6.80–7.35, m, 8H, Ar**H**. δ_C ($CDCl_3$; 50 MHz) 28.4, 46.4, 48.7, 66.6, 79.7, 110.9, 121.1, 126.7, 127.2, 127.9, 156.2.

15-Benzyl-1,12,15-triaza-3,4 : 9,10-dibenzo-5,8-dioxacyclo-heptadecane (2)

Benzyl chloride (353 mg, 2.79 mmol) in acetonitrile (50 cm^3) was added dropwise to a refluxing suspension of (8) (1.00 g, 1.86 mmol) and sodium carbonate (0.48 g, 4.50 mmol) in acetonitrile (100 cm^3). The reaction mixture was maintained under reflux for an additional 24 h with rapid stirring and was then cooled to room temperature and filtered. The filtrate was evaporated and the residue was partitioned between water and dichloromethane. The aqueous phase was separated and extracted with two further portions of dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate and the solution then evaporated. Chromatography of the residue on silica gel using 50% ethyl acetate/hexane as the eluent led to the isolation of the intermediate diprotected product as a white microcrystalline solid (1.05 g, 90%); MS (ES) *m/z*, 632.4 ($M+H^+$). This product (1.00 g, 1.58 mmol) was stirred at room temperature for 2 h with excess trifluoroacetic acid (12.0 g). The solution was then taken to dryness on a rotary evaporator, methanol was added and the solution again taken to dryness. This procedure was repeated a further two times to ensure full evaporation of any remaining trifluoroacetic acid. Aqueous sodium carbonate (50 cm^3 of a 15% solution) was added to the residue and the resulting mixture extracted three times with dichloromethane. The combined organic phases were dried with anhydrous sodium sulfate, filtered, then the solvent was removed under reduced pressure to yield (2) as an orange viscous oil (642 mg, 93%) (Found: $M+H^+$, 431.2575. $C_{27}H_{33}N_3O_2$ requires 431.2573). δ_H ($CDCl_3$; 300 MHz) 2.53, s, 4H, $NHCH_2CH_2NCH_2Ar$; 2.62, s, 4H, $NHCH_2CH_2NCH_2Ar$; 3.21, 4H, $ArCH_2N(CH_2)_2$); 3.47, s, 2H, N**H**; 3.75, s, 4H, $ArCH_2NH$; 4.42, s, 4H, OCH_2CH_2O; 6.89–7.26, m, 13H, Ar**H**. δ_C ($CDCl_3$; 50 MHz) 46.3, 50.2, 53.8, 57.9, 67.4, 111.9, 121.7, 127.3, 128.6, 129.1, 129.6, 131.8, 138.6, 157.5.

*1,15-Bis(*tert*-butoxycarbonyl)-1,12,15-triaza-3,4 : 9,10-dibenzo-5,8-dioxacycloheptadecane (9)*

After (8) was separated, successive gradient elution of the column (from 20% ethyl acetate/hexane to 100% ethyl acetate) yielded (9) (1.74 g, 26%) as a viscous pink oil (Found: $M+H^+$, 542.3228. $C_{30}H_{43}N_3O_6$ requires 542.3224). δ_H ($CDCl_3$; 200 MHz) 1.42, s, 9H, $ArCH_2NCOOC(CH_3)_3$; 1.48, br, 9H, $NHCH_2CH_2NCOOC(CH_3)_3$; 2.78, m, 2H, $NHCH_2CH_2$; 3.30, m, 6H, Boc–NCH_2CH_2N(–Boc)CH_2; 3.87, s, 2H, $ArCH_2NH$; 4.37, m, 4H, OCH_2CH_2O; 4.57, d, 2H, $ArCH_2N$–Boc; 6.88–7.30, m, 8H, Ar**H**. δ_C ($CDCl_3$; 50 MHz) 28.4, 43.5, 44.8, 46.6, 47.0, 47.6, 48.3, 66.8, 67.2, 79.6, 79.7, 111.2, 112.0, 121.2, 121.6, 126.6, 128.2, 128.4, 129.0, 130.4, 151.1, 155.6, 156.1, 156.6.

Linked Derivative (12)

A solution of α,α′-dibromo-*p*-xylene (0.32 g, 1.21 mmol) in acetonitrile and tetrahydrofuran (1 : 1, 40 cm^3) was added dropwise to a refluxing suspension of (8) (1.46 g, 2.70 mmol) and sodium carbonate (0.32 g, 3.00 mmol) in acetonitrile (150 cm^3). The reaction mixture was maintained at reflux for an additional 24 h with rapid stirring, allowed to cool to room temperature, then filtered. The filtrate was evaporated and the residue was partitioned between water and dichloromethane. The aqueous phase was separated and extracted with two further portions of dichloromethane. The combined organic phases were dried with anhydrous sodium sulfate and the solution then evaporated to dryness. The residue was recrystallized from 40% ethyl acetate/hexane to yield (12) (0.85 g, 59%) (Found: C, 69.2; H, 8.0; N, 7.1%. $C_{68}H_{92}N_6O_{12}$ requires C, 68.9; H, 7.8; N, 7.1%. Found: $M+H^+$, 1185.6870. $C_{68}H_{93}N_6O_{12}$ requires $M+H^+$, 1185.6845). δ_H ($CDCl_3$; 200 MHz) 1.31, s, 36H, $(CH_3)_3$; 2.68–2.35, s, 8H, Boc–NCH_2CH_2N–xylyl; 3.42–3.10, s, 8H, Boc–NCH_2CH_2N–xylyl; 3.48, s, 4H, NCH_2ArCH_2N; 4.36, s, 8H, OCH_2CH_2O; 4.53, s, 8H, $ArCH_2N$; 6.78–7.32, m, 20H, Ar**H**. δ_C ($CDCl_3$; 50 MHz) 29.0, 45.7, 52.8, 59.6, 67.2, 67.3, 80.1, 111.5, 121.8, 127.8, 128.7, 129.0, 129.7, 138.5, 156.7, 156.9.

Linked Derivative (13)

To (12) (2.49 g, 2.10 mmol) in dichloromethane (30 cm^3) was added trifluoroacetic acid (30.0 g) with vigorous stirring at room temperature. Stirring was continued for 2 h. The solution was then taken to dryness on a rotary evaporator, methanol was added, and the solution again taken to dryness. This procedure was repeated a further two times to ensure evaporation of any remaining trifluoroacetic acid. Aqueous sodium carbonate (15%, 50 cm^3) was added to the residue, which was then extracted three times with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was recrystallized from acetone to yield (13) as a colourless solid (1.33 g, 81%) (Found: C, 73.0; H, 7.8; N, 10.7%. $C_{48}H_{60}N_6O_4$ requires C, 73.4; H, 7.7; N, 10.7%. Found: $M+H^+$, 785.4721. $C_{48}H_{61}N_6O_4$ requires 785.4748). δ_H ($CDCl_3$; 200 MHz) 2.44, m, 8H, $NHCH_2CH_2N$–xylyl; 2.58, br, 12H, $NHCH_2CH_2N$–xylyl; 3.16, s, 4H, NCH_2ArCH_2N; 3.72, s, 8H, $ArCH_2NH$; 4.41, s, 8H, OCH_2CH_2O; 6.86–7.22, m, 20H, Ar**H**. δ_C ($CDCl_3$; 50 MHz) 45.3, 48.3, 51.6, 58.6, 67.8, 113.1, 121.6, 124.7, 129.4, 129.9, 131.9, 136.9, 157.3.

Linked Derivative (14)

A solution of α,α′-dibromo-*p*-xylene (0.66 g, 1.76 mmol) in 20% tetrahydrofuran/acetonitrile (80 cm^3) was added dropwise to a refluxing suspension of (9) (3.20 g, 5.54 mmol) and sodium carbonate (0.66 g, 6.25 mmol) in acetonitrile (280 cm^3). The reaction mixture was maintained under reflux for an additional 24 h with rapid stirring and it was then cooled to room temperature and filtered. After the solvent was removed by rotary evaporation, the yellow solid that remained was dissolved in ethyl acetate (15 cm^3). Excess hexane was added to the solution to yield a sticky yellow precipitate. The clear solution above the precipitate was decanted and discarded. The precipitate was recrystallized from ethyl acetate/hexane to yield (14) as a colourless solid (2.46 g, 83%) (Found: C, 69.3; H, 8.1; N, 6.9%. $C_{68}H_{92}N_6O_{12}$ requires C, 68.9; H, 7,8; N, 7.09%. Found: $M+H^+$, 1185.6787. $C_{68}H_{93}N_6O_{12}$ requires 1185.6845). δ_H ($CDCl_3$; 200 MHz) 1.30–1.55, m, 36H, $(CH_3)_3$; 2.76, br, 4H, Boc–NCH_2CH_2N–xylyl; 3.38, br, 12H, Boc–NCH_2CH_2N(Boc)CH_2; 3.76, br, 8H, $ArCH_2N$(xylyl)CH_2; 4.45, br, 8H, OCH_2CH_2O; 4.58, br, 4H, $ArCH_2N$–Boc; 6.97–7.39, m, 20H, Ar**H**. δ_C ($CDCl_3$; 50 MHz) 28.4, 43.6, 44.8, 45.4, 51.1, 51.5, 58.7, 67.0, 79.0, 79.2, 79.6, 111.1, 111.3, 120.8, 121.3, 126.9, 127.9, 128.4, 129.0, 129.3, 130.9, 138.3, 155.2, 155.6, 156.0, 156.3, 156.6.

Linked Derivative (15)

Precursor (14) (2.12 g, 1.79 mmol) was stirred at room temperature for 2 h with excess trifluoroacetic acid (20.0 g). The solution was then taken to dryness on a rotary evaporator, methanol was added and the solution was again taken to dryness. This procedure was repeated a further two times to ensure evaporation of any remaining trifluoroacetic acid. Aqueous sodium carbonate (50 cm^3 of a 15% solution) was added to the residue and the resulting mixture extracted with dichloromethane three times. The combined organic phases were dried with anhydrous sodium sulfate and then taken to dryness. The residue that remained was recrystallized from acetone to yield (15) as a colourless solid (1.02 g, 73%) (Found: C, 73.6; H, 7.6; N, 10.7%. $C_{48}H_{60}N_6O_4$ requires C, 73.4; H, 7.7; N, 10.7%. Found: $M+H^+$, 785.5). δ_H ($CDCl_3$; 200 MHz) 2.33–2.72, m, 20H, **H**$NCH_2CH_2NHCH_2CH_2N$–xylyl; 3.45, s, 4H, CH_2ArCH_2; 3.55, br, 4H, $ArCH_2NH$; 3.78, br, 4H, $ArCH_2N$–xylyl; 4.28, br, 8H, OCH_2CH_2O; 6.87–7.36, m, 20H, Ar**H**. δ_C ($CDCl_3$; 50 MHz) 46.6, 48.8, 51.0, 51.6, 55.3, 59.0, 66.6, 67.0, 110.8, 111.5, 120.5, 120.9, 127.3, 128.6, 131.0, 132.2, 137.8, 157.5, 157.7.

Structure Determination

Crystal data for (4).HNO_3. $C_{34}H_{40}N_4O_5$, *M* 584.70, monoclinic, space group $P2_1/n$ (non-std., no.14), *a* 14.9322(10), *b* 12.2162(8), *c* 17.4693(11) Å, β 105.9970(10)°, *V* 3063.3(3) $Å^3$, *Z* 4, D_c 1.268 Mg/m^3, colourless plates, λ(Mo Kα) 0.71073 Å, μ(Mo Kα) 0.086 mm^{-1}, *F*(000) 1248.

Data Collection, Structure Solution and Refinement

A crystal of dimensions 0.2 × 0.4 × 0.45 mm^3 was attached to a thin glass fibre and mounted on a Bruker SMART CCD 3-circle diffractometer employing graphite monochromated Mo Kα radiation generated from a sealed tube. Cell dimensions were obtained from a least squares refinement for selected reflections. Data were collected at 298(2) K using ω scans for 19658 reflections in the theta range 2.06 to 28.39° (97.3% completeness). These were reduced to 7477 independent reflections (R_{merge} 0.0276) in the index ranges $-19 \le h \le 16$, $-16 \le k \le 14$, $-21 \le l \le 22$, which were used for structure solution and refinement uncorrected for absorption effects.[11] The structure was solved by direct methods and refined on $||F||^2$ by full-matrix least-squares methods using SHELXTL software.[12] After preliminary refinement, H atoms (H1F and H2F) on the central amine group (N1) were located in a difference-Fourier synthesis. Anisotropic thermal parameters were employed for all non-hydrogen atoms, while a riding atom model was used for all non-amine hydrogen atoms placed in idealized positions. In final refinement cycles 396 parameters were varied with 0 restraints, which included positional and isotropic thermal parameters for H1F and H2F. Final refinement converged to $R_1(F)$ 0.071, $wR_2(F^2)$ 0.131 for all data and $R_1(F)$ 0.046, $wR_2(F^2)$ 0.117 for data with $I > 2\sigma(I)$. A final difference-Fourier synthesis showed no electron densities outside the range –0.26 to 0.46 e $Å^3$. A full set of data defining the crystal structure has been deposited with the Cambridge Crystallographic Data Centre (CCDC 186157).

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