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New *N*-acyl, *N*-alkyl, and *N*-bridged derivatives of *rac*-6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline

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Abstract—The preparation of potential new ligand systems based on the *rac*-1,1′,2,2′,3,3′,4,4′-octahydro-6,6′,7,7′-tetramethoxy-1,1′-bisisoquinoline skeleton has been investigated. Syntheses of *N*-(2-bromobenzyl), *N*-(3-acetoxybenzyl), *N*-acetyl, *N*-chloroacetyl, *N*-chlorocarbonyl, *N*-ethoxycarbonyl and *N*-*tert*-butyloxycarbonyl derivatives and five macrocyclic, polyether containing derivatives are described.

Chiral C_2-symmetric agents[1] are popular in asymmetric synthesis because their use normally precludes complications due to formation of diastereomeric transition states. Moreover, such reagents are often readily available in two enantiomerically pure forms. This permits their use in processes leading to complementary stereochemical outcomes. For example, axially chiral binaphthyl derivatives, including the well-known Noyori (±)-BINAP phosphine ligands,[2] and related (+) and (−)-BINOL derivatives, have seen enormous success in this regard as ligands for metals in catalytic processes including asymmetric hydrogenation,[3] sulfide oxidation,[4] cyanosilylation,[5] and ene reactions.[6] They have also been used as resolving agents. Chiral C_2-symmetric diamines have similarly found manifold uses in asymmetric synthesis and as ligands in catalytic reagent systems; bis-oxazolidinemethanes derived from various amino acids serve as ligands for Cu during catalytic oxidations, while 2,2′-diaminobinaphthyl[7] and derivatives of *trans*-cyclohexanediamine and *threo*-1,2-diphenylethanediamine have been used widely in different applications, including resolution. Recent interest has turned to new, more specialised ligands[8] and to novel combinations of these technologies.[9,10] 1,1′-Bisisoquinoline derivatives offer similar opportunities in both fully aromatic [atropisomeric (axially chiral)] and reduced [configurational (centrally chiral) or atropisomeric (axially chiral)] forms, and it is our intention to develop novel ligands for these purposes based on the versatile *rac*-1,1′,2,2′,3,3′,4,4′-octahydro-6,6′,7,7′-tetramethoxy-1,1′-bisisoquinoline skeleton.

In this paper, we describe the synthesis of a range of *N*-substituted bis-tetrahydroisoquinoline derivatives and certain *N*-strapped macrocyclic polyether 1,1′-bisisoquinolines. Conditions are established for the preparation of isoquinoline-derived crown ethers, further evidence is provided for conserved molecular structures for amide derivatives of the reduced heterocycles, and a method is described for the asymmetric reduction of bis-imine **1** to yield scalemic bis-amine **3**.

1. Results and discussion

The relative stereochemistry of *racemic* and *meso* forms of octahydrobisisoquinoline derivatives has been the subject of several investigations over the past ninety years.[11–17] However, much of the known chemistry of the reduced 1,1′-bisisoquinoline dimeric ring skeleton was elucidated during a single study of compound **1** and its partially reduced derivatives **2** and **3** that was directed towards novel dopaminergic agents based on intramolecular oxidative aryl–aryl coupling reactions.[15] Bischler–Napieralski synthesis of bisimine **1** using $POCl_3$,[15] pyrophosphoryl chloride,[18] or triflic anhydride/DMAP[19] reagents followed by diastereoselective reduction using $NaBH_3CN$ provides a ready source of the *racemic* secondary amine **3**.[15] Amine **3** was an attractive intermediate for further development and was the starting point for this investigation.

Racemic amine **3** was subjected to a range of *N*-acylation conditions, all of which gave smooth reaction at both nitrogens. Thus, treatment with Ac_2O and $ClCH_2COCl$ afforded amides **4** and **5**, while reaction with 1.2 mole equiv. of $COCl_2$ gave a 3:5 mixture of the chloroformyl derivative, **6**, and cyclic urea **7**. Subsequent reaction of chloroformamide **6** with EtOH in the presence of K_2CO_3 did not yield the expected urethane **8**, but instead gave the cyclic urea **7** in 70% yield. Solvolysis had clearly caused

Keywords: 1,1′-bisisoquinolines; crown ethers; macrocycles; asymmetric reduction; ligands; NMR spectroscopy.

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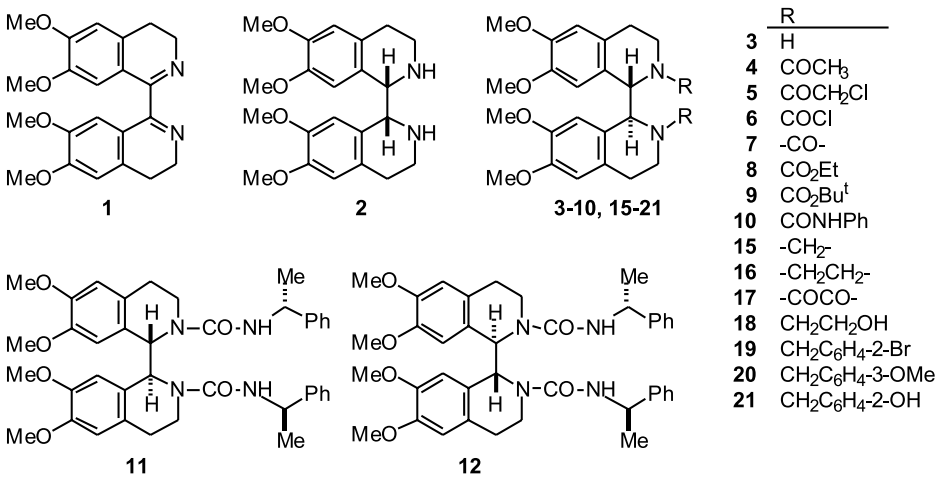
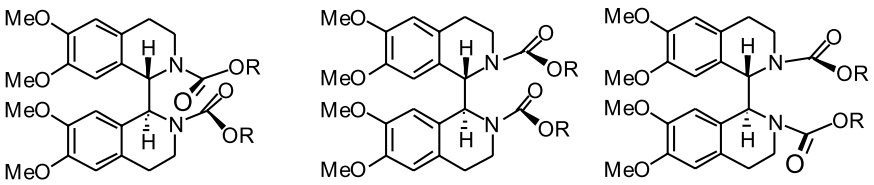


deacylation of one nitrogen and permitted cyclisation to occur subsequently through the chloroformyl group of the other; the role of EtOH or adventitious water in the reaction was not determined.

Direct treatment of amine **3** with $ClCO_2Et$ did give urethane **8**. The product was isolated as prisms in 84% yield but as a 36:45:19 mixture of three diastereomers, which had not been noted previously. The first of the two major isomers was symmetrical and the other unsymmetrical, while the third isomer was also symmetrical, according to NMR spectroscopic analysis. The origin of the isomers was almost certainly the restricted rotation that would have been present about the amide groups, which is normally slow on the NMR timescale and would give the observed three different rotameric forms of the molecule, namely **8a**–**c**.

Treatment of amine **3** with PhNCO afforded the expected *N*-phenylurea derivative **10** in 87% yield. Single crystal X-ray crystallographic analysis‡ revealed a very similar molecular structure to that observed for urethane **8** (see Supplementary Material). In this case the ^{1}H NMR spectrum of the product in d_6-DMSO at ambient temperature showed broad signals for most of the protons. At 365 K the majority of signals sharpened to reveal a single C_2 symmetric substance. Symmetry was most clearly seen through the corresponding *N*,*N*′-di-*tert*-butyloxycarbonyl (Boc) derivative **9** as again a mixture of three diastereomers **9a**–**c**. In this case the isomers appeared in a 38:47:15 ratio of symmetrical, unsymmetrical and symmetrical derivatives, respectively, and again they could not be separated by chromatography.



An X-ray crystal structure determination† revealed an unusual unit cell with two molecules of one configuration and one of the opposite configuration, thereby making it chiral. Closer inspection showed that within the molecular structure (see Fig. 1) the heterocyclic core contained offset isoquinoline rings joined by an axial C1–C1′ bridging bond, consistent with earlier findings.[20] There was also a single major configuration at nitrogen with the urethane carbonyl group dipoles opposed to one another. Similarly, acylation of amine **3** with di-*tert*-butyloxydicarbonate gave the appearance of a single singlet resonance at δ 5.38 from the benzylic protons at C1. Similar treatment of bis-amine **3** with a stoichiometric amount of (*R*)-(+)-α-methylbenzyl-isocyanate gave the corresponding urea derivative **11/12** in 84% yield. However in this case most of the signals in the ^{1}H NMR spectrum in d_6-DMSO at room temperature were sharp and the remaining signals became sharp at 365 K. Surprisingly, even at the higher temperature, only one set of signals could be observed, despite the likelihood of diastereomeric products. Furthermore, careful TLC

† X-ray crystallographic data for *rac*-2,2′-di(ethoxycarbonyl)-6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline **8** (CCDC 193035): formula $C_{28}H_{36}N_2O_8$, M=550, tetragonal, space group $I4_1$, a=12.785(1), b=12.785(1), c=50.770(8) Å, β=90°, V=8299(2)Å^3, D_{calc}=1.27 cm^{-3}, Z=24, μ(Cu Kα)=7.31 cm^{-1}. $2\theta_{max}$=50°. The number of reflexions was 1341 considered observed out of 2165 unique data. Final residuals R, R_w were 0.065, 0.080. Atomic coordinates, bond lengths and angles, and thermal parameters are shown below.

‡ X-Ray crystallographic data for *rac*-2,2′-di(phenylaminocarbonyl)-6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline **10** (CCDC 193034): formula $C_{36}H_{38}N_4O_6$, M=622, triclinic, space group P-1, a=10.915(5), b=12.148(6), c=13.084(6) Å, β=82.34(3)°, V=1538(1) Å^3, D_{calc}=1.34 cm^{-3}, Z=2, μ(Cu Kα=7.12 cm^{-1}. $2\theta_{max}$=70°. The number of reflexions was 4071 considered observed out of 5833 unique data. Final residuals R, R_w were 0.060, 0.077. Atomic coordinates, bond lengths and angles, and thermal parameters are shown below.

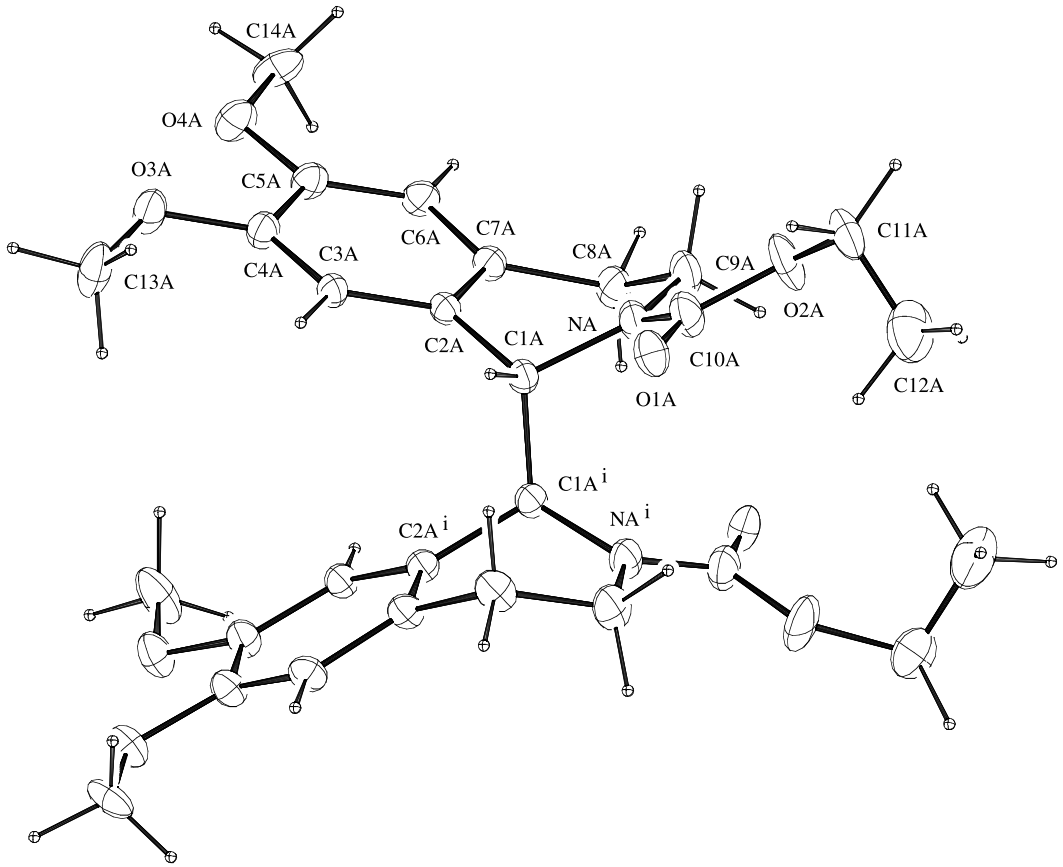
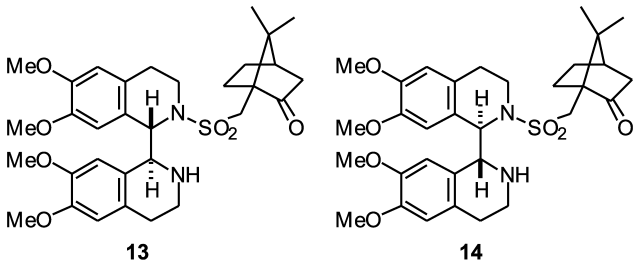


Figure 1. ORTEP diagram of urethane derivative **8** with crystallographic numbering.

chromatographic analysis failed to detect isomers. Therefore it could not be determined if the product was a single diastereomer or a mixture of two.

Interestingly, sulfonylation of **3** using a normalised stoichiometric amount of (*D*)-(+)-camphorsulfonyl chloride gave, after chromatography, an equimolar mixture of diastereoisomers **13** and **14** in 87% yield, each of which, from NMR and mass spectrometry, contained only one camphorsulfonyl group. Repeated chromatography on alumina eventually afforded a pure sample of one of the isomers, but the relative configuration of the pure sulfonamide as **13** or **14** could not be determined.



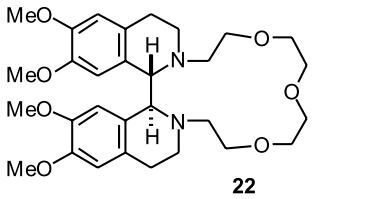
13 **14**

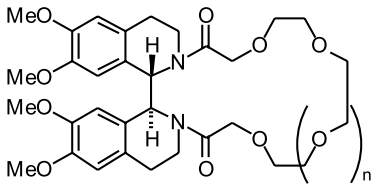
In contrast to this broad range of *N*-acylation and *N*-sulfonylation reactions, *N*-alkylation initially appeared limited in scope. Alkylation could not be achieved using simple alkyl chlorides or tosylates, nor with ethylene oxide, but was found to occur with CH_2Cl_2, 1,2-dibromoethane, 2-bromoethanol, and 2-bromo-, 2-acetoxy- and 3-methoxybenzyl bromide reagents.

Reaction with CH_2Cl_2 as solvent, in the presence of K_2CO_3 was slow and required 3 days to go to completion, but the product **15**[15] was obtained in 94% yield. Treatment with 1,2-dibromoethane in the presence of K_2CO_3, was repeated several times using varying ratios of reactants, from one mole equivalent of the alkyl halide to use of dibromoethane as solvent, but again only the cyclic product **16**, a substance previously obtained[15] by reduction of the corresponding oxamide **17**, could be isolated. Clearly the intramolecular process leading to cyclisation was favoured over separate reactions on nitrogen. In contrast, alkylation of **3** with 2-bromoethanol, and 2-bromo- and 3-methoxybenzyl bromide reagents afforded the expected products, **18**–**20**, in 57, 81 and 87% yields, respectively. Treatment with 2-acetoxybenzyl bromide gave a mixture of products that resulted from partial deacylation of the phenolic groups after alkylation had occurred. The mixture was hydrolysed under basic conditions to give the expected bis-phenol **21** after workup in 68% overall yield.

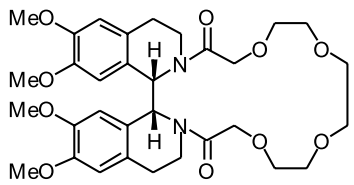
1.1. Asymmetric reduction of bis-imine 1

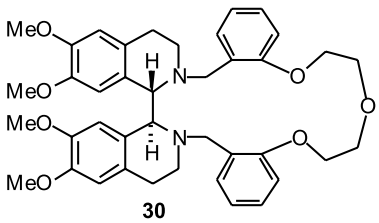
In the long term, access to homochiral bis-amine **3** and its derivatives is essential if the compounds are to be useful as asymmetric ligands. Our preliminary attempts to achieve resolution of **3** through diastereomeric salt formation and through derivative formation were discouraging. The one exception was the case of sulfonamide **13/14**, which was a substance that could be separated after tedious chromatography, but was deemed impractical as a derivative for resolution. We turned to asymmetric reduction of bis-imine **1**





23 n = 1
24 n = 2
25 n = 3
26 n = 4





as a more satisfactory solution, and application of amino acid modified borohydride reagents proved moderately successful.

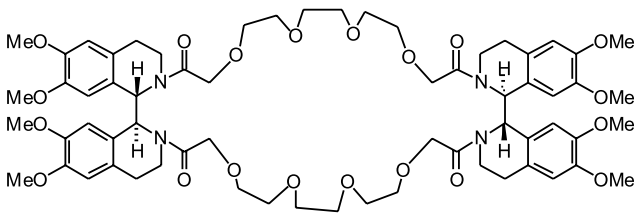
Reduction of imines, including 1-substituted 3,4-dihydroisoquinolines, proceeds with good asymmetric induction using a reagent prepared from $NaBH_4$ and various *N*-protected amino acids.[21] The reaction is reported to proceed with highest induction in the presence of the *N*-benzyloxycarbonylprolinate ligand. Unfortunately, treatment of bis-imine **1** with $NaBH_4$ and 3 mole equiv. of (*S*)-*N*-benzyloxycarbonylproline afforded only the *meso* reduction product **2**, although in 78% yield. However, replacement of the $NaBH_4$ with $NaBH_3CN$ and use of 2 mole equiv. of the amino acid derivative at 0°C to room temperature gave a mixture of diastereomers **2** and **3** in 25 and 57% yields, respectively. The latter isomer was treated with (*D*)-camphorsulfonyl chloride as described above to yield an 85:15 mixture of diastereomers in 87% yield. Repetition of the reaction at 45°C gave reduction products **2** and **3** in 25 and 66% yields, respectively, and a 62:38 mixture of diastereomeric camphorsulfonamide derivatives of **3**. There is clearly room for improvement in these results, but there is a strong indication that satisfactory asymmetric reduction can be achieved. Further development of the asymmetric reduction approach to these homochiral ligands is planned for the future.

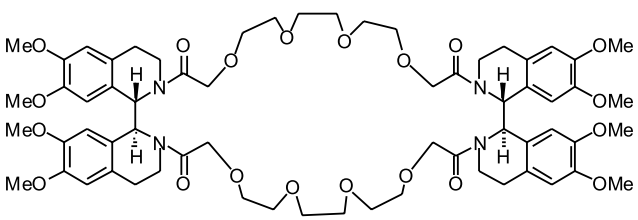
1.2. Preparation of macrocyclic derivatives

A major objective of this work was to investigate the synthesis of chiral racemic, macrocyclic and azacrown ether cavities based on the heterocyclic core of bis-amine **3**. Alkylation at nitrogen, as a pathway to these derivatives, was again initially discouraging due to the already mentioned lack of reactivity of suitable alkyl chlorides and tosylates. Thus, treatment of compound **3** with variously sized ethyleneglycol chlorides and tosylates in the presence of a wide spectrum of alkoxide and carbonate bases in alcohol, THF, Et_2O, CH_2Cl_2 and MeCN solvents yielded only recovered starting materials. Eventually, treatment with tetraethyleneglycol diiodide in MeCN in the presence of cesium carbonate afforded the desired diazacrown ether **22** in reasonable yield and purity. The product was however difficult to purify completely and the reaction towards higher homologues was not pursued.

In an alternative strategy to macrocyclic compounds, the chloroacetyl derivative **5** was used in place of bis-amine **3** and found to react readily with tri-, tetra-, penta- and hexaethyleneglycol to yield macrocyclic diamido analogues **23**–**26** of increasing ring size. The smallest-ringed amidocrown, compound **23**, was isolated in equal amounts with both its *meso* diastereoisomer **27** and an equal mixture of diastereomeric substances **28** and **29**. The latter substances clearly resulted from intermolecular condensation, but such by-products were not observed in any of the reactions leading to higher homologues **24**–**26**. Hence formation of **28** and **29** was attributed to the relatively small ring size being created in efforts to make **23**. Treatment of chloroacetamide **5** with ethyleneglycol itself under the same reaction conditions gave a mixture of products from which the oxamide **17**[15] was isolated in 57% yield. This strange result was reproducible and must have resulted from the small size of the incipient bridge; it probably also involved an oxidative process.

Interestingly, the methylene protons of the acetamido portion of macrocycles **23**–**26**, **28** and **29** were diastereotopic, as could be seen through their appearance in the ^1H NMR spectra as AB quartet signals. This was consistent with the non-equivalence of the corresponding signals from the bis-chloroacetamide **5**. Moreover, there





was a steady decrease in the difference in chemical shift of the proton signals as one progressed along the series **23** to **26**. This steady change could be interpreted as an indicator of the decreasing conformational constraints on the polyether part of the molecules. The observation that the *meso* diastereomer **27** had diastereotopic protons with the same difference in chemical shift as the *racemic* isomer **23** was consistent with this interpretation.

Advantage was also taken of the availability of bis(hydroxybenzyl) derivative **21**, prepared earlier, to test its potential as an intermediate in macrocycle formation. It underwent reaction with diethyleneglycol ditosylate under standard crown ether forming reaction conditions to yield the dibenzo-fused macrocycle **30** in 86% yield. Similar to the amide situation above, there was diastereotopicity in the benzylic protons of both the acyclic and macrocyclic derivatives, **21** and **30**, respectively. In this instance, there was a large difference (0.91 ppm) in chemical shifts between the diastereotopic protons of **30** compared to the relatively small differences (0.20–0.36 ppm) of the corresponding proton signals from the acyclic *N*-benzyl derivatives **19**-**21**. The difference was noted but there was insufficient information to decide if this was a structural indicator.

These successes clearly pave the way for a much broader investigation into the synthesis and chemical characterisation of macrocyclic derivatives, and a study of their supramolecular properties. In particular, a study of the degree to which complexation and the orientation about the bisisoquinoline bridging bond are related will have bearing on the utility of these substances and will be described in due course.

2. Experimental

^{1}H and ^{13}C NMR chemical shift assignments of the following compounds were made through a combination of H–H COSY, NOESY, HSQC and HMBC experiments, and in some cases DEPT 135, DEPT 90 experiments, at 300 or 500 MHz and comparisons of chemical shifts with those of other fully characterised derivatives.

2.1. Preparation of *N*-derivatives

2.1.1. Treatment of bis-amine 3 with acetic anhydride. Acetic anhydride (5 mL) and bis-amine **3** (0.100 g, 0.260 mmol) were treated together at 50°C for 20 min then at ambient temperature for 2 h. The mixture was poured on to ice and the precipitate collected and washed with H_2O. Chromatography on silica gel (EtOAc) then recrystallization of the main fraction from EtOAc gave *rac-2,2′-di(ethanoyl)-6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline* ***4*** as white needles (0.102 g, 84%) mp 225–226°C; [Found: C, 66.32; H, 6.58; N, 5.86. $C_{26}H_{32}N_2O_6$ requires C, 66.65; H, 6.88; N, 5.98%]; ν_{max} (Nujol) 1605, 1505, 1245, 1215, 1110, 1000, 920, 850 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.11 (6H, s, 2×COCH_3), 2.85 (2H, m, $H_\alpha4$ and $H_\beta4'$), 3.41 (2H, m, $H_\beta4$ and $H_\alpha4'$), 3.39 (6H, s, 7-OCH_3 and 7′-OCH_3), 3.48 (2H, m, $H_\alpha3$ and $H_\beta3'$), 3.82 (6H, s, 6-OCH_3 and 6′-OCH_3), 3.98 (2H, m, $H_\beta3$ and $H_\alpha3'$), 5.44 (2H, s, *H*1 and *H*1′), 5.62 (2H, s, *H*8 and *H*8′), 6.69 (2H, s, *H*5 and *H*5′); δ_C (75.6 MHz, $CDCl_3$) 22.1 (C2″ and C2‴), 27.8 (C4 and C4′), 43.4 (C3 and C3′), 55.5 (7-OCH_3 and 7′-OCH_3), 56.0 (6-OCH_3, 6′-OCH_3, C1 and C1′), 110.9 (C5 and C5′), 113.4 (C8 and C8′), 126.2 (C8a and C8′a), 127.3 (C4a and C4′a), 146.3 (C7 and C7′), 148.3 (C6 and C6′), 170.5 (C1″ and C1‴); *m/z* (EI) 468 (M^+, absent), 425 (M−43, 4), 411 (7), 368 (4), 308 (5), 307 (14), 289 (15), 279 (73), 251 (18), 248 (39), 234 (100), 193 (5), 192 (59), 176 (18), 149 (24), 109 (7), 97 (8), 86 (36), 84 (60), 71 (15), 57 (20), 49 (43%).

2.1.2. Treatment of bis-amine 3 with chloroacetyl chloride. Chloroacetyl chloride (0.40 mL, 5.20 mmol) was added to bis-amine **3** (1.00 g, 2.60 mmol) in glacial AcOH (4.5 mL) and the solution warmed at 40–50°C for 30 min. NaOAc (0.8 g) in H_2O (20 mL) was added to the warm solution and the mixture cooled in ice. The precipitate was collected, washed with H_2O, and recrystallized from EtOAc to give *rac-2,2′-di(chloroethanoyl)-6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline* ***5*** as white prisms suitable for X-ray crystallographic analysis[20] (1.30 g, 92%) mp 218–219°C; [Found: C, 57.82; H, 5.59; N, 5.07. $C_{26}H_{30}N_2O_6Cl_2$ requires C, 58.11; H, 5.63; N, 5.21%]; ν_{max} (Nujol) 1655, 1605, 1500, 1450, 1395, 1370, 1255, 1225, 1200, 1115, 1015, 970, 920, 890, 870, 850, 780 cm^{-1}. δ_H (500 MHz, $CDCl_3$) 2.92 (2H, m, $H_\alpha4$ and $H_\beta4'$), 3.40 (6H, s, 7-OCH_3 and 7′-OCH_3), 3.52 (2H, m, $H_\beta4$ and $H_\alpha4'$), 3.54 (2H, m, $H_\alpha3$ and $H_\beta3'$), 3.86 (6H, s, 6-OCH_3 and 6′-OCH_3), 4.07 (2H, m, $H_\beta3$ and $H_\alpha3'$), 4.10 (2H, d, J=12.8 Hz, $H_\alpha2''$ and $H_\beta2'''$), 4.15 (2H, d, J=12.8 Hz, $H_\beta2''$ and $H_\alpha2'''$), 5.42 (2H, s, *H*1 and *H*1′), 5.66 (2H, s, *H*8 and *H*8′), 6.73 (2H, s, H5 and H5′); δ_C (75.6 MHz, $CDCl_3$) 27.6 (C4 and C4′), 42.8 (C3 and C3′), 42.9 (C2″ and C2‴), 55.6 (7-OCH_3 and 7′-OCH_3), 56.0 (6-OCH_3 and 6′-OCH_3), 57.0 (C1 and C1′), 110.9 (C5 and C5′), 113.4 (C8 and C8′), 125.3 (C8a and C8′a), 127.1 (C4a and C4′a), 146.5 (C7 and C7′), 148.6 (C6 and C6′), 166.7 (C2″ and C2‴); *m/z* (EI) 536 (M^+, absent), 270 (M+2/2, 35), 268 (M/2, 100), 192 (59), 176 (30%).

2.1.3. Treatment of bis-amine 3 with phosgene. Commercial $COCl_2$ in toluene (0.30 mL, 20%) was added at rt to a solution of bis-amine **3** (100 mg, 0.260 mmol) in CH_2Cl_2 (40 mL). Within 30 min the mixture began to turn yellow and deposit a solid. After 2 h the solution was diluted with CH_2Cl_2 (50 mL), washed with H_2O (2×20 mL) and the organic phase dried over $MgSO_4$. Evaporation gave a mixture of two compounds as an off-white solid (110 mg). Silica gel chromatography (EtOAc) afforded, in order of increasing R_f: *rac-2,2′-di(chlorocarbonyl)-6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline* ***6*** as colourless prisms (41 mg, 31%) mp 201–203°C (EtOAc) suitable for X-ray crystallographic analysis;[20] [Found: C, 56.18; H, 5.07; N, 5.39. $C_{24}H_{26}N_2O_6Cl_2$ requires C, 56.59; H, 5.14; N, 5.50%]; ν_{max} (Nujol) 1732, 1605, 1510, 1255, 1230, 1120, 1040, 1015, 890 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.86 (2H, ddd, J=16.4, 5.6, ca. 5.1 Hz, $H_\alpha4$ and $H_\beta4'$), 3.32 (2H, ddd, J=16.4, 9.8, 6.2 Hz, $H_\beta4$ and $H_\alpha4'$), 3.41 (6H, s, 7-OCH_3 and 7′-OCH_3), 3.70 (2H, ddd, J=11.8, 6.2, ca. 5.1 Hz, $H_\alpha3$ and $H_\beta3'$), 3.85 (6H, s, 6-OCH_3 and 6′-OCH_3), 4.08 (2H, ddd, J=11.8, 6.2, ca. 5.1 Hz, $H_\beta3$ and $H_\alpha3'$), 5.12 (2H, s, *H*1 and *H*1′), 5.62 (2H, s, *H*8

and *H*8′), 6.73 (2H, s, *H*5 and *H*5′; δ_C (75.6 MHz, $CDCl_3$) 27.3 (C4 and C4′), 46.5 (C3 and C3′), 55.7 (7-OCH_3 and 7′-OCH_3), 56.1 (6-OCH_3 and 6′-OCH_3), 61.0 (C1 and C1′), 110.9 (C5 and C5′), 112.9 (C8 and C8′), 124.1 (C8a and C8′a), 127.3 (C4a and C4′a), 146.6 (C7 and C7′), 148.9 (C6 and C6′), 150.9 (C1″ and C1‴); *m/z* (EI) 508 (M^+, absent), 410 (25), 256 (M+2/2, 20), 254 (M^+/2, 61), 192 (20), 191 (100), 176 (39%); and *5,6,7,9,10,11,15b,15c-octahydrodi-isoquinolino[2,1-c:1′,2′-e]imidazol-8-one* **7** as colourless prisms (57 mg, 53%) mp 245–246°C (EtOAc); ν_{max} (Nujol) 1685, 1610, 1510, 1460, 1450, 1410, 1355, 1255, 1225, 1095, 1030, 1000, 890, 850, 790 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.51 (2H, m, H_α5 and H_β11), 3.02 (2H, m, H_β5 and H_α11), 3.06 (2H, m, H_α6 and H_β10), 3.88 (6H, s, 2-OCH_3 and 14-OCH_3), 3.92 (6H, s, 3-OCH_3 and 13-OCH_3), 4.13 (2H, m, H_β6 and H_α10), 4.78 (2H, s, *H*15b and *H*15c), 6.62 (2H, s, *H*1 and *H*15), 6.84 (2H, s, H4 and H12); δ_C (75.6 MHz, $CDCl_3$) 26.2 (C5 and C11), 39.3 (C6 and C10), 56.0 (2-OCH_3 and 14-OCH_3), 56.3 (3-OCH_3 and 13-OCH_3), 61.1 (C15b and C15c), 108.3 (C4 and C12), 112.2 (C1 and C15), 127.7 (C15a and C15d), 127.8 (C4a and C11a), 148.1 (C2 and C14), 148.5 (C3 and C13), 160.2 (C8); *m/z* 411 (M+1, 6), 410 (M^+, 25), 409 (M−1, 5), 192 (18), 191 (100), 176 (32%); HRMS (ES): M+Na^+, found 433.1726. $C_{23}H_{26}N_2O_5Na$ requires 433.1734.

Conversion of chloroformamide **6** to imidazolone **7**. A mixture of **6** (0.074 g, 0.15 mmol) and K_2CO_3 (0.040 g, 0.29 mmol) in absolute EtOH (30 mL) was heated at reflux for 3 h under vigorous stirring whereupon the mixture turned yellow. The mixture was cooled to rt, filtered, and the filtrate evaporated to dryness. Recrystallization of the residue from EtOAc gave imidazolone **7** as colourless prisms (0.042 g, 70%) mp 245–247°C with identical t.l.c., ^1H NMR and ^{13}C NMR characteristics as the product from above.

2.1.4. Treatment of bis-amine 3 with ethyl chloroformate. Ethyl chloroformate (0.079 g, 0.73 mmol) was added slowly to a mixture of bis-amine **3** (0.14 g, 0.36 mmol) and K_2CO_3 (0.12 g, 0.84 mmol) in CH_2Cl_2 (20 mL). The mixture was heated at reflux for 5 h and then cooled to rt and filtered. The filtrate was washed with H_2O (2×15 mL) and dried over $MgSO_4$. Evaporation of solvent gave an off-white solid that was column chromatographed on silica gel. Elution with EtOAc gave a single fraction that crystallized from EtOAc to give three isomeric forms of *rac-2,2′-di(ethoxycarbonyl)-6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline* ***8*** as white prisms suitable for X-ray crystallographic analysis (0.16 g, 84%) mp 139–145°C; ν_{max} (Nujol) 1685, 1605, 1340, 1300, 1265, 1220, 1120, 1090, 1020, 930, 920, 870 cm^{-1}; *m/z* (EI) 529 (M+1, 0.3), 528 (M^+, absent), 326 (1), 264 (M/2, 100), 236 (35), 192 (32), 176 (29), 97 (22%); HRMS: M+Na^+, found 551.2364. $C_{28}H_{36}N_2O_8Na$ requires *m/z* 551.2364. ^1H NMR spectroscopic analysis showed a major symmetrical isomer, a major unsymmetrical isomer and a minor symmetrical isomer in the ratio 36:45:19. The first major isomeric product **8a** had δ_H (300 MHz, $CDCl_3$) 1.20 (6H, t, *J*=7.2 Hz, CH_2CH_3 and $CH_2'CH_3'$), 2.62–3.25 (4H, m, $(H4)_2$ and $(H4')_2$), 3.40 (6H, s, 7-OCH_3 and 7′-OCH_3), 3.45–3.95 (4H, m, $(H3)_2$ and $(H3')_2$), 3.79 (6H, s, 6-OCH_3 and 6′-OCH_3), 4.15 (4H, m, CH_2CH_3 and $CH_2'CH_3'$), 5.00 (2H, s, *H*1 and *H*1′), 5.64 (2H, s, *H*8 and *H*8′), 6.66 (2H, s, H5 and H5′); δ_C (75.6 MHz, $CDCl_3$) 14.7 (CH_2CH_3 and $C'H_2C'H_3$), 27.3 (C4 and C4′), 41.1 (C3 and C3′), 55.5 (7-OCH_3 and 7′-OCH_3), 55.9 (6-OCH_3 and 6′-OCH_3), 58.3 (C1 and C1′), 61.1 (CH_2CH_3 and $C'H_2C'H_3$), 111.0 (C5 and C5′), 113.2 (C8 and C8′), 126.4 (C8a and C8a′), 127.6 (C4a and C4a′), 146.0 (C7 and C7′), 148.1 (C6 and C6′), 156.4 (CO and C′O). The unsymmetrical isomer **8b** had δ_H (300 MHz, $CDCl_3$) 1.20, 1.31 (6H, 2×t, *J*=7.2 Hz, CH_2CH_3 and $CH_2'CH_3'$), 2.62–3.25 (4H, m, $(H4)_2$ and $(H4')_2$), 3.40, 3.42 (6H, 2×s, 7-OCH_3 and 7′-OCH_3), 3.45-3.95, m, $(H3)_2$ and $(H3')_2$; 3.79 (6H, s, 6-OCH_3 and 6′-OCH_3), 4.10 (4H, m, CH_2CH_3 and $CH_2'CH_3'$), 4.94, 5.15 (2H, 2×d, *J*=9.4 Hz, *H*1 and *H*1′), 5.61, 5.73 (2H, 2×s, *H*8 and *H*8′), 6.62, 6.63 (2H, 2×s, *H*5 and *H*5′); δ_C (75.6 MHz, $CDCl_3$): δ 14.62, 14.67 (CH_2CH_3 and $C'H_2C'H_3$), 27.26, 27.31 (C4 and C4′), 40.4, 41.0 (C3 and C3′), 55.5 (7-OCH_3 and 7′-OCH_3), 55.9 (6-OCH_3 and 6′-OCH_3), 57.97, 58.0 (C1 and C1′), 61.28, 61.36 (CH_2CH_3 and $C'H_2C'H_3$), 110.9, 111.2 (C5 and C5′), 113.1, 113.4 (C8 and C8′), 125.7, 126.3 (C8a and C8a′), 127.2, 127.8 (C4a and C4a′), 145.9, 146.3 (C7 and C7′), 148.1, 148.2 (C6 and C6′), 155.5 (CO and C′O). The minor symmetrical isomer **8c** had δ_H (300 MHz, $CDCl_3$) 1.20 (6H, t, *J*=7.2 Hz, CH_2CH_3 and $CH_2'CH_3'$), 2.62–3.25 (4H, m, $(H4)_2$ and $(H4')_2$), 3.40 (6H, s, 7-OCH_3 and 7′-OCH_3) 3.45–3.95 (4H, m, $(H3)_2$ and $(H3')_2$), 3.79 (6H, s, 6-OCH_3 and 6′-OCH_3), 4.05 (4H, m, CH_2CH_3 and $CH_2'CH_3'$), 5.06 (2H, s, *H*1 and *H*1′), 5.64 (2H, s, *H*8 and *H*8′), 6.60 (2H, s, *H*5 and *H*5′); δ_C (75.6 MHz, $CDCl_3$) 14.7 (CH_2CH_3 and $C'H_2C'H_3$), 27.18 (C4 and C4′), 40.0 (C3 and C3′), 55.5 (7-OCH_3 and 7′-OCH_3), 55.9 (6-OCH_3 and 6′-OCH_3), 58.0 (C1 and C1′), 61.5 (CH_2CH_3 and $C'H_2C'H_3$), 111.0 (C5 and C5′), 113.2 (C8 and C8′), 125.4 (C8a and C8a′), 127.4 (C4a and C4a′), 146.2 (C7 and C7′), 148.3 (C6 and C6′), 156.2 (CO and C′O).

2.1.5. Treatment of bis-amine 3 with di-*tert*-butyloxydicarbonate. 4-(Dimethylamino)pyridine (0.127 g, 1.04 mmol) and di-*tert*-butyloxydicarbonate (2.73 g, 12.40 mmol) were added to a well-stirred suspension of bis-amine **3** (2.00 g, 5.20 mmol) in CH_3CN (70 mL) under argon. After 4 h, the solvent was evaporated and the residue was partitioned between $CHCl_3$ (60 mL) and 1 M $KHSO_4$ (30 mL). The $CHCl_3$ extracts were washed sequentially with 1 M $KHSO_4$ (4×30 mL), 1 M $NaHCO_3$ (1×25 mL) and H_2O (2×25 mL), and subsequently dried over Na_2SO_4. Solvent was evaporated and the residue chromatographed on silica gel using an EtOAc/light petroleum gradient. The EtOAc fraction, which was major, crystallized from MeOH to give a 38:47:15 mixture of three isomeric forms of *rac-2,2′-di-(tert-butyloxycarbonyl)-6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline* ***9*** as clusters of thin white needles (1.362 g, 89%) mp 143–147°C; [Found: C, 65.69; H, 7.32; N, 4.52. $C_{32}H_{44}N_2O_8$ requires C, 65.73; H, 7.58; N, 4.79%]; ν_{max} (Nujol) 1680, 1600, 1510, 1460, 1340, 1280, 1180, 1120, 1090 cm^{-1}; *m/z* (EI) 585 (M+1, 3), 584 (M^+, 7), 485 (6), 484 (15), 427 (23),411 (15), 368 (15), 352 (25), 340 (20), 293 (18) 292 (100%). The major symmetrical diastereomer **9a** had δ_H (300 MHz, $CDCl_3$) 1.46 (18H, s, $C(CH_3)_3$ and $C'(CH_3)_3$), 2.71–3.24 (4H, m, $(H4)_2$ and $(H4')_2$), 3.41–3.83 (4H, m, $(H3)_2$ and $(H3')_2$), 3.48 (6H, s, 7-OCH_3 and 7′-OCH_3), 3.83 (6H, s, 6-OCH_3 and 6′-OCH_3), 5.00 (2H, s, *H*1 and *H*1′), 5.74 (2H, s, *H*8 and

*H*8′), 6.67 (2H, s, H5 and H5′). δ_C (75.6 MHz, $CDCl_3$) 27.4 (C4 and C4′), 28.4 (C(CH_3)$_3$ and C′(CH_3)$_3$), 41.4 (C3 and C3′), 55.4 (7-OCH_3 and 7′-OCH_3), 55.9 (6-OCH_3 and 6′-OCH_3), 57.7 (C1 and C1′), 79.6 (*C*(CH_3)$_3$ and *C*′(CH_3)$_3$), 111.0 (C5 and C5′), 113.2 (C8 and C8′), 127.0 (C8a and C8′a), 127.8 (C4a and C4a′), 145.9 (C7 and C7′), 148.0 (C6 and C6′), 155.4 (CO and C′O). The unsymmetrical isomeric product **9b** had δ_H (300 MHz, $CDCl_3$) 1.45, 1.52 (18H, 2×s, C(CH_3)$_3$ and C′(CH_3)$_3$), 2.71–3.24 (4H, m, (*H*4)$_2$ and (*H*4′)$_2$), 3.41, 3.83 (4H, 2×m, (*H*3)$_2$ and (*H*3′)$_2$), 3.43 (6H, s, 7-O*CH*$_3$ and 7′-O*CH*$_3$), 3.83 (6H, s, 6-O*CH*$_3$ and 6′-O*CH*$_3$), 4.87, 5.14 (2H, 2×d, *J*=9.7 Hz, H1 and H1′), 5.53, 5.75 (2H, 2×s, H8 and H8′), 6.65, 6.66 (2H, 2×s, H5 and H5′); δ_C (75.6 MHz, $CDCl_3$) 27.4, 27.5 (C4 and C4′), 28.4, 28.5 (C(*C*H_3)$_3$ and C′(*C*H_3)$_3$), 39.8, 41.6 (C3 and C3′), 55.4, 55.6 (7-OCH_3 and 7′-OCH_3), 55.8, 56.0 (6-OCH_3 and 6′-OCH_3), 57.0, 58.4 (C1 and C1′), 79.1, 80.1 (*C*(CH_3)$_3$ and *C*′(CH_3)$_3$), 110.8, 111.2 (C5 and C5′), 113.2, 113.5 (C8 and C8′), 126.2, 126.8 (C8a and C8a′), 127.2, 127.9 (Ca4 and Ca4′), 145.8, 146.3 (C7 and C7′), 148.05, 148.09 (C6 and C6′), 154.1, 155.1 (CO and C′O). The minor symmetrical rotomeric isomer **9c** had δ_H (300 MHz, $CDCl_3$) 1.44 (18H, s, C(*CH*$_3$)$_3$ and C′(*CH*$_3$)$_3$), 2.71–3.24 (4H, m, (*H*4)$_2$ and (*H*4′)$_2$), 3.61, 4.21 (4H, 2×m, (*H*3)$_2$ and (*H*3′)$_2$), 3.36 (6H, s, 7-O*CH*$_3$ and 7′-O*CH*$_3$), 3.82 (6H, s, 6-O*CH*$_3$ and 6′-O*CH*$_3$), 5.01 (2H, s, H1 and H1′), 5.53 (2H, s, H8 and H8′), 6.64 (2H, s, H5 and H5′); δ_C (75.6 MHz, $CDCl_3$) 27.7 (C4 and C4′), 28.3 (C(*C*H_3)$_3$ and C′(*C*H_3)$_3$), 38.9 (C3 and C3′), 55.4 (7-OCH_3 and 7′-OCH_3), 55.9 (6-OCH_3 and 6′-OCH_3), 57.6 (C1 and C1′), 79.1 (*C*(CH_3)$_3$ and *C*′(CH_3)$_3$), 111.1 (C5 and C5′), 113.5 (C8 and C8′), 125.8 (C8a and C8′a), 127.3 (C4a and C4′a), 146.0 (C7 and C7′), 148.2 (C6 and C6′), 154.2 (CO and C′O).

2.1.6. Treatment of bis-amine 3 with phenyl isocyanate. Phenyl isocyanate (0.062 g, 0.52 mmol) was added over 5 min to a stirred solution of bis-amine **3** (0.100 g, 0.26 mmol) in dry CH_2Cl_2 (15 mL) at 10°C under argon. Stirring was continued for 30 min before the mixture was diluted with CH_2Cl_2 (20 mL), the solution washed with H_2O (15 mL), and the organic layer dried ($MgSO_4$). Evaporation gave an off-white solid that was recrystallized from EtOH to give *rac-2,2′-di(phenylaminocarbonyl)-6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline **10*** as white prisms suitable for X-ray crystallographic analysis (0.140 g, 87%) mp 250–251°C; [Found: C, 69.19; H, 6.10; N, 8.83. $C_{36}H_{38}N_4O_6$ requires C, 69.44; H, 6.15; N, 9.00%]; ν_{max} (Nujol) 3350, 1640, 1590, 1500, 1440, 1350, 1300, 1230, 1210, 1115, 1020, 1005, 920, 840, 750, 690 cm^{-1}; δ_H (500 MHz, d_6-DMSO): δ 2.58–2.82 (2H, m, H_α4 and H_β4′), 3.32–3.55 (4H, m, H_β4, H_α4′, H_α3 and H_β3′), 3.44 (6H, br s, 7-O*CH*$_3$ and 7′-O*CH*$_3$), 3.75 (6H, s, 6-O*CH*$_3$ and 6′-O*CH*$_3$), 3.80-3.94 (2H, m, H_β3 and H_α3′), 5.38 (2H, s, *H*1 and *H*1′), 5.96 (2H, br s, *H*8 and *H*8′), 6.82 (2H, s, *H*5 and *H*5′), 6.95 (2H, t, *J*=7.2 Hz, *H*6″ and *H*6‴), 7.23 (4H, t, *J*=7.7 Hz, *H*5″, *H*5‴, *H*7″ and *H*7‴), 7.51 (4H, d, *J*=8.2 Hz, *H*4″, *H*4‴, *H*8″ and *H*8‴), 8.49 (2H, br s, 2×N*H*); δ_C (75.6 MHz, d_6-DMSO) 26.7 (C4 and C4′), 41.1 (C3 and C3′), 55.5 (7-OCH_3 and 7′-OCH_3), 55.9 (6-OCH_3 and 6′-OCH_3), 57.6 (br, C1 and C1′), 111.7 (C5 and C5′), 113.8 (C8 and C8′), 120.7 (C6″ and C6‴), 122.1 (C5″, C5‴, C7″ and C7‴), 126.4 (br, C8a and C8′a), 128.1 (C4a and C4′a), 128.4 (C4″, C4‴, C8″ and C8‴), 140.7 (C3″ and C3‴), 146.3 (C7 and C7′), 148.4 (C6 and C6′), 155.5 (C1″ and C1‴); *m/z* (EI) 622 (M^+, absent), 311 (M/2, 10), 264 (6), 236 (8), 193 (9), 192 (100), 176 (23), 119 (49), 91 (48), 69 (49%).

2.1.7. Treatment of bis-amine 3 with (*R*)-(+)-α-methylbenzyl isocyanate. Repetition of reaction (treatment of bis-amine **3** with phosgene) using (*R*)-(+)-α-methylbenzyl isocyanate (0.766 g, 5.21 mmol) and bis-amine **3** (1.00 g, 2.60 mmol) gave *rac-2,2′-di((R)-1-phenylethyl)aminocarbonyl)-6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline **11*** and/or **12** as white needles (1.115 g, 84%) mp 212–214°C; ν_{max} (Nujol) 3270, 1625, 1510, 1450, 1370, 1260, 1210, 1130, 1030 cm^{-1}; δ_H (300 MHz, d_6-DMSO) 1.50 (6H, d, *J*=7.8 Hz, NHCHC*H*$_3$ and NH′CH′C*H*$_3$′), 1.88 (2H, m, H_α4 and H_β4′), 2.39 (2H, m, H_β4 and H_α4′), 3.13 (2H, m, H_α3 and H_β3′), 3.51 (6H, br s, 7-O*CH*$_3$ and 7′-O*CH*$_3$), 3.66 (2H, m, Hβ3 and Hα3′), 3.71 (6H, s, 6-OCH_3 and 6′-OCH_3), 5.05 (2H, q, *J*=14.5, 7.3 Hz, NHC*H*CH$_3$ and NH′C*H*′CH$_3$′), 5.24 (2H, s, *H*1 and *H*1′), 6.11 (2H, s, *H*8 and *H*8′), 6.63 (2H, s, 2×N*H*), 6.64 (2H, s, *H*5 and *H*5′), 7.14 (2H, t, *J*=7.2 Hz, H6″ and H6‴), 7.24 (4H, t, *J*=7.6 Hz, H5″, H5‴, H7″ and H7‴), 7.36 (4H, d, *J*=7.3 Hz, H4″, H4‴, H8″ and H8‴); δ_C (75.6 MHz, d_6-DMSO) 23.0 (NHCH*C*H$_3$ and NHCH*C*H$_3$), 26.6 (C4 and C4′), 41.5 (C3 and C3′), 50.3 (NH*C*HCH$_3$ and NH*C*HCH$_3$), 56.3 (7-OCH_3 and 7′-OCH_3), 56.7 (6-OCH_3 and 6′-OCH_3), 58.4 (C1 and C1′), 112.9 (C5 and C5′), 114.9 (C8 and C8′), 126.2 (C6″ and C6‴), 126.6 (C5″, C5‴, C7″ and C7‴), 128.4 (C4″, C4‴, C8″ and C8‴), 128.6 (C8a and C8′a), 128.9 (C4a and C4′a), 146.6 (C3″ and C3‴), 147.4 (C7 and C7′), 149.3 (C6 and C6′), 157.6 (C1″ and C1‴); *m/z* (EI) 680 (M+2, 7), 679 (M+1, 20), 678 (M^+, 5), 411 (4), 353 (3), 359 (M/2, 7), 192 (100), 176 (3%); HRMS: MH^+, found 679.8249. $C_{40}H_{46}N_4O_6$+H requires 679.8245.

2.1.8. Treatment of bis-amine 3 with (*D*)-(+)-10-camphorsulfonyl chloride. (*D*)-(+)-10-Camphorsulfonyl chloride (1.31 g, 5.2I mmol) was added to a mixture of bis-amine **3** (1.00 g, 2.60 mmol) and Et_3N (0.41 mL, 5.23 mmol) in CH_2Cl_2 (25 mL). The resultant mixture was allowed to stir at ambient temperature for 34 h. The reaction mixture was then diluted with CH_2Cl_2 (20 mL), and the solution washed successively with brine (20 mL) and H_2O (3×30 mL), dried over Na_2SO_4, and evaporated to give a yellow gum that was flash-chromatographed on silica gel (EtOAc) to give yellow gum (1.85 g, 87%). ^1H NMR spectroscopic analysis showed the presence of a 1:1 mixture of two diasteroisomers. Attempted fractional crystallization failed, but preparative tlc of a sample on commercial alumina plates, with multiple development with EtOAc gave from one fraction a single isomer, *(1R,1′R)-or(1S,1′S)-2-[[(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)sulfonyl]-6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′1-octaahydro-1,1′-bisisoquinoline **13** or **14*** as a yellow gum; ν_{max} (Nujol) 3030, 1425, 1585, 1485, 1450, 1360, 1250, 1220, 1185, 1130, 1020, 895, 850 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.62 (3H, s, 7″-C*H*$_3$), 0.98 (3H, s, 7″-C*H*$_3$), 1.36 (1H, ddd, *J*=13.7, 9.4, 4.2 Hz, H_a5″), 1.70 (1H, ddd, *J*=13.7, 9.1, 4.0 Hz, H_a6″), 1.85 (1H, d, *J*=18.4 Hz, H_a2″), 1.98 (1H, m, H_b5″), 2.01 (1H, dd, *J*=4.3, 4.2 Hz, *H*4″), 2.25 (1H, ddd, *J*=8.1, 4.2, 3.4 Hz, H_b2″), 2.36 (1H, ddd, *J*=14.7, 10.0, 3.8 Hz, H_b6″), 2.73 (1H, m, H_a4′), 2.80 (1H, m, H_a4), 2.85 (1H, m, H_b4′), 2.90 (1H, m, H_a3′), 2.98 (1H, d, *J*=14.7 Hz,

$SO_2CH_aH_b$), 3.00 (1H, m, H_b4), 3.27 (1H, m, H_b3'), 3.65 (3H, s, 7′-OCH_3), 3.67 (3H, s, 7-OCH_3), 3.82 (3H, s, 6′-OCH_3), 3.83 (1H, d, J=14.7 Hz, $SO_2CH_aH_b$), 3.86 (1H, m, H_a3), 3.87 (3H, s, 6-OCH_3), 4.18 (1H, m, H_b3), 4.39 (1H, d, J=5.7 Hz, $H1'$), 5.28 (1H, d, J=5.7 Hz, $H1$), 6.25 (1H, br s, $H8'$), 6.30 (1H, br s, $H8$), 6.59 (1H, s, $H5'$), 6.64 (1H, s, $H5$); δ_C (75.6 Hz, $CDCl_3$) 19.4 (CH_3), 19.6 (CH_3), 24.9 (C6″), 26.9 (C5″), 27.4 (C4), 29.2 (C4′), 40.5 (C3′), 41.4 (C3), 42.5 (C3″), 42.7 (C4″), 47.7 (C7″), 48.5 (SO_2CH_2), 55.5 (7′-OCH_3), 55.9 (7-OCH_3), 55.7 (6′-OCH_3), 56.0 (6-OCH_3), 57.8 (C1), 58.0 (C1″), 60.4 (C1′), 111.4 (C5′), 111.45 (C8′), 111.7 (C5), 112.4 (C8), 125.0 (C8a), 125.5 (C8′a), 127.0 (C4a), 128.5 (C4′a), 146.2, 147.1, 147.8 and 148.4 (C6, C6′, C7 and C7′), 214.9 (CO); *m/z* (EI) 598 (M^+, 100%); HRMS: M+H, found 599.2785. $C_{32}H_{42}N_2SO_7$+H requires 599.2785.

2.1.9. Treatment of bis-amine 3 with excess 1,2-dibromoethane. 1,2-Dibromoethane (0.453 g, 2.4 mmol) was added to bis-amine **3** (0.421 g, 1.1 mmol) and K_2CO_3 (0.33 g, 2.4 mmol) in dry CH_3CN (15 mL), and the mixture heated at reflux for 3 h. The mixture was then cooled, filtered, and the filtrate washed with H_2O (2×15 mL) and dried over $MgSO_4$. Evaporation gave a yellow solid that was recrystallized from EtOAc to give *rac-2,2′-ethano-6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline* ***16*** as white needles (0.319 g, 71%) mp 223–227°C (lit.[15] 226–228°C); δ_C (75.6 MHz, $CDCl_3$) 27.5 (br C4 and C4′), 45.8 (br C3 and C3′), 48.4 (br C1″ and C1‴), 55.1 (7-OCH_3 and 7′-OCH_3), 55.8 (6-OCH_3 and 6′-OCH_3), 58.3 (C1 and C1′), 111.3 (C5 and C5′), 112.7 (br C8 and C8′), 126.4 (C8a and C8′a), 127.0 (C4a and C4′a), 145.5 (C7 and C7′), 147.6 (C6 and C6′).

2.1.10. Treatment of bis-amine 3 with 2-bromoethanol. 2-Bromoethanol (0.12 mL, 1.1 mmol) in CH_2Cl_2 (5 mL) was added to a well-stirred mixture of bis-amine **3** (0.20 g, 0.53 mmol) and K_2CO_3 (0.73 g, 5.38 mmol) in CH_2Cl_2 (20 mL). The mixture was heated at reflux overnight, cooled to rt, filtered, and the filtrate washed with H_2O (2×10 mL), brine (10 mL) and dried over $MgSO_4$. Evaporation gave a mixture of two compounds as an off-white solid (0.22 g). Silica gel chromatography with a gradient of EtOAc/MeOH afforded *rac-2,2′-di(hydroxyethyl)-6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline* ***18*** as a colourless amorphous solid (0.14 g, 57%) mp 174–178°C (EtOAc); (Found: HRMS *m/z* 495.2408. $C_{26}H_{36}N_2O_6Na$ requires 495.2465). ν_{max} (Nujol) 3400, 1600, 1215, 1110, 1050, 1015, 870, 850, 830 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.55 (2H, dd, J=8.2, 4.1 Hz, $H_\alpha4$ and $H_\beta4'$), 2.77 (4H, m, $(H1'')_2$ and $(H1''')_2$), 2.90 (2H, m, $H_\beta4$ and $H_\alpha4'$), 3.00 (2H, m, $H_\alpha3$ and $H_\beta3'$), 3.21 (6H, s, 7-OCH_3 and 7′-OCH_3), 3.49 (2H, m, $H_\beta3$ and $H_\alpha3'$), 3.75 (4H, m, $(H2'')_2$ and $(H2''')_2$), 3.76 (6H, s, 6-OCH_3 and 6′-OCH_3), 3.77 (2H, s, $H1$ and $H1'$), 5.38 (2H, s, $H8$ and $H8'$), 6.55 (2H, s, $H5$ and $H5'$); δ_C (75.6 MHz, $CDCl_3$) 23.0 (C4 and C4′), 45.5 (C3 and C3′), 54.4 (C1″ and C1‴), 55.2 (7-OCH_3 and 7′-OCH_3), 55.8 (6-OCH_3 and 6′-OCH_3), 60.5 (C2″ and C2‴), 64.4 (C1 and C1′), 110.8 (C5 and C5′), 114.3 (C8 and C8′), 124.5 (C8a and C8′a), 126.7 (C4a and C4′a), 146.0 (C7 and C7′), 147.8 (C6 and C6′); *m/z* (EI) 473 (M+1, 100), 472 (M^+, absent), 237 (5), 236 (14), 234 (3%); HRMS: M+Na, 495.2408. $C_{26}H_{36}N_2O_6Na$ requires 495.2465.

2.1.11. Treatment of bis-amine 3 with 2-bromobenzyl bromide. Repetition of the procedure (Treatment of bis-amine **3** with phosgene) using 2-bromobenzyl bromide (2.30 g, 9.20 mmol), K_2CO_3 (1.30 g, 9.30 mmol), and bisamine **3** (1.61 g, 4.20 mmol) in CH_3CN (200 mL) gave a yellow-brown gum that was chromatographed on silica gel (EtOAc/light petroleum) to give *rac-2,2′-di(2-bromobenzyl)-6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline* ***19*** as colourless prisms (2.43 g, 81%) mp 85–87°C (EtOAc); [Found: C, 59.69; H, 5.38; N, 3.57. $C_{36}H_{38}N_2O_4Br_2$ requires C, 59.85; H, 5.30; N, 3.88%]; ν_{max} (Nujol) 1595, 1300, 1260, 1220, 1135, 1015, 855 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.60 (2H, m, $H_\alpha4$ and $H_\beta4'$), 2.60 (2H, m, $H_\beta4$ and $H_\alpha4'$), 2.60 (2H, m, $H_\alpha3$ and $H_\beta3'$), 3.20 (2H, m, $H_\beta3$ and $H_\alpha3'$), 3.67 (6H, s, 7-OCH_3 and 7′-OCH_3), 3.77 (6H, s, 6-OCH_3 and 6′-OCH_3), 3.80 (2H, d, J=ca. 13.9 Hz, $H_\alpha1''$ and $H_\beta1'''$), 4.14 (2H, s, $H1$ and $H1'$), 4.16 (2H, d, J=13.9 Hz, $H_\beta1''$ and $H_\alpha1'''$); 6.41 (2H, s, $H8$ and $H8'$), 6.87 (2H, s, $H5$ and $H5'$), 7.10 (2H, t, J=7.7 Hz, $H6''$ and $H6'''$), 7.25 (2H, m, $H5''$ and $H5'''$), 7.53 (2H, d, J=8.2 Hz, $H7''$ and $H7'''$), 7.65 (2H, d, J=7.7 Hz, $H4''$ and $H4'''$); δ_C (75.6 MHz, $CDCl_3$) 26.9 (C4 and C4′), 46.6 (C3 and C3′), 55.5 (7-OCH_3, 7′-OCH_3, 6-OCH_3 and 6′-OCH_3), 58.7 (C1″ and C1‴), 65.9 (C1 and C1′), 110.4 (C5 and C5′), 112.1 (C8 and C8′), 124.4 (C8a and C8′a), 126.9 (C5″ and C5‴), 127.7 (C2″ and C2‴), 127.9 (C4a and C4′a), 128.2 (C7″ and C7‴), 130.9 (C4″ and C4‴), 132.6 (C5″ and C5‴), 138.6 (C3″ and C3‴), 145.6, (C7 and C7′), 146.8 (C6 and C6′); *m/z* 724 (M^+ ($^{81}Br_2$), 58), 723 (M(^{81}Br,^{79}Br)+1, 100), 721 (M($^{79}Br_2$)+1, 50), 192 (20), 191 (100), 176 (39%).

2.1.12. Treatment of bis-amine 3 with 3-methoxybenzyl chloride. 3-Methoxybenzyl chloride (0.090 g, 0.58 mmol) and K_2CO_3 (0.075 g, 2.2 mmol) were added to a warm solution of bisamine **3** (0.100 g, 0.260 mmol) in CH_3CN (50 mL) and the mixture was heated at reflux overnight, then cooled to rt and filtered. The filtrate was evaporated to give a yellow solid that was redissolved in CH_2Cl_2 (20 mL) and the solution washed with H_2O (2×15 mL), then dried and evaporated to dryness. The residue was recrystallized from EtOAc to give *rac-2,2′-di(3-methoxybenzyl)-6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline* ***20*** as colourless needles (141 mg, 87%) mp 147–149°C; ν_{max} (Nujol): 1610, 1585, 1505, 1480, 1460, 1365, 1310, 1270, 1240, 1220, 1185, 1140, 1075, 1055, 1035, 1010, 990, 960, 865, 835, 800, 780, 695 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.51 (2H, m, $H_\alpha4$ and $H_\beta4'$), 2.52 (2H, m, $H_\beta4$ and $H_\alpha4'$), 2.66 (2H, m, $H_\alpha3$ and $H_\beta3'$), 3.21 (2H, m, $H_\beta3$ and $H_\alpha3'$), 3.68 (6H, s, 7-OCH_3 and 7′-OCH_3), 3.77 (6H, s, 6-OCH_3 and 6′-OCH_3 or 3″-OCH_3 and 3‴-OCH_3), 3.79 (6H, s, 3″-OCH_3 and 3‴-OCH_3 or 6-OCH_3 and 6′-OCH_3), 4.10 (2H, s, $H1$ and $H1'$), 3.49 (2H, d, J=14.0 Hz, $H_\alpha1''$ and $H_\beta1'''$), 4.22 (2H, d, J=14.0 Hz, $H_\beta1''$ and $H_\alpha1'''$), 6.37 (2H, s, $H8$ and $H8'$), 6.82 (2H, dd, J=8.2, ca. 2.0 Hz, $H5''$ and $H5'''$), 7.03 (2H, partially obscured d, J=ca. 8 Hz, $H7''$ and $H7'''$), 7.05 (4H, br s, $H3''$, $H3'''$, $H5$ and $H5'$), 7.24 (2H, t, J=8.2 Hz, $H6''$ and $H6'''$); δ_C (75.6 MHz, $CDCl_3$) 27.5 (C4 and C4′), 46.8 (C3 and C3′), 55.2 (3″-OCH_3 and 3‴-OCH_3), 55.6 (7-OCH_3 and 7′-OCH_3), 55.7 (6-OCH_3 and 6′-OCH_3), 59.4 (C1″ and C1‴), 66.1 (C1 and C1′), 110.4 (C5 and C5′), 112.1 (C8 and C8′), 112.2 (C4″ and C4‴), 114.6 (C3″ and C3‴), 121.1 (C5″ and C5‴), 128.1 (C8a and C8′a), 128.3 (C4a and C4′a), 129.2 (C3″ and

C3‴), 141.7 (C2″ and C2‴), 145.9 (C7 and C7′), 146.9 (C6 and C6′), 159.8 (C4″ and C4‴); *m/z* (ES) 624 (M^+, absent), 625 (M+1, 100%); HRMS: M+H, 625.3241. $C_{38}H_{44}N_2O_6$+H requires 625.3271.

2.1.13. Treatment of bis-amine 3 with 2-(bromomethyl)-phenyl acetate. 2-(Bromomethyl)phenyl acetate (427 mg, 1.86 mmol) and anhydrous K_2CO_3 (0.269 g, 1.95 mmol) were added to a boiling solution of bisamine **3** (0.341 g, 0.888 mmol) in CH_3CN (100 mL). The mixture was heated at reflux overnight then cooled to rt, filtered and the filtrate was evaporated to give a yellow gum (0.498 g). The crude products (1.00 g total) from two such reactions were heated together at reflux with KOH (150 mg) in EtOH (20 mL) containing H_2O (0.5 mL) for 2 h. The mixture was cooled in ice and the resulting precipitate collected, washed with cold EtOH, and recrystallized from CH_2Cl_2/EtOAc (2:8) to give *rac-2,2′-di(2-hydroxybenzyl)-6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline* ***21*** as colourless prisms (0.721 g, 71%) mp 138–141°C; [Found: C, 71.09; H, 7.14; N, 4.41. $C_{36}H_{40}N_2O_6{\cdot}0.5H_2O$ requires C, 71.38; H, 6.82; N, 4.62%]; ν_{max} (Nujol) 1590, 1505, 1480, 1460, 1155, 1260, 1240, 1225, 1100, 1015, 860, 760 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.54 (2H, dd, *J*=11.3, 6.2 Hz, H_α4 and H_β4′), 2.93 (2H, m, H_β4 and H_α4′), 3.09 (2H, dd, *J*=15.4, 7.2 Hz, H_α3 and H_β3′), 3.25 (2H, m, H_β3 and H_α3′), 3.42 (6H, s, 7-OCH_3 and 7′-OCH_3), 3.65 (2H, d, *J*=13.6 Hz, H_α1″ and H_β1‴), 3.65 (2H, s, *H*1 and *H*1′), 3.84 (6H, s, 6-OCH_3 and 6′-OCH_3), 3.85 (2H, d, *J*=13.6 Hz, H_β1″ and H_α1‴), 5.50 (2H, s, *H*8 and *H*8′), 6.60 (2H, s, *H*5 and *H*5′), 6.72 (2H, t, *J*=7.2 Hz, *H*6″ and *H*6‴), 6.92 (2H, d, *J*=7.2 Hz, *H*7″ and *H*7‴), 7.17 (2H, d, *J*=7.2 Hz, *H*4″ and *H*4‴), 7.19 (2H, t, *J*=8.2 Hz, *H*5″ and *H*5‴); δ_C (75.6 MHz, $CDCl_3$) 21.6 (C4 and C4′), 41.4 (C3 and C3′), 55.4 (6-OCH_3 and 6′-OCH_3), 55.9 (7-OCH_3 and 7′-OCH_3), 55.0 (C1″ and C1‴), 63.5 (C1 and C1′), 111.5 (C5 and C5′), 114.7 (C8 and C8′), 116.4 (C4″ and C4‴), 119.1 (C6″ and C6‴), 122.2 (C7″ and C7‴), 124.1 (C8a and C8′a), 125.6 (C4a and C4′a), 129.0 (C5″ and C5‴), 129.2 (C7″ and C7‴), 145.8 (C7 and C7′), 148.3 (C6 and C6′), 158.2 (C2″ and C2‴); *m/z* (EI) 597 (M+1, 100), 596 (M^+, absent), 491 (9), 298 (7), 157 (9%).

2.2. Reduction of bis-imine 1 with (*S*)-*N*-benzyloxycarbonylproline/$NaBH_3CN$

A solution of bis-imine **1** (0.11 g, 0.29 mmol) in THF (20 mL) was added dropwise under argon at −25°C to a stirred suspension of (*S*)-*N*-benzyloxycarbonylprolinate-borane complex (prepared by the addition of (*S*)-*N*-benzyloxycarbonylproline (2.02, 8.10 mmol) in dry THF (6 mL) to an ice-cooled suspension of $NaBH_3CN$ (0.25 g, 4.05 mmol) in dry THF (5 mL). The mixture was stirred for 16 h in the ice bath as the temperature was allowed to rise, then worked up and purified as described above to give a 70:30 mixture of (±)-6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline **3** and *meso*-6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline **2** (0.091 g, 82%) as measured by ^1H NMR spectroscopic analysis. Treatment of the (±)-**3** with camphorsulfonyl chloride at room temperature for 34 h gave a product 87% yield which from ^1H NMR spectroscopic analysis revealed an 85:15 mixture of diastereomers **14a/b**.

The same reduction was repeated under similar conditions but at 45°C to give a 73:27 mixture of (±)-**3** and *meso* **2** bis-amines (0.101 g, 91%). The (±)-**3** yielded a 62:38 diastereomeric mixture as camphorsulfonamide **14a/b**.

2.3. Macrocycle formation

2.3.1. From bis-amine 3 with CH_2Cl_2. A mixture of bis-amine **3** (0.116 g, 0.30 mmol) and K_2CO_3 (0.12 g, 0.84 mmol) was heated at reflux in CH_2Cl_2 (10 mL) for 3 days. The reaction mixture was filtered, the solid washed with CH_2Cl_2 (10 mL) and the filtrate washed with H_2O (2×15 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave an off-white solid that was recrystallized from ethanol to give 2,3,13,14-tetramethoxy-5,6,7,9,10,11,15b,15c-octahydro-8*H*-isoquino-[1′,2′,5,1]imidazo[4,3-a]isoquinoline **15** as long white needles (0.113 g, 94%) mp 209–212°C (lit.[15] 197–199°C); δ_H (300 MHz, $CDCl_3$) 2.83 (2H, m, H_α5 and H_β11), 2.91 (2H, m, H_β5 and H_α11), 3.09 (2H, m, H_α6 and H_β10), 3.30 (2H, m, H_β6 and H_α10), 3.65 (6H, s, 2-OCH_3 and 14-OCH_3), 3.88 (6H, s, 3-OCH_3 and 13-OCH_3), 4.03 (2H, s, *H*15b and *H*15c), 4.38 (2H, s, $(H8)_2$), 6.21 (2H, s, *H*1 and *H*15), 6.72 (2H, s, *H*4 and *H*12); δ_C (75.6 MHz, $CDCl_3$) 26.7 (C5 and C11), 46.7 (C6 and C10), 55.9 (2-OCH_3 and 14-OCH_3), 56.0 (3-OCH_3 and 13-OCH_3), 65.9 (C15b and C15c), 76.1 (C8), 111.6 (C4 and C12), 112.4 (C1 and C15), 123.6 (C4a and C11a), 127.1 (C1a and C15a), 146.9 (C2 and C14), 148.6 (C3 and C13).

2.3.2. From bis-amine 3 with tetra(ethylene glycol) diiodide. A solution of tetra(ethylene glycol) diiodide (0.216 g, 0.52 mmol) in dry CH_3CN (25 mL) was added to a mixture of bis-amine **3** (0.200 g, 0.52 mmol) and Cs_2CO_3 (0.510 g, 1.56 mmol) in dry CH_3CN (170 mL) under argon at rt. The resulting mixture was heated at reflux for 3 days. The mixture was cooled, filtered, and the residue washed with CH_2Cl_2 (3×5 mL). The filtrate was washed with H_2O (3×15 mL), dried over $MgSO_4$, and evaporated to dryness to give *rac-6,6′,7,7′-tetramethoxy-2,2′-(3″,6″,9″-trioxaundecano)-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline* ***22*** (0.198 g, 70%) as a dark gum that was difficult to bring to absolute purity. ν_{max} (Nujol): 1678, 1625, 1594, 1512, 1494, 1465, 1378, 134, 1263, 1226, 1166, 1139, 1085, 1031, 995, 961, 811, 750 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.48 (2H, m, H_a4 and H_b4′), 2.85 (2H, m, H_a3 and H_b3′), 3.09 (2H, m, H_b4 and H_a4′), 3.17 (2H, m, H_b3 and H_a3′), 3.54 (6H, s, 7-OCH_3 and 7′-OCH_3), 3.55–3.87 (8H, m, *H*1″, *H*2″, *H*4″, *H*5″, *H*7″, *H*8″, *H*10″ and *H*11″), 3.71 (6H, s, 6-OCH_3 and 6′-OCH_3), 4.09 (2H, s, *H*1 and *H*1′), 6.31 (2H, s, *H*8 and *H*8′), 6.49 (2H, s, *H*5 and *H*5′); δ_C (75.6 MHz, $CDCl_3$) 26.3 (C1 and C1′), 45.9 (C3 and C3′), 53.7, 65.4, 70.0, 70.5 (C1″, C2″, C4″, C5″, C7″, C8″, C10″ and C11″), 55.4 (7-OCH_3 and 7′-OCH_3), 55.9 (6-OCH_3 and 6′-OCH_3), 68.8 (C1 and C1′), 110.1 (C5 and C5′), 113.2 (C8 and C8′), 127.5 (C8a and C8′a), 145.5 (C4a and C4′a), 145.5 (C7 and C7′), 146.9 (C6 and C6′); *m/z* (EI) 543 (M+1, 5), 542 (M^+, 14), 527 (25), 350 (13), 218 (62), 205 (100), 191 (90,), 190 (98), 176 (71), 150 (47), 146 (28), 43 (38%). The crude gum by ^1H NMR spectroscopic analysis showed a single, relatively pure product. When the gum was column chromatographed (EtOAc/light petroleum) on alumina, three different fractions were obtained which showed the same mass fragmentation pattern.

2.3.3. From bis-chloroacetamide derivative 5 with ethylene glycol. Ethylene glycol (0.035 g, 0.559 mmol) and KOBu^t (0.132 g, 1.173 mmol) in dry THF (120 mL) were heated together at reflux for 2 h. A solution of bis-chloroacetamide **5** (0.300 g, 0.559 mmol) in dry THF (40 mL) was then added dropwise to the cloudy solution and the mixture heated at reflux for 2 days whereby it turned yellow. The mixture was cooled, solvent removed under reduced pressure, and the resulting gum redissolved in CH_2Cl_2 (50 mL). The solution was washed with H_2O (3×15 mL), 1 M HCl (3×10 mL), brine (2×10 mL) then H_2O (2×20 mL), dried over $MgSO_4$ and evaporated to give an off-white solid (0.25 g). Silica gel chromatography using a gradient of EtOAc/MeOH gave from the major fraction *rac*-6,6′,7,7′-tetramethoxy-2,2′-oxalyl-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline **17** as white needles (0.14 g, 57%) mp 251–253°C (acetone) (lit.[15] 254–259°C); ν_{max} (Nujol) 1675, 1600, 1310, 1255, 1215, 1185, 1115, 1010, 940, 855, 800 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.79 (2H, m, $H_\alpha4$ and $H_\beta4'$), 2.85 (2H, m, $H_\alpha3$ and $H_\beta3'$), 3.00 (2H, m, $H_\beta4$ and $H_\alpha4'$), 3.31 (6H, s, 7-OCH_3 and 7′-OCH_3), 3.85 (6H, s, 6-OCH_3 and 6′-OCH_3), 4.61 (2H, s, *H*1 and *H*1′), 4.97 (2H, m, $H_\beta3$ and $H_\alpha3'$), 5.39 (2H, s, *H*8 and *H*8′), 6.70 (2H, s, *H*5 and *H*5′); δ_C (75.6 MHz, $CDCl_3$) 30.0 (C4 and C4′), 40.1 (C3 and C3′), 55.2 (7-OCH_3 and 7′-OCH_3), 56.0 (6-OCH_3 and 6′-OCH_3), 63.1 (C1 and C1′), 111.0 (C5 and C5′), 114.2 (C8 and C8′), 120.7 (C8a and C8′a), 129.5 (C4a and C4′a), 146.4 (C7 and C7′), 148.6 (C6 and C6′), 157.4 (2×CO); *m*/*z* (ES) 461 (M+Na, 49), 439 (M+1, 100), 413 (7), 385 (5), 385 (5), 260 (10), 280 (9), 260 (10), 219 (20), 105 (14%).

2.3.4. From bis-chloroacetamide derivative 5 with tri(ethylene glycol). Tri(ethylene glycol) (0.028 g, 0.18 mmol) and KOH (0.104 g, 0.37 mmol) in dry THF (100 mL) were heated at reflux for 2 h. A solution of the bis-chloroacetamide **5** (0.100 g, 0.18 mmol) in dry THF (140 mL) was added slowly using a syringe pump to this mixture, which was then heated at reflux for 2 days and finally evaporated under reduced pressure. The residual gum was dissolved in CH_2Cl_2 (50 mL), and the solution washed with H_2O (3×10 mL), 1 M HCl (2×10 mL), brine (2×10 mL) and H_2O (2×15 mL), dried over Na_2SO_4, and evaporated to dryness to give a yellow oil (0.089 g). The oil was subjected to flash column chromatography (alumina) using EtOAc to give yellow gum (0.064 g, 59%) that solidified after standing at room temperature. ^{1}H NMR spectroscopic analysis showed the presence of three components in equal amounts. Preparative tlc on alumina plates with multiple development using a gradient of EtOAc/light petroleum afforded in order of decreasing R_f: *rac-6,6′,7,7′-tetramethoxy-2,2′-(1″,14″-dioxo-3″,6″,9″,12″-tetraoxatetradecano)-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline* ***23*** (0.012 g) as a yellow oil; ν_{max} (Nujol) 1650, 1510, 1340, 1255, 1220, 1120, 1015, 930, 860 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.80 (2H, dt, *J*=5.3, 5.7 Hz, $H_\alpha4$ and $H_\beta4'$), 3.34 (2H, m, $H_\alpha3$ and $H_\beta3'$), 3.43 (6H, s, 7-OCH_3 and 7′-OCH_3), 3.45 (2H, m, $H_\beta4$ and $H_\alpha4'$), 3.51–3.75 (6H, m, *H*4″, *H*11″, *H*5″, *H*10″, *H*7″ and *H*8″), 3.87 (2H, m, $H_\beta3$ and $H_\alpha3'$), 3.85 (6H, s, 6-OCH_3 and 6′-OCH_3), 4.10 (2H, d, *J*=14.3 Hz, H_a2'' and H_b13''), 4.50 (2H, d, *J*=14.3 Hz, H_b2'' and H_a13''), 5.37 (2H, s, *H*1 and *H*1′), 5.67 (2H, s, *H*8 and *H*8′), 6.71 (2H, s, *H*5 and *H*5′); δ_C (75.6 MHz, $CDCl_3$) 27.5 (C4 and C4′), 41.5 (C3 and C3′), 55.7 (7-OCH_3 and 7′-OCH_3), 56.1 (6-OCH_3 and 6′-OCH_3), 56.7 (C1 and C1′), 69.9 (C2″ and C13″), 70.7 (C4″ and 11″), 70.9 (C5″ and C10″), 70.95 (C7″ and C8″), 111.0 (C5 and C5″), 113.4 (C8 and C8″), 126.1 (C8a and C8′a), 127.5 (C4a and C4′a), 146.4 (C7 and C7′), 148.4 (C6 and C6′), 169.3 (2×CO); *m*/*z* (ES) 637 (M+23, 29), 632 (M+18, 9), 615 (M+1, 100%), 614 (M$^+$, absent); HRMS: found, M+Na 637.2727. $C_{32}H_{42}N_2O_{10}Na$ requires 637.2731; and an equimolar mixture of *N,N:N′,N′-bis(1,14-dioxo-3,6,9,12-tetraoxatetradecamethylene)(1S*,1′S*:1S*,1′S*)di(6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline)* ***28*** *and N,N:N′,N′-bis(1,14-dioxo-3,6,9,12-tetraoxatetradecamethylene)(1S*,1′R*:1S*,1′R*)di(6,6′,7,7′-tetramethoxy-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline)* ***29*** as yellow oil (0.019 g); ν_{max} (Nujol, CH_2Cl_2) 1650, 1510, 1340, 1255, 1220, 1120, 1020, 930, 860 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.87 (2H, dt, *J*=ca. 5.3, 2.3 Hz, $H_\alpha4$ and $H_\beta4'$), 3.39 (2H, m, $H_\alpha3$ and $H_\beta3'$), 3.42, 3.43 (total 6H, 2×s, 7-OCH_3 and 7′-OCH_3), 3.56 (2H, m, $H_\beta4$ and $H_\alpha4'$), 3.58–3.77 (6H, m, *H*4″, *H*11″, *H*5″, *H*10″, *H*7″ and *H*8″), 3.85 (6H, s, 6-OCH_3 and 6′-OCH_3), 3.93 (2H, m, $H_\beta3$ and $H_\alpha3'$), 4.24 (2H, 2×d, *J*=14.7, 14.7 Hz, H_a2'' and H_b13''), 4.30 (2H, br d, *J*=14.7 Hz, H_b2'' and H_a13''), 5.41, 5.42 (total 2H, 2×s, *H*1 and *H*1′), 5.65, 5.66 (total 2H, 2×s, *H*8 and *H*8′), 6.71, 6.72 (total 2H, 2×s, *H*5 and *H*5′); δ_C (75.6 MHz, $CDCl_3$) 27.5 (C4 and C4′), 41.2 (C3 and C3′), 55.5 (7-OCH_3 and 7′-OCH_3), 55.9 (6-OCH_3 and 6′-OCH_3), 56.3 (C1 and C1′), 69.7 (C2″ and C13″), 70.3 (C4″ and C11″), 70. 5 (C5″ and C10″), 70.8 (C7″ and C8″), 110.8 (C5 and C5′), 113.4 (C8 and C8′), 125.8 (C8a and C8′a), 127.2 (C4a and C4′a), 146.3 (C7 and C7′), 148.3 (C6 and C6′), 169.2 (2×CO); *m*/*z* (ES) 1251 (M+23, 45), 1228 (M$^+$, absent), 1229 (M+1, 100%); HRMS: found, M+Na 637.2726. $C_{32}H_{42}N_2O_{10}Na$ requires 637.2731; and *meso-6,6′,7,7′-tetramethoxy-2,2′-(1″,14″-dioxo-3″,6″,9″,12″-tetra-oxatetradecano)-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline* ***27*** (0.01 g) as yellow oil; ν_{max} (Nujol, CH_2Cl_2) 1730, 1650, 1510, 1330, 1305, 1255, 1220, 1120, 1020, 930, 860 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.85 (2H, dt, *J*=5.3, 5.7 Hz, $H_\alpha4$ and $H_\beta4'$), 3.33 (2H, m, $H_\alpha3$ and $H_\beta3'$), 3.45 (2H, m, $H_\beta4$ and $H_\alpha4'$), 3.45 (6H, s, 7-OCH_3 and 7′-OCH_3), 3.56-3.77 (6H, m, *H*4″, *H*5″, *H*7″, *H*8″, *H*10″ and *H*11″), 3.88 (2H, m, $H_\beta3$ and $H_\alpha3'$), 3.86 (6H, s, 6-OCH_3 and 6′-OCH_3), 4.12 (2H, d, *J*=14.3 Hz, H_a2'' and H_b13''), 4.50 (2H, d, *J*=14.3 Hz, H_b2'' and H_a13''), 5.39 (2H, s, *H*1 and *H*1′), 5.69 (2H, s, *H*8 and *H*8′), 6.73 (2H, s, *H*5 and *H*5′); δ_C (75.6 MHz, $CDCl_3$) 27.5 (C4 and C4′), 41.5 (C3 and C3′), 55.6 (7-OCH_3 and 7′-OCH_3), 56.0 (6-OCH_3 and 6′-OCH_3), 56.7 (C1 and C1′), 69.8 (C2″ and C13″), 70.6 (C4″ and C11″), 70.8 (C5″, C10″, C7″ and C8″), 110.9 (C5 and C5′), 113.4 (C8 and C8′), 126.0 (C8a and C8′a), 127.4 (C4a and C4′a), 146.3 (C7 and C7′), 148.4 (C6 and C6′), 169.3 (2×CO); *m*/*z* (ES) 637 (M+23, 46), 632 (M+18, 29), 615 (M+1, 100%), 614 (M$^+$, absent); HRMS: found M+Na 637.2735. $C_{32}H_{42}N_2O_{10}Na$ requires 637.2731.

2.3.5. From bis-chloroacetamide derivative 5 with tetra(ethylene glycol). Tetra(ethylene glycol) (0.180 g, 0.93 mmol) and KOBu^t (0.104 g, 1.86 mmol) in dry THF (150 mL) were heated together at reflux for 2 h. Bis-chloroacetamide **5** (0.500 g, 0.93 mmol) in dry THF (250 mL) was added slowly using a syringe pump and the

resulting mixture was heated at reflux for 2 days. Workup as in (ii) gave a brown gum that was subjected to column chromatography on alumina. Elution with EtOAc gave *rac-6,6′,7,7′-tetramethoxy-2,2′-(1″,17″-dioxo-3″,6″,9″,12″,15″-pentaoxaheptadecano)-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bis-isoquinoline* ***24*** as a hygroscopic foam (0.41 g, 67%) that crystallized from EtOAc upon slow but complete evaporation of the solvent mp 86–89°C; [Found: C, 62.12; H, 7.20; N, 4.33. $C_{34}H_{46}N_2O_{11}$ requires C, 61.99; H, 7.04; N, 4.25%]; ν_{max} (Nujol) 1630, 1505, 1450, 1340, 1255, 1220, 1110, 1015, 930, 850 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.85 (2H, m, $H_\alpha4$ and $H_\beta4'$), 3.41 (2H, m, $H_\alpha3$ and $H_\beta3'$), 3.42 (6H, s, 7-OCH_3 and 7′-OCH_3), 3.50 (2H, m, $H_\beta4$ and $H_\alpha4'$), 3.60–3.84 (8H, m, *H*4″, *H*14″, *H*5″, *H*13″, *H*7″, *H*11″, *H*8″, and *H*10″), 3.85 (6H, s, 6-OCH_3 and 6′-OCH_3), 3.97 (2H, m, $H_\beta3$ and $H_\alpha3'$), 4.11 (2H, d, *J*=14.7 Hz, H_a2'' and H_b19''), 4.34 (2H, d, *J*=14.7 Hz, H_b2'' and H_a19''), 5.44 (2H, s, *H*1 and *H*1′), 5.64 (2H, s, *H*8 and *H*8′), 6.70 (2H, s, *H*5 and *H*5′); δ_C (75.6 MHz, $CDCl_3$): δ 27.5 (C1 and C1′), 41.2 (C3 and C3′), 55.5 (7-OCH_3 and 7′-OCH_3), 56.0 (6-OCH_3 and 6′-OCH_3), 56.4 (C1 and C1′), 69.9 (C2″ and C19″), 70.37 (C4″ and C18″), 70.41 (C5″ and C16″), 70.78 (C8″ and C13″), 70.87 (C7″ and C14″), 70.92 (C10″ and C11″), 110.7 (C5 and C5′), 113.3 (C8 and C8′), 125.8 (C8a and C8′a), 127.2 (C4a and C4′a), 146.2 (C7 and C7′), 148.3 (C6 and C6′), 169.3 (2×CO); *m/z* (ES) 682 (M+24, 40), 681 (M+23, 43), 674 (M+18, 21), 659 (M+1, 100%), 658 (M^+, absent).

2.3.6. From bis-chloroacetamide derivative 5 with penta(ethylene glycol). Penta(ethylene glycol) (0.133 g, 0.60 mmol) and KOBu^t (0.132 g, 1.173 mmol) in dry THF (120 mL) was heated at reflux for 2 h. Bis-chloroacetamide **5** (0.300 g, 0.60 mmol) in dry THF (40 mL) was added slowly using a syringe pump, and the mixture heated at reflux for 2 days. Workup as in (ii) gave a yellow gum that was chromatographed on alumina using EtOAc as eluent to give *rac-6,6′,7,7′-tetramethoxy-2,2′-(1″,20″-dioxo-3″,6″,9″,12″,15″,18″-hexaoxaicosano)-1,1′,2,2′,3,3′,4,4′-octa-hydro-1,1′-bisisoquinoline* ***25*** (0.24 g, 57%) as a hygroscopic foam mp 69-72°C; ν_{max} (Nujol) 1640, 1505, 1455, 1345, 1255, 1220, 1120, 1020, 930, 855 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.81 (2H, m, $H_\alpha4$ and $H_\beta4'$), 3.37 (2H, m, $H_\alpha3$ and $H_\beta3'$), 3.38 (6H, s, 7-OCH_3 and 7′-OCH_3), 3.48 (2H, m, $H_\beta4$ and $H_\alpha4'$), 3.58–3.70 (6H, m, *H*7″, *H*14″, *H*8″, *H*13″, *H*10″ and *H*11″), 3.73 (2H, m, *H*5″ and *H*16″), 3.75 (2H, m, *H*4″ and *H*17″), 3.81 (6H, s, 6-OCH_3 and 6′-OCH_3), 3.93 (2H, m, $H_\beta3$ and $H_\alpha3'$), 4.12 (2H, d, *J*=14.7 Hz, H_a2'' and H_b19''), 4.28 (2H, d, *J*=15.1 Hz, H_b2'' and H_a19''), 5.39 (2H, s, *H*1 and *H*1′), 5.61 (2H, s, *H*8 and *H*8′), 6.68 (2H, s, *H*5 and *H*5′); δ_C (75.6 MHz, $CDCl_3$) 27.6 (C1 and C1′), 41.3 (C3 and C3′), 55.6 (7-OCH_3 and 7′-OCH_3), 56.0 (6-OCH_3 and 6′-OCH_3), 56.5 (C1 and C1′), 69.8 (C2″ and C19″), 70.4 (C4″ and C17″), 2×70.6, 70.7 (C7″, C14″, C8″, C13″, C10″ and C11″), 71.0 (C5″ and C16″), 110.9 (C5 and C5′), 113.4 (C8 and C8′), 125.9 (C8a and C8′a), 127.3 (C4a and C4′a), 146.4 (C7 and C7′), 148.4 (C6 and C6′), 169.5 (2×CO); *m/z* (ES) 726 (M+24, 76), 720 (M+18, 27), 704 (M+2, 100%), 702 (M^+, absent); HRMS: found M+Na 725.3258. $C_{36}H_{50}N_2O_{12}Na$ requires 725.3255.

2.3.7. From bis-chloroacetamide derivative 5 with hexa(ethylene glycol). Hexa(ethylene glycol) (0.63 g, 9.31 mmol) and KOBu^t (0.219 g, 1.955 mmol) in dry THF (170 mL) was heated at reflux for 2 h. Bis-chloroacetamide **5** (0.500 g, 0.931 mmol) in dry THF (40 mL) was added slowly using a syringe pump and the mixture heated at reflux for 2 days. Workup as in (ii) gave an off-white gum that was redissolved in CH_2Cl_2 and precipitated with light petroleum to give *rac-6,6′,7,7′-tetramethoxy-2,2′-(1″,23″-dioxo-3″,6″,9″,12″,15″,18″,21″-heptaoxatricosano)-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline* ***26*** as an off-white semi-solid (0.43 g, 62%) mp 48–51°C; [Found: C, 60.79; H, 7.15; N, 3.62. $C_{38}H_{54}N_2O_{13}$ requires C, 61.11; H, 7.29; N, 3.75%]; ν_{max} (Nujol) 1640, 1510, 1450, 1345, 1255, 1220, 1110, 1020, 930, 855 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.81 (2H, dt, *J*=4.1, 5.2 Hz, $H_\alpha4$ and $H_\beta4'$), 3.33 (2H, m, $H_\alpha3$ and $H_\beta3'$), 3.37 (6H, s, 7-OCH_3 and 7′-OCH_3), 3.45 (2H, m, $H_\beta4$ and $H_\alpha4'$), 3.53–3.75 (12H, m, *H*4″, *H*20″, *H*5″, *H*19″, *H*7″, *H*17″, *H*8″, *H*16″, *H*10″, *H*14″, *H*11″ and *H*13″), 3.80 (6H, s, 6-OCH_3 and 6′-OCH_3), 3.89 (2H, dt, $H_\beta3$ and $H_\alpha3'$), 4.13 (2H, d, *J*=14.7 Hz, H_a2'' and H_b22''), 4.24 (2H, d, *J*=14.7 Hz, H_b2'' and H_a22''), 5.36 (2H, s, *H*1 and *H*1′), 5.60 (2H, s, *H*8 and *H*8′), 6.67 (2H, s, *H*5 and *H*5′); δ_C (75.6 MHz, $CDCl_3$) 27.4 (C4 and C4′), 41.2 (C3 and C3′), 55.5 (7-OCH_3 and 7′-OCH_3), 55.9 (6-OCH_3 and 6′-OCH_3), 56.4 (C1 and C1′), 69.5 (C2″ and C22″), 70.3 (C4″ and C20″), 70.54, 2×70.56, 70.6 (C7″, C17″, C8″, C16″, C10″, C14″, C11″ and C13″), 70.7 (C5″ and C19″), 110.7 (C5 and C5″), 113.2 (C8 and C8″), 125.7 (C8a and C8′a), 127.2 (C4a and C4′a), 146.2 (C7 and C7′), 148.2 (C6 and C6′), 169.3 (2×CO); *m/z* (ES) 769 (M+23, 66), 764 (M+18, 79), 747 (M+1, 100%), 746 (M^+, absent).

2.3.8. From bis-phenol 21 with di(ethylene glycol) di-*p*-tosylate. A mixture of the bis-phenol **21** (0.17 g, 0.28 mmol) and KOBu^t (0.12 g, 0.28 mmol) in dry CH_3CN (35 mL) was heated at reflux under argon for 1 h. A solution of di(ethylene glycol) di-*p*-tosylate (0.17 g, 0.28 mmol) in CH_3CN (10 mL) was added to this mixture over 15 min. After complete addition the resulting mixture was heated at reflux for 2 days whereupon a white suspension was observed and tlc (alumina) analysis showed the formation of a new product with lower R_f value than the starting material. The mixture was cooled and the solvent was evaporated under reduced pressure to give a white solid that was redissolved in CH_2Cl_2 (70 mL) and the solution washed with H_2O (2×20 mL), 1 M HCl (2×10 mL), brine (1×10 mL), 1 M K_2CO_3 (1×10 mL) then H_2O (2×20 mL). The organic layer was dried over $MgSO_4$ and evaporated to dryness under reduced pressure to give a white gum (0.23 g). Chromatography of the product on alumina using EtOAc as eluant followed by recrystallization of the main fraction from acetone gave *rac-6,6′,7,7′-tetramethoxy-2,2′-(2″,3″:11″,12″-dibenzo-4″,7″,10″-trioxatridecano)-1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-bisisoquinoline* ***30*** as white needles (0.16 g, 86%) mp 146–148°C (Found: HRMS *m/z* 667.3371. $C_{40}H_{47}N_2O_7$ requires 667.3377). ν_{max} (Nujol) 1595, 1470, 1440, 1330, 1300, 1050, 930, 865 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 2.43 (2H, m, $H_\alpha3$ and $H_\beta3'$), 2.47 (2H, m, $H_\alpha4$ and $H_\beta4'$), 3.02 (2H, m, $H_\beta4$ and $H_\alpha4'$), 3.25 (2H, m, $H_\beta3$ and $H_\alpha3'$), 3.71 (2H, obs. d, *J*=ca. 14.3 Hz, H_a1'' and H_b13'''), 3.74 (6H, s, 6-OCH_3 and 6′-OCH_3), 3.82 (2H, m, H_a6'' and H_b8''), 3.90 (6H, s, 7-OCH_3 and 7′-OCH_3), 3.96 (2H, m, H_b6'' and H_a8''), 4.19 (2H, m, H_a5'' and H_b9''), 4.31 (2H, m, H_a5'' and H_b9''), 4.62 (2H, d, *J*=ca. 14.3 Hz, H_b1'' and H_a13'''), 6.29 (2H, s, *H*5 and *H*5′),

6.89 (2H, d, J=7.9 Hz, $H7''$ and $H7'''$), 6.99 (2H, t, J=7.5 Hz, $H6''$ and $H6'''$), 7.23 (2H, t, J=7.5 Hz, $H5''$ and $H5'''$), 7.60 (2H, d, J=7.1 Hz, $H4''$ and $H4'''$), 7.66 (2H, s, $H8$ and $H8'$); δ_C (75.6 MHz, $CDCl_3$) 29.6 (C4 and C4′), 49.9 (C3 and C3′), 53.6 (C1″ and C1‴), 55.4 (6-OCH_3 and 6′-OCH_3), 55.6 (7-OCH_3 and 7′-OCH_3), 66.9 (C1 and C1′), 67.0 (C5″ and C9″), 69.6 (C6″ and C8″), 109.9 (C5 and C5′), 110.8 (C8 and C8′), 110.9 (C4″ and C4‴), 111.0 (H7″ and H7‴), 120.6 (C6″ and C6‴), 127.0 (C4″ and C4‴), 128.0 (C8a, C8′a, C4a and C4′a); 127.9 (C5″ and C5‴), 129.1 (C2″ and C2‴), 145.6 (C7 and C7′), 146.3 (C6 and C6′), 156.2 (C3″ and C3‴); m/z (ES) 667 (M+1, 100%); HRMS: found M+1 667.3371. $C_{40}H_{46}N_2O_7$+H requires 667.3377. ^1H and ^{13}C NMR assignments were confirmed through H–H COSY, NOESY, HSQC and HMBC experiments at 600 MHz.

Crystallographic data (excluding structure factors) for **8** and **10** have been deposited with the Cambridge Crystallographic Data Centre as the supplementary publication numbers CCDC 193035 and CCDC 193034, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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