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Synthesis of thiacrown and azacrown ethers based on a spiroacetal framework

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Abstract—A novel class of thiacrown and azacrown ethers incorporating the 1,7-dioxaspiro[5.5]undecane spiroacetal ring system was prepared by reaction of ditosylate **5** with the appropriate dithiols **9a–c** or protected diamine **12a**. Spiroacetal ditosylate **5** in turn, was prepared from diol **3** via ozonolysis of bisallyl ether **7** followed by tosylation of the derived diol **8**.

1. Introduction

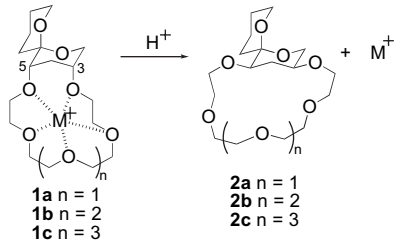
The discovery of crown ethers by Charles J. Pedersen in 1967[1] has led to the synthesis of numerous macrocycles and the study of their complexing abilities. Many macrocycles have been synthesised due to their close resemblance to biological systems. Alternatively, functionality has been introduced into the crown ether structure providing molecules that are potentially capable of mimicking various biological macromolecular systems.

One such 'privileged scaffold'[2] of biological relevance is the spiroacetal structure. The spiroacetal ring system enjoys widespread occurrence in insects, plants, microbes, fungi and marine organisms.[3] The isolation of the spiroacetal-containing ionophore, monensin, in 1967[4] together with its reported cation binding properties prompted extensive interest in the synthesis of spiroacetal ionophores.

To date, a limited number of spiroacetal-based crown ethers have been synthesised,[5] however, our research group was the first to incorporate the 1,7-dioxaspiro[5.5]undecane spiroacetal ring system into a crown ether structure.[6] Several spiroacetal crown ethers of type **1** and **2** were synthesised and their potential to act as pH dependent ionophores was evaluated. The spiroacetal structure **1a–c** chosen for this study was derived from a 1,7-dioxaspiro[5.5]undecane ring system containing two axial hydroxyl groups at C-3 and C-5. Upon treatment with acid the spiroacetal ring in crown ethers **1a–c** undergoes ring opening followed by reclosure to form spiroacetals **2a–c** where the two alkoxy substituents adopt more thermodynamically favoured equatorial positions.

The association constants of these spiroacetal-based crown ethers were evaluated using Li^+, Na^+, K^+, Cs^{2+} and NH_4^+ ions and it was established that the diaxial crown ethers **1a–c** exhibited better binding ability than the diequatorial crown ethers **2a–c**. This result was explained by the fact that the two oxygen atoms at C-3 and C-5 in the equatorial crown ethers **2a–c** were further removed from the metal centre and could not contribute to the binding.

In theory it is possible for the diaxial crown ethers to complex metal ions that can be released upon exposure to acid (Scheme 1). The potential ability of these spiroacetal crown ethers to act as pH dependent ionophores is highly desirable for separation science. We therefore herein report our related work on the synthesis of spiroacetal thiacrown and azacrown ethers. These spiroacetal-based thiacrown and azacrown ethers provide valuable compounds with interesting possibilities for environmental and medicinal chemistry.



Scheme 1.

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2. Results and discussion

According to the retrosynthesis outlined (Scheme 2), the synthesis of the thiacrown and azacrown ethers can be carried out following two possible pathways. The first approach (Route A) involves reaction between spiroacetal diol **3** and an appropriate β-chloroethyl sulfide or amine. This method was effected in a similar manner to the method previously used to prepare oxygenated spiroacetal crown ethers **1a–c** and **2a–c**.

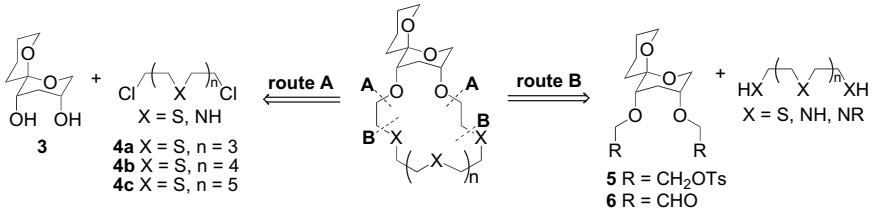
The second approach (Route B) involves reaction of a dithiol or diamine with an electrophilic group attached to the spiroacetal framework. A suitable electrophile is the ditosylate **5** that can undergo reaction with a dithiol or a protected diamine. Alternatively, the electrophilic group could be aldehyde **6**. This latter method is more amenable for the construction of azacrown ethers rather than thiacrown ethers. The spiroacetal-containing electrophile can be synthesised from the parent spiroacetal diol **3** that has already been prepared by our research group.[7]

Initially our attention focused on the synthesis of spiroacetal thiacrown ethers following Route A via the synthesis of diol **3** and several β-chloroethyl sulfides **4a–c**. The β-chloroethyl sulfides [*caution*: blister-causing agents] were prepared by treatment of the corresponding alcohols with thionyl chloride.[8] We then investigated methods for the alkylation step that had been successfully employed by Brimble and Johnston,[6] and Kellogg and Buter[9] in related systems. Spiroacetal diol **3** was treated with NaH in THF or Cs_2CO_3 in DMF, then β-chloroethyl sulfide was added slowly under high dilution techniques. Unfortunately, the desired alkylation was not successful with the dianion formed from diol **3** acting as a base, resulting in elimination of the β-chloroethyl sulfide to form the corresponding diene.

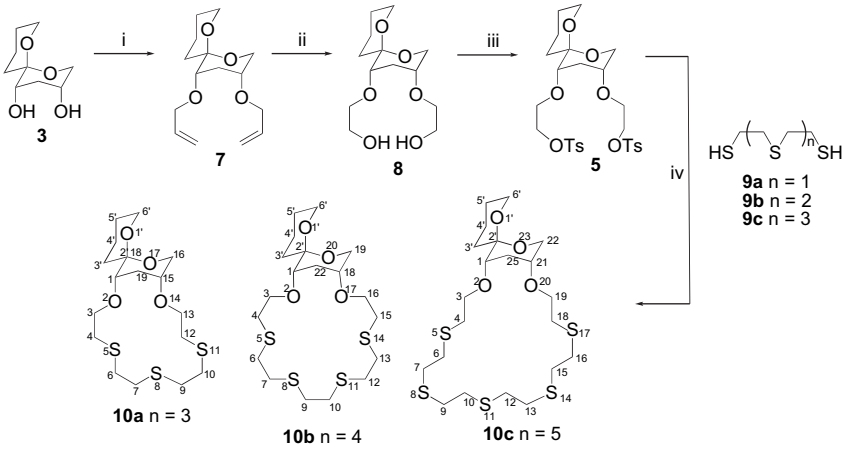
Disappointed by the inability to effect reaction of the spiroacetal diol **3** with β-chloroethyl sulfide via Route A, our attention next focused on the alternative disconnection summarised as Route B in Scheme 2. This approach required synthesis of spiroacetal ditosylate **5** that contains two leaving groups. Spiroacetal ditosylate **5** was synthesised from diol **3** via reductive ozonolysis of bisallyl ether **7** followed by tosylation of derived diol **8**. Reaction of ditosylate **5** with the requisite dithiols **9a–c** successfully afforded the desired spiroacetal thiacrown ethers **10a–c** in 86%, 68% and 64% yields, respectively (Scheme 3).

It was established that the thiacrown ethers **10a–c** thus formed adopted an axial position on the spiroacetal ring based on the coupling constants observed for the CHO protons in the ^{1}H NMR spectra. Thus, thiacrown **10a** exhibited a triplet at δ_H 3.09 with $J_{1,19}$ 3.4 Hz that was assigned to 1-H establishing that 1-H occupied an equatorial position. 15-H resonated as a multiplet at δ_H 3.37, however, the double double doublet at δ_H 1.91, with $J_{19ax,19eq}$ 15.2, $J_{19ax,1}$ 3.4 and $J_{19ax,15}$ 3.4 Hz assigned to 19-H_{ax} established that 15-H is also equatorial.

In the ^{1}H NMR spectrum recorded for thiacrown **10b**, 1-H resonated as a triplet at δ_H 3.09 with $J_{1,22}$ 3.7 Hz. 18-H



Scheme 2.



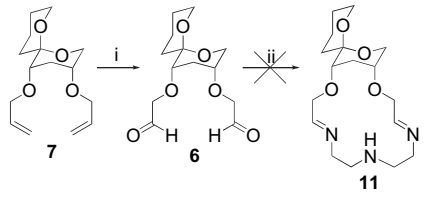
Scheme 3. *Reagents and conditions*: (i) NaH, THF, reflux, 30 min, then allyl bromide (2.0 equiv), 18 h, 84%; (ii) ozone, MeOH, −78 °C, 15 min, then $NaBH_4$, room temp, 18 h, 75%; (iii) ^{n}BuLi, THF, −78 °C, 30 min, then TsCl, 30 min, room temp, 16 h, 90%; (iv) Cs_2CO_3, DMF, 60 °C, **5** and **9a–c** in DMF added over 2.5 h, **10a** 86%, **10b** 68%, **10c** 64%.

resonated as a double double double doublet at δ_H 3.37 with $J_{18eq,22ax}$ 3.7, $J_{18eq,22eq}$ 3.7, $J_{18eq,19ax}$ 3.7 and $J_{18eq,19eq}$ 3.7 Hz, suggesting that 1-H and 18-H occupied equatorial positions. A double double doublet at δ_H 1.97 with $J_{22ax,22eq}$ 14.8, $J_{22ax,18}$ 3.7 and $J_{22ax,1}$ 3.7 Hz was assigned to the axial proton 22-H_{ax}. 22-H_{eq} resonated as a double double double doublet at δ_H 2.07 with $J_{22eq,22ax}$ 14.8, $J_{22eq,1}$ 3.7, $J_{22eq,18}$ 3.7 and $J_{22eq,19eq}$ 1.9 Hz, thus confirming that 1-H and 18-H were in fact equatorial.

In the ^{1}H NMR spectrum of thiacrown **10c**, 1-H resonated as a triplet at δ_H 3.08 with $J_{1,25}$ 3.8 Hz. 25-H_{ax} resonated as a double double doublet at δ_H 1.95 with $J_{25ax,25eq}$ 14.8, $J_{25ax,1}$ 3.8 and $J_{25ax,21}$ 3.8 Hz, confirming that 1-H and 21-H adopt equatorial positions and that the thiacrown ether was linked through the axial positions.

Having successfully prepared thiacrown ethers **10a–c** that are embedded in a spiroacetal framework, our attention next turned to the synthesis of the azacrown ethers **14a–c** via Route B (Scheme 2). Reaction between an appropriate electrophilic spiroacetal with a diamine should afford desired azacrown ethers, however, the synthesis of azacrown ethers proved to be more difficult than anticipated. Two factors needed to be taken into account, namely, the sensitivity of the spiroacetal ring system and the need for protection of the diamine.

We initially investigated the synthesis of the azacrown ethers via an intermediate macrocyclic imine **11** by the addition of a diamine to spiroacetal dialdehyde **6** (Scheme 4). Spiroacetal dialdehyde **6** was prepared from bisallyl ether **7** via ozonolysis followed by reduction of the ozonide with dimethyl sulfide. However, reaction of dialdehyde **6** and commercially available diethylenetriamine in refluxing benzene with removal of the water by azeotropic distillation was not successful. The non-templated synthesis of macrocyclic-Schiff bases[10] has been successful in rigid compounds, however, in the present work this procedure only afforded polymeric material.



Scheme 4. *Reagents and conditions*: (i) ozone, MeOH, −78 °C, 15 min, then $(CH_3)_2S$, room temp, 18 h, 86%; (ii) diethylenetriamine, benzene, reflux.

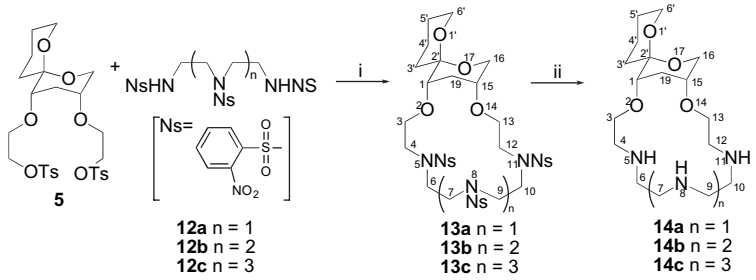
We next reassessed our strategy to access spiroacetal azacrown ethers **14a–c**, deciding that reaction of a protected diamine with spiroacetal ditosylate **5** was an appropriate option. The choice of protecting group for the amine was primarily based on the conditions required for their subsequent removal because of the sensitivity of the spiroacetal functionality. It was determined that the most appropriate protecting group would be the *o*-nosylate group used by Fukuyama et al.[11] Pleasingly, reaction of protected triamine **12a** and ditosylate **5** in THF at reflux under high dilution conditions yielded the protected azacrown ether **13a** (Scheme 5). Subsequent deprotection using thiophenol and potassium carbonate afforded the desired azacrown ether **14a**. Disappointingly, subsequent attempts to synthesise the related protected spiroacetal azacrown ethers **14b** and **14c** from ditosylate **5** proved difficult with no reaction observed. Attempts to vary the conditions did not lead to any successful outcome.

In order to confirm the axial orientation of azacrown ethers **13a** and **14a** we once again referred to the coupling constants observed for the CHO protons in the ^{1}H NMR spectra. In the ^{1}H NMR spectrum of protected azacrown ether **13a**, 1-H resonated as triplet at δ_H 3.03 with $J_{1,19}$ 3.0 Hz, establishing that 1-H adopted an equatorial position.

Unfortunately, 15-H resonated as a broad singlet at δ_H 3.24 and 19-CH_2 resonated as a multiplet at δ_H 2.03 precluding confirmation of the equatorial orientation for 15-H. In the case of azacrown ether **14a**, 1-H resonated as triplet at δ_H 3.04 with $J_{1,19}$ 3.2 Hz whilst 15-H resonated as a broad singlet at δ_H 3.29.

3. Summary

The synthesis of novel spiroacetal thiacrown ethers **10a–c** has been successfully achieved. Reaction between the requisite dithiols **9a–c** and the spiroacetal ditosylate **5** afforded the desired thiacrown ethers in good yields. Disappointingly, only the synthesis of spiroacetal azacrown ether **14a** was successful. Metal binding studies using these spiroacetal thiacrown and azacrown ethers will be reported in due course.



Scheme 5. *Reagents and conditions*: (i) NaH, reflux, 30 min, then **5** over 3 h, 18 h, **13a** 27%, **13b** 0%, **13c** 0%; (ii) K_2CO_3, PhSH, DMF, **14a** 84%.

4. Experimental

4.1. General

All reactions were conducted in flame-dried or oven-dried glassware unless otherwise noted. Tetrahydrofuran was dried over sodium/benzophenone and distilled prior to use. Dimethylformamide was distilled from calcium hydride and used immediately. Flash chromatography was performed using Merck Kieselgel 60 (230–400 mesh) with the indicated solvents. Thin layer chromatography (TLC) was carried out on precoated silica plates (Merck Kieselgel 60 F_{254} or Riedel-de Haen Kieselgel SF_{254}) and compounds were visualised by UV fluorescence or by staining with vanillin in methanolic sulfuric acid and heating. Infrared spectra were recorded with a Shimadzu FTIR-8300 spectrometer or Perkin Elmer Spectrum One Fourier Transform IR spectrometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}) with the following abbreviations: s=strong, m=medium, w=weak and br=broad. ^1H and ^{13}C NMR spectra were obtained using a Bruker DRX 400 or Varian Mercury 400 or Bruker Avance 300 spectrometer. All chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane as internal standard (^1H) or relative to $CDCl_3$ (^{13}C) and J values are given in hertz. ^1H NMR data are tabulated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. High resolution mass spectra were recorded using a VG70-SE spectrometer operating at a nominal accelerating voltage of 70 eV. Chemical ionisation (CI) mass spectra were obtained with ammonia as reagent gas. Fast atom bombardment (FAB) mass spectra were obtained using 3-nitrobenzyl alcohol as the matrix. 2-Mercaptoethyl sulfide **9a** was purchased from Aldrich.

4.1.1. [3*R,5*S**,6*S**]-1,7-Dioxaspiro[5.5]undecan-3,5-diyl bisallyl ether 7.** [3*R**,5*S**,6*S**]-1,7-Dioxaspiro[5.5]-undecan-3,5-diol **3** (0.22 g, 1.17 mmol) in tetrahydrofuran (5 mL) was added to a suspension of sodium hydride (0.08 g, 3.51 mmol) in tetrahydrofuran (10 mL). The reaction mixture was heated under reflux for 0.5 h, allyl bromide (0.22 mL, 2.51 mmol) was then added dropwise and the reaction heated under reflux for a further 18 h. After cooling, the reaction was quenched with sodium dihydrogen phosphate (7 mL, 10% w/v) and extracted with ethyl acetate (5×20 mL). The combined extracts were washed with water (15 mL) and dried over sodium sulfate. Removal of the solvent under reduced pressure gave a yellow oil that was purified by flash chromatography using hexane–ethyl acetate (4:1) as eluent to afford the *title compound* **7** as a pale yellow oil (0.26 g, 84%); found (CI, NH_3): MH^+, 269.17533. $C_{15}H_{25}O_4$ requires MH, 269.17528; ν_{max}(film)/cm^{-1} 1646 (w, C=C); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.41 (1H, ddd, $J_{11ax,11eq}$ 13.6, $J_{11ax,10ax}$ 13.6 and $J_{11ax,10eq}$ 4.3 Hz, 11-Hax), 1.48–1.82 (4H, m, 9-CH_2 and 10-CH_2), 1.91–2.02 (2H, m, 4-CH_2), 2.14 (1H, dt, $J_{11eq,11ax}$ 13.6 and $J_{11eq,10}$ 2.5 Hz, 11-Heq), 3.16 (1H, t, $J_{5,4}$ 4.7 Hz, 5-H), 3.45 (1H, dddd, $J_{3,2ax}$ 4.1, $J_{3,2eq}$ 4.1, $J_{3,4ax}$ 4.1 and $J_{3,4eq}$ 4.1 Hz, 3-H), 3.60–3.81 (3H, m, OCH_2), 4.13 (1H, ddt, J_{gem} 12.9, $J_{1'A,2'}$ 5.4 and $J_{1'A,3'}$ 1.5 Hz, 1′-H_A), 5.13 (2H, d, $J_{3'B,2'}$ 10.3 Hz, 2×3′-H_B), 5.25 (2H, ddd, $J_{3'A,2'}$ 17.2, $J_{3'A,1'A}$ 1.5 and $J_{3'A,1'B}$ 1.5 Hz, 2×3′-H_A), 5.85–5.97 (2H, m, 2×2′-H); δ_C (75 MHz; $CDCl_3$; Me_4Si) 17.9 (CH_2, C-10), 25.2 (CH_2, C-9), 27.1 (CH_2, C-4), 28.5 (CH_2, C-11), 61.1 (CH_2, C-8), 62.8 (CH_2, C-2), 69.7, 70.6 (CH_2, 2×OCH_2), 70.7 (CH, C-3), 76.0 (CH, C-5), 97.4 (quat C-6), 116.54, 116.55 (CH_2, 2×C-3′), 135.27, 135.29 (CH, 2×C-2′); *m*/*z* (CI, NH_3) 269 (MH^+, 17%), 211 (100), 127 (38), 101 (78), 84 (42), 71 (47).

4.1.2. [3*R,5*S**,6*S**]-1,7-Dioxaspiro[5.5]undecan-3,5-diyl bis(2-*p*-toluenesulfonyl) ethyl ether 5.** *n*-Butyllithium (0.41 mL of a 1.6 mol dm^{-1} solution in hexane, 0.66 mmol) was added to a solution of [3*R**,5*S**,6*S**]-1,7-dioxaspiro-[5.5]undecan-3,5-diyl bis(2-hydroxy-ethyl) ether **8** in tetrahydrofuran (8 mL) at −78 °C. The mixture was stirred for 0.5 h. A solution of tosyl chloride (0.15 g, 0.79 mmol) in tetrahydrofuran (5 mL) was added and the mixture stirred for a further 0.5 h at −78 °C. The reaction was then taken out of the cooling bath, allowed to warm to room temperature and left to stir for 16 h. The reaction was quenched with sodium dihydrogen phosphate solution (5 mL, 10% w/v) and extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over magnesium sulfate and the solvent removed in vacuo to yield a pale yellow oil. Purification by flash chromatography using hexane–ethyl acetate (3:2) as eluent yielded the *title compound* **5** as a colourless oil (0.17 g, 90%); found (FAB): MH^+, 585.18336. $C_{27}H_{37}O_{10}S_2$ requires MH, 585.18282; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.25 (1H, ddd, $J_{11ax,11eq}$ 14.3, $J_{11ax,10ax}$ 14.3 and $J_{11ax,10eq}$ 4.3 Hz, 11-Hax), 1.45–1.56 (3H, m, 9-CH_2 and 10-H_A or 10-H_B), 1.65–1.76 (1H, m, 10-H_A or 10-H_B), 1.83–2.02 (3H, m, 4-CH_2 and 11-Heq), 2.44 (6H, s, 2×$ArCH_3$), 3.07 (1H, t, $J_{5,4}$ 3.9 Hz, 5-H), 3.34 (1H, dddd, $J_{3,2ax}$ 3.2, $J_{3,2eq}$ 3.2, $J_{3,4ax}$ 3.2 and $J_{3,4eq}$ 3.2 Hz, 3-H), 3.56–3.79 (8H, m, 2-CH_2, 8-CH_2 and 2×C-1′), 4.08–4.14 (4H, m, 2×CH_2OTs), 7.31–7.79 (8H, m, Ar-H); δ_C (75 MHz; $CDCl_3$; Me_4Si) 17.9 (CH_2, C-10), 21.6 (CH_3, Ar-CH_3), 25.1 (CH_2, C-9), 26.0 (CH_2, C-4), 29.6 (CH_2, C-11), 61.1 (CH_2, C-8), 62.3 (CH_2, C-2), 66.5, 67.5 (CH_2, 2×C-1′), 69.5, 69.6 (CH_2, 2×CH_2OTs), 72.2 (CH, C-3), 77.6 (CH, C-5), 96.5 (quat, C-6), 127.9, 127.9, 129.83, 129.84 (CH, 4×Ar), 133.0, 133.0, 144.75, 144.81 (quat, 2×Ar-CH_3 and 2×$ArSO_2$); *m*/*z* (FAB) 585 (MH^+, 6%), 369 (45), 199 (27), 154 (100), 136 (72), 91 (33).

4.1.3. [3*R,5*S**,6*S**]-1,7-Dioxaspiro[5.5]undecan-3,5-diyl diacetaldehyde 6.** [3*R**,5*S**,6*S**]-1,7-Dioxaspiro-[5.5]undecan-3,5-diyl bisallyl ether **7** (0.19 g, 0.71 mmol) was dissolved in methanol (10 mL) and the solution cooled to −78 °C. Ozone was bubbled through the solution until a pale blue colour persisted (10–15 min). Excess ozone was discharged by passing oxygen and nitrogen through the flask. The reaction was taken out of the cooling bath and dimethyl sulfide (0.16 mL, 2.1 mmol) was added. The reaction was allowed to warm to room temperature and left to stir for 16 h. The volatiles were removed in vacuo to yield an oil that was purified by flash chromatography using 8% methanol in dichloromethane to yield the *title compound* **5** as a colourless viscous oil (0.17 g, 86%). Found (EI): M^+, 272.12576. $C_{13}H_{20}O_6$ requires M, 272.12599; ν_{max}(film)/cm^{-1} 1733 (s, C=O); δ_H (400 MHz; $CDCl_3$) 1.43 (1H, ddd, $J_{11ax,11eq}$ 13.5, $J_{11ax,10ax}$ 13.5 and $J_{11ax,10eq}$ 4.8 Hz, 11-Hax), 1.51–1.64 (3H, m, 9-CH_2, 10-H_A or 10-H_B), 1.69–1.83 (1H, m, 10-H_A or 10-H_B), 2.04–2.22 (3H, m, 4-CH_2 and 11-Heq), 3.21 (1H, t, $J_{5,4}$ 3.8 Hz, 5-H), 3.44–3.46 (1H, m, 3-H), 3.64–3.79 (4H, m, 2-CH_2 and 8-CH_2),

3.96–4.28 (4H, m, 2×O*CH*$_2$CHO), 9.68–9.74 (2H, m, 2×HC═O); δ_C (75 MHz; $CDCl_3$) 17.9 (CH_2, C-10), 25.0 (CH_2, C-9), 26.5 (CH_2, C-4), 29.8 (CH_2, C-11), 61.2 (CH_2, C-8), 61.8 (CH_2, C-2), 74.5, 75.4 (CH_2, 2×O*CH*$_2$CHO), 72.7 (CH, C-3), 76.8 (CH, C-5), 96.6 (quat, C-6), 201.1, 201.3 (quat, 2×C═O); *m/z* (EI) 272 (M^+, 1%), 172 (10), 101 (100), 69 (81), 43 (27).

4.1.4. [3*R,5*S**,6*S**]-1,7-Dioxaspiro[5.5]undecan-3,5-diyl bis(2-hydroxyethyl) ether 8.** [3*R**,5*S**,6*S**]-1,7-Dioxaspiro[5.5]undecan-3,5-diyl bisallyl ether **7** (75 mg, 0.28 mmol) was dissolved in methanol (8 mL) and the solution cooled to −78 °C. Ozone was bubbled through the solution until a pale blue colour persisted (10–15 min). Excess ozone was removed by passing oxygen through the solution. The reaction was taken out of the cooling bath and sodium borohydride (42 mg, 1.12 mmol) was added. The reaction was allowed to warm to room temperature and left to stir for 16 h. The solution was diluted with brine (5 mL) and the methanol removed. The aqueous solution was extracted with dichloromethane (5×15 mL). The combined extracts were dried over sodium sulfate and the dichloromethane removed under reduced pressure. The pale yellow oil was purified by flash chromatography using 8% MeOH in CH_2Cl_2 to afford the *title compound* **8** (120 mg, 75%) as colourless needles mp 62–65 °C. Found (EI): M^+, 276.15725. $C_{13}H_{24}O_6$ requires M, 276.15729; ν_{max}(film)/cm^{-1} 3628–3290 (br s, OH); δ_H (400 MHz; $CDCl_3$) 1.31 (1H, ddd, $J_{11ax,11eq}$ 13.6, $J_{11ax,10ax}$ 13.6 and $J_{11ax,10eq}$ 4.5 Hz, 11-Hax), 1.49–1.62 (3H, m, 9-CH_2, 10-H_A or 10-H_B), 1.73–1.82 (1H, m, 10-H_A or 10-H_B), 1.98 (1H, ddd, $J_{4ax,4eq}$ 15.1, $J_{4ax,5}$ 3.6 and $J_{4ax,3}$ 3.6 Hz, 4-Hax), 2.11–2.29 (2H, m, 4-Heq and 11-Heq), 3.11 (1H, t, $J_{5,4}$ 3.6 Hz, 5-H), 3.37–3.41 (1H, m, 3-H), 3.47–3.84 (12H, m, 2-CH_2, 8-CH_2, 2×1′-CH_2 and 2×*CH*$_2$OH); δ_C (75 MHz; $CDCl_3$) 18.1 (CH_2, C-10), 25.1 (CH_2, C-9), 26.0 (CH_2, C-4), 31.1 (CH_2, C-11), 60.9 (CH_2, C-8), 61.0 (CH_2, C-2), 61.5, 61.6 (CH_2, 2×C-1′), 70.9, 71.3 (CH_2, 2×*CH*$_2$OH), 72.2 (CH, C-3), 77.2 (CH, C-5), 96.1 (quat, C-6); *m/z* (EI) 276 (M^+, 0.4%), 158 (10), 101 (41), 88 (95), 73 (42), 69 (23), 45 (100).

4.1.5. [1*S,15*R**,18*S**]-Spiro[2,14,17-trioxa-5,8,11-trithiabicyclo[13.3.1]-nonadecane-18,2′-tetrahydropyran] 10a.** A solution of the spiroacetal ditosylate **5** (100 mg, 0.17 mmol) in dimethylformamide (5 mL) and a solution of the 2-mercaptoethyl sulfide **9a** (220 mg, 0.17 mmol) in dimethylformamide (5 mL) were added from separate addition funnels over 2.5 h to a vigorously stirred suspension of caesium carbonate (170 mg, 0.51 mmol) in dimethylformamide (20 mL) at 60 °C. The mixture was left to stir for 16 h. The reaction mixture was then filtered through a short pad of Celite and the filter cake washed with dichloromethane (3×15 mL). The solvent was removed under reduced pressure to yield a yellow oil that was purified by flash chromatography using hexane–ethyl acetate (4:1) as eluent to afford the *title compound* **10a** (58 mg, 86%) as a pale yellow oil; found (EI): M^+, 394.13104. $C_{17}H_{30}O_4S_3$ requires M, 394.13063; δ_H (400 MHz; $CDCl_3$) 1.26 (1H, ddd, $J_{3'ax,3'eq}$ 13.6, $J_{3'ax,4'ax}$ 13.6 and $J_{3'ax,4'eq}$ 4.4 Hz, 3′-Hax), 1.51–1.57 (3H, m, 5′-CH_2 and 4′-H_a or 4′-H_B), 1.73–1.81 (1H, m, 4′-H_A or 4′-H_B), 1.91 (1H, ddd, $J_{19ax,19eq}$ 15.2, $J_{19ax,15}$ 3.4 and $J_{19ax,1}$ 3.4 Hz, 19-Hax), 2.15–2.25 (2H, m, 19-Heq and 3′-Heq), 2.72–2.82 (12H, m, 6×CH_2S), 3.09 (1H, t, $J_{1,19}$ 3.4 Hz, 1-H), 3.37 (1H, m, 15-H), 3.41 (1H, ddd, $J_{A,B}$ 6.8, $J_{3A,4A}$ 9.0 and $J_{3A,4B}$ 9.0 Hz, 3-H_A), 3.55–3.68 (4H, m, 16-CH_2 and 13-CH_2), 3.72–3.82 (3H, m, 3-H_B and 6′-CH_2); δ_C (100 MHz; $CDCl_3$) 18.0 (CH_2, C-4′), 24.3 (CH_2, C-19), 25.2 (CH_2, C-5′), 31.2 (CH_2, C-3′), 31.4, 31.8, 32.3, 32.4, 33.2, 33.5 (CH_2, 6×CH_2S), 60.9 (CH_2, C-6′), 62.2 (CH_2, C-16), 70.1 (CH_2, C-13), 70.3 (CH_2, C-3), 72.0 (CH, C-15), 77.2 (CH, C-1), 96.6 (quat, C-18); *m/z* (EI) 394 (M^+, 23%), 120 (54), 103 (57), 87 (100), 61 (76), 41 (46).

4.1.6. [1*S,18*R**,21*S**]-Spiro[2,17,20-trioxa-5,8,11,14-tetrathiabicyclo[16.3.1]-docosane-21,2′-tetrahydropyran] 10b.** The *title compound* **10b** was prepared from the spiroacetal ditosylate **5** (140 mg, 0.24 mmol), 3,6-dithiaoctane-1,8-dithiol **9b** (50 mg, 0.24 mmol) and caesium carbonate (230 mg, 0.72 mmol) using a similar procedure to that described above for crown ether **10a**. The crude product was purified by flash chromatography using hexane–ethyl acetate (4:1) as eluent to afford the *title compound* **10b** (75 mg, 68%) as a colourless oil; found (EI): M^+, 454.13397. $C_{19}H_{34}O_4S_4$ requires M, 454.13400; δ_H (400 MHz; $CDCl_3$) 1.32 (1H, ddd, $J_{3'ax,3'eq}$ 13.6, $J_{3'ax,4'ax}$ 13.6 and $J_{3'ax,4'eq}$ 4.4 Hz, 3′-Hax), 1.49–1.60 (3H, m, 5′-CH_2 and 4′-H_A or 4′-H_B), 1.71–1.79 (1H, m, 4′-H_A or 4′-H_B), 1.97 (1H, ddd, $J_{22ax,22eq}$ 14.8, $J_{22ax,18}$ 3.7 and $J_{22ax,1}$ 3.7 Hz, 22-Hax), 2.07 (1H, dddd, $J_{22eq,22ax}$ 14.8, $J_{22eq,1}$ 3.7, $J_{22eq,18}$ 3.7 and $J_{22eq,19eq}$ 1.9 Hz, 22-Heq), 2.12 (1H, dt, $J_{3'eq,3'ax}$ 13.6 and $J_{3'eq,4'}$ 2.8 Hz, 3′-Heq), 2.72–2.82 (16H, m, 8×CH_2S), 3.09 (1H, t, $J_{1,22}$ 3.7 Hz, 1-H), 3.37 (1H, dddd, $J_{18eq,22ax}$ 3.7, $J_{18eq,22eq}$ 3.7, $J_{18eq,19ax}$ 3.7 and $J_{18eq,19eq}$ 3.7 Hz, 18-H), 3.55–3.78 (8H, m, 6′-CH_2, 19-CH_2, 16-CH_2 and 3-CH_2); δ_C (100 MHz; $CDCl_3$) 17.9 (CH_2, C-4′), 25.2 (CH_2, C-5′), 26.4 (CH_2, C-22), 30.2 (CH_2, C-3′), 32.01, 32.04, 32.41, 32.46, 32.49, 32.52, 33.15, 33.18 (CH_2, 8×CH_2S), 61.0 (CH_2, C-6′), 62.1 (CH_2, C-19), 69.2 (CH_2, C-16), 70.5 (CH_2, C-3), 71.9 (CH, C-18), 77.2 (CH, C-1), 96.5 (quat, C-21); *m/z* (EI) 454 (M^+, 19%), 131 (42), 120 (71), 87 (100), 61 (74), 41 (35).

4.1.7. [1*S,21*R**,24*S**]-Spiro[2,20,23-trioxa-5,8,11,14,17-pentathiabicyclo[19.3.1]-pentacosane-24,2′-tetrahydropyran] 10c.** The *title compound* **10c** was prepared from the spiroacetal ditosylate **5** (0.27 g, 0.46 mmol), 3,6,9-trithiaundecane-1,11-dithiol **9c** (0.13 g, 0.46 mmol) and caesium carbonate (0.45 g, 1.4 mmol) using a similar procedure to that described above for crown ether **10a**. The crude product was purified by flash chromatography using hexane–ethyl acetate (4:1) as eluent to afford the *title compound* **10c** (0.15 g, 64%) as a pale yellow oil; found (EI): M^+, 514.13764. $C_{21}H_{38}O_4S_5$ requires M, 514.13737; δ_H (400 MHz; $CDCl_3$) 1.32 (1H, ddd, $J_{3'ax,3'eq}$ 13.3, $J_{3'ax,4'ax}$ 13.3 and $J_{3'ax,4'eq}$ 4.3 Hz, 3′-Hax), 1.46–1.60 (3H, m, 5′-CH_2 and 4′-H_A or 4′-H_B), 1.66-1.82 (1H, m, 4′-H_A or 4′-H_B), 1.95 (1H, ddd, $J_{25ax,25eq}$ 14.8, $J_{25ax,21}$ 3.8 and $J_{25ax,1}$ 3.8 Hz, 25-Hax), 2.05–2.14 (2H, m, 3′-Heq and 25-Heq), 2.69–2.84 (20H, m, 10×CH_2S), 3.08 (1H, t, $J_{1,25}$ 3.8 Hz, 1-H), 3.53 (1H, br s, 21-H), 3.55–3.79 (8H, m, 6′-CH_2, 22-CH_2, 3-CH_2 and 19-CH_2); δ_C (100 MHz; $CDCl_3$) 17.9 (CH_2, C-4′), 25.2 (CH_2, C-5′), 26.1 (CH_2, C-25), 30.3 (CH_2, C-3′), 31.9, 32.1, 32.30, 32.32, 32.4, 32.5, 32.6, 32.7, 32.9, 33.0 (CH_2, 10×CH_2S), 61.0 (CH_2, C-6′),

62.0 (CH_2, C-22), 69.2 (CH_2, C-19), 70.1 (CH_2, C-3), 71.9 (CH, C-21), 77.1 (CH, C-1), 96.5 (quat, C-24); *m/z* (EI) 514 (M^+, 13%), 120 (72), 105 (54), 87 (100), 61 (72), 41 (32).

4.1.8. [1*S,15*R**,18*S**]-Spiro[2,14,17-trioxa-5,8,11-tris(2-nitro-benzenesulfonyl)-5,8,11-triazabicyclo-[13.3.1]nonadecane-18,2′-tetrahydropyran] 13a.** To a solution of the Ns-protected triamine **12a** (46 mg, 0.07 mmol) in tetrahydrofuran (20 mL) was added sodium hydride (5 mg, 0.17 mmol) and the resulting mixture heated under reflux for 30 min. A solution of [3*R**,5*S**,6*S**]-1,7-dioxaspiro[5.5]undecan-3,5-diyl bis(2-*p*-toluenesulfonyl) ethyl ether **5** (41 mg, 0.07 mmol) in tetrahydrofuran (5 mL) was added over 3 h and the reaction mixture was heated under reflux for a further 20 h. The solvent was removed under reduced pressure to yield a tan oil, which was purified by flash chromatography using ethyl acetate–hexane (4:1) as eluent to afford the *title compound* **13a** (17 mg, 27%) as a colourless oil; found (FAB): MH^+, 899.18910. $C_{35}H_{43}N_6O_{16}S_3$ requires MH, 899.18977; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.30–1.34 (1H, m, 3′-Hax), 1.51–1.59 (4H, m, 4′-CH_2 and 5′-CH_2), 1.96 (1H, dt, $J_{11eq,11ax}$ 13.5 and $J_{11eq,10}$ 2.1 Hz, 3′-Heq), 2.03–2.07 (2H, m, 19-CH_2), 3.03 (1H, t, $J_{1,19}$ 3.0 Hz, 1-H), 3.24 (1H, br s, 15-H), 3.38–3.88 (20H, m, 6′-CH_2, 16-CH_2, 3-CH_2, 13-CH_2 and 6×CH_2N), 7.61–8.11 (12H, m, Ar); δ_C (75 MHz; $CDCl_3$; Me_4Si) 18.2 (CH_2, C-4′), 25.1 (CH_2, C-5′), 27.5 (CH_2, C-19), 31.6 (CH_2, C-3′), 48.4, 48.6, 49.8, 49.9, 50.9, 51.0 (CH_2, 6×CH_2N), 60.5 (CH_2, C-6′), 60.9 (CH_2, C-16), 71.1 (CH_2, C-13), 71.9 (CH_2, C-3), 72.0 (CH, C-15), 77.2 (CH, C-1), 96.1 (quat, C-18), 124.2, 124.4, 131.2, 131.5, 132.0, 132.0, 132.1, 132.2, 132.4, 133.6, 133.7, 133.8 (18×Ar); *m/z* (EI) 899 (MH^+, 0.6%), 368 (11), 194 (57), 181 (60), 167 (91), 101 (85), 71 (100).

4.1.9. [1*S,15*R**,18*S**]-Spiro[2,14,17-trioxa-5,8,11-triazabicyclo[13.3.1]-nonadecane-18,2′-tetrahydropyran] 14a.** Thiophenol (5 mg, 0.05 mmol) was added to a stirred mixture of the [1*S**,15*R**,18*S**]-spiro[2,14,17-trioxa-5,8,11-tris(2-nitro-benzenesulfonyl)-5,8,11-triazabicyclo-[13.3.1]nonadecane-18,2′-tetrahydropyran] **13a** (10 mg, 0.01 mmol) and K_2CO_3 (21 mg, 0.15 mmol) in dimethylformamide (5 mL). The resulting solution was stirred at room temperature for 18 h. The solvent was removed under reduced pressure to yield a tan residue that was redissolved in H_2O–$CHCl_3$ (3:5). The organic phase was separated and the aqueous layer extracted with $CHCl_3$ (5×5 cm^3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and the solvent concentrated. The residue was purified by flash chromatography using CH_2Cl_2–MeOH (20:1), then CH_2Cl_2–MeOH–30% NH_4OH (20:1) as eluents to afford the *title compound* **14a** (3.2 mg, 84%) as a viscous tan oil; found (FAB): MH^+, 344.25423. $C_{17}H_{34}N_3O_4$ requires MH, 344.25493; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.32–1.36 (1H, m, 3′-Hax), 1.55–1.70 (4H, m, 4′-CH_2 and 5′-CH_2), 1.96 (1H, m, 3′-Heq), 2.17 (2H, m, 19-CH_2), 3.04 (1H, m, 1-H), 3.29 (1H, br s, 15-H), 3.55–3.84 (8H, m, 3-CH_2, 6′-CH_2, 13-CH_2 and 16-CH_2); *m/z* (EI) 344 (MH^+, 2%), 299 (52), 287 (73), 226 (61), 153 (58), 99 (68), 56 (100), 44 (75). ^{13}C NMR data were not acquired for this compound as there was insufficient material to give a satisfactory signal to noise ratio.

4.1.10. N^1,N^3,N^5-Tris(2-nitrobenzenesulfonyl)-1,5-diamino-3-azapentane 12a. A solution of diethylenetriamine (0.25 g, 2.4 mmol) and triethylamine (0.5 mL, 3.9 mmol) were added to a stirred solution of 2-nitrobenzenesulfonyl chloride (1.61 g, 7.7 mmol) in dichloromethane (20 mL) at 0 °C. The reaction mixture was stirred for 20 h. The solvent was removed in vacuo and the residue dissolved in H_2O–$CHCl_3$. The organic layer was separated and the aqueous layer extracted with $CHCl_3$ (3×10 mL). The extracts were washed with saturated $NaHCO_3$ (15 mL) and dried over Na_2SO_4. Removal of the solvent and purification by flash chromatography using hexane–ethyl acetate (3:2) afforded the *title compound* **12a** (1.27 g, 80%) as a yellow solid; mp 70–74 °C; found (FAB): MH^+, 659.05478. $C_{22}H_{23}N_6O_{12}S_3$ requires MH, 659.05361; ν_{max}(film)/cm^{-1} 3323 (w, NH); δ_H (400 MHz; $CDCl_3$) 3.33 (4H, m, 2×CH_2NH), 3.54 (4H, t, *J*=6.1 Hz, 2×CH_2N), 5.72 (2H, t, *J*=6.1 Hz, NH); δ_C (100 MHz; $CDCl_3$) 42.3 (C-1), 49.0 (C-2), 124.5, 124.7, 125.6, 131.0, 131.4, 132.1, 132.6, 133.0, 133.9, 134.5, 135.9 (18×Ar); *m/z* (FAB) 659 (MH^+, 10%), 154 (100), 136 (73).

4.1.11. 3,6-Dithiaoctane-1,8-dithiol 9b. Dithiol **9b** was prepared from the appropriate β-chloroethyl sulfide using well established literature procedures.[8] 1,8-Dichloro-3,6-dithiaoctane (0.22 g, 1.0 mmol) was treated with Cs_2CO_3 (1.0 mmol) and thioacetic acid (2.0 mmol) in MeOH to afford the corresponding caesium thiolate. Lithium aluminium hydride (0.17 g, 4.5 mmol) was added to a solution of the crude 4,7-dithiaoctane-1,10-dithiyldiacetate (0.5 g, 1.8 mmol) in diethyl ether using the procedure described by Edema et al.[8c] Excess lithium aluminium hydride was quenched with saturated ammonium chloride (10 mL). The reaction mixture was extracted with ethyl acetate (3×20 mL), washed with water (15 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the product purified by flash chromatography using dichloromethane as eluent to yield dithiol **9b** as a white solid (0.34 g, 89%); found (EI): M^+, 21399764. $C_{12}H_{22}O_2S_5$ requires M, 213.99784; δ_H (300 MHz; $CDCl_3$) 1.69–1.77 (2H, m, SH), 2.71–2.80 (12H, m, CH_2S).

4.1.12. 3,6,9-Trithiaundecane-1,11-dithiol 9c. Dithiol **9c** was prepared from the appropriate β-chloroethyl sulfide **4c** using the procedures described by Wolf et al.[8a] and de Groot et al.[8b] 1,11-Dichloro-3,6,9-trithiaundecane **4c** (0.28 g, 1.0 mmol) was treated with Cs_2CO_3 (1.0 mmol) and thioacetic acid (2.0 mmol) in MeOH to afford the corresponding caesium thiolate. Lithium aluminium hydride (0.17 g, 4.5 mmol) was added to a solution of the crude 4,7,10-trithiaundecane-1,13-dithiyldiacetate (0.64 g, 1.8 mmol) in diethyl ether using the procedure described by Edema et al.[8c] Excess lithium aluminium hydride was quenched with saturated ammonium chloride (10 mL). The reaction mixture was extracted with ethyl acetate (3×20 mL). The extracts were washed with water (15 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the product purified by flash chromatography using dichloromethane as eluent to yield dithiol **9c** as a white solid (0.34 g, 68%); found (EI): M^+, 274.00046. $C_8H_{18}S_5$ requires M, 274.00121; δ_H (300 MHz; $CDCl_3$) 1.68–1.77 (2H, m, SH), 2.67–2.81 (16H, m, CH_2S); *m/z* (EI) 274 (M^+, 0.7%), 120 (39), 61 (100).

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References and notes

1. Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017–7036.
2. For an example, see: Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939–9953.
3. Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617–1661.
4. Agtrap, A.; Chamberlin, J. W.; Pinkerton, M.; Steinrauf, L. *J. Am. Chem. Soc.* **1967**, *89*, 5737–5739.
5. (a) Lee, W. Y.; Park, C. H.; Kim, S. S. *J. Am. Chem. Soc.* **1993**, *115*, 1184–1185; (b) Lee, W. Y.; Park, C. H. *J. Org. Chem.* **1993**, *58*, 7149–7157; (c) Garcia, C.; Pointud, Y.; Jeminet, G.; Dugat, D.; Beltran, J. L. *Tetrahedron: Asymmetry* **1998**, *9*, 4253–4265; (d) McGarvey, G. J.; Stepanian, M. W.; Bressette, A. R.; Sabat, M. *Org. Lett.* **2000**, *2*, 3453–3456.
6. Brimble, M. A.; Johnston, A. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 265–270.
7. Brimble, M. A.; Johnston, A. D.; Furneaux, R. H. *J. Org. Chem.* **1998**, *63*, 471–479.
8. (a) Wolf, R. E.; Hartman, J. R.; Foxman, B. M.; Cooper, S. R. *J. Am. Chem. Soc.* **1987**, *109*, 4328–4335; (b) de Groot, B.; Loeb, S. J. *Inorg. Chem.* **1989**, *28*, 3573–3578; (c) Edema, J. J. H.; Buter, J.; Kellogg, R. M. *Tetrahedron* **1994**, *50*, 2095–2098.
9. (a) Buter, J.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1980**, 466; (b) Buter, J.; Kellogg, R. M. *J. Org. Chem.* **1981**, *46*, 4481–4485.
10. (a) Lindoy, L. F. *The Chemistry of Macrocyclic Ligand Complexes*; Cambridge University Press: Cambridge, UK, 1989; p 48; (b) Owsten, P. G.; Peters, R.; Ramsammy, E.; Tasker, P. A.; Trotter, J. *J. Chem. Soc., Chem. Commun.* **1980**, 1218–1220; (c) Ray, J. K.; Haldar, M. K.; Gupta, S.; Kar, G. K. *Tetrahedron* **2000**, *56*, 909–912.
11. (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373–6374; (b) Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831–5834.