Steps Towards a Practical Synthesis of Macrocyclic Bisbenzylisoquinolines

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There are more than 400-reported bisbenzylisoquinoline alkaloids, many with interesting biological activity, but the reported syntheses are long and low yielding. As a result, there have been no systematic attempts at exploitation of the potential therapeutic applications. The concept of a sulfur 'stitch', restricting the conformational freedom of intermediates in the synthesis, will potentially allow analogues of the natural products to be prepared using relatively efficient routes. The synthesis of intermediate sulfur heterocycles is reported, based on 2,8-dimethylphenoxathiin, leading *via* 2,8-bis(bromomethyl)phenoxathiin-10,10-dioxide to a synthesis of 3,4,8,9-tetrahydro-13-oxa-6-thia-2,10-diazapentacene, a key potential intermediate on the route to a variety of macrocyclic bisbenzylisoquinolines.

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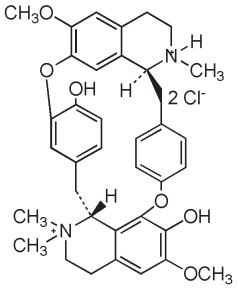
Introduction.

More than 400 bisbenzylisoquinolines (BBIQ's) have been reported from natural sources [1-4]. Of these, by far the best known is tubocurarine **1**, which was used for many years as a surgical muscle relaxant before being superseded by synthetic analogues. Other macrocyclic BBIQ's have been reported to have potentially useful biological activity, for example several have antimalarial activity; isotetrandrine **2** shows an IC_{50} of 70ng/ml against a multidrug resistant strain of *Plasmodium falciparum* [5,6]. Despite this, there has been no systematic attempt to develop routes of general applicability, perhaps because the numerous syntheses of individual members of the series are long and low-yielding. The problems associated with syntheses of macrocyclic BBIQ's are two-fold. First, it is necessary to link benzene rings, through an ether oxygen or directly through carbon, while maintaining suitable substitution for formation and elaboration of two benzylisoquinolines. Secondly, the relatively complex product of this linkage, which is inherently very flexible, must be cyclised to give a large ring; the size of the ring depends on the type of BBIQ being formed. The ring closure itself is sterically hindered and statistically improbable, relative to competing intermolecular reactions and decomposition of the intermediate.



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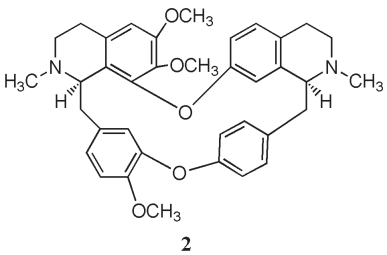

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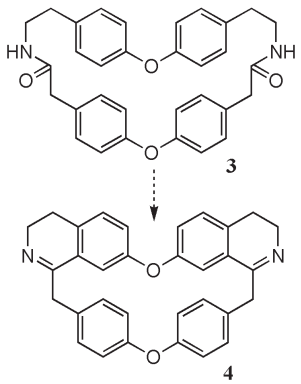
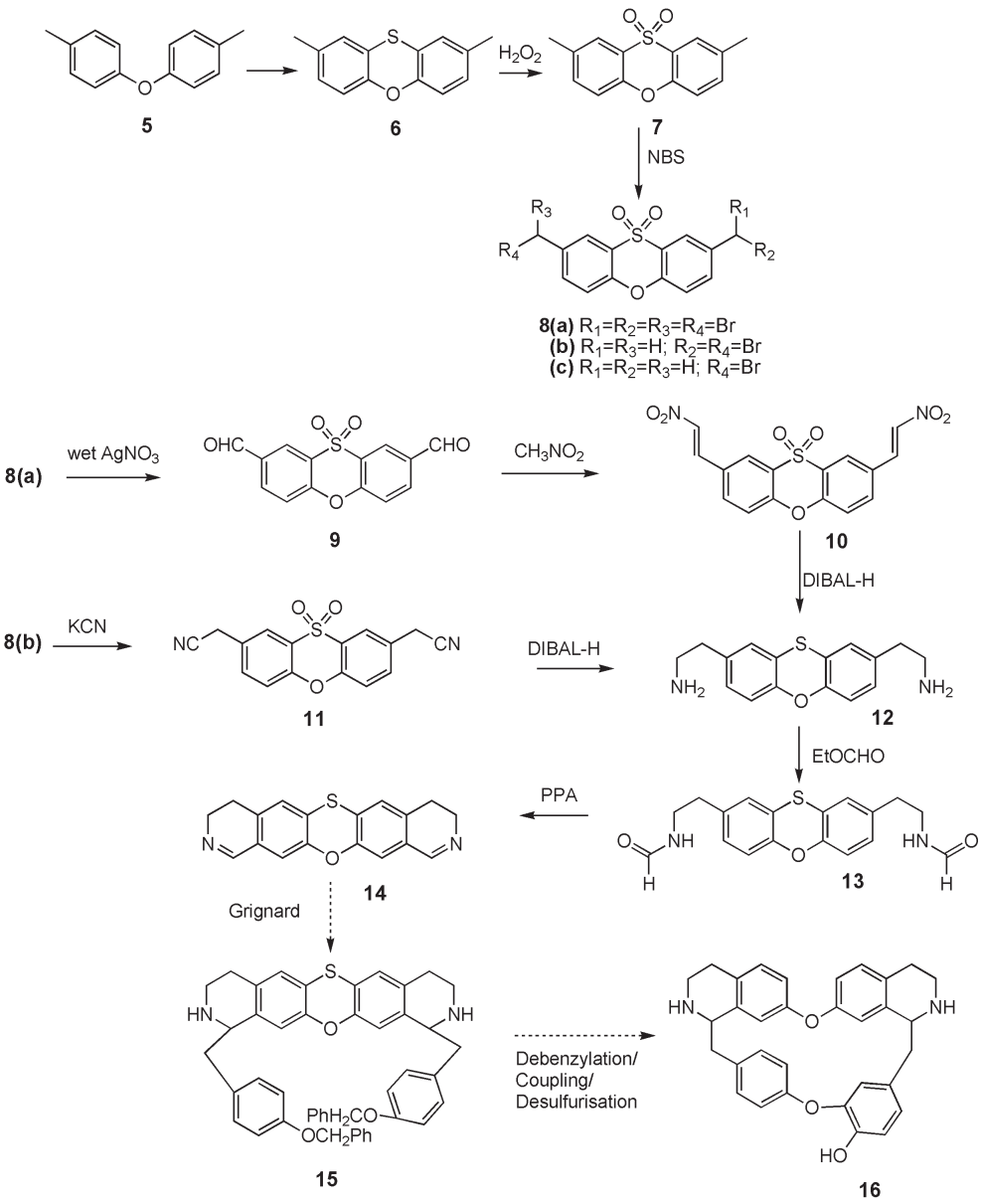
An approach to the synthesis of a stripped-down analogue is exemplified by the unsuccessful attempt [7] to cyclise the simple bis-amide **3** under Bischler-Napieralski conditions, to the BBIQ **4** (Scheme 1). In practice, the formation of the bis-amide **3**, which is itself macrocyclic, was

Scheme 1



3 **4**

Scheme 2



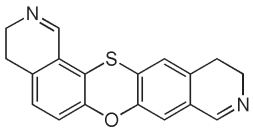
only possible in very dilute solution. This limited the practicality of the method and discouraged investigation into further Bischler-Napieralski reactions with **3**.

It seemed possible that a stepwise approach to the macrocycle could be achieved by the incorporation of a sulfur 'stitch,' which would hold the BBIQ in an appropriate conformation for cyclization (Scheme 2). The sulfur could be removed later [8]. The use of such a 'stitch' is an example of a more general approach using 'disposable tethers' [9], in which two parts of a molecule are held together until they have reacted and are then disconnected. Most disposable tethers are based on silicon, but there are a few examples of the use of sulfur; unlike the potential use described here, the earlier use of sulfur was as a passive weak point, with no electronic involvement of the sulfur in facilitating a reaction [10].

We here report all stages of the proposed synthesis (Schemes 2 and 3), up to the preparation of the pentacyclic BBIQ **25**, which we were unable to obtain in sufficient quantities to go further in the time available. However, it seems probable that the concept of the 'sulfur stitch' could be used in other contexts, temporarily activating a ring to electrophilic attack as well as tethering two parts of the molecule, where macrocycles present synthetic difficulties. The synthesis of BBIQ's such as **16** remains a worthwhile target, in view of the potential biological activity.

Results and Discussion.

The key pentacyclic intermediate **14** was synthesised by two routes from the common tricyclic intermediate **7** (Scheme 2). An Ullman reaction gave *p*-tolyl ether, which cyclised to the dimethylphenoxathiin **6** on heating with sulfur and aluminium chloride [11]. While bromination of **6** with *N*-bromosuccinimide was possible, concomitant oxidation to the sulfoxide and the sulfone gave a complex mixture of products. The sulfur was therefore oxidised to the sulfone **7** prior to bromination. Depending on the conditions employed, bromination could be controlled to give either the tetrabromo **8a** or the dibromo derivative **8b** as the major product. Either could be used to give 2,8-di(2-aminoethyl)phenoxathiin **12**, as in Scheme 2, using potassium cyanide with **8b** or nitromethane with the dialdehyde derived from **8a**, followed by reduction with a large excess of DIBAL. Reaction with DIBAL also regenerated the sulfide link, necessary to facilitate ring closure after formylation; it would not be expected that the sulfone would undergo Bischler-Napieralski ring closure owing to its strong electron-withdrawing effect. Ring closure of the *N*,*N*'-diformyl derivative of **12** to give the pentacyclic amine **14** was successful, although three products were formed. The major isomer was the expected linear compound **14**, with smaller amounts of the angular isomer **17** and possible traces of **18**. It was not considered worth separating the isomers prior to further reaction, since HPLC was required for this purpose and the mixture of amines showed signs of decomposition in solution.



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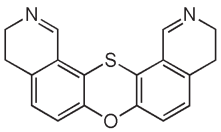

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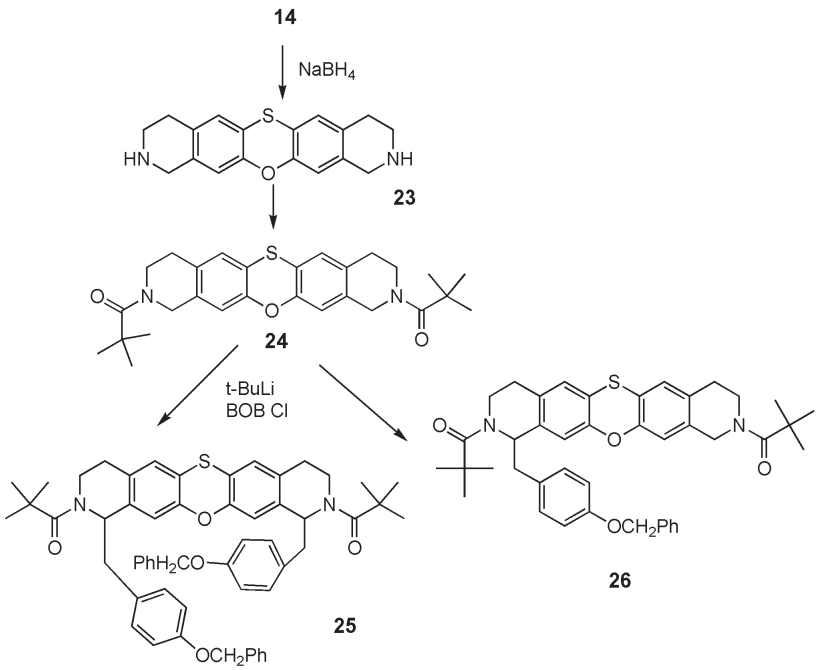
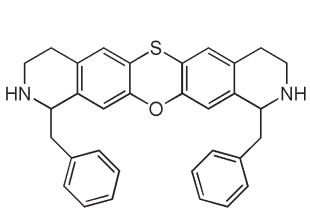
Synthesis of the pentacyclic amine **14** was intended to be followed by Grignard reaction [12] with 4-benzyloxybenzyl (BOB) chloride to give **15**, which after deprotection would allow phenolic oxidative coupling to give the macrocycle; desulfurisation would give the target compound **16** (Scheme 2). When initial attempts at Grignard reactions with **14** failed, it was decided to investigate model compounds involving only half of the desired structure, which are comparatively readily available.

3,4-Dihydroisoquinoline was synthesised in high yield by cyclisation of *N*-formyl phenethylamine in polyphosphoric acid and reacted readily with benzyl magnesium bromide to give 1-benzyl-1,2,3,4-tetrahydroisoquinoline in good yield. A similar reaction with a mixture of **14**, **17** and possibly **18** also succeeded, giving a mixture of the bis-benzyl isoquinolines **19**, **20** and possible traces of **21**. Unfortunately, reaction of 3,4-dihydroisoquinoline with BOB chloride failed, although the Grignard reagent formed from BOB chloride could be successfully coupled with benzaldehyde to give the alcohol **22**.

The poor prospects with the Grignard route led to consideration of an alternative, involving N-derivatisation,

Scheme 3





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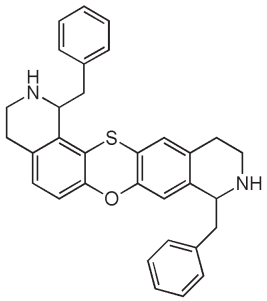

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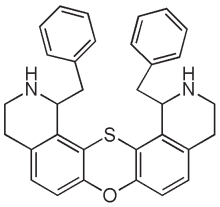

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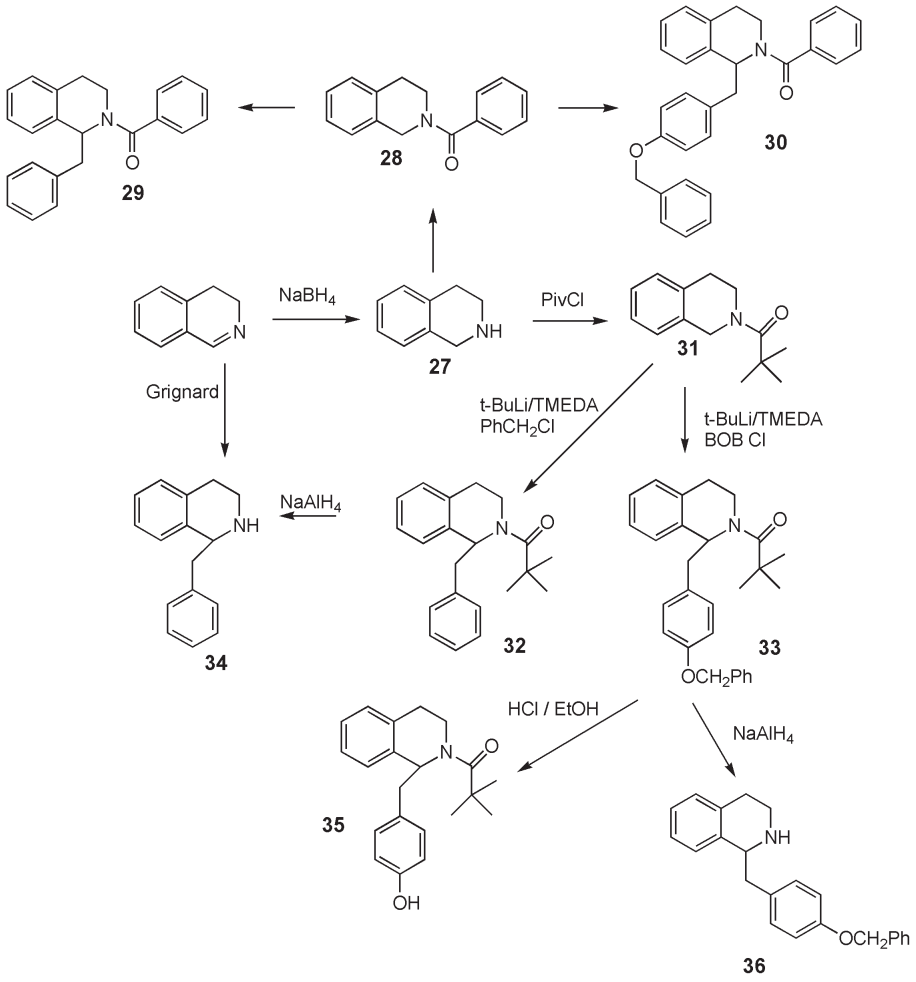
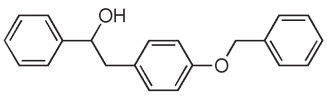
lithiation and alkylation (Scheme 3). This route had the advantage that the N-substituents would tend to push the 1-benzyl groups in the adduct **25** (Scheme 3) towards each other, potentially favouring the later oxidative coupling reaction required to form the macrocycle. The first choice for the *N*-substituent was benzoyl, which would be relatively easy to remove later, however, while the model benzoyl amide **28** formed readily from 1,2,3,4-tetrahydroisoquinoline **27 (**Scheme 4), reaction with benzyl halides after lithiation to give **29** and **30** was poor. We therefore changed to pivaloyl (**31** in Scheme 4), which worked very well, once we changed to the conditions for alkylation employed by Seebach *et al* [13]. The simple benzyl adduct **32** was obtained in 77% and the BOB adduct **33** in 95% yield. As anticipated, both showed an upfield shift of H-8 of the isoquinoline, indicating that the benzyl or benzyl-

Scheme 4





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oxybenzyl group was pushed away from the pivaloyl substituent, and potentially towards the other benzyl group in a future BBIQ intermediate, such as **25** in Scheme 3. The BOB adduct **33** was readily *O*-debenzylated in a mixture of concentrated hydrochloric acid and ethanol to give **35**.

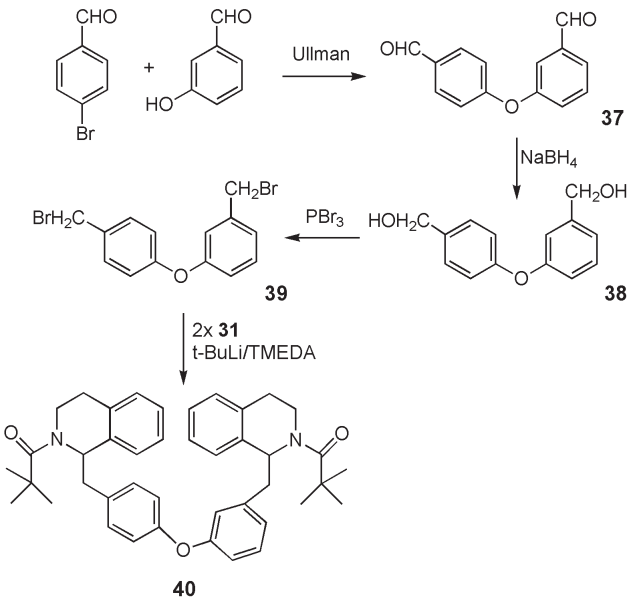
Removal of *N*-pivaloyl substituents is potentially a problem; Seebach *et al* reported that acidic and alkaline hydrolysis and aminolysis were all unsuccessful, while reductive cleavage furnished mixtures of the NH and N-neopentyl tetrahydroisoquinolines [13]. Ultimately, the best conditions were similar to those used by Isabelle and Seebach [14] and Zakharkin *et al* [15], who used sodium aluminium hydride in dry tetrahydrofuran; this gave a 36% yield of **34** from **32** and a 44% yield of **36** from **33**. The mixture of pentacyclic compounds **14**, **17** and possibly **18** was readily reduced with sodium borohydride, without being separated, and converted to the di-pivaloyl derivatives, of which only the major isomer **24** is shown in Scheme 3 for simplicity. The mixture of isomers suffered oxidation in solution, but the major component could be separated by flash chromatography, provided that this was carried out quickly.

The pentacyclic diamide **24**, as a mixture with its isomers, was subjected to a total of twelve attempts at alkylation with BOB chloride, of which only one gave any indication of success in forming **25**, in a calculated yield of 13%, with a small amount of the mono-alkylated derivative **26**. There was insufficient material for an attempt at deprotection and oxidative coupling. In view of the very high yields obtained with the monomer, this outcome is difficult to explain.

To avoid the necessity for phenolic oxidative coupling, it was decided to work with an already coupled tail unit, the dibrominated ether **39**, which was prepared by Ullman reaction of two aldehydes (Scheme 5), followed by reduction with sodium borohydride and bromination with phosphorus tribromide. Ether **39** was tested by alkylating the simple pivaloylated tetrahydroisoquinoline **31**, giving the BBIQ **40** as a mixture of stereoisomers, in 77% yield. Unfortunately, attempts at coupling **39** with the five-ring compound **24** were unsuccessful, giving complex mixtures from which it was not possible to isolate any identifiable material. The standard use of tetramethylethylenediamine in these reactions is a problem, since it was shown on several occasions to form adducts by direct *N*-alkylation with the benzyl halides, a side reaction which will become more serious if the required *C*-alkylation is slow. A more sterically hindered diamine, such as tetraethylethylenediamine, might solve this problem.

Our failure to reach our ultimate goal is frustrating, especially since new antimalarials are badly needed. If the problem can be traced to steric obstruction to alkylation by the pivaloyl groups in **24**, it is possible that the use of other *N*-substituents might succeed. In particular, the use of chiral substituents, as pioneered by Meyer [16], offers the prospect of steric control of alkylation at C-1 of the tetrahydroisoquinoline, which is potentially important for the biological activity.

Scheme 5



EXPERIMENTAL

Nmr spectra were recorded in deuteriochloroform unless stated otherwise.

4,4'-Dimethyldiphenyl ether (**5**).

(A) *p*-Cresol (100.0 g, 0.924 mol) was dissolved in methanol (50 cm^3) and added to a solution of sodium hydroxide (37.0 g, 0.924 mol) in 85% methanol/water (200 cm^3). The solvent was removed at 60 °C under reduced pressure and the solid material dried *in vacuo* at 100 °C for 4 h to give the sodium salt as a white solid in quantitative yield. Cuprous oxide (Cu_2O, 27.4 g, 0.192 mol), *p*-bromotoluene (65.0 g, 0.380 mol) and the dried sodium phenoxide (25.0 g, 0.192 mol) were dissolved in dimethylacetamide (25 cm^3) and heated under reflux for 72 h under nitrogen. Dilute hydrochloric acid (7%, 200 cm^3) was added and the precipitated product was extracted with ethyl acetate. The crude product was purified on a silica gel column; the first fraction was *p*-bromotoluene, and the second was *p*-tolyl ether, which solidified upon standing (12.5 g, 33%) [17].

(B) *p*-Bromotoluene (15.0 g, 0.087 mol) was dissolved in toluene (30.0 g, 0.326 mol) to which was added *p*-cresol (15.7 g, 0.145 mol, 1.65 molar excess), followed by cesium carbonate (40.0 g, 0.122 mol, 1.4 molar excess), 1-naphthoic acid (21.14 g, 0.122 mol), copper(I) chloride (0.34 g, 5.00 mol%) and ethyl acetate (1.00 g, 5.00 mol%). Finally, molecular sieve (5 Å) (21.90 g) was added. The reaction mixture was heated under reflux for 24 h under nitrogen. Toluene was distilled off under reduced pressure and the remaining slurry was poured into iced hydrochloric acid (7%, 150 cm^3) and the mixture extracted with ether (3 x 150 cm^3). The ether layer was separated, washed 3 times with sodium hydroxide solution (20%), dried (magnesium sulfate), filtered and evaporated under reduced pressure to give the crude product, which solidified upon standing (13.20 g). Recrystallization from ether gave *p*-tolyl ether as white crystals (10.05 g, 58%) [18], mp 47-49 °C, [lit.,[17] 49-50 °C]; ^{1}H nmr: δ (270MHz) 2.22 (s, 6H, CH_3), 6.78 (dd, J = 7.8, 1.8 Hz, 4H, Ar-H), 7.03 (dd, J = 8.1, 2.0 Hz, 4H, Ar-H); hrms: found 198.10448, calculated for $C_{14}H_{14}O$; 198.10447.

2,8-Dimethylphenoxathiin (**6**).

p-Tolyl ether (55.38 g, 0.279 mol) was first melted in a 3-necked round bottom flask. Ground aluminium chloride (26.5 g, 0.199 mol), and sulphur (8.95 g, 0.279 mol) were added and the mixture was heated to 100 °C for 15 h with stirring under nitrogen. The green solution was poured into iced hydrochloric acid (10%, 100 cm^3), stirred for 2 h, and extracted with ether (3 x 300 cm^3). The organic layer was dried (magnesium sulfate), filtered and evaporated under reduced pressure to give a green oil. The oil was purified by Kügelrohr distillation; *p*-tolyl ether distilled between 100-115°C at 0.3-0.4 mmHg, while the phenoxathiin (**6**) distilled between 125-150°C at 0.3-0.4 mmHg as a pale yellow oil. Crystallisation gave **6** as a white solid (14.6 g, 35%), mp 69-71 °C (from methanol) (lit.,[19] 73-74 °C); ^{1}H nmr: δ (270MHz) 2.24 (s, 6H, CH_3), 6.84-6.88 (m, 6H, Ar-H); hrms: found 228.06027, calculated for $C_{14}H_{12}OS$; 228.06089.

2,8-Dimethylphenoxathiin-10,10-dioxide (**7**).

2,8-Dimethylphenoxathiin (8.0 g, 0.035 mol) was suspended in a mixture of glacial acetic acid (60 cm^3) and aqueous hydrogen peroxide (30%, 60 cm^3). The suspension was heated to reflux and left stirring for 48 h. More hydrogen peroxide solution (20 cm^3) was added and the solution was heated for a further 3 h. The reaction mixture was diluted with iced water (30 cm^3) to give the sulphone **7** as a white precipitate (8.3 g, 91%), mp 172-175 °C, (Lit. [20] 178 °C); R_F 0.32 (toluene); ir: 1366s (S=O), 1147s (S=O) cm^{-1}; ^{1}H nmr: δ (250MHz) 2.44 (s, 6H, CH_3), 7.24 (d, J = 8.4 Hz, 2H, Ar-H), 7.45 (dd, J = 2.1, 8.4 Hz, 2H, Ar-H), 7.85 (d, J = 1.5 Hz, 2H, Ar-H); hrms: found 260.05183, calculated for $C_{14}H_{12}O_3S$; 260.05072.

2,8-Di(bromomethyl)phenoxathiin-10,10-dioxide (**8b**).

To a refluxing solution of 2,8-dimethylphenoxathiin-10,10-dioxide (3.00 g, 0.012 mol) in tetrachloromethane (65 cm^3) was added *N*-bromosuccinimide (4.10 g, 0.023 mol, 2 *M* excess) portionwise. 3-Chloroperoxybenzoic acid (0.10 g, 0.580 mmol) was added and the mixture was heated under reflux (78-80 °C) for 22 h. The solution was diluted with chloroform (200 cm^3) and washed with sodium bicarbonate solution (10%, 3 x 100 cm^3). The organic layer was separated, dried (magnesium sulfate), filtered, and evaporated under reduced pressure to give the crude product (4.5 g). Recrystallisation from toluene gave **8b** as a white crystalline solid (2.70 g, 56%), mp 198-201°C; ^{1}H nmr: δ (250MHz) 4.54 (s, 4H, -CH_2Br), 7.40 (d, J = 8.6 Hz, 2H, Ar-H), 7.68 (dd, J = 2.2, 8.7 Hz, 2H, Ar-H), 8.07 (d, J = 2.2Hz, 2H, Ar-H); hrms: found 415.87273, calculated for $C_{14}H_{10}O_3S^{79}Br_2$; 415.87174.

Anal. Calcd for $C_{14}H_{10}O_3SBr_2$: C, 40.22; H, 2.41; S, 7.67. Found: C, 40.20; H, 2.31; S, 7.97.

Two alternative major products were formed if the reflux period was changed. These were isolated from the crude product by flash chromatography on silica gel, Kieselgel 60, Merck, 0.040-0.063 using toluene as mobile phase, followed by recrystallisation from toluene, as follows:

2-(Bromomethyl)-8-methylphenoxathiin-10,10-dioxide (**8c**).

This was the first material to be eluted from the column described above and was the major product upon heating under reflux for less than 15 h, mp 150-153 °C (from toluene); ^{1}H nmr: δ (250MHz) 2.45 (s, 3H, CH_3), 4.53 (s, 2H, CH_2Br), 7.28 (d, J = 8.6 Hz, 1H, Ar-H), 7.35 (d, J = 8.7 Hz, 1H, Ar-H), 7.43 (dd, J = 2.1, 8.7 Hz, 1H, Ar-H), 7.66 (dd, J = 2.2, 8.7 Hz, 1H, Ar-H), 7.84 (d, J = 1.8 Hz, 1H, Ar-H), 8.05 (d, J =2.2 Hz, 1H, Ar-H); hrms: found 339.94675, calculated for $C_{14}H_{11}O_3S^{81}Br$; 339.95918.

2,8-Di(dibromomethyl)phenoxathiin-10,10-dioxide (**8a**).

This was the major product from chromatography as above if refluxing more than 30 h, mp 245-248 °C (from toluene). In a typical experiment **7** (4.00 g, 0.017 mol) gave **8a** (5.25 g, 52%); ^{1}H nmr: δ (250MHz) 6.70 (s, 2H, $CHBr_2$), 7.49 (d, J = 8.8 Hz, 2H, Ar-H), 7.99 (dd, J = 2.3, 8.8 Hz, 2H, Ar-H), 8.17 (d, J = 2.3 Hz, 2H, Ar-H); hrms: found 498.75389, calculated for $C_{14}H_8O_3S^{81}Br_3$; 498.76829.

Anal. Calcd for $C_{14}H_8O_3SBr_4$: C, 29.20; H, 1.40; Br, 55.5; S, 5.57. Found: C, 29.36; H, 1.04; Br, 55.94; S, 6.09.

2,8-Di(cyanomethyl)phenoxathiin-10,10-dioxide (**11**).

2,8-Di(bromomethyl)phenoxathiin-10,10-dioxide (**8b**) (5.50 g, 0.013 mol) was added to absolute ethanol (300 cm^3) under reflux in a 500 mL round bottom flask. Potassium cyanide (2.57 g, 0.039 mol, in 50 cm^3 water) was added to the suspension and the mixture was heated under reflux for 3 h with stirring, poured into water (1 L) and extracted with chloroform/methanol (7:3, 3 x 500 cm^3). The organic layers were combined, dried (magnesium sulfate), filtered and evaporated under reduced pressure to yield the crude product as a yellow solid (3.91 g). The product was triturated with hot toluene and filtered to give the desired product as a pink solid (3.59 g, 88%), mp 220-225 °C, R_F=0.66 (toluene/acetone 1:1); ir 2256m (CN), 1147s (S=O), 1287, s (S=O) cm^{-1}; ^{1}H nmr: δ (250MHz) 3.88 (s, 4H, CH_2CN), 7.45 (d, J = 8.7 Hz, 2H, Ar-H), 7.69 (dd, J = 2.2, 8.7 Hz, 2H, Ar-H), 8.03 (d, J = 2.1H z, 2H, Ar-H); hrms: found 310.04231, calculated for $C_{16}H_{10}O_3N_2S$; 310.04121.

2,8-Di(2-aminoethyl)phenoxathiin (**12**).

Dry dioxane (350 cm^3, redistilled) was placed in a 500 mL 3-necked round-bottomed flask. Diisobutylaluminium hydride (1.0 M in toluene, 129 cm^3, 0.129 mol) was added dropwise over 1 h under nitrogen, which was passed through a Dririte apparatus. 2,8-Dicyanomethyl phenoxathiin-10,10-dioxide (**11**, 2.67 g, 8.628 mmol, dissolved in 40 cm^3 dioxane) was added to the reaction mixture dropwise over 30 min. The solution was heated

under reflux for 5 days: a grey precipitate appeared after 3 days. The reaction mixture was left to cool to room temperature, and water was added dropwise under nitrogen until effervescence ceased. The toluene/dioxane layer was separated, partly evaporated, extracted with sodium hydroxide (20%) and the mixture extracted with chloroform (3 x 200 cm^3). The separated aqueous layer was again extracted with chloroform (2 x 300 cm^3). The chloroform extracts were combined, dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the required product as a yellow oil (2.09 g, 85%). The oil was dissolved in a small amount of dry methanol, added dropwise to ethereal hydrogen chloride and the precipitate was collected by filtration to give the amine (**12**) hydrochloride as a pale yellow solid, which was dried *in vacuo*; this material was slightly hygroscopic, mp 202-205°C (from dry methanol). The salt was dissolved in a small amount of methanol, diluted with chloroform and basified with sodium hydroxide (conc.). The free amine was extracted with chloroform (2 x 200 cm^3). The organic extracts were combined, dried (magnesium sulfate), filtered and evaporated to give the base as a yellow oil (1.92 g, 77%). A sample of the oil (0.50 g) was further purified by Kügelrohr distillation. The amine distilled between 240-250 °C at 0.4mmHg as a yellow oil (0.23 g); ir: 3367br (NH) cm^{-1}; ^{1}H nmr: δ (250MHz) 1.62 (br s, 4H, NH_2), 2.59 (t, J = 6.7 Hz, 4H, Ar-CH_2), 2.85 (t, J = 6.7 Hz, 4H, N-CH_2), 6.86-6.89 (m, 6H, Ar-H); hrms: found 286.11358, calculated for $C_{16}H_{18}N_2OS$; 286.11399.

2,8-Diformylphenoxathiin-10,10-dioxide (**9**).

2,8-Di(dibromomethyl)phenoxathiin-10,10-dioxide (**8a**) (22.00 g, 0.038 mol) and ethanol (300 cm^3) were heated to 50 °C in a 500 mL round bottomed flask. To the stirring suspension, a hot solution of silver nitrate (25.96 g, 0.153 mol) in ethanol (100 cm^3) and water (30 cm^3) was added. The yellow mixture was stirred rapidly under reflux for 1 h, cooled to room temperature and diluted with water (100 cm^3). The aqueous layer was extracted with chloroform (3 x 200 cm^3) and the organic layer separated, dried (magnesium sulfate), filtered and evaporated under reduced pressure to yield a pale yellow oil (15.20 g). Crystallisation from chloroform/hexane gave the dialdehyde as a white solid (9.68 g, 88%) mp 185-190°C, R_F=0.37 (ethyl acetate/hexane 1/1); ir: 2860w (C-HO), 1696s (C=O), 1299s (S=O), 1144s (S=O) cm^{-1}; ^{1}H nmr: δ (250MHz) 7.63 (d, J = 8.7 Hz, 2H, Ar-H), 8.25 (dd, J = 1.9, 8.7 Hz, 2H, Ar-H), 8.61 (d, J = 1.9 Hz, 2H, Ar-H), 10.09 (s, 2H, CHO); hrms: found 288.01028, calculated for $C_{14}H_8O_5S$; 288.00925.

2,8-Di(2-nitroethenyl)phenoxathiin-10,10-dioxide (**10**).

To a solution of 2,8-diformylphenoxathiin-10,10-dioxide (**9**) (1.40 g, 4.86 mmol) in methanol (10 cm^3) was added nitromethane (0.742 g, 0.012 mol) and the solution stirred at 0 °C. Potassium hydroxide (6.13 g, 0.109 mol) dissolved in methanol (40 cm^3) was added dropwise over 30 min. The mixture was stirred at 0 °C for another 30 min and poured into hydrochloric acid solution (20%, 200 cm^3). The suspension was allowed to stir overnight in the acidic solution. After 24 h, the yellow suspension formed was filtered to give a yellow solid (2.50 g), which was washed and then triturated with hot ether to give the dinitroethenyl dioxide as a pale yellow solid (1.20 g, 66%), mp >300 °C (decomp.); ir: 1509s (N-O), 1341s (N-O), 1293s (S=O), 1146s (S=O) cm^{-1}; ^{1}H nmr: δ (250MHz) 7.55 (d, J = 8.7 Hz, 2H, Ar-H), 7.64 (d, J = 13.6 Hz, 2H, CH=C*H*-NO_2), 7.87 (dd, J = 2.0, 7.9 Hz, 2H, Ar-H), 8.05 (d, J = 13.6 Hz, 2H, C*H*=CH-NO_2), 8.27 (d, J = 2.0 Hz, 2H, Ar-H); hrms: found 374.02169, calculated for $C_{16}H_{10}N_2O_7S$; 374.02087.

2,8-Di(2-aminoethyl)phenoxathiin (**12**) from 2,8-Di(2-nitroethenyl)phenoxathiin-10,10-dioxide (**10**).

2,8-Di-(2-nitroethenyl)phenoxathiin-10,10-dioxide (2.74 g, 7.31 mmol) was placed in a 3-necked round bottomed flask to which was added distilled dioxane (500 cm^3, dry) and diisobutylaluminium hydride (1.0 *M* in toluene, 109 cm^3, 0.109 mol) dropwise over 1 h under nitrogen. The solution was heated under reflux for 5 days with stirring. The colour of the solution changed from pink to yellow after the initial addition of diisobutylaluminium hydride and persisted for 2 days followed by formation of a grey precipitate on the third day. The reaction mixture was left to cool to room temperature then water was added dropwise under nitrogen until the effervescence ceased. The organic layer was collected and the aqueous layer made strongly basic with sodium hydroxide and extracted with chloroform. The combined chloroform extracts were dried (magnesium sulfate), filtered and evaporated to give a yellow oil (1.60 g), which was dissolved in a small amount of methanol and added dropwise to ethereal hydrogen chloride to give the diamine (**12**) hydrochloride as a pale yellow solid (1.97 g, 75%), identical to the product described above.

2,8-Di-(*N*-formylaminoethyl)phenoxathiin (**13**).

2,8-Di(2-aminoethyl)phenoxathiin (**12**) (2.403 g, 8.39 mmol) was dissolved in hot ethanol (100 cm^3) and ethyl formate (50 cm^3) was added. The reaction mixture was heated under reflux for 24 h with stirring after which time an nmr sample showed some starting material still present in the reaction mixture. Ethanol (10 cm^3) and ethyl formate (10 cm^3) were added and the reaction mixture was heated under reflux for an additional 24 h. The solvent was removed under reduced pressure, and then the mixture was diluted with hydrochloric acid solution (10%, 40 cm^3) and extracted with chloroform (3 x 100 cm^3). The organic layer was dried (magnesium sulfate), filtered, and the solvent removed under reduced pressure to give the required product as a semi-solid yellow material (2.82 g, 98%); R_F = 0.32 (ethyl acetate/methanol 9/1); ir: 3276br (NH), 1660br (C=O) cm^{-1}; ^{1}H nmr: δ (400MHz; 50°C) 2.72 (t, J = 6.8 Hz, 4H, Ar-CH_2), 3.47 (m, 4H, CH_2-N), 6.16 (br s, 2H, NH), 6.96-6.93 (m, 6H, Ar-H), 8.03 (s, 2H, CHO); hrms: found 342.10283, calculated for $C_{18}H_{18}N_2O_3S$; 342.10382.

3,4,8,9-Tetrahydro-13-oxa-6-thia-2,10-diazapentacene (**14**).

Polyphosphoric acid (30.00 g) was added to 2,8-di-(2-formylaminoethyl)phenoxathiin (**13**) (340 mg, 0.994 mmol) and the reaction mixture was heated in a sand bath (200-220 °C) with vigorous stirring for 1 h, allowed to cool to 50 °C then poured into iced sodium hydroxide solution (10%, 500 cm^3) with stirring. The mixture was extracted with chloroform (2 x 200 cm^3) and the organic layer dried (magnesium sulfate), filtered, and evaporated under reduced pressure to yield a brown oil, which solidified upon drying to a glassy solid material with no distinct melting point (0.299 g, 98%). 400MHz nmr showed that the product was a mixture of the *para-para* cyclized isomer (**14**) and the *ortho-para* cyclised isomer (**17**). The integral ratio of the imine proton (-CH=N-) for the two isomers in the mixture was 81:19 respectively in eight experiments. Reverse phase hplc (Hypersil basic deactivated silica, C18 250x4.6 μm column,

mobile phase; A, 0.1 *M* ammonium acetate and ammonium hydroxide (pH=7.4), B, acetonitrile, mixed on line in the ratio 35:65) showed 2 peaks with retention times 13.30 min (23.6%) and 14.26 min (76.4%). Data for the major isomer (**14**)**,** obtained from the mixture, were as follows: ir: 1619s, (C=N) cm^{-1}; ^1H nmr: δ (250MHz) 2.67 (t, J = 7.9 Hz, 4H, Ar-CH_2), 3.75 (m, 4H, CH_2-N), 6.87 (s, 2H, Ar-H), 6.91 (s, 2H, Ar-H), 8.28 (t, J = 2.1 Hz, 2H, CH=N); hrms: found 306.08189, calculated for $C_{18}H_{14}N_2OS$; 306.08268.

3,4-Dihydroisoquinoline.

To *N*-phenethylformamide (4.46 g, 0.029 mol) was added polyphosphoric acid (50.00 g) in a 100 mL round bottom flask. The reaction mixture was heated in a sand bath to 200-220 °C with stirring for 1 h, allowed to cool to 50 °C, then poured into iced sodium hydroxide (10% w/v, 1L) with vigorous stirring. The black mixture was extracted with chloroform (3 x 100 cm^3). The chloroform layer was separated, dried (magnesium sulfate), filtered and evaporated under reduced pressure to give the isoquinoline as a brown oil (3.90 g, 99%), giving the expected ir, nmr and ms data and identical with the product described elsewhere [21].

1-Benzyl-1,2,3,4-tetrahydroisoquinoline (**34**) from 3,4-Dihydroisoquinoline.

To magnesium turnings (0.713 g, 0.029 mol) in a three-necked round-bottomed flask was added tetrahydrofuran (15 cm^3, dry), and iodine (catalytic amount). After 10 minutes, 1-2 drops of 1,2-dibromoethane were added, after which time stirring was continued until the colour of the iodine disappeared (30 min). The mixture was cooled to –10 °C and benzyl chloride (1.445 g, 0.011 mol, in 20 cm^3 of tetrahydofuran) was added dropwise over 1 h. The reaction mixture was cooled to –78 °C and 3,4-dihydroisoquinoline (1.00 g, 7.620 mmol) dissolved in tetrahydrofuran (10 cm^{-3}, dry) was added in over 10 min. Stirring was continued for 3 h at -78 °C and then overnight at room temperature. Water was added and the product was extracted with ether, dried (magnesium sulfate), filtered and evaporated under reduced pressure to give the title compound as a yellow oil (1.620 g). The oil was dissolved in ether (3 cm^3, dry) and poured onto ethereal hydrogen chloride solution. The hydrochloride salt (mp 187-189 °C. Lit. [14] 192 °C) was collected by filtration and washed with dry ether. On basification this salt gave 1-benzyl-1,2,3,4-tetrahydroisoquinoline as a yellow oil (1.250 g, 73%); ir: 3330, broad, (NH) cm^{-1}; ^1H nmr: δ (250MHz) 1.27 (br s, 1H, NH), 2.72-2.99 (m, 4H, 2 x CH_2), 3.19-3.31 (m, 2H, CH_2), 4.23 (dd, J = 3.4, 9.8 Hz, 1H, N-CH), 7.11-7.37 (m, 9H, Ar-H); hrms: found 223.13512, calculated for $C_{16}H_{17}N$; 223.13610.

Benzylation of Mixed 5-Ring Heterocycles (14) and (17) to Give Impure 1,11-Dibenzyl-1,2,3,4,8,9,10,11-octahydro-13-oxa-6-thia-2,10-diazapentacene (19).

3,4,8,9-Tetrahydro-13-oxa-6-thia-2,10-diazapentacene (**14** in a mixture with **17**, obtained as above, 0.190 g, 0.621 mmol) was dissolved in tetrahydrofuran (50 cm^3, dry). Benzylmagnesium chloride (2.0 *M* in tetrahydrofuran, 3 cm^3) was added dropwise at room temperature with stirring. The stirring was continued over night. Water was added dropwise and the solvent was removed at room temperature and then the residue was extracted with chloroform. The organic layer was extracted with acetic acid (5%, 20 cm^3). The acidic layer was collected and basified with concentrated potassium hydroxide to pH 11 and then extracted with chloroform (3 x 50 cm^3). The organic layer was dried (magnesium sulfate) filtered, and the solvent removed under reduced pressure to give the product as a brown solid (0.205 g, 67%). Nmr indicated a mixture of isomers, the major isomer (**19**) and a small amount of (**20**). Attempts were made to separate the isomers but the product oxidised rapidly in solution. Data for the major isomer (**19**) were as follows: ir: 3420br (NH) cm^{-1}; ^1H nmr: δ (250MHz) 1.67 (br s, 2H, NH exch), 2.70-2.98 (m, 8H, CH_2), 3.20-3.27 (m, 4H, CH_2), 4.13 (dd, J = 3.1, 9.4 Hz, 2H, CH-N), 6.85 (s, 2H, Ar-H), 6.91 (s, 2H, Ar-H), 7.15-7.55 (m, 10H, Ar-H); hrms: found 490.21095, calculated for $C_{32}H_{30}N_2OS$; 490.20789. Tlc (basic alumina, methanol) showed three spots at R_F = 0.68 (oxidation product, increasing with time), R_F = 0.55 (presumed to be **20**, minor) and R_F = 0.52 (**19**, major isomer).

1-Phenyl-2-(4′-benzyloxyphenyl)ethanol (**22**).

All glassware and solid starting materials were oven dried before use. Tetrahydrofuran was sodium-dried over night. Benzaldehyde and 1,2-dibromoethane were distilled before use. Magnesium turnings (480 mg, 19.74 mmol) were placed in a 3-necked flask fitted with a reflux condenser in a closed system filled with dry, deoxygenated nitrogen. Tetrahydrofuran (8 cm^3) was added to cover the magnesium surface followed by a few crystals of iodine and the flask was kept undisturbed for 10 minutes. After the stirring was started a few drops of 1,2-dibromoethane were added. Stirring was continued at room temperature until the colour of the iodine disappeared (10 min). The flask was heated to 50 °C to initiate the reaction then cooled to -10 °C to control the vigorous reaction. After 30 min, benzyloxybenzyl chloride (1.200 g, 5.146 mmol) dissolved in tetrahydrofuran (20 cm^3) was added dropwise over a period of 1 h with vigorous stirring at a temperature ranging from -10 to -15 °C. Stirring was maintained for a further 30 min. at -10 °C. The flask was cooled to -78 °C before adding benzaldehyde (544 mg, 5.126 mmol, dissolved in 10 cm^3 of tetrahydrofuran). The mixture was stirred for an additional 4 h at -78 °C after which time it was left stirring overnight at room temperature. The reaction was quenched with ammonium chloride solution, stirred for 3 h then extracted with ether. The ether layer was washed with water (60 cm^3), dried (magnesium sulfate), filtered and the solvent was removed under reduced pressure to give a semi-solid yellow material (2.540 g). The crude product was triturated with hexane/chloroform (3:1, 2 x 20 cm^3) to remove residual benzaldehyde. Recrystallization from chloroform/ether gave the phenylethanol (**22**) as white crystals (0.560 g, 36%), mp 136-140 °C, R_F = 0.26 (hexane/ethyl acetate 3:1); ir: 3311br (OH) cm^{-1}; ^1H nmr: δ (250MHz) 2.47 (br s, 1H, OH**,** D_2O exch.), 2.94 (dd, J = 3.2, 14.3 Hz, 1H, CH_2-C*H*), 3.25 (dd, J = 9.8, 14.3 Hz, 1H, CH_2-C*H*), 4.82 (dd, J = 3.4, 9.8 Hz, 1H, CH_2-C*H*), 4.97 (s, 2H, OCH_2), 6.91 (dd, J = 2.7, 8.4 Hz, 2H, O-Ar-H), 7.23 (dd, J = 2.3, 8.2 Hz, 2H, O-Ar-H), 7.27-7.43 (m, 10H, Ar-H); hrms: found 304.14575, calculated for $C_{21}H_{20}O_2$; 304.14633. The phenylethanol (**22**) decomposed in solution, for example if chloroform solutions were stored overnight.

1,2,3,4-Tetrahydroisoquinoline (**27**).

3,4-Dihydroisoquinoline (3.00 g. 0.038 mol) was dissolved in absolute ethanol (60 cm^3). Sodium borohydride (1.44 g, 0.038 mol) was added and the mixture was heated under reflux at 90 °C

for 1 h, after which time it was left overnight at room temperature. Ethanol was removed under reduced pressure, and the residue was extracted with ether (2 x 100 cm^3). The organic layer was washed with water, dried (magnesium sulfate), filtered and the solvent was removed under reduced pressure to give the desired product as a brown oil (4.510 g, 89%), identical with the material described previously [13,14,22]; ir: 3400-3200br (NH) cm^{-1}; ^1H nmr: δ (250MHz) 1.71 (s, 1H, NH), 2.78 (t, J = 6.1 Hz, 2H, Ar-C*H*$_2$-CH_2-N), 3.12 (t, J = 6.1 Hz, 2H, Ar-CH_2-C*H*$_2$-N), 3.99 (s, 2H, Ar-CH_2-NH), 6.98-7.16 (m, 4H, Ar-H); hrms: found 133.08956, calculated for $C_9H_{11}N$; 133.08915.

N-Benzoyl-1,2,3,4-tetrahydroisoquinoline (28).

To a solution of tetrahydroisoquinoline (**27**, 10.00 g, 0.075 mol) in pyridine (50 cm^3, dry) at 0 °C was added benzoyl chloride (15.80 g, 0.115 mol) over 1 h. After an additional 3 h at 0 °C, the mixture was filtered. The filtrate was evaporated under reduced pressure, and the residue was dissolved in dichloromethane and extracted with water (50 cm^3). The organic layer was then washed with sodium hydroxide solution (1 *M*, 2 x 20 cm^3), hydrochloric acid (10%, 2 x 10 cm^3) and brine (40 cm^3). The organic layer was dried (magnesium sulfate), filtered and evaporated under reduced pressure to give a brown oil (17.04 g). The crude product was purified by flash chromatography using a silica gel column and eluted with *n*-hexane/ethyl acetate (1:1). The product was obtained as a thick yellow oil, which crystallized from ethanol to give the *N*-benzoyltetrahydroisoquinoline as a pale yellow solid (9.63 g, 54%), R_F = 0.65 (hexane/ethyl acetate 1:1), mp 127-129°C. {Lit. [23] 126-128°C}; ir: 1630s (C=O) cm^{-1}; ^1H nmr: δ (250MHz), (2 conformers at R.T.) 2.88 (br t, J = 6.2 Hz, 2H, Ar-CH_2-CH_2-N), 3.64 (br s, 1.32H, Ar-CH_2-CH_2-N), 3.99 (br s, 0.67H, Ar-CH_2-CH_2-N-), 4.59 (br s, 0.66H, Ar-CH_2-NH), 4.91 (br s, 1.34H, Ar-CH_2-NH), 7.17-7.30 (m, 4H, Ar-H), 7.44-7.58 (m, 5H, Ar-H); ^1H nmr: δ (400MHz; DMSO-d_6), (1 conformer, 87°C) 2.90 (t, J = 6.2 Hz, 2H, Ar-C*H*$_2$-CH_2-N), 3.69 (t, J = 5.9 Hz, 2H, Ar-CH_2-C*H*$_2$-N), 4.68 (s, 2H, Ar-CH_2-NH), 7.13-7.19 (m, 4H, Ar-H), 7.41-7.48 (m, 5H, Ar-H); ^{13}C nmr: δ_C (100MHz; DMSO-d_6, 57°C) 27.6 (CH_2CH_2N), 28.7 (CH_2CH_2N), 44.6 ($ArCH_2N$), 127.0, 127.1, 127.3, 127.6, 129.3, 129.5, 130.4, 134.0, 135.3 and 137.2 (C_6H_4 and C_6H_5), 170 (C=O); hrms: found 237.11760, calculated for $C_{16}H_{15}NO$; 237.11536.

N-Pivaloyl-1,2,3,4-tetrahydroisoquinoline (**31**).

To a solution of 1,2,3,4-tetrahydroisoquinoline (**27**, 20.00 g, 0.150 mol) in pyridine (100 cm^3, dry) at 0 °C was added pivaloyl chloride (27.16 g, 0.225 mol) over 10 min. After an additional 3 h at 0 °C, the solution was taken up with dichloromethane, extracted with dilute hydrochloric acid (7%, 40 cm^3) and extracted 3 times with dichloromethane. The organic layer was washed sequentially with sodium hydroxide (1 *M*, 2 x 50 cm^3), hydrochloric acid (10%, 2 x 50 cm^3) and brine (50 cm^3). The organic layer was dried (magnesium sulfate), filtered and evaporated under reduced pressure to give the crude product as a semi-solid material (37.34 g). Crystallization from hexane gave the amide (**31**) as white crystals (28.78 g, 88%), mp 67-69°C (Lit., [13,22] 65°C); ir: 1623s, (C=O) cm^{-1}; ^1H nmr: δ (250MHz) 1.31 (s, 9H, t-Bu-H), 2.87 (t, J = 5.9 Hz, 2H, Ar-CH_2-CH_2-N), 3.85 (t, J =5.8 Hz, 2H, Ar-CH_2-CH_2-N), 4.76 (s, 2H, Ar-CH_2-N), 7.14-7.22 (m, 4H, Ar-H); hrms: found 217.14716, calculated for $C_{14}H_{19}NO$; 217.146664.

1-(4-Benzyloxybenzyl)-2-benzoyl-1,2,3,4-tetrahydroisoquinoline (**30**).

To 100 cm^3 of dry tetrahydrofuran was added diisopropyl amine (2.79 g, 3.6 cm^3, 27.65 mmol) and n-butyl lithium (2.5 M in hexane, 10.16 cm^3) at -80 °C under nitrogen. The mixture was stirred for 20 min at -80 °C, then *N*-benzoyltetrahydroisoquinoline (**28**, 2.00 g, 8.43 mmol, in 20 cm^3 of tetrahydrofuran) was added over 5 min, giving a purple-blue intermediate. After 2 h at -78 °C, 4-benzyloxybenzyl chloride (1.96 g, 8.43 mmol) was added in 10 cm^3 of tetrahydrofuran. The reaction mixture was left stirring for 5 h at -80 °C, after which time it was left stirring overnight at room temperature. Ammonium chloride solution (20 cm^3, saturated) was added and the solution was allowed to warm to room temperature. The reaction mixture was extracted with ether (200 cm^3), the organic layer was separated, washed with brine (50 cm^3) dried (magnesium sulfate), filtered and the solvent was removed under reduced pressure to give a brown oil (3.76 g). ^1H nmr of the crude product showed the desired 1-(4-benzyloxybenzyl)-2-benzoyl-1,2,3,4-tetrahydroisoquinoline to be a minor component in the mixture. Sufficient was separated for nmr, using hplc (Si60 semi-prep, hexane/ethyl acetate (70/30), 6 ml/min); the required material (**R_T** 7.7 min) constituted 10% of the mixture. No attempt was made to collect this product on a large scale; ^1H nmr: δ (400MHz, 57°C) 2.63 (m, 1H, Ar-C*H*$_2$-CH_2-N), 2.91-4.12 (m, 1H, Ar-C*H*$_2$-CH_2-N), (m, 1H, Ar-CH_2-C*H*$_2$-N) and 4.18 (m, 1H, Ar-CH_2-C*H*$_2$-N), 5.09 (s, 2H, OCH_2), 6.39 (t, J = 6.4 Hz, 1H, CH-N), 7.0-7.51 (m, 18H, Ar-H); ms: found 433.11, calculated for $C_{30}H_{27}NO_2$; 433.20.

Lithiation/alkylation of *N*-Acyltetrahydroisoquinolines.

General Procedure.

Note: quantities are given separately for each preparation.

To a cooled solution of the amide and tetramethylethylene diamine in tetrahydrofuran (50 cm^3) was added *t*-butyllithium (1.7 *M* in pentane). The resulting deep-red solution was stirred for 20 min at -78 °C before adding the electrophile dissolved in tetrahydrofuran. After stirring (as described below), the solution was treated with water and warmed to room temperature. The mixture was poured into water and extracted with chloroform (3 x 150 cm^3, unless otherwise indicated). The combined organic layers were collected, washed with water, dried (magnesium sulfate) and the solvent was removed under reduced pressure to give the crude product, which was purified by chromatography or recrystallization or by a combination of both. The components of each experiment carried out were separated using np-hplc (as described individually, below).

1-Benzyl-2-benzoyl-1,2,3,4-tetrahydroisoquinoline (**29**).

Amide: *N*-benzoyl-1,2,3,4-tetrahydroisoquinoline (**28**, 3.48 g, 14.7 mmol); tetramethylethylenediamine (2.2 cm^3, 1.69 g, 14.70 mmol); *t*-butyllithium (8.65 cm^3); benzyl chloride, (1.86 g, 17.7 mmol, in tetrahydrofuran 10 cm^3); stirred for 24 h at -78 °C. A blue-purple colour persisted for 5 h. After work-up as above, the crude yellow oil (4.47 g) was purified using hplc (semi-prep Si60 column, hexane/ethyl acetate 70/30). One major peak (R_T 16.8 min) was collected and evaporation gave a sticky semi-solid, identified as the benzylbenzoylisoquinoline (**29**, 2.63 g, 55%); ir: 1631s (C=O) cm^{-1}; ^1H nmr: δ (400MHz), (2 conformers, R.T) 2.58-2.95 (m, 2H), 3.16-3.36 (m, 2H), 3.43-4.91 (comprising signals at 3.43-3.66, m and 4.91, m with a combined integral of 2H),

6.07 (t, J = 6.8 Hz, 1H, CH-N), 6.68 (d, J = 7.2 Hz, 1H, Ar-H), 6.92 (d, J =7.5 Hz, 1H, Ar-H), 7.11-7.37 (m, 12H, Ar-H). hrms: found 328.16983, calculated for $C_{23}H_{22}NO$; 328.17014. This compound has been reported to be an oil, from an alternative synthesis [24].

1-Benzyl-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline (**32**).

Amide: *N*-pivaloyl-1,2,3,4-tetrahydroisoquinoline, (**31**, 1.74 g, 8.00 mmol); tetramethylethylenediamine (1.2 cm^3, 8.00 mmol, 0.929 g); t-butyllithium (4.94 cm^3, 8.40 mmol); benzyl chloride (1.012 g, 8.00 mmol, in 5 cm^3 tetrahydrofuran) stirred for 2 h at -78 °C. A deep red colour persisted for 20 min. After work-up as above, the crude yellow semi-solid (2.722 g) was recrystallized from ether/hexane to give **32** as a white solid, mp 98-100 °C, [lit. [14] 101 °C] (1.69 g, 69%); ir: 1614s (C=O) cm^{-1}; ^{1}H nmr: δ (250MHz) 1.20 (s, 9H, t-Bu**),** 2.68-2.76 (dt, J = 3.3H z, 1H, Ar-C*H*$_2$-CH_2-N), 2.88-3.01 (m, 1H, Ar-C*H*$_2$-CH_2-N), 3.11 (d, J = 6.7 Hz, 2H, Ph-CH_2), 3.33-3.54 (m, 1H, Ar-CH_2-C*H*$_2$-N), 4.17 (br s,1H, Ar-CH_2-C*H*$_2$-N), 5.85 (t, J =6.7 Hz, 1H, CH-N), 6.91-6.94 (d, J = 7.2 Hz, 1H, Ar-H), 7.10-7.29 (m, 8H, Ar-H); hrms: found 308.20137, calculated for $C_{21}H_{26}NO$; 308.20144.

Anal. Calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.77; H, 7.92; N, 4.88.

1-(4-Benzyloxybenzyl)-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline (**33**).

Amide: *N*-pivaloyl-1,2,3,4-tetrahydroisoquinoline (**31**, 1.74 g, 8.00 mmol); tetramethylethylenediamine (1.2 cm^3, 8.00 mmol, 0.93 g); t-butyllithium (5.0 cm^3, 8.40 mmol, 1.07 *M* excess); benzyloxybenzyl chloride (1.86 g, 8.00 mmol, in 10 cm^3 tetrahydrofuran); stirred for 2 h at -78 °C. A deep red colour persisted for 15 min. Work-up as above gave a yellow oil (2.99 g) which was crystallised from ether/hexane to give **33** as fine white crystals (3.15 g, 95%) mp 121-122 °C (Lit. [25] 121-122°C); ir: 1611s (C=O) cm^{-1}; ^{1}H nmr: δ (250MHz; 20°C) 1.21 (s, 9H, t-Bu), 3.11 (d, J =6.9 Hz, 2H, Ph-CH_2), 2.68-3.51 (m, 2H, Ar-C*H*$_2$-CH_2-N and m, 1H, Ar-CH_2-C*H*$_2$-N), 4.14 (br s,1H, Ar-CH_2-C*H*$_2$-N), 5.05 (s, 2H, OCH_2), 5.83 (br s, 1H, CH-N), 6.85-7.46 (m, 13H, Ar-H); ^{1}H nmr: δ (400MHz; 57 °C) 1.23 (s, 9H, t-Bu), 2.69-2.73 (ddd, J = 3.3, 3.9, 16.1 Hz, 1H, Ar-C*H*$_2$-CH_2-N), 2.90-2.98 (ddd, J = 5.6, 13.7, 16.1 Hz, 1H, Ar-C*H*$_2$-CH_2-N), 3.11 (d, J = 6.7 Hz, 2H, Ph-CH_2), 3.34-3.42 (ddd, J = 3.9, 13.7, 15.6 Hz, 1H, Ar-CH_2-C*H*$_2$-N), 4.18 (br d, J = 14.3 Hz,1H, Ar-CH_2-C*H*$_2$-N), 5.06 (s, 2H, OCH_2), 5.81 (t, J = 6.7 Hz, 1H, CH-N), 6.85 (dd, J = 2.8, 8.6 Hz, 2H, Ar-H), 6.94 (dd, J = 2.2, 7.6 Hz, 1H, Ar-H), 7.05 (dd, J = 2.2, 8.5 Hz, 2H, Ar-H), 7.10-7.18 (m, 3H, Ar-H), 7.31-7.45 (m, 5H, Ar-H).

Anal. Calcd for $C_{28}H_{31}NO_2$: C, 81.33; H, 7.56; N, 3.39. Found: C, 81.06; H, 7.42; N, 3.32.

1-(4-Hydroxybenzyl)-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline (**35**).

A mixture of 1-benzyloxybenzyl-2-pivaloyl-tetrahydroisoquinoline (**33**, 0.200 g, 4.84 mmol), concentrated hydrochloric acid solution (20 cm^3), and absolute ethanol (30 cm^3) was heated at 80 °C overnight. The mixture was kept stirring overnight under a nitrogen atmosphere. Water (20 cm^3) was added and ethanol was evaporated under reduced pressure. The residue was taken up in chloroform, then dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give the crude hydroxybenzylisoquinoline as a yellow gum (0.236 g), which was crystallized from ether/hexane to give the title compound as white crystals (85 mg, 54%), R_F = 0.34 (chloroform/ether 3/1), mp 227-229 °C; ir: 3291, br (OH), 1604s (C=O) cm^{-1}; ^{1}H nmr: δ (400MHz) 1.23 (s, 9H, t-Bu), 3.06 (d, J = 6.4 Hz, 2H, Ph-CH_2), 2.73-2.77 (m, 1H, Ar-C*H*$_2$-CH_2-N), 2.94-3.01 (m, 1H, Ar-C*H*$_2$-CH_2-N), 3.44-3.51 (m, 1H, Ar-CH_2-C*H*$_2$-N), 4.21 (br s, 1H, Ar-CH_2-C*H*$_2$-N), 5.84 (br s, 1H, CH-N), 5.97 (br s, 1H, OH, D_2O exch.), 6.98 (d, J = 8.4 Hz, 2H, Ar-H), 6.96 (d, J = 7.0 Hz, 1H, Ar-H), 7.03 (d, J = 8.4 Hz, 2H, Ar-H), 7.10-7.18 (m, 3H, Ar-H); hrms: found 323.18864, calculated for $C_{21}H_{25}NO_2$; 323.18853.

Removal of the *N*-Pivaloyl Group from 1-Benzyl-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline (**32**) to Give 1-Benzyl-1,2,3,4-tetrahydroisoquinoline (**34**).

A solution of 1-benzyl-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline (**32**, 3.28 g, 10.68 mmol) in hydrochloric acid (2.0 *M*, 30 cm^3) was heated under reflux for 24 h. The mixture was cooled in an ice bath, ether (200 cm^3) was added and the solution was made alkaline with potassium hydroxide pellets (pH 11). The mixture was extracted with ether (3 x 100 cm^3), dried (magnesium sulfate), filtered and evaporated under reduced pressure to give an oil (1.92 g). The oil was poured into ethereal hydrogen chloride solution, and the salt was collected by filtration and washed with ether (40 cm^3). The solid was basified and extracted with chloroform to give the 1-benzyl tetrahydroisoquinoline (**34**, 0.852 g, 36%) as a yellow oil, identical with the compound described above.

1-(4-Benzyloxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**36**).

To a solution of *N*-pivaloyl-1-(4-benzyloxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**33**, 300 mg, 0.725 mmol, in 20 cm^3 of dry tetrahydrofuran) stirred at 0 °C was added a solution of sodium aluminium hydride (78 mg, 1.450 mmol, 2.5 *M* excess, in 25 cm^3 of dry tetrahydrofuran). The mixture was allowed to warm slowly to room temperature, and then heated under reflux for 90 h under nitrogen. The reaction mixture was left for two more days at room temperature; water (20 cm^3) was added followed by ether (100 cm^3). The basic products were extracted with dilute hydrochloric acid (2 *M*, 100 cm^3), separated, rebasified with potassium hydroxide solution (10%, w/v) and extracted with chloroform (3 x 150 cm^3). After drying (magnesium sulfate) and removal of the solvents under reduced pressure, the benzyloxybenzylisoquinoline was obtained as a pale yellow oil (105 mg, 44%), R_F = 0.61 (ethyl acetate/n-hexane, 1:1); ir: 3332w (NH) cm^{-1}; ^{1}H nmr: δ_H (250MHz; $CDCl_3$) 1.87 (1H, br, NH, D_2O exch.), 2.81-2.98 (4H, m, CH_2), 3.21-3.25 (2H, m, CH_2), 4.16 (1H, dd, *J* 3.3, 9.8Hz, CH-N), 5.07 (2H, s, OCH_2), 6.94 (2H, d, *J* 7.6Hz, Ar-H), 7.11-7.47 (11H, m, Ar-H); hrms: found 329.17705, calculated for $C_{23}H_{23}NO$; 329.17796. This compound oxidised very rapidly when exposed to air.

1,2,3,4,8,9,10,11-Octahydro-13-oxa-6-thia-2,10-diazapentacene (**23**),

3,4,8,9-Tetrahydro-13-oxa-6-thia-2,10-diazapentacene (**14**), in a mixture with **17** (*ca* 20%) and a possible trace of **18** (see above), (0.570 g, 1.86 mmol) was dissolved in absolute ethanol (50 cm^3). An excess of sodium borohydride (0.211 g, 5.58 mmol) was added very carefully. The reaction mixture was heated under reflux for 1 h and left stirring overnight at 80 °C. The solvent was evaporated under reduced pressure and the solid material was dissolved in chloroform (100 cm^3) and washed with water. The water

layer was collected and extracted again with chloroform (3 x 100 cm^3). The organic layers were combined, dried (magnesium sulfate), filtered and evaporated to yield a brown gum (0.496 g, 86%). ^1H nmr showed a mixture of two isomers, with an integral ratio of 80:20 based on the Ar-C*H*$_2$-NH protons. A sample (50 mg) was taken and the two isomers were separated for identification on a basic alumina preparative tlc plate using ethyl acetate/methanol (1:9). The system showed two spots with one compound being major. The major spot, with R_F = 0.67, was collected as a brown gum (30 mg) and shown to be the linear isomer (**23**), from reduction of **14**. Less than 5 mg of the isomer from reduction of **17**, 1,2,3,4,9,10,11,12-octahydro-7-oxa-14-thia-2,10-diazabenzo[*a*]naphthacene, was obtained in this experiment. It was observed that the crude mixture was undergoing rapid oxidative decomposition; therefore it was taken directly to the next stage. Data for the linear isomer 1,2,3,4,8,9,10,11-octahydro-13-oxa-6-thia-2,10-diazapentacene: ir: 3302br (NH) cm^{-1}; ^1H nmr: δ (250MHz) 1.67 (br s, 2H, NH), 2.67 (t, J = 6.4 Hz, 4H, Ar-C*H*$_2$-CH$_2$-N), 3.09 (t, J = 5.9 Hz, 4H, Ar-CH$_2$-C*H*$_2$-N), 3.92 (s, 4H, Ar-CH$_2$-NH), 6.63 (s, 2H, Ar-H), 6.81 (s, 2H, Ar-H); hrms: found 310.11131, calculated for $C_{18}H_{18}N_2OS$; 310.11399.

1-[10-(2,2-Dimethylpropanoyl)-3,4,8,9,10,11-hexahydro-1*H*-13-oxa-6-thia-2,10-diazapentacene-2-yl]-2,2-dimethylpropan-1-one (**24**).

To a solution of **23** (in a mixture with its minor isomer (see above)) (0.496 g, 1.599 mmol) in pyridine (10 cm^3) at 0 °C was added 3 *M* excess of pivaloyl chloride (0.578 g, 4.79 mmol, in 2 cm^3 of pyridine) over 10 min. The mixture was stirred for 3 h at 0 °C, taken up in chloroform (200 cm^3) and washed with dilute hydrochloric acid (7%, 3 x 100 cm^3). The organic layer was washed with sodium hydroxide solution (1 *M*, 2 x 40 cm^3), hydrochloric acid (10%, 2 x 40 cm^3), brine (40 cm^3), dried (magnesium sulfate), filtered and evaporated under reduced pressure to give a brown oil, which solidified upon drying (0.626 g, 82%). ^1H nmr showed 2 peaks in the ratio of 77:23, based on the Ar-C*H*$_2$-N protons. Normal phase hplc (analytical scale Hypersil 5 silica (250x4.60mm) column, 0.5 mg/ml sample conc., 2 ml/min flow rate, and hexane/ethyl acetate (70:30) as mobile phase) showed 3 peaks running close to each other in the ratio of 65:30:5, representing 3 isomers. Three fractions (R_T = 41, 43, 47 min) were collected by repeated use of a semi-prep column (Si60 silica, 6ml/min flow rate, 5mg/ml concentration, and hexane/ethyl acetate (70:30) as mobile phase). Ms showed that the first two fractions (at 41 and 43 minutes) were product isomers but ^1H nmr did not give good spectra. Further hplc investigation revealed that new peaks were appearing and the old fractions disappearing, indicating that the product was decomposing. The major isomer was separated on a flash silica column using ethyl acetate/hexane (1:1) as mobile phase. Sufficient **24** was obtained for identification; ir: 1627s (C=O) cm^{-1}; ^1H nmr: δ (250MHz) 1.32 (s, 18H, t-Bu), 2.78 (t, J = 5.5 Hz, 4H, Ar-C*H*$_2$-CH$_2$-N), 3.82 (t, J = 5.7 Hz, 4H, Ar-CH$_2$-C*H*$_2$-N), 4.67 (s, 4H, Ar-CH$_2$-N), 6.77 (s, 2H, Ar-H), 6.86 (s, 2H, Ar-H); hrms: found 478.22999, calculated for $C_{28}H_{34}N_2O_3S$; 478.22901. During the process of purification, new spots appeared on tlc (silica, ethyl acetate/hexane 1:1).

Attempted Synthesis of 1-[1,11-Bis-(4-benzyloxybenzyl)-10-(2,2-dimethylpropanoyl)-3,4,8,9,10,11-hexahydro-1*H*-13-oxa-6-thia-2,10-diazapentacene-2-yl]-2,2-dimethylpropan-1-one (**25**).

The *N*-pivaloyl pentacycle (**24**) and benzyloxybenzyl chloride were dried under high vacuum at room temperature for 12 h. Tetramethylethylenediamine was redistilled. *t*-Butyl lithium was from a freshly opened bottle. Tetrahydrofuran was dried and degassed before use. Glassware was dried in an oven overnight. The nitrogen was oxygen free and was passed throughout the experiment through a Dririte apparatus. The reaction was conducted in a very dry environment in a closed system. To a cooled solution (-78 °C) of **24**, obtained as described above (0.400 g, 0.836 mmol) and tetramethylethylenediamine (0.252 cm^3, 1.67 mmol, 2 *M* excess) in tetrahydrofuran (30 cm^3) was added *t*-butyl lithium (0.983 cm^3, 2.07 *M* excess, 1.7 *M* in pentane) under nitrogen. The deep red solution was stirred at –78 °C for 20 min before adding benzyloxybenzyl chloride (0.388 g, 1.67 mmol, in 15 cm^3 of tetrahydrofuran) dropwise over 1 h. The deep red colour persisted for 30 min after adding the benzyloxybenzyl chloride. The mixture was stirred at -78 °C for 10 h then left for 38 h at room temperature. Water (6 cm^3) was added cautiously to the reaction mixture and the solvent removed under reduced pressure. The residue was shaken with water (100 cm^3) and the products extracted with chloroform (3 x 100 cm^3). The organic layer was washed with water and brine, dried (magnesium sulfate), filtered and evaporated under reduced pressure to yield a brown solid (1.232 g). Tlc on silica (ethyl acetate/hexane, 1:1) showed a spot, R_F = 0.64, that was different from starting material and appeared orange-red upon spraying with vanillin-sulphuric acid. A very dense spot appeared at R_F = 0.0. Lc-ms was used to investigate a small sample of the crude product (5 mg), using a Luna 3μ C18 column in a Thermoquest Automass multi gc/lc-ms with electrospray. With a flow rate throughout of 0.6 ml/min, the solvents used were A: acetonitrile/water (70:30) B: acetonitrile. Elution started with system A for five min, then gradient mixing started between solvents A and B for 20 min, until 100% B, which was continued for 10 min. The lc-ms chromatogram showed 6 major peaks. The mass corresponding to each peak was determined using the selective ion tracing technique, in each case as the sodium adduct, and showed a mass corresponding to **25** at R_T = 23.97 min, M^+ 894. Direct crystallization (chloroform/methanol (50:50)) from the crude reaction mixture (1.232 g) gave *N,N′*-bis-(4-benzyloxybenzyl)-*N,N,N′,N′*-tetramethylethane-1,2-diammonium chloride (23 mg) as white crystals, mp 232-233 °C: ^1H nmr: δ (250MHz; CD_3OD) 3.14 (s, 12H, N^+-(C*H*$_3$)$_4$), 4.03 (s, 4H, N^+-C*H*$_2$-C*H*$_2$-N^+), 4.63 (s, 4H, Ar-C*H*$_2$-N^+), 5.12 (s, 4H, OCH$_2$), 7.14 (d, J = 8.6 Hz, 4H, Ar-H), 7.25-7.45 (m, 10H, Ar-H), 7.57 (d, J = 8.6 Hz, 4H, Ar-H); hrms (fab): found 511.33105 (MH^+-Cl_2, 50%), calculated for $C_{34}H_{43}N_2O_2$; 511.33245. ^1H nmr of the remaining crude product at this stage showed distinctive, dominant peaks for *N*-(4-benzyloxybenzyl)-*N*-(*N′,N′*-dimethylamino)ethane-*N,N*-dimethylammonium chloride, which was the major product in the nmr spectrum of the crude material, ^1H nmr: δ_H (250MHz; $CDCl_3/CD_3OD$) 2.22 (s, 6H, N-(CH$_3$)$_2$), 2.74 (br s, 2H, N^+-CH$_2$-C*H*$_2$-N), 3.24 (s, 6H, N^+-(CH$_3$)$_2$), 3.78 (br s, 2H, N^+-C*H*$_2$-CH$_2$-N), 5.07 (s, 2H, Ar-CH$_2$-N^+) and (s, 2H, OCH$_2$), 6.95 (d, J = 8.6 Hz, 2H, Ar-H), 7.27-7.36 (m, 5H, Ar-H), 7.55 (d, J = 8.6 Hz, 2H, Ar-H); ms(fab): found 313 (M^+-Cl, 100%), calculated for $C_{20}H_{29}N_2O$; 313. The crude mixture (1.199 g) was further separated by flash chromatography using ethyl acetate/hexane (1:1). Three fractions were collected, each of which gave an orange-pink colour on tlc (silica, ethyl acetate/hexane 1:1) when

sprayed with vanillin/sulphuric acid. The first of these (R_F = 0.81, 35 mg) was a mixture of unidentified, probably oxidised material. The second fraction (R_F = 0.65, 73 mg, 13%) gave nmr spectra consistent with the required product (**25**) as the major constituent, ^{1}H nmr: δ (250MHz) 1.23 (s, 18H, t-Bu), 2.59-3.20 {10H (m, 2H, Ar-C*H*$_{2eq}$-CH$_2$-N), (m, 2H, Ar-C*H*$_{2ax}$-CH$_2$-N), (m, 4H, Ph-CH$_2$) and (m, 2H, Ar-CH$_2$-C*H*$_{2ax}$-N)}, 4.19 (m, 2H, Ar-CH$_2$-C*H*$_{2eq}$-N), 5.05 (s, 4H, OCH$_2$), 5.78 (br s, 2H, Ar-CH-N), 6.65-7.42 (m, 22H, Ar-H). The third fraction (R_F = 0.5, 55 mg, 7%) was impure mono-substituted compound (**26**); ^{1}H nmr: δ (250MHz) 1.25 (s, 9H, t-Bu), 1.35 (s, 9H, t-Bu), 2.80 (t, 2H, Ar-C*H*$_2$-CH$_2$-N), 2.52-3.23 (5H (m, 1H, Ar-C*H*$_{2eq}$-CH$_2$-N), (m, 1H, Ar-C*H*$_{2ax}$-CH$_2$-N), (m, 2H, Ph-CH$_2$) and (m, 1H, Ar-CH$_2$-C*H*$_{2ax}$-N)), 3.83 (t, J = 5.7 Hz, 2H, Ar-CH$_2$-C*H*$_2$-N), 4.21 (m, 1H, Ar-CH$_2$-C*H*$_{2eq}$-N), 4.69 (s, 2H, Ar-CH$_2$-N), 5.05 (s, 2H, OCH$_2$), 5.75 (br s, 1H, Ar-CH-N), 6.81-7.42 (m, 13H, Ar-H); hrms(fab): found 675.32127, calculated for $C_{42}H_{47}N_2O_4S$; 675.32566.

3,4′-Diformyldiphenyl Ether (**37**).

All starting materials and glassware were oven dried (110 °C) before use. In a 500 ml three necked flask, 4-bromobenzaldehyde (12.64 g, 68 mmol) was added to a mixture of 3-hydroxybenzaldehyde (9.36 g, 76 mmol) and potassium carbonate (10.59 g, 76 mmol). To the mixture, tris[2-(methoxyethoxy)ethyl]amine (2.46 g, 7.60 mmol) and copper (I) chloride (0.87 g, 8.80 mmol) were added in pyridine (100 cm^3, dry). Molecular sieve (10.0 g, 4 Å) was added. The reaction mixture was heated under reflux with stirring for 96 h under nitrogen. Excess pyridine was distilled off and the remaining slurry was poured into iced hydrochloric acid (100 cm^3) and extracted with ether. The organic layer was washed with sodium hydroxide (20% w/v, 3 x 50 cm^3), dried (magnesium sulfate), filtered and evaporated under reduced pressure to give a brown oil (13.70 g). The crude oil was purified using Kügelrohr distillation. The oil, which distilled between 150-160 °C at 0.5-0.7 mmHg, crystallised from ether to give the diformyl ether as a yellow solid (7.50 g, 49%), mp 59-62 °C; ir: 2840m (CHO), 1681s (C=O) cm^{-1}; ^{1}H nmr: δ (250MHz) 7.11 (dd, J = 1.9, 9.3 Hz, 2H, Ar-H), 7.37 (ddd, J = 1.97, 2.5, 8.0 Hz, 1H, Ar-H), 7.57 (m, 2H, Ar-H), 7.73 (ddd, J = 1.9, 2.4, 7.5 Hz, 1H, Ar-H), 7.91 (dd, J = 2.4, 9.2 Hz, 2H, Ar-H), 9.95 (s, 1H, CHO), 10.01 (s, 1H, CHO); hrms: found 226.06210, calculated for $C_{14}H_{10}O_3$; 226.06299.

Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.32; H, 4.46. Found: C, 74.14; H, 4.58.

3,4′-Di(hydroxymethyl)diphenyl Ether (**38**).

3,4′-Diformyldiphenyl ether (**37**, 6.67 g, 0.029 mol) was dissolved in ethanol (50 cm^3) in a 100 ml round bottom flask and stirred at 0 °C. Sodium borohydride (3.33 g, 0.088 mol) was added portionwise and the mixture was stirred for 24 h. Ethanol was evaporated to dryness under reduced pressure and the mixture dissolved in glacial acetic acid (50 cm^3), poured into iced water (300 cm^3) and extracted with chloroform (300 cm^3). The chloroform layer was washed with sodium hydroxide (20% w/v, 100 cm^3), dried (magnesium sulfate), filtered and evaporated under reduced pressure to give **38** as a white solid (4.697 g, 70%) mp 84-86 °C (from ether); ir: 3397-3207br (OH) cm^{-1}; ^{1}H nmr: δ (250MHz) 4.65 (s, 2H, C*H*$_2$OH), 4.67 (s, 2H, C*H*$_2$OH), 6.95 (dd, J = 2.9, 9.2 Hz, 1H, Ar-H), 7.02 (m, 3H, Ar-H), 7.10 (dd, J = 2.3, 7.5 Hz, 1H, Ar-H), 7.26 (dd, J = 1.5, 6.8 Hz, 1H, Ar-H), 7.32 (dd, J = 1.7, 8.1 Hz, 2H, Ar-H); hrms: found 230.09438, calculated for $C_{14}H_{14}O_3$; 230.09429.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.01; H, 6.13. Found: C, 72.65; H, 6.09.

3,4′-Di(bromomethyl)diphenyl Ether (**39**).

3,4′-Di(hydroxymethyl)diphenyl ether (**38**, 1.00 g, 4.34 mmol) was dissolved with stirring in ether (100 cm^3, dry) to which excess phosphorous tribromide (5.88 g, 0.021 mol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 24 h, then poured into water (200 cm^3) and extracted with chloroform. The chloroform layer was washed with sodium bicarbonate solution (10%, w/v) and water (50 cm^3), dried (MgSO$_4$), filtered and evaporated under reduced pressure to yield **39** as a yellow gum (1.303 g, 84%). Nmr indicated that the product was pure; since it was expected to be a potent lachrymator, it was used without further purification; ir: 598s (CBr) cm^{-1}; ^{1}H nmr: δ (250MHz) 4.46 (s, 2H, CH$_2$Br), 4.52 (s, 2H, CH$_2$Br), 6.94-7.01 (m, 3H, Ar-H), 7.07 (dd, J = 2.2, 1.8 Hz, 1H, Ar-H), 7.18 (dd, J 1.3, 7.6 Hz, 1H, Ar-H), 7.27-7.42 (dd, J = 7.3, 7.8 Hz 1H, and dd, J = 2.1, 7.6 Hz, 2H, Ar-H); hrms: found 357.92146, calculated for $C_{14}H_{12}O^{81}Br_2$; 357.92140.

2-(2,2-Dimethylpropanoyl)-1-(3-{4-[(2-(2,2-dimethylpropanoyl)-1,2,3,4-tetrahydro-1-isoquinolinyl)methyl]phenoxy}benzyl)-1,2,3,4-tetrahydroisoquinoline (**40**).

N-Pivaloyl-1,2,3,4-tetrahydroisoquinoline (**31**, 1.59 g, 7.317 mmol) and freshly distilled tetramethylethylenediamine (1.10 cm^3, 0.85 g, 7.316 mmol) were placed in a 3 necked 250 ml round-bottomed flask containing tetrahydrofuran (50 cm^3, dry). The flask was cooled to -78 °C, and then *t*-butyl lithium (6.45 cm^3, 1.5 *M* excess, 1.7 *M* in pentane) was added under nitrogen. The deep red solution was stirred for 20 min at (-78 °C) before adding **39** (1.30 g, 3.65 mmol, in 10 cm^3 of tetrahydrofuran) dropwise over 1 h. After stirring for 10 h at -78 °C, and 62 h at room temperature, the reaction mixture was quenched with water (10 cm^3) and the solvent partially removed under reduced pressure. The residue was poured into water (200 cm^3), and extracted with chloroform (3 x 100 cm^3). The combined organic layers were washed with water and brine, dried (magnesium sulfate), filtered and concentrated under reduced pressure to give crude **40** (2.230 g). The product was purified using a Sephadex LH-20 column (25.5cm x 2.5cm) with chloroform as mobile phase, to give **40** as a yellow oil (1.47 g, 65%), R_F = 0.89 (silica, n-hexane/ethyl acetate (1:1) orange-red with vanillin/sulphuric acid; ir: 1624s (C=O) cm^{-1}; ^{1}H nmr: δ (400MHz; 50 °C) 1.21 (s, 9H, t-Bu), 1.23 (s, 9H, t-Bu), 3.10 (d, J = 6.7 Hz, 4H, 2 x Ph-*CH*$_2$), 2.68-2.74 (m, 2H, Ar-C*H*$_2$-CH$_2$-N), 2.88-2.99 (m, 2H, Ar-C*H*$_2$-CH$_2$-N), 3.35-3.45 (m, 2H, Ar-CH$_2$-C*H*$_2$-N), 4.18 (br s, 2H, Ar-CH$_2$-C*H*$_2$-N), 5.82 (t, J = 5.4 Hz, 2H, CH-N), 6.73 (s, 1H, Ar-H), 6.79-6.93 (m, 5H, Ar-H), 7.03-7.21 (m, 10H, Ar-H); ^{1}H nmr: δ (250MHz; R.T.) 1.23 (br s, 18H, 2 x t-Bu), 3.10 (d, J = 6.4 Hz, 4H, Ph-CH$_2$), 2.65-2.99 (m, 4H, Ar-C*H*$_2$-CH$_2$-N), 3.25-4.18 (m, 4H, Ar-CH$_2$-C*H*$_2$-N), 5.81 (br s, 2H, CH-N), 6.80-7.21 (m, 16H, Ar-H); hrms: found 629.37246, calculated for $C_{42}H_{49}N_2O_3$; 629.37432.

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