Pergamon

Tetrahedron, Vol. 53, No. 51, pp. 17477-17488, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)10196-X

The Synthesis of Bisanthraquinone Derivatives as DNA Bisintercalating Agents

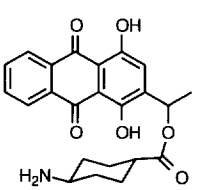
Ping Ge[a] and Richard A. Russell*

School of Biological and Chemical Sciences, Deakin University, Geelong, Victoria, Australia 3217
[a] Present address: Department of Chemistry, University of Rochester Rochester, NY 14627-0216

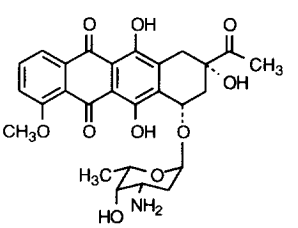
Abstract: The linked bisanthraquinone derivatives **4a-c** were synthesized as DNA bisintercalating agents. Starting from the aldehyde **7**, the linking chain was introduced via a Grignard reaction to afford the ethers **9a-c**. Subsequent anodic oxidation of these products, followed by annelation with the anion of phthalide **5** affordedthe linked anthraquinones **12**. The target compounds were then obtained by selective esterification with the acid **14**, followed by deprotection with anhydrous hydrogen chloride.
© 1997 Elsevier Science Ltd.

INTRODUCTION

DNA intercalating agents are one of the most important classes of anticancer drugs and are widely used in the clinic. Examples of such drugs are the anthracycline antibiotics, the ellipticine alkaloids and the synthetic mitoxantrone and acridines.[1] In each case the mode of DNA intercalation has been well documented by a variety of studies including NMR and X-ray crystallography methods.[2] The concept of bisintercalating agents evolved from the view that more efficacious antagonists of DNA replication might be developed by combining two intercalating agents in a single molecule. Such bifunctional ligands in which both chromophores would intercalate simultaneously should have enhanced affinity for DNA and slower dissociation rates.[3] As a consequence they could compete more effectively with DNA processing enzymes for binding sites on the genome. Additionally it was argued that their larger sized binding site may lead to greater selectivity in terms of nucleotide sequence recognition and as a consequence the toxicity of bisintercalators may be more easily controlled or modified. The isolation of naturally occuring quinoxalines such as Triostin A and Echinomycin together with the related Luzopeptin has done much to keep alive the concept of DNA bisintercalating agents as potential therapeutic agents.[4]



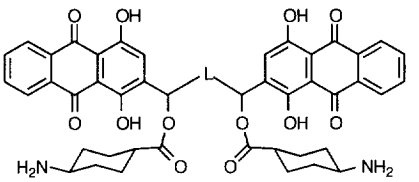
1



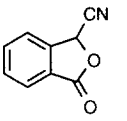
2

In the course of designing simpler anthracycline analogs as potential anticancer agents, we recently synthesized a series of anthraquinone derivatives such as **1** as a mimic of daunomycin **2**.[5] Preliminary

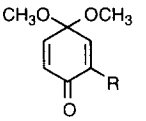
evaluation of **1** as an inhibitor of the *in vitro* growth of P388 cell line showed that its activity was comparable to that of 4-demethoxydaunomycin. In the light of this result we reasoned that if two molecules of **1** were joined by a linker (L) it might be possible to create a new class of totally synthetic DNA bisintercalators **3** with potent biological activity. In this paper we report the synthesis of compounds **4a-c** which extends the limited range of previously reported anthracycline based intercalators.[6]



3



5



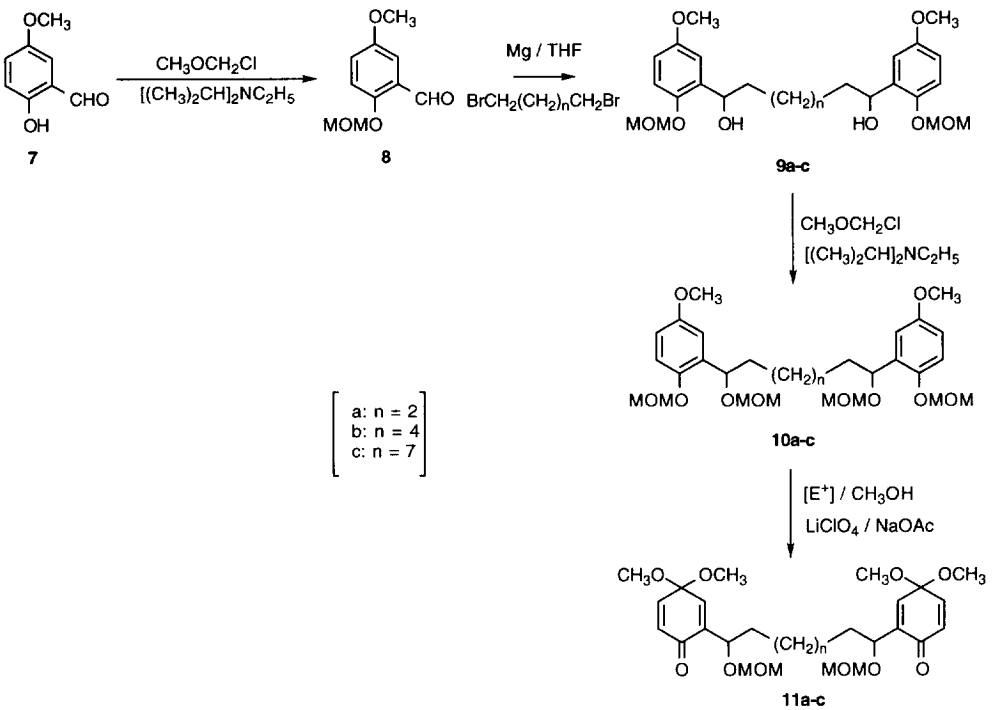
6

RESULTS AND DISCUSSION

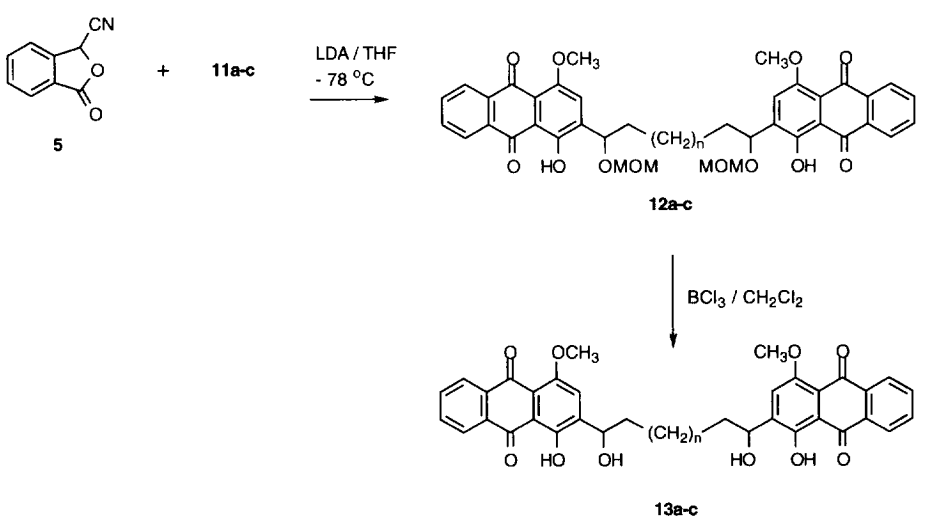
Our initial strategic problem focused on the choice between convergent or divergent syntheses. The latter approach offered the possibilities of employing our earlier work[7] based on the cyanophthalide **5** annelation of linked *p*-quinone monoacetals **6** which in their own right could be prepared by directed electrochemicaloxidation.

Starting from the aldehyde **7**, the phenolic hydroxyl group was protected as methoxymethyl (MOM) ether to afford **8**. The linkers (L) were successfully introduced by reacting this latter aldehyde with *bis*-Grignard reagents, as shown in Scheme 1. This afforded the linked diols **9a-c** in moderate to good yields [8] and these products could be directly converted to the corresponding MOM ethers **10a-c** without further purification. Anodic oxidation of the ethers **10a-c** in anhydrous methanol containing lithium perchlorate and anhydrous sodium acetate afforded the *bis-p*-quinone monoacetals **11a-c**. These oxidations were monitored by both the decrease in cell current, to about 7mA, and the decrease of the UV absorption at 287 nm. The resulting *bis-p*-quinone monoacetals **11a-c**, readily underwent hydrolysis to the corresponding quinones, and as a consequence were used without further purification for the subsequent annelation reactions. Regiospecific *bis*-annelation of acetals **11a-c** was readily accomplished with the anion of 3-cyanophthalide *via* an addition-elimination process [7] and the resulting *bis*-anthraquinones **12a-c** were purified by column chromatography on buffer washed silica gel (Scheme 2). This adsorbant gave high recovery rates and minimised irreversible binding, features not observed with normal untreated silica. Concomitant deprotection and demethylation of compounds **12a-c** with boron trichloride produced the corresponding 1,4-dihydroxyanthraquinones **13a-c**.

These compounds were only sparingly soluble in commonly used solvents and were difficult to recrystallize. Notwithstanding the fine precipitates obtained directly from the reaction were sufficiently pure to utilize in the subsequent step.

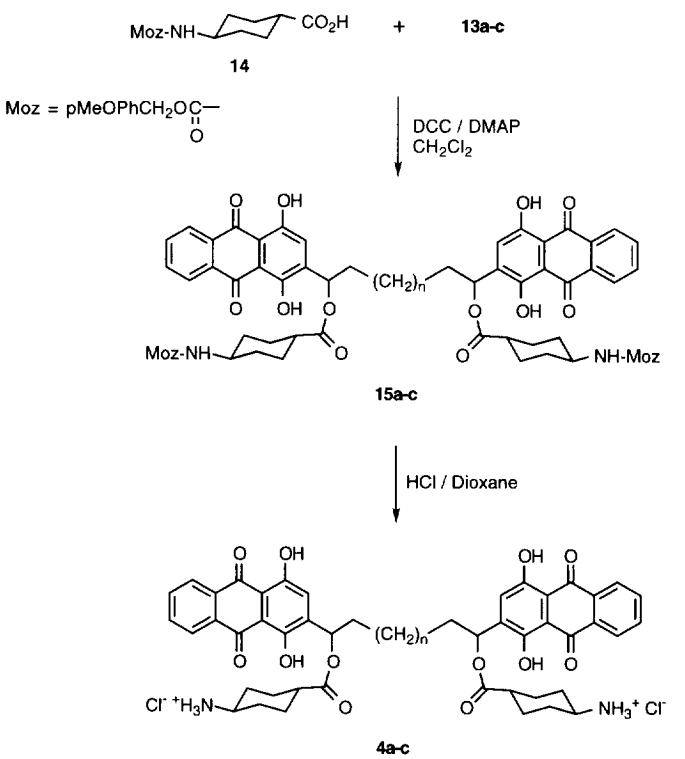


Scheme 1



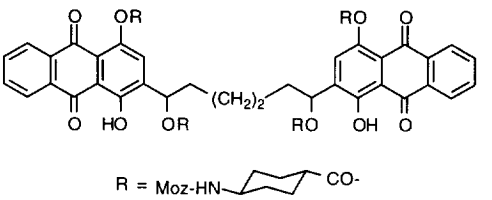
Scheme 2

Selective esterification of the side chain alcohols in **13a-c** proved difficult. Whilst the protected *trans*-4-amino-1-cyclohexanecarboxylic acid **14** was readily synthesized from 4-aminobenzoic acid,[9] our initial attempts to esterify this acid using benzenesulfonyl chloride and the quinone **13a** failed to yield any of the desired product **15a**. Accordingly we turned our attention to dicyclohexylcarbodiimide/4-dimethylaminopyridine (DCC/DMAP) which had been reported previously to be an effective coupling reagent in the preparation of daunomycinone peptide derivatives.[10] When we applied this methodology, using two equivalent of **14**, most of the starting bisanthraquinone was recovered unchanged. If four equivalent of the protected acid **14** were used the reaction mixture afforded a complex array of products. When the ratio of **14** to **13a** was further increased to eight equivalent, as noted in the preceeding paper,[5] all the *bis*-anthraquinone was transformed into a tetraester **16**. However on prolonged standing this latter reaction afforded a new major product identified as the diester **15a**, which was readily purified by column chromatography. This behaviour, although not rigorously understood, proved to be general across the whole series of related compounds and provided reliable access to the required esters. Finally deprotection of the MOZ amide with hydrogen chloride in dioxane afforded the target compounds **4a-c** (Scheme 3).



Scheme 3

Throughout this synthetic sequence the linked compounds (Scheme 1-3) appeared as homogeneous by tlc analysis, but as expected that they were clearly a mixture of diastereomers as evidenced by their melting points and doubling of some signals in their ^{1}H NMR spectra. However these spectroscopic differences were usually small and of no diagnostic value. Separation of these diastereomers or asymmetric synthesis may be accomplished at a later stage, following further biological evaluation of the compounds described in this paper. Preliminary results suggest that the bisintercalating molecules reported herein are less effective inhibitors of *in vitro* growth in the P388 cell line than the simple anthraquinones described in the accompanying paper.



16

EXPERIMENTAL SECTION

General experimental methods have been reported in the preceeding paper. [5]

2-Methoxymethyloxy-5-methoxybenzaldehyde (8)

To a solution of **7** (5.5 g, 36.2 mmol) in dichloromethane (50 ml) were added diisopropyl ethylamine (9.7 ml, 55 mmol) and chloromethyl methyl ether (4.1 ml, 54 mmol). The resulting yellow solution was stirred at room temperature for 4 h, then water (17 ml) was added. The mixture was stirred for a further 1 h after which the organic layer was separated, washed with sodium hydroxide (5%, 11 ml), water (10 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified by short path distillation (150 °C / 1mm) to afford **8** as light yellow oil (6.0 g, 85%). ^{1}H NMR ($CDCl_3$) δppm: 3.50 (s, 3H, OCH_3), 3.82 (s, 3H, 5-OCH_3), 5.22 (s, 2H, $C\underline{H}_2OCH_3$), 7.10 (dd, 1H, J = 3.2 and 8.7 Hz, 4-H), 7.20 (d, 1H, J = 8.7 Hz, 3-H), 7.31 (d, 1H, J = 3.1 Hz, 6-H), 10.50 (s, 1H, -CHO).

1,8-Bis(2-methoxymethyloxy-5-methoxyphenyl)-1,8-octanediol(9b)

A mixture of 1,6-dibromohexane (2 ml, 13.78 mmol), magnesium turnings (1.8 g, 75 mmol) and a crystal of iodine in THF (30 ml) was refluxed for 1.5 h under nitrogen. The resulting solution of the Grignard reagent was added to a solution of **8** (1.8 g, 9.7 mmol) in THF (50 ml) at -50 °C, and the reaction allowed to be warmed to room temperature. After being stirred for a further 3h at rt, the reaction was quenched by adding water (10 ml), and diluted with diethyl ether (30 ml). The organic layer was separated and the aqueous layer was extracted with diethyl ether (30 ml). The combined ethereal extracts were combined, washed with water (5 ml), brine (5 ml) and dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by column chromatography (silica gel, eluting with 40% ethyl acetate in petroleum ether) to afford the product as white solid (1.05 g, 47%), mp 89-92 °C. ^{1}H NMR ($CDCl_3$) δppm: 1.20-1.80 (m, 12H, 6 x CH_2), 2.40 (br, 2H, 2 x OH), 3.50 (s, 6H, 2 x OCH_3), 3.80 (s, 6H, 2 x 5'-OCH_3), 4.90 (m, 2H, 2 x CH), 5.15 (s, 4H, 2

x $OC\underline{H}_2OCH_3$), 6.75 (dd, 2H, J = 3.1 and 8.9 Hz, 2 x 4'-H), 6.93 (d, 2H, J = 3.1 Hz, 2 x 6'-H), 7.05 (d, 2H, J = 8.9 Hz, 2 x 3'-H). Anal. Calcd for $C_{26}H_{38}O_8$: C, 65.25; H, 8.00. Found: C, 65.36; H, 8.07.

1,6-Bis(2-methoxymethyloxy-5-methoxyphenyl)-1,6-dimethoxymethyloxyhexane(10a)

A mixture of 1,4-dibromobutane (2.85 g, 13 mmol), magnesium turnings (1.6 g, 66 mmol) and a crystal of iodine in THF (30 ml) was refluxed for 1.5 h under nitrogen. This Grignard reagent was added to a solution of **8** (1.98 g, 10 mmol) in THF (50 ml) at -50 °C. The resulting mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched by adding water (10 ml), then diluted with diethyl ether (30 ml). The organic layer was separated. The aqueous layer was extracted with diethyl ether (30 ml). All the ethereal extracts were combined, washed with water (5 ml), brine (5 ml) and dried over anhydrous sodium sulfate. Solvent was removed to afford a light yellow oil residue **9a** which was dissolved in dichloromethane (30 ml). To this was added diisopropyl ethylamine (3.6 ml, 20 mmol) and chloromethyl methyl ether (1.5 ml, 20 mmol). The resulting yellow solution was stirred at room temperature for 5 h, then water (10 ml) was added. The mixture continued to stir for 1 h. The organic layer was separated, washed with water (10 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residual oil was purified by column chromatography (silica gel, eluting with 25 % ethyl acetate in petroleum ether) to afford the product as white solid (760 mg, 29% overall), mp 70 - 74 °C. ^{1}H NMR ($CDCl_3$) δppm: 1.40-1.80 (m, 8H, 4 x CH_2), 3.341 (s, 3H, OCH_3), 3.344 (s, 3H, OCH_3), 3.43 (s, 6H, 2 x OCH_3), 3.74 (s, 6H, 2 x 5'-OCH_3), 4.50 (s, 4H, 2 x $OC\underline{H}_2OCH_3$), 4.98 (m, 2H, 2 x CH), 5.07 (s, 4H, 2 x $OC\underline{H}_2OCH_3$), 6.70 (dd, 2H, J = 3.1 and 8.9 Hz, 2 x 4'-H), 6.92 (d, 2H, J = 3.1 Hz, 2 x 6'-H), 6.99 (d, 2H, J = 8.9 Hz, 2 x 3'-H). ^{13}C NMR ($CDCl_3$) 25.5, 25.6 (C3 and C4), 36.9, 37.0 (C2, C5), 55.5 (4 x OCH_3), 55.8 (2 x PhO$\underline{C}$H-), 71.66, 71.69 (C1, C6), 94.5 (2 x OCH_2O), 95.2 (2 x PhO$\underline{C}H_2$O-), 112.4 (2 x C4'), 112.9, 113.0 (2 x C3'), 115.6, 115.7 (2 x C6'), 133.2 (2 x C1'), 148.8 (2 x C5'), 154.9 (2 x C2'). MS (EI) m/z: 538 (M^+). Anal. Calcd for $C_{28}H_{42}O_{10}$: C, 62.43; H, 7.86. Found: C, 62.56; H, 7.95.

1,8-Bis(2-methoxymethyloxy-5-methoxyphenyl)-1,8-dimethoxymethyloxyoctane(10b)

To a solution of **9b** (240 mg, 0.5 mmol) in dichloromethane (2 ml) were added diisopropyl ethylamine (0.36 ml, 2 mmol) and chloromethyl methyl ether (0.15 ml, 2 mmol). The resulting solution was stirred at room temperature for 5 h, then water (0.35 ml) was added. The mixture continued to stir for 1 h. The organic layer was separated, washed with water (1 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residual oil was purified by column chromatography (silica gel, eluting with 25 % ethyl acetate in petroleum ether) to afford the product as colorless oil (287 mg, 100%). ^{1}H NMR ($CDCl_3$) δppm: 1.30-1.80 (m, 12H, 6 x CH_2), 3.36 (s, 6H, 2 x OCH_3), 3.45 (s, 6H, 2 x OCH_3), 3.75 (s, 6H, 2 x 5'-OCH_3), 4.52 (s, 4H, 2 x $OC\underline{H}_2OCH_3$), 5.02 (dd, 2H, J = 5 and 7.9 Hz, 2 x CH), 5.09 (s, 4H, 2 x $OC\underline{H}_2OCH_3$), 6.71 (dd, 1H, J = 3.2 and 9 Hz, 2 x 4'-H), 6.93 (d, 2H, J = 3.2 Hz, 2 x 6'-H), 6.99 (d, 2H, J = 9 Hz, 2 x 3'-H). MS (EI) m/z: 566 (M^+). Anal. Calcd for $C_{30}H_{46}O_{10}$: C, 63.58; H, 8.18. Found: C, 63.88; H, 8.40.

1,11-Bis(2-methoxymethyloxy-5-methoxyphenyl)-1,11-dimethoxymethyloxyundecane(10c)

A mixture of 1,11-dibromoundecane (15 ml, 73 mmol), magnesium turnings (10 g, 0.36 mol) and a crystal of iodine in THF (300 ml) was refluxed for 1.5 h under nitrogen. This Grignard reagent was added to a solution of **8** (11 g, 56 mmol) in THF (150 ml) at -50 °C. The resulting mixture was warmed to room

temperature and stirred for 3 h. The reaction was quenched by adding water (50 ml), then diluted with diethyl ether (300 ml). The organic layer was separated. The aqueous layer was extracted with diethyl ether (100 ml). All the ethereal extracts were combined, washed with brine (35 ml) and dried over anhydrous sodium sulfate. Solvent was removed to afford a light yellow oil residue **9c** which was dissolved in dichloromethane (90 ml). To this were added diisopropyl ethylamine (22.7 ml, 120 mmol) and chloromethyl methyl ether (9.6 ml, 120 mmol). The resulting yellow solution was stirred at room temperature for 5 h, then water (30 ml) was added. The mixture continued to stir for 1 h. The organic layer was separated, washed with water (25 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residual oil was purified by column chromatography (silica gel, eluting with 25 % ethyl acetate in petroleum ether) to afford the product as light yellow oil (8.1 g, 47 % overall). ^{1}H NMR ($CDCl_3$) δppm: 1.20-1.80 (m, 18H, 9 x CH_2), 3.38 (s, 6H, 2 x OCH_3), 3.48 (s, 6H, 2 x OCH_3), 3.78 (s, 6H, 2 x 5'-OCH_3), 4.55 (s, 4H, 2 x $OC\underline{H}_2OCH_3$), 5.03 (dd, 2H, J = 5.0 and 7.8 Hz, 2 x CH), 5.14 (s, 4H, 2 x $OC\underline{H}_2OCH_3$), 6.73 (dd, 2H, J = 3.1 and 9 Hz, 2 x 4'-H), 6.95 (d, 2H, J = 3.1 Hz, 2 x 6'-H), 7.01 (d, 2H, J = 9 Hz, 2 x 3'-H). ^{13}C NMR ($CDCl_3$) δppm: 25.7 (C4 and C8), 29.32, 29.37, 29.4 (C3, C5, C6, C7, C9), 36.9 (C2, C10), 55.5 (4 x OCH_3), 55.8 (2 x PhO$\underline{C}H_3$), 77.8 (C1, C11), 94.6 (2 x OCH_2O), 95.2 (2 x PhO$\underline{C}H_2O$-), 112.4 (2 x C4'), 113.0 (2 x C3'), 115.6 (2 x C6'), 133.4 (2 x C1'), 148.8 (2 x C5'), 154.9 (2 x C2'). MS (EI) m/z: 608 (M^+). Anal. Calcd for $C_{33}H_{52}O_{10}$: C, 65.11; H, 8.61. Found: C, 65.19; H, 8.73.

General Procedure for the Synthesis of Compounds 12a-c

Step 1. Anodic oxidation

Compound **10** (1 mmol) was dissolved in dry methanol (100 ml) containing sodium acetate (0.5 g) and lithium perchlorate (2.0 g) and then anodically oxidized in a divided cell at a controlled anode potential of 1.3V. The completion of the oxidation was determined by both a low cell current (from 276 mA to 7 mA) and the disappearance of the UV absorption at 287 nm. The solution was then poured into a 50% brine/water (30 ml). Sodium hydrogen carbonate (5%, 5 ml) was added to keep the solution basic. The resulting mixture was extracted with diethyl ether (40 ml x 3). The combined extracts were washed with water (10 ml), brine (10 ml), dried over anhydrous sodium sulfate and filtered. The solvent was removed to afford **11** which was directly used for the annelation.

Step 2. Cyanophthalide annelation

To a solution of butyl lithium (1.3 M, 1.6 ml, 2 mmol) in dry THF (2 ml) was added dropwise diisopropylamine (0.29 ml, 2 mmol) at 0 °C under nitrogen. After stirred for 20 min, the pale yellow solution was cooled to -78 °C. To this was added a solution of **5** [11] (320 mg, 2 mmol) in THF (1.5 ml) to give a yellow mixture, then a solution of the above bis *p*-quinone monoacetal **11** in THF (1.5 ml) was added. The resulting mixture was stirred for 30 min then gradually warmed to room temperature. After stirred for 6 h, the reaction mixture was poured into 50% brine/water (10 ml), and extracted with dichloromethane (40 ml x 2). The extracts were combined, washed with water (5 ml), brine (5 ml), and dried over anhydrous sodium sulfate. The solvent was removed and the residue was purified by column chromatography (buffered silica gel, eluting with 0.5% methanol in dichloromethane) to afford **12** as a red solid.

1,6-Bis(1-hydroxy-4-methoxyanthracene-9,10-dion-2-yl)-1,6-dimethoxymethyloxyhexane (12a)

The title compound is prepared in 61% yield (262 mg) from compound **10a** (330 mg, 0.6 mmol) and **5** (190 mg, 1.2 mmol), melt at 82 °C but turned into solid, then melt at 191°C (dec.).

11a: ^{1}H NMR ($CDCl_3$) δppm: 1.30-1.70 (m, 8H, 4 x CH_2), 3.35 (s, 6H, 2 x OCH_3), 3.37 (m, 12H, 4 x OCH_3), 4.60 (s, 4H, 2 x $C\underline{H}_2OCH_3$), 4.65 (m, 2H, 2 x CH), 6.21 (d, 2H, J = 9 Hz, 2 x 6'-PhH), 6.82 (d, 2H, J = 9 Hz, 2 x 5'-PhH), 6.84 (s, 2H, 2 x 3'-PhH).

12a: ^{1}H NMR ($CDCl_3$) δppm: 1.40-1.90 (m, 8H, 4 x CH_2), 3.37 (s, 3H, OCH_3), 3.38 (s, 3H, OCH_3), 4.00 (s, 3H, 4'-OCH_3), 4.01 (s, 3H, 4'-OCH_3), 4.58 (d, 2H, J = 17.5 Hz, 2 x $C\underline{H}OCH_3$), 4.64 (d, 2H, J = 17.5 Hz, 2 x $C\underline{H}OCH_3$), 5.17 (m, 2H, 2 x CH), 7.56 (s, 2H, 2 x 3'-PhH), 7.75 (m, 4H, 6' and 7'-PhH), 8.25 (m, 4H, 5' and 8'-PhH), 13.34 (s, 1H, 1'-OH), 13.36 (s, 1H, 1'-OH). ^{13}C NMR ($CDCl_3$) δppm: 25.1, 25.2 (C3 and C4), 35.87, 35.93 (C2 and C5), 55.9 (OCH_3), 56.9 ($PhOCH_3$), 72.1, 72.2 (C1 and C6), 95.5 (OCH_2O), 115.7 (9'a), 118.2 (4'a), 120.5 (3'), 126.5 (5'/8'), 127.5 (8'/5'), 132.5 (10'a/8'a), 133.4 (6'/7'), 134.9 (7'/6'), 135.3 (8'a/10'a), 141.7 (2'), 154.2 (1'), 155.1 (4'), 181.9 (10'), 189.7 (9'). MS (FAB) m/z: 711 (M^+). IR (KBr) cm^{-1} 3527(m), 3037(m), 2938 (s), 1664 (s), 1630 (s), 1592 (s), 1570 (s), 1460 (s), 1455 (s), 1423 (s), 1355 (s), 1243 (s), 1218 (s), 1174 (s), 1149 (s), 1122 (s), 1099 (s), 1037 (s). Anal. Calcd for $C_{40}H_{38}O_{12}$: C, 67.60; H, 5.39. Found: C, 67.49; H, 5.28.

1,8-Bis(1-hydroxy-4-methoxyanthracene-9,10-dion-2-yl)-1,8-dimethoxymethyloxyoctane(12b)

The title compound is prepared in 65% yield (477 mg) from compound **10b** (566 mg, 1 mmol) and **5** (320 mg, 2 mmol), mp 61 - 64 °C.

11b: ^{1}H NMR ($CDCl_3$) δppm: 1.20-1.70 (m, 12H, 6 x CH_2), 3.37 (s, 6H, 2 x OCH_3), 3.38 (m, 12H, 4 x OCH_3), 4.5 (s, 4H, 2 x $C\underline{H}_2OCH_3$), 4.63 (m, 2H, 2 x CH), 6.25 (d, 2H, J = 10.5 Hz, 2 x 6'-PhH), 6.82 (d, 2H, J = 10.5 Hz, 2 x 5'-PhH), 6.84 (s, 2H, 2 x 3'-PhH).

12b: ^{1}H NMR ($CDCl_3$) δppm: 1.30-1.90 (m, 12H, 6 x CH_2), 3.40 (s, 6H, 2 x OCH_3), 4.05 (s, 6H, 2 x 4'-OCH_3), 4.62 (d, 2H, J = 17.5 Hz, 2 x $C\underline{H}OCH_3$), 4.65 (d, 2H, J = 17.5 Hz, 2 x $C\underline{H}OCH_3$), 5.19 (dd, 2H, J= 4.6 and 6.2 Hz, 2 x CH), 7.56 (s, 2H, 2 x 3'-PhH), 7.79 (m, 4H, 6' and 7'-PhH), 8.27 (m, 4H, 5' and 8'-PhH), 13.40 (s, 2H, 2 x 1'-OH). ^{13}C NMR ($CDCl_3$) δppm: 25.5 (C4 and C5), 29.5 (C3 and C6), 36.1 (C2 and C7), 56.0 (OCH_3), 57.0 ($PhOCH_3$), 72.2 (C1 and C8), 95.8 (OCH_2O), 115.7 (9'a), 118.2 (4'a), 120.5 (3'), 126.5 (5'/8'), 127.5 (8'/5'), 132.5 (10'a/8'a), 133.5 (6'/7'), 135.0 (7'/6'), 135.4 (8'a/10'a), 142.2 (2'), 154.5 (1'), 155.2 (4'), 182.0 (10'), 189.8 (9'). MS (FAB) m/z: 739 (M^+). IR (KBr) cm^{-1} 3447(m), 3070(m), 2931 (s), 2851 (s), 1664 (s), 1630 (s), 1592 (s), 1570 (s), 1456 (s), 1423 (s), 1355 (s), 1244 (s), 1217 (s), 1173 (s), 1151 (s), 1122 (s), 1098 (s), 1038 (s). Anal. Calcd for $C_{42}H_{42}O_{12}$: C, 68.28; H, 5.73. Found: C, 68.01; H, 5.59.

1,11-Bis(1-hydroxy-4-methoxyanthracene-9,10-dion-2-yl)-1,11-dimethoxymethyloxyundecane(12c)

The title compound is prepared in 70% yield (220 mg) from compound **10c** (290 mg, 0.47 mmol) and **5** (140 mg, 0.86 mmol), melt at 56 °C first, then 98 °C.

11c: ^{1}H NMR ($CDCl_3$) δppm: 1.20-1.70 (m, 18H, 9 x CH_2), 3.35 (m, 18H, 6 x OCH_3), 4.45 (s, 2H, $C\underline{H}_2OCH_3$), 4.56 (s, 2H, $C\underline{H}_2OCH_3$), 4.62 (m, 2H, 2 x CH), 6.25 (d, 2H, J = 10.5 Hz, 2 x 6'-PhH), 6.82 (d, 2H, J = 10.5 Hz, 2 x 5'-PhH), 6.84 (s, 2H, 2 x 3'-PhH).

12c: ^{1}H NMR ($CDCl_3$) δppm: 1.20-1.80 (m, 18H, 9 x CH_2), 3.40 (s, 6H, 2 x OCH_3), 4.02 (s, 6H, 2 x 4'-OCH_3), 4.60 (d, 2H, J = 17.5 Hz, 2 x $C\underline{H}OCH_3$), 4.62 (d, 2H, J = 17.5 Hz, 2 x $C\underline{H}OCH_3$), 5.16 (m, 2H, 2 x CH), 7.54 (s, 2H, 2 x 3'-PhH), 7.76 (m, 4H, 6' and 7'-PhH), 8.25 (m, 4H, 5' and 8'-PhH), 13.36 (s, 1H, 1'-OH),

13.37 (s, 1H, 1'-OH). ^{13}C NMR ($CDCl_3$) δppm: 25.5 (C4 and C8), 29.14, 29.17, 29.26, 29.29, 29.36 (C3, C5, C6, C7, C9), 36.1 (C2, C10), 55.9 (OCH_3), 56.9 ($PhOCH_3$), 72.2 (C1 and C11), 95.5 (OCH_2O), 115.7 (9'a), 118.2 (4'a), 120.5 (3'), 126.5 (5'/8'), 127.5 (8'/5'), 132.5 (10'a/8'a), 133.4 (6'/7'), 135.0 (7'/6'), 135.4 (8'a/10'a), 141.9 (2'), 154.5 (1'), 155.1 (4'), 181.9 (10'), 189.7 (9'). MS (FAB) m/z: 781 (M^+). IR (KBr) cm^{-1} 3528 (m), 3071 (m), 2926 (s), 2851 (s), 1664 (s), 1630 (s), 1593 (s), 1570 (s), 1455 (s), 1423 (s), 1355 (s), 1243 (s), 1216 (s), 1173 (s), 1153 (s), 1098 (s), 1038 (s). Anal. Calcd for $C_{45}H_{48}O_{12}$: C, 69.22; H, 6.20. Found: C, 69.18; H, 6.28.

General Procedure for the Synthesis of Compounds 13a-c

To a solution of **12** (1 mmol) in dry dichloromethane (80 ml) was added boron trichloride (1.0 M, 8 ml, 8 mmol) at -78 °C under nitrogen. The resulting purple solution was stirred for 1 h then allowed to warm to room temperature. The stirring was continued for 2 h then quenched by adding water (4 ml) at 0 °C. The mixture was extracted with dichloromethane. The extract was washed with water, brine and dried. The solvent was evaporated to a small volume. The red precipitate was separated and thoroughly washed with dichloromethane or purified by column chromatography (buffered silica gel, eluting with 0.5% methanol in dichloromethane) to afford the product as a red solid.

1,6-Bis(1,4-dihydroxyanthracene-9,10-dion-2-yl)-1,6-hexanediol (13a)

The title compound is prepared in 95% yield (550 mg) from compound **12a** (696 mg, 0.98 mmol) and boron trichloride (1.0 M, 8 ml, 8 mmol), mp 215-218 °C. ^1H NMR ($CDCl_3$) δppm: 0.9 -1.80 (m, 8H, 4 x CH_2), 5.05 (m, 2H, 2 x CH), 7.45 (s, 2H, 2 x 3'-PhH), 7.85 (m, 4H, 2 x 5' and 8'-PhH), 8.35 (m, 4H, 2 x 6' and 7'-PhH), 12.91 (s, 2H, 2 x 4'-PhOH), 13.47 (s, 2H, 2 x 1'-PhOH). Anal. Calcd for $C_{34}H_{26}O_{10}$: C, 68.69; H, 4.38. Found: C, 68.74; H, 4.34.

1,8-Bis(1,4-dihydroxyanthracene-9,10-dion-2-yl)-1,8-octanediol (13b)

The title compound is prepared in 86% yield (134 mg) from compound **12b** (185 mg, 0.25 mmol) and boron trichloride (1.0 M, 2 ml, 2 mmol), mp 203 - 205 °C. ^1H NMR ($CDCl_3$ + DMSO-d_6) δppm: 1.10-1.80 (m, 12H, 6 x CH_2), 5.0 (m, 2H, 2 x CH), 7.45 (s, 2H, 2 x 3'-PhH), 7.78 (m, 4H, 2 x 5' and 8'-PhH), 8.30 (m, 4H, 2 x 6' and 7'-PhH), 12.90 (s, 2H, 2 x 4'-PhOH), 13.38 (s, 2H, 2 x 1'-PhOH). Anal. Calcd for $C_{36}H_{30}O_{10}\cdot 0.75H_2O$: C, 67.97; H, 4.99. Found: C, 67.85; H, 5.02.

1,11-Bis(1,4-dihydroxyanthracene-9,10-dion-2-yl)-1,11-undecanediol (13c)

The title compound is prepared in 90% yield (120 mg) from compound **12c** (156 mg, 0.2 mmol) and boron trichloride (1.0 M, 1.6 ml, 1.6 mmol), mp 167 - 170 °C. ^1H NMR ($CDCl_3$) δppm: 1.20-1.90 (m, 18H, 9 x CH_2), 5.02 (m, 2H, 2 x CH), 7.42 (s, 2H, 2 x 3'-PhH), 7.82 (m, 4H, 2 x 5' and 8'-PhH), 8.33 (m, 4H, 2 x 6' and 7'-PhH), 12.92 (s, 2H, 2 x 4'-PhOH), 13.49 (s, 2H, 2 x 1'-PhOH). Anal. Calcd for $C_{39}H_{36}O_{10}\cdot 0.25H_2O$: C, 70.00; H, 5.50. Found: C, 70.03; H, 5.42.

General Procedure for the Synthesis of Compounds 15a-c

To a solution of DCC (2 mmol) in dry dichloromethane (10 ml) was added compound **14** [9] (500 mg, 1.6 mmol) at room temperature. The resulting mixture was stirred for 10 min. 4-Dimethylaminopyridine (1.6 mmol) and **13** (0.2 mmol) were then added. The resulting mixture was stirred for 4 days at room temperature. The solid was filtered off and the filtrate was evaporated to dryness. The red residue was purified by column chromatography (buffered silica gel, eluting with dichloromethane) to afford the product as a red solid.

1,6-Bis(1,4-dihydroxyanthracene-9,10-dion-2-yl)-1,6-bis[[trans-4-[N-[(4-methoxybenzyl)oxy]carbonyl]-amino]cyclohexylcarbonyloxy]-hexane (15a)

The title compound is prepared in 91% yield (217 mg) from compound **13a** (120 mg, 0.2 mmol), DCC (400 mg, 1.9 mmol), **14** (500 mg, 1.6 mmol) and DMAP (200 mg, 1.6 mmol), mp 221 - 223 °C (dec.). ^{1}H NMR ($CDCl_3$) δppm: 1.00 - 2.18 (m, 24H, 4 x CH_2 and 16H in cyclohexyl), 2.30 (m, 2H, 2 x 1-H of cyclohexyl), 3.50 (m, 2H, 2 x 4-H of cyclohexyl), 3.80 (s, 6H, 2 x $PhOCH_3$), 4.58 (m, 2H, 2 x NH), 5.00 (s, 4H, 2 x $PhCH_2O$), 6.15 (m, 2H, 2 x CH), 6.86 (d, 4H, J = 8.8 Hz, 2 x 3 and 5-PhH in Moz-), 7.21 (s, 2H, 2 x 3'-PhH), 7.28 (d, 4H, J = 8.8 Hz, 2 x 2 and 6-PhH in Moz-), 7.82 (m, 4H, 2 x 5' and 8'-PhH), 8.32 (m, 4H, 2 x 6' and 7'-PhH), 12.86 (s, 1H, 4'-PhOH), 12.87 (s, 1H, 4'-PhOH), 13.30 (s, 1H, 1'-PhOH), 13.31 (s, 1H, 1'-PhOH). ^{13}C NMR ($CDCl_3$) δppm: 25.4 (C3 and 4), 27.49, 27.56 (C2, C6 in cyclohexyl), 32.2 (C3, C5 in cyclohexyl), 33.8 (C2 and C5), 42.2 (C1 in cyclohexyl), 49.2 (C4 in cyclohexyl), 55.2 (OCH_3), 66.4 ($PhCH_2O$-), 69.4 (C1 and C6), 112.3 (C9'a), 112.8 (C4'a), 114.0 (C3, C5 in Moz-), 124.9 (C3'), 127.2, 127.3 (C5', C8'), 128.8 (C1 in Moz-), 130.2 (C2, C6 in Moz-), 133.6, 133.63 (C10'a, C8'a), 134.7, 134.78 (C6', C7'), 143.0 (C2'), 155.2 (C1'), 155.9 (CONH), 157.7 (C4'), 159.8 (C4 in Moz-), 174.5 (-CO_2-), 187.0 (C10'), 187.6 (C9').

1,8-Bis(1,4-dihydroxyanthracene-9,10-dion-2-yl)-1,8-bis[[trans-4-[N-[(4-methoxybenzyl)oxy]carbonyl]-amino]cyclohexylcarbonyloxy]-octane (15b)

The title compound is prepared in 70% yield (169 mg) from compound **13b** (125 mg, 0.2 mmol), DCC (400 mg, 1.9 mmol), **14** (500 mg, 1.6 mmol) and DMAP (200 mg, 1.6 mmol), mp 87 - 90 °C. ^{1}H NMR ($CDCl_3$) δppm: 1.10 - 2.20 (m, 28H, 6 x CH_2 and 16H in cyclohexyl), 2.30 (m, 2H, 2 x 1-H of cyclohexyl), 3.50 (m, 2H, 2 x 4-H of cyclohexyl), 3.80 (s, 6H, 2 x $PhOCH_3$), 4.60 (m, 2H, 2 x NH), 5.00 (s, 4H, 2 x $PhCH_2O$), 6.22 (m, 2H, 2 x CH), 6.87 (d, 4H, J = 8.7 Hz, 2 x 3 and 5-PhH in Moz-), 7.23 (s, 2H, 2 x 3'-PhH), 7.28 (d, 4H, J = 8.7 Hz, 2 x 2 and 6-PhH in Moz-), 7.82 (m, 4H, 2 x 5' and 8'-PhH), 8.32 (m, 4H, 2 x 6' and 7'-PhH), 12.89 (s, 2H, 2 x 4'-PhOH), 13.32 (s, 2H, 2 x 1'-PhOH). ^{13}C NMR ($CDCl_3$) δppm: 25.0 (C3 and 6), 27.5, 27.6 (C2, C6 in cyclohexyl), 28.8 (C4 and C5), 32.2 (C3, C5 in cyclohexyl), 34.4 (C2 and C7), 42.2 (C1 in cyclohexyl), 49.2 (C4 in cyclohexyl), 55.12 (OCH_3), 66.4 ($PhCH_2O$-), 69.5 (C1 and C8), 112.2 (C9'a), 112.7 (C4'a), 114.0 (C3, C5 in Moz-), 124.9 (C3'), 127.2, 127.3 (C5', C8'), 128.8 (C1 in Moz-), 130.2 (C2, C6 in Moz-), 133.63 (C10'a, C8'a), 134.7, 134.8 (C6', C7'), 143.3 (C2'), 155.2 (C1'), 155.9 (CONH), 157.8 (C4'), 159.8 (C4 in Moz-), 174.5 (-CO_2-), 187.0 (C10'), 187.6 (C9'). IR (KBr) cm^{-1} 3388 (m), 3325 (m), 2930 (s), 2860 (s), 1719 (s), 1626 (s), 1511 (s), 1423 (s), 1262 (s), 1247 (s), 1174 (s), 1037 (s).

1,11-Bis(1,4-dihydroxyanthracene-9,10-dion-2-yl)-1,11-bis[[trans-4-[N-[(4-methoxybenzyl)oxy]-carbonyl]amino]cyclohexylcarbonyloxy]-undecane (15c)

The title compound is prepared in 91% yield (172 mg) from compound **13c** (100 mg, 0.15 mmol), DCC (400 mg, 1.9 mmol), **14** (500 mg, 1.6 mmol) and DMAP (200 mg, 1.6 mmol), mp 74-76 °C. ^{1}H NMR ($CDCl_3$) δppm: 1.05 - 2.18 (m, 34H, 9 x CH_2 and 16H in cyclohexyl), 2.35 (m, 2H, 2 x 1-H of cyclohexyl), 3.45 (m, 2H, 2 x 4-H of cyclohexyl), 3.80 (s, 6H, 2 x $PhOCH_3$), 4.60 (m, 2H, 2 x NH), 5.00 (s, 4H, 2 x $PhCH_2O$), 6.13 (m, 2H, 2 x CH), 6.87 (d, 4H, J = 8.7 Hz, 2 3 and 5-PhH in Moz-), 7.24 (s, 2H, 2 x 3'-PhH), 7.28 (d, 4H, J = 8.7 Hz, 2 x 2 and 6-PhH in Moz-), 7.82 (m, 4H, 2 x 5' and 8'-PhH), 8.33 (m, 4H, 2 x 6' and 7'-PhH), 12.89 (s, 2H, 2 x 4'-PhOH), 13.32 (s, 1H, 1'-PhOH), 13.33 (s, 1H, 1'-PhOH). ^{13}C NMR ($CDCl_3$) δppm: 25.1 (C3 and 9), 27.5, 27.6 (C2, C6 in cyclohexyl), 28.9, 29.1 (C4, C5, C7 and C8), 29.15 (C6), 32.2 (C3, C5 in cyclohexyl), 34.5 (C2 and C10), 42.2 (C1 in cyclohexyl), 49.2 (C4 in cyclohexyl), 55.2 (OCH_3), 66.4 ($PhCH_2O$-), 69.6 (C1 and C11), 112.2 (C9'a), 112.7 (C4'a), 114.1 (C3, C5 in Moz-), 125.0 (C3'), 127.2, 127.3 (C5', C8'), 128.8 (C1 in Moz-), 130.2 (C2, C6 in Moz-), 133.7 (C10'a, C8'a), 134.7, 134.8 (C6', C7'), 143.3 (C2'), 155.3 (C1'), 155.9 (CONH), 157.8 (C4'), 159.8 (C4 in Moz-), 174.5 (-CO_2-), 187.0 (C10'), 187.6 (C9'). IR (KBr) cm^{-1} 3333 (S), 2935 (s), 2857 (s), 1717 (s), 1628 (s), 1592 (S), 1514 (s), 1248 (s), 1176 (s), 1036 (s).

General Procedure for the Synthesis of Compounds 4a-c

To a solution of **15** (0.1 mmol) in dry dichloromethane (1.5 ml) was added hydrogen chloride in dioxane (1.3 M, 1.5 ml) at room temperature. The resulting red solution was stirred for 2 h. The red crystals were then separated, washed thoroughly with dry dioxane and diethyl ether to give the product as orange crystals.

1,6-Bis(1,4-dihydroxyanthracene-9,10-dion-2-yl)-1,6-bis[(trans-4-amino)cyclohexylcarbonyloxy]-hexane dihydrochloride (4a)

The title compound is prepared in 87% yield (81 mg) from compound **15a** (120 mg, 0.1 mmol), mp 247 °C (dec.). ^{1}H NMR (DMSO-d_6) δppm: 1.30 - 2.10 (m, 24H, 4 x CH_2 and 16H in cyclohexyl), 2.40 (m, 2H, 2 x 1-H of cyclohexyl), 2.95 (m, 2H, 2 x 4-H of cyclohexyl), 6.0 (t, 2H, J = 6.2 Hz, 2 x CH), 7.29 (s, 1H, 3'-PhH), 7.30 (s, 1H, 3'-PhH), 8.0 (m, 10H, 2 x 5', 8'-PhH and 2 x NH_3), 8.20 (m, 4H, 2 x 6' and 7'-PhH), 12.61 (s, 1H, 4'-PhOH), 12.64 (s, 1H, 4'-PhOH), 13.15 (s, 1H, 1'-PhOH), 13.19 (s, 1H, 1'-PhOH). ^{13}C NMR (DMSO-d6) δppm: 23.8 (C3 and 4), 26.3, 26.4 (C2, C6 in cyclohexyl), 29.2 (C3, C5 in cyclohexyl), 33.3 (C2 and C5), 40.9 (C1 in cyclohexyl), 48.5 (C4 in cyclohexyl), 68.7 (C1 and C6), 112.4 (C9'a), 112.9 (C4'a), 124.7 (C3'), 127.0 (C5', C8'), 133.1, 133.2 (C10'a, C8'a), 135.4, 135.6 (C6', C7'), 142.1 (C2'), 154.0 (C1'), 156.7 (C4'), 173.9 (-CO_2-), 186.8 (C10'), 187.7 (C9'). MS (FAB) m/z: 845 (M^+). IR (KBr) cm^{-1}: 3419 (s), 3038 (s), 2935 (s), 2874 (s), 1732 (s), 1621 (s), 1579 (s), 1428 (s), 1259 (s), 1234 (s). Anal. Calcd for $C_{48}H_{50}Cl_2N_2O_{12}$: C, 62.81; H, 5.45; N, 3.05. Found: C, 62.77; H, 5.35; N, 3.09.

1,8-Bis(1,4-dihydroxyanthracene-9,10-dion-2-yl)-1,8-bis[(trans-4-amino)cyclohexylcarbonyloxy]-octane dihydrochloride (4b)

The title compound is prepared in 91% yield (67 mg) from compound **15b** (94 mg, 0.08 mmol), mp 210 °C (dec.). ^{1}H NMR (DMSO-d_6) δppm: 1.20 - 2.10 (m, 28H, 6 x CH_2 and 16H in cyclohexyl), 2.42 (m, 2H, 2 x 1-H of cyclohexyl), 3.00 (m, 2H, 2 x 4-H of cyclohexyl), 6.0 (m, 2H, 2 x CH), 7.30 (s, 2H, 2 x 3'-PhH), 7.95 (m, 4H, 2 x 5' and 8'-PhH), 8.15 (m, 10H, 2 x 6' and 7'-PhH, 2 x NH_3), 12.60 (s, 2H, 2 x 4'-PhOH), 13.14 (s, 2H, 2 x 1'-PhOH). ^{13}C NMR (DMSO-d_6) δppm: 24.5 (C3 and 6), 26.2, 26.4 (C2, C6 in cyclohexyl), 28.1 (C4 and C5), 29.1 (C3, C5 in cyclohexyl), 33.8 (C2 and C7), 42.5 (C1 in cyclohexyl), 48.5 (C4 in cyclohexyl), 68.8

(C1 and C8), 112.3 (C9'a), 112.8 (C4'a), 124.6 (C3'), 126.9, 127.0 (C5', C8'), 133.0, 133.1 (C10'a, C8'a), 135.4, 135.5 (C6', C7'), 142.3 (C2'), 154.0 (C1'), 156.7 (C4'), 174.0 (-CO_2-), 186.7 (C10'), 187.6 (C9'). MS (FAB) m/z: 873 (M^+). IR (KBr) cm^{-1}: 3416 (s), 3005 (s), 2934 (s), 2861 (s), 1738 (s), 1621 (s), 1582 (s), 1426 (s), 1256 (s), 1234 (s).

1,11-Bis(1,4-dihydroxyanthracene-9,10-dion-2-yl)-1,11-bis[(trans-4-amino)cyclohexylcarbonyloxy]-undecane dihydrochloride (4c)

The title compound is prepared in 82% yield (97 mg) from compound **15c** (150 mg, 0.12 mmol), mp 215 °C (dec.). ^1H NMR (DMSO-d_6) δppm: 1.20 - 2.08 (m, 34H, 9 x CH_2 and 16H in cyclohexyl), 2.42 (m, 2H, 2 x 1-H of cyclohexyl), 3.98 (m, 2H, 2 x 4-H of cyclohexyl), 6.0 (m, 2H, 2 x CH), 7.30 (s, 2H, 2 x 3'-PhH), 8.00 (m, 10H, 2 x 5', 8'-PhH and 2 x NH_3), 8.22 (m, 4H, 2 x 6' and 7'-PhH), 12.64 (s, 2H, 2 x 4'-PhOH), 13.17 (s, 1H, 1'-PhOH), 13.19 (s, 1H, 1'-PhOH). MS (FAB) m/z: 915 (M^+). IR (KBr) cm^{-1}: 3425 (s), 3013 (s), 2938 (s), 2855 (s), 1733 (s), 1622 (s), 1583 (s), 1263 (s), 1233 (s).

REFERENCES

1. (a) Baguley, B. C. *Anti-Cancer Drug Des.* **1991**, *6*, 1-35. (b) Denny, W. A. *Anti-Cancer Drug Des.* **1989**, *4*, 241-263. (c) Krohn, K. *Tetrahedron* **1990**, *46*, 291-318. (d) Auclair, C. *Arch. Biochem. Biophys.* **1987**, *257*, 1-14.
2. (a) Neidle, S.; Abraham, Z. *CRC Critical Rev. Biochem.* **1984**, *17*, 73-121. (b) Dautant, A.; Langlois D'Estaintot, B.; Gallois, B.; Brown, T.; Hunter, W.N. *Nucleic Acids Res.* **1995**, *23*, 1710-1716. (c) Frederick, C. A.; Williams, L. D.; Ughetto, G.; van der Marel, G. A.; van Boom, J. H.; Rich, A.; Wang, A. H. *Biochemistry* **1990**, *29*, 2538-2549. (d) Chen, H.; Patel, D. J. *J. Mol. Biol.* **1995**, *246*, 164-179.
3. Wakelin, L. P. *Med. Res. Rev.* **1986**, *6*, 275-340.
4. (a) Low, C. M. L.; Drew, H. R.; Waring, M. J. *Nucleic Acids Res.* **1984**, *12*, 4865-4879. (b) Crothers, D. M. *Biopolymers* **1968**, *6*, 575-584. (b) Chaires, J.B.; Leng, F.; Przewloka, T.; Fokt, I.; Ling, Y.H.; Perez-Soler, R.; Priebe, W. *J. Med. Chem.* **1997**, *40*, 261-266.
5. Ge, P.; Russell, R. A. *Tetrahedron.* submitted.
6. (a) Henry, D. W.; Tong, G. L. U.S. Patent 4, **1978**, *112*, 217. (b) Apple, M. A.; Yanagisawa, H.; Hut, C. A. Amer. Assoc. Cancer Res. Abstracts No. 675, **1978**. (c). Brownlee, R. T. C.; Cacoli, P.; Chandler, C. J.; Phillips, D. R.; Scourides, P. A.; Reiss, J. A. *J. Chem. Soc. Chem. Commun.* **1986**, 659-661.
7. (a) Russell, R. A.; Pilley, B. A.; Irvine, R. W.; Warrener, R. N. *Aust. J. Chem.* **1987**, *40*, 311-323. (b) Mitchell, A. S.; Russell, R. A. *Tetrahedron* **1995**, *51*, 5207-5236. (c) Mitchell, A. S.; Russell, R. A. *Tetrahedron* **1997**, *53*, 4387-4410.
8. Russell, R. A.; Day, A. I.; Pilley, B. A.; Leavy, P. J.; Warrener, R. N. *J. Chem. Soc. Chem. Commun.* **1987**, 1631-1633.
9. Wang, Z. Q.; Feng, D. W.; Zhang, C. N. *Acta Pharm. Sinica* **1984**, *19*, 349-356.
10. Ge, P.; Wang, Z. Q.; Zhang, C. N. *Acta Pharm. Sinica* **1987**, *22*, 254-263.
11. Russell, R. A.; Pilley, B. A. *Synth. Commun.* **1986**, *16*, 425-430.

(*Received in UK* 1 *September* 1997; *accepted* 16 *October* 1997)