Synthesis of Sequence-Selective C8-Linked Pyrrolo[2,1-*c*][1,4]benzodiazepine DNA Interstrand Cross-Linking Agents

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An efficient convergent synthesis of a homologous series of C8-linked pyrrolobenzodiazepine dimers with remarkable DNA interstrand cross-linking activity and potent *in vitro* cytotoxicity is reported. The "amino thioacetal" cyclization procedure was used to produce the electrophilic DNA-interactive N10−C11 imine moiety during the final synthetic step. In order to construct the key A-ring fragments (**9a**−**d**), a versatile convergent approach has been developed to join two units of vanillic acid with α,ω-dihaloalkanes of varying length to provide the required bis(4-carboxy-2-methoxyphenoxy)alkanes while avoiding the formation of mixtures of monoalkylated and bisalkylated products.

DNA-binding molecules are presently attracting interest due to their involvement in carcinogenesis and their use as antitumor agents and probes of DNA structure.[1] The pyrrolobenzodiazepine (PBD) family of DNA-binding antitumor antibiotics was discovered in early 1960 with the isolation of anthramycin, and, since then, the group has been extensively studied as a potential source of antitumor agents and DNA probes.[2] To date, 13 members, including such compounds as tomaymycin (**1**), chicamycin (**2**), neothramycin (**3**), and DC-81 (**4**) (Figure 1) have been isolated from various *Streptomyces* species, and there is now extensive evidence that they exert their biological activity through covalent binding to the exocyclic N2 of guanine in the minor groove of DNA.[2] The molecules have a right-handed twist which allows them to follow the curvature of the minor groove of B-form double-stranded DNA spanning three base pairs. Fluorescence, NMR, molecular modeling, and DNA footprinting-type studies have all contributed to a detailed knowledge of the structure of PBD−DNA adducts, including the stereochemistry of the aminal linkage formed, the orientation of the molecule in the minor groove, and the preferred binding sequence (i.e., 5′-Pu-G-Pu).[2a] More

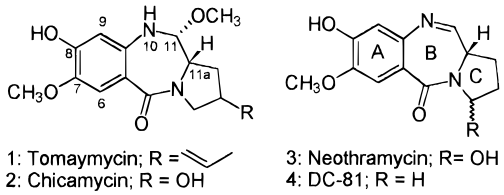

Figure 1.

recent studies have started to relate the DNA-binding affinity and sequence-selectivity of the PBDs to their biological activity.[2a,3a] A recent development has been the linking of two PBD units through their C7[4] - or C8[5]-positions to give bisfunctional alkylating agents capable of cross-linking DNA. One C8-linked dimer, DSB-120 (**14a**), is a remarkably efficient interstrand DNA cross-linker, being approximately 300- and 50-fold more efficient than the clinically used cross-linking agents, melphalan and cisplatin, respectively.[5a] It is also approximately equivalent in efficiency to the CC-1065 based AT-specific cross-linking agent, U-77779.[6] DSB-120 is highly cytotoxic in a number of murine and human cell lines with IC_{50} values as low as 0.5 nM. Molecular

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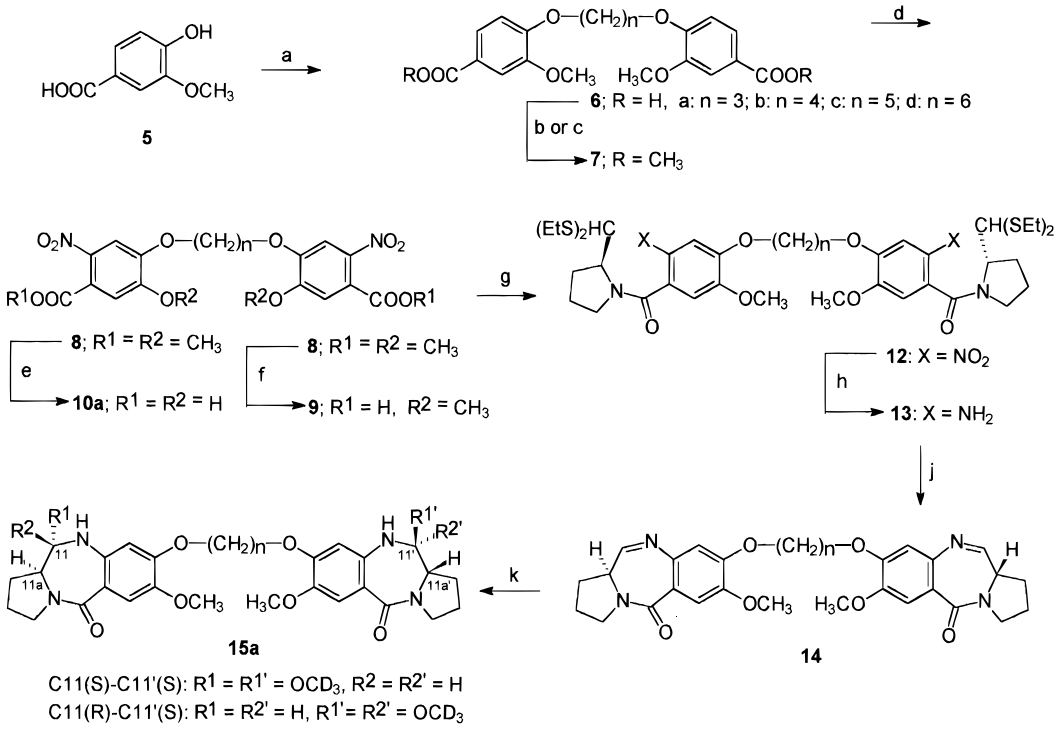
Scheme 1[a]



[a] (a) $I(CH_2)_nI$; $n = 3-6$, THF, NaOH, Δ, 48 h; (b) (i) $(COCl)_2$, THF, DMF, 18 h; (ii) MeOH, 4 h; (c) Me_2SO_4, K_2CO_3, acetone, Δ, 4 h; (d) $SnCl_4$, HNO_3, CH_2Cl_2, −20 °C, 20 min; (e) NaOH, THF, Δ, 12 h; (f) 1 N NaOH, THF, 40 °C, 6 h; (g) (i) $(COCl)_2$, THF, DMF, rt, 18 h; (ii) (2*S*)-pyrrolidine-2-carboxaldehyde diethyl dithioacetal (**11**), Et_3N, 0 °C, 18 h; (h) $SnCl_2 \cdot 2H_2O$, MeOH; (j) $HgCl_2$, $CaCO_3$, MeCN, H_2O, 6 h, rt; (k) CD_3OD.

modeling[5a,7] and NMR[5a,8] experiments indicate that for DSB-120 (i.e., **14**, $n = 3$) spatial separation of the PBD units is optimal for spanning six base-pairs with a preference for 5′-PuGATCPy or 5′-PyGATCPu sequences, and that it actively recognizes the embedded $d(GATC)_2$ sequence. Studies with short oligonucleotides containing defined binding sites have shown that the extended dimer with $n = 5$ (**14c**) is capable of spanning two guanines separated by three base pairs. Furthermore, a significant correlation between DNA-binding affinity, cross-linking efficiency, and cytotoxicity has been found, with the $n = 3$ and $n = 5$ homologues (**14a** and **14c)** displaying optimal effects compared to dimers with an even number of methylenes in the linker.[5b,9] In addition, the dimer adducts appear difficult to repair and there is no cross-resistance with cisplatin in some cell lines.[9] The synthesis of pyrrolobenzodiazepines has recently been reviewed.[10] An efficient synthesis of DSB-120 and related C8-linked pyrrolobenzodiazepine dimers of varying linker length has now been achieved and is reported here.

Our initial objective was to tether two PBD units through their C8-positions *via* a flexible α,ω-alkyl ether linkage with a view to extending the number of spanned base-pairs recognized, thus enhancing DNA sequence-selectivity. Dimers of this type should have the potential to form interstrand cross-links, in addition to possible adducts resulting from monoalkylation. The natural product DC-81 (**4**)[11] was chosen as the monomer PBD unit, and an efficient synthetic pathway developed to provide the target dimers **14a**−**d** in useful quantities and in a stereochemically homogenous form. The overall synthetic strategy is shown in Scheme 1 and is based on formation of the crucial electrophilic N10−C11 imine moiety by cyclization of the B-rings during the last synthetic step. Although there are several methods by which this might be accomplished,[10] using either a linear (e.g., coupling of **9a**−**d** to proline or pyrrolidinemethanol) or convergent (e.g., coupling to either the acetal or thioacetal fragment of type **11**[12]), we chose the latter approach as the amino thioacetal procedure has been successfully applied to the synthesis of a number of PBDs including prothracarcin[12] and DC-81.[11]

A versatile approach was developed to join two units of vanillic acid (**5**) with α,ω-dihaloalkanes of varying length to provide the dimer acids **6a**−**d**. There was initial concern about the possible formation of mixtures of monoalkylated, bisalkylated, and/or elimination products. However, after investigating many different reaction conditions, a procedure involving the reflux of **5** with diiodoalkanes in the presence of aqueous NaOH and THF for 48 h with the exclusion of light was developed that afforded **6a**−**d** in 60−84% yields with no apparent formation of monoalkylated or elimination products. Dibromo- and dichloroalkanes gave inferior yields compared to the diiodo- compounds, and varying the chain length from $n = 3$ to 6 did not appear to affect the efficiency of the reaction.

The next step involved nitration of the aromatic A-rings at the C2-position which usually proceeds smoothly

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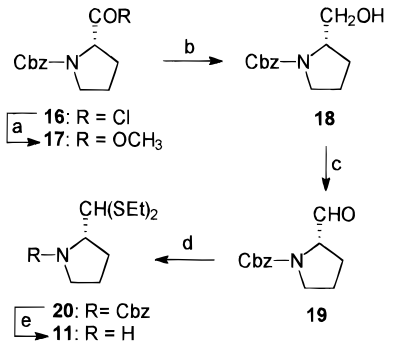
Scheme 2[a]



[a] (a) MeOH, 0 °C; (b) $LiBH_4$, THF, 16 h; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (d) EtSH, TMS-Cl, CH_2Cl_2; (e) TMS-I, CH_2Cl_2.

using $SnCl_4/HNO_3$[11a] in the case of vanillic acid analogues. However, all attempts to nitrate the vanillic acid dimers of type **6** failed using a variety of different reaction conditions, including $NaNO_3/H_2SO_4$, $SnCl_4/HNO_3$, and H_2SO_4/HNO_3. It was concluded that this problem was related to the insoluble nature of the dimer acids **6**. Following conversion to their corresponding methyl esters (**7a**−**d**) in high yield (90−94%) by treatment with either Me_2SO_4/K_2CO_3/acetone or $(COCl)_2/CH_3OH$ (preferred), nitration using $SnCl_4/HNO_3$ in CH_2Cl_2 proceeded smoothly at −20 °C to afford the corresponding arylnitro esters **8a**−**d** in good yield (65−75%). An initial attempt to hydrolyze the methyl ester **8a** by refluxing in aqueous NaOH gave a high melting solid (>350 °C), identified by NMR as the phenolic hydrolysis product (**10a**) in which demethylation of the aromatic ethers had occurred. The electron-withdrawing *p*-nitro groups may be responsible for this phenomenon.[13] However, mild hydrolysis of the esters in aqueous NaOH/THF at 40 °C for 6 h afforded **9a**−**d** in 90−95% yield.

Coupling of nitro acids **9a**−**d** with (2*S*)-pyrrolidine-2-carbaldehyde diethyl dithioacetal (**11**)[12] afforded the bisamides **12a**−**d** in 65−76% yield. Previously, we have reported[12] the preparation of the thioacetal **11** via DIBAL-H-mediated reduction of the Cbz-protected proline ester **17**[14] (i.e., **17** → **19**) (Scheme 2). However, DIBAL-H reduction is often problematic as the yield is only moderate, and it is usually necessary to isolate the aldehyde from both unreacted starting material and the alcohol **18** resulting from over reduction. As an alternative large-scale procedure, the ester **17** prepared via the acid chloride **16**, was reduced with lithium borohydride to afford the alcohol **18** in 79% yield. Swern oxidation[15] of **18** could then be performed on a large scale (∼30 g) to provide **19** in 88% yield. Conversion of this material to the thioacetal **20**, followed by deprotection to give **11**, represented a viable alternative synthesis of this key intermediate.

Reduction of the nitro thioacetal intermediates **12a**−**d** to give the amino thioacetals **13a**−**d** in 60−64% yields was achieved with $SnCl_2 \cdot 2H_2O$. Cyclization[12] with $HgCl_2/CaCO_3$ in CH_3CN/H_2O afforded the target C8-linked dimers (**14a**−**d**; 60−83%), which were characterized by NMR and MS. The relatively large optical rotation values for these final products suggested that the stereochemistry at C11a was retained throughout the synthesis.

Both the ^1H and ^{13}C NMR spectra were consistent with the structures of the target dimers **14a**−**d**. For example, for **14a** the H11 proton of the N10−C11 imine moiety gave a diagnostic doublet at δ 7.66 with a coupling constant of J = 4.4 Hz. Similarly, the C11 carbon appeared as a methine signal at δ 162.4 identified by a DEPT experiment. Further characteristic features were the central methylene protons of the linker, which appeared as a multiplet at δ 2.01−2.17 (2H), and the two neighboring methylenes attached to the phenolic C8-oxygens, which appeared as a multiplet at δ 4.22−4.33 (4H). Interestingly, although the correct molecular ions ($MH^{+\bullet}$) could be obtained for **14a**−**d** by FAB ionization, all attempts at EI-MS gave the surprising result of molecular ions at $M^{+\bullet} + 2$.

A further characteristic of the PBD ring system is the electrophilicity of the N10−C11 imine functionality that is responsible for the DNA-binding of these compounds.[2] The electrophilic properties of **14a** were studied by dissolving it in CD_3OD and monitoring the reaction at C11 (to give diastereomers of type **15a**) by ^1H NMR. The chemical shifts and coupling patterns of the C11 carbon and proton are diagnostic for this addition reaction.[16] The first spectrum examined (after 10 min) indicated that reaction with CD_3OD was approximately 90% complete. The H11 signal for the N10−C11 imine at δ 7.66 and the two aromatic signals (H6 and H9) at δ 6.85 and δ 7.51 had nearly disappeared and had been replaced with three new sets of aromatic signals (one major, one minor, and one trace). New H11 signals at δ 4.58 (s) and δ 4.40 (d, J = 9.0 Hz) were also observed. Based on the possible structures of adducts of type **15a**, it is evident that methanol can approach from either the *re* or *si* face of the N10−C11 imine moiety to give rise to three possible diastereoisomers: C11(*S*)−C11′(*S*), C11(*R*)−C11′(*S*) or C11(*R*)−C11′(*R*). Based on the initial ratio of the H11 signals observed [H11(*R*):H11(*S*), 20:80], the major and minor isomers were considered to be the C11(*S*)−C11′(*S*) and C11(*R*)−C11′(*S*) diastereomers (**15a**), respectively. After 4 h the ratio had not changed significantly, although the trace isomer had disappeared completely indicating that reaction was complete. Interestingly, under identical conditions, reaction of DC-81 with CD_3OD provides an initial predominance [C11(*R*):C11(*S*), 0.6:1] of the C11(*S*) isomer, although reaction is complete within 5 min.[11b] However, after 24 h, epimerization of the dimer to a slight predominance of the C11(*R*)−C11′(*S*) isomer occurred [H11(*R*):H11(*S*), 1:0.8], suggesting that a structural feature of the dimer may slow the kinetics of nucleophilic attack at the N10−C11 imine moiety and subsequent epimerization of the new C11-substituent compared to the monomer compounds. As with DC-81, conversion of the methyl ether forms back to the N10−C11 imine (**14a**) could be achieved by two cycles of dissolving in dry $CHCl_3$, followed by evaporation of the solvent *in vacuo* at 25−40 °C.[11b]

The DNA binding affinity of the PBD dimers **14a**−**d** was examined by thermal denaturation studies.[5a,b] An increase in helix melting temperature (ΔT_m) of up to 15.1 °C (e.g., for **14a**) was observed compared to untreated control DNA after incubation at 37 °C for 18 h (5:1 mol ratio of DNA−ligand for 100 μM dm^{-3}, phosphate buffer, pH 7.0). In the same experiment, the monomer (DC-81, **4**) gives only a small increase in T_m (0.7 °C), consistent with the notion that the PBD dimers form stable inter-

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strand cross-links. The DNA cross-linking efficiency of dimers **14a**−**d** was investigated using an assay[17] involving linear double-stranded DNA derived from the plasmid pBR322. Following complete denaturation to the single-stranded form, the presence of an interstrand cross-link results in renaturation to double-stranded DNA during electrophoresis in a neutral agarose gel. Compounds **14a** (n = 3) and **14c** (n = 5) are broadly similar in cross-linking efficiency (i.e. concentration required for 50% cross-linking of pBR322 DNA = 0.055 and 0.070 μmol dm^{-3} for **14a** and **14c**, respectively), whereas dimers **14b** (n = 4) and **14d** (n = 6) are approximately 18- and 14-fold less efficient, respectively. These results are consistent with the determined ΔT_m values, which reflect the differences in ability of the compounds to stabilize DNA helix−coil transitions. The number of base pairs spanned by the dimers and their sequence-selectivity are described in the introduction.[5a,7,8]

In vitro cytotoxicity data in human K_{562} and rodent ADJ/PC6 (e.g., **14a**: IC_{50} = 0.0005 μM in PC6 for a 4-day exposure) cell lines correlate with both the thermal denaturation data and the cross-linking efficiencies.[5b] Considering the lower activity (e.g., IC_{50} = 0.33 μM in PC6) of the monomer DC-81 (**4**),[5b,11b] these results suggest that the interstrand cross-links probably represent the cytotoxic lesions leading to cell death.

Conclusions

In conclusion, an efficient route has been developed for the synthesis of DNA-binding interstrand cross-linking agents of type **14a**−**d**, which span up to seven base pairs and have exquisite DNA cross-linking and cytotoxic properties. The synthesis should be adaptable to prepare analogues with modified linkers and substituents at various positions. A structure-activity study is presently underway in the Portsmouth laboratory with a view to the development of possible clinical candidates.

Experimental Section

General Methods. Melting points (mp) were determined on a Gallenkamp P1384 digital melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded using a Perkin-Elmer 297 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL GSX 270 MHz FT-NMR spectrometer operating at 20 °C ±1 °C. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. Spin multiplicities are described as: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), p (pentuplet), or m (multiplet). Mass spectra (MS) were recorded using a JEOL JMS-DX 303 GC mass spectrometer (EI mode: 70 eV, source 117−147 °C). Accurate molecular masses (HRMS) were determined by peak matching using perfluorokerosene (PFK) as an internal mass marker, and FAB mass spectra were obtained from a glycerol/thioglycerol/trifluoroacetic acid (1:1:0.1) matrix with a source temperature of 180 °C. Optical rotations at the Na-D line were obtained at ambient temperature using a Perkin-Elmer 141 polarimeter. Elemental analyses were carried out by the Department of Pharmaceutical Chemistry at the School of Pharmacy, 29-39 Brunswick Square, London WC1N 1AX. Analytical results were generally within ±0.2% of the theoretical values. Flash chromatography was performed using Aldrich flash chromatography "Silica Gel-60" (E. Merck, 230−400 mesh). Thin-layer chromatography (TLC) was performed using GF_{254} silica gel (with fluorescent indicator) on glass plates. All solvents and reagents, unless otherwise stated, were supplied by Aldrich Chemical Company Ltd and were used as supplied. Anhydrous solvents were prepared by distillation under a dry nitrogen atmosphere in the presence of an appropriate drying agent and were stored over 4 Å molecular sieves or sodium wire. Petroleum ether refers to the fraction boiling at 60−80 °C.

Bis(4-carboxy-2-methoxyphenoxy)alkanes 6a−d. A solution of the appropriate diiodoalkane (29.7 mmol) in THF (50 mL) was added dropwise over a period of 4 h to a vigorously stirred solution of vanillic acid (10 g, 59.5 mmol) in THF (100 mL) and aqueous NaOH (225 mL, 0.05 M) at 65 °C in the absence of light (foil-wrapped flask). After reflux for 48 h in the dark, the suspension was cooled, washed with hexane (3 × 100 mL) and the THF removed by evaporation *in vacuo*. The aqueous residue was acidified to pH 1 with concd HCl and the resultant precipitate filtered, dried, and recrystallized from glacial acetic acid to afford the corresponding dimer acid as a light crystalline solid:

1′,3′-Bis(4-carboxy-2-methoxyphenoxy)propane (6a). Mp 238−240 °C; Yield = 9.39 g (84% from 8.8 g of diiodopropane); ^{1}H NMR (DMSO-d_6): δ 2.23 (t, 2H, J = 6.0 Hz), 3.80 (s, 6H), 4.20 (t, 4H, J = 6.0 Hz), 7.09 (d, 2H, J = 8.4 Hz), 7.45 (d, 2H, J = 1.8 Hz), 7.54 (dd, 2H, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 12.76 (bs, 2H); ^{13}C NMR ($CDCl_3$): δ 28.4, 55.4, 64.8, 111.9, 112.0, 122.9, 123.0, 148.3, 151.6, 167.0; IR (KBr) 3600−2000, 1680, 1600, 1515, 1465, 1430, 1345, 1310, 1270, 1225, 1180, 1140, 1115, 1030, 990, 970, 950, 925, 875, 850, 825, 765, 725, 645 cm^{-1}; EIMS m/z (relative intensity) 376 ($M^{+\bullet}$, 28), 360 (3), 249 (2), 209 (45), 165 (29), 153 (16), 151 (19), 137 (19), 121 (7), 78 (15), 44 (100); HRMS: Calcd for 376.1158 ($C_{19}H_{20}O_8$). Found 376.1146.

1′,4′-Bis(4-carboxy-2-methoxyphenoxy)butane (6b). Mp 248−249 °C; Yield = 9.45 g (82% from 9.2 g of diiodobutane); ^{1}H NMR (DMSO-d_6): δ 1.92−1.95 (m, 4H), 3.80 (s, 6H), 4.09−4.13 (m, 4H), 7.05 (d, 2H, J = 8.5 Hz), 7.45 (s, 2H), 7.56 (dd, 2H, J_1 = 8.5 Hz, J_2 = 2.0 Hz), 12.4 (bs, 2H); ^{13}C NMR (DMSO-d_6): δ 25.3, 55.3, 67.9, 111.7, 111.9, 122.8, 148.3, 151.9, 167.0, 172.0; IR (KBr) 3380−2200, 1680, 1580, 1500, 1450, 1405, 1330, 1290, 1260, 1210, 1130, 1100, 1015, 985, 755, 745 cm^{-1}; EIMS m/z (relative intensity) 390 ($M^{+\bullet}$, 14), 223 (100), 181 (58), 168 (28), 153 (15), 55 (94), 44 (11). Anal. Calcd for $C_{20}H_{22}O_8$: C, 61.52; H, 5.69. Found C, 61.09; H, 5.89.

1′,5′-Bis(4-carboxy-2-methoxyphenoxy)pentane (6c). Mp 219−220 °C; Yield = 8.62 g (72% from 9.6 g of diiodopentane); ^{1}H NMR (DMSO-d_6): δ 1.57−1.67 (m, 2H), 1.77−1.85 (m, 4H), 3.80 (s, 6H), 4.05 (t, 4H, J = 6.4 Hz), 7.05 (d, 2H, J = 8.5 Hz), 7.45 (s, 2H), 7.55 (dd, 2H, J_1 = 8.6 Hz, J_2 = 2.0 Hz), 12.31 (bs, 2H); ^{13}C NMR (DMSO-d_6): δ 22.2, 28.2, 55.4, 68.1, 111.7, 111.9, 123.1, 148.3, 152.0, 167.0, 172.0; IR (KBr) 3400−2100, 1680, 1580, 1500, 1450, 1415, 1290, 1270, 1220, 1175, 1125, 1010, 935, 865, 805, 785, 750 cm^{-1}; EIMS m/z (relative intensity) 404 ($M^{+\bullet}$, 9), 237 (37), 223 (5), 181, 168, 93 (7), 69 (87), 55 (14), 44 (100). Anal. Calcd for $C_{21}H_{24}O_8$: C, 62.36; H, 5.99. Found C, 62.31; H, 6.21.

1′,6′-Bis(4-carboxy-2-methoxyphenoxy)hexane (6d). Mp 203−204 °C; Yield = 7.42 g (60% from 10.0 g of diiodohexane); ^{1}H NMR (DMSO-d_6): δ 1.47−1.51 (m, 4H), 1.74−1.89 (m, 4H), 3.80 (s, 6H), 4.04 (t, 4H, J = 6.5 Hz), 7.02 (d, 2H, J = 8.5 Hz), 7.44 (s, 2H), 7.53 (dd, 2H, J_1 = 8.5, J_2 = 1.95 Hz), 12.04 (bs, 2H); ^{13}C NMR (DMSO-d_6): δ 25.1, 28.5, 55.7, 68.4, 112.3, 112.8, 123.1, 148.7, 152.2, 166.9, 171.7; EIMS m/z (relative intensity) 418 ($M^{+\bullet}$, 24), 251 (12), 181 (10), 168 (100), 153 (19), 125 (6), 93 (7), 83 (75), 65 (9), 55 (89), 44 (11), 41 (31); IR (KBr) 3300−2200, 1680, 1600, 1515, 1450, 1410, 1290, 1260, 1225, 1120, 1100, 1020, 990, 945, 810, 785, 755 cm^{-1}; HRMS: Calcd for 404.1471 ($C_{21}H_{24}O_8$). Found 404.1469.

Bis[2-methoxy-4-(methoxycarbonyl)phenoxy]alkanes 7a−d. Method A: A mixture of the appropriate bis-(4-carboxy-2-methoxyphenoxy)alkane **6a**−**d** (10.0 mmol), dimethyl sulfate (2.78 g, 20.0 mmol), and K_2CO_3 (30.0 mmol) in dry acetone (100 mL) was refluxed for 2 h until TLC indicated reaction was complete. The acetone was removed *in vacuo* and crushed ice added to the residue. The resulting solid was filtered, washed with water, and dried to afford the corresponding ester as a light brown solid:

(17) Hartley, J. A.; Berardini, M. D.; Souhami, R. L. *Anal. Biochem.* **1990**, *19*, 131.

Method B: DMF (2 drops) was added to a stirred suspension of oxalyl chloride (3.1 g, 24.4 mmol, 2.4 equiv) and the appropriate bis(4-carboxy-2-methoxyphenoxy)alkane (10 mmol) in dry THF (25 mL), and stirring was continued for 6 h. The THF was removed by evaporation *in vacuo*, and the resultant solid dissolved in dry MeOH (60 mL). After stirring for a further 2 h, the MeOH was removed *in vacuo* and the residue triturated with water (30 mL). The resultant solid was collected by filtration:

1′,3′-Bis[2-methoxy-4-(methoxycarbonyl)phenoxy]propane (7a). Mp 153−155 °C; Yield = 3.8 g (94% from 3.76 g of **6a**); ^{1}H NMR ($CDCl_3$): δ 2.39−2.43 (m, 2H), 3.89 (s, 6H), 3.90 (s, 6H), 4.30 (t, 4H, J = 6.1 Hz), 6.93 (d, 2H, J = 8.5 Hz), 7.54 (d, 2H, J = 2.0 Hz), 7.64 (dd, 2H, J_1 = 8.5 Hz, J_2 = 2.0 Hz); ^{13}C NMR ($CDCl_3$): δ 28.9, 52.0, 56.0, 65.4, 111.7, 112.3, 122.8, 123.5, 148.9, 152.2, 166.9; IR (KBr) 2940, 1710, 1600, 1510, 1460, 1435, 1410, 1340, 1290, 1270, 1215, 1180, 1130, 1100, 1060, 1025, 975, 870, 760, 720 cm^{-1}; EIMS m/z (relative intensity) 404 ($M^{+\bullet}$, 92), 373 (19), 256 (3), 223 (100), 195 (49), 191 (58), 171 (18), 164 (39), 151 (51), 135 (12), 119 (20), 107 (11), 85 (61), 83 (90), 59 (23), 43 (24); EIHRMS m/z Calcd for 404.1472 ($C_{21}H_{24}O_8$). Found 404.1457.

1′,4′-Bis[2-methoxy-4-(methoxycarbonyl)phenoxy]butane (7b). Mp 151−152 °C; Yield = 5.98 g (92% from 6.06 g of **6b**); ^{1}H NMR ($CDCl_3$): δ 2.06−2.10 (m, 4H), 3.89 (s, 6H), 3.91 (s, 6H), 4.16−4.20 (m, 4H), 6.89 (d, 2H, J = 10.4 Hz), 7.52 (d, 2H, J = 2.0 Hz), 7.64 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$): δ 25.8, 52.0, 68.5, 111.4, 112.2, 122.5, 123.5, 148.8, 152.4, 166.9; IR (KBr) 2920, 2900, 1720, 1580, 1520, 1390, 1370, 2840, 1270, 1250, 1220, 1150, 1125, 1085; EIMS m/z (relative intensity) 418 ($M^{+\bullet}$, 7), 237 (55), 205 (2.33), 195 (22), 151 (12), 135 (2), 55 (29), 44 (7), 41 (4); EIHRMS m/z Calcd for 418.1661 ($C_{22}H_{26}O_8$). Found 418.1695.

1′,5′-Bis[2-methoxy-4-(methoxycarbonyl)phenoxy]pentane (7c). Mp 127−128 °C; Yield = 6.12 g (90% from 7.27 g of **6c**); ^{1}H NMR ($CDCl_3$): δ 2.06−2.10 (m, 4H), 3.89 (s, 6H), 3.91 (s, 6H), 4.18 (m, 4H), 6.89 (d, 2H, J = 10.4 Hz), 7.52 (d, 2H, J = 2.0 Hz), 7.65 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$): δ 22.5, 28.7, 52.0, 56.0, 68.9, 111.4, 112.3, 122.5, 123.5, 148.9, 152.5, 166.9; IR (KBr) 2920, 1720, 1600, 1510, 1435, 1410, 1290, 1270, 1210, 1175, 1130, 1000 cm^{-1}; EIMS m/z (relative intensity) 432 ($M^{+\bullet}$, 34), 401 (76), 354 (49), 251 (48), 216 (75), 195 (100), 182 (63), 151 (32), 69 (56), 44 (77), 41 (40); EIHRMS m/z Calcd for 432.1833 ($C_{23}H_{28}O_8$). Found 432.1881.

1′,6′-Bis[2-methoxy-4-(methoxycarbonyl)phenoxy]hexane (7d). Mp 126−127 °C; Yield = 4.06 g (91% from 4.18 g of **6d**); ^{1}H NMR ($CDCl_3$): δ 1.56 (m, 4H), 1.90 (m, 4H), 3.89 (s, 6H), 3.91 (s, 6H), 4.09 (m, 4H), 6.87 (d, 2H, J = 8.4 Hz), 7.63 (d, 2H, J = 2.0 Hz), 7.66 (d, 2H, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$): δ 25.7, 28.9, 51.9, 56.0, 68.7, 111.4, 112.3, 122.4, 123.5, 148.8, 152.5, 166.9; IR (KBr) 2925, 2860, 1430, 1700, 1595, 1500, 1410, 1340, 1290, 1270, 1220, 1180, 1130, 1000; EIMS m/z (relative intensity) 446 ($M^{+\bullet}$, 100), 432 (9), 415 (20), 391 (20), 282 (25), 251 (9), 211 (11), 182 (155), 151 (73), 85 (28), 69 (4), 55 (39), 44 (5); EIHRMS m/z Calcd for 446.1995 ($C_{24}H_{30}O_8$). Found 446.2049.

Bis[2-methoxy-4-(methoxycarbonyl)-5-nitrophenoxy]alkanes 8a−d. A freshly prepared mixture of $SnCl_4$ (6.48 g, 24.9 mmol) and fuming nitric acid (2.0 g, 31.7 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 5 min to a stirred solution of the appropriate methyl ester **7a**−**d** (4.0 g, 10.0 mmol) in CH_2Cl_2 (60 mL) at −25 °C (dry ice/CCl_4). The mixture was maintained at the same temperature for a further 10 min, quenched with water (150 mL), and then allowed to return to room temperature. The organic layer was separated and the aqueous phase extracted with ethyl acetate (2 × 100 mL). The combined organic phase was dried (Na_2SO_4) and evaporated *in vacuo* to afford the corresponding nitroaryl ester as a brown gum which was crystallized from ethyl acetate/hexane to afford yellow prisms:

1′,3′-Bis[2-methoxy-4-(methoxycarbonyl)-5-nitrophenoxy]propane (8a). Mp 165−168 °C; Yield = 3.52 g (72% from 4.0 g of **7a**); ^{1}H NMR ($CDCl_3$): δ 2.43 (m, 2H), 3.90 (s, 6H), 3.95 (s, 6H), 4.32 (t, 4H, J = 6.0 Hz), 7.06 (s, 2H), 7.49 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 28.6, 53.3, 56.6, 65.6, 108.1, 110.9, 121.9, 149.5, 152.8, 167.0; IR (KBr) 2940, 1710, 1600, 1575, 1520, 1420, 1355, 1280, 1250, 1210, 1175, 1140, 1045, 990, 960, 870, 830, 750 cm^{-1}; EIMS m/z (relative intensity) 494 ($M^{+\bullet}$, 94), 463 (14), 449 (8), 404 (3), 285 (3), 268 (28), 267 (29), 240 (32), 236 (68), 222 (94), 207 (6) 194 (45), 164 (19), 151 (15), 122 (14), 109 (9), 86 (47), 84 (73), 75 (12), 59 (29), 49 (100), 41 (73); EIHRMS m/z Calcd for 494.1173 ($C_{21}H_{22}N_2O_{12}$). Found 494.1170.

1′,4′-Bis[2-methoxy-4-(methoxycarbonyl)-5-nitrophenoxy]butane (8b). Mp 180−182 °C; Yield = 3.45 g (68% from 4.18 g of **7b**); ^{1}H NMR ($CDCl_3$): δ 2.10−2.14 (m, 4H), 3.91 (s, 6H), 3.96 (s, 6H), 4.23 (t, 4H, J = 10.9 Hz), 7.03 (s, 2H), 7.44 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 25.6, 53.2, 56.5, 69.2, 107.3, 110.8, 121.5, 141.1, 149.6, 152.7, 166.3; IR (KBr) 2940, 1720, 1590, 1520, 1450, 1425, 1570, 1340, 1280, 1210, 1140, 1040; EIMS m/z (relative intensity) 508 ($M^{+\bullet}$, 12), 476 (2), 445 (1), 281 (63), 250 (3), 240 (14), 196 (24), 182 (6), 55 (45), 44 (7); EIHRMS m/z Calcd for 508.1329 ($C_{22}H_{24}N_2O_{12}$). Found 508.1326.

1′,5′-Bis[2-methoxy-4-(methoxycarbonyl)-5-nitrophenoxy]pentane (8c). Mp 147−149 °C; Yield = 3.90 g (75% from 4.3 g of **7c**); ^{1}H NMR ($CDCl_3$): δ 1.71−1.76 (m, 2H), 1.93−2.04 (m, 4H), 3.91 (s, 6H), 3.96 (s, 6H), 4.10−4.16 (m, 4H), 7.08 (s, 2H), 7.44 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 22.5, 28.5, 53.2, 56.5, 69.3, 107.9, 110.9, 121.5, 141.2, 149.8, 152.8, 166.4; IR (KBr) 2920, 1430, 1720, 1600, 1580, 1530, 1350, 1280, 1260, 1130, 1040; EIMS m/z (relative intensity) 522 ($M^{+\bullet}$, 17), 491 (30), 296 (39), 264 (75), 251 (27), 196 (55), 182 (35), 69 (12), 55 (92), 44 (12), 41 (58); EIHRMS m/z Calcd for 522.1486 ($C_{23}H_{26}N_2O_{12}$). Found 522.1486.

1′,6′-Bis[2-methoxy-4-(methoxycarbonyl)-5-nitrophenoxy]hexane (8d). Mp 132−134 °C; Yield = 3.44 g (65% from 4.40 g of **7d**); ^{1}H NMR ($CDCl_3$): δ 1.55−1.58 (m, 4H), 1.89−1.93 (m, 4H), 3.91 (s, 6H), 3.96 (s, 6H), 4.11 (t, 4H, J = 13.2 Hz), 7.07 (s, 2H), 7.44 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 25.5, 28.6, 53.3, 56.6, 69.4, 107.8, 110.9, 121.4, 141.1, 149.9, 152.7, 166.4; EIMS m/z (relative intensity) 537 ($M^{+\bullet}$, 22), 507 (14), 505 (20), 477 (27), 257 (17), 254 (24), 252 (15), 240 (16), 210 (28), 198 (98), 112 (32), 107 (38), 85 (100), 81 (99); EIHRMS m/z Calcd for 536.1653 ($C_{24}H_{28}N_2O_{12}$). Found 536.1642.

Bis(4-carboxy-2-methoxy-5-nitrophenoxy)alkanes 9a−d. A suspension of the appropriate methyl ester **8a**−**d** (approximately 1.0 g) in a mixture of THF (20 mL) and aqueous NaOH (1 M, 20 mL) was stirred at 40 °C for 6 h until TLC (ethyl acetate/hexane, 1:1) indicated that reaction was complete. The THF was removed by evaporation *in vacuo*, and the remaining aqueous solution adjusted to pH 1 with concd HCl. The resulting precipitate was collected by filtration and dried to afford the nitro acid as a yellow solid:

1′,3′-Bis(4-carboxy-2-methoxy-5-nitrophenoxy)propane (9a). Mp 243−246 °C; Yield = 0.91 g (95% from 1.02 g of **8a**); ^{1}H NMR (DMSO-d_6): δ 2.25 (t, 2H, J = 5.9 Hz), 3.90 (s, 6H), 4.27 (t, 4H, J = 5.9 Hz), 7.29 (s, 2H), 7.62 (s, 2H), 13.6 (bs, 2H); ^{13}C NMR (DMSO-d_6): δ 28.0, 56.3, 65.7, 108.0, 111.2, 121.1, 141.3, 149.1, 151.7, 165.9; IR (KBr) 3620−2280, 1700, 1595, 1570, 1515, 1460, 1415, 1350, 1270, 1210, 1180, 1135, 1045, 930, 880, 810, 750, 730, 645 cm^{-1}; EIMS m/z (relative intensity) 467 ($MH^{+\bullet}$, 1), 450 (1), 436 (3), 423 (8), 378 (4), 268 (1), 255 (4), 236 (4), 210 (7), 194 (2), 182 (7), 164 (14), 153 (2), 123 (3), 91 (6), 77 (3), 55 (5), 44 (100); EIHRMS m/z Calcd for 466.0860 ($C_{19}H_{18}N_2O_{12}$). Found 466.0871.

1′,4′-Bis(4-carboxy-2-methoxy-5-nitrophenoxy)butane (9b). Mp 282−284 °C; Yield = 0.967 g (93% from 1.10 g of **8b**); ^{1}H NMR (DMSO-d_6): δ 1.93−1.96 (m, 2H), 3.89 (s, 6H), 4.18−4.25 (m, 4H), 7.27 (s, 2H), 7.56 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 24.9, 56.3, 68.6, 107.7, 111.1, 120.9, 141.3, 149.3, 151.7, 166.0; IR (KBr) 3620−2280, 1700, 1595, 1570, 1515, 1460, 1415, 1350, 1270, 1210, 1180, 1135, 1045, 930, 880, 810, 750, 730, 645 cm^{-1}.

1′,5′-Bis(4-carboxy-2-methoxy-5-nitrophenoxy)pentane (9c). Mp 283−285 °C; Yield = 826 mg (90% from 0.97 g of **8c**); ^{1}H NMR (DMSO-d_6): δ 1.56−1.59 (m, 2H), 1.81−1.86 (m, 4H), 3.92 (s, 6H), 4.11−4.15 (m, 4H), 7.29 (s, 2H), 7.58 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 21.9, 27.9, 56.3, 68.9, 107.7, 111.1, 120.8, 141.4, 149.4, 151.7, 165.9; IR (KBr) 3620−2280, 1700, 1595, 1570, 1515, 1460, 1415, 1350, 1270, 1210, 1180, 1135, 1045, 930, 880, 810, 750, 730, 645 cm^{-1}.

1′,6′-Bis(4-carboxy-2-methoxy-5-nitrophenoxy)hexane (9d). Mp 222−224 °C; Yield = 785 mg (90% from 0.92 g of **8d**); ^{1}H NMR (DMSO-d_6): δ 1.48 (m, 4H), 1.76−1.77 (m, 4H), 3.91 (s, 6H), 4.09−4.11 (m, 4H), 7.23 (s, 2H), 7.57 (s, 2H); ^{13}C NMR (DMSO-d_6): δ 24.9, 28.8, 56.3, 68.9, 107.7, 111.2, 120.8, 141.4, 149.4, 151.7, 166.0; IR (KBr) 3620−2280, 1700, 1595, 1570, 1515, 1460, 1415, 1350, 1270, 1210, 1180, 1135, 1045, 930, 880, 810, 750, 730, 645 cm^{-1}.

1′,3′-Bis(4-carboxy-2-hydroxy-5-nitrophenoxy)propane (10a). NaOH (0.5 M, 15 mL) was added to a solution of **8a** (0.7 g, 1.5 mmol) in THF (20 mL), and the solution refluxed for 12 h until TLC (EtOAc/hexane, 1:1) indicated that reaction was complete. The THF was removed *in vacuo* and the residue acidified to pH 1 with HCl. The resulting precipitate was collected by filtration and dried to afford **10a** as a yellow solid (0.54 g, 82%): ^{1}H NMR (DMSO-d_6): δ 2.24 (t, 2H, J = 5.86 Hz), 4.30 (t, 4H, J = 5.86 Hz), 7.09 (s, 2H), 7.60 (s, 2H), 10.72 (bs, 2H), 13.35 (bs, 2H); ^{13}C NMR (DMSO-d_6): δ 28.0, 65.5, 108.7, 114.9, 122.2, 139.7, 147.8, 150.8, 166.2; IR (KBr) 3600, 3450, 3350−2300, 1690, 1610, 1570, 1510, 1430, 1380, 1345, 1280, 1260, 1190, 1045, 950, 870, 830, 750, 720, 640 cm^{-1}; EIMS m/z (relative intensity) 407 ($M^{+\bullet}$, 3), 382 (5), 354 (7), 326 (5), 269 (4), 219 (10), 207 (6), 192 (3), 164 (3), 138 (7), 136 (6), 98 (4), 91 (100).

1,1′-[[(Alkane-α,ω-diyl)dioxy]bis[(2-nitro-5-methoxy-1,4-phenylene)carbonyl]]bis[pyrrolidine-2-carboxaldehyde ethyl dithioacetal] 12a−d. *N*,*N*-Dimethylformamide (2 drops) was added to a stirred suspension of the dimer acid (1.07 mmol) and oxalyl chloride (0.34 g, 2.69 mmol, 2.5 equiv) in dry THF (15 mL), and stirring was continued for 4 h. After evaporation of the THF *in vacuo*, the resultant yellow residue was redissolved in dry THF (10 mL) and added dropwise over a period of 25 min to a vigorously stirred suspension of (2*S*)-pyrrolidine-2-carbaldehyde diethyl thioacetal[12] (2.68 mmol, 2.5 equiv), Et_3N (0.46g, 4.5 mmol, 4.2 equiv), and ice/water (0.6 mL) cooled in an ice bath. The mixture was then warmed to room temperature and stirred for a further 1.5 h. After removal of the THF by evaporation *in vacuo*, the residue was diluted with water (2 × 50 mL) and extracted with EtOAc (3 × 25 mL). The aqueous phase was adjusted to pH 3 with concd HCl and also extracted with EtOAc (2 × 50 mL). The combined organic phase was washed with water (3 × 25 mL) and brine (3 × 25 mL) and dried (anhyd $MgSO_4$) and the solvent removed by evaporation *in vacuo* to afford a dark red oil which was purified by flash chromatography (EtOAc/hexane, 1:1; TLC: EtOAc/hexane, 3:2) to afford the corresponding bis(amide) as a pale yellow oil. These compounds failed to produce significant parent ions by mass spectrometry using a number of different ionization techniques:

1,1′-[[(Propane-1,3-diyl)dioxy]bis[(2-nitro-5-methoxy-1,4-phenylene)carbonyl]]bis[pyrrolidine-2-carboxaldehyde diethyl dithioacetal] (12a). Yield = 685 mg (76% from 0.5 g of **9a**); ^{1}H NMR ($CDCl_3$): δ 1.25−1.38 (m, 14H), 1.76−2.47 (m, 8H), 2.67−2.87 (m, 8H), 3.21−3.30 (m, 4H), 3.95 (s, 6H) 4.30−4.35 (m, 4H), 4.67−4.74 (m, 2H), 4.87 (d, 2H, J = 3.9 Hz), 6.83 (s, 2H), 7.72 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 15.0, 24.6, 26.3, 26.6, 27.2, 50.2, 52.8, 56.5, 61.1, 65.6, 108.4, 109.3, 128.5, 137.2, 148.2, 154.5, 166.5; IR (neat) 2930, 1625, 1570, 1510, 1445, 1420, 1370, 1330, 1270, 1215, 1050, 750 cm^{-1}.

1,1′-[[(Butane-1,4-diyl)dioxy]bis[(2-nitro-5-methoxy-1,4-phenylene)carbonyl]]bis[pyrrolidine-2-carboxaldehyde diethyl dithioacetal] (12b). Yield = 590 mg (65% from 0.51 g of **9b**); ^{1}H NMR ($CDCl_3$): δ 1.32−1.38 (m, 14H), 1.70−2.40 (m, 10H), 2.67−2.85 (m, 8H), 3.89−3.95 (m, 10H), 4.11−4.22 (m, 6H), 4.72−4.87 (m, 2H), 4.88 (d, 2H, J = 3.84 Hz), 6.82 (s, 2H), 7.69 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 15.0, 24.6, 26.3, 26.6, 27.2, 29.7, 50.2, 52.8, 56.5, 61.1, 69.1, 108.0, 109.2, 128.2, 137.2, 148.3, 154.4, 166.6; IR (neat) 2935, 1630, 1570, 1515, 1445, 1420, 1370, 1330, 1270, 1220, 1050, 750 cm^{-1}.

1,1′-[[(Pentane-1,5-diyl)dioxy]bis[(2-nitro-5-methoxy-1,4-phenylene)carbonyl]]bis[pyrrolidine-2-carboxaldehyde diethyl dithioacetal] (12c). Yield = 640 mg (70% from 0.52 g of **9c**); ^{1}H NMR ($CDCl_3$): δ 1.31−1.38 (m, 14H), 1.66−2.32 (m, 18H), 2.67−2.85 (m, 8H), 3.22−3.30 (m, 4H), 3.95 (s, 6H), 3.97−4.16 (m, 4H), 4.67−4.71 (m, 2H), 4.73 (d, 2H, J = 6.59 Hz), 6.83 (s, 2H), 7.68 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 15.1, 22.5, 24.6, 26.3, 27.2, 50.2, 52.8, 56.5, 61.1, 69.2, 108.1, 109.3, 128.2, 137.3, 148.4, 154.4, 166.6; IR (neat) 2920, 1630, 1570, 1510, 1450, 1420, 1370, 1330, 1270, 1220, 1050, 750 cm^{-1}.

1,1′-[[(Hexane-1,6-diyl)dioxy]bis[(2-nitro-5-methoxy-1,4-phenylene)carbonyl]]bis[pyrrolidine-2-carboxaldehyde diethyl dithioacetal] (12d). Yield = 617 mg (67% from 0.53 g of **9d**); ^{1}H NMR ($CDCl_3$): δ 1.34−1.36 (m, 12H), 1.58−1.60 (m, 4H), 1.82−2.30 (m, 12H), 2.70−2.83 (m, 8H), 3.22−3.30 (m, 4H), 3.95 (s, 6H), 4.11−4.14 (m, 4H), 4.68−4.75 (m, 2H), 4.88 (d, 2H, J = 3.9 Hz), 6.83 (s, 2H), 7.68 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 15.0, 24.6, 25.7, 26.3, 26.6, 27.2, 28.7, 50.2, 52.8, 56.5, 61.1, 69.4, 108.1, 109.2, 128.1, 137.3, 148.5, 154.4, 166.6; IR (neat) 2925, 1630, 1575, 1515, 1445, 1430, 1375, 1335, 1265, 1230, 1045, 745 cm^{-1}.

1,1′-[[(Alkane-α,ω-diyl)dioxy]bis[(2-amino-5-methoxy-1,4-phenylene)carbonyl]]bis[pyrrolidine-2-carboxaldehyde diethyl dithioacetal] 13a−d. A solution of the dinitro thioacetal (0.59 mmol) and $SnCl_2{\cdot}2H_2O$ (1.37 g, 6.0 mmol) in methanol (15 mL) was refluxed for 40 min until TLC (EtOAc/hexane, 4:1) indicated that reaction was complete. The solvent was removed by evaporation *in vacuo* and the residue cooled to 0 °C and then treated with saturated $NaHCO_3$ solution. The resulting solid was triturated with ethyl acetate (2 × 50 mL), and the mixture was allowed to stir at room temperature for up to 4 h. The suspension was filtered through a short bed of Celite, which was rinsed with ethyl acetate (2 × 50 mL). The combined filtrate was evaporated *in vacuo* to afford the corresponding diamino thioacetal as a light yellow foam. Further purification by flash chromatography (ethyl acetate) afforded a yellow oil which, due to potential stability problems,[12] was briefly characterized by IR and/or ^{1}H NMR and then used directly in the next step:

1,1′-[[(Propane-1,3-diyl)dioxy]bis[(2-amino-5-methoxy-1,4-phenylene)carbonyl]]bis[pyrrolidine-2-carboxaldehyde diethyl dithioacetal] (13a). Yield = 297 mg (64% from 0.5 g of **12a**); IR (neat) 3425, 3315, 2930, 1720, 1620, 1590, 1505, 1460, 1455, 1400, 1260, 1165, 1030, 750 cm^{-1}.

1,1′-[[(Butane-1,4-diyl)dioxy]bis[(2-amino-5-methoxy-1,4-phenylene)carbonyl]]bis[pyrrolidine-2-carboxaldehyde diethyl dithioacetal] (13b). Yield = 285 mg (60% from 0.51 g of **12b**); ^{1}H NMR ($CDCl_3$): δ 1.21−1.49 (m, 12H), 1.50−1.80 (m, 4H), 1.85−2.04 (m, 4H), 2.23−2.41 (m, 4H), 2.64−2.90 (m, 8H), 3.61−3.80 (m, 10H; including singlet for 6H at 3.77), 4.19−4.30 (m, 4H), 4.56−4.81 (m, 6H), 6.29 (s, 2H), 6.83 (s, 2H); IR (neat) 3430, 3320, 2930, 1710, 1620,1590, 1505, 1465, 1455, 1410, 1265, 1165, 1030, 750 cm^{-1}.

1,1′-[[(Pentane-1,5-diyl)dioxy]bis[(2-amino-5-methoxy-1,4-phenylene)carbonyl]]bis[pyrrolidine-2-carboxaldehyde diethyl dithioacetal] (13c). Yield = 310 mg (64% from 0.52 g of **12c**); IR (neat) 3430, 3320, 2930, 1710, 1620, 1590, 1505, 1465, 1455, 1410, 1265, 1165, 1030, 750 cm^{-1}.

1,1′-[[(Hexane-1,6-diyl)dioxy]bis[(2-amino-5-methoxy-1,4-phenylene)carbonyl]]bis[pyrrolidine-2-carboxaldehyde diethyl dithioacetal] (13d). Yield = 291 mg (60% from 0.52 g of **12d**); IR (neat) 3430, 3320, 2930, 1710, 1620, 1590, 1505, 1465, 1455, 1410, 1265, 1165, 1030, 750 cm^{-1}.

1,1′-[(Alkane-α,ω-diyl)dioxy]bis[(11a*S*)-7-methoxy-1,2,3,11a-tetrahydro-5*H*-pyrrolo[1,2-*c*][1,4]benzodiazepin-5-one] 14a−d. A suspension of the diamino thioacetal (0.65 mmol), $HgCl_2$ (0.867 g, 3.20 mmol), and $CaCO_3$ (0.317 g, 3.20 mmol) in CH_3CN/H_2O (4:1, 15 mL) was stirred slowly at rt for 2.5 h until TLC ($MeOH/CHCl_3$, 1:4) indicated a complete loss of starting material. After removal of the CH_3CN/H_2O by evaporation *in vacuo*, the resulting residue was dissolved in MeOH (15 mL) and filtered through Celite. The solvent was evaporated *in vacuo* and the residue purified by column chromatography eluting with methanol/chloroform (1:19) to afford the corresponding dimer as a light yellow oil. The unusual behavior of the dimers in the mass spectrometer (see text) precluded high resolution analysis:

1,1′-[(Propane-1,3-diyl)dioxy]bis[(11a*S*)-7-methoxy-1,2,3,11a-tetrahydro-5*H*-pyrrolo[1,2-*c*][1,4]benzodiazepin-5-one] (14a). Yield = 289 mg (83% from 0.51 g of **13a**); ^{1}H NMR ($CDCl_3$): δ 2.01−2.17 (m, 2H), 2.28−2.45 (m, 8H), 3.50−3.87 (m, 6H), 3.92 (s, 6H), 4.22−4.33 (m, 4H), 6.85 (s, 2H), 7.51

(s, 2H), 7.66 (d, 2H, J = 4.4 Hz); ^{13}C NMR ($CDCl_3$): δ 24.2, 28.8, 29.6, 46.7, 53.7, 56.1, 65.4, 110.7, 111.6, 120.3, 140.6, 147.8, 150.6, 162.4, 164.6; FAB MS m/z 533 ($MH^{+\bullet}$); EIMS m/z 534 ($MH_2^{+\bullet}$); $[\alpha]^{23}_D$ = +330° (c = 0.6, $CHCl_3$).

1,1′-[(Butane-1,4-diyl)dioxy]bis[(11a*S*)-7-methoxy-1,2,3,11a-tetrahydro-5*H*-pyrrolo[1,2-*c*][1,4]benzodiazepin-5-one] (14b). Yield = 232 mg (65% from 0.52 g of **13b**); ^{1}H NMR ($CDCl_3$): δ 2.02−2.17 (m), 2.29−2.34 (m, 7H), 3.50−3.87 (m), 3.93 (s, 6H), 4.12−4.21 (m, 4H), 6.81 (s, 2H), 7.50 (s, 2H), 7.66 (d, 2H, J = 4.4 Hz); ^{13}C NMR ($CDCl_3$): δ 24.2, 25.7, 29.6, 46.7, 53.7, 56.1, 65.4, 110.7, 111.6, 120.3, 140.6, 147.8, 150.6, 162.4, 164.6; FAB MS m/z 547 ($MH^{+\bullet}$); EIMS m/z 548 ($MH_2^{+\bullet}$); $[\alpha]^{23}_D$ = +50.0° (c = 0.012, $CHCl_3$).

1,1′-[(Pentane-1,5-diyl)dioxy]bis[(11a*S*)-7-methoxy-1,2,3,11a-tetrahydro-5*H*-pyrrolo[1,2-*c*][1,4]benzodiazepin-5-one] (14c). Yield = 220 mg (60% from 0.53 g of **13c**); ^{1}H NMR ($CDCl_3$): δ 1.61−1.66 (m), 1.95−2.04 (m), 2.28−2.30 (m), 3.57−3.84 (m), 3.93 (s), 3.97−4.07 (m), 6.80 (s, 2H), 7.51 (s, 2H), 7.64 (d, 2H, J = 11.9 Hz); ^{13}C NMR ($CDCl_3$): δ 22.5, 24.2, 28.6, 29.7, 46.7, 53.7, 56.2, 68.5, 110.4, 111.5, 120.1, 140.6, 147.8, 150.8, 162.4, 164.7; FAB MS m/z 561 ($MH^{+\bullet}$); EIMS m/z 562 ($MH_2^{+\bullet}$); $[\alpha]^{23}_D$ = +47.8° (c = 0.4, $CHCl_3$).

1,1′-[(Hexane-1,6-diyl)dioxy]bis[(11a*S*)-7-methoxy-1,2,3,11a-tetrahydro-5*H*-pyrrolo[1,2-*c*][1,4]benzodiazepin-5-one] (14d). Yield = 303 mg (82% from 0.53 g of **13d**); ^{1}H NMR ($CDCl_3$): δ 1.54−1.56 (m, 4H), 1.89−2.08 (m, 8H), 2.11−2.33 (m, 4H), 3.47−3.85 (m, 6H), 3.89 (s, 6H), 4.03−4.09 (m, 4H), 6.80 (s, 2H), 7.50 (s, 2H), 7.66 (d, 2H, J = 4.4 Hz); ^{13}C NMR ($CDCl_3$): δ 24.2, 25.7, 28.8, 29.6, 46.6, 53.7, 56.2, 68.8, 110.4, 111.5, 120.1, 140.6, 147.8, 150.8, 162.4, 164.7; FAB MS m/z 575 ($MH^{+\bullet}$); EIMS m/z 576 ($MH_2^{+\bullet}$); $[\alpha]^{23}_D$ = +470.5° (c = 0.18, $CHCl_3$).

Conversion of Imines 14a−d to Carbinolamine Methyl Ethers 15a−d. Conversion of the imines **14a−d** to their methyl ether forms could be achieved by dissolving in CH_3OH; for example for **14a**: ^{1}H NMR (CD_3OD, major isomer **15a**, C11(*S*)−C11′(*S*)): δ 2.0−2.4 (m, 10H), 3.3 (s, 6H), 3.42−3.71 (m, 6H), 3.8 (s, 6H), 4.18−4.30 (m, 4H), 4.40 (d, 2H, J = 9.0 Hz), 6.61 (s, 2H), 7.90 (s, 2H). A small amount of the minor isomer C11(*R*)−C11′(*S*) [C11(*S*)−C11′(*R*)] was evident from signals at 4.58 (s, H11), 6.38 (s), and 7.36 (s).

(2*S*)-*N*-(Benzyloxycarbonyl)-2-(hydroxymethyl)pyrrolidine (18). Lithium borohydride (1.6 g, 73 mmol) was added in portions (~0.5 g) to a vigorously stirred solution of methyl (2*S*)-(benzyloxycarbonyl)pyrrolidine-2-carboxylate (**17**) (12.7 g, 48 mmol) in dry THF (100 mL) at 0 °C under a nitrogen atmosphere. The mixture was allowed to stir overnight at room temperature and was then cooled in an ice/salt bath, diluted with water (50 mL), and acidified by dropwise addition of HCl (50 mL, 2 N). The resulting suspension was extracted with EtOAc (3 × 30 mL), and the combined organic phase was washed with water (100 mL). The aqueous fractions were back-extracted with EtOAc (30 mL), and the combined organic phase was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to afford **18**[15] as a pale yellow oil (9.0 g, 79%). ^{1}H NMR ($CDCl_3$): δ 1.53−2.09 (m, 4H), 3.34−3.63 (m, 4H), 3.85−4.02 (m, 1H), 4.32−4.44 (m, 1H), 5.14 (s, 2H), 7.33−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 24.0, 28.6, 47.3, 60.7, 66.9, 67.3, 127.9, 128.1, 128.5, 136.5, 157.1.

(2*S*)-*N*-(Benzyloxycarbonyl)pyrrolidine-2-carboxaldehyde (19). A solution of DMSO (27.3 mL, 0.37 mol, 2.84 equiv) in dry CH_2Cl_2 (65 mL) was added slowly via a double-tipped needle to a stirred solution of oxalyl chloride (93 mL, 0.184 mol, 1.41 equiv) in anhydrous CH_2Cl_2 at −45 °C under a N_2 atmosphere. After stirring for 25 min, a solution of the alcohol **18** (30.9 g, 0.131 mol) in dry CH_2Cl_2 (65 mL) was added dropwise over a period of 15 min. The resulting white suspension was stirred for 2 h after which time TLC (EtOAc/hexane, 1:1) indicated that reaction was complete. Triethylamine (92 mL, 0.655 mol, 5.0 equiv) in anhydrous CH_2Cl_2 (65 mL) was added dropwise, and the solution was allowed to warm slowly to room temperature. The reaction mixture was then diluted with CH_2Cl_2 (250 mL) and washed successively with 5% HCl (1 × 100 mL), water (1 × 150 mL), and brine (1 × 150 mL). The combined aqueous phase was back-extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic phase was dried (Na_2SO_4) and evaporated *in vacuo* to give an oily residue which was purified by flash chromatography on silica gel (EtOAc/petroleum ether 60−80 °C, 1:2) to afford **19**[15] (27 g, 88%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$): δ 1.78−2.15 (m, 4H), 3.50−3.61 (m, 2H), 4.20 + 4.39 (2m, 1H), 5.12 + 5.17 (2s, 2H), 7.26−7.36 (m, 5H), 9.48 + 9.59 (2d, 1H); ^{13}C NMR ($CDCl_3$): δ 23.7, 24.5, 26.6, 27.8, 46.7, 47.3, 64.9, 65.3, 67.2, 128.0, 128.1, 128.5, 136.2, 137.3, 200.0.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **6a−d**, **7a,b**, **8a−d**, **9a−d**, **10a**, **12a,d**, **13a**, **14a−d**, **15a**, **18**, and **19**. COSY and HETCOR 2-D spectra are also provided for compounds **14a** and **14b** (47 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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