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APPROACH TO THE SYNTHESIS OF (+)-IFFORESTINE. MODEL STUDIES DIRECTED AT THE TETRACYCLIC FRAMEWORK

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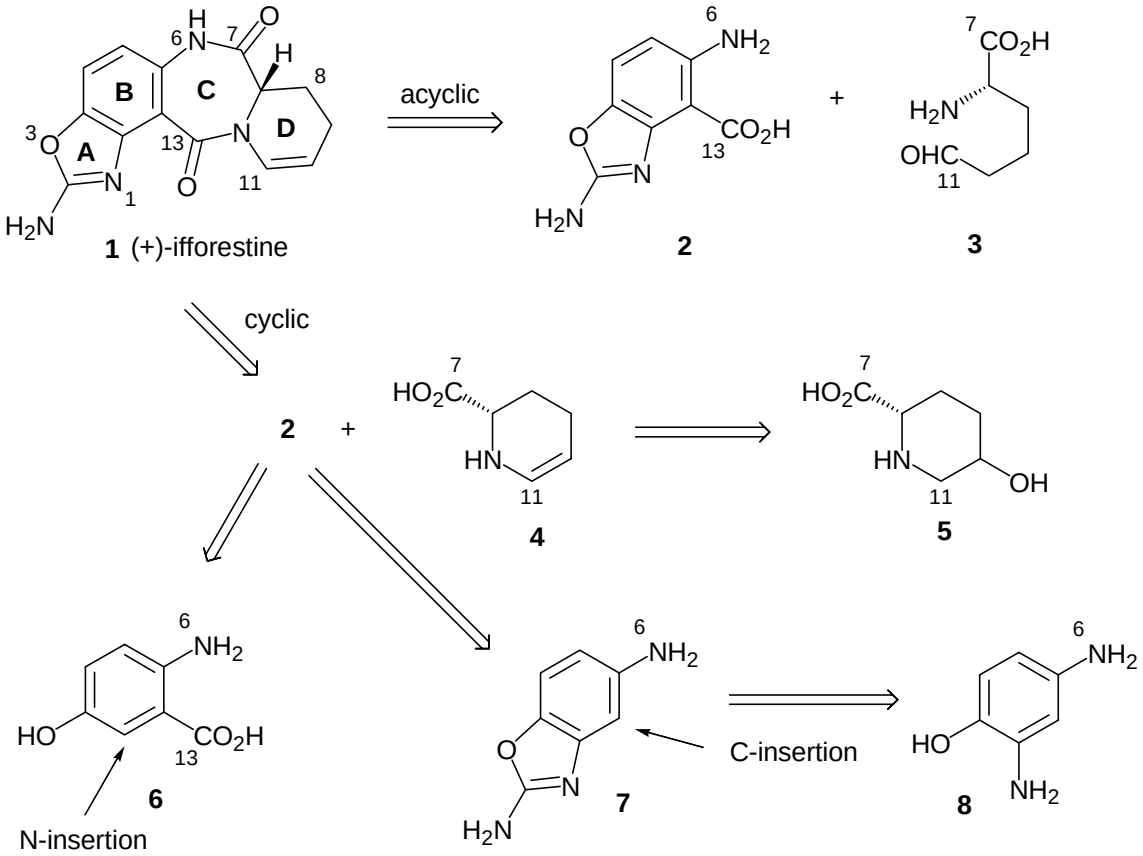
Abstract - In order to design an effective asymmetric synthesis of (+)-ifforestine, model approaches to the construction of the tetracyclic ring system have been investigated. These studies have identified two key synthons, a functionalized isatoic anhydride and a pipecolic acid derivative, as suitable AB- and D-ring portions for creation of the crucial diazopinedione C-ring.

INTRODUCTION

The *Isotropis* genus has nine species indigenous to Australia, five of which have been reported to be toxic.[1] In Western Australia, *Isotropis forrestii* is an annual herb that has been reported to pose the highest risk to livestock. Ingestion of relatively small amounts of this plant may cause sudden death. It has been speculated that acute cardiac failure precipitates this initial response while those animals that survive the initial acute reaction may die later as a consequence of renal failure.[2] Bioassay-directed isolation from *Isotropis forrestii* afforded the novel alkaloid (+)-ifforestine (**1**) as the active toxin that reproduced the acute renal proximal necrosis exhibited by the whole plant.[3] Given that this compound represented only 0.007% of the dry weight of the whole plant, a synthetic strategy was required to provide further material for pathomechanistic studies.

Logical primary retrosynthesis of (+)-ifforestine based on the two amide linkages, and thus the creation of the diazopinedione ring C, might proceed through a condensation approach with either an *acyclic* or *cyclic* partner (Scheme 1). This analysis affords an aromatic AB ring segment (**2**) along with either the acyclic chiron (**3**) or cyclic L-pipecolic acid chiron (**4**) serving to provide the D ring. Initial model studies were directed at determining the optimum choice of these C-ring-forming condensation options. After due consideration of available precursors, further analysis of the aromatic AB synthon (**2**) revealed two

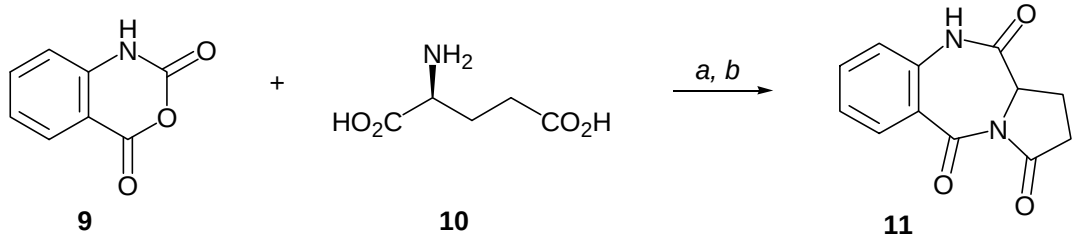
primary options through which to approach its construction (Scheme 1). These were based either on an *N*-insertion approach on the hydroxyanthranilic acid (**6**) or *C*-insertion on the amine (**7**) or its precursor (**8**).



Scheme 1 Primary retrosynthetic analysis of (+)-ifforestine

RESULTS & DISCUSSION

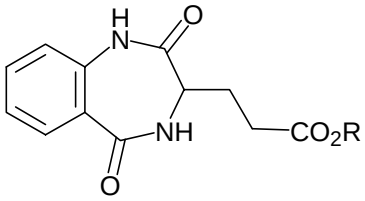
BCD-Ring Approaches: An initial approach using an acyclic D-ring chiron followed a literature precedent for related frameworks.[4] Thus, the two-step condensation of isatoic anhydride (**9**) with L-glutamic acid was carried out to produce the tricycle (**10**) (Scheme 2). Modification of the original protocol was required to ensure a high yield (>75%) and afforded pure product (**11**) without need for chromatography. However, contrary to the related literature, the product proved to be racemic.



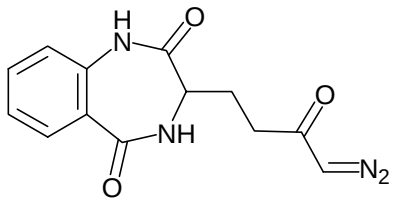
a. $Et_3N/THF\text{-}H_2O$; *b.* $Ac_2O/HOAc$, reflux or $(CF_3CO)_2O/CF_3CO_2H$, 120°C

Scheme 2

The tricyclic product (**11**) was used to test possible pyrrolidone ring-expansion protocols that could provide the required tetrahydropyridine D-ring. As a first approach, regioselective reduction of the pyrrolidone carbonyl was attempted. This proved to be ineffective under a range of conditions and hydride reagents. Complex mixtures resulted, an occurrence that has been noted in the literature.[5,6] It was, however, possible to cleanly open the pyrrolidone ring to afford either the acid (**12**) or ester (**13**). Surprisingly, this ester resisted efforts to directly produce the corresponding aldehyde (REDAL, DIBAL), instead simply reforming the tricyclic **11**. Attempts were also made to produce the diazoketone (**15**) from acid (**12**) (oxalyl chloride/diazomethane). Again, the sole product was the recyclized **11**.



12 R = H
13 R = Me
14 R = Bn



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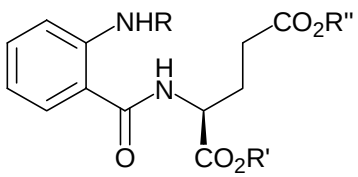
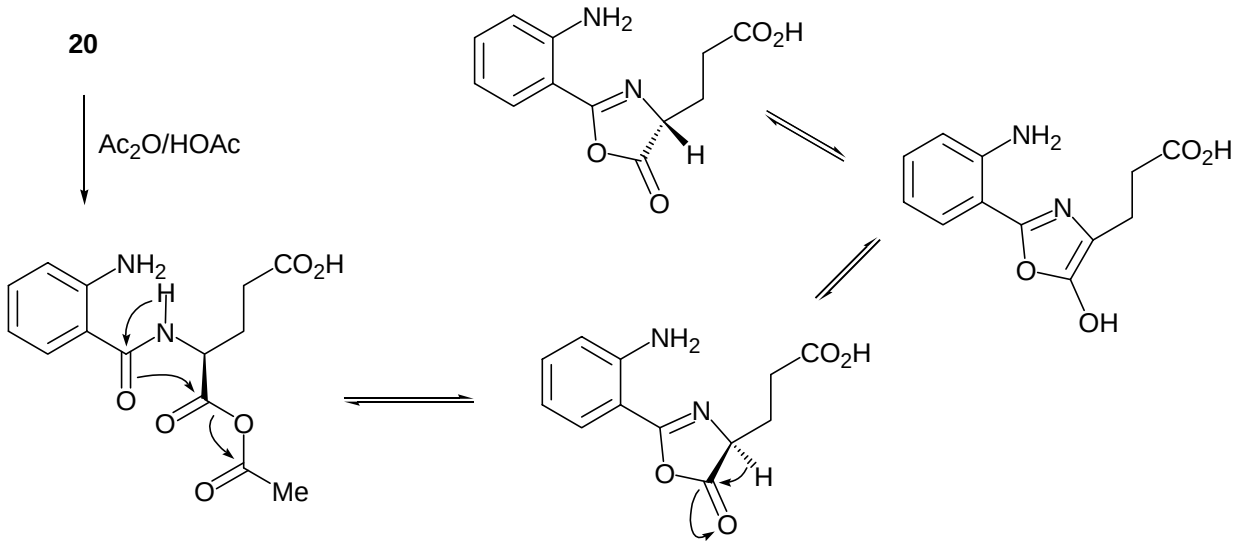


16 R = H; R' = R'' = Me
17 R = Bn; R' = R'' = H
18 R = Bn; R' = R'' = Me
19 R = Bn; R' = H; R'' = Me
20 R = R' = R'' = H
21 R = R' = H; R'' = Me
22 R = R' = H; R'' = Bn

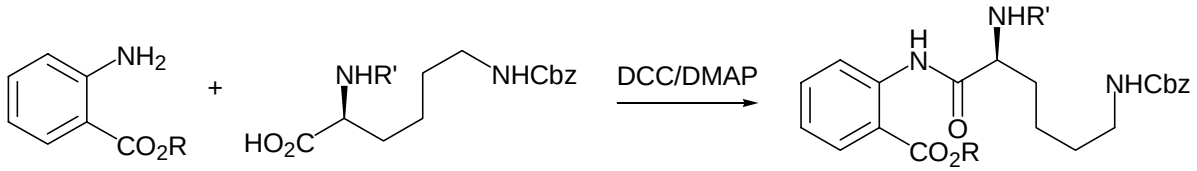
The possible routes to racemisation were also investigated. The intermediate in the stepwise condensation was initially thought to be the bicyclic diamide (**12**). However, esterification of this intermediate produced the diester (**16**) rather than the anticipated monoester **(13**). From this it was clear that racemisation occurred in the second forcing step with TFA. To obviate this, creation of the C-ring was attempted under milder reaction conditions.

Activation of the aromatic amino substituent as the *N*-benzyl derivative was carried out *via* the appropriately modified isatoic anhydride. Various intermediates (**17-19**) from this approach, however, showed no increased propensity to cyclize. Peptide coupling agents, specifically hydroxybenzotriazole, proved more successful and led in good yield to bicyclic products (**12-14**) when applied to the crude intermediates (**20-22**). Again, however, these proved to be racemic. It seems likely that racemisation occurs *via* an oxazolone intermediate as depicted for intermediate (**20**) in Scheme 3.[7,8]

In an effort to circumvent potential oxazolone participation, anthranilic acid derivatives (**23-25**) were substituted for the isatoic anhydride. In addition, L-glutamic acid was replaced by L-lysine derivatives (**27-28**) to allow for later direct elaboration to the tetrahydropyridine D-ring. Whilst the initial coupling proceeded in good yield (Scheme 4), all of the intermediate products (**28-31**) proved resistant to clean cyclization and afforded inseparable mixtures.



Scheme 3



23 R = H
24 R = Bn
25 R = Et

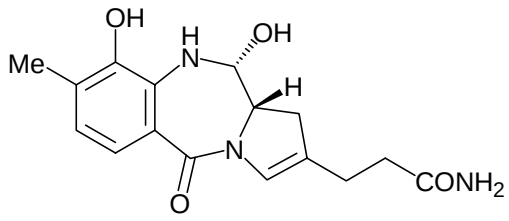
26 R' = Cbz
27 R' = Boc

28 R = H; R' = Cbz
29 R = Bn; R' = Cbz
30 R = Et; R' = Cbz
31 R = Et; R' = Boc

Scheme 4

The alternative approach *via* suitable cyclic D-ring chirons was based on the observable similarities between the ifforestine skeleton and members of the anthramycin group of antitumour antibiotics (eg: (+)-anthramycin (**32**)).[9,10] Methodologies related to these were thus potentially applicable to our situation.[11-13] Using this chemistry, isatoic anhydride and 4-hydroxy-L-proline afforded the benzodiazepinedione (**33**) in good yield (80%). The initial target from this alcohol was the alkene (**35**). Surprisingly, this dehydration proved difficult by a variety of standard methodologies (H_2SO_4/DMSO/160°C; DBU/$ClCH_2CH_2Cl$/84°C; $POCl_3$/Py; $FeCl_3/SiO_2$). Alternative approaches *via* halide formation and dehydrohalogenation proved equally ineffective. Alkene (**35**) was finally secured in overall 61% from **33** *via* elimination of the corresponding mesylate (**34**). This latter series of reactions thus provided rapid, economical access to the dihydropyrrole analogue of the BCD-ring system. It was envisaged that the corresponding tetrahydropyridine system would be available *via* analogous reaction with the corresponding L- hydroxypipecolic acid chiron.

Related to the above studies, alcohol (**33**) was oxidized to ketone (**36**). Treatment of this compound under Shapiro conditions[14] also failed to produce the alkene (**35**) and, in addition, it also resisted various attempts at ring expansion.



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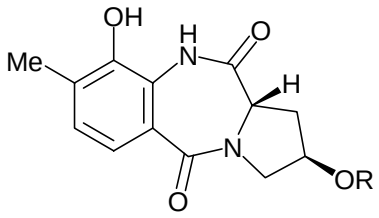
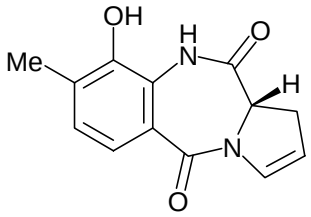


33 R = H
34 R = Ms



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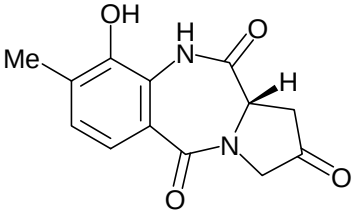
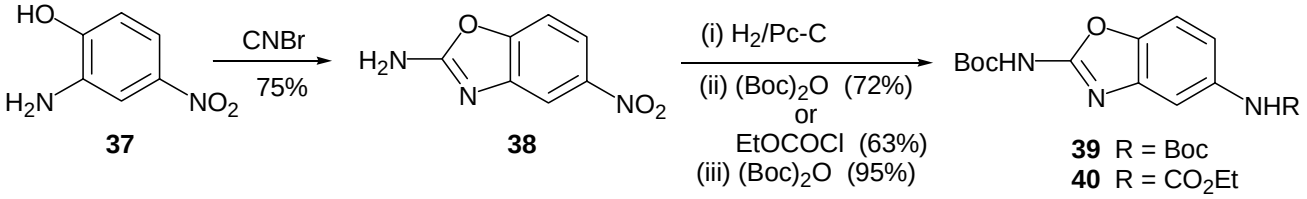
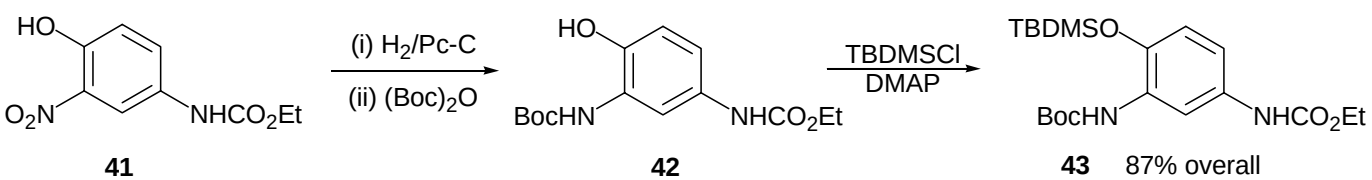


36

Aromatic Synthon Studies: As outlined in Scheme 1, efforts were concentrated primarily on *N*-insertion and *C*-insertion approaches on precursors of type (**6**) and (**7**) respectively. The approach to *C*-insertion was envisaged *via* a directed *ortho* metallation (DoM) procedure[15] on appropriately substituted variants of **7** followed by carbanion quench to insert a carboxyl group. Thus, the Boc protected 2-aminobenzoxazoles (**39**) and (**40**) were prepared from 2-amino-4-nitrophenol (**37**)[16] (Scheme 5). These substrates provide differing degrees of steric congestion at C4 by way of either the Boc- (**39**) or ethyl carbamate- (**40**) activation of the aromatic amino group. Although two regioisomeric *ortho* positions exist, it was hoped that the oxazolamine ring nitrogen might provide additional chelation to direct metallation to C4 rather than C6. Unfortunately, extensive study of DoM reactions (*t*-BuLi, *n*-BuLi, NaHMDS bases and CO_2, ethyl chloroformate, diethyl oxalate electrophiles)[17-19] with both substrates (**39**) and (**40**) proved unsuccessful, providing instead complex mixtures. The high polarity of the product components, combined with a tendency to rapidly darken, suggested that oxazolamine ring-opening had occurred. To obviate the above possibility, substrate (**43**) was prepared, but again no clean carboxylation was observed.



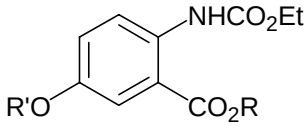
37 **38** **39** R = Boc
40 R = CO_2Et



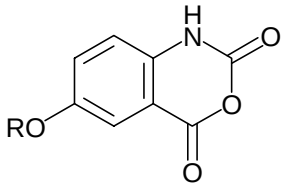
41 **42** **43** 87% overall

Scheme 5

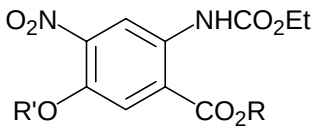
The major pathway for *N*-substitution was envisaged to be nitration, and a variety of possible substrates were investigated. In the first instance, the amino group of **6** was protected as the carbamate to give **44** under conditions that obviated the simultaneous formation of the carbonate (**45**). This choice of *N*-protection was based on the ease with which conversion of α-carboxy-*N*-carbamates (*cf* **44**) to the cyclic anhydrides could be effected.[20]



44 R = R' = H
45 R = H; R' = EtO.CO
46 R = Me; R' = H
47 R = R' = Bn
48 R = H; R' = Bn



49 R = H
50 R = Ac
51 R = Bn



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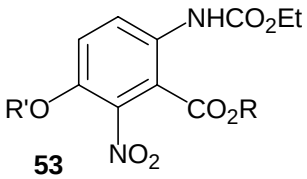


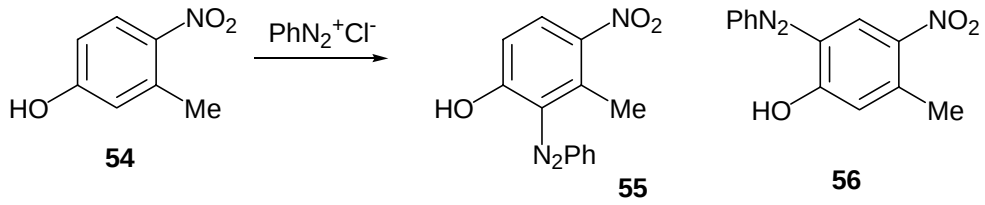
53

R = Me; R' = H 1 : 1.6 regiomixture
R = R' = Bn 1 : 4.0 regiomixture

All attempts at direct nitration of **44** under a variety of reported conditions (*eg.* ^{i}PrNO/TFA; HNO_3/Et_2O[21,22]; $Cu(NO_3)_2/MeNO_2$[23]) led to complex TLC product profiles. Any purification of these polar components was thought to be hindered by the free carboxylic acid. To obviate this, the cyclic derivatives (**49**) and (**50**) were prepared. Although these were smoothly formed, both failed as nitration substrates. In the case of phenol (**49**), multiple polar products were again observed, whilst for acetate (**50**), deactivation of the aromatic system simply afforded starting material. To modify the reactivity of the aromatic system, the anhydride (**51**) was prepared *via* ether (**48**)**.** However, nitration attempts consistently returned starting material.

Alternative use of the methyl ester (**46**) as a nitration substrate proved marginally more successful and, although the overall yield was low (~16%), produced the desired regioisomer (**53a**) as the major product. Further tuning of the aromatic core *via* the ester (**47**) gave further improvement and the nitration product (**53b**) was produced in a favorable 80:20 ratio along with its regioisomer (**52b**).

In a single alternative approach, the nitrocresol (**54**) was *N*-functionalized by diazophenyl insertion (Scheme 6). Although unstable, the product mixture could be characterized by rapid ^{1}H NMR. Unfortunately, the desired regioisomer (**55**) was the very minor component of the mixture with **56** as was shown by the presence of two singlets (δ 7.90 and 8.05) for the major regioisomer and two doublets (δ 6.91 and 7.95 with J = 7.5 Hz) for the minor regioisomer. The poor regioselectivity and apparent instability discouraged further pursuit of this approach.



Scheme 6

CONCLUSION

Although the above *N*-substitution approaches were less than optimum, they proved to be better than the alternative *C*-substitution route. Overall, given the above results with the model systems, current work is directed at adequate sourcing of the required L-hydroxypipecolic synthon, optimization of the *N*-insertion process, and final assembly of natural (+)-ifforestine.

ACKNOWLEDGEMENT

The authors thank Murdoch University for support and Professor R. G. F. Giles for his input.

EXPERIMENTAL

General.

NMR spectra were recorded on a Bruker Avance DPX-300 (^{1}H, 300 MHz; ^{13}C, 75.5 MHz). Unless otherwise indicated, all spectra were run in deuterochloroform at ambient (25°C) temperature with tetramethylsilane as an internal standard. HRMS were measured on a VG Autospec Mass Spectrometer. HPLC was carried out on a GBC LC 1150 system using a 25 cm Chiracell OD or an Alltech Econosil C18 column with UV detector set at 254 nm. IR spectra were recorded on a Perkin Elmer 1720-X Fourier Transform Spectrometer. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Optical rotations were obtained on an Optical Activity PolAAr 2001 polarimeter.

Column chromatography refers to dry packed columns of Merck silica gel 60 (70-230 mesh) with pre-absorption onto Merck silica gel 60 (35-70 mesh). Thin layer chromatography was carried out on aluminium plates coated with Kieselgel 60 F_{254} and developed with UV irradiation or with ceric sulphate (general), ninhydrin (amines and amino acids), bromocresol green (acids), cobalt thiocyanate (amines) or vanadium (V)-sulfuric acid reagent (general). Radial chromatography was performed on a Harrison Research Ltd. “Chromatotron” with Merck silica gel 60 PF_{254}.

Hexanes refers to the fraction of petroleum distillate that boils in the range 65-70°C. Sodium bicarbonate, sodium carbonate and salt solutions were all used as saturated solutions. Calcium chloride and magnesium sulfate drying reagents were dried in an oven at 200°C for 3 h (and

cooled in a vacuum desiccator) prior to use. All solvents were distilled prior to use. Solvents were dried according to standard methods and stored in amber bottles over activated 3Å molecular sieves (5% w/v). All other reagent chemicals were purchased from the Sigma-Aldrich Chemical Company and were further purified where stated. Butyllithium was standardised in a similar manner to a literature report except that *N*-pivaloyl-*o*-methylaniline was used as the reagent.[24] All quoted yields refer to isolated compounds obtained after chromatography, distillation or recrystallisation, unless otherwise stated.

(±)-2,3,3a,4,5–Pyrolo[2,1-*c*][1,4]benzodiazepine-1,4,10–trione (11)

L-Glutamic acid (**10**, 1.523 g, 10.4 mmol), triethylamine (2.10 g, 2.9 mL, 0.208 mol) and distilled water (10 mL) were swirled until dissolution was complete. Isatoic anhydride (**9**) (2.00 g, 10.4 mmol) dissolved in THF (2.5 mL) was then added. The reaction mixture was left to stand at rt for 24 h with occasional stirring. The solvent was evaporated and the residue diluted with chloroform (25 mL) and dried ($MgSO_4$). The concentrated residue was transferred to a glass ampoule with the aid of trifluoroacetic anhydride (25 mL). The ampoule was sealed under vacuum and heated at 120°C for 2 h. After cooling the solvent was evaporated or distilled for recycling. The residue was dissolved in ethyl acetate (50 mL), water (30 mL) added and the mixture shaken to precipitate the product. The product was filtered, washed with water (10 mL) then ether (20 mL) and recrystallised from acetone (1.78 g, 75%): mp 245°C; IR (KBr) 1763, 1693, 1658 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.90 (s, 1H, NH), 7.03 (dd, 1H, J = 1.5 and 8 Hz, H9), 6.74 (dt, 1H, J = 1.5 and 8 Hz, H7), 6.44 (dt, 1H, J = 1 and 8 Hz, H8), 6.37 (dd, 1H, J = 1 and 8 Hz, H6), 3.79 (d, 1H, J = 8 Hz, NH), 1.83 (m, 2H, H2), 1.69 (m, 1H, H3), 1.33 (m, 1H, H3); ^{13}C NMR δ 173, 169, 164, 136, 131, 126, 124, 121, 55.8, 30.9, 17.7. Anal. Calcd for $C_{12}H_{10}N_2O_3$: C 62.61; H 4.38; N 12.17. Found: C 62.67; H 4.39, N 12.45.

(±)-3-[2-Ethylcarboxy]-1,4-benzodiazepine-2,5-dione (12)

Method (1). To a solution of the triamide (**11**, 1.15 g, 5 mmol) in DMF (10 mL) was added a solution of 1N KOH (10 mL). The reaction was stirred at ambient temperature for 0.5 h then acidified with 1N HCl (15 mL). The precipitate was filtered, washed with water (10 mL), ether (10 mL), and then air dried to give a white solid (1.19 g, 96%) that recrystallised from MeOH, mp 226-228°C; IR (KBr) 1718, 1686, 1646 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.10 (br s, 1H, $CO_2\underline{H}$), 10.40 (s, 1H, PhNH), 8.49 (d, 1H, J = 5.5 Hz, NH), 7.73 (dd, 1H, J = 1.5 and 8 Hz, H7), 7.49 (dt, 1H, J = 1.5 and 8 Hz, H9), 7.20 (dt, 1H, J = 1 and 8 Hz, H8), 7.08 (dd, 1H, J = 1 and 8 Hz, H10), 3.68 (dt, 1H, J = 6 and 8 Hz, H4), 2.34 (m, 2H, H2), 1.98 (ddt, 1H, J = 4.5, 7 and 8 Hz,

H3), 1.81 (ddt, 1H, J = 3, 6.5 and 7 Hz, H3); ^{13}C NMR δ 174, 171, 168, 137, 130, 126, 124, 121, 51.0, 29.9, 23.2; Anal. Calcd for $C_{12}H_{12}N_2O_2$: C 58.06, H 4.87, N 11.28. Found: C 57.85, H 4.85, N 11.19.

Method (2). L-Glutamic acid (**10**) (0.735 g, 5.0 mmol) was dissolved in distilled water/DMF (6 mL/3 mL), diisopropylethylamine (1.0 mL, 11.0 mmol) and a solution of isatoic anhydride (**9**) (0.815 g, 5 mmol) in DMF (3 mL) added and the reaction stirred at 60 ^{0}C for 1.5 h. The solvent was evaporated, the residue dissolved in DMF (10 mL) and cooled to 0°C then hydroxybenzotriazole (0.764 g, 5.0 mmol) and dicyclohexylcarbodiimide (1.13 g, 5.5 mmol) added. The reaction was stirred at 0 ^{0}C for 1 h and rt for 20 h, the solvent evaporated and the residue triturated with acetone (~20 mL). The precipitate collected by filtration (0.460 g, 40%) was recrystallised from MeOH.

(±)-Methyl 3-(2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepin-3-yl)propanoate (13)

Method (1). The triamide (**11**, 0.460 g, 2.0 mmol) was stirred in MeOH (10 mL) and TEA (0.28 mL, 0.204 g, 2.0 mmol) for 10 min at ambient temperature. The solvent was evaporated and the residue recrystallised from acetone as needles (0.510 g, 97%), mp 184-186°C; IR (KBr) 1733, 1681, 1662 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.40 (s, 1H, PhNH), 8.49 (d, 1H, J = 5.5 Hz, NH), 7.73 (dd, 1H, J = 1.5 and 8 Hz, H7), 7.50 (dt, 1H, J = 1.5 and 8 Hz, H9), 7.20 (dt, 1H, 1 and 8 Hz, H8), 7.09 (dd, 1H, J = 1 and 8 Hz, H10), 3.69 (dt, 1H, J = 6 and 8 Hz, H4), 3.54 (s, 3H, OMe), 2.34 (m, 2H, H2), 1.75 (m, 1H, H2); ^{13}C NMR δ 173, 171, 168, 137, 132, 130, 126, 124, 121, 51.3, 50.9, 29.6, 23.1; Anal. Calcd for $C_{13}H_{14}N_2O_4$: C 58.06, H 4.87, N 11.28. Found: C 57.85, H 4.85, N 11.19.

Method (2). 5-Methyl-L-glutamate (0.805 g, 5.0 mmol), isatoic anhydride (**9**, 0.815 g, 5.0 mmol) and diisopropylethylamine (0.5 mL, 5.5 mmol) were stirred in dry DMF (10 mL) at 60°C for 3 h. The solution was cooled to 0°C, hydroxybenzotriazole (0.675 g, 5.0 mmol) and dicyclohexylcarbodiimide (1.13 g, 5.5 mmol) added and stirring continued for 1 h at 0°C then 19 h at ambient temperature. The urea was filtered, the filter cake washed with DMF (5 mL) and the solvent evaporated (1 mm Hg, 60°C). The residue was triturated with EtOAc (~20 mL) to yield an off-white solid (0.735 g). The mother liquor was chromatographed on silica gel (40 g) with gradient elution of EtOAc in hexanes (50% → 75%) to give further product (0.265 g, total yield 1.00 g, 76%). The combined products were recrystallised from acetone.

(±)-Benzyl 3-(2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepin-3-yl)propanoate (14)

5-Benzyl-L-glutamate (2.32 g, 10.0 mmol) was suspended in DMF (15 mL) and diisopropylethylamine (1.92 mL, 1.1 mmol). Isatoic anhydride (**9**, 1.63 g, 10.0 mmol) in DMF (5 mL) was added and the reaction stirred at 60°C for 3 h. The reaction was cooled to ambient temperature, hydroxybenzotriazole (1.53 g, 10.0 mmol) and dicyclohexylcarbodiimide (2.27 g, 11.0 mmol) added and stirring continued for 1 h. The urea was filtered, the filter cake washed with a little DMF (5 mL) and the solvent evaporated (1 mmHg, 60°C). The residue was triturated with EtOAc (20 mL) to yield a white precipitate of (**14**, 2.01 g, 40%) that recrystallised from acetone, mp 182-185°C; IR (KBr) 1745, 1686, 1670 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.40 (s, 1H, NH), 8.50 (d, 1H, J = 6 Hz, NH), 7.73 (dd, 1H, J = 1.5 and 8 Hz, H3), 7.50 (ddd, 1H, J = 1.5 and 8 Hz, H5), 7.31 (m, 5H, PhH), 7.21 (dt, 1H, J = 1 and 8 Hz, H4), 7.11 (dd, 1H, J = 1 and 8 Hz, H6), 5.05 (s, 2H, $PhCH_2$), 3.71 (dt, 1H, J = 6 and 7.5 Hz, H9), 2.07 (m, 1H, H10), 1.87 (m, 1H, H10), 1.60 (m, 1H, H11), 1.15 (m, 1H, H11); ^{13}C NMR δ 172, 171, 168, 137, 136, 132, 130, 128, 126, 124, 121, 65.4, 50.9, 29.9, 23.2; Anal. Calcd for $C_{19}H_{18}N_2O_4$: C 67.45, H 5.36, N 8.28. Found: C 67.41 H 5.38, N 8.28.

Dimethyl 2(*S*)-*N*-[2-aminobenzoyl]glutamate (16)

Isatoic anhydride (**9**, 0.897 g, 5.5 mmol) was dissolved in dry DMF (10 mL) with dry triethylamine (1.01 g, 1.39 mL, 0.01 mol) and L-glutamic acid (**10**, 0.735 g, 5 mmol) added. The flask was left to stand at ambient temperature for 4 days under a drying tube, with occasional stirring. The solvent was evaporated (1mmHg, 80°C) and the residue diluted with dry MeOH and c.H_2SO_4 (1 mL). The mixture was heated under reflux for 3 h, the solvent evaporated and the residue applied to a silica column (65 g). Elution with a 10-50% gradient of EtOAc in hexanes returned 1.41 g (96%) of product (**16**) that was recrystallised from ether/hexanes as off white needles, mp 81-82°C; IR (KBr) 1743, 1724, 1621 cm^{-1}; $[\alpha]_D^{22}$ –50.7° (*c* = 1.0, MeOH); ^1H NMR δ 7.41 (dd, 1H, J = 1.5 and 8 Hz, H7), 7.19 (dt, 1H, J = 1.5 and 8 Hz, H9), 6.98 (d, 1H, J = 7.5, NH), 6.68-6.66 (m, 2H, H8 and H10), 5.35 (br s, 2H, NH_2), 4.75 (dt, 1H, J = 5 and 7.5 Hz, H2), 2.49 (dt, 1H, J = 7 and 17 Hz, H4), 2.42 (dt, 1H, J = 7 and 17 Hz, H4), 2.28 (ddt, 1H, J = 5, 7 and 14 Hz, H3), 2.11 (m, 1H, H3); ^{13}C NMR δ 174, 172, 169, 149, 133, 128, 117, 116, 115, 52.6, 51.9, 51.7, 30.2, 27.1; Anal. Calcd for $C_{14}H_{18}N_2O_5$: C 57.14, H 6.16, N 9.52. Found: C 56.94, H 6.19, N 9.39.

2(S)-*N*-[2-(*N*-Benzylamino)benzoyl]glutamic acid (17)

N-Benzylisatoic anhydride (1.26 g, 5.0 mmol), L-glutamic acid (**10**, 0.805 g, 5.5 mmol) and triethylamine (1.21 g, 1.66 mL, 0.012 mol) were suspended in dry DMSO (10 mL). The reaction mixture was stirred at 50°C for 1.5 h, under a paraffin bubbler (until gas evolution ceased), poured into $NaHCO_3$ (25 mL) and extracted with EtOAc (2 x 20 mL). The aqueous phase was acidified with 5N HCl and extracted with EtOAc (5 x 20 mL). The combined organics were dried ($MgSO_4$) and concentrated to a powder (1.068 g, 63%) that recrystallised from ether/hexanes, mp 163.5-164.5°C; IR (KBr) 1711, 1645 cm^{-1}; $[\alpha]_D^{21}$ –27.4° (*c* = 1.0, MeOH); ^1H NMR (DMSO-d_6) δ 12.40 (br s, 2H, CO_2H), 8.47 (dd, 1H, J = 1 and 8 Hz, NH), 8.16 (t, 1H, J = 5.5 Hz, PhNH), 7.66 (dd, 1H, J = 1 and 8 Hz, H7), 7.31 (m, 4H, H9 and PhH), 7.22 (m, 2H, PhH), 6.62 (d, 1H, J = 8 Hz, H10), 6.57 (t, 1H, J = 8 Hz, H8), 4.36 (m, 3H, H2 and $PhCH_2$), 2.36 (t, 2H, J = 7.5 Hz, H4), 2.08 (m, 1H, H3), 1.95 (m, 1H, H3); ^{13}C NMR δ 174, 173, 170, 149, 140, 132, 129, 128, 127, 115, 114, 112, 51.7, 46.1, 30.4, 25.8; Anal. Calcd for $C_{19}H_{20}N_2O_2$: C 64.04, H 5.66, N 7.86. Found: C 63.83, H 5.66, N 7.60.

Dimethyl 2(*S*)-*N*-[2-(*N*-benzylamino)benzoyl]glutamate (18)

The diacid (**17**, 0.908 g, 2.6 mmol) was dissolved in methanol (25 mL) and conc. H_2SO_4 (1 mL). The mixture was heated at reflux temperature for 2 h, the excess solvent evaporated, and the residue diluted with $NaHCO_3$ (20 mL) and extracted with EtOAc (5 x 10 mL). The combined organic phases were dried ($MgSO_4$), concentrated and chromatographed (SiO_2, 40 g) with gradients of EtOAc in hexanes (10% → 20%). The homogenous, pale yellow residue (0.741 g, 74%) was recrystallised from ether/ hexanes, mp 79-80°C; IR (KBr) 1754, 1725, 1629 cm^{-1}; $[\alpha]_D^{21}$ –47.8° (c = 1.0, MeOH); ^1H NMR δ 8.17 (br s, 1H, PhNH), 7.46 (dd, 1H, J = 1.5 and 8 Hz, H7), 7.33 (m, 4H, H9 and PhH), 7.25 (m, 2H, PhH), 6.93 (d, 1H, J = 7.5 Hz, CONH), 6.66-6.64 (m, 2H, H8 and H10), 4.76 (ddd, 1H, J = 5, 7 and 8 Hz, H2), 4.40 (s, 2H, $PhCH_2$), 3.78 (s, 3H, OMe), 3.67 (s, 3H, OMe), 2.52 (dt, 1H, J = 7 and 17 Hz, H4), 2.45 (dt, 1H, J = 7 and 17 Hz, H4), 2.30 (ddt, 1H, J = 5, 7 and 14 Hz, H3), 2.14 (ddt, 1H, J = 7, 8 and 14 Hz, H3); ^{13}C NMR δ 174, 172, 170, 150, 139, 133, 129, 128, 127, 115, 114, 112, 52.6, 51.9, 47.1, 30.2, 27.1; Anal. Calcd for $C_{21}H_{24}N_2O_5$: C 65.61, H 6.29, N 7.29. Found: C 65.46, H 6.61, N 7.21.

(*S*)-2-{2-[2-(2-benzylamino)phenyl]-2-oxoethyl}-5-methoxy-5-oxopentanoic acid (19)

5-Methyl-L-glutamate (0.805 g, 0.05 mol), *N*-benzylisatoic anhydride (1.26 g, 0.05 mol) and triethylamine (1.40 mL, 1.02 g, 0.10 mol) were combined with dry DMSO (10 mL) and stirred at 50°C for 4 h (until gas evolution ceased). The resulting clear solution was concentrated (60°C and 1 mmHg), diluted with $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The

aqueous phase was acidified to pH 1 with 5N HCl and extracted with EtOAc (3 x 20 mL). The combined organics were dried ($MgSO_4$) and concentrated to a TLC homogenous solid (1.48 g, 80%) that recrystallised as prisms from ether/hexanes, mp 144-146°C; IR (KBr) 1731, 1712, 1627 cm^{-1}; $[\alpha]_D^{21}$ –25.0° (*c* = 1.0, MeOH); ^1H NMR (DMSO-d_6) δ 12.70 (br s, 1H, CO_2H), 8.49 (d, 1H, J = 7.5 Hz, NH), 8.13 (br s, 1H, NH), 7.66 (dd, 1H, J = 1.5 and 8 Hz, H7), 7.36-7.14 (m, 6H, PhH and H9), 6.62 (d, 1H, J = 8 Hz, H10), 6.57 (t, 1H, J = 8 Hz, H8), 4.36 (m, 3H, H4 and PhC$\underline{H}_2$), 2.45 (m, 2H, H2), 2.10 (m, 1H, H3), 1.99 (m, 1H, H3); ^{13}C NMR δ 173, 172, 170, 149, 140, 133, 129, 128, 127, 115, 114, 112, 51.6, 51.4, 46.1, 30.2, 25.7; Anal. Calcd for $C_{20}H_{22}N_2O_5$: C 64.84, H 5.99, N 7.57. Found: C 64.58, H 6.08, N 7.39.

2-({2,6-*Bis*[(benzyloxycarbonyl)amino]hexanoyl}amino)benzoic acid (28)

*N*α,*N*ε-Carbobenzyloxy-L-lysine (**26**, 1.036 g, 2.5 mmol) was dissolved in dry CH_2Cl_2 (15 mL), 4-dimethylaminopyridine (0.305 g, 2.5 mmol) and dicyclohexylcarbodiimide (0.567 g, 2.75 mmol) added and the flask cooled to 0 ^0C. Anthranilic acid (**23**, 0.343 g, 2.5 mmol) was dissolved in dry CH_2Cl_2 (3 mL) with the aid of triethylamine (0.38 mL, 0.275 g, 2.75 mmol). This solution was slowly added to the 0 ^0C solution over 2 min, stirred for 1 h at 0°C, and then at ambient temperature for 3 h. The urea was filtered and the cake washed with ether (50 mL). The organic solution was washed with 0.2 N HOAc (3 x 10 mL), then brine (10 mL), and dried ($MgSO_4$). Solvent removal gave the product (1.14 g, 85%), mp 128.5-130.5°C (from acetone/hexanes); $[\alpha]_D^{23}$ –18.4° (c = 1.0, $CHCl_3$); ^1H NMR δ 11.60 (s, 1H, CO_2H), 11.50 (s, 1H, NH), 8.65 (d, 1H, J = 8.5 Hz, H5′), 8.07 (d, 1H, J = 7.5 Hz, H2′), 7.55 (m, 1H, H3′), 7.29 (m, 10H, OCH_2Ar), 7.11 (m, 1H, H4′), 5.71 (m, 1H, NH), 5.08 (m, 5H, OC$\underline{H}_2$Ar and NH), 3.17 (m, 2H, H6), 2.00-1.40 (m, 6H, H3-H5); ^{13}C NMR δ 171, 170, 157, 156, 141, 136, 134, 132, 128, 123, 120, 115, 67.4, 67.1, 66.6, 56.1, 40.5, 32.4, 22.3; Anal. Calcd for $C_{29}H_{31}N_3O_7$: C 65.30, H 5.86, N 7.88. Found: C 65.40, H 5.74, N 8.01.

Benzyl 2-({2,6-*bis*[(benzyloxycarbonyl)amino]hexanoyl}amino)benzoate (29)

A solution of benzyl anthranilate (**24**, 1.14 g, 5.0 mmol) in CH_2Cl_2 (5 mL) was slowly added to a solution of *N*α,*N*ε-Cbz-L-lysine (**26**, 2.07 g, 5.0 mmol), hydroxybenzotriazole (0.675 g, 5.0 mmol) and dicyclohexylcarbodiimide (1.24 g, 6.0 mmol) in CH_2Cl_2 (20 mL) at 0°C. The reaction was stirred overnight (16 h), filtered, concentrated and applied to a silica column (40 g). The product was eluted from the column with gradients of EtOAc in hexanes (10% → 35%) to give a white powder (2.68 g, 86%) that recrystallised as needles from acetone/hexanes, mp 122-124°C; IR (KBr) 1691 cm^{-1}; $[\alpha]_D^{23}$ –16.8° (*c* = 1.0, $CHCl_3$); ^1H NMR δ 11.50 (s, 1H, NH), 8.69 (d, 1H, J

= 7.5 Hz, H5′), 8.07 (d, 1H, J = 8 Hz, H2′), 7.52 (dt, 1H, J = 1.5 and 8 Hz, H3′), 7.34 (m, 15H, PhH), 7.08 (t, 1H, J = 7.5 Hz, H4′), 5.72 (d, 1H, J = 7 Hz, NH), 5.29 (AB, 2H, J = 12 Hz, PhC$\underline{H_2}$OC=O), 5.09 (m, 4H, PhC$\underline{H_2}$OC=O and PhC$\underline{H_2}$O), 4.91 (br s, 1H, N$\underline{H}$), 4.37 (m, 1H, H2), 3.18 (m, 2H, H6), 2.00-1.42 (m, 6H, H3-H5); ^{13}C NMR δ 170, 168, 157, 141, 136, 135, 134, 131, 128, 123, 120, 115, 67.1, 67.0, 66.6, 56.1, 40.2, 32.0, 29.4, 22.2; Anal. Calcd for $C_{36}H_{37}N_3O_7$: C 69.30, H 5.98, N 6.74. Found: C 69.50, H 5.95, N 6.54.

Ethyl 2-({2,6-*bis*[(benzyloxycarbonyl)amino]hexanoyl}amino)benzoate (30)

A solution of ethyl anthranilate (**25**, 0.825 g, 5.0 mmol) in CH_2Cl_2 (5 mL) was slowly added to a stirred solution of *N*α, *N*ε-Cbz-L-lysine (**26**, 2.07 g, 5.0 mmol), hydroxybenzotriazole (0.675 g, 5.0 mmol) and dicyclohexylcarbodiimide (1.55 g, 7.5 mmol) in CH_2Cl_2 (20 mL) at 0°C. The reaction was stirred for 24 h, filtered, concentrated and applied to a silica column (40 g) that was eluted with gradients of EtOAc in hexanes (10% → 100%). The white solid product (**30**, 1.99 g, 71%) was recrystallised from ether/hexanes, mp 70-72°C; IR (KBr) 1691 cm^{-1}; $[\alpha]_D^{23}$ –15.8° (*c* = 1.0, $CHCl_3$); ^{1}H NMR δ 11.60 (s, 1H, NH), 8.68 (d, 1H, J = 8.5 Hz, H5′), 8.04 (dd, 1H, J = 1.5 and 8 Hz, H2′), 7.52 (dt, 1H, J = 1 and 8 Hz, H3′), 7.31 (m, 10H, PhH), 7.09 (dt, 1H, J = 1 and 8 Hz, H4′), 5.71 (m, 1H, NH), 5.08 (m, 4H, $PhCH_2$), 4.90 (m, 1H, NH), 4.35 (m, 3H, OC$\underline{H_2}$CH$_3$ and H2), 3.17 (m, 2H, H6), 1.80-1.42 (m, 6H, H3-H5), 1.37 (t, 3H, J = 7 Hz, OCH$_2$C$\underline{H_3}$); ^{13}C NMR δ 171, 168, 157, 156, 141, 137, 136, 134, 131, 129, 128, 123, 120, 115, 67.1, 66.6, 61.5, 56.2, 40.3, 33.9, 32.2, 22.3, 14.1; Anal. Calcd for $C_{31}H_{35}N_3O_7$: C 66.30, H 6.29, N 7.48. Found: C 66.40, H 6.60, N 7.37.

Ethyl 2-({2-(*tert*-butyloxycarbonyl)amino-6-(benzyloxycarbonyl)amino]hexanoyl}amino)-benzoate (31)

*N*α–Boc, *N*ε-carbobenzyloxy-L-lysine (**27**, 0.950 g, 2.5 mmol) and hydroxybenzotriazole (0.335 g, 2.5 mmol) were dissolved in THF (20 mL). Dicyclohexylcarbodiimide (0.545 g, 2.75 mmol) was added followed by a solution of ethyl anthranilate (**25**, 0.415 g, 2.5 mmol) in THF (5 mL). The reaction was stirred at 0 ^{0}C for 2 h then for 3 h at ambient temperature. The reaction was concentrated and chromatographed (SiO_2, 40 g) with gradients of EtOAc in hexanes (10 % → 50 %). Any mixed product fractions were re-chromatographed on a 2 mm Chromatotron plate with elutions of 20%, 35% and 50% EtOAc in hexanes. The combined product (0.820 g, 62%) was recrystallised from ether/hexanes, mp 99-100°C; IR (KBr) 1714, 1688 cm^{-1}; $[\alpha]_D^{23}$ –28.8° (*c* = 1.0, $CHCl_3$); HRMS Calcd for $C_{28}H_{37}N_3O_7$: 527.2632; Found: 527.2682; ^{1}H NMR δ 11.60 (s,

1H, NH), 8.71 (dd, 1H, J = 1 and 8 Hz, H5′), 8.04 (dd, 1H, J = 1.5 and 8 Hz, H2′), 7.56 (dt, 1H, J = 1.5 and 8 Hz, H4′), 7.34 (m, 5H, PhH), 7.09 (dt, 1H, J = 1 and 8 Hz, H3′), 5.33 (br.s, 1H, NH), 5.08 (s, 2H, PhCH$_2$), 4.99 (br s, 1H, NH), 4.34 (q, 2H, J = 7 Hz, OCH$_2$CH$_3$), 4.32 (m, 1H, H2), 3.19 (m, 2H, H16), 1.92-1.36 (m, 6H, H3-H5), 1.46 (s, 9H, *t*-OBu), 1.39 (t, 3H, J = 7 Hz, OCH$_2$CH$_3$); ^{13}C NMR δ 171, 168, 156, 155, 141, 137, 134, 131, 128, 123, 120, 115, 80.0, 66.6, 61.4, 55.7, 40.5, 32.3, 29.5, 28.3, 22.5, 14.2; Anal. Calcd for $C_{28}H_{37}N_3O_7$: C 63.73, H 7.07, N 7.96. Found: C 63.60, H 7.50, N 8.07.

(2*R*,11a*S*)-2-Hydroxy-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (33)

Prepared in 90% yield from isatoic anhydride (**9**, 4.89 g, 0.03 mol) and 4-hydroxy-L-proline (3.277 g, 0.025 mol) according to the reported procedure.[25]

(2*R*,11a*S*)-2-[(Methylsulfonyl)oxy]-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine-5,11-dione (34) and (2*S*, 11a*S*)-2-chloro-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1, 4]benzodiazepine-5,11-dione

The alcohol (**33**, 0.232 g, 1.0 mmol) was dissolved in dry pyridine (2 mL) and cooled to 0°C under a stream of dry N_2. Methanesulfonyl chloride (0.155 mL, 0.229 g, 2.0 mmol) was added dropwise over 10 min and the reaction left to stir for 15 h. The solvent was evaporated and the residue applied to a short silica gel column (12 g) and eluted with CH_2Cl_2 (100 mL) and gradients of EtOAc in CH_2Cl_2 (25% → 50%). This gave a less polar product (0.031 g, 5 %) that recrystallised from EtOAc and was identified as the chloro compound: mp 204-207°C; IR (KBr) 1697, 1616 cm^{-1}; $[\alpha]_D^{21}$ +345° (*c* = 0.5, MeOH), ^{1}H NMR (DMSO-d$_6$) δ 10.55 (s, 1H, NH), 7.81 (dd, 1H, J = 1.5 and 8 Hz, H6), 7.53 (dt, 1H, J = 1.5 and 8 Hz, H8), 7.22 (dt, 1H, J = 1 and 8 Hz, H7), 7.16 (dd, 1H, J = 1 and 8 Hz, H9), 4.73 (m, 1H, H2), 4.26 (dd, 1H, J = 3.5 and 9 Hz, H11a), 4.08 (dd, 1H, J = 4.5 and 13 Hz, H3), 3.66 (ddd, 1H, J = 1, 3 and 13 Hz, H3), 2.86 (ddt, 1H, J = 1, 3 and 14 Hz, H1), 2.60 (ddd, 1H, J = 6, 9 and 14 Hz, H1); ^{13}C NMR δ 170, 165, 137, 131, 125, 124, 121, 56.2, 55.8, 54.9, 35.1; Anal. Calcd for $C_{12}H_{11}N_2O_2Cl{\cdot}1/2\ C_4H_8O_2$: C 57.05, H 5.13, N 9.50. Found: C 57.05, H 5.14, N 9.53.

Further elution and concentration gave the product mesylate (**34**) as a colorless powder (0.283 g, 91%) that recrystallised from EtOAc as prisms, mp 204-205°C; IR (KBr) 1697, 1624 cm^{-1}, $[\alpha]_D^{21}$ +368° (*c* = 1.0, MeOH), ^{1}H NMR (DMSO-d$_6$) δ 10.68 (s, 1H, NH), 7.81 (dd, 1H, J = 1.5 and 8 Hz, H8), 7.25 (dt, 1H, J = 1 and 8 Hz, H7), 7.15 (d, 1H, J = 8 Hz, H9), 5.34 (m, 1H, H2), 4.33 (t, 1H, J = 7.5 Hz, H11a), 4.09 (d, 1H, J = 13.5 Hz, H3), 3.71 (dd, 1H, J = 4.5 and 13.5 Hz,

H3), 3.26 (s, 3H, OCH_3), 2.92 (ddd, 1H, J = 5.5, 7.5 and 14.5 Hz, H1), 2.34 (ddt, 1H, J = 2.5, 7.5 and 14.5 Hz, H1); ^{13}C NMR δ 170, 165, 136, 132, 130, 125, 124, 122, 78.5, 54.8, 52.0, 37.7, 32.6; Anal. Calcd for $C_{13}H_{14}N_2O_4S$: C 50.32, H 4.55, N 9.03. Found: C 50.21, H 4.72, N 9.00.

(11a*S*)-1,10,11,11a-Tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (35)

Resublimed KO^{t}Bu (0.246 g, 2.2 mmol) was dissolved in dry DMSO (2 mL) under N_2 at rt. A solution of the mesylate (**34**, 0.310 g, 1 mmol) in dry DMSO (2 mL) was added to the stirred solution *via* syringe. The reaction was stirred for 0.5 h then quenched with brine (10 mL) and ether (30 mL), the layers separated and the aqueous phase re-extracted with ether (3 x 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated to a white solid (**35**, 0.180 g, 84%) that recrystallised from EtOAc, mp 212-215°C; IR (KBr) 1697, 1610 cm^{-1}; $[\alpha]_D^{21}$ +723° (*c* = 1.0, MeOH); ^1H NMR (DMSO-d_6) δ 10.66 (s, 1H, NH), 7.81 (dd, 1H, J = 1 and 8 Hz, H6), 7.53 (ddd, 1H, J = 1, 1.5 and 8 Hz, H8), 7.25 (dt, 1H, J = 1 and 8 Hz, H7), 7.16 (dd, 1H, J = 1 and 8 Hz, H9), 6.89 (dt, 1H, J = 2.5 and 4 Hz, H3), 5.45 (dt, 1H, J = 2 and 4 Hz, H2), 4.59 (dd, 1H, J = 3.5 and 11 Hz, H11a), 3.34 (m, 1H, H1), 2.78 (ddt, 1H, J = 2.5, 11 and 17 Hz, H1); ^{13}C NMR δ 169, 162, 136, 133, 131, 127, 126, 124, 122, 113, 55.5, 30.3; Anal. Calcd for $C_{12}H_{10}N_2O_2$: C 67.28, H 4.71, N 13.08. Found; C 66.98, H 4.71, N 13.08.

(11a*S*)-1,3,10,11,11a-Pentahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-2,5,11-trione (36)

The alcohol (**33**, 2.32 g, 0.01 mol) was dissolved in acetone (150 mL) in a 1L round bottom flask equipped with a condenser, a mechanical stirrer and a dropping funnel. The solution was heated at reflux while a chromic acid solution (20 mL) was slowly added over 30 min. After complete addition, EtOAc (150 mL) was added, the layers separated and the organic phase washed with sat. $NaHCO_3$ (3 x 20 mL) then dried ($MgSO_4$). The residue upon evaporation was chromatographed over silica gel (50 g) with gradients of EtOAc in hexanes (50% → 100%). The resultant off-white solid (0.475 g, 21%) was recrystallised from EtOAc/hexanes, mp 217-222°C (decomp); IR (KBr) 1765, 1697, 1618 cm^{-1}; $[\alpha]_D^{21}$ +484° (*c* = 1.0, MeOH); ^1H NMR (DMSO-d_6) δ 10.72 (s, 1H, NH), 7.81 (dd, 1H, J = 1.5 and 8 Hz, H6), 7.27 (dt, 1H, J = 1 and 8 Hz, H7), 7.17 (dd, 1H, J = 19.5 Hz, H3), 3.88 (d, 1H, J = 19.5 Hz, H3), 3.17 (dd, 1H, J = 3.5 and 19 Hz, H1), 2.87 (ddd, 1H, J = 1.5, 10 and 19 Hz, H1); ^{13}C NMR δ 208, 170, 166, 136, 130, 126, 124, 122, 54.1, 52.8, 36.8.

2,5-Diamino-*bis*-(*N*-*t*-butoxycarbonyl)benzoxazole (39)

2-Amino-5-nitrobenzoxazole[15] (**38**, 0.895 g, 5.0 mmol) was suspended in MeOH (50 mL),

Pd/C (10%, 0.09 g) added and the mixture stirred under 1 atmosphere of H_2 overnight (15 h). The reaction was self-indicating, with the orange color of the nitro compound being discharged. The solvent was evaporated and the residue diluted with dry THF (30 mL). Et_3N (0.83 mL, 0.606 g, 6.0 mmol), hydroxylamine hydrochloride (0.034 g, 0.5 mmol) and *t*-butyl pyrocarbonate (2.72 g, 0.0125 mole) were added and the reaction stirred at ambient temperature for 48 h under a gentle stream of dry N_2. The solvent was evaporated and the residue applied to a silica column with eluted with gradients of EtOAc in hexanes (20% → 50%). The product (**39**, 0.913 g, 52%) was recrystallised from benzene/hexanes: mp 133-135°C; IR (KBr) 1756, 1725 cm^{-1}; HRMS Calcd for $C_{17}H_{24}N_3O_5$: 350.1718; Found (M^+ + 1): 350.1716; ^1H NMR δ 7.97 (br s, 1H, NH), 7.88 (br s, 1H, NH), 6.96 (m, 2H, H6 and H7), 1.71 (s, 9H, O-*t*-Bu), 1.52 (s, 9H, O-*t*-Bu); ^{13}C NMR δ 154, 153, 150, 139, 135, 128, 115, 109, 106, 86.3, 28.3, 28.1; Anal. Calcd for $C_{17}H_{23}N_3O_5$: C 58.44, H 6.64. Found: C 58.80, H 6.64.

2,5-Diamino-N_2-(*t*-butoxycarbonyl)-N_5-(ethoxycarbonyl)benzoxazole (40)

2-Amino-5-nitrobenzoxazole[15] (**34**, 0.895g, 0.005 mole) was suspended in MeOH (50 mL), Pd/C (10%, 0.09 g) added and the mixture stirred under 1 atmosphere of H_2 overnight (15 h). The reaction was self-indicating, with the orange colour of the nitro compound being discharged. The solvent was evaporated and the residue diluted with dry THF (30 mL), Et_3N (0.76 mL, 0.55 g, 5.5 mmol) and ethyl chloroformate (0.52 mL, 0.59 g, 5.5 mmol) and the reaction stirred at ambient temperature for 1 h. The solvent was evaporated and the residue applied to a silica column (40 g) that was eluted with gradients of EtOAc in hexanes (20% → 50%). The intermediate N_5-Boc product (0.694 g, 63%) was recrystallised from EtOAc as needles: mp 190-191°C; IR (KBr) 1706 cm^{-1}; HRMS Calcd for $C_{10}H_{11}N_3O_3$: 221.0800; Found (M^+ + 1); 222.0878; ^1H NMR (DMSO-d_6) δ 9.46 (s, 1H, NH), 7.34 (m, 3H, NH_2 and H3), 7.12 (m, 1H, H6), 7.00 (m, 1H, H5), 4.11 (q, 2H, J = 7 Hz, $OC\underline{H}_2CH_3$), 1.31 (t, 3H, J = 7 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR δ 163, 153, 144, 143, 135, 110, 107, 106, 59.9, 14.5; Anal. Calcd for $C_{10}H_{11}N_3O_3$: C 54.30, H 5.01, N 19.00. Found: C 54.22, H 5.01, N 18.94.

The above intermediate carbamate (0.608 g, 2.75 mmol) was heated at reflux in THF (10 mL) with *t*-butyl pyrocarbonate for 6 h. The solvent was removed and the residue applied to a silica column (40 g) and eluted with EtOAc/hexanes (25% → 100%) to give the product (**40**, 0.805 g, 91%) which was recrystallised from ether: mp 141-145°C; IR (KBr) 1721, 1670 cm^{-1}; ^1H NMR δ 7.99 (br s, 1H, NH), 7.91 (br s, 1H, NH), 6.98 (m, 3H, PhH), 4.22 (q, 2H, J = 7 Hz, $OC\underline{H}_2CH_3$), 1.70 (s, 9H, O-*t*-Bu), 1.30 (t, 3H, J = 7 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR δ 154, 153, 139, 134, 128, 115, 109, 106, 86.4, 61.3, 28.1, 14.6; Anal. Calcd for $C_{15}H_{19}N_3O_5$: C 56.07, H

5.96, N 13.08. Found: C 56.21, H 5.95, N 13.11.

4-Amino-2-nitro-*N*-ethoxycarbonylphenol (41)

2-Nitro-4-aminophenol (0.77 g, 5.0 mmol) was heated at reflux temperature for 0.5 h in dry dioxane (25 mL) with ethyl chloroformate (0.52 g, 0.6 mL, 6.0 mmol). The solvent was evaporated and the residue applied to a silica column (40 g) with gradients of EtOAc in hexanes (10% → 20%). The resultant homogenous solid (**41**, 1.0 g, 88%) was recrystallised as needles from ether/hexanes: mp 83-84°C; IR (KBr) 1712 cm^{-1}; ^{1}H NMR δ 10.40 (s, 1H, N<u>H</u>), 8.18 (d, 1H, J = 2.5 Hz, H3), 7.63 (dd, 1H, J = 2.5 and 9 Hz, H5), 7.12 (d, 1H, J = 9 Hz, H6), 6.80 (br s, 1H, OH), 4.24 (q, 2H, J = 7 Hz, OC<u>H</u>$_2$CH$_3$), 1.32 (t, 3H, J = 7 Hz, OCH$_2$C<u>H</u>$_3$); ^{13}C NMR δ 153, 151, 133, 130, 129, 120, 114, 61.3, 14.0; Anal. Calcd for $C_9H_{10}N_2O_5$: C 47.78, H 4.46, N 12.4. Found: C 47.92, H 4.48, N 12.4.

***N*$_2$-(*t*-Butoxycarbonyl)-*N*$_4$-ethoxycarbonyl-2,4-diaminophenol (42)**

The aminophenol (**41**, 0.77 g, 5.0 mmol) was heated at reflux temperature for 0.5 h in dry dioxane (25 mL) with ethyl chloroformate (0.52 g, 0.6 mL, 6.0 mmol). The solvent was evaporated and the residue taken up in THF (20 mL), 10% Pd/C (0.11 g) and *t*-butyl pyrocarbonate (1.31 g, 6.0 mmol) added. The mixture was stirred under 1 atmosphere of H_2 pressure for 24 h. The solvent was evaporated and the residue applied to a silica column (40 g) and eluted with 25% EtOAc/hexanes. The product (**42**, 1.36 g, 92%) was recrystallised from ether/hexanes: mp 110-111°C; IR (KBr) 1705, 1698 cm^{-1}; HRMS Calcd for $C_{14}H_{20}N_2O_5$: 296.1372; Found (M^+ + 1): 227.1450; ^{1}H NMR δ 7.93 (br s, 1H, N<u>H</u>), 7.46 (br s, 1H, NH), 6.88 (m, 1H, H5), 6.76 (d, 1H, J = 8.5 Hz, H6), 6.59 (br.s, 1H, H3), 4.19 (q, 2H, J = 7 Hz, OC<u>H</u>$_2$CH$_3$), 1.51 (s, 9H, O-*t*-Bu), 1.28 (t, 3H, J = 7 Hz, OCH$_3$C<u>H</u>$_3$); ^{13}C NMR δ 154, 143, 131, 126, 118, 116, 81.7, 61.3, 28.3, 14.5; Anal. Calcd for $C_{14}H_{20}N_2O_5$: C 56.73, H 6.81, N 9.46. Found: C 57.13, H 7.01, N 9.33.

***t*-Butyldimethylsilyl-*N*$_2$-*t*-butoxycarbonyl-*N*$_4$-ethoxycarbonyl-2,4-diaminophenol (43)**

2-Nitro-4-aminophenol (0.77 g, 5.0 mmol) treated as above for intermediates (**41**) and (**42**) and, without isolation, the residue taken up in dry DMF (10 mL). Imidazole (0.68 g, 0.01 mole) and TBDMSCl (0.904 g, 0.06 mol) were added and the reaction stirred at ambient temperature for 1 h. The solvent was evaporated and the residue applied to a silica (40 g) column that was eluted with EtOAc gradients in hexanes (10% → 20%). The TLC homogenous product (**43**, 1.84 g, 90%) was recrystallised from ether/hexanes: mp 135-137°C;

IR (KBr) 1714, 1686 cm^{-1}; HRMS Calcd for $C_{20}H_{34}N_2O_5Si$: 410.2237; Found (M^+ + 1): 411.2315; ^1H NMR δ 7.86 (br s, 1H, N<u>H</u>), 7.14 (m, 1H, H5), 6.93 (br s, 1H, NH), 6.73 (d, 1H, J = 8.5 Hz, H6), 6.49 (br s, 1H, H3), 4.19 (q, 2H, OC<u>H</u>$_2$CH$_3$), 1.50 (s, 9H, *t*-Bu), 1.31 (t, 3H, J = 7 Hz, OCH$_2$C<u>H</u>$_3$), 1.02 (s, 9H, *t*-BuSi), 0.22 (s, 6H, OSi(CH$_3$)$_2$; ^{13}C NMR δ 153, 152, 139, 130, 117, 112, 109, 79.9, 60.6, 27.8, 25.3, 17.7, 14.1, -4.89.

2-Amino-*N*-ethoxycarbonyl-5-hydroxybenzoic acid (44)

2-Amino-5-hydroxybenzoic acid (2.29 g, 0.015 mole) was dissolved in 5% $NaHCO_3$ (30 mL), cooled to 5°C and ethyl chloroformate (1.89 g, 1.67 mL, 0.0175 mole) slowly added along with 1N NaOH to maintain the pH at 8.4. The reaction was stirred for 1 h after complete addition, acidified to pH 2 with 1N HCl and filtered. The filter cake was washed with 1N HCl (100 mL), air dried and eluted down a silica column with ether/hexanes (1:1). The product (2.91 g, 86%) was recrystallised from EtOAc as a powder: mp 217-220°C; IR (KBr) 1704, 1660 cm^{-1}; HRMS Calcd for $C_{10}H_{11}NO_5$: 225.0637; Found: 225.0634; ^1H NMR (MeOH-d_4) δ 8.14 (d, 1H, J = 9 Hz, H3), 7.50 (br s, 1H, H6), 7.03 (m, 1H, H4), 5.09 (br s, 3H, OH and NH), 4.19 (q, 2H, J = 7 Hz, OC<u>H</u>$_2$CH$_3$), 1.32 (t, 3H, J = 7 Hz, OCH$_2$C<u>H</u>$_3$); ^{13}C NMR 169, 154, 151, 133, 121, 120, 116, 60.5, 13.4

Methyl 6-amino-*N*-ethoxycarbonyl-3-hydroxybenzoate (46)

2-Amino-5-hydroxybenzoic acid (0.765 g, 5.0 mmol) and ethyl chloroformate (0.814 g, 0.75 mL, 7.5 mmol) were heated at reflux temperature in dry dioxane (25 mL) for 2 h. The solvent was evaporated, the residue diluted with dry MeOH (50 mL) and thionyl chloride (5 mL, 64 mmol) added. The reaction was heated at reflux temperature for 2 h, concentrated and applied to a silica column. Elution with EtOAc in hexanes (10% → 20%) gave 1.00 g (84%) of homogenous product (**46**) that was recrystallised from ether/hexanes as needles: mp 139-141°C; IR (KBr) 1726, 1682 cm^{-1}, ^1H NMR δ 10.10 (s, 1H, NH), 8.24 (d, 1H, J = 9 Hz, H5), 7.47 (d, 1H, J = 3 Hz, H2), 7.05 (dd, 1H, J = 3 Hz and 9 Hz, H4), 5.76 (br s, 1H, OH), 4.22 (q, 2H, J = 7 Hz, OC<u>H</u>$_2$CH$_3$), 3.89 (s, 3H, OCH$_3$), 1.31 (t, 3H, J = 7 Hz, OCH$_2$C<u>H</u>$_3$); ^{13}C NMR δ 168, 154, 150, 135, 122, 121, 116, 115, 61.1, 52.1, 14.3.

Benzyl 2-amino-5-benzyloxy-*N*-ethoxycarbonylbenzoate (47)

2-Amino-5-hydroxybenzoic acid (0.765 g, 5.0 mmol) and ethyl chloroformate (0.814 g, 0.72 mL, 7.5 mmol) were heated in dry dioxane (25 mL) at reflux temperature for 2 h. The solvent

was evaporated, the residue dissolved in dry DMF (10 mL), K_2CO_3 (2.07 g, 0.015 mol) and benzyl bromide (1.88 g, 1.31 mL, 0.011 mol) added and the reaction stirred under N_2 for 2 h at ambient temperature. The reaction was diluted with water (50 mL) and extracted with ether (3 x 20 mL). The ether extract was concentrated and applied to a silica column that was eluted with 10% EtOAc in hexanes. The TLC homogenous product (**47**, 1.63 g, 80%) was recrystallised as needles from ether/hexanes: mp 63-64°C; IR (KBr) 1729, 1682 cm^1; ^1H NMR ($CDCl_3$) δ 10.2 (s, 1H, NH), 8.35 (d, 1H, J = 9 Hz, H3), 7.62 (d, 1H, J = 3 Hz, H6), 7.40 (m, 10H, $OCH_2\underline{Ph}$), 7.19 (dd, 1H, J = 3 and 9 Hz, H4), 5.34 (s, 2H, $OC\underline{H_2}Ph$), 5.04 (s, 2H, $OC\underline{H_2}Ph$), 4.21 (q, 2H, J = 7 Hz, $OC\underline{H_2}CH_3$), 1.31 (t, 3H, J = 7 Hz, $OCH_2C\underline{H_3}$); ^{13}C NMR δ 167, 154, 153, 137, 136, 135, 129, 128, 127, 126, 122, 120, 116, 115, 70.5, 67.0, 61.1, 14.5; Anal. Calcd for $C_{23}H_{23}NO_5$: C 71.1, H 5.55, N 3.45. Found: C 71.1, H 5.72, N 3.45.

6-Amino-3-benzyloxy-*N*-ethoxycarbonylbenzoic acid (48)

The benzyl ester (**47**, 0.405 g, 1.0 mmol) and KOH (0.112 g, 2.0 mmol) were heated at reflux in MeOH/H_2O (10 mL, 3:1) for 2 h. The reaction was cooled and acidified with 1N HCl (2 mL). The precipitate was filtered, air dried and recrystallised from ether/hexanes as needles (0.281 g, 89%): mp 159-160°C; IR (KBr) 1730, 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.94 (s, 1H, CO_2H), 8.39 (d, 1H, J = 9 Hz, H3), 7.69 (d, 1H, J = 3 Hz, H6), 7.37 (m, 5H, $OCH_2\underline{Ph}$), 7.24 (dd, 1H, J = 3 and 9 Hz, H4), 5.07 (s, 2H, $OC\underline{H_2}Ph$), 4.24 (q, 2H, J = 7 Hz, $OC\underline{H_2}CH_3$), 1.34 (t, 3H, J = 7 Hz, $OCH_2C\underline{H_3}$); ^{13}C NMR δ 173, 154, 153, 136, 129, 128, 127, 124, 121, 116, 114, 70.6, 61.4, 14.6; Anal. Calcd for $C_{17}H_{17}NO_5$: C 64.75, H 5.43, N 4.44. Found: C 64.63, H 5.40, N 4.46.

6-Hydroxyisatoic anhydride (49)

2-Amino-5-hydroxybenzoic acid (1.53 g, 0.01 mol), dry dioxane (50 mL) and ethyl chloroformate (1.3 g, 1.5 mL, 0.015 mol) were heated at reflux under a $CaCl_2$ drying tube until complete dissolution was achieved (~2 h). The reaction mixture was cooled and oxalyl chloride (1.52 g, 1.02 mL, 0.012 mole) added with caution. The reaction mixture was heated at reflux temperature for a further 1h, at which point TLC indicated 100% conversion. The solvent was evaporated and the compound (**49**) was used directly without further purification. This compound was fully characterised as the acetate derivative (**50** below).

6-Acetoxyisatoic anhydride (50)

2-Amino-5-hydroxybenzoic acid (1.53 g, 0.01 mol), dry dioxane (50 mL) and ethyl chloroformate (1.3 g, 1.5 mL, 0.015 mol) were heated at reflux under a $CaCl_2$ drying tube until complete dissolution was achieved (~2 h). The solvent volume was reduced to half and acetyl chloride (2.36 g, 2.1 mL, 0.03 mol) added and heating at reflux temperature continued for 1 h. The solvent was evaporated and the residue recrystallised from acetone to afford the acetate (**50**) as prisms (1.83 g, 83%): mp 204-206°C; IR (KBr) 1768, 1749, 1697 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.80 (br s, 1H, N<u>H</u>), 7.67 (m, 1H, H6), 7.53 (m, 1H, H3), 7.19 (m, 1H, H4), 2.29 (s, 3H, OC=O<u>CH</u>$_3$); ^{13}C NMR δ 169, 159, 147, 146, 140, 131, 116, 111, 20.7; Anal. Calcd for $C_{10}H_7NO_5$: C 54.31, H 3.19, N 6.33. Found: C 54.33, H 3.15, N 6.32.

6-Benzyloxyisatoic anhydride (51)

The acid (**48**, 0.472 g, 1.5 mmol) was dissolved in dry THF (15 mL), oxalyl chloride (1 mL) added and the reaction heated at reflux temperature for 2 h. The solvent was evaporated, ether (10 mL) added to the residue and the mixture heated under reflux for 10 min. The precipitate was filtered, washed with a little ether (10 mL) and recrystallised from EtOAc to give the product (**51**) as prisms (0.350 g, 87%): mp 218-220°C; IR (KBr) 1748, 1696 cm^{-1}; HRMS Calcd for $C_{15}H_{11}NO_4$: 269.0688; Found (M^+ + 1): 270.0766; ^1H NMR (DMSO-d_6) δ 11.60 (s, 1H, NH), 7.40 (m, 7H, CH_2<u>Ph</u>, H7 and H5), 7.12 (d, 1H, J = 8.5 Hz, H4), 5.16 (s, 2h, OC<u>H</u>$_2$Ph); ^{13}C NMR δ 160, 154, 147, 136, 135, 128, 126, 117, 111, 110, 69.7; Anal. Calcd for $C_{15}H_{11}NO_4$: C 66.91, H 4.12, N 5.20. Found: C 66.52, H 4.15, N 5.21.

Methyl 2-amino-*N*-ethoxycarbonyl-5-hydroxy-4-nitrobenzoate (52a) and Methyl 6-amino-*N*-ethoxycarbonyl-3-hydroxy-2-nitrobenzoate (53a)

The methyl ester (**46**, 0.239 g, 1.0 mmol) was dissolved in THF (5 mL) and acetic anhydride (0.5 mL). Cupric nitrate (0.121 g, 1.0 mmol) was added and the reaction stirred for 1 h. The solvent was evaporated and the residue applied to a short silica column (10 g) and eluted with EtOAc (100 mL). The eluant was evaporated and the mixture purified by repeated chromatography on a 2 mm Chromatotron plate with CH_2Cl_2 in hexanes (50% → 100%). The 4-nitro compound (**52a**, 18 mg, 6%) eluted first: mp 119-121°C; IR (KBr) 1707 cm^{-1}; HRMS Calcd for $C_{11}H_{13}N_2O_7$: 285.0724; Found (M^+ + 1): 285.0722; ^1H NMR δ 10.00 (br s, 2H, OH and NH), 9.22 (s, 1H, H3), 7.82 (s, 1H, H6), 4.27 (m, 2H, OC<u>H</u>$_2$CH$_3$), 3.98 (s, 3H, OC<u>H</u>$_3$), 1.34 (t, 3H, J = 7 Hz, OCH$_2$C<u>H</u>$_3$); ^{13}C NMR δ 166, 154, 148, 136, 134, 123, 122, 115, 61.6, 53.1, 14.4.

Further elution produced the 2-nitro isomer (**53a**, 29 mg, 10%): mp 140.5-142°C; IR (KBr) 1708 cm^{-1}; ^{1}H NMR δ 9.76 (br s, 1H, NH), 8.29 (d, 1H, J = 9.5 Hz, H5), 7.72 (br s, 1H, OH), 7.24 (d, 1H, J = 9.5 Hz, H4), 4.22 (q, 2H, J = 7 Hz, $OC\underline{H}_2CH_3$), 3.91 (s, 3H, OCH_3), 1.32 (t, 3H, J = 7 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR δ 166, 154, 150, 132, 130, 123, 61.9, 53.7, 14.4. Satisfactory microanalysis was not obtained for either product.

Benzyl 6-amino-3-benzyloxy-*N*-ethoxycarbonyl-2-nitrobenzoate (53b) and Benzyl 2-amino-*N*-ethoxycarbonyl-5-benzyloxy-3-nitrobenzoate (52b)

The benzyl ester (**47**, 0.405 g, 1.0 mmol) was dissolved in acetic anhydride (2.5 mL) and cupric nitrate (0.244 g, 1.0 mmol) added. The reaction was stirred at ambient temperature for 2 h, diluted with water (50 mL) and extracted with ether (3 x 20 mL). The extract was concentrated and applied to a 2 mm Chromatotron plate that was eluted with gradients of EtOAc in hexanes (10% → 20%) repeatedly until the two compounds were separated. The first, the 2-nitro isomer (**53b**) was a pale yellow solid (102 mg, 23%) was recrystallised from ether/hexanes: mp 81-82°C; IR (KBr) 1745, 1695 cm^{-1}; ^{1}H NMR δ 9.26 (br s, 1H, NH), 7.78 (d, 1H, J = 7 Hz, H4 or H6), 7.66 (d, 1H, J = 7 Hz, H4 or H6), 7.39 (m, 10H, $OCH_2\underline{Ph}$), 5.32 (s, 2H, $OC\underline{H}_2Ph$), 5.06 (s, 2H, $OC\underline{H}_2Ph$), 4.14 (q, 2H, J = 7 Hz, $OC\underline{H}_2CH_3$), 1.25 (t, 3H, J = 7 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR δ 165, 154, 144, 135, 134, 128, 127, 126, 122, 115, 70.7, 67.7, 62.0, 14.0; Anal. Calcd for $C_{24}H_{22}N_2O_7$: C 63.99, H 4.92, N 6.22. Found: C 63.71, H 4.96, N 6.20.

The second compound to elute, the 4-nitro isomer (**52b**, 25 mg, 6%, orange solid) was also recrystallised from ether/hexanes: mp 126-128°C; IR (KBr) 1729 cm^{-1}; ^{1}H NMR δ 9.36 (br s, 1H, NH), 8.37 (d, 1H, J = 2.5Hz, H5), 7.36 (m, 10H, $OCH_2\underline{Ph}$), 7.21 (d, 1H, J = 2.5 Hz, H4), 5.30 (s, 2H, $OC\underline{H}_2Ph$), 5.14 (s, 2H, $OC\underline{H}_2Ph$), 4.20 (q, 2H, J = 7 Hz, $OC\underline{H}_2CH_3$), 1.31 (t, 3H, J = 7 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR δ 164, 154, 145, 143, 135, 134, 133, 128, 127, 123, 120, 111, 71.8, 68.7, 61.6, 14.4; Anal. Calcd for $C_{24}H_{22}N_2O_7$: C 63.99, H 4.92, N 6.22. Found: C 63.65, H 4.89, N 6.18.

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