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Synthesis of Pyrrolo[2,1-*c*][1,4]benzodiazepines *via* an Intramolecular Aza-Wittig Reaction. Synthesis of the Antibiotic DC-81

Pedro Molina*, Isidora Díaz, Alberto Tárraga

Departamento de Química Orgánica, Facultad de Químicas, Universidad de Murcia
Campus de Espinardo, E-30071 Murcia, Spain.

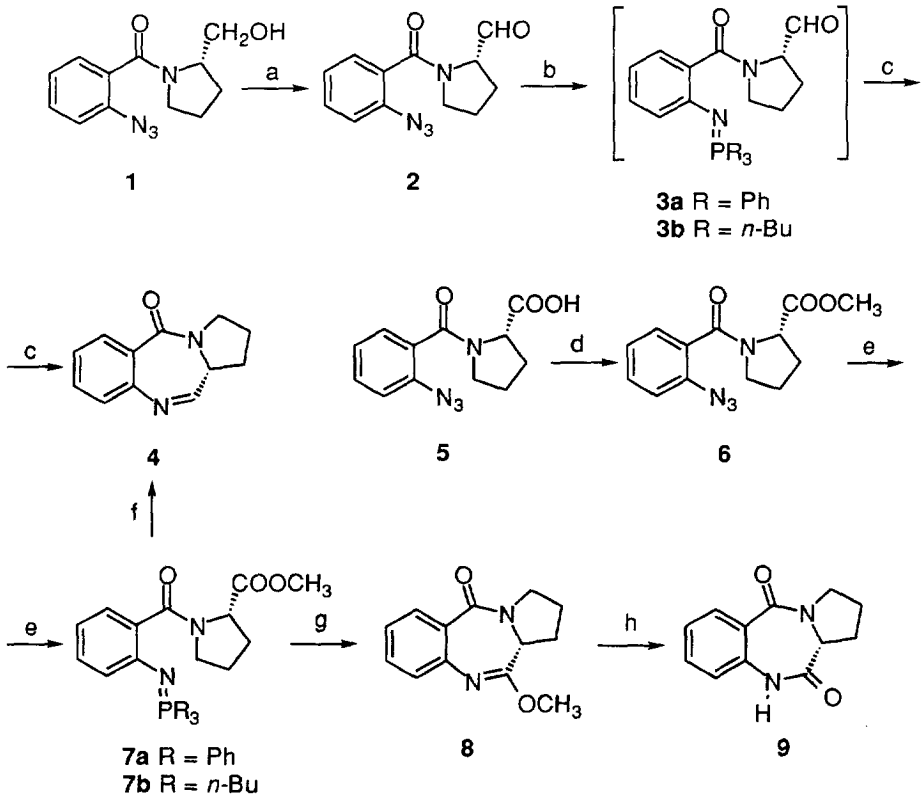
Abstract: A new and efficient synthesis of the pyrrolo[2,1-*c*][1,4]benzodiazepine ring system has been carried out using, as a key step, an intramolecular aza Wittig reaction of the appropriately substituted *N*-(2-azidobenzoyl)pyrrolidine-2-carboxaldehydes. The parent unsubstituted PBD **4** and the natural product DC-81 have been prepared in the imine form in good overall yields.

The pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) group of antitumor antibiotics[1]: anthramycin, tomaymycin, DC-81, neothramycins A and B, prothracarcin, pretomaymycin, sibiromycin and several others, exert their biological activity by covalently binding to the N2 of guanine in the minor groove of DNA, via an electrophilic imine or carbinolamine functionality at N10-C11. The resulting DNA-antibiotic adduct inhibits DNA replication[2]. Preparation of compounds in this group involves a) hydride reduction of a seven-membered cyclic dilactam[3], b) reductive cyclization of an acyclic nitro aldehyde[4], c) reduction of cyclic iminothioethers[5], d) cyclization of amino acetals[6] or thioacetals[7], e) photochemical ring expansion of *N*-pentenylphthalimides[8], and f) palladium catalyzed carbonylation of *o*-haloanilides[9].

The intramolecular aza-Wittig reaction has been utilized for the synthesis of five-, six and seven-membered azaheterocycles and several successful examples of the synthesis of natural products using this cyclization reaction as the key step have been reported[10]. We herein report a new method to the synthesis of the pyrrolo[2,1-*c*][1,4]benzodiazepine ring system and its application to synthesis of the natural product DC-81. Our approach is based on the formation of the seven-membered ring through an intramolecular aza-Wittig reaction. This allows cyclization of the diazepine ring to take place under neutral and extremely mild reaction conditions and involves a simple and rapid work-up procedure.

The starting *o*-azidobenzamide derivative **1** was easily prepared in 94% yield from the readily available *o*-azidobenzoyl chloride[11] and *L*-prolinol. Oxidation with pyridinium chlorochromate (PCC) at room temperature provided **2** in 81% yield. Staudinger reaction of compound **2** with tertiary phosphines under mild conditions directly led to the pyrrolo[2,1-*c*][1,4]benzodiazepine **4** in yields ranging from 90 to 93%. When triphenylphosphine was used, the formation of the iminophosphorane **3a** was carried at 0°C and the conversion **3**→**4** was completed in 1 h at room temperature. However, when the more reactive tributylphosphine was used

as cyclisating agent, formation of **3b** was performed at lower temperature (-10°C) and completion of the cyclization reaction required a shorter period of time (30 min).

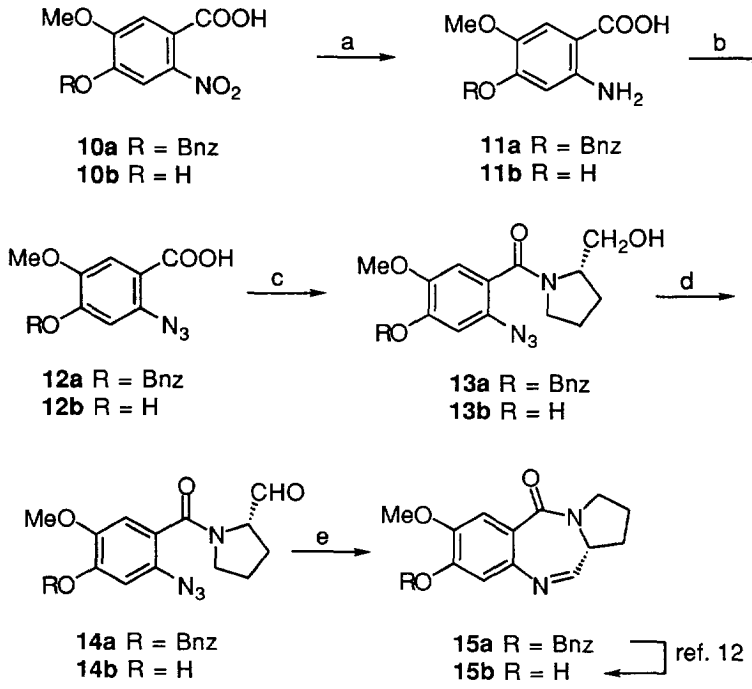


Reagents and conditions: **a**) PCC, CH_2Cl_2, r.t., **b**) TPP, Et_2O, 0°C (for **3a**), or *n*-Bu_3P, Et_2O, -10°C (for **3b**).**c**) Et_2O, r.t. 1 h (for **3a**), or Et_2O, r.t. 30 min (for **3b**), **d**) $SOCl_2$, benzene, r.t., then CH_3OH r.t. **e**) TPP, CH_2Cl_2, r.t.,**f**) DIBAL, Et_2O, -78°C → r.t. **g**) toluene, 140°C sealed tube, 24 h (for **7a**), or toluene, reflux, 3 h (for **7b**), **h**) H_2O,reflux, 30 min.

An alternative route consists of using *L*-proline as precursor of the pyrrolidine ring. Thus, *o*-azidobenzamide **5**, available in 82% yield from *o*-azidobenzoyl chloride and *L*-proline, was converted into the methyl ester derivative **6** in 96% yield. Iminophosphorane **7a** was obtained in 72% yield by reaction with triphenylphosphine at room temperature. Reduction of iminophosphorane **7a** with DIBAL furnished **4** in 57% yield. Both routes afforded the pyrrolo[2,1-*c*][1,4]benzodiazepine **4** in the N10-C11 imine form as a stable yellow oil.

On the other hand, iminophosphoranes **7** were converted, by heating, into the iminoether **8**, in yields ranging from 82 to 85%. This intramolecular aza-Wittig reaction, involving an ester functionality, was carried out in toluene in a sealed tube at 140°C for 24 h (for **7a**) or at reflux temperature for 3 h (for **3b**). The conversion iminoether **8** to dilactam **9** was achieved in 91% yield by heating in water.

We have applied this methodology to the synthesis of the natural product DC-81. The readily available 4-benzyloxy-5-methoxy-2-nitrobenzoic acid[12] **10a** was converted into the *o*-aminobenzoic acid derivative **11a** by the action of the system Fe/HCl (84%), which by diazotization followed by azidation provided the *o*-azidobenzoic acid derivative **12a** (69%). Compound **12a** was converted into the *o*-azidobenzamide **13a** by sequential treatment with thionyl chloride and *L*-prolinol. Oxidation of **13a** with PCC in dichloromethane at room temperature afforded **14a** (73%), which was converted into **15a** by the action of triphenylphosphine at room temperature (92%).which in turn could be converted into DC-81, **15b**, in a straighforward manner[12].



10a R = Bnz
10b R = H

11a R = Bnz
11b R = H

12a R = Bnz
12b R = H

13a R = Bnz
13b R = H

14a R = Bnz
14b R = H

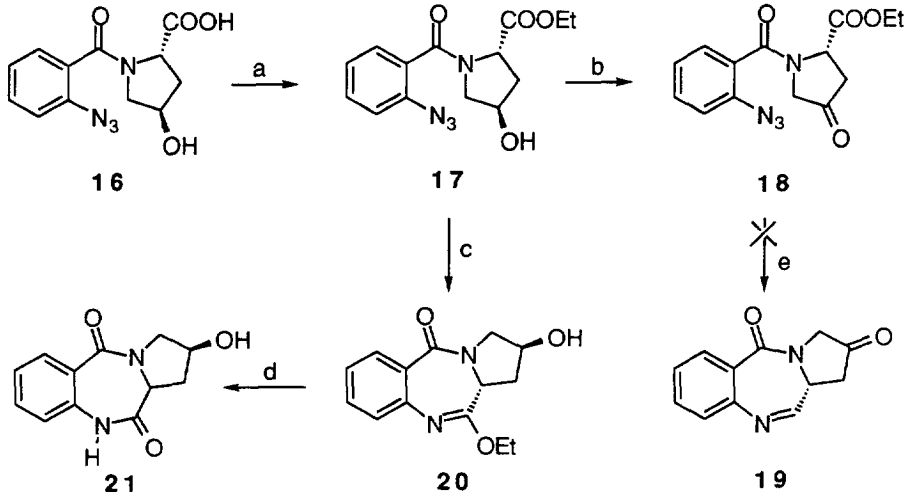
15a R = Bnz
15b R = H

Reagents and conditions: a) Fe, HCl, EtOH/AcOH/H_2O, **b)** $NaNO_2$, H_2SO_4/H_2O, 0°C, then NaN_3, **c)** $SOCl_2$, benzene, reflux, then *L*-prolinol, CH_2Cl_2/H_2O, Na_2CO_3, **d)** PCC, CH_2Cl_2, r.t., **e)** TPP, CH_2Cl_2, r.t.

An alternative approach has been developed in order to overcome the problems associated with the deprotection of the benzyl ether at the final synthetic step[6]. To this end, the 6-nitrovanillinic acid **10b** was reduced by catalytic hydrogenation (H_2/Pd-C) to give the *o*-aminobenzoic acid **11b** in 93% yield, which was converted by diazotization and further azidation into the *o*-azidobenzoic acid **12a** in 84% yield. The one-pot conversion of compound **12a** into the amide **14a** was achieved in an overall yield of 68% by the following sequence: a) treatment with oxalyl chloride and further reaction with *(S)*-prolinol and by oxidation with PCC in dichloromethane at room temperature. Cyclization of **14a** with triphenylphosphine in dichloromethane at room temperature provided, after chromatographic separation, **15a** (DC-81) in 79 % yield. The optical rotation of this

product $[\alpha]_{D23}$= +315 (c = 0.53, $CHCl_3$) was similar to the one reported for synthetic DC-81[12] and higher than the one reported for natural product[13].

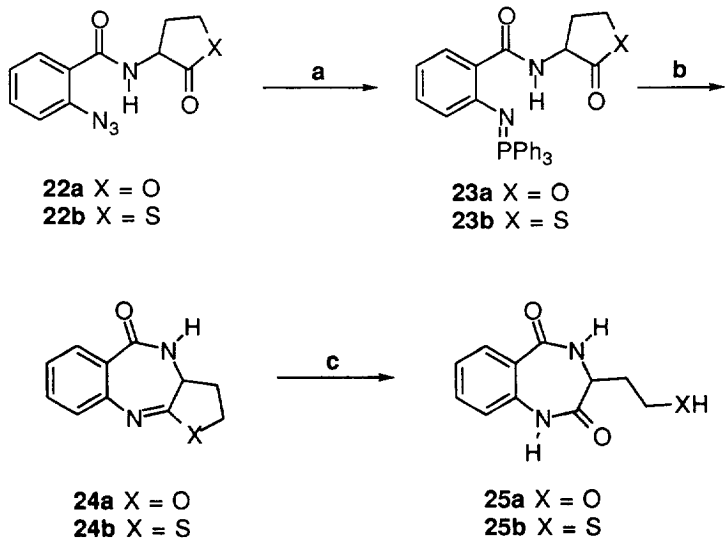
Keeping these results in mind, we turned our attention to the synthesis of prothracarcin, a pyrrolo[1,4]benzodiazepine with antitumor activity isolated from *Streptomyces umbrosis*[14], by using this methodology. Two approaches to the synthesis of this compound have been recently reported[7b,9b]. The *o*-azidobenzamide derivative **16**, prepared in 58% yield from *o*-azidobenzoyl chloride and 4-hydroxy-*L*-proline, was converted into the ethyl ester **17** in 92% yield by using the system DCC/DMAP as condensating agent. Compound **17** was oxidized by PCC in dichloromethane at room temperature to give **18** in 71% yield. Sequential treatment of 18 with triphenylphosphine in dichloromethane, reduction with DIBAL and further heating did not afford the desired pyrrolo[1,4]benzodiazepine **19**, which is a valuable precursor of the prothracarcin[15]. However, treatment of **17**, with tributhylphosphine at room temperature provided the pyrrolo[1,4]benzodiazepine **20**, in near quantitative yield. Conversion of iminoether **20** into the dilactam **21** was achieved in 96% yield, by heating in water.



Reagents and conditions: a) EtOH, DCC, 4-DMAP, r.t., **b)** PCC, CH_2Cl_2, r.t., **c)** PBu_3, 2 h. r.t., or 1 h. reflux, **d)** CH_2Cl_2, silica gel, **e)** i) PPh_3, CH_2Cl_2, ii) DIBAL

Finally, this methodology has also been applied to the preparation of [1,4] benzodiazepines fused to a saturated heterocyclic ring. Thus, reaction of *o*-azidobenzoyl chloride with α-amino-γ-butyrolactone hydrobromide or homocysteine thiolactone hydrochloride in DMF and in the presence of triethylamine, afforded the corresponding amides **22a** and **22b** in 78% and 87% yield, respectively. Staudinger reaction of *o*-azidobenzamides **22** with TPP in dichloromethane at room temperature provided the iminophosphoranes **23a** (72%) and **23b** (98%), respectively. When iminophosphorane **23a** was treated at 160°C in a sealed tube, an intramolecular aza-Wittig reaction took place to give the highly unstable **24a** which underwent easy hydrolitic ring opening. Compound **25a** can also be obtained directly from **22a** by treatment with tri-*n*-butyl phosphine at 0°C and further heating in toluene of the resulting iminophosphorane. Similarly, compound **24b** was obtained in 61% yield from **22b** by treatment with tri-*n*-butylphosphine and further heating. However, iminophospho-

rane **23b** did not undergo intramolecular aza-Wittig reaction even at temperatures higher than 150°C. Compound **24b** underwent hydrolitic ring opening to give **25b**.



Reagents and conditions: a) TPP, CH_2Cl_2, r.t. or *n*-Bu_3P, toluene, 0°C, **b)** toluene, sealed tube 160°C or toluene reflux, **c)** H_2O.

In conclusion, the results reported here show that the intramolecular aza-Wittig reaction affords a new and versatile entry to pyrrolo[2,1-*c*][1,4]benzodiazepines in their imine form, using a simple work-up procedure, and an extension of this methodology using substituted prolines has also been developed.

Experimental.

All melting points were determined on a Kofler hot-plate melting point apparatus and are uncorrected. IR spectra were obtained as Nujol emulsions or films on a Nicolet 5DX spectrophotometer. NMR spectra were recorded on a Bruker AC 200 (200 MHz) or a Varian Unity 300 (300 MHz). Mass spectra were recorded on a Hewlett-Packard 5993C spectrometer. Microanalyses were performed on a Perkin-Elmer 240C instrument.

Preparation of 2-Azido-4-benzyloxy-5-methoxybenzoic acid **12a**

To a suspension of the corresponding amine **11a** (0.98 g, 3.96 mmol) cooled to 0°C in a mixture of water (4.5 ml) and conc. H_2SO_4 (0.8 ml) a solution of $NaNO_2$ (0.359 g, 5.2 mmol) in water (3.2 ml) was added dropwise and the reaction mixture was stirred at 0°C for 30 min. Then, a cooled solution of NaN_3 (0.478 g, 7.3 mmol) in water (3 ml) was added. After stirring at room temperature for 12 h., a precipitated was formed which was separated by filtration and suspended in boiling ethyl acetate. After filtration and solvent removal a solid

was obtained which crystallized from ether/n-hexane (1:1) to give **12a** as yellow needles; m.p. 147-149°C. (Found: C, 60.08; H, 4.25; N, 13.86. $C_{15}H_{13}N_3O_4$ requires: C, 60.20; H, 4.38; N, 14.04). i.r. (Nujol): 2105, 1687, 1575, 1521, 1461, 1376, 1269, 1211, 1185, 736, 697 cm^{-1}; ^1H n.m.r. δ (DMSO d_6): 3.79 (s, 3H), 5.21 (s, 2H), 6.96 (s, 1H), 7.37-7.45 (m, 6H). ^{13}C n.m.r. δ (DMSO d_6): 55.9, 70.2, 106.5, 114.0, 115.2, 127.9, 128.1, 128.5, 133.0, 136.2, 146.0, 151.5, 165.7; m/z (%): 299 (M^+, 1), 273 (9), 271 (4), 149 (8), 136 (8), 108 (5), 91 (100), 77 (3), 69 (13).

Preparation of 2-Azido-4-hydroxy-5-methoxybenzoic acid **12b.**

To a solution of the amine **11b**[16] (0.73 g, 4 mmol) in 6N HCl (16 ml) a solution of $NaNO_2$ (0.29 g, 4.24 mmol) in water (6 ml) was added in one portion. After stirring for 30 min, the reaction mixture was added dropwise to a solution of NaOAc (7.91 g, 96 mmol) and NaN_3 (0.28 g, 4.24 mmol) in water (16 ml) and stirred at room temperature for 2 h. The resulting solid was separated by filtration, washed with water (2x30 ml) and crystallized from ether/n-hexane (1:1) to give **12b** as yellow needles; m.p. 167°C. (Found: C, 45.79; H, 3.43; N, 20.20. $C_8H_7N_3O_4$ requires: C, 45.94; H, 3.37; N, 20.09). i.r. (Nujol): 3500-2400, 2106, 1662, 1597, 1526, 1467, 1374, 1281, 1186, 831, 781 cm^{-1}; ^1H n.m.r. δ (DMSO d_6): 3.80 (s, 3H), 6.72 (s, 1H), 7.37 (s, 1H), 10.43 (br. s, 1H0, 12.66 (br. s, 1H). ^{13}C n.m.r. δ (DMSO d_6): 56.0, 107.9, 113.6, 114.8, 133.5, 145.0, 151.5, 165.9; m/z (%): 209 (M^+, 14), 181 (33), 137 (47), 125 (23), 122 (100), 110 (11), 94 (23), 82 (13), 77 (12), 68 (51), 53 (68)..

General Procedure for the Preparation of (2S)-N-(2-azidoaroyl)-2-hydroxymethyl pyrrolidines **1** *and* **13a-b.**

To a solution of *S*-prolinol (1.52 g,15 mmol) in dichloromethane (30 ml) an aqueous solution (30 ml) of potassium carbonate (3.18 g, 30 mmol) was added in one portion. After stirring for 5 min. a solution of the corresponding *o*-azido aroyl chloride (15 mmol) in dry dichloromethane (20 ml) was added, and the resultant mixture was stirred at room temperature under nitrogen for 4h. The organic layer was separated, washed with water (2x30 ml) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residual product was chromatographed on a silica gel column with diethyl ether/ethyl acetate (1:1).

1: (94%), m.p. 98-100°C (white needles, from diethyl ether/*n*-hexane) (Found: C, 58.48; H, 5.61; N, 22.69. $C_{12}H_{14}N_4O_2$ requires: C, 58.53; H, 5.73; N, 22.75). i.r. (Nujol): 3313, 2131, 1605, 1496, 1456, 1433, 1374, 1300, 1168, 1087, 1034, 771, 755 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.64-1.92 (m, 3H, 4-H_2 and 3-H), 2.15-2.24 (m, 1H, 3-H), 3.20-3.36 (m, 2H, 5-H_2), 3.70-3.89 (m, 2H, CH_2O), 4.31-4.40 (m, 1H, 2-H), 4.75 (br. s, 1H, OH), 7.17-7.23 (m, 2H), 7.31 (dd, 1H, J=8.1, J=1.5 Hz), 7.44 (dt, 1H, J=7.6, J=1.5 Hz). ^{13}C n.m.r. δ ($CDCl_3$): 24.5 (4-C), 28.6 (3-C) 49.6 (5-C), 61.3 (2-C), 66.5 (CH_2OH), 118.5, 125.3, 127.8, 129.3, 130.7, 136.0, 169.0 (C=O); m/z (%): 246 (M^+, 3), 228 (16), 218 (2), 215 (10). 187 (100), 160 (3), 146 (38), 132 (5), 120 (17), 104 (4), 92 (16), 90 (77), 70 (5), 63 (21).

13a: yellow oil; (98%) (Found: C, 62.90; H, 5.66; N, 14.42. $C_{20}H_{22}N_4O_4$ requires: C, 62.82; H, 5.80; N, 14.65). i.r. (film): 3393, 2115, 1632, 1614, 1517, 1468, 1455, 1434, 1391, 1247, 1215, 1181, 1080, 737, 700 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.65-1.88 (m, 3H, 4-H_2 and 3-H), 2.13-2.18 (m, 1H, 3-H), 3.25-3.36 (m, 2H, 5-H_2), 3.69-3.85 (m, 2H, CH_2O), 3.84 (s, 3H, OCH_3), 4.29-4.37 (s, 1H, 2-H), 4.74 (br. s, 1H, OH), 5.17 (s, 2H, OCH_2), 6.67 (s, 1H. 3´-H), 6.83 (s, 1H, 6´-H), 7.29-7.46 (m, 5H). ^{13}C n.m.r. δ ($CDCl_3$): 24.3 (4-C), 28.4 (3-C) 49.5 (5-C), 56.2 (OCH_3), 61.0 (2-C), 66.3 (CH_2OH), 71.2 (OCH_2Ph), 104.4, 110.8, 121.4, 127.3, 128.1, 128.2, 128.6, 135.9, 147.2, 149.7, 168.6 (C=O); m/z (%): 382 (M^+, 1), 355 (5), 323 (10), 256 (5), 231 (20), 136 (8), 91 (100).

13b: yellow oil; (90%) (Found: C, 53.22; H, 5.48; N, 19.30. $C_{13}H_{16}N_4O_4$ requires: C, 53.42; H, 5.52; N, 19.17). i.r. (film): 3393, 3260, 2113, 1662, 1613, 1519, 1469, 1435, 1258, 1214, 1171, 1078, 735 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.65-2.08 (m, 3H, 4-H_2 and 3-H), 2.11-2.21 (m, 1H, 3-H), 3.26-3.44 (m, 2H, 5-H_2), 3.72-3.88 (m, 2H, CH_2OH), 3.84 (s, 3H, OCH_3), 4.30-4.40 (m, 1H, 2-H), 6.10 (br. s, 2H), 6.72 (s, 1H), 6.79 (s, 1H). ^{13}C n.m.r. δ ($CDCl_3$): 24.4 (4-C), 28.5 (3-C), 49.6 (5-C), 56.3 (OCH_3), 61.0 (2-C), 66.2 (CH_2OH), 105.24, 110.3, 120.0, 129.1, 144.8, 148.3, 169.1 (C=O); m/z (%): 292 (M^+, 2), 264 (3), 236 (2), 233 (17), 220 (11), 219 (100), 218 (60), 193 (35), 180 (9), 166 (7), 150 (6), 122 (3), 84 (4).

General Procedure for the Preparation of (2S)-N-(2-azidoaroyl)-pyrrolidine-2-carboxaldehyde **2** *and* **14a-b.**

To a solution of the corresponding (2S)-N-(2-azidoaroyl)-2-hydroxymethyl pirrolidines **1, 13a** or **13b** (15 mmol) in dry dichloromethane (120 ml), pyridinium chlorochromate (5.27 g, 25 mmol) was added. The reaction mixture was stirred at room temperature for 4 h and then diethyl ether (60 ml) was added and the mixture filtered off through celite. The resultant filtrate was extracted with hot ether (3x20 ml) and the solvent removed under reduced pressure to give a residue which was chromatographed on a silica gel solumn using ether/ethyl acetate (1:1) as eluent, for **2** and **14b**, and dichloromethane/ ethyl acetate (10:1), for **14a**.

2: as a mixture of *syn* and *anti* rotamers (5:1); yellow oil (81%); (Found: C, 58.89; H, 4.86; N, 22.81. $C_{12}H_{12}N_4O_2$ requires: C, 59.01; H, 4.95; N, 22.94). i.r. (film): 2137, 1732, 1640, 1560, 1579, 1490, 1451, 1420, 1293, 757, 681 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$) 1.80-2.27 (m, 4H, 3-H_2 and 4-H_2), 3.18-3.46 (m, 1.66H, 5-H), 3.65-3.80 (m, 0.33H, 5-H), 4.10-4.21 (m, 0.16H, 2-H), 4.53-4.67 (m, 0.83H, 2-H), 7.11-7.30 (m, 2H), 7.32-7.50 (m, 2H), 9.25 (d, 0.16H, J=2.0 Hz, CHO), 9.68 (d, 0.83H, J=2.1 Hz, CHO).^{13}C n.m.r. δ ($CDCl_3$): 22.7 and 24.7 (4-C), 26.3 and 27.7 (3-C), 46.5 and 48.4 (5-C), 64.6 and 66.2 (2-C), 118.4, 125.0 and 125.1, 127.9 and 128.3, 128.4, 130.7 and 130.8, 136.1, 167.4 (C=O), 197.8 and199.2 (CHO); m/z (%): 244 (M^+, 1), 216 (7), 187 (100), 160 (8), 146 (55), 132 (19), 118 (8), 104 (5), 90 (98), 77 (8), 70 (8), 63 (30).

14a: as a mixture of *syn* and *anti* rotamers (4:1); yellow oil (73%); (Found: C, 63.30; H, 5.28; N, 14.66. $C_{20}H_{20}N_4O_4$ requires: C, 63.15; H, 5.30; N, 14.73). i.r. (film): 2114, 1733, 1628, 1607, 1514, 1455, 1431, 1386, 1249, 1202, 1080, 913, 734 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$) 1.84-2.30 (m, 4H, 3-H_2 and 4-H_2), 3.31-3.51 (m, 1.6H, 5-H_2), 3.70-3.95 (m, 0.4H, 5-H_2), 3.83 (s, 2.4H, OCH_3), 3.87 (s, 0.6H, OCH_3), 4.18-4.26 (m, 0.2H, 2-H), 4.60 (m, 0.8H, 2-H) 5.14 (s, 0.4H. OCH_2Ph), 5.19 (s, 1.6H, OCH_2Ph), 6.61 (s, 0.2H, 6′-H), 6.69 (s, 0.8H, 6′-H), 6.79 (s, 0.2H, 3′-H), 6.87 (s, 0.8H, 3′-H), 7.28-7.48 (m, 5H), 9.28 (d, 0.2H, J=1.8 Hz, CHO), 9.68 (d, 0.8H, J= 1.8 Hz, CHO).^{13}C n.m.r. δ ($CDCl_3$): 22.8 and 24.8 (4-C), 26.3 and 27.8 (3-C), 46.7 and 48.8 (5-C), 56.2 and 56.3 (OCH_3), 64.7 and 66.4 (2-C), 71.25 (OCH_2Ph), 104.2 and 104.4, , 111.1 and 111.4, 120.6 and 120.7, 127.4, 128.2, 128.6, 128.7, 135.8 and 135.9, 147.2, 147.3, 149.9, 150.0, 167.1 and 167.3 (CON), 197.9 and 199.3 (CHO); m/z (%): 380 (M^+, 1), 352 (4), 323 (26), 255 (7), 232 (11), 231 (43), 136 (2), 91 (100).

14b:as a mixture of *syn* and *anti* rotamers (5:1); yellow oil (73%); (Found: C, 53.61; H, 4.90; N, 19.16. $C_{13}H_{14}N_4O_4$ requires: C, 53.79; H, 4.86; N, 19.30). i.r. (film): 3250, 2114, 1732, 1630, 1519, 1435, 1251, 1079, 742 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$) 1.82-2.30 (m, 4H, 3-H_2 and 4-H_2), 3.21-3.50 (m, 1.66H, 5-H_2), 3.68-3.90 (m, 0.33H, 5-H_2), 3.83 (s, 2.5H. OCH_3), 3.87 (s, 0.5H, OCH_3), 4.11-4.25 (m, 0.33H, 2-H), 4.52-4.68 (m, 1.66H, 2-H), 6.72 (s, 0.16H), 6.75 (s, 0.83H), 6.78 (s, 0.16H), 6.81 (s, 0.83H), 9.25 (d, 0.16H, J=2.0 Hz, CHO), 9.67 (d, 0.83H, J=2.0 Hz, CHO); m/z (%): 290 (M^+, 2), 262 (8), 233 (27), 219 (100), 218 (55), 193 (21).

General Procedures for the preparation of (11a S)-1,2,3,11a-tetrahydro-5H-pyrrolo [2,1-c][1,4]arenodiazepin-5-ones **4** *and* **15a-b.**

To a solution of **2, 14a** or **14b** (5 mmol) in dry diethyl ether (10 ml) cooled to 0°C an equimolecular amount of the appropriate phosphine in the same solvent (15 ml) was added dropwise. The mixture was stirred at room temperature under argon for 30 min, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column using chloroform/methanol (95:5) as eluent to give **4** (0.93 g, 93% yield),**15a** (1.55g, 92% yield), or **15b** (0.97g, 79% yield). The i.r. spectrum, mass spectrum and the whole pattern of ^{1}H and ^{13}C n.m.r. signals were identical to the previously reported[6,7,12] Compound **15b** ^{13}C n.m.r (75 MHz, $CDCl_3$) δ 24.2, 29.7, 46.7, 53.7, 56.2, 70.8, 111.3, 111.7, 120.6, 127.4, 128.2, 128.7, 136.2, 140.5, 148.0, 150.5, 162.5, 164.7.

(2S)-N-(2-Azidobenzoyl)pyrrolidine-2-carboxylic acid **5.**

To a solution of L-proline (1.5 g, 10 mmol) and triethyl amine (2.22 g, 22 mmol) in water (15 ml) cooled to 0°C a solution of *o*-azidoaroyl chloride (1.81 g, 10 mmol) in dry THF (10 ml) was added dropwise for a period of 20 min. The reaction mixture was then stirred at room temperature for 2h and then the organic solvent removed under vacuum. The resultant aqueous solution was acidified until pH=1 by addition of concentrated HCl and the solid formed was separated by filtration and crystallized from benzene to give **5** in 82% yield, as a mixture of *syn* and *anti* rotamers (9:2), with m.p. 160-162°C (white needles) (Found: C, 55.43; H, 4.57; N, 21.40. $C_{12}H_{12}N_4O_3$ requires: C, 55.38; H, 4.65; N, 21.53). i.r. (Nujol): 3398-2588, 2129, 1744, 1693, 1597, 1574, 1461, 1432, 1291, 1229, 886, 775, 758 cm^{-1}; ^{1}H n.m.r. δ ($CDCl_3$) 1.83-2.38 (m, 4H, 3-H_2 and 4-H_2), 3.26-3.41 (m, 1.64H, 5-H_2), 3.70-3.81 (m, 0.36H, 5-H_2), 4.19 (dd, 0.18H, J=7.5Hz, J=2.7Hz, 2-H), 4.74 (dd, 0.82H, J=8.1Hz, J=4.5Hz, 2-H), 7.09-7.27 (m, 2H), 7.35 (dd, 1H, J=7.6Hz, J=1.4 Hz), 7.45 (dt, 1H, J=7.7Hz, J=1.5 Hz), 9.42 (br. s, 1H).^{13}C n.m.r. δ ($CDCl_3$): 22.7 and 24.6 (4-C), 28.6 and 31.1 (3-C), 46.2 and 48.8 (5-C), 59.3 and 60.4 (2-C), 118.5 and 118.6, 125.1 and 125.2, 128.2 and 128.6, 130.6, 130.7 and 131.0, 136.5, 158.7 (CON, 173.5 (COOH); m/z (%): 260 (M^+, 4), 232 (19), 216 (11), 188 (19), 187 (100), 171 (3), 160 (13), 146 (13), 119 (18), 104 (4), 92 (16), 90 (35), 70 (10), 63 (18).

Methyl (2S)-N-(2-Azidobenzoyl)pyrrolidine-2-carboxylate **6.**

To a suspension of **5** (1.5 g, 5.77 mmol) in benzene (40 ml) $SOCl_2$ (4 ml) was added and then it was stirred at room temperature for 4 h. After cooling in an ice bath anhydrous methanol (20 ml) was added and the mixture stirred at room temperature for an additional 2h. The solvent was removed under reduced pressure, and the residue was disolved into dichloromethane (40 ml), and then sequentially washed with $NaHCO_3$ (3x15 ml) and water (2x15 ml) and dried over $MgSO_4$. Finally the organic solvent was removed and the resultant residue chromatographed on a silica gel column with diethyl ether as eluent to give **6**, as a mixture of *syn* and *anti* rotamers (3:1), which was crystallized from diethyl ether/petroleum ether (40°-60°) (1:1) in 96% yield as white needles, m.p. 70-72°C (Found: C, 56.78; H, 5.09; N, 20.21. $C_{13}H_{14}N_4O_3$ requires: C, 56.93; H, 5.14; N, 20.43). i.r. (Nujol): 2141, 1755, 1631, 1455, 1427, 1302, 1200, 1166, 781, 764, 679. cm^{-1}; ^{1}H n.m.r. δ ($CDCl_3$) 1.84-2.39 (m, 4H, 3-H_2 and 4-H_2), 3.30-3.50 (m, 1.5H, 5-H), 3.52 (s, 0.75H, COOMe), 3.78 (s, 2.25H, COOMe), 3.72-3.90 (m, 0.5H, 5-H), 4.20 (dd, 0.25H, J=8.6 Hz, J=3.0 Hz, 2-H), 4.68 (dd, 0.75H, J=8.4 Hz, J=4.2 Hz, 2-H), 7.11-7.25 (m, 2H), 7.33-7.47 (m, 2H).^{13}C n.m.r. δ ($CDCl_3$): 24.6 and 22.9 (4-C), 29.5 and 31.2 (3-C), 46.3 and 48.4 (5-C), 52.1 and 52.3 (OCH_3), 58.5 and 60.3 (2-C), 118,4 and 118.5, 124.9 and 125.0, 128.2 and 128.4, 128.9, 130.5 and 130.6, 136.3, 167.0 (CON), 172.4 (COOMe); m/z (%):

274 (M^+, 2), 246 (16), 187 (69), 160 (6), 146 (29), 132 (9), 119 (21), 104 (7), 92 (2), 90 (100), 77 (15), 63 (44), 59 (23).

Methyl N-[2-(Triphenylfosforanylidene)aminobenzoyl]pyrrolidine-2-carboxylate **7a.**

To a solution of triphenyl phosphine (10 mmol) in dry dichloromethane (20 ml) cooled to 0°C a solution of an equimolecular amount of the methyl ester **6** (2.74 g, 10 mmol) in the same solvent (20 ml) was added. The solution was allowed to warm to room temperature and stirred, under nitrogen, for 8 h. The solvent was removed under reduced pressure and the residue was purified by crystallization in benzene/hexane (4:1) to give a mixture of *syn* and *anti* rotamers of **7a**, as yellow needles; m.p.149-151 °C (Found: C, 73.39; H, 5.62; N, 5.44. $C_{31}H_{29}N_2PO_3$ requires: C, 73.22; H, 5.75; N, 5.51). i.r. (Nujol): 1744, 1642, 1591, 1477, 1455, 1415, 1353, 1206, 1110, 996, 753, 719, 696 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$) 1.60-2.31 (m, 4H), 3.42, (s 1H, 3.78 and 3.89 (two s, in total 2H), 3.48-4.02 (m, 2H), 4.70-4.82 (m, 1H), 6.36-6.43 (m, 1H), 6.56-6.70 (m, 1H), 6.80-6.91 (m, 1H), 7.10-7.28 (m, 1H), 7.36-7.60 (m, 9H), 7.60-7.82 (m, 6H); m/z (%): 508 (M^+, 6), 380 (24), 352 (17), 277 (100), 230 (12), 201 (15), 199 (12), 183 (17), 146 (26), 90 (10), 77 (27), 51 (15).

(11a S)-1,2,3,11a-Tetrahydro-11-methoxy-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one **8.**

To a solution of **6** (1,37 g, 5 mmol) in dry toluene (15 ml) cooled to 0°C a solution of 85% *n*-Bu_3P (1.19 g, 5 mmol) in the same solvent (30 ml) was added dropwise. The reaction mixture was stirred at room temperature under argon for 3 h and then heated at reflux for 3 h. After cooling, the solvent was removed under reduced pressure and the residue was recrystallized from dry hexane to give **8** (82%, colourless needles, m.p. 119-121°C.(Found: C, 67.69; H, 6.09; N, 12.33. $C_{13}H_{14}N_2O_2$ requires: C, 67.81; H, 6.13; N, 12.17) i.r. (Nujol): 1661, 1632, 1600, 1463, 1413, 1328, 1235, 1184, 1007, 766 cm^{-1}; ^1H n.m.r. (300 MHz, $CDCl_3$) δ 1.94-2.12 (m, 3H, 2-H_2 and 1-H_1), 2.56-2.67 (m, 1H, 1-H_1), 3.45-3.56 (m, 1H, 3-H_1), 3.80-3.88 (m, 1H, 3-H_1), 3.89 (s, 3H, OCH_3), 3.98 (d, 1H, J=6.3 Hz, 11a-H), 7.12-7.23 (m, 2H), 7.44 (dt, 1H, J=7.2, 1.8 Hz, 8-H), 7.98 (dd, 1H, J=7.6, 1.8 Hz, 6-H); ^{13}C n.m.r (75 MHz, $CDCl_3$) δ 24.0, 26.6, 46.8, 54.5, 54.6, 124.1, 126.4, 127.4, 130.2, 131.6, 144.1, 162.4, 165.8; m/z (%) 230 (M^+, 15), 161 (12), 146 (100), 120 (45), 92 (16), 90 (62), 68 (10).

(11a S)-2,3,5,10,11,11a-Hexahydro-1H-pyrrolo[2,1-c][1,4]benzodiazepin-5,11-dione **9.**

A solution of **8** (2.3 g, 10 mmol) in water (50 ml) was heated under reflux for 30 min and on cooling the corresponding white needles formed were separated by filtration to give **9** in 91% yield. The m.p., i.r. spectrum, mass spectrum and the whole pattern of ^1H and ^{13}C n.m.r. signals were identical to the previously reported[9].

(2S, 4R)-N-(2-Azidobenzoyl)-4-hydroxypyrrolidine-2-carboxylic acid **16.**

A solution of *L*-hydroxyproline (1,3 g, 9.4 mmol) and triethylamine (2.2 g, 2.2 mmol) in water (20 ml) was allowed to warm at 40°C and then a solution of *o*-azidobenzoyl chloride (1.81 g, 10 mmol) in THF (20 ml) was added dropwise under nitrogen. The reaction mixture was stirred at 50°C for 24 h, the organic solvent removed at reduced pressure and the resulting solution acidified to pH=1 with concentrated HCl. The resulting solid was separated by filtration and crystallized from benzene to give a mixture of *syn* and *anti* rotamers (3:1) **16** in 58% yield, as white needles, m.p. 136-138°C.(Found: C,52.30 ; H, 4.26; N, 20.24. $C_{12}H_{12}N_4O_4$ requires: C, 52.17; H, 4.38; N, 20.28) i.r. (Nujol): 3335, 2400-3100, 2133, 1741, 1692, 1621, 1495, 1452, 1300, 1196, 1153, 1077, 1004, 751 cm^{-1}; ^1H n.m.r. (300 MHz, DMSO d_6) δ 1.94-2.29 (m, 2H), 3.05 (d,

0.75H, J=10.8 Hz), 3.40-3.58 (m, 1.25H), 4.22-4.31 (m, 1H), 4.35-4.50 (m, 1H), 5.11 (br. s, 0.75 H), 5.21 (br. s, 0.25H), 7.17-7.60 (m, 4H), 12.81 (br. s, 1H); ^{13}C n.m.r (75 MHz, DMSO d_6) δ 37.7 and 39.4(3-C), 54.2 and 56.5 (5-C), 57.5 and 58.9 (2-C), 67.4 and 68.7 (4-C), 119.6, 125.0 and 125.3, 128.2 and 128.5, 128.9, 130.8 and 131.0, 135.9, 166.2 and 166.5, 173.2 and 173.4; m/z (%) 276 (M^+, 1), 248 (23), 203 (37), 185 (39), 160 (26), 147 (39), 146 (36), 132 (26), 120 (61), 119 (93), 118 (19), 104 (14), 90 (100), 86 (17), 77 (19).

Ethyl (2S, 4R)-N-(2-Azidobenzoyl)-4-hydroxypyrrolidine-2-carboxylate **17.**

To a solution of **16** (0.8 g, 3 mmol) in dry CH_2Cl_2 (15 ml) and dry ethanol (15 ml), DCC (0.6 g, 3 mmol) and 4-DMAP (51 mg, 0.45 mmol) were added and the solution was then stirred at room temperature under nitrogen for 24 h. The solvent was removed and CH_2Cl_2 (15 ml) was added to give a white solid which was separated by filtration. The resulting filtrate was then concentrated to dryness under reduced pressure and chromatographed on a silica gel column with diethyl ether/ethyl acetate (1:1) as eluent, to give a yellow oil, identified as a mixture of *syn* and *anti* rotamers of **17**, in 92% yield; (Found: C, 55.09; H, 5.26; N, 18.33 $C_{14}H_{16}N_4O_4$ requires: C, 55.26; H, 5.30; N, 18.41) i.r. (Nujol): 3398, 2130, 1741, 1621, 1491, 1455, 1432, 1297, 1195, 1087, 914, 734 cm^{-1}; ^1H n.m.r. (200 MHz, $CDCl_3$) δ 1.03 (t, 0.6H, J=7.1 Hz), 1.30 (t, 2.4H, J=7.1 H), 2.05-2.41 (m, 2H), 3.21 (d, 0.8H, J=10.3 Hz), 3.53-3.91 (m, 1.2 H), 4.11 (q, 0.4H, J=7.1 Hz), 4.22 (q, 1.6H, J=7.1 Hz), 7.10-7.25 (m, 2H), 7.30-7.35 (m, 1H), 7.39-7.47 (m, 1H); ^{13}C n.m.r (50 MHz, $CDCl_3$) δ 14.0 and 14.1 (CH_3), 37.9 and 39.5 (3-C), 54.7 and 56.3 (5-C), 57.6 and 59.1 (2-C), 59.2 and 61.2 (OCH_2), 68.5 and 69.7 (4-C), 119.6, 124.8 and 125.0, 128.4, 128.5, 130.8, 136.5, 167.4 and 167.8 (CON), 171.2 and 172.0 (COOEt); m/z (%) 304 (M^+, 1), 276 (25), 224 (10), 203 (97), 185 (73), 160 (7), 146 (34), 132 (5), 120 (20), 90 (39), 86 (68), 84 (100).

Ethyl (2S)-N-(2-Azidobenzoyl)-4-oxopyrrolidine-2-carboxylate **18.**

To a solution of **17** (0.6 g, 2 mmol) in dry CH_2Cl_2 (15 ml), was added PCC (0.7 g, 3.4 mmol). The reaction mixture was stirred at room temperature for 24 h and then diethyl ether (15 ml) was added. The resultant suspension was filtered through cellite and the filtrate was extracted with hot ether (3x20 ml), the solvent removed under reduced pressure and the residue chromatographed on a silica gel column using ether/ethyl acetate (1:1) as eluent to give a yellow oil identified as a mixture of *syn* and *anti* rotamers (2:1) of **18**, in 71% yield; (Found: C, 55..55; H, 4.42; N, 18.60 $C_{14}H_{14}N_4O_4$ requires: C, 55.69; H, 4.67; N, 18.53) i.r. (Nujol): 2131, 1767, 1741, 1650, 1450, 1374, 1300, 1189, 1147, 1033, 916, 755, 733 cm^{-1}; ^1H n.m.r. (300 MHz, $CDCl_3$) δ 1.17 (t, 1H, J=7.1 Hz, CH_3), 1.33 (t, 1H, J=7.1 Hz, CH_3), 2.64 (dd, 1H, J=20.0, J=2.1 Hz, 3-H), 2.97 (dd, 1H, J=20.0 Hz, J=10.5 Hz, 3-H), 3.64-4.12 (m, 2H) (5-H), 4.15-4.39 (m, 2H), 4.58 (d, 0.66 H, J=10.5 Hz, 2-H), 5.23 (dd, 0.33H, J=10.5 Hz, J=2.4 Hz), 2-H), 7.16-7.38 (m, 3H), 7.49 (t, 1H, J=7.8 Hz); ^{13}C n.m.r (75 MHz, $CDCl_3$) δ 13.9 and 14.0 (CH_3), 40.2 and 41.5 (3-C), 51.9 and 53.8 (5-C), 55.2 and 57.6 (2-C), 61.8 and 61.9 (OCH_2), 118.4 and 118.5, 125.1 and 125.2, 127.5, 128.2 and 128.6, 131.2, 136.2, 167.5 and 167.7 (CON), 170.4 and 170.6 (COOEt), 206.7 and 206.8 (4-C); m/z (%) 302 (M^+, 2), 274 (30), 201 (85), 173 (36), 147 (13), 146 (93), 120 (13), 119 (32), 118 (27), 90 (100), 86 (28), 84 (44).

(11aS, 2R)-11-Ethoxy-1,2,3,11a-tetrahydro-2-hydroxy-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one **20.**

To a solution of 85% *n*-PBu_3 (0.24 g, 1 mmol) in dry toluene (5 ml), a solution of **17** (0.3 g, 1 mmol), in the same solvent (5 ml) was added and the reaction mixture was stirred at 0°C, under nitrogen, for 2 h. The

solvent was removed under vacuum and a mixture of diethyl ether /hexane (1:1) was added from which compound **20** was separated as a yellow oil in 95% yield; (Found: C, 64.46; H, 6.16; N, 10.81 $C_{14}H_{16}N_2O_3$ requires: C, 64.60; H, 6.20; N, 10.76) i.r. (Nujol): 3355, 1648, 1602, 1455, 1412, 1372, 1314, 1257, 1222, 1148, 1097, 1035, 769 cm^{-1}; ^1H n.m.r. (300 MHz, $CDCl_3$) δ 1.27 (t, 3H, J=7.7 Hz), 2.01-2.18 (m, 1H0, 2.68-2.79 (m, 1H), 2.65-3.74 (m, 2H), 4.11 (t, 1H, J=7.3 Hz), 4.20-4.41 (m, 3H), 4.52 (t, 1H, J=4.3 Hz), 4.56 (br. s, 1H), 7.06-7.17 (m, 2H), 7.41 (t, 1H, J=7.5 Hz), 7.86 (t, 1H, J=7.8 Hz); ^{13}C n.m.r (75 MHz, $CDCl_3$) δ 13.9, 34.5 (1-C), 53.6 (11a-C), 54.3 (3-C), 63.3, 68.3 (2-C), 123.9, 126.3, 126.4, 130.1, 131.5, 144.3 (9a-C), 161.3 (11-C), 166.6 (5-C).

(11aS, 2R)-2,3,5,10,11,11a-Hexahydro-2-hydroxy-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dion **21**

To a solution of **20** (0.26g, 1 mmol) in CH_2Cl_2 silica gel (0.4 g) was added, and the resultant suspension was stirred at room temperature for 12 h. Then, the silica gel was separated by filtration, washed with ethanol (2x10 ml) and evaporated to dryness under vacuum. The residue was then crystallized from water to give **21** in 96% yield (m.p. 198-200°C). The m.p., i.r. spectrum, mass spectrum and the whole pattern of ^1H and ^{13}C n.m.r. signals were identical to the previously reported[15].

General Procedure for the Preparation of α-(o-Azido)benzoylamino-γ-butyrolactone **22a** *or thiolactone* **22b.**

To a solution of the corresponding α-amino-γ-butyrolactone hydrobromide or homocysteine thiolactone hydrochloride (10 mmol) and triethylamine (20 mmol) in dry DMF (30 ml), an equimolecular amount of *o*-azidobenzoyl chloride was added dropwise. The reaction mixture was stirred at room temperature for 4 h. and then poured into ice/water. The resulting precipitate was filtered and crystallized from ethanol.

22a: 73%; m.p. 145-147°C (colourless prisms) (Found: C, 53.75; H, 3.78; N, 22.56. $C_{11}H_{10}N_4O_3$ requires: C, 53.66; H, 4.09; N, 22.75); i.r. (Nujol) 3298, 2135, 1771, 1649, 1534, 1485, 1455, 1287, 1220, 1170, 1017, 954, 758 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 2.25-2.40 (m, 1H), 2.85-2.95 (m, 1H), 4.30-4.39 (m, 1H), 4.54 (t, 1H, J = 9.1 Hz), 4.70-4.79 (m, 1H), 7.19-7.28 (m, 2H), 7.53 (dt, 1 H, J=8.5 Hz, J=1.5 Hz), 8.16 (dd, 1H, J = 7.8 Hz, J=1.5 Hz), 8.24 (d, 1H, J= 4.0 Hz).^{13}C n.m.r. δ ($CDCl_3$): 30.2, 49.8, 66.2, 118.5, 123.4, 125.2, 132.4, 133.1, 137.5, 164.9, 173.3; m/z (%): 246 (M^+, 2), 218 (100), 160 (23), 120 (12), 105 (12), 92 (10), 90 (23), 77 (13), 63 (20).

22b: 88%; m.p. 162-164°C (white needles) (Found: C, 50.29; H, 3.71; N, 21.23. $C_{11}H_{10}N_4O_2S$ requires: C, 50.37; H, 3.84; N, 21.36); i.r. (Nujol) 3264, 2125, 1711, 1644, 1517, 1465, 1446, 1296, 1023, 915, 756 cm^{-1}; ^1H n.m.r. δ (DMSO d_6): 2.19-2.39 (m, 1H), 2.44-2.54 (m, 1H), 3.28-3.50 (m, 2H), 4.74-4.88 (m, 1H) 7.26 (t, 1H, J=7.5 Hz), 7.36 9d, 1H, J=8.2 Hz), 7.51-7.60 (m, 2H), 8.64 (d, 1H, J=8.2 Hz).^{13}C n.m.r. δ (DMSO d_6): 26.8, 29.9, 58.7, 119.8, 124.9, 127.4, 129.8, 131.8, 136.7, 165.5, 205.0; m/z (%): 262 (M^+, 4), 234 (9), 173 (21), 146 (32), 134 (22), 120 (24), 118 (11), 105 (10), 92 (29), 90 (100), 77 (18), 73 (48).

General Procedure for the Preparation of α-[(o-Triphenylphosphoranylideneamino)benzoyolamino]-γ-butyrolactone **23a** *or thiolactone* **23b.**

To a cooled at 0°C solution of triphenylphosphine (10 mmol) in dichloromethane (15 ml) a solution of an equimolecular amount of the corresponding azido derivative **22** in the same solvent (15 ml) was added. After stirring at room temperature for 12 h and solvent removal, a yellow solid was obtained which was crystallized from benzene/hexane (4:1) to give **23.**

23a: 78%; m.p. 214-215°C (yellow prisms) (Found: C, 72.38; H, 5.30; N, 5.67. $C_{29}H_{25}N_2O_3P$ requires: C, 72.49; H, 5.24; N, 5.83); i.r. (Nujol) 1778, 1646, 1538, 1470, 1439, 1389, 1269, 1154, 1110, 979, 731, 696

cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.79-2.01 (m, 1H), 2.53-2.69 (m, 1H), 4.13-4.35 (m, 2H), 4.82-4.96 (m, 1H), 6.45 (d, 1H, J=8.1 Hz), 6.72 (t, 1H, J = 7.2 Hz), 6.92 (dt, 1H, J=7.8 Hz, J=1.8 Hz), 7.42-7.61 (m, 9H), 7.64-7.75 (m, 6H), 8.23 (td, 1H, J=7.8 Hz, J=2.2 Hz), 12.04 (d, 1H, J=7.6 Hz).^{13}C n.m.r. δ ($CDCl_3$): 30.3, 48.4, 65.5, 117.7, 122.6 (d, J^{P-C}=12 Hz), 123.9 (d, J^{P-C}=20.4 Hz;), 128.3, 129.1 (d, J^{P-C}=12.1 Hz), 129.1 (d, J^{P-C}=100 Hz), 131.3, 131.4 (d, J^{P-C}=2.4 Hz), 132.5 (d, J^{P-C}=9.8 Hz), 150.26 (d, J^{P-C}=3 Hz), 168.7 (d, J^{P-C}=1.4 Hz), 175.7; m/z (%): 480 (M^+, 37), 408 (16), 380 (56), 352 (61), 277 (57), 262 (21), 201 (69), 198 (20), 191 (15), 185 (16), 183 (100), 173 (10), 152 (22), 146 (40), 108 (25), 90 (20), 77 (29), 51 (22).

23b: 93%; m.p. 208-210°C (yellow prisms) (Found: C, 70.30; H, 4.97; N, 5.70. $C_{29}H_{25}N_2O_2SP$ requires: C, 70.15; H, 5.07; N, 5.64); i.r. (Nujol) 3418, 1702, 1643, 1469, 1438, 1330, 1269, 1110, 1013, 756, 721, 695 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.57-1.80 (m, 1H), 2.57-2.70 (m, 1H), 3.03-3.12 (m, 1H), 3.21-3.36 (m, 1H), 4.95-5.10 (m, 1H), 6.45 (d, 1H, J=8.0 Hz), 6.71 (dt, 1H, J=7.4 Hz, J=1.0 Hz), 6.90 (dt, 1H, J=7.5 Hz, J=1.9 Hz), 7.44-7.60 (m, 9H), 7.63-7.74 (m, 6H), 8.23 (td, J=7.9 Hz, J=2.2 Hz), 11.90 (d, 1H, J=8.0 Hz).^{13}C n.m.r. δ ($CDCl_3$): 27.2, 32.0, 58.9, 117.6, 122.6 (d, J^{P-C}=12 Hz), 124.0 (d, J^{P-C}=20.5 Hz), 128.3, 129.1 (d, J^{P-C}=12.1 Hz), 129.1 (d, J^{P-C}=100 Hz), 131.2, 131.5 (d, J^{P-C}=2.2 Hz), 132.5 (d, J^{P-C}=29.7 Hz), 150.3, 168.4 (d, J^{P-C}=1.5 Hz), 205.4; m/z (%): 496 (M^+, 10), 468 (19), 381 (100), 352 (92), 277 (91), 262 (15), 218 (49), 201 (46), 199 (20), 185 (20), 183 (73), 162 (72), 152 (23), 134 (24), 107 (20), 102 (18), 92 (13), 90 (22), 88 (16), 77 (74).

2,3,3a-4-Tetrahydro-5-H-thieno[2,3-b][1,4]benzodiazepine-5-one **24b.**

To a cooled at 0°C solution of *n*-tributylphosphine (10 mmol) in dichloromethane (15 ml) a solution of an equimolecular amount of the corresponding azido derivative **22b** in the same solvent (15 ml) was added. After stirring at room temperature for 12 h, the reaction mixture was heated under reflux for 8 h. The solvent was then evaporated under reduced pressure and the residue crystallized from ethanol to give **24b**, as red prisms in 61% yield, m.p. 216-218°C (Found: C, 60.38; H, 4.42; N, 12.71. $C_{11}H_{10}N_2OS$ requires: C, 60.53; H, 4.62; N, 12.83); i.r. (Nujol) 3148, 1645, 1616, 1596, 1466, 1450, 1384, 1112, 863, 822, 783 cm^{-1}; ^1H n.m.r. δ (DMSO d_6): 2.29-2.41 (m, 2H), 3.36-3.59 (m, 2H), 3.98-4.07 (m, 1H), 7.16 (d, 1H, J=8.0 Hz), 7.25 (dd 1H, J=7.8 Hz, J=1.2 Hz), 7.52 (dt, 1H, J=7.5 Hz, J=1.3 Hz), 7.79 (dd, 1H, J=7.8 Hz, J=1.2 Hz), 8.83 (d, 1H, J=3.5 Hz). (^{13}C n.m.r. δ (DMSO d_6): 31.7, 32.0, 53.7, 124.7, 125.3, 126.9, 130.4, 131.6; 147.4, 167.7, 181.8; m/z (%): 218 (M^+, 10), 185 (13), 162 (100), 134 (32), 102 (18), 90 (22), 76 (18), 63 (12), 50 (22).

1,2,3,4,5-Pentahydro-3-(2-hydroxyethyl)-[1,4]-benzodiazepine-2,5-dione **25a.**

This compound was obtained following the same procedure described for the preparation of **24b** but during the work up of the reaction, hydrolysis and ring opening of the previously fused benzodiazepine **24a** formed took place to give **25a** which was crystallized, as orange needles, from ethanol; (72% yield) m.p 236-238°C (Found: C, 59.87; H, 5.60; N, 12.55. $C_{11}H_{12}N_2O_3$ requires: C, 59.99; H, 5.49; N, 12.72); i.r. (Nujol) 3428, 3192, 1683, 1661, 1608, 1453, 1416, 1227, 1063, 1046, 759 cm^{-1}; ^1H n.m.r. δ (DMSO d_6) 1.70-1.84 (m, 1H), 1.90-2.08 (m, 1H), 3.41-3.63 (m, 2H), 3.77-3.86 (m, 1H), 4.01 (br. s, 1H), 7.12 (d, 1H, J=8.0 Hz), 7.76 (d, 1H, J=7.7 Hz), 7.52 (t, 1H, J=7.6 Hz), 8.50 (d, 1H, J=5.4 Hz), 10.47 (s, 1H). ^{13}C n.m.r. δ (DMSO d_6): 31.0 48.7, 56.9, 121.1, 124.1, 126.5, 130.6, 132.3, 136.9, 168.2, 171.8; m/z (%) 220 (M^+, 37), 202 (6), 176 (36), 147 (61), 146 (27), 120 (100), 119 (46), 92 (40), 90 (10), 65 (16).

3-(2-Mercaptoethyl)-[1,4]-benzodiazepine-2,5-dione **25b**.

To a solution of **24b** (0.22 g, 1 mmol) in DMSO (10 ml) water (2 ml) was added and the solution stirred for 2 h at room temperature. The resulting solid was filtered and crystallized from ethanol to give **25b**, as white needles (98% yield) m.p. 266-267°C (Found: C, 55.79; H, 5.18; N, 11.98. $C_{11}H_{12}N_2O_2S$requires: C, 55.91; H, 5.12; N, 11.86); i.r. (Nujol) 3171, 3053, 1682, 1666, 1608, 1455, 1410, 1379, 1231, 1160, 1031 cm^{-1}; ^1H n.m.r. δ (DMSO d_6) 1.90-2.08 (m, 1H), 2.08-2.31 (m, 1H), 2.65-2.91 (m, 2H), 3.42-3.65 (m, 1H), 7.13 (d, 1H, J=7.8 Hz), 7.26 (t, 1H, J=7.5 Hz), 7.54 (t, 1H, J=7.2 Hz), 7.75 (d, 1H, J=7.5 Hz), 8.61 (d, 1H, J=5 Hz), 10.47 (s, 1H). ^{13}C n.m.r. δ (DMSO d_6): 27.6, 33.8, 50.9, 121.5, 124.8, 126.4, 130.8, 132.9, 136.8, 168.5, 171.7.

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References and Notes.

1. a) Thurston, D.E. Advances in the Study of Pyrrolo[2,1-c][1,4]benzodiazepine (PBD) Antitumor Antibiotics in *Molecular Aspects of Anticancer Drug-DNA Interactions*. b) Neidle, S.; Waring, M.J. Eds.; The Macmillan Press Ltd, 1993, Vol. 1, pp. 54-88.
2. a) Hurley, L.H. *J. Antibiot.* **1977**, *30*, 349 and references therein. b) Hurley, L.H.; Lasswell, W.L.; Ostrander, J.M.; Parry, R. *Biochemistry* **1979**, *18*, 4230. c) Petrusek, R.L.; Anderson, G.L.; Garner, T.F.; Quinton, F.L.; Fannin, L.; Kaplan, D.J.; Zimmer, S.G.; Hurley, L.H. *Biochemistry* **1981**, *20*, 1111. d) Hurley, L.H.; Needham-Van Devander, D.R. *Acc. Chem. Res.* **1986**, *19*, 230.
3. a) Leimgruber, W.; Batcho, A.D.; Czajkowski, R.C. *J. Am. Chem. Soc.* **1968**, *90*, 5641. b) Kaneko, T.; Wong, H.; Doyle, T. W. *Tetrahedron Lett.* **1983**, 5165. c) Thurston, D.E.; Kaumaya, P.T.P.; Hurley, L.H. *Tetrahedron Lett.***1984**, 2649. d) Suggs, J.W.; Wang, Y.S.; Lee, K.S. *Tetrahedron Lett.* **1985**, 4871.
4. a) Langlois, N.; Bourrel, P.; Andriamialisoa, R.Z. *Heterocycles* **1986**, *24*, 777. b) Thurston, D.E.; Langley, D.R.; *J. Org. Chem.* **1986**, *51*, 705.
5. Kaneko, T.; Wong, H.; Doyle, T.W. *Tetrahedron Lett.* **1983**, 24.
6. Bose, D.S.; Jones, G.B.; Thurston, D.E. *Tetrahedron* **1992**, *48*, 751.
7. a) Langley, D.R.; Thurston, D.E. *J. Org. Chem.* **1987**, *52*, 91. b) Courtney, S.M.; Thurston, D.E. *Tetrahedron Lett.* **1993**, 5327.
8. a) Mazzocchi, P.H.; Schuda, A.D. *Heterocycles* **1985**, *23*, 1603. b) Weidner-Wells, M.A.; DeCamp, A.; Mazzocchi, P.H. *J. Org. Chem.* **1989**, *54*, 5746.
9. a) Mori, M.; Kimura, M.; Uozumi, Y.; Ban, Y. *Tetrahedron Lett.* **1985**, 5947. b) Mori, M.; Uozumi, Y.; Kimura, M.; Ban, Y. *Tetrahedron*, **1986**, *42*, 3793. c) Mori, M.; Uozumi, Y.; Ban, Y. *Heterocycles* **1986**, *24*, 1257. d) Mori, M.; Uozumi, Y.; Ban, Y. *J. Chem. Soc. Chem. Commun.* **1986**, 841.
10. See review: Molina, P.; Vilaplana, M.J. *Synthesis* **1994**, 1197.
11. Ardakan, M.N. *J. Chem. Soc. Perkin Trans. I* **1983**, 2501.
12. Thurston, D.E.; Murty, V.S.; Langley, D.R.; Jones, G.B. *Synthesis* **1990**, 81.

13. JP 58,180,487 [83,180,487] (Cl. CO7D487/04) Kyowa Hakko Kogyo Co., Ltd. Jpn., Kokai Tokkyo Koho, Appl. 21 Oct 1983, 82/63, 630, 16 Apr 1982 (Chem. Abs. 1984, 100: 173150k).
14 a) Shimizu, K.; Kawamoto, I.; Tomita, F.; Morimoto, M.; Fujimoto, K. *J. Antibiotics* **1982**, *35*, 972. b) Tozuda, Z.; Takaya, T. *J. Antibiotics* **1983**, *36*, 142.
15 Peña, M.R.; Stille, J.K. *J. Am. Chem. Soc.* **1989**, *111*, 5417.
16 Mori, M.; Minoru, I.; Ikeda, T.; Ban, Y. *Heterocycles* **1984**, *22*, 253.

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