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An expedient synthesis of 7-*O*-functionalised pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones

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Abstract—An efficient synthetic route to 7-hydroxypyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione, an important potential ligand for the DNA minor groove, has been developed. Simultaneous reduction of nitro and hydrogenolysis of the *O*-benzyl in *N*-(5-benzyloxy-2-nitrobenzoyl)-L-proline methyl ester, followed by thermal cyclisation, gave 7-hydroxypyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione. This was alkylated to give the prop-2-ynyl ether. Reaction of benzyl hex-5-ynoate with $B_{10}H_{14}$ and deprotection with HBr gave 4-(1,2-dicarbaclosododecaboran(12)-1-yl)butanoic acid. This acid was coupled with the tricyclic phenol to give 5,11-dioxo-2,3-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-7-yl 4-(1,2-dicarbaclosododecaboran(12)-1-yl)butanoate.

1. Introduction

The tricyclic pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones **1** (Fig. 1) are structurally related to the well-known benzodiazepine-2,5-diones **2**. The substituted benzodiazepine-2,5-diones have been used for a number of applications, including as a template for design and assembly of peptidomimetic agents,[1] as anxiolytic drugs,[2] as anticonvulsants[3] and as herbicides.[4] The principal use to date of the pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones **1** has been as important synthetic intermediates[5–8] in the assembly of the potent DNA-binding pyrrolo[2,1-*c*][1,4]-benzodiazepine-5-ones (PBDs) **3**. However, they also have recently been recognised[9,10] as weaker and non-covalent ligands for the DNA minor groove. In the structure of the highly potent PBDs, the optimum site for attachment of additional ligands for the DNA minor groove is the 6-position, since slender groups and linkers joined at this point will lie along the floor of the minor groove.[11,12] Substituents at the 7-position are predicted to protrude from the minor groove; Guiotto et al.[13] have noted that such 7-substituents do, nevertheless, subtly influence the biological activity of the PBDs. Since we rationalised that a substituent attached to the 7-position of the pyrrolo[2,1-*c*]-[1,4]benzodiazepine-5,11-diones through an appropriate linker would be held non-covalently near the opening of the DNA minor groove, we have sought to devise an efficient synthesis of the 7-*O*-substituted diones.

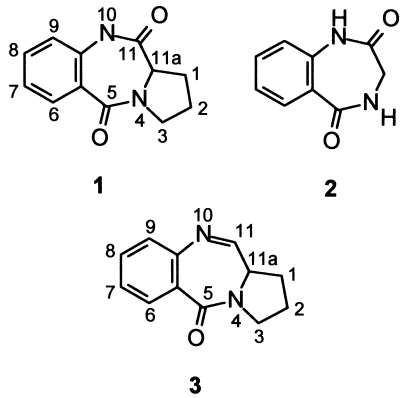

Figure 1. General structures of pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones **1**, 1,4-benzodiazepine-2,5-diones **2** and pyrrolo[2,1-*c*][1,4]benzodiazepine-5-ones (PBDs) **3**.

2. Results and discussion

In our initial approach (Scheme 1), the *O*-prop-2-ynyl substituent was introduced early in the synthesis, before the closure of the 7-membered ring. 5-Hydroxy-2-nitrobenzaldehyde **5** was oxidised in excellent yield to the corresponding acid **6** with hot basic hydrogen peroxide; in this process, it was essential to heat **5** very rapidly in the sodium hydroxide solution and to add the hydrogen peroxide as rapidly as technically feasible, to avoid Cannizzaro-type side reactions. The acid **6** was converted to its methyl ester **7**. Alkylation with 3-bromopropyne was achieved in 54% yield and the carboxylic acid was exposed again by hydrolysis of the intermediate ester **8**, giving 2-nitro-5-(prop-2-ynyloxy)benzoic acid **9**. The chiral pyrrolidine unit was then introduced by conversion to the acid

Keywords: pyrrolobenzodiazepine; cyclisation; carborane; neutron capture therapy; hydrogenoloysis.

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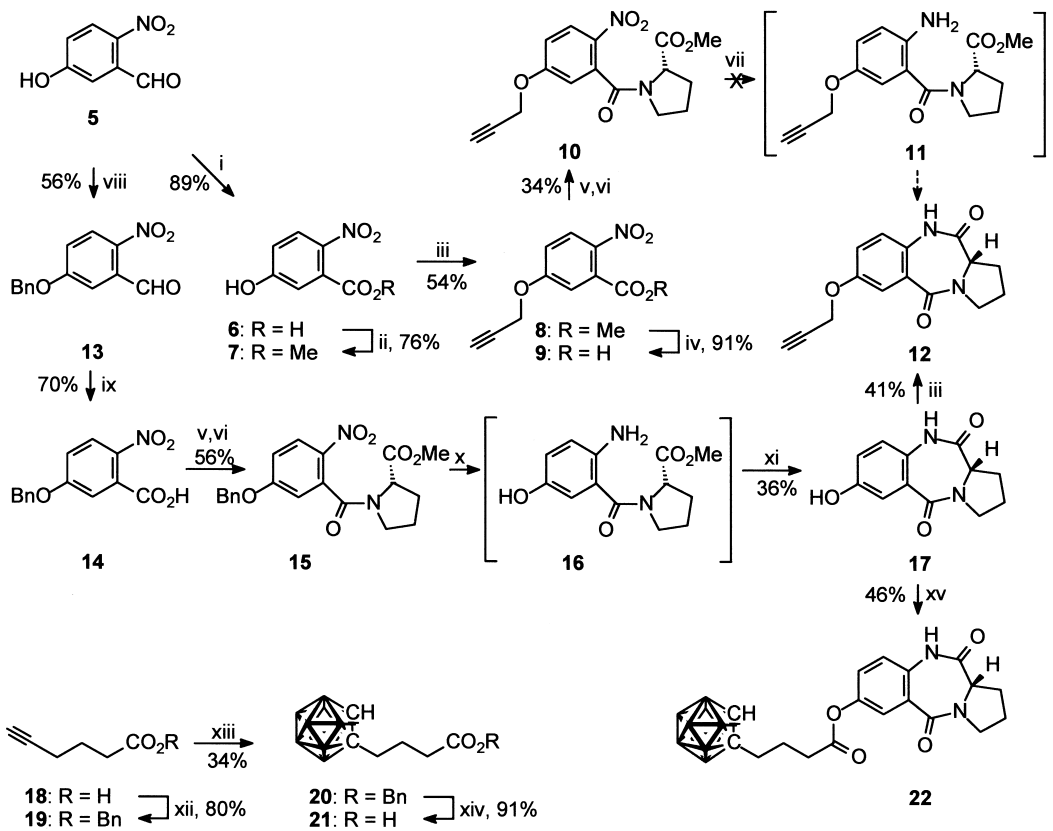

Scheme 1. Synthesis of 7-hydroxypyrrolo[2,1,*c*][1,4]benzodiazepine-5,11-diones **17** and reaction to form the exemplary ether **12** and the ester **22**. In the icosahedra, the unmarked vertices represent BH. *Reagents*: (i) H_2O_2, NaOH, H_2O, Δ; (ii) MeOH, $SOCl_2$, Δ; (iii) NaH, $BrCH_2C{\equiv}CH$, DMF, NaI, Δ; (iv) NaOH, aq. MeOH; (v) $(COCl)_2$, DMF, THF; (vi) ProOMe, Et_3N, DMAP, THF, CH_2Cl_2; (vii) various reductants; (viii) $KOBu^t$, BnBr, DMF, Δ; (ix) $KMnO_4$, Me_2CO, H_2O; (x) H_2, Pd/C, THF, MeOH; (xi) DMF, Δ; (xii) DBU, BnBr, MeCN; (xiii) $B_{10}H_{14}$, MeCN, Δ; (xiv) HBr, AcOH; (xv) **21**, DCC, HOBt, DMF.

chloride and coupling with L-proline methyl ester, forming the tertiary amide **10** in moderate yield. At this point, selective reduction of nitro to amino, followed by in situ ring closure of the proposed intermediate **11**, was investigated. This route has been used for the synthesis of a number of pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones.[4,14] Several agents have been reported[15] to reduce nitro groups selectively in the presence of other potentially reducible moieties. However, using the propargyl ether **10** as a substrate, metal-based reagents (e.g. $SnCl_2$) gave intractable mixtures of products whereas the $NaBH_4$/Pd/C combination surprisingly reduced the alkyne to the corresponding propyloxy group, as well as reducing the nitro function.

In the second route (Scheme 1), the phenolic oxygen in **5** was protected with benzyl in the first step. Oxidation of **13** with permanganate then gave the corresponding acid **14**, which was coupled with L-proline methyl ester via its acid chloride. Now, treatment with hydrogen and palladium effected both the required reduction of the nitro group in **15** and hydrogenolysis of the benzyl protection. The exposed phenolic OH in intermediate **16**, as a potent electron-donating group, activates the amine as a nucleophile to effect the closure of the diazepinedione ring. Simple alkylation of the phenolate anion of the resulting tricycle **17** with 3-bromopropyne afforded the required 7-*O*-prop-2-ynyl pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione **12**.

With the demonstration of an efficient route to the tricyclic phenol **17** and of alkylation thereof, an example of an ester was also prepared (Scheme 1). As part of a programme of investigation of tumour-targeted boron clusters for applications in boron neutron capture therapy (BNCT),[16] we have previously reported[17] the synthesis of 4-(1,2-dicarba-*closo*dodecaboran(12)-1-yl)butanoic acid **21** through hydrolysis of the corresponding nitrile. However, this hydrolysis can be unreliable and an alternative synthesis of **21** was developed. Hex-5-ynoic acid **18** was selectively alkylated at oxygen, in the presence of DBU to give its previously unreported benzyl ester **19**. The carborane (1,2-dicarba*closo*dodecaborane) icosahedron in **20** was then assembled by heating this alkyne with decaborane(14) in the presence of a Lewis base (acetonitrile). Protection of the carboxylic acid is essential, since decaborane(14) is incompatible with acidic hydrogens under the vigorous reaction conditions. Debenzylation of the carborane ester **20** with hydrogen bromide gave the required carboranebutanoic acid **21** in excellent yield without degradation of the boron cage. A carbodiimide coupling then joined this acid to 7-hydroxypyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione **17** to give the target ester **22**. Results of biochemical and biostructural studies on **22** will be reported elsewhere.

3. Conclusion

In this paper, we report a short, efficient and reliable synthesis of 7-hydroxypyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione **17**, along with alkylation and esterification of the

phenol therein. The ready availability of this compound will facilitate the development of new agents that bind non-covalently in the minor groove of DNA, with substituents held in or near the top of this groove.

4. Experimental

4.1. General

Procedures were conducted at room temperature, except where noted. Solutions in organic solvents were dried with anhydrous magnesium sulphate. The chromatographic stationary phase was silica gel. NMR spectra were obtained of solutions in $CDCl_3$, except where noted. IR spectra were obtained of samples as KBr discs, except where noted. Brine refers to saturated aqueous sodium chloride, THF refers to tetrahydrofuran, DMF refers to dimethylformamide. Melting points are uncorrected.

4.1.1. 5-Hydroxy-2-nitrobenzoic acid (6). 5-Hydroxy-2-nitrobenzaldehyde **5** (1.0 g, 6.0 mmol) in aq. NaOH (10%, 10 mL) was placed in a pre-heated oil bath (100°C). Aqueous H_2O_2 (28% v/v, 15 mL) was added dropwise during 10 min and the mixture was boiled under reflux for 16 h. The solution was acidified to pH 2 with aq. H_2SO_4 (10%) and extracted twice with EtOAc. The combined extracts were washed with water and brine and were dried. Evaporation gave **6** (980 mg, 89%) as a yellow solid: mp 170–172°C (lit.[20] mp 171–172°C); NMR ($(CD_3)_2SO$) δ_H 7.01 (2H, m, 4,6-H_2), 7.97 (1H, d, J=9.5 Hz, 3-H), 11.22 (1H, br, ArOH), 13.6 (1H, br, CO_2H).

4.1.2. Methyl 5-hydroxy-2-nitrobenzoate (7). $SOCl_2$ (430 mg, 3.7 mmol) was added dropwise during 10 min to **6** (980 mg, 5.3 mmol) in MeOH (125 mL) and the mixture was boiled under reflux for 16 h. The evaporation residue, in EtOAc, was washed with water and brine and was dried. Evaporation gave **6** (800 mg, 76%) as a pale yellow solid: mp 101–103°C; IR ν_{max} 3300, 1724, 1520, 1350 cm^{-1}; NMR ($(CD_3)_2SO$) δ_H 3.94 (3H, s, Me), 6.97 (1H, d, J=8.6, 2.7 Hz, 4-H), 7.02 (1H, dd, J=2.7, 0.5 Hz, 6-H), 8.01 (1H, dd, J=8.6, 0.5 Hz, 3-H); MS (EI^+) m/z 197.0326 (M) ($C_8H_7NO_5$ requires 197.0324).

4.1.3. Methyl 2-nitro-5-(prop-2-ynyloxy)benzoate (8). Ester **7** (500 mg, 2.5 mmol) in dry DMF (2.2 mL) was added to sodium hydride (60% in oil, 72 mg, 2.8 mmol) in dry DMF (3.5 mL) at 0°C under N_2. The mixture was warmed to 20°C and then rapidly cooled to 0°C. NaI (380 mg, 2.5 mmol) and 3-bromopropyne (80% in toluene, 910 mg, 7.7 mmol) were added and the mixture was boiled under reflux for 18 h. The evaporation residue, in EtOAc, was washed with sat. aq. NH_4Cl, water and brine. Drying, evaporation and chromatography (hexane/EtOAc 7:3) gave **8** (320 mg, 54%) as a pale yellow oil; IR (film) ν_{max} 2120, 1730, 1520, 1340 cm^{-1}; NMR δ_H 2.60 (1H, t, J=2.4 Hz, C≡CH), 3.94 (3H, s, Me), 4.81 (2H, d, J=2.4 Hz, CH_2), 7.16 (2H, m, 4,6-H_2), 8.10 (1H, dd, J=8.6, 0.5 Hz, 3-H); MS (CI^+) m/z 236 (M+H), 204 (M+H−OMe), 178.

4.1.4. 2-Nitro-5-(prop-2-ynyloxy)benzoic acid (9). Ester **8** (270 mg, 1.1 mmol) was stirred with NaOH (100 mg, 2.5 mmol) in water (1.0 mL) and MeOH (5.0 mL) for 23 h. The MeOH was evaporated. The residue was acidified with aq. HCl (2 M) and was extracted twice with EtOAc. The combined extracts were washed with brine and were dried. Evaporation gave **9** (230 mg, 91%) as a white solid: mp 164–167°C; IR ν_{max} 3100–2800, 2120, 1700, 1510, 1340 cm^{-1}; NMR δ_H 3.70 (1H, t, J=2.3 Hz, C≡CH), 5.00 (2H, d, J=2.3 Hz, CH_2), 7.40 (2H, m,4,6-H_2), 8.10 (1H, d, J=8.0 Hz, 3-H); NMR δ_C 57.3, 78.8, 80.1, 116.6, 117.6, 127.2, 132.6, 140.3, 161.3, 166.9; MS m/z (FAB^+) 222.0397 (M+H) ($C_{10}H_7NO_5$ requires 222.0402).

4.1.5. *N*-(2-Nitro-5-(prop-2-ynyloxy)benzoyl)-L-proline methyl ester (10). Acid **9** (70 mg, 320 μmol) was stirred with DMF (50 μL) and oxalyl chloride (3.26 g, 26 mmol) in dry THF (2.0 mL) for 4.5 h. The evaporation residue, in THF (3.0 mL), was added to L-proline methyl ester (102 mg, 620 μmol), Et_3N (68 mg, 0.67 mmol) and 4-dimethylaminopyridine (5 mg) in THF (2.2 mL) and CH_2Cl_2 (1.0 mL) and the mixture was stirred for 16 h. Evaporation and chromatography (EtOAc/hexane 1:9) gave **10** (36 mg, 34%) as a colourless oil: IR (film) ν_{max} 3260, 2120, 1730, 1570, 1330 cm^{-1}; NMR δ_H 2.08–2.18 (3H, m, proline β-H_2 and γ-H), 2.61 (1H, t, J=2.4 Hz, C≡CH), 2.39 (1H, m, proline γ-H), 3.25 (1H, m, proline δ-H), 3.38 (1H, br m, proline δ-H), 3.81 (3H, s, Me), 4.78 (1H, m, proline α-H), 4.82 (2H, d, J=2.4 Hz, OCH_2), 7.03 (1H, d, J=2.9 Hz, Ar 6-H), 7.11 (1H, dd, J=9.0, 2.9 Hz, Ar 4-H), 8.21 (1H, d, J=9.1 Hz, Ar 3-H); NMR δ_C 14.1, 24.6, 29.5, 48.3, 52.3, 56.5, 58.4, 60.3, 76.5, 114.3, 115.6, 127.1, 135.5, 162.0, 165.9, 172.2; MS (CI^+) m/z 333 (M+H), 278 (M−OC_3H_3), 204 (M−prolineOMe), 128.

4.1.6. 2-Nitro-5-phenylmethoxybenzaldehyde (13). 5-Hydroxy-2-nitrobenzaldehyde **5** (1.00 g, 5.9 mmol) was stirred with $KOBu^t$ (670 mg, 5.9 mmol) in dry DMF (28 mL) for 20 min under N_2. Bromomethylbenzene (1.10 g, 6.4 mmol) was added and the mixture was boiled under reflux for 23 h. The evaporation residue, in EtOAc, was washed with water and brine and was dried. Evaporation and chromatography (EtOAc/hexane 3:7) gave **13** (860 mg, 56%) as an orange solid: mp 66–68°C (lit.[18] yellow oil); NMR δ_H 4.91 (2H, s, CH_2), 6.95 (1H, dd, J=8.8, 2.9 Hz, Ar 4-H), 7.10–7.26 (6H, m, Ph-H_5+Ar 6-H), 7.85 (1H, d, J=8.8 Hz, Ar 3-H), 10.14 (1H, s, CHO).

4.1.7. 5-Benzyloxy-2-nitrobenzoic acid (14). $KMnO_4$ (920 mg, 5.8 mmol), in acetone (50 mL) and water (50 mL), was added dropwise during 20 min to **13** (1.01 g, 3.9 mmol) and the mixture was stirred for 23 h. The solution was acidified to pH 2 with aq. HCl (10%) and extracted twice with EtOAc. The combined extracts were washed with water and brine and were dried. Evaporation gave **14** (750 mg, 70%) as a pale yellow solid: mp 132–134°C (lit.[19] mp 143–144°C); NMR δ_H 5.16 (2H, s, CH_2), 7.10 (1H, dd, J=8.9, 2.7 Hz, Ar 4-H), 7.27 (1H, d, J=2.7 Hz, Ar 6-H), 7.39 (5H, m, Ph-H_5), 7.98 (1H, d, J=8.9 Hz, Ar 3-H), 10.71 (1H, s, CO_2H).

4.1.8. *N*-(5-Benzyloxy-2-nitrobenzoyl)-L-proline methyl ester (15). Oxalyl chloride (13.2 g, 103 mmol) was added dropwise to **14** (420 mg, 1.5 mmol) and DMF (0.05 mL) in CH_2Cl_2 (5.0 mL) during 25 min and the mixture was stirred

for 3 h. Evaporation gave the crude acid chloride, which, in CH_2Cl_2 (10 mL), was added to a suspension of L-proline methyl ester (760 g, 4.6 mmol), Et_3N (470 mg, 4.6 mmol) and 4-dimethylaminopyridine (5 mg) in CH_2Cl_2 (5.0 mL). The mixture was stirred for 18 h. The evaporation residue, in EtOAc, was washed with water and brine and was dried. Evaporation and chromatography (EtOAc) gave **15** (0.33 g, 56%) as white solid: mp 157–158°C; IR ν_{max} 1730, 1570, 1338 cm^{-1}; NMR δ_H 2.03–2.09 (3H, m, proline β-H_2 and γ-H), 2.31 (1H, m, proline γ-H), 3.17 (1H, m, proline δ-H), 3.27 (1H, m, proline δ-H), 3.79 (3H, s, Me), 4.74 (1H, m, proline α-H), 5.16 (2H, s, OCH_2), 7.00 (1H, d, J=2.7 Hz, Ar 6-H), 7.02 (1H, dd, J=8.9, 2.7 Hz, Ar 4-H), 7.38 (5H, m, Ph-H_5), 8.16 (1H, d, J=8.9 Hz, Ar 3-H); NMR δ_C 24.7, 29.6, 48.3, 58.4, 70.9, 113.9, 115.5, 127.0, 127.5, 128.4, 128.6, 134.9, 135.5, 137.6, 163.0, 163.2, 165.8, 172.1; MS (EI^+) m/z 385.1432 (M) ($C_{20}H_{21}N_2O_6$ requires 385.1399).

4.1.9. 7-Hydroxy-2,3-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine-5,11(10*H*,11a*H*)-dione (17). Compound **15** (480 mg, 1.3 mmol) was treated with H_2 in the presence of Pd/C (10%, 50 mg) in THF (5 mL) and MeOH (45 mL) for 10 h. The mixture was filtered (Celite®). The evaporation residue, in dry DMF (30 mL), was boiled under reflux for 2 d. The evaporation residue, in EtOAc, was washed with water and brine and was dried. Evaporation and chromatography (EtOAc/MeOH 99:1) gave **17** (105 mg, 36%) as a white solid; mp 213–214°C; IR ν_{max} 3400, 3196, 1659 cm^{-1}; NMR δ_H 1.80 (1H, m, 1-H_β), 1.88–1.96 (2H, m, 2-H_2), 2.48 (1H, m, 1-H_α), 3.43 (1H, m, 3-H), 3.56 (1H, m, 3-H), 4.07 (1H, m, 11a-H), 6.94–6.92 (2H, m, 8,9-H_2), 7.15 (1H, d, J=2.7 Hz, Ar 6-H), 9.36 (1H, s, 7-OH), 10.21 (1H, s, NH); MS (EI^+) m/z 233.0927 (M) ($C_{12}H_{13}N_2O_3$ requires 234.0926).

4.1.10. 7-(2-Propynyloxy)-2,3-dihydro-1*H*-pyrrolo[2,1-*c*]-[1,4]benzodiazepine-5,11-(10*H*,11a*H*)-dione (12). Compound **17** (50 mg, 220 μmol) was stirred with NaH (60% in oil, 5.3 mg, 220 μmol) in dry DMF (4.0 mL) under N_2 at 0°C for 15 min, then at 45°C for 15 min. The mixture was rapidly cooled to 0°C, sodium iodide (32 mg, 220 μmol) and 3-bromopropyne (80% in toluene, 62 mg, 520 μmol) were added and the mixture was boiled under reflux for 18 h. The evaporation residue, in EtOAc, was washed with sat. aq. NH_4Cl, water and brine. Drying, evaporation and preparative layer chromatography (hexane/EtOAc 7:3) gave **12** (24 mg, 41%) as a yellow solid; mp >230°C; IR ν_{max} (KBr) 3227 (N–H), 2116 (C≡C), 1686 (C=O) cm^{-1}; NMR δ_H 1.95–1.98 (3H, m, 2-H_2 and 1-H_β), 2.46 (1H, t, J=2.3 Hz, C≡C-H), 2.68 (1H, m, 1-H_α), 3.54 (1H, m, 3-H), 3.75 (1H, m, 3-H), 4.00 (1H, br d, J=5.9 Hz, 11a-H), 4.67 (2H, d, J=2.3 Hz, OCH_2), 6.88 (1H, d, J=8.9 Hz, 9-H), 7.05 (1H, dd, J=8.9, 3.1 Hz, 8-H), 7.49 (1H, d, J=3.1 Hz, 6-H), 8.03 (1H, br, N–H); MS (EI^+) m/z 270.1007 (M) ($C_{15}H_{14}N_2O_3$ requires 270.1004).

4.1.11. Phenylmethyl hex-5-ynoate (19). Hex-5-ynoic acid **18** (5.2 g, 46 mmol) was stirred with 1,8-diazabicyclo-[4,5,6]undec-7-ene (10.2 g, 69 mmol) and bromomethyl-benzene (21.1 g, 124 mmol) in dry MeCN (160 mL) for 24 h under Ar. Aq. HCl (2 M, 200 mL) was added and the mixture was extracted twice with Et_2O. Drying, evaporation and chromatography (pentane/Et_2O 19:1) gave **19** (7.5 g, 80%) as a colourless oil: IR ν_{max} (film) 2111, 1734 cm^{-1}; NMR δ_H 1.86 (2H, qn, J=7 Hz, 3-H_2), 1.99 (1H, t, J=2.6 Hz, 6-H), 2.26 (2H, td, J=7.0, 2.6 Hz, 4-H_2), 2.51 (2H, t, J=7.7 Hz, 2-H_2), 5.14 (2H, s, $PhCH_2$), 7.34–7.38 (5H, m, Ph-H_5); MS (FAB^+) m/z 203.1076 (M+H) ($C_{13}H_{15}O_2$ requires 203.1072).

4.1.12. Phenylmethyl 4-(1,2-dicarba*closo*dodecaboran(12)-1-yl)butanoate (20). Decaborane(14) ($B_{10}H_{14}$; 1.3 g, 10.9 mmol) was stirred with dry MeCN (17 mL) for 3.5 h. Ester **19** (2.17 g, 10.9 mmol) was added and the mixture was boiled under reflux for 5 d. Evaporation and chromatography (hexane/EtOAc; 3:2) gave **20** (1.19 g, 34%) as a white wax: mp IR ν_{max} 1698, 2343 cm^{-1}; NMR δ_H 1.81 (2H, m, 3-H_2), 2.20 (10H, br q, J=$_{BH}$ ca. 150 Hz, $B_{10}H_{10}$), 2.21 (2H, m, 2-H_2), 2.35 (2H, t, J=7.0 Hz 4-H_2), 3.50 (1H, br s, carborane 2-H), 5.11 (2H, s, CH_2O), 7.34–7.40 (5H, m, Ph-H_5); MS (EI) m/z 322.2721 (M) ($^{12}C_{13}H_{24}{}^{11}B_{10}O_2$ requires 322.2707), 321.2748 (M) ($^{12}C_{13}H_{24}{}^{11}B_9{}^{10}B_1O_2$ requires 321.2743), (M) 320.2779 ($^{12}C_{13}H_{24}{}^{11}B_8{}^{10}B_2O_2$ requires 320.2779), 319.2806 (M) ($^{12}C_{13}H_{24}{}^{11}B_7{}^{10}B_7O_2$ requires 320.2841), 318.2841 (M) ($^{12}C_{13}H_{24}{}^{11}B_6{}^{10}B_4O_2$ requires 318.2841).

4.1.13. 4-(1,2-Dicarba*closo*dodecaboran(12)-1-yl)butanoic acid (21). Ester **20** (110 mg, 0.34 mmol) was stirred with HBr (30% in AcOH) (4.0 mL) in CH_2Cl_2 (6.0 mL) for 3 h. Evaporation (80°C, 0.1 torr) gave **21** (38 mg, 91%) as a white solid: mp 157–159°C (lit.[17]155–157°C); NMR ($(CD_3)_2SO$) δ_H 1.62 (2H, m, 3-H_2), 2.20 (10H, br, $B_{10}H_{10}$), 2.21–2.30 (4H, m, 2,4-H_4), 5.19 (1H, br, carborane 2-H), 12.22 (1H, br, OH).

4.1.14. 5,11-Dioxo-2,3-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepin-7-yl (1,2-dicarba*closo*dodecacarborane-(12)-1-yl)butanoate (22). Compound **21** (7.0 mg, 30 μmol) was stirred with **17** (6.8 mg, 30 μmol), dicyclohexylcarbodiimide (6.0 mg, 30 μmol) and 1-hydroxybenzotriazole (1.0 mg, 7.4 μmol) in dry DMF (3.0 mL), under N_2 for 6.5 h. The evaporation residue, in EtOAc, was cooled to 0°C and filtered. Evaporation and chromatography (EtOAc/hexane 3:2) gave **22** (6.0 mg, 46%) as a white solid; mp 89–91°C; NMR δ_H 1.85 (2H, m, $CH_2CH_2CH_2$), 1.93–1.98 (3H, m, 2-H_{2+}1-H_β), 2.30–2.52 (2H, m, carborane-CH_2), 2.4 (10H, br q, J=$_{B-H}$ 150 Hz, $B_{10}H_{10}$), 2.53 (2H, t, J=7.0 Hz, CH_2CO_2), 2.68 (1H, m, 1-H_α), 3.49–3.57 (2H, m, 3-H and carborane 2-H), 3.75 (1H, m, 3-H), 4.04 (1H, br d, J=5.9 Hz, 11a-H), 6.91 (1H, d, J=8.4 Hz, 9-H), 7.14 (1H, dd, J=8.4, 2.7 Hz, 8-H), 7.63 (1H, d, J=2.7 Hz, 6-H), 7.90 (1H, br, NH); MS (FAB^+) m/z 446.3126 (M+H) ($^{12}C_{18}H_{29}{}^{11}B_9{}^{10}B_1N_2O_4$ requires 446.3139), 445.3149 (M+H) ($^{12}C_{18}H_{29}{}^{11}B_8{}^{10}B_2N_2O_4$ requires 445.3139), 444.3172 (M+H) ($^{12}C_{18}H_{29}{}^{11}B_7{}^{10}B_3N_2O_4$ requires 444.3167), 443.3153 (M+H) ($^{12}C_{18}H_{29}{}^{11}B_6{}^{10}B_4N_2O_4$ requires 443.3203).

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