1 PERKIN

New derivatives of the 1,2-benzodiazepine ring system

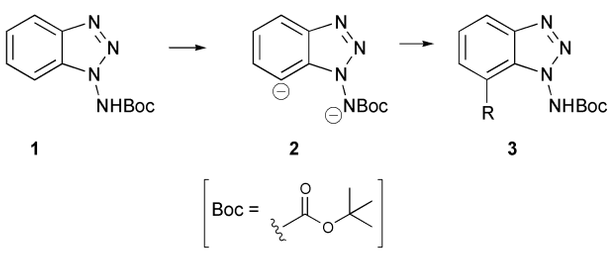
David W. Knight * and Paul B. Little

Chemistry Department, Cardiff University, P.O. Box 912, Cardiff, UK CF10 3TB

Received (in Cambridge, UK) 14th July 2000, Accepted 18th August 2000
First published as an Advance Article on the web 27th October 2000

The adducts **10**, formed in high yield by condensations between the benzotriazole dianion **2** and enals **9**, undergo smooth oxidation by manganese(IV) oxide to provide the expected conjugated enones. These then cyclise at varying rates, depending upon the substitution pattern around the enone function, by intramolecular Michael addition of the NHBoc group to provide examples **13** of a novel ring system based upon a 4,5,6,7-tetrahydro-1,2-benzodiazepine core. Allylic acetates **16** derived from the initial adducts **10** also undergo cyclisations *via* the derived π-allyl palladium complexes **15** to provide examples of the corresponding 4,5-dihydro-1,2-benzodiazepinenes **17**, but in a less general manner.

Despite the enormous advances in pharmaceutical design and synthesis in recent times, the bulk of commercially successful products are still based upon heterocyclic ring systems.[1] Clearly, therefore, there is a continuing need for the definition of routes to novel heterocyclic arrays. We have recently described methods for the generation of the dianion **2** from the parent benzotriazole derivative **1** (Scheme 1).[2] This can be used in a



1 2 3

Scheme 1

number of ways for the elaboration of the 7-substituted homologues **3**, precursors of *ortho*-substituted benzynes. During this work, the high nucleophilicity of the *N*-amino group in such aminobenzotriazoles manifested itself in a number of ways. For example, the deprotected free amines **4** were very rapidly transformed into the corresponding imines **5** when dissolved in

4 5

acetone. This reaction was so facile that exposure to even traces of this solvent had to be avoided at all times. The *N*-Boc function in derivatives **1** and **3** is also highly nucleophilic. During the early stages of our studies in this area, chromatographic solvent systems based on ethyl acetate were often used, which resulted in the isolation of variable amounts of by-products (5–20%, depending on time of exposure), manifested by the appearance of a new singlet at *ca.* δ_H 2.5. These were identified as the *N*-acetyl derivatives **6**, formed by reaction between the NHBoc group and ethyl acetate. Hence, this and related solvents were always avoided in subsequent work. Perhaps the most definitive example of this phenomenon is the unavoidable formation of the bis(Boc) derivative **7** during protection of the parent 1-aminobenzotriazole.[2] (Fortunately, selective

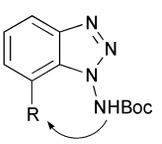
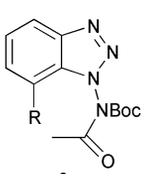
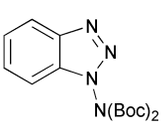


Fig. 1

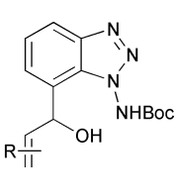


6



7

hydrolysis of one of these groups occurs upon exposure to warm methanolic sodium hydroxide to provide excellent yields of the mono(Boc) derivative **1**.) We reasoned that it ought to be possible to exploit this level of nucleophilicity in a more positive way by using various types of bond formation between the NHBoc function and electrophilic centres in the newly introduced 7-substituents in the derivatives **3** (Fig. 1). As condensations between the dianion **2** and conjugated aldehydes and ketones resulted in exclusive [1,2]-addition to give the adducts **8**,[2] we have examined opportunities for the manipulation of the resulting allylic alcohol function in order to generate such systems. Herein, we report that intramolecular additions to the derived enones and to allylic acetates both provide routes to a novel 1,2-benzodiazepine ring system.[3]

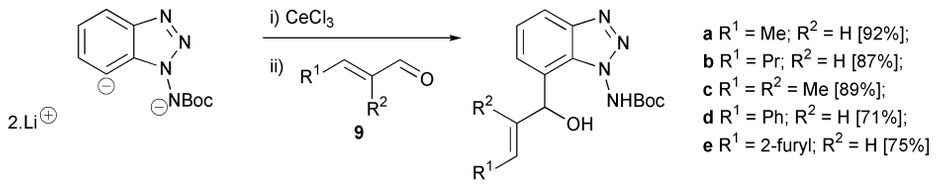


8

Results and discussion

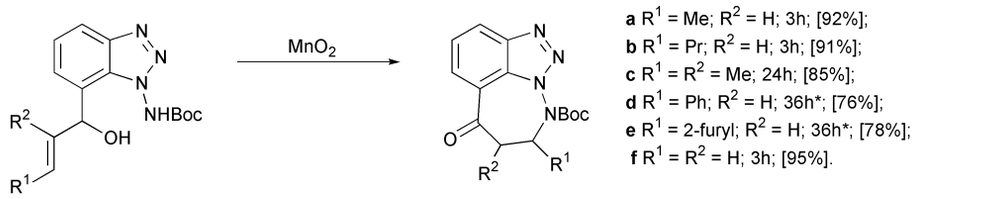
Condensations between representative enals **9** and dianion **2** were best carried out after modification of the initial dilithio derivative of dianion **2** by the addition of cerium(III) chloride, resulting in increases in yields of 10–15%. Isolated yields of the resulting allylic alcohols **10** thus ranged from good to excellent (71–92%; Scheme 2). The simplest member **12** of the series was prepared by an alternative route in which the dianion **2** was

 DOI: 10.1039/b005696k



2 **9** **10**

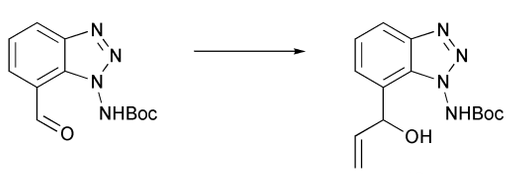
Scheme 2 Condensations between dianion **2** and enals.



10 a-e; 12 **13**

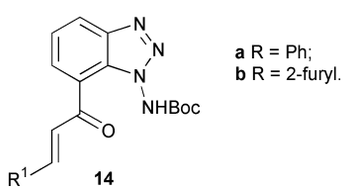
Scheme 3 Formation of [1,2]benzodiazepin-7-one derivatives.

formylated using DMF as the electrophile and the resulting aldehyde **11**[2] reacted with vinylmagnesium chloride at 0 °C in THF. This gave an essentially quantitative yield of the desired adduct **12**. When the allylic alcohol **10a**, derived from crotonaldehyde, was treated with activated manganese(IV) oxide, prepared by the Attenburrow method,[4] in dichloromethane at ambient temperature, TLC analysis indicated the formation of a single, less polar product after 3 hours (Scheme 3). Filtration and evaporation gave a single compound, isolated in 92% yield, which was evidently devoid of an enone function but which did contain a new carbonyl group (ν_{max} 1674 cm^{-1}; δ_C 194.0 ppm), consistent with the expected formation of an aryl ketone. Further, the ^{1}H and ^{13}C spectra, when obtained at 300 K, showed very broadened resonances and it was only when these spectra were run at 340 K that useful analysis could be carried out. This clearly showed the presence of an ABX system; all of these data were consistent with formation of the novel benzodiazepinone structure **13a**. It is presumed that the line broadening was due either to rotation of the NHBoc function or to pseudorotation around the newly formed ring. Hence, in this case, the high nucleophilicity of the NHBoc function must have facilitated an intramolecular Michael addition, while oxidation of the allylic alcohol **10a** to the corresponding enone proceeded. Attempts to observe the latter intermediate by either TLC or ^{1}H NMR were not successful, indicating that the Michael addition is faster than oxidation. Exposure to other oxidants including Jones reagent or pyridinium chlorochromate (PCC) failed to generate the enone cleanly.



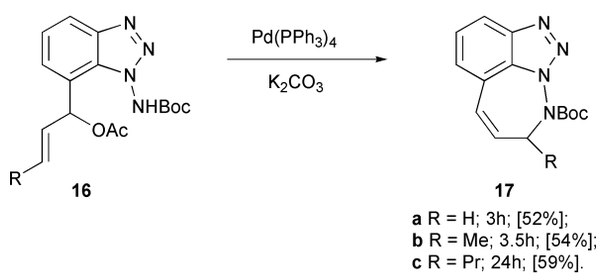
11 **12**

The other alkyl-substituted allylic alcohols **10b**,**c** were similarly converted into the substituted benzodiazepinones **13b**,**c** in excellent isolated yields. While oxidation of the alcohol **10c** was significantly slower, the product **13c** was nevertheless isolated in excellent yield and as a single diastereoisomer, which we presume had the *trans* stereochemistry although this was not proven with certainty as, due to the rotameric nature of the compound, only low quality NOE data could be obtained. In contrast, oxidation of the cinnamaldehyde-derived alcohol **10d** was even slower but was completed cleanly after 36 h. However, the product, although not fully characterised, was evidently the enone **14a** according to both infrared and NMR data. Fortunately, in terms of the aims of this study, addition of a slight excess of triethylamine to the reaction mixture, after completion of the oxidation step, triggered a smooth intramolecular Michael addition to this poorer acceptor function and the anticipated heterocycle **13d** was isolated in 76% yield. The enone **14b** proved similarly recalcitrant in terms of the Michael addition until triethylamine was added and gave a similarly good isolated yield of the anticipated product **13e**. Returning to the simplest allylic alcohol **12**, the parent heterocycle **13f** was obtained in less than 3 h without the need to add triethylamine, as expected.



14

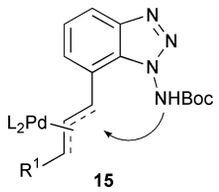
We then turned to our second strategy, in which formation of an intermediate π-allyl species **15** (Fig. 2) was a central feature.[5] For this, we required the allylic acetates **16** which, in the cases of the parent alcohol **12** or the distally alkylated derivatives **10a**,**b**, were selectively formed by exposure to acetic anhydride. Subsequent reaction[6] of the parent acetate **16a** with catalytic amounts of $Pd(PPh_3)_4$ and an equivalent of potassium carbonate in THF at ambient temperature resulted in disappearance of the starting material after 3 h (Scheme 4). A



16 **17**

Scheme 4

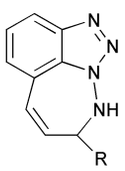
single product **17a** was subsequently separated by column chromatography, which evidently had the expected benzodiazepine structure. Similarly, the methyl-substituted acetate **16b** gave the corresponding heterocycle **17b** but the slightly larger propyl group of acetate **16c** slowed the cyclisation



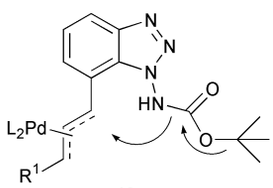
15

Fig. 2

significantly. However, after 24 h, a 59% isolated yield of the expected product **17c** was secured. In all three cases, varying amounts (5–20%) of the corresponding free amines **18** were observed; presumably, these are formed by loss of the Boc group during cyclisation as indicated in structure **19**, as at no stage are the reactants exposed to acidic conditions. Taking the formation of these three amines **18** into account, overall yields of these heterocycles are thus respectable; higher yields were not obtained, despite modifications to the reaction conditions including heating and changes both of solvent and of catalyst.

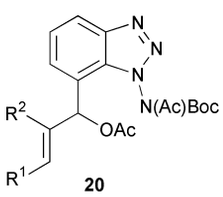


18



19

Unfortunately, the very nucleophilicity upon which this chemistry relies precluded extensions to this approach. When attempts were made to form the corresponding acetates from the allylic alcohols **10c** and **10d**, we were surprised to find, in the light of the foregoing results, that the products instead were the bis-acetylated species **20**. In view of the mechanism indicated in structure **19**, it was reasoned that this might not be a drawback in terms of formation of the ring system **18**. However, many attempts to cyclise these intermediates under increasingly vigorous conditions failed to produce the desired heterocycles. Presumably, the nitrogen function is now both too hindered and not sufficiently nucleophilic to participate in such cyclisations.



20

a $R^1 = R^2 = Me$;
b $R^1 = Ph$; $R^2 = H$.

In conclusion, this chemistry has defined a simple approach to a new benzodiazepine ring system which, despite some limitations, should be applicable to the elaboration of many derivatives beyond those reported herein. Not unexpectedly, in none of the foregoing examples was formation of the related five-membered derivatives observed. Presumably, ring strain prevents the generation of such products, despite the opportunity for their formation, by attack either onto the aryl ketone function in enones **14** and relatives or onto the benzylic position in the π-allyl complexes **15**. Efforts to further exploit the nucleophilicity of the amino function in such aminobenzotriazoles in the formation of other, novel ring systems are underway.

Experimental

For general experimental details see ref. 2.

Generation of dianion 2 and condensations with 2-enals: general procedure

Anhydrous cerium(III) chloride was prepared from the heptahydrate by drying in a vacuum oven (140 °C, 0.1 mmHg, 4 days) with regular crushing. Anhydrous cerium(III) chloride (1.1 eq.) was slurried in dry tetrahydrofuran (30 ml $mmol^{-1}$) for 16 h under dry nitrogen. In a separate vessel butyllithium (1.6 M solution in hexanes, 2.2 eq.) was added to a stirred solution of dry tetraglyme (5 eq.) in dry tetrahydrofuran (10 ml $mmol^{-1}$) maintained at −78 °C under dry nitrogen. Stirring was continued for 0.5 h, after which a solution of 1-(*N*-Boc-amino)-benzotriazole **6** (*n* mmol) in dry tetrahydrofuran (10 ml $mmol^{-1}$) was added slowly *via* syringe. The resulting deep purple dianion solution was stirred for 0.5 h at −78 °C; concurrently the cerium(III) chloride suspension was cooled to −78 °C and titrated with butyllithium (1.6 M solution in hexanes) until the first faint but permanent orange end point (typically 0.1 ml $mmol^{-1}$). The dianion solution was then rapidly transferred *via* syringe to the cerium(III) chloride suspension. The reaction mixture was stirred at −78 °C for 3 h, before rapid addition of freshly purified electrophile (1.1 eq.) in THF (1 ml $mmol^{-1}$). The reaction mixture was slowly warmed to ambient temperature and stirring was continued for 16 h, before the reaction was quenched with saturated ammonium chloride (10 ml $mmol^{-1}$). The resulting mixture was carefully acidified using 2 M hydrochloric acid and extracted with ether (3 × 30 ml $mmol^{-1}$). The combined extracts were washed with saturated aqueous sodium bicarbonate (10 ml $mmol^{-1}$), water (10 ml $mmol^{-1}$) and brine (10 ml $mmol^{-1}$), then dried and evaporated to give crude material which was subjected to column chromatography (20 g silica $mmol^{-1}$) using petrol–diethyl ether (7 : 3) to obtain the purified product, unless otherwise stated.

(*E*)-1-(*tert*-Butoxycarbonylamino)-7-(1′-hydroxybut-2′-en-1′-yl)-1*H*-1,2,3-benzotriazole 10a

Following the general procedure, treatment of dianion **2** generated from the aminobenzotriazole **1** (0.234 g, 1 mmol) with freshly distilled (*E*)-but-2-enal **9a** (0.082 ml, 1.1 mmol) gave alcohol **10a** as a brown solid which recrystallised from ether–petrol to yield the *allylic alcohol* **10a** as colourless crystals (0.279 g, 92%), mp 115–118 °C, ν_{max}/cm^{-1} 3267, 2980, 1750, 1456, 1370, 1253, 1160, 1049, 967 and 751; δ_H 1.30–1.59 (9H, br s, $C(CH_3)_3$), 1.66 (3H, d, *J* 7.1, 4′-H), 2.55–2.65 (1H, br s, OH), 5.55–5.66 (2H, m, C*H*OH and 3′-H), 5.74 (1H, ddd, *J* 15.4, 5.9 and 1.5, 2′-H), 7.26 (1H, t, *J* 7.1, 5-H), 7.41 (1H, d, *J* 7.1, 6-H), 7.97 (1H, d, *J* 7.1, 4-H) and 8.51–8.62 (1H, br s, NH); δ_C 18.3 (4′-CH_3), 28.5 ($C(CH_3)_3$), 71.2 (1′-CHOH), 84.2 ($C(CH_3)_3$), 120.5, 124.8 (both CH), 126.8 (C), 127.0 (both CH), 130.2 (C), 131.8 (CH) and 154.2 (C=O); *m*/*z* (ES) 305 ($M^+ + 1$, 100%) [Found: C, 59.31; H, 6.69; N, 18.50. $C_{15}H_{20}N_4O_3$ requires C, 59.18; H, 6.63; N, 18.42%].

(*E*)-1-(*tert*-Butoxycarbonylamino)-7-(1′-hydroxyhex-2′-en-1′-yl)-1*H*-1,2,3-benzotriazole 10b

Following the general procedure, treatment of dianion **2** generated from the aminobenzotriazole **1** (0.234 g, 1 mmol) with freshly distilled (*E*)-hex-2-enal **9b** (0.12 ml, 1.1 mmol) yielded the *alcohol* **10b** as a colourless crystalline solid (0.289 g, 87%), mp 138–144 °C, ν_{max}/cm^{-1} 3264, 2960, 2932, 2873, 1753, 1457, 1394, 1370, 1252, 1160, 1116, 1048, 969 and 771; δ_H 0.78 (3H, t, *J* 7.4, 6′-CH_3), 1.28 (2H, quintet, *J* 7.4, 5′-CH_2), 1.35–1.50 (9H, br s, $C(CH_3)_3$), 1.94 (2H, q, *J* 7.4, 4′-CH_2), 3.25–3.51 (1H, br s, OH), 5.58 (1H, app d, *J* 7.4, 1′-C*H*OH), 5.61 (1H, app t, *J* 6.0, 3′-H), 5.72 (1H, app dd, *J* 15.0 and 6.0, 2′-H), 7.19 (1H, t, *J* 7.1, 5-H), 7.41 (1H, d, *J* 7.1, 6-H), 7.72 (1H, d, *J* 7.1, 4-H) and 8.95–9.05 (1H, br s, NH); δ_C 13.8 (6′-CH_3), 22.2 ($C(CH_3)_3$), 28.1 (5′-CH_2), 34.4 (4′-CH_2), 70.5 (1′-C*H*OH), 83.8 ($C(CH_3)_3$), 120.0, 124.5, 126.7 (all CH), 126.7, 129.8 (both C), 130.3, 134.2 (both CH), 145.2 (C) and 153.9 (C=O); *m*/*z* (ES) 333 ($M^+ + 1$, 100%) and 98 (92) [Found: C, 61.27; H, 7.42; N, 16.88. $C_{17}H_{24}N_4O_3$ requires C, 61.43; H, 7.28; N, 16.85%].

(*E*)-1-(*tert*-Butoxycarbonylamino)-7-(1′-hydroxy-2′-methylbut-2′-en-1′-yl)-1*H*-1,2,3-benzotriazole 10c

By the general procedure, treatment of dianion **2** generated from the aminobenzotriazole **1** (0.234 g, 1 mmol) with freshly distilled (*E*)-2-methylbut-2-enal **9c** (0.097 ml, 1.1 mmol) yielded the *allylic alcohol* **10c** as a colourless crystalline solid (0.283 g, 89%), mp 134–136 °C, ν_{max}/cm^{-1} 3246, 2978, 1749, 1449, 1370, 1253, 1159, 1050 and 748; δ_H 1.29–1.50 (9H, br s, C(CH_3)$_3$), 1.54 (3H, d, *J* 9.9, 4′-CH_3), 1.62 (3H, s, 2′-CH_3), 3.49–3.60 (1H, br s, OH), 5.20–5.36 (1H, app br s, 3′-H), 5.47–5.52 (1H, app br s, 1′-H), 7.22 (1H, t, *J* 7.9, 5-H), 7.40 (1H, d, *J* 7.9, 6-H), 7.77 (1H, d, *J* 7.9, 4-H) and 8.95–9.05 (1H, br s, NH); δ_C 13.8 (4′-CH_3), 14.0 (2′-CH_3), 28.5 (C(CH_3)$_3$), 74.1 (1′-CHOH), 83.2 (C(CH$_3$)$_3$), 119.9, 122.9, 124.8, 127.5 (all CH), 128.6, 130.3, 136.4, 145.2 (all C) and 154.2 (C=O); *m*/*z* (ES) 319 (M$^+$ + 1, 100%), 263 (10) and 175 (11) [Found: C, 60.26; H, 7.08; N, 17.88. $C_{16}H_{22}N_4O_3$ requires C, 60.36; H, 6.97; N, 17.60%].

(*E*)-1-(*tert*-Butoxycarbonylamino)-7-(1′-hydroxy-3′-phenylprop-2′-en-1′-yl)-1*H*-1,2,3-benzotriazole 10d

By the general procedure, treatment of dianion **2** generated from the aminobenzotriazole **1** (0.234 g, 1 mmol) with freshly distilled (*E*)-cinnamaldehyde **9d** (0.138 ml, 1.1 mmol) yielded the *allylic alcohol* **10d** as a colourless crystalline solid (0.26 g, 71%), mp 153–155 °C, ν_{max}/cm^{-1} 3260, 2981, 1749, 1495, 1370, 1273, 1156, 1049 and 969; δ_H 1.35–1.78 (9H, br s, C(CH_3)$_3$), 2.78–2.93 (1H, br s, OH), 5.93 (1H, d, *J* 5.3, 1′-H), 6.52 (1H, dd, *J* 15.6 and 5.3, 2′-H), 6.68 (1H, app d, *J* 15.6, 3′-H), 7.26–7.41 (6H, m, 6 × Ar-H), 7.58 (1H, d, *J* 7.2, 6-H), 7.98 (1H, d, *J* 7.2, 4-H) and 8.55 (1H, br s, NH); δ_C 28.4 (C(CH_3)$_3$), 70.9 (1′-CHOH), 84.4 (C(CH$_3$)$_3$), 120.8, 125.0 (both CH), 126.5 (C), 127.1, 127.3, 128.6, 129.1, 129.8, 132.7 (all CH), 136.4, 146.1 (both C) and 158.9 (C=O); *m*/*z* (ES) 367 (M$^+$ + 1, 74%) [Found: C, 65.56; H, 6.16; N, 15.43. $C_{20}H_{22}N_4O_3$ requires C, 65.56; H, 6.05; N, 15.29%].

1-(*tert*-Butoxycarbonylamino)-7-[3′-(2-furyl)-1′-hydroxyprop-2′-en-1′-yl]-1*H*-1,2,3-benzotriazole 10e

Following the general procedure, treatment of dianion **2** generated from the aminobenzotriazole **1** (0.234 g, 1 mmol) with freshly distilled (*E*)-3-(2-furyl)prop-2-enal **9e** (0.134 g, 1.1 mmol) yielded the *allylic alcohol* **10e** as a brown solid (0.267 g, 75%), mp 88–91 °C, ν_{max}/cm^{-1} 3285, 2979, 1747, 1371, 1326, 1158 and 797; δ_H (323 K) 1.38–1.43 (9H, br s, C(CH_3)$_3$), 2.50–2.55 (1H, br s, OH), 5.92–5.99 (1H, br s, 1′-H), 6.28 (1H, d, *J* 3.2, 4″-H), 6.39 (1H, dd, *J* 3.2 and 2.9, 3″-H), 6.45–6.54 (2H, m, 2′- and 3′-H), 7.32–7.41 (2H, m, 2″- and 5-H), 7.65 (1H, d, *J* 7.5, 6-H), 8.03 (1H, d, *J* 7.5, 4-H) and 8.29–8.32 (1H, br s, NH); δ_C 28.3 (C(CH_3)$_3$), 70.3 (1′-CHOH), 84.3 (C(CH$_3$)$_3$), 109.6, 111.9, 120.3, 120.5, 125.0 (all CH), 126.4 (C), 127.5, 128.3 (both CH), 130.2 (C), 142.7 (CH), 145.5, 152.2 (both C) and 154.2 (C=O).

1-(*tert*-Butoxycarbonylamino)-7-(1′-hydroxyprop-2′-en-1′-yl)-1*H*-1,2,3-benzotriazole 12

Vinylmagnesium chloride (4 eq. of a 15% solution in THF) was added dropwise to a stirred solution of aldehyde **11**[2] (0.251 g, 1 mmol) in dry ether at 0 °C. TLC analysis showed that the reaction was complete after 5 min. Excess Grignard reagent was destroyed by the dropwise addition of water (10 ml). The organic layer was separated and the aqueous layer extracted with ether (3 × 10 ml). The combined organic solutions were washed with water (10 ml) and brine (10 ml) then dried and evaporated to yield a crude product which was purified by column chromatography (3:7 ether–petrol), followed by recrystallisation from dichloromethane–petrol, to give the *allylic alcohol* **12** as a colourless crystalline solid (0.267 g, 92%), mp 125–127 °C, ν_{max}/cm^{-1} 3392, 2984, 2253, 1749, 1477, 1395, 1371, 1274, 1258, 1100, 990, 912, 804 and 742; δ_H 1.31–1.78 (9H, app br d, C(CH_3)$_3$), 2.88 (1H, s, OH), 5.29–5.32 (2H, m, 2 × 3′-H), 5.73 (1H, app d, *J* 5.0, 1′-H), 6.20 (1H, ddd, *J* 17.2, 10.4 and 4.9, 2′-H), 7.34 (1H, t, *J* 8.2, 5-H), 7.51 (1H, d, *J* 8.2, 6-H), 7.91 (1H, d, *J* 8.2, 4-H) and 8.61 (1H, br s, NH); δ_C 28.5 (C(CH_3)$_3$), 71.1 (1′-CH), 84.2 (C(CH$_3$)$_3$), 117.2 (CH$_2$), 120.6, 124.9 (both CH), 126.3 (C), 127.5 (CH), 130.2 (C), 138.8 (CH), 145.6 (C) and 154.1 (C=O); *m*/*z* (ES) 291 (M$^+$ + 1, 100%), 235 (50) and 179 (24) [Found: C, 57.95; H, 6.38; N, 18.23. $C_{14}H_{18}N_4O_3$ requires C, 57.92; H, 6.25; N, 19.3%].

General oxidation–cyclisation protocol for formation of 1,2-benzodiazepinones 13

The allylic alcohol (*n* mmol) was stirred in dichloromethane (20 ml mmol^{-1}) at ambient temperature; manganese(IV) oxide (3.0 g mmol^{-1}) was added with vigorous stirring. The progress of the reaction was monitored by TLC; after all the starting material had been consumed, the reaction mixture was passed through a plug of Celite, which was then washed with copious dichloromethane. The combined filtrates were dried and evaporated to yield the crude benzodiazepinone which was purified by column chromatography.

4-*N*-(*tert*-Butoxycarbonyl)-5-methyl-4,5,6,7-tetrahydro[1,2,3]-triazolo[4,5,1-*jk*][1,2]benzodiazepin-7-one 13a

Benzotriazole **10a** (0.50 g, 1.6 mmol) was subjected to the general oxidation–cyclisation protocol to yield the *benzodiazepinone* **13a** as colourless crystals (0.45 g, 92%), mp 138–140 °C, ν_{max}/cm^{-1} 2978, 1739, 1674, 1594, 1370, 1297, 1157 and 806; δ_H (300 K) 1.04–1.18 (3H, br d, 5-CH_3), 1.30–1.42 (9H, br s, C(CH_3)$_3$), 3.12 (1H, br d, *J* ~ 17, 6-H$_A$), 3.30 (1H, br d, *J* ~ 17, 6-H$_B$), 4.80–4.97 (1H, br res., 5-H), 7.49 (1H, t, *J* 7.6, 10-H), 8.24 (1H, d, *J* 7.6, 9-H) and 8.29 (1H, d, *J* 7.6, 11-H); δ_H (340 K) 1.21 (3H, d, *J* 7.2, 5-CH_3), 1.37–1.45 (9H, br s, C(CH_3)$_3$), 3.14 (1H, dd, *J* 18.3 and 4.4, 6-H$_A$), 3.32 (1H, dd, *J* 18.3 and 3.8, 6-H$_B$), 4.58 (1H, m, 5-H), 7.51 (1H, app t, *J* 7.9, 10-H), 8.29 (1H, d, *J* 7.9, 9-H) and 8.32 (1H, d, *J* 7.9, 11-H); δ_C (340 K) 19.6 (5-CH_3), 28.3 (C(CH_3)$_3$), 50.2 (CH$_2$), 50.2 (CH), 85.4 (C(CH$_3$)$_3$), 120.1 (C), 125.1, 127.1, 131.0 (all CH), 154.1 and 194.0 (both C=O); *m*/*z* (ES) 303 (M$^+$ + 1, 100%) and 247 (74) [Found: C, 59.30; H, 5.96; N, 18.44. $C_{15}H_{18}N_4O_3$ requires C, 59.59; H, 6.00; N, 18.53%].

4-*N*-(*tert*-Butoxycarbonyl)-5-propyl-4,5,6,7-tetrahydro[1,2,3]-triazolo[4,5,1-*jk*][1,2]benzodiazepin-7-one 13b

Benzotriazole **10b** (0.60 g, 1.8 mmol) was subjected to the general oxidation–cyclisation protocol to yield the *benzodiazepinone* **13b** as colourless crystals (0.54 g, 91%), mp 145–149 °C, ν_{max}/cm^{-1} 2963, 2934, 2874, 1732, 1674, 1596, 1458, 1297, 1294, 1160, 1026 and 1001; δ_H 0.82 (3H, br t, *J* 7.0, 3′-CH_3), 1.10–1.52 (13H, br res., 1′- and 2′-CH$_2$ and C(CH_3)$_3$), 3.20 (1H, br d, *J* ~ 17, 6-H$_A$), 3.30 (1H, br d, *J* ~ 17, 6-H$_B$), 4.62–4.83 (1H, br res., 5-H), 7.58 (1H, t, *J* 7.9, 10-H), 8.31 (1H, d, *J* 7.9, 9-H) and 8.36 (1H, d, *J* 7.9, 11-H); δ_C 13.8 (CH$_3$), 20.2 (CH$_2$), 28.3 (C(CH_3)$_3$), 49.8 (CH$_2$), 53.9 (CH), 85.3 (C(CH$_3$)$_3$), 120.0 (C), 125.1, 127.0 (both CH), 128.9 (C), 131.0 (CH), 145.2 (C), 154.3 and 193.2 (both C=O); *m*/*z* (ES) 331 (M$^+$ + 1, 100%) [Found: C, 62.04; H, 7.01; N, 16.55. $C_{17}H_{22}N_4O_3$ requires C, 61.80; H, 6.71; N, 16.96%].

***trans*-4-*N*-(*tert*-Butoxycarbonyl)-5,6-dimethyl-4,5,6,7-tetrahydro[1,2,3]triazolo[4,5,1-*jk*][1,2]benzodiazepin-7-one 13c**

Benzotriazole **10c** (0.25 g, 0.80 mmol) was subjected to the general oxidation–cyclisation protocol to yield the *benzodiazepinone* **13c** as colourless crystals (0.215 g, 85%), mp 139–143 °C, ν_{max}/cm^{-1} 2980, 2936, 1732, 1676, 1595, 1456, 1371, 1301, 1258, 1157, 1119, 1106 and 1018; δ_H 1.01 (3H, d, *J* 7.4, 5-CH_3), 1.39–1.54 (12H, m, 6-CH$_3$ and C(CH_3)$_3$), 3.21 (1H, br quintet,

$J \sim 6.9$, 6-H), 4.88 (1H, br quintet, $J \sim 6.9$, 5-H), 7.69 (1H, t, J 7.6, 10-H) and 8.31–8.35 (2H, m, 9- and 11-H); δ_C 12.4, 15.3 (both CH_3), 28.8 ($C(CH_3)_3$), 54.2, 56.1 (both CH), 85.8 ($C(CH_3)_3$), 120.7 (C), 125.1, 127.0 (both CH), 129.3 (C), 131.0 (CH), 145.2 (C), 154.7 and 196.0 (both C=O); *m*/*z* (ES) 317 ($M^+ + 1$, 100%), 245 (40) and 240 (42) [Found: $M^+ + 1$, 317.1616. $C_{16}H_{21}N_4O_3$ requires *M*, 317.1614].

4-*N*-(*tert*-Butoxycarbonyl)-5-phenyl-4,5,6,7-tetrahydro[1,2,3]-triazolo[4,5,1-*jk*][1,2]benzodiazepin-7-one 13d

Benzotriazole **10d** (0.25 g, 0.68 mmol) was stirred in dichloromethane (20 ml) at ambient temperature; manganese(IV) oxide (2.3 g) was added with vigorous stirring. The progress of the reaction was monitored by TLC; after 36 h, all the starting material had been converted into *enone* **14a**, a small sample of which showed ν_{max}/cm^{-1} 3258, 2982, 1750, 1660, 1604, 1576, 1494, 1448, 1412, 1273, 1253, 1226, 1158, 1094, 1016, 772 and 697; δ_H 1.32–1.63 (9H, br s, $C(CH_3)_3$), 7.50–7.56 (5H, m, 5 × Ar-H), 7.61 (1H, t, J 7.5, 5-H), 7.99 (1H, d, J 15.6, 2′-H), 8.18 (2H, app d, J 7.5, 4- and 6-H), 8.21–8.30 (1H, br s, NH) and 8.92 (1H, d, J 15.6, 3′-H).

To the enone **14a**, in dichloromethane (20 ml) (*i.e.* the foregoing reaction mixture) was added triethylamine (0.14 ml, 1.5 eq.) and stirring continued for a further 3 h before the mixture was passed through a plug of Celite, which was then washed with copious dichloromethane. The combined filtrates were dried and evaporated to yield a crude product which was purified by column chromatography to yield the *benzodiazepinone* **13d** as yellow crystals (0.189 g, 76%), mp 153–157 °C, ν_{max}/cm^{-1} 2780, 1728, 1673, 1595, 1498, 1450, 1371, 1323, 1292, 1268, 1152, 1076, 1045 and 985; δ_H 1.46–1.64 (9H, br s, $C(CH_3)_3$), 3.67 (1H, br dd, $J \sim 16$ and 3, 6-H_A), 5.05 (1H, br dd, $J \sim 16$ and 3, 6-H_B), 6.12–6.20 (1H, m, 5-H), 7.00–7.19 (4H, m), 7.35 (1H, d, J 7.6, Ar-H), 7.45 (1H, t, J 7.6, 10-H), 8.15 (1H, d, J 7.6, 9-H) and 8.25 (1H, d, J 7.6, 11-H); δ_C 28.3 ($C(CH_3)_3$), 47.2 (CH_2), 85.8 ($C(CH_3)_3$), 119.7 (C), 124.7, 126.7, 126.9, 128.6 (all CH), 128.8 (C), 129.1, 130.7 (both CH), 134.3, 145.2 (both C), 154.2 and 174.0 (both C=O); *m*/*z* (ES) 365 ($M^+ + 1$, 100%), 245 (22) and 240 (20) [Found: $M^+ + 1$, 365.1616. $C_{20}H_{21}N_{40}O_3$ requires *M*, 365.1614].

(*tert*-Butoxycarbonylamino)-7-(3′-furyl-1-oxoprop-2′-en-1′-yl)-1*H*-1,2,3-benzotriazole 14b and 4-*N*-(*tert*-butoxycarbonyl)-5-furyl-4,5,6,7-tetrahydro[1,2,3]triazolo[4,5,1-*jk*][1,2]benzodiazepin-7-one 13e

Benzotriazole **10e** (0.15 g, 0.42 mmol) was stirred in dichloromethane (10 ml) at ambient temperature and manganese(IV) oxide (1.3 g) was added with vigorous stirring. The progress of the reaction was monitored by TLC and after 36 h, all the starting material had been converted into *enone* **14b**. An aliquot was removed from the reaction mixture, filtered and evaporated to leave a residue which showed: δ_H 1.32–1.35 (9H, br s, $C(CH_3)_3$), 6.51 (1H, dd, J 3.3 and 1.8, Ar-H), 6.74 (1H, dd, J 3.3 and 1.8, Ar-H), 7.32 (1H, d, J 15.5, 3′-H), 7.46–7.53 (3H, m, 2′-, 5- and Ar-H), 7.95 (1H, d, J 7.1, 6-H), 8.23 (1H, d, J 7.1, 4-H) and 8.51 (1H, s, NH); δ_C 28.3 ($C(CH_3)_3$), 83.7 ($C(CH_3)_3$), 113.4, 118.0, 121.1, 124.4 (all CH), 124.6 (C), 125.3 (CH), 130.1 (C), 130.2, 133.1, 146.2 (all CH), 151.1 (C), 153.7 and 189.7 (both C=O).

To the remaining reaction mixture, triethylamine (0.08 ml, 1.5 eq.) was then added and stirring was continued for a further 3 h before the mixture was passed through a plug of Celite and the residue was washed with copious dichloromethane. The combined filtrates were dried and evaporated to yield a crude product which was purified by column chromatography to yield the *benzodiazepinone* **13e** as yellow crystals (0.12 g, 78%), mp 153–157 °C, ν_{max}/cm^{-1} 2984, 1732, 1674, 1595, 1373, 1284, 1251 and 1153; δ_H 1.42–1.50 (9H, br s, $C(CH_3)_3$), 3.52 (1H, dd, J 12.0 and 3.5, 6-H_A), 3.58 (1H, dd, J 12.0 and 3.5, 6-H_B), 5.85–5.89 (2H, m, 2 × furyl-β-H), 5.96–5.99 (1H, m, 5-H), 7.01–7.04 (1H, m, Ar-H), 7.47 (1H, t, J 7.4, 10-H), 8.22 (1H, d, J 7.4, 9-H) and 8.28 (1H, d, J 7.4, 11-H), *m*/*z* (ES) 355 ($M^+ + 1$, 100%) and 298 (24) [Found: $M^+ + 1$, 355.1407. $C_{18}H_{19}N_4O_4$ requires *M*, 355.1406].

4-*N*-(*tert*-Butoxycarbonyl)-4,5,6,7-tetrahydro[1,2,3]triazolo-[4,5,1-*jk*][1,2]benzodiazepin-7-one 13f

Benzotriazole **12** (1.00 g, 3.4 mmol) was subjected to the general oxidation–cyclisation protocol to yield the parent *benzodiazepinone* **13f** as colourless crystals (0.93 g, 95%), mp 164–167 °C, ν_{max}/cm^{-1} 2984, 2926, 1739, 1675, 1594, 1398, 1313, 1242 and 1153; δ_H 1.47–1.62 (9H, br s, $C(CH_3)_3$), 3.28–3.42 (2H, app br s, 6-CH_2), 4.05–4.42 (2H, app br s, 5-CH_2), 7.58 (1H, t, J 7.8, 10-H), 8.32 (1H, d, J 7.8, 9-H) and 8.41 (1H, d, J 7.8, 10-H); δ_H (330 K) 1.47–1.50 (9H, br s, $C(CH_3)_3$), 3.30 (2H, app br t, J 5.4, 6-CH_2), 4.12–4.26 (2H, m, 5-CH_2), 7.56 (1H, t, J 7.8, 10-H), 8.33 (1H, d, J 7.8, 9-H) and 8.35 (1H, d, J 7.8, 11-H); δ_C 28.4 ($C(CH_3)_3$), 44.4, 45.2 (both CH_2), 85.5 ($C(CH_3)_3$), 119.6 (C), 125.1, 127.1 (both CH), 128.4 (C), 131.1 (CH), 145.5 (C), 153.7 and 194.5 (both C=O); *m*/*z* (ES) 289 ($M^+ + 1$, 100%), 233 (24) and 142 (29) [Found: C, 58.13; H, 5.41; N, 19.14. $C_{14}H_{16}N_4O_3$ requires C, 58.33; H, 5.59; N, 19.14%].

1-(*tert*-Butoxycarbonylamino)-7-(1′-acetyloxyprop-2′-en-1′-yl)-1*H*-1,2,3-benzotriazole 16a

Acetic anhydride (0.5 ml, ~5 mmol) was added to benzotriazole **12** (0.291 g, 1 mmol) in dichloromethane (10 ml) containing 4-(*N*,*N*-dimethylamino)pyridine (~5 mg). The reaction mixture was stirred overnight and diluted with dichloromethane (20 ml). The resulting solution was washed with water (10 ml) and brine (10 ml), then dried and evaporated to give a brown solid which was recrystallised from dichloromethane–petrol to yield the *acetate* **16a** as a beige crystalline solid (0.256 g, 77%), mp 116–118 °C, ν_{max}/cm^{-1} 3274, 2982, 1731, 1496, 1395, 1254, 1159, 1052, 993, 929 and 750; δ_H 1.32–1.54 (9H, br s, $(C(CH_3)_3)$), 2.10 (3H, s, $CH_3C(O)O$), 5.26 (1H, d, J 17.2, 3′-H_A), 5.31 (1H, d, J 10.5, 3′-H_B), 6.11 (1H, ddd, J 17.2, 10.5 and 5.1, 2′-H), 6.93 (1H, d, J 5.1, 1′-H), 7.40 (1H, t, J 7.6, 5-H), 7.58 (1H, d, J 7.6, 6-H), 8.04 (1H, d, J 7.6, 4-H) and 8.44–8.56 (1H, br s, NH); δ_C 21.6 ($CH_3C(O)O$), 28.5 ($C(CH_3)_3$), 70.4 (CHOAc), 84.3 ($C(CH_3)_3$), 118.4 (CH_2), 121.2 (CH), 122.5 (C), 125.0 (CH), 128.9 (C), 135.4 (CH), 145.4 (C), 153.5 and 170.4 (both C=O); *m*/*z* (APCI) 333 ($M^+ + 1$, 100%) [Found: C, 58.02; H, 6.39; N, 16.73. $C_{16}H_{20}N_4O_4$ requires C, 57.82; H, 6.07; N, 16.87%].

(*E*)-1-(*tert*-Butoxycarbonylamino)-7-(1′-acetyloxyhex-2′-en-1′-yl)-1*H*-1,2,3-benzotriazole 16c

Benzotriazole **10b** (0.33 g, 1 mmol) was subjected to the foregoing acetylation conditions to give the *acetate* **16c** as a light brown, crystalline solid (0.281 g, 75%); δ_H 0.76 (3H, t, J 8.1, 6′-CH_3), 1.10–1.54 (11H, br m, 5′-CH_2 and $C(CH_3)_3$), 1.86 (2H, app q, J 7.6, 4′-CH_2), 1.99 (3H, s, $CH_3(O)O$), 5.65–5.78 (2H, m, 2′- and 3′-H), 6.80 (1H, d, J 5.7, 1′-CHOAc), 7.30 (1H, t, J 7.2, 5-H), 7.49 (1H, d, J 7.2, 6-H), 7.91 (1H, d, J 7.2, 4-H) and 8.40–8.46 (1H, br s, NH); δ_C 14.1, 21.7 (both CH_3), 22.3 (CH_2), 28.5 ($C(CH_3)_3$), 34.7 (5′-CH_2), 70.4 (1′-CHOAc), 84.2 ($C(CH_3)_3$), 120.8, 124.7, 125.0 (all CH), 126.5, 129.7 (both C), 120.7, 135.2 (both CH), 145.3 (C), 153.6 and 162.1 (both C=O).

(*E*)-1-(*tert*-Butoxycarbonylacetamido)-7-(1′-acetyloxy-2′-methylbut-2′-en-1′-yl)-1*H*-1,2,3-benzotriazole 20a

Benzotriazole **10c** (0.319 g, 1 mmol) was subjected to the foregoing acetylation conditions to give the *bis(acetate)* **20a** as a light brown crystalline solid (0.281 g, 72%), mp 128–131 °C, ν_{max}/cm^{-1} 2982, 1744, 1430, 1371, 1289, 1228, 1146, 1028, 916,

835 and 750; δ_H 1.36 (9H, s, C(CH_3)$_3$), 1.68 (1H, s, 3′-CH_3), 1.72 (3H, d, *J* 9.0, 4′-CH_3), 2.16 (3H, s, CH_3C(O)O), 2.60 (3H, s, CH_3C(O)N), 5.38 (1H, q, *J* 9.0, 3′-H), 6.42 (1H, s, 1′-H), 7.41 (1H, t, *J* 7.8, 5-H), 7.56 (1H, d, *J* 7.8, 6-H) and 8.05 (1H, d, *J* 7.8, 4-H); δ_C 13.8, 14.1, 21.5, 25.8 (all CH_3), 27.9 (C(CH_3)$_3$), 79.6 (CH), 87.4 (C(CH_3)$_3$), 120.8 (CH), 122.3 (C), 125.0, 125.9, 127.7 (all CH), 130.3, 132.9, 145.4 (all C), 150.2, 169.2 and 170.0 (all C=O); *m*/*z* (ES) 403 (M^+ + 1, 100%) and 303 (24).

(*E*)-1-(*tert*-Butoxycarbonylacetamido)-7-(1′-acetyloxy-3′-phenylprop-2-en-1′-yl)-1*H*-1,2,3-benzotriazole 20b

Benzotriazole **10d** (0.37 g, 1 mmol) was subjected to the foregoing acetylation conditions to give the *bis(acetate)* **20b** as a brown crystalline solid (0.35 g, 78%), mp 120–123 °C, ν_{max}/cm^{-1} 3463, 3230, 2960, 1744, 1648, 1457, 1371, 1252, 1160, 1106, 1021, 951, 802 and 751; δ_H 1.22 (9H, s, C(CH_3)$_3$), 2.02 (3H, s, CH_3C(O)O), 2.45 (3H, s, CH_3C(O)N), 6.19 (1H, dd, *J* 15.4 and 5.3, 2′-H), 6.37 (1H, app d, *J* 15.4, 3′-H), 6.70 (1H, d, *J* 5.3, 1′-H), 7.13–7.29 (5H, m, 5 × Ar-H), 7.32 (1H, t, *J* 7.2, 5-H), 7.55 (1H, d, *J* 7.2, 6-H) and 7.98 (1H, d, *J* 7.2, 4-H); δ_C 21.1, 25.9 (both CH_3), 27.9 (C(*C*H_3)$_3$), 70.7 (1′-CHOAc), 87.4 (*C*(CH_3)$_3$), 119.9, 121.2 (both CH), 122.6 (C), 125.9, 127.2, 128.1, 128.5, 128.8, 129.0, 129.1, 135.8 (all CH), 135.8, 144.5 (both C), 150.1, 169.5 and 169.9 (all C=O); *m*/*z* (ES) 451 (M^+ + 1, 100%) and 351 (30).

General protocol for the palladium catalysed formation of 4,5-dihydrobenzodiazepines 17

Acetate **16** (*n* mmol, 1 eq.) in THF (10 ml $mmol^{-1}$) was stirred under nitrogen with anhydrous potassium carbonate (1 eq.) at ambient temperature. Tetrakis(triphenylphosphine)-palladium(0) (20 mol%) was added as a solution in THF (5 ml $mmol^{-1}$). The resulting mixture was stirred at ambient temperature until TLC analysis showed complete consumption of starting material. Water (10 ml $mmol^{-1}$) was added and stirring continued for 2 h. The organic layer was separated and the aqueous layer extracted with ether (2 × 10 ml $mmol^{-1}$). The combined organic solutions were washed with water (10 ml $mmol^{-1}$) and brine (10 ml $mmol^{-1}$), then dried and evaporated to give a crude product which was subjected to column chromatography (eluent, 1 : 4 ether–petrol).

4-*N*-(*tert*-Butoxycarbonyl)-4,5-dihydro[1,2,3]triazolo[4,5,1-*jk*]-[1,2]benzodiazepine 17a

Acetate **16a** (0.250 g, 0.67 mmol) was subjected to the general palladium cyclisation protocol to yield the *1,2-benzodiazepine* **17a** as an orange crystalline solid (0.095 g, 52%), mp 120–123 °C, ν_{max}/cm^{-1} 2978, 1742, 1435, 1405, 1370, 1240, 1153, 1012, 850, 813 and 748; δ_H 1.25–1.49 (9H, br s, C(CH_3)$_3$), 3.98 (1H, app d, *J* 16.6, 5-H_A), 4.92 (1H, dd, *J* 16.6 and 6.8, 5-H_B), 6.31 (1H, dd, *J* 11.3 and 6.8, 6-H), 6.80 (1H, dd, *J* 11.3 and 1.6, 7-H), 7.35–7.40 (2H, m, 9- and 10-H) and 7.95 (1H, dd, *J* 7.2 and 4.8, 11-H); δ_C 28.2 (C(*C*H_3)$_3$), 50.5 (CH_2), 84.6 (*C*(CH_3)$_3$), 119.8 (CH), 121.4 (C), 125.4, 128.2, 130.1, 130.5 (all CH), 130.6, 144.9 (both C) and 155.5 (C=O); *m*/*z* (APCI) 273 (M^+ + 1, 52%) and 217 (100) [Found: M^+ + 1, 273.1384. $C_{14}H_{17}N_4O_2$ requires *M*, 273.1351].

4-*N*-(*tert*-Butoxycarbonyl)-5-methyl-4,5-dihydro[1,2,3]-triazolo[4,5,1-*jk*][1,2]benzodiazepine 17b

The acetate **16b** was prepared by the general procedure and used directly in the cyclisation. Acetate **16b** (0.250 g, 0.64 mmol) was subjected to the general palladium cyclisation protocol to yield the *1,2-benzodiazepine* **17b** as an orange crystalline solid (0.098 g, 54%), mp 120–124 °C, ν_{max}/cm^{-1} 2962, 2926, 2854, 1739, 1674, 1595, 1459, 1365, 1266 and 1158; δ_H 1.20 (3H, d, *J* 11.6, 5-CH_3), 1.35–1.40 (9H, br s, C(CH_3)$_3$), 5.28–5.36 (1H, m, 5-H), 6.33 (1H, dd, *J* 11.3 and 6.8, 6-H), 6.68 (1H, d, *J* 11.3, 7-H), 7.32–7.42 (2H, m, 9- and 10-H) and 7.95 (1H, d, *J* 7.2, 11-H); δ_C 17.9 (CH_3) 31.3 (C(*C*H_3)$_3$), 82.8 (*C*(CH_3)$_3$), 118.2, 119.3, 124.1 (all CH), 125.0 (C), 125.6, 126.3 (both CH), 130.5, 144.2 (both C) and 154.7 (C=O) [Found: M^+ + 1, 287.1511. $C_{15}H_{19}N_4O_2$ requires *M*, 287.1508].

4-*N*-(*tert*-Butoxycarbonyl)-5-propyl-4,5-dihydro[1,2,3]triazolo-[4,5,1-*jk*][1,2]benzodiazepine 17c

Acetate **16c** (0.208 g, 0.5 mmol) was subjected to the general palladium cyclisation protocol to yield the *1,2-benzodiazepine* **17c** as an orange crystalline solid (0.092 g, 59%), mp 125–128 °C, ν_{max}/cm^{-1} 2961, 2873, 1738, 1504, 1456, 1370, 1290, 1257, 1156, 1117, 1040, 841, 813 and 749; δ_H 0.88 (3H, t, *J* 7.4, 3′-CH_3), 1.22–1.47 (13H, m, 1′- and 2′-CH_2 and C(CH_3)$_3$), 5.12–5.20 (1H, m, 5-H), 6.34 (1H, dd, *J* 11.6 and 6.8, 6-H), 6.65 (1H, d, *J* 11.6, 7-H), 7.32–7.41 (2H, m, 9- and 10-H) and 7.93 (1H, d, *J* 7.7, 11-H); δ_C 12.5 (CH_3), 26.7 (CH_2), 27.8 (C(*C*H_3)$_3$), 26.7, 32.1 (CH_2), 82.8 (*C*(CH_3)$_3$), 118.0, 119.7, 124.0 (all CH), 125.0 (C), 125.4, 126.4 (both CH), 130.1, 144.1 (both C) and 154.4 (C=O); *m*/*z* (APCI) 315 (M^+ + 1, 47%), 279 (96) and 199 (100) [Found: M^+ + 1, 315.1819. $C_{17}H_{23}N_4O_2$ requires *M*, 315.1821].

Acknowledgements

We are grateful to the EPSRC Mass Spectrometry Service at University College, Swansea for the provision of high resolution mass spectral data, to Mrs F. Godwin for helpful assistance and to Cardiff University for financial support.

References

1 *Comprehensive Medicinal Chemistry*, ed. P. G. Sammes, Pergamon Press, Oxford, 1990; R. Silverman, *The Organic Chemistry of Drug Design and Drug Action*, Academic Press, 1992; *Burger's Medicinal Chemistry and Drug Discovery*, ed. M. E. Wolff, J. Wiley and Sons, Chichester, 1997.
2 M. A. Birkett, D. W. Knight, P. B. Little and M. B. Mitchell, *Tetrahedron*, 2000, **56**, 1013; D. W. Knight and P. B. Little, *J. Chem. Soc.*, *Perkin Trans. 1*, 2000, 2343.
3 For a preliminary communication, see D. W. Knight and P. B. Little, *Tetrahedron Lett.*, 1997, **38**, 5037.
4 J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.*, 1952, 1094.
5 S. Godleski, *Comprehensive Organic Synthesis*, Pergamon Press, Oxford, 1991, **4**, 585; J. Tsuji, *Palladium Reagents and Catalysts*, J. Wiley and Sons, Chichester, 1995; C. G. Frost, J. Howarth and J. M. J. Williams, *Tetrahedron: Asymmetry*, 1992, **3**, 1089.
6 G. J. Dawson, J. F. Bower and J. M. J. Williams, *Contemp. Org. Synth.*, 1996, **3**, 4.