Directed deprotonation of 7-methyl-1-aminobenzotriazole: an approach to *ortho*-substituted benzyne precursors

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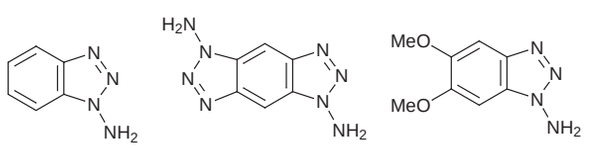
Lateral deprotonation of *N*-Boc-1-amino-7-methylbenzotriazole 7 using BuLi–TMEDA leads to the synthetically useful dianion 18, which can be alkylated and which condenses smoothly with a range of aldehydes, ketones and epoxides to provide derivatives (19, 20 and 21 respectively), which are potentially useful in the generation of substituted benzynes.

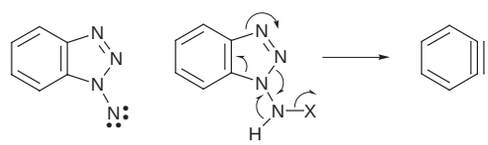
The chemistry of benzynes is now sufficiently well understood that, despite their high reactivity, these intermediates have found many applications in synthesis.[1] Methods for their generation are based upon a wide variety of elimination reactions, ranging from the classical elimination of 'HX' from a halobenzene and many more recently developed but related benzenoids,[1,2] to the regiocontrolled, overall removal of halogen from a 1,2-dihalobenzene and the disintegration of anthranilic acid upon diazotization. Other regiospecific methods feature chemical- or light-induced decomposition of a range of benzo-fused heterocycles, such as phthaloyl peroxide, diazalactones and benzocyclobutanedione. Of these, perhaps the most popular is 1-aminobenzotriazole **1**, probably because it is more stable than many of the foregoing intermediates. As has recently been pointed out,[2] a serious drawback in this area in general is the lack of short routes to such benzyne precursors, especially when these are substituted. Some relatively complex precursors have been prepared,[3] but these are often derived from bromobenzenes and regioselectivity problems can arise, both during their synthesis as well as in the key benzyne trapping step. In the specific case of 1-aminobenzotriazole derivatives, Hart's group have prepared the double derivative **2** and have successfully used it to effectively generate bis-benzyne, although most likely this and subsequent trapping reactions occur in a stepwise manner.[4] The symmetrical aminobenzotriazole **3** has been used



1 **2** **3**

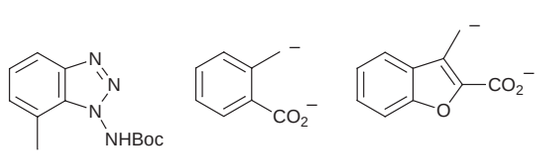
as a precursor during an approach to benzo[*c*]phenanthridines which featured trapping the benzyne with a vinyl isocyanate.[5] A few other simple derivatives have been prepared by Campbell and Rees (see below).[6]

A further attraction of using 1-aminobenzotriazole **1** as a benzyne precursor is the generally very mild, essentially neutral and anhydrous conditions required to effect fragmentation. Generally, exposure to an oxidizing agent such as lead(IV) acetate, *N*-bromosuccinimide, nickel peroxide or iodobenzene diacetate, at temperatures as low as −78 °C is sufficient. Originally,[6] it was suggested that these oxidations generated the nitrene **4** which rapidly disintegrated with the loss of two molecules of nitrogen to give benzyne; however, an equally plausible mechanism in many instances involves formation of an *N*-substituted derivative (**5**; X = Br, OAc) which then decomposes as indicated to give benzyne **6**. These methods are also effective for the generation of higher homologues such as 2,3-dehydronaphthalene and dehydrophenanthrene[7] and even 1,8-didehydronaphthalene, a 1,3-diradical form of *meta*-naphthyne.[8] Similar mechanisms lead to benzyne **6** from other 1-aminobenzotriazole derivatives, but by formation of a nitrogen-centred anion, rather than by oxidation; examples include the decomposition of the lithium salt of 1-(benzotriazolyl)-4-tosyltetrazene[9] and photoinduced elimination from lithium 1-tosylamidobenzotriazole.[10] Another approach, designed to proceed *via* nitrene **4** features deoxygenation of 1-nitrosobenzotriazole using ethyl diphenylphosphinite.[11]



4 **5** **6**

It was against this background that we wondered whether it would be possible to deprotonate the 7-methylbenzotriazole derivative **7** to give a synthetically useful dianionic species. The reasoning behind this was on two counts. Firstly, a deprotonated *N*-*tert*-butoxycarbonyl (Boc) function is well established as a powerful directing group for metallation, often referred to as a remote directing effect, which has found many useful applications.[12] In principle, other amine protecting groups could be used, but the Boc function has the dual attractions of ease of removal and, crucially, a quaternary carbon centre adjacent to the carboxylate group, hence excluding the possibility of deprotonation at this site, in contrast to most other such derivatives. Secondly, 'benzylic' methyl groups, when deprotonated, tend to provide highly nucleophilic and less basic carbanions than, for example, the corresponding aryl carbanions.[13] This is amply demonstrated by the utility of the toluic acid dianion **8**,[14] the inspiration behind our development of the related benzofurancarboxylic acid dianion **9**.[15] Herein, we report in full on our experiments in pursuit of this idea.[16]



7 **8** **9**

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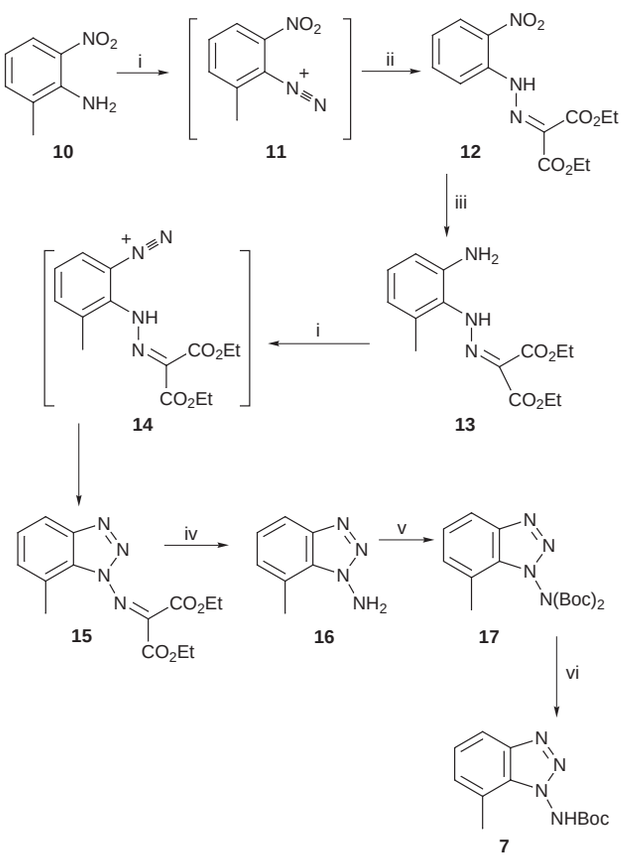
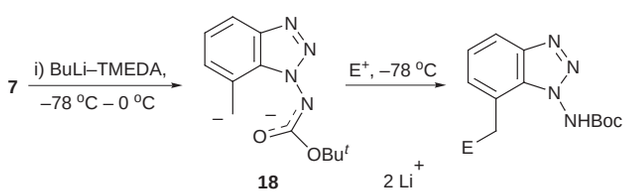
The required *N*-Boc-1-aminobenzotriazole **7** was prepared, following the route described by Campbell and Rees[6] but with some modifications, as outlined in Scheme 1. Diazotization of



Scheme 1 *Reagents*: (i) $NaNO_2$, HCl, 0 °C; (ii) $CH_2(CO_2Et)_2$, NaOAc, H_2O, 5 °C; (iii) 10% Pd-C, *c*-C_6H_{10}, EtOH, 80 °C; (iv) 10 M HCl (aq.), MeOH, 50 °C; (v) $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2, 20 °C; (vi) 2 M NaOH (aq.), MeOH, 50 °C

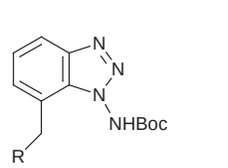
the commercial nitroaniline **10** and immediate trapping of the resulting diazonium salt **11** in a buffered, aqueous emulsion of diethyl malonate led to good yields of the iminomalonate **12**. A later modification wherein the buffer was potassium carbonate did not provide any benefit in this case.[17] Subsequent reduction of the nitro group using the original method (1 atmosphere H_2, 10% Pd–C, MeOH) did not go to completion in our hands; while use of higher hydrogen pressures (*e.g.* 80 atmospheres) solved this problem, yields of the amine **13** were not high, due to over-reduction. Rigby's modification[17] using platinum oxide was an improvement but we found that transfer hydrogenation, as reported by Johnstone,[18] using a combination of 10% Pd–C and cyclohexene in boiling ethanol to be especially efficient and convenient in leading cleanly to amine **13**. Following the original method,[6] this was then diazotized; the resulting salt **14** underwent rapid cyclization to give the protected aminobenzotriazole **15** in excellent yield. In our hands, the final hydrolysis gave poor conversions under the original conditions (10 M hydrochloric acid, 20 °C); by adding methanol and warming to 50 °C, however, excellent yields of the benzotriazole **16** were secured. Exposure of this amine to di-*tert*-butyl dicarbonate [Boc anhydride, $(Boc)_2O$] under the usual conditions led not to the expected *N*-Boc derivative **7**, but rather to the bis-Boc adduct **17**; when one equivalent of the dicarbonate was used, a mixture of the bis-adduct **17** and starting amine **16** was obtained, indicating, not unreasonably, that the amino group is especially nucleophilic. Such bis-carbamates are well-established species;[19] fortunately, in this case, selective removal of one of the Boc groups could be achieved by hydrolysis using 2 M sodium hydroxide in aqueous methanol at 50 °C to deliver a good overall yield of the required mono-Boc intermediate **7**.

Initial trials of the key metallation step, aimed at generating dianion **18**, were run using iodomethane as electrophile. We were unsure as to whether selective carbon alkylation would be possible, especially in view of the evident nucleophilicity of the neutral *N*-Boc function. In any event, ^1H NMR analysis was sufficient to determine if *C*-metallation and subsequent methylation had occurred. In the event, despite some promising colour changes, both *n*- and *sec*-butyllithium in tetrahydrofuran at various temperatures only provided low (~10%) conversions to the 7-ethyl derivative **19a**, as did Schlösser's base [KOBu^t, BuLi].[20] At −78 °C, the more powerful base combination of butyllithium and tetramethylethylenediamine [TMEDA] in THF was equally ineffective but, on warming to −40 °C, a much higher conversion, but to a mixture of both *C*- and *N*-methylated products, was observed. A set of optimum conditions (Scheme 2) turned out to be deprotonation using this base

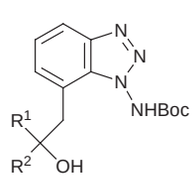


Scheme 2

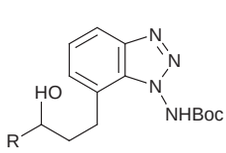
system between −78 and 0 °C followed by re-cooling to −78 °C, at which temperature, selective *C*-methylation was essentially complete and led to a 95% isolated yield of the 7-ethyl derivative **19a**. Above 0 °C, much lower yields were obtained, indicating that the dianion **18** is unstable in THF above this temperature. Alkylation with iodoethane was also successful and regioselective, giving the 7-propyl derivative **19b** in 90% yield, indicating that the dianion **18** will be suitable for the elaboration of many other 7-alkyl derivatives. High regioselection was also found with the more reactive alkyl bromide, leading to the butenyl derivative **19c** in 85% isolated yield; at higher temperatures, *N*-allylation became a significant side reaction.



19a R = Me;
b R = Et;
c R = $CH_2CH{=}CH_2$



20a R^1 = Ph; R^2 = H;
b R^1 = 2-furyl; R^2 = H;
c R^1 = C_5H_{11}; R^2 = H;
d R^1 = $CH{=}C(Me)(CH_2)_2CH{=}CMe_2$; R^2 = H
e R^1 = R^2 = Me;
f R^1 = R^2 = c-$(CH_2)_5$



21a R = Et;
b R = Me; [(*S*)–enant]
c R = Ph [(*R*)–enant]

Perhaps not surprisingly, condensations of dianion **18** with aromatic aldehydes proceeded very smoothly to give the alcohols **20a** and **20b** from benzaldehyde and furan-2-carbaldehyde respectively, in high yields. More significantly, condensations with hexanal and citral also led to the expected products (**20c** and **20d**), although in slightly reduced yields, possibly due to competing enolization. Despite this, condensations with two enolizable ketones, acetone and cyclohexanone, were efficient,

giving the homologous alcohols **20e** and **20f** in good yields. Finally, the dianion **17** is evidently highly nucleophilic as it is also alkylated by monosubstituted epoxides with the expected regiospecificity. Although a little slower than condensations with carbonyls, such couplings gave excellent yields of the alcohols **21**, without the need to add a typical epoxide activator, such as a Lewis acid. This is fortunate in the case of styrene oxide as, presumably, such an activator would seriously compromise the regioselectivity of this homologation.

This method is therefore another exemplification of the utility of the *N*-Boc function in remote directed metallation and has provided a contribution to methodology for the preparation of some functionalized benzyne precursors which were previously very difficult to obtain. The use of the aminobenzotriazole adducts reported herein for the synthesis of dihydrobenzofurans and chromans, by intramolecular trapping of the derived benzynes by the hydroxy groups, has been reported by us in brief,[21] suggesting that this methodology will have a number of applications in this area.

Experimental

General details

Infra-red spectra were obtained using a Perkin-Elmer 1720 FTIR spectrometer using liquid films on sodium chloride plates or, if solids, chloroform solutions. ^{1}H NMR spectra were obtained using a Perkin-Elmer R32a instrument operating at 90 MHz (90) or a Bruker WM-250 instrument operating at 250 MHz. A JEOL EX270 spectrometer operating at 67.5 MHz was used to obtain ^{13}C NMR spectra. All spectra were recorded using dilute solutions in deuteriochloroform, with tetramethylsilane as the internal standard, *J* values are given in Hz. Mass spectra were obtained in the EI mode using either an AEI MS 902 or a VG 7070E instrument operating at 70 eV. Unless stated otherwise, all reactions were performed under dry nitrogen and all organic solutions from aqueous work-ups were dried by brief exposure to anhydrous magnesium sulfate followed by filtration. CC refers to column chromatography using silica gel [SORBSIL® C60-H (40–60 mm)] and the eluents specified. Petrol refers to light petroleum with bp 60–80 °C.

Diethyl 2-[(2′-amino-6′-methylphenyl)hydrazono]propanedioate 13

To a stirred suspension of 10% palladium on charcoal (0.5 g) in ethanol (75 ml) at ambient temperature was added portionwise diethyl 2-[(2′-nitro-6′-methylphenyl)hydrazono]propanedioate **12**[6] (10.0 g, 31 mmol) followed by cyclohexene (15.26 g, 186 mmol).[18] The resulting mixture was stirred and refluxed for 1.75 h then allowed to cool to ambient temperature and filtered through Celite. The solid was washed with ethanol (2 × 50 ml) and the combined filtrates cooled to 0 °C. The resulting suspension was filtered to give the *amine* **13** (5.51 g, 61%) as orange crystals, mp 103–104 °C (lit.,[6] mp 100–101 °C); δ_H 1.59 (3H, t, *J* 7.1, CH_3), 1.66 (3H, t, *J* 7.1, CH_3), 2.60 (3H, s, 6′-CH_3), 4.33 (2H, q, *J* 7.1, OCH_2), 4.43 (2H, q, *J* 7.1, OCH_2), 5.57 (2H, br s, NH), 6.52 (1H, dd, *J* 7.8 and 1.0, 5′-H), 6.61 (1H, dd, *J* 7.8 and 1.0, 3′-H), 6.82 (1H, dd, *J* 7.8 and 7.8, 4′-H) and 13.54 (1H, br s, NH).

1-Amino-7-methylbenzotriazole 16

Diazotization of the foregoing amine, as described by Campbell and Rees,[6] gave the iminylbenzotriazole **15**, mp 67–68 °C (lit.,[6] mp 64–65 °C) in 75–80% yield, on a 5–10 g scale. To a stirred solution of the iminylbenzotriazole **15** (8.52 g, 28 mmol) in methanol (200 ml) stirred and heated to 50 °C was added concentrated hydrochloric acid (10 M, 50 ml). After 3.5 h at this temperature, the solution was cooled and the solvents evaporated. The residue was taken up in 2 M hydrochloric acid (300 ml) and the resulting solution washed with diethyl ether (3 × 20 ml), then neutralized using solid sodium carbonate and extracted with diethyl ether (3 × 150 ml). The combined extracts were dried and evaporated and the residue crystallized from toluene to give the *amine* **16** (3.45 g, 83%) as an amorphous, colourless powder, mp 116–118 °C (lit.,[6] mp 116–118 °C); δ_H 2.90 (3H, s, 7-CH_3), 5.88 (2H, br s, NH_2), 7.32–7.38 (2H, m, 5- and 6-H) and 7.90 (1H, dd, *J* 6.6 and 2.1, 4-H); *m/z* 148 (M^+, 7%), 120 (25), 119 (26), 92 (14), 91 (100), 77 (14), 65 (40) and 51 (21).

1-[Bis(*tert*-butoxycarbonyl)amino]-7-methylbenzotriazole 17

To a stirred solution of the aminobenzotriazole **16** (1.00 g, 6.76 mmol), triethylamine (1.50 g, 15 mmol) and 4-dimethylaminopyridine (50 mg) in dry dichloromethane (40 ml) maintained at 0 °C was added dropwise a solution of di-*tert*-butyl dicarbonate (3.24 g, 15 mmol) in dichloromethane (1 ml). The resulting solution was stirred for 48 h without further cooling then poured into saturated aqueous sodium hydrogen carbonate (10 ml). The separated organic layer was washed with water (10 ml) and brine (10 ml) then dried and evaporated to leave a brown gum which was crystallized from hexane–ethyl acetate (1:1) to give the bis-*Boc derivative* **17** (2.10 g, 89%) as an amorphous, colourless powder, mp 113–115 °C; ν_{max}/cm^{-1} 2933, 1807, 1774, 1613, 1458, 1372, 1346, 1309, 1145, 1125, 996, 862 and 842; δ_H 1.38 (18H, s, 2 × Bu^t), 2.49 (3H, s, 7-CH_3), 7.23–7.27 (2H, m, 5- and 6-H) and 7.85–7.89 (1H, m, 4-H); δ_C 15.92 (7-CH_3), 27.64 [2 × C(*C*H_3)$_3$], 85.75 [2 × *C*(CH$_3$)$_3$], 118.17 (CH), 119.91 (C), 124.67 (CH), 129.70 (CH), 130.93 (C), 144.37 (C) and 148.70 (2 × CO); *m/z* (FAB) 349 (M^+ + H, 7%), 249 (7) and 149 (100) (Found: C, 58.5; H, 7.2; N, 16.0. $C_{17}H_{24}N_4O_4$ requires C, 58.6; H, 7.0; N, 16.1%).

1-(*tert*-Butoxycarbonyl)amino-7-methylbenzotriazole 7

To a stirred solution of the foregoing bis-Boc benzotriazole **17** (2.21 g, 6.34 mmol) in methanol (40 ml) maintained at 50 °C was added 2 M aqueous sodium hydroxide (5 ml). After 40 min, the solvent was evaporated and the brown residue dissolved in dichloromethane (50 ml). The resulting solution was washed with water (20 ml) and brine (20 ml) then dried and evaporated to leave a yellow solid. CC [petrol–ethyl acetate (3:1)] gave the mono-*Boc derivative* **7** (1.47 g, 98%) as an oil which solidified upon high-vacuum drying to give an amorphous, colourless powder, mp 105–106 °C; ν_{max}/cm^{-1} 3404, 2931, 1755, 1611, 1457, 1155, 1117, 1064, 1014, 907 and 867; δ_H 1.45 (9H, br s, Bu^t), 2.62 (3H, s, 7-CH_3), 7.22–7.30 (2H, m, 5- and 6-H), 7.82–7.87 (1H, m, 4-H) and 8.35 (1H, br s, NH); δ_C 16.05 (7-CH_3), 27.91 [C(*C*H_3)$_3$], 83.40 [*C*(CH$_3$)$_3$], 117.56 (CH), 120.88 (C), 124.56 (C), 129.51 (CH), 131.30 (C), 144.28 (C) and 153.69 (CO); *m/z* (FAB) 249 (M^+ + H, 100%), 149 (95) and 134 (47) (Found: C, 58.2; H, 6.7; N, 22.8. $C_{12}H_{16}N_4O_2$ requires C, 58.1; H, 6.5; N, 22.6%).

Metallation and homologation of 1-(*tert*-butoxycarbonyl)amino-7-methylbenzotriazole 7: general procedure

Butyllithium (1.6 M in hexanes, 2.2 equiv.) was added to a stirred solution of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, 2.2 equiv.) in dry tetrahydrofuran (10 ml mmol^{-1} of benzotriazole **7**) maintained below −70 °C in a solid carbon dioxide–acetone bath. After 0.25 h, a solution of the benzotriazole **7** (1 equiv.) in dry tetrahydrofuran (1 ml mmol^{-1}) was added dropwise *via* syringe. The resulting burgundy-red solution was stirred for 5 min then allowed to warm to 0 °C and kept at this temperature for 0.5 h, to complete formation of dianion **18**, before recooling to below −70 °C. A solution of the electrophile (1.1 equiv.) in dry tetrahydrofuran (1 ml mmol^{-1}) was then added. Unless otherwise stated, the resulting solution was stirred at this temperature for 1 h then quenched by the addition of saturated aqueous ammonium chloride (10 ml mmol^{-1}) and allowed to warm to ambient temperature. The solution was then acidified using 2 M hydrochloric acid and extracted with diethyl ether (3 × 30 ml mmol^{-1}). The combined extracts were dried and evaporated and the residue subjected to

column chromatography, typically using petrol–ethyl acetate (3 : 1) as eluent.

1-(*tert*-Butoxycarbonyl)amino-7-ethylbenzotriazole 19a

By the general procedure, treatment of dianion **18** generated from benzotriazole **7** (0.050 g, 0.2 mmol) with dry iodomethane (0.014 ml, 0.22 mmol) gave the 7-*ethyl derivative* **19a** (0.050 g, 95%) as a colourless oil; ν_{max}/cm^{-1} 3399, 3220, 2934, 2854, 1756, 1608, 1461, 1154, 1118, 1080, 1003, 903 and 866; δ_H 1.32 (3H, t, *J* 7.5, 7-CH_2CH_3), 1.51 (9H, br s, Bu^t), 3.07 (2H, q, *J* 7.5, 7-CH_2CH_3), 7.29–7.32 (2H, m, 5- and 6-H), 7.86–7.89 (1H, m, 4-H) and 8.27 (1H, s, NH); δ_C 14.96 (CH_3), 23.12 (CH_2), 28.10 [C(CH_3)$_3$], 83.89 [*C*(CH_3)$_3$], 118.04 (CH), 124.86 (C), 127.41 (CH), 127.98 (CH), 130.85 (C), 144.86 (C) and 153.48 (CO); *m*/*z* 262 (M$^+$, 6%), 189 (25), 178 (20), 119 (12), 118 (18), 105 (22), 91 (14) and 77 (14) and 57 (100) (Found: M$^+$, 262.1405. $C_{13}H_{18}N_4O_2$ requires *M*, 262.1429).

1-(*tert*-Butoxycarbonyl)amino-7-propylbenzotriazole 19b

By the general procedure, treatment of dianion **18** generated from benzotriazole **7** (0.050 g, 0.2 mmol) with dry iodoethane (0.018 ml, 0.22 mmol) gave the 7-*propyl derivative* **19b** (0.050 g, 90%) as a colourless oil; ν_{max}/cm^{-1} 3397, 3228, 2931, 2855, 1756, 1608, 1458, 1154, 1121, 1090, 1004 and 906; δ_H 0.97 (3H, t, *J* 7.5, 3′-CH_3), 1.51 (9H, br s, Bu^t), 1.60–1.80 (2H, m, 2′-CH_2), 2.95 (2H, dist. t, *J* 7.5, 1′-CH_2), 7.27–7.33 (2H, m, 5- and 6-H), 7.87 (1H, dd, *J* 6.4 and 2.9, 4-H) and 8.26 (1H, br s, NH); δ_C 14.08 (CH_3), 24.20 (CH_2), 28.10 [C(CH_3)$_3$], 32.31 (CH_2), 83.88 [*C*(CH_3)$_3$], 118.10 (CH), 124.71 (C), 125.71 (C), 128.98 (CH), 131.20 (C), 144.92 (C) and 153.43 (CO); *m*/*z* 276 (M$^+$, 5%), 203 (10), 192 (6), 163 (7), 151 (13), 113 (8), 91 (12) and 57 (100) (Found: M$^+$, 276.1615. $C_{14}H_{20}N_4O_2$ requires *M*, 276.1586).

1-(*tert*-Butoxycarbonyl)amino-7-(but-3′-en-1′-yl)benzotriazole 19c

By the general procedure, treatment of dianion **18** generated from benzotriazole **7** (0.124 g, 0.5 mmol) with dry allyl bromide (0.067 g, 0.55 mmol) gave the 7-*butenyl derivative* **19c** (0.122 g, 85%) as a colourless powder, mp 87–88 °C; ν_{max}/cm^{-1} 3395, 3218, 2989, 2932, 2859, 1756, 1640, 1610, 1457, 1153, 1098, 994, 912 and 867; δ_H 1.49 (9H, br s, Bu^t), 2.45 (2H, app. q, *J ca.* 7.5, 2′-CH_2), 3.06 (2H, t, *J* 7.5, 1′-CH_2), 5.02 (1H, br d, *J* 10, =CH_c), 5.05 (1H, br d, *J* 17.0, =CH_t), 5.81–5.91 (1H, m, =CH), 7.21–7.30 (2H, m, 5- and 6-H), 7.85 (1H, dd, *J* 6.6 and 2.6, 4-H) and 8.69 (1H, s, NH), δ_C 28.10 [C(CH_3)$_3$], 29.56 (CH_2), 34.73 (CH_2), 83.82 [*C*(CH_3)$_3$], 115.64 (=CH_2), 118.18 (CH), 124.70 (C), 125.11 (C), 128.90 (CH), 131.02 (C), 137.30 (CH), 144.92 (C) and 153.43 (CO); *m*/*z* [FAB] 289 (M$^+$ + H, 61%), 273 (7), 249 (16), 223 (98), 189 (11) and 57 (100) (Found: M$^+$ + H, 289.1674. $C_{15}H_{21}N_4O_2$ requires *M*, 289.1664) (Found: C, 62.4; H, 7.0; N, 19.2. $C_{15}H_{20}N_4O_2$ requires C, 62.5; H, 7.0; N, 19.4%).

1-(*tert*-Butoxycarbonyl)amino-7-(2′-hydroxy-2′-phenyl)ethylbenzotriazole 20a

Following the general procedure, reaction between benzotriazole **7** (0.124 g, 0.5 mmol) and freshly distilled benzaldehyde (0.06 g, 0.5 mmol) gave the *alcohol* **20a** (0.15 g, 85%) as a pale yellow oil, ν_{max}/cm^{-1} 3270 (br), 2990, 1754, 1606, 1492, 1456, 1153, 910 and 638; δ_H 1.48 (9H, br s, Bu^t), 3.20 (1H, dd, *J* 14.4 and 3.5, 1′-H_a), 3.28 (1H, dd, *J* 14.4 and 9.1, 1′-H_b), 4.90 (1H, dd, *J* 9.1 and 3.5, 2′-H), 7.21–7.38 (7H, m, 5-, 6- and Ph-H), 7.74 (1H, dd, *J* 7.3 and 1.9, 4-H) and 9.49 (1H, s, NH); δ_C 28.14 [C(CH_3)$_3$], 40.27 (1′-CH_2), 75.29 (2′-CH), 83.57 [*C*(CH_3)$_3$], 118.75 (CH), 121.64 (C), 124.68, 125.72, 128.05, 128.60, 130.42 (all CH), 131.25, 143.74, 144.92 (all C) and 154.12 (CO); *m*/*z* [FAB] 355 (M$^+$ + H, 42%), 299 (50), 154 (38), 136 (25), 107 (31), 95 (41), 83 (55), 69 (97) and 57 (100) (Found: M$^+$ + H, 355.1741. $C_{19}H_{23}N_4O_3$ requires *M*, 355.1770) (Found: C, 64.4; H, 6.2; N, 15.7. $C_{19}H_{22}N_4O_3$ requires C, 64.4; H, 6.3; N, 15.8%).

1-(*tert*-Butoxycarbonyl)amino-7-[2′-hydroxy-2′-(furan-2-yl)-ethyl]benzotriazole 20b

By the general procedure, condensation of dianion **18** from benzotriazole **7** (0.124 g, 0.5 mmol) with freshly distilled furan-2-carbaldehyde (0.055 g, 0.55 mmol) gave the *alcohol* **20b** (0.139 g, 81%) as a thick oil; ν_{max}/cm^{-1} 3592, 3380, 3308, 2936, 1754, 1608, 1487, 1457, 1153, 1115, 1006, 911 and 862; δ_H 1.40 (9H, br s, Bu^t), 3.29–3.39 (2H, m, 1′-CH_2), 4.89 (1H, dd, *J* 7.6 and 5.5, 2′-H), 6.11–6.30 (2H, m), 7.13–7.32 (3H, m), 7.70 (1H, dd, *J* 6.9 and 2.5, 4-H) and 9.49 (1H, s, NH); δ_C 28.12 [C(CH_3)$_3$], 36.29 (1′-CH_2), 68.57 (2′-CH), 83.59 [*C*(CH_3)$_3$], 106.37, 110.46, 119.01 (all CH), 121.02 (C), 124.70, 130.41 (both CH), 131.26 (C), 142.15 (CH), 144.78 (C), 154.12 (CO) and 155.67 (C); *m*/*z* (FAB) 345 (M$^+$ + H, 11%), 327 (5), 289 (20), 271 (11), 137 (29), 91 (33), 81 (60), 69 (44) and 57 (100) (Found: M$^+$ + H, 345.1567. $C_{17}H_{21}N_4O_4$ requires *M*, 345.1563).

1-(*tert*-Butoxycarbonyl)amino-7-(2′-hydroxyheptyl)benzotriazole 20c

By the general procedure, reaction between dianion **18**, generated from the benzotriazole **7** (0.124 g, 0.5 mmol), and hexanal (0.053 g, 0.55 mmol), followed by stirring at −78 °C for 3 h gave the *alcohol* **20c** (0.096 g, 55%) as a colourless oil; ν_{max}/cm^{-1} 3262, 2930, 2858, 1754, 1458, 1370, 1156, 1118, 993, 908 and 864; δ_H 0.91 (3H, t, *J* 6.6, 7′-CH_3), 1.16–1.62 (8H, m, 3′-, 4′-, 5′- and 6′-CH_2), 1.51 (9H, br s, Bu^t), 2.96–3.04 (2H, m, 1′-CH_2), 3.80–3.95 (1H, m, 2′-H), 7.25–7.32 (2H, m, 5- and 6-H), 7.86 (1H, dd, *J* 7.6 and 1.6, 4-H) and 9.27 (1H, s, NH); δ_C 14.02 (7′-CH_3), 22.55, 25.12 (both CH_2), 28.07 [C(CH_3)$_3$], 31.79, 37.41, 37.49 (all CH_2), 72.58 (2′-CH), 83.24 [*C*(CH_3)$_3$], 118.31 (CH), 122.12 (C), 124.58, 130.01 (both CH), 131.08, 144.42 (both C) and 154.14 (CO) and 155.67 (C); *m*/*z* (FAB) 349 (M$^+$ + H, 68%), 293 (62), 275 (12), 249 (23) and 57 (100) (Found: M$^+$ + H, 349.2234. $C_{18}H_{29}N_4O_3$ requires *M*, 349.2240).

(*E*)-1-(*tert*-Butoxycarbonyl)amino-7-(4′,8′-dimethyl-2′-hydroxynona-3′,7′-dienyl)benzotriazole 20d

By the general procedure, reaction between dianion **18** generated from the benzotriazole **7** (0.124 g, 0.5 mmol) and citral (0.084 g, 0.55 mmol), followed by stirring at −78 °C for 3 h gave the *alcohol* **20d** (0.106 g, 53%) as a colourless oil; ν_{max}/cm^{-1} 3270, 2990, 2933, 1750, 1606, 1492, 1456, 1155, 1153, 910 and 890; δ_H 1.52 (9H, br s, Bu^t), 1.60 (3H, br s, =CCH_3), 1.65 (3H, br s, =CCH_3), 1.66 (3H, br s, =CCH_3), 2.02–2.17 (4H, m, 5′- and 6′-CH_2), 3.08–3.11 (2H, m, 1′-CH_2), 4.60–4.80 (1H, m, 2′-H), 5.08–5.25 (2H, m, 3′- and 7′-H), 7.24–7.33 (2H, m, 5- and 6-H), 7.88 (1H, dd, *J* 7.6 and 1.3, 4-H) and 9.39 (1H, s, NH); δ_C 16.71, 17.77 (both CH_3), 25.71 (CH_2), 25.75 (CH_3), 28.20 [C(CH_3)$_3$], 37.60, 39.56 (both CH_2), 68.57 (2′-CH), 83.57 [*C*(CH_3)$_3$], 118.78 (CH), 121.30 (C), 123.72, 124.48, 126.27, 130.43 (all CH), 131.38, 132.03, 139.46, 144.81 (all C) and 154.12 (CO); *m*/*z* (FAB) 401 (M$^+$ + H, 18%), 345 (11), 327 (12), 192 (13), 154 (16), 69 (38) and 57 (100) (Found: M$^+$ + H, 401.2549. $C_{22}H_{33}N_4O_3$ requires *M*, 401.2552).

1-(*tert*-Butoxycarbonyl)amino-7-(2′-hydroxy-2′-methylpropyl)-benzotriazole 20e

Following the general procedure, reaction between benzotriazole **7** (0.434 g, 1.75 mmol) and dry acetone (0.15 ml, 2 mmol) at −78 °C for 3 h gave the *alcohol* **20e** (0.386 g, 83%) as a colourless powder, mp 160–162 °C; ν_{max}/cm^{-1} 3208 (br), 2993, 2860, 1755, 1609, 1490, 1458, 1116, 964, 900, 868, 837 and 644; δ_H 1.35 (6H, s, 2 × CH_3), 1.52 (9H, br s, Bu^t), 2.98 (2H, s, 1′-CH_2), 3.27 (1H, br s, OH), 7.17 (1H, dd, *J* 7.6 and 1.0, 6-H), 7.28 (1H, dd, *J* 7.6 and 7.6, 5-H), 7.75 (1H, dd, *J* 7.6 and 1.0, 4-H) and 9.61 (1H, s, NH); δ_C 28.17 [C(CH_3)$_3$], 29.67 (2 × CH_3), 42.98 (1′-CH_2), 71.28 (2′-C), 83.02 [*C*(CH_3)$_3$], 118.65 (CH), 120.71 (C), 124.33, 131.21, (both CH), 131.29, 144.38 (both C) and 154.64 (CO); *m*/*z* (FAB) 307 (M$^+$ + H, 100%), 251 (55), 233 (10), 207 (14), 154 (17) and 136 (17) (Found: M$^+$ + H,

307.1778. $C_{15}H_{23}N_4O_3$ requires *M*, 307.1770) (Found: C, 58.6; H, 7.2; N, 18.5. $C_{15}H_{22}N_4O_3$ requires C, 58.8; H, 7.2; N, 18.3%).

1-(*tert*-Butoxycarbonyl)amino-7-[(1′-hydroxycyclohexyl)-methyl]benzotriazole 20f

Following the general procedure, reaction between benzotriazole **7** (0.124 g, 0.50 mmol) and dry, freshly distilled cyclohexanone (0.06 g, 0.55 mmol) at −78 °C for 3 h gave the *alcohol* **20f** (0.107 g, 62%) as a colourless powder, mp 152–154 °C; ν_{max}/cm^{-1} 3252 (br), 2934, 2856, 1754, 1457, 1156, 971 and 912; δ_H 1.51 (9H, br s, Bu^t), 1.11–1.60 (10H, m, 5 × CH_2), 2.81 (1H, br s, OH), 2.99 (2H, s, 1′-CH_2), 7.18 (1H, dd, *J* 8.0 and 1.0, 6-H), 7.27 (1H, dd, *J* 8.0 and 8.0, 5-H), 7.77 (1H, dd, *J* 8.0 and 1.0, 4-H) and 9.61 (1H, s, NH); δ_C 21.91 (2 × CH_2), 25.52 (2 × CH_2), 28.11 [C(CH_3)$_3$], 37.54 (CH_2), 42.05 (1′-CH_2), 72.00 (2′-C), 82.93 [*C*(CH_3)$_3$], 118.20 (CH), 120.09 (C), 124.15, 131.09 (both CH), 131.14, 144.42 (both C) and 154.14 (CO); *m*/*z* (FAB) 347 (M^+ + H, 49%), 291 (39), 273 (10), 247 (10), 229 (7), 154 (21), 136 (16), 91 (17), 81 (24), 69 (30) and 57 (100) (Found: M^+ + H, 347.2096. $C_{18}H_{27}N_4O_3$ requires *M*, 347.2083) (Found: C, 62.4; H, 7.7; N, 15.9. $C_{18}H_{26}N_4O_3$ requires C, 62.4; H, 7.6; N, 16.2%).

(±)-1-(*tert*-Butoxycarbonyl)amino-7-(3′-hydroxypentyl)benzotriazole 21a

Following the general procedure, reaction between benzotriazole **7** (0.570 g, 2.3 mmol) and dry, freshly distilled 1,2-epoxybutane (0.23 ml, 2.4 mmol) at −78 °C followed by stirring at −60 °C for 3 h gave the *alcohol* **21a** (0.645 g, 86%) as a colourless oil; ν_{max}/cm^{-1} 3285, 2934, 2856, 1754, 1458, 1156, 984 and 912; δ_H 0.91 (3H, t, *J* 7.4, 5′-CH_3), 1.46 (9H, br s, Bu^t), 1.71–1.90 (4H, m, 2′- and 4′-CH_2), 2.28 (1H, br s, OH), 3.10 (2H, dist. t, *J ca*. 7.3, 1′-CH_2), 3.35–3.50 (1H, m, 3′-H), 7.23–7.32 (2H, m, 5- and 6-H), 7.83–7.89 (1H, m, 4-H) and 9.53 (1H, br s, NH); δ_C 9.83 (5′-CH_3), 25.64 (CH_2), 27.94 [C(CH_3)$_3$], 30.12, 38.04 (both CH_2), 72.24 (3′-CH), 82.27 [*C*(CH_3)$_3$], 117.75, 124.71 (both CH), 125.46 (C), 128.77 (CH), 130.75, 144.56 (both C) and 154.07 (CO); *m*/*z* (FAB) 321 (M^+ + H, 16%), 265 (13), 247 (10), 221 (13), 154 (9), 107 (12), 95 (18), 81 (21), 69 (39) and 57 (100) (Found: M^+ + H, 321.1925. $C_{16}H_{25}N_4O_3$ requires *M*, 321.1927).

(*S*)-1-(*tert*-Butoxycarbonyl)amino-7-(3′-hydroxybutyl)benzotriazole 21b

Following the general procedure, reaction between benzotriazole **7** (0.248 g, 1.0 mmol) and (*S*)-(−)-propylene oxide (77 µl, 1.1 µmol) at −78 °C for 5 h, followed by gradual warming to ambient temperature gave the *alcohol* **21b** (0.236 g, 78%) as a colourless oil; $[a]_D^{25}$ −20.1 (*c* 1, CH_2Cl_2); ν_{max}/cm^{-1} 3191, 2990, 2932, 2850, 1748, 1608, 1458, 1154, 1118, 1002, 949, 901 and 866; δ_H 1.22 (3H, d, *J* 6.2, 4′-CH_3), 1.45 (9H, br s, Bu^t), 1.78–1.88 (2H, m, 2′-CH_2), 3.10 (2H, t, *J* 7.5, 1′-CH_2), 3.70–3.78 (1H, m, 3′-H), 7.27–7.30 (2H, m, 5- and 6-H), 7.84 (1H, dd, *J* 5.9 and 3.3, 4-H) and 9.51 (1H, br s, NH); δ_C 23.70 (4′-CH_3), 25.90 (2′-CH_2), 28.10 [C(CH_3)$_3$], 40.44 (1′-CH_2), 67.18 (3′-CH), 83.60 [*C*(CH_3)$_3$], 118.09, 124.90 (both CH), 125.40 (C), 129.03 (CH), 130.92, 144.77 (both C) and 154.05 (CO); *m*/*z* (FAB) 307 (M^+ + H, 32%), 251 (21), 233 (13), 207 (17), 154 (16), 136 (13), 107 (10), 91 (16), 69 (20) and 57 (100) (Found: M^+ + H, 307.1772. $C_{15}H_{23}N_4O_3$ requires *M*, 307.1770).

(*R*)-1-(*tert*-Butoxycarbonyl)amino-7-(3′-hydroxy-3′-phenylpropyl)benzotriazole 21c

Following the general procedure, reaction between benzotriazole **7** (0.397 g, 1.6 mmol) and (*S*)-(−)-styrene oxide (0.204 g, 1.7 mmol) at −78 °C for 6 h, followed by gradual warming to ambient temperature during 1 h gave the *alcohol* **21c** (0.244 g, 52%) as a colourless oil; $[a]_D^{25}$ +27.0 (*c* 1, CH_2Cl_2); ν_{max}/cm^{-1} 3191, 2990, 2934, 2852, 1751, 1608, 1456, 1155, 1111, 1009 and 908; δ_H 1.43 (9H, br s, Bu^t), 2.01–2.06 (2H, m, 2′-CH_2), 3.05 (2H, br t, *J* 6.9, 1′-CH_2), 4.55–4.65 (1H, m, 3′-H), 7.22–7.35 (7H, m, 5-, 6-H and Ph-H), 7.78 (1H, dd, *J* 6.0 and 3.3, 4-H) and 9.46 (1H, br s, NH); δ_C 25.99 (2′-CH_2), 28.29 [C(CH_3)$_3$], 39.89 (1′-CH_2), 73.46 (3′-CH), 83.61 [*C*(CH_3)$_3$], 118.10, 124.91 (both CH), 125.23 (C), 125.99, 127.78, 128.48, 128.61, 128.77, 128.97 (all CH), 131.74, 144.03, 144.76 (all C) and 154.77 (CO); *m*/*z* (FAB) 369 (M^+ + H, 19%), 313 (12), 295 (8), 251 (6), 154 (19), 136 (16), 107 (12), 91 (21), 77 (17), 69 (11) and 57 (100) (Found: M^+ + H, 369.1913. $C_{20}H_{25}N_4O_3$ requires *M*, 369.1927) (Found: C, 65.4; H, 6.6; N, 15.3. $C_{20}H_{24}N_4O_3$ requires C, 65.2; H, 6.6; N, 15.2%).

Acknowledgements

We are very grateful to Dr J. A. Ballantine and the EPSRC MS centre, Swansea for some high resolution mass spectral data and to SB Pharmaceuticals (Tonbridge) and the EPSRC for financial support under the CASE scheme.

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Paper 8/03251C
Received 29*th April* 1998
Accepted 25*th May* 1998