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1-Aminobenzotriazole functionalisation using directed metallation: new routes to chromanes and chromenes using intramolecular benzyne trapping by alcohols

David W. Knight and Paul B. Little

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

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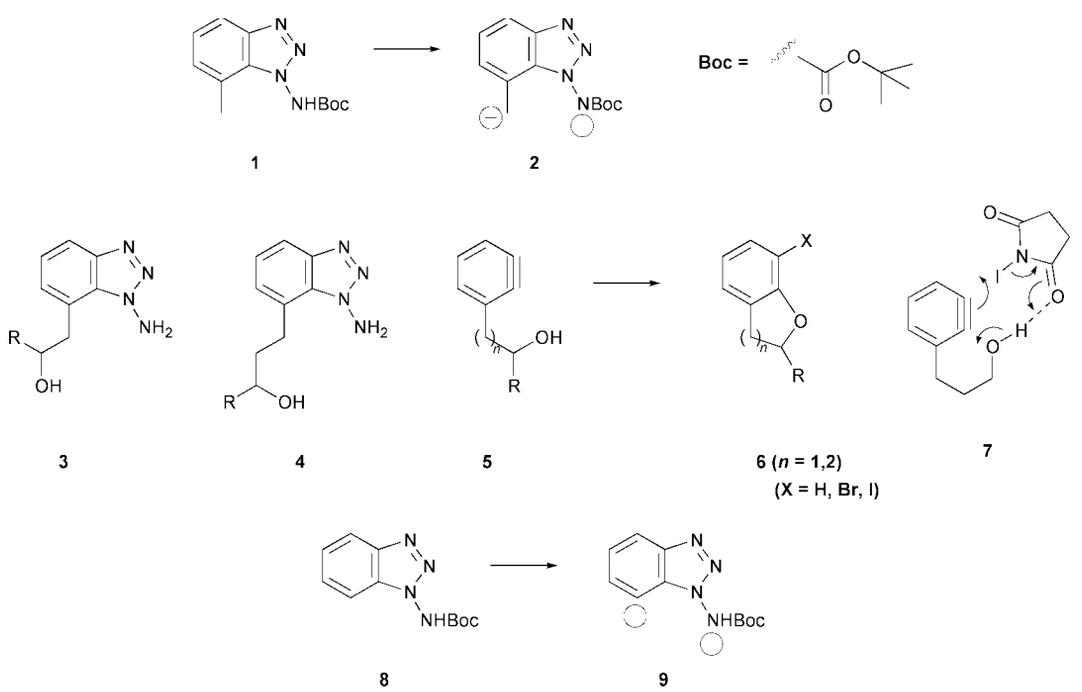
Metallation of 1-(*tert*-butoxycarbonylamino)benzotriazole **8** leads to the dianionic species **9** which undergoes smooth reactions with a range of electrophiles, under appropriate conditions. The derived iodide **30** undergoes efficient Sonogashira coupling with a range of alk-1-yn-3-ols to provide the expected arylalkynes **33**, total or partial reduction of which leads to the arylpropanols **34** and the (*Z*)-allylic alcohols **40** respectively. *N*-Deprotection and exposure to *N*-iodosuccinimide then led to smooth benzyne generation and intramolecular trapping by the hydroxy functions with iodine incorporation to give the iodochromanes **35** and iodochromenes **41** respectively, in respectable overall yields.

Despite being classic examples of reactive intermediates, benzynes have enjoyed applications in a plethora of synthetic pathways.[1] However, one of the major drawbacks associated with benzyne chemistry is the relative lack of general approaches to substituted examples. As a contribution to this, we have recently reported that the principle of lateral deprotonation[2] can be used to facilitate the generation of the dianionic species **2** from the parent aminobenzotriazole **1**, using BuLi–TMEDA in tetrahydrofuran at low temperature (Scheme 1).[3] Subsequent condensations with aldehydes or epoxides, amongst other electrophiles, provided excellent yields of the *ortho*-substituted benzyne precursors **3** and **4** respectively, following deprotection of the 1-amino group. The elaboration of these species gave us the opportunity to explore the prospects for trapping benzynes by hydroxy functions in an intramolecular manner. Perhaps surprisingly, successful examples of this type of transformation had not been reported to date, before these studies, although many alkaloid syntheses have been reported which rely on similar trapping, but by nitrogen nucleophiles.[1] The classical methods for generating benzynes from 1-aminobenzotriazoles rely on oxidation of the 1-amino group, using either lead(IV) acetate or *N*-bromosuccinimide;[4] these are in marked contrast to the more common and highly basic methods for benzyne generation from halo- and dihalobenzenes. Hence, we were able to examine such intramolecular trapping reactions using an unionized hydroxy function and it seems likely that this is the basis of the resulting highly efficient cyclisations of the presumed benzynes [**5**; $n = 1,2$] to the dihydrobenzofurans [**6**; $n = 1$] and chromanes [**6**; $n = 2$].[3] When lead(IV) acetate was used, unsubstituted products (**6**; X = H) were obtained; however, a significant bonus when *N*-bromosuccinimide was used as oxidant, was that an additional brom-



Scheme 1

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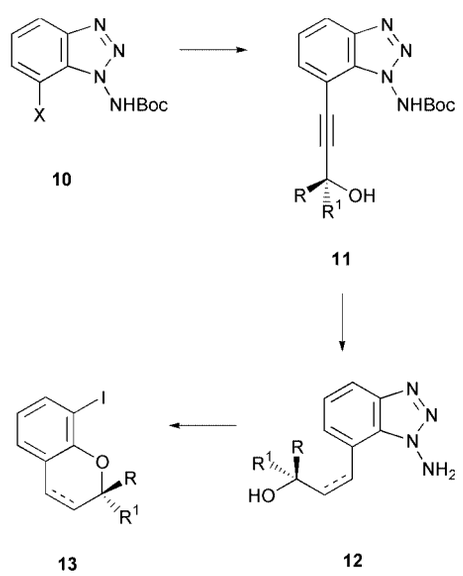
ine atom was incorporated [*i.e.* **6**; X = Br].[4] This finding was enhanced, both in terms of overall yield and synthetic utility, with the discovery that *N*-iodosuccinimide (NIS) led very efficiently to the corresponding iodides [**6**; X = I], thereby providing the potential for the introduction of a wide variety of functional groups at this position. Although not proven, this transformation may involve a hydrogen-bonded species **7**;[3] it has also been suggested that an *N*-nitrene may be involved in the pathway to the benzyne intermediates.[4]

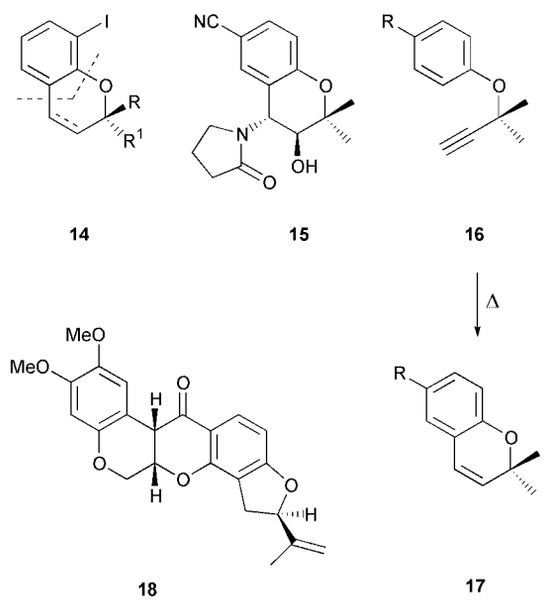
The success of this scheme led us to consider more efficient routes to the *ortho*-substituted 1-aminobenzotriazoles **3** and **4**. One of the drawbacks of the foregoing methods is associated with the preparation of the starting material **1**. Although the chemistry, originally developed by Campell and Rees,[4] is relatively straightforward, reliable and efficient, five steps are required to obtain the protected aminobenzotriazole **1** from commercial 2-methyl-6-nitroaniline. We were attracted to the idea that it might be possible to generate the parent dianion **9** from the more readily available aminobenzotriazole **8** (Scheme 1). Clearly, if this were viable, condensations with a variety of electrophiles ought to be possible, although such sp^2-centred carbanions are usually less nucleophilic than similar sp^3-centred species such as dianion **2**.[5] What attracted us more was the prospect of using dianion **9** to generate various intermediates **10** in which the added group 'X' would be a trialkyltin, halogen or boronic acid residue, hence allowing the possibility of homologations by various palladium(0)-catalysed processes including the Stille, Suzuki, Heck and Sonogashira methods, for example (Scheme 2). We anticipated that such couplings



Scheme 2

could be used to access a range of unsaturated derivatives **11**, for example, and thence the saturated or (*Z*)-allylic systems **12**, the latter either directly or by alkyne semi-reduction, and finally the chromane and chromene derivatives **13**, following *N*-deprotection, benzyne generation using NIS and intramolecular cyclisation. We reasoned that this scheme would offer a number of advantages. Firstly, the intermediates **10** could be available efficiently in only three steps from very cheap, commercially available benzotriazole (see below), given that these steps could be optimized or, in the case of the last metallation step, that the dianion **9** could indeed be generated and displayed the required reactivity.[6] Secondly, such couplings would add a further degree of flexibility to our initial routes based on dianion **2** and, significantly, would obviate the need to expose potentially sensitive and more complex addends to strongly basic conditions. Finally, more asymmetric approaches to alk-1-yn-3-ols have been established[7] and hence all the later intermediates and products [**11** to **13**] could be accessed as single enantiomers. In summary, this scheme overall can be represented by the disconnections indicated in formula **14**.

Both chromanes and chromenes are ubiquitous in nature and display a wide range of biological activities, and many synthetic approaches have been established to these compounds and their analogues, although not all are amenable to the elaboration of single enantiomers.[8] More recently, purely synthetic derivatives, such as cromakalim **15** have been found to be highly selective and unique potassium channel activators.[9] These have been prepared from the corresponding chromenes **17**, which in turn are obtained from aryl propargyl† ethers **16** which undergo a spectacular series of thermal reorganizations, initiated by a Claisen rearrangement. This chromene synthesis, due originally to Iwai and Ide,[10] was often used with relish by Leslie Crombie to test the mechanistic skills of his colleagues and co-workers and it is no coincidence that one of the main players in the discovery of cromakalim, G. Stemp, is an ex-member of the Crombie group, which also made its own significant contributions to chromene synthesis.[11] Of course, one of the more spectacular examples of the chromane ring found in nature occurs in the insecticidal molecule rotenone **18**, which was the



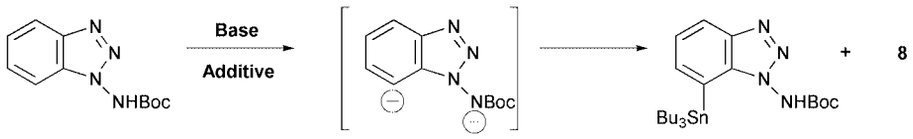
subject of a prolonged series of seminal biosynthetic studies by Crombie and Whiting[12] and often referred to by Crombie as "the queen of molecules". Herein, we report in full our recent contribution to both chromane and chromene synthesis, based on the benzyne chemistry outlined above.[13]

Results and discussion

The first objective was to define an optimized route to 1-aminobenzotriazole **20**. The method favoured by Campbell and Rees during their seminal work in this area[4] was a four step process, starting from 2-nitroaniline (see above). While successful in our hands and although the chemistry is amenable to large-scale preparations, the overall yield was *ca.* 20% and the intermediates were poorly crystalline and not particularly easy to handle. A much briefer alternative appeared to be direct *N*-amination of benzotriazole **19** using hydroxylamine-*O*-sulfonic acid as the electrophile in hot (80 °C) aqueous potassium hydroxide.[4] However, this is not without its problems, as the corresponding 2-isomer **21** is formed as a by-product, amounting to approximately 25% of the product under these aqueous conditions (Scheme 3). Attempts to modify this reaction were restricted

† IUPAC name for propargyl is prop-2-ynyl.

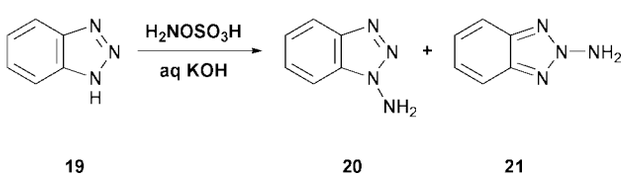
Table 1 Generation of dianion **9**: optimisation and trapping by Bu_3SnCl[a]



8 **9** **23**

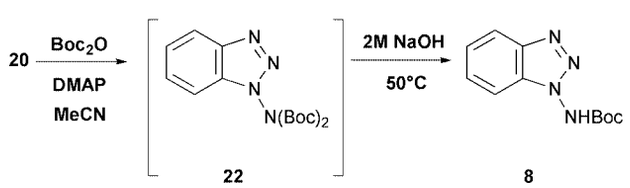
Entry	Base	Additive	Solvent	Ratio of products	
				23	**8**
1	BuLi	—	THF	0	100
2	BuLi[b]	TMEDA	THF	64	36
3	BuLi	TMEDA	Et_2O	71	29
4	t-BuLi	—	THF	61	39
5	LDA	—	THF	0	100
6	t-BuOK–BuLi	—	THF	44	56
7	BuLi	12-Crown-4	THF	100	0
8	BuLi	20 mol% 12-c-4	THF	23	77
9	BuLi	Tetraglyme	THF	89	11
10	BuLi	Tetraglyme[c]	THF	99	1

[a] Reactions were performed at −78 °C using 2.2 equivalents of the base and additive, unless stated otherwise. The ratios of products were for essentially quantitative material balances and were determined from ^{1}H NMR integrations. [b] When 3.3 equivalents of base and additive were used, the result was almost identical. [c] 5 equivalents of tetraglyme were used.



19 **20** **21**

Scheme 3



22 **8**

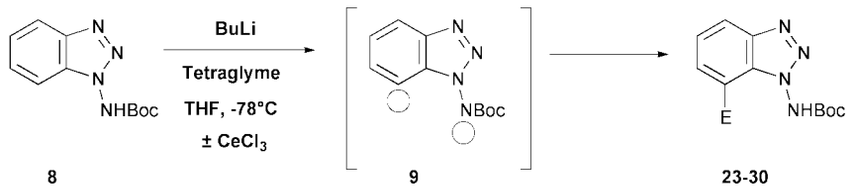
Scheme 4

to relatively low temperatures because rearrangement of the 1-amino isomer **20** to the 2-isomer **21**, which is not a benzyne precursor, becomes significant above *ca.* 50 °C.[4,14] Thus, all modifications were carried out by careful addition of the sulfonic acid to a solution of benzotriazole **19**, allowing the natural exotherm to keep the temperature of the reaction mixture at 50 °C. Under these conditions in water, the desired 1-isomer **20** was obtained selectively, but in only 32% yield. Surprisingly, in ethanol, the conversion was nearly quantitative, but the product was formed in a 2:1 ratio in favour of the unwanted 2-isomer **21**. The reaction failed in acetonitrile but regioselectively delivered a 62% yield of the 1-isomer **20** in dioxane containing 5% water. (In pure dioxane, the reaction had a dangerous tendency to produce uncontrollable exotherms.) Eventually, guided by literature reports of the *N*-amination of indole,[15] we found that dimethylformamide (DMF) containing 5% water, again to allow moderation of the exotherm, was an optimum solvent system, delivering around 70% of the 1-isomer **20**, uncontaminated by the 2-isomer **21**. Dilution of the DMF with toluene to assist in the work-up failed, as little reaction occurred. Final isolation of the aminobenzotriazole **20** was achieved by evaporation and purification *via* its hydrochloride or by filtration through silica gel using a solvent gradient. In common with the corresponding 7-methyl derivative **1**,[3] it proved impossible to add a single butoxycarbonyl (Boc) group to the highly nucleophilic amino function in aminobenzotriazole **20**. Instead, treatment with two equivalents of di-*tert*-butyl dicarbonate [Boc_2O] delivered excellent yields of the bis-Boc derivative **22**, which was then selectively and efficiently hydrolysed using aqueous methanolic sodium hydroxide at 50 °C to give the required *N*-Boc derivative **8**. Fortunately, this whole process could be carried out in a single flask and hence was only wasteful of the Boc_2O reagent (Scheme 4).

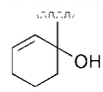
We were therefore in a position to study the central metallation idea, that of generating the dianion **9** (Scheme 1). We used tributyltin chloride as a test electrophile, both because it is known to react unambiguously with carbon nucleophiles and also because this would provide one of the desired intermediates [**10**; X = $SnBu_3$ (= **23**)] for the projected Pd(0)-catalysed coupling reactions (Scheme 2). The initial results are presented in Table 1. In all cases, the whole process was performed using 2.2 equivalents of both the base and any additive (usually in tetrahydrofuran at −78 °C) until the electrophile had been added, when the mixture was allowed to warm slowly to ambient temperature. Product ratios, for what were essentially quantitative material balances, were deduced from the integrals of ^{1}H NMR spectra of the crude products. Butyllithium alone was ineffective (entry 1) but in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) it delivered an encouraging 2:1 ratio in favour of the desired product **23** (entry 2).[3] Use of ether as solvent or *tert*-butyllithium as base gave results similar to this (entries 3, 4) while lithium diisopropylamide failed to give any of the desired dianion **9** (entry 5), and Schlosser's base[16] gave a 1:1 mixture (entry 6). It was only when we turned to ether-based additives that improvements were achieved. Thus, the addition of 2.2 equivalents of 12-crown-4 gave an essentially quantitative conversion (entry 7) but, unfortunately when only 20 mol% was used, this reverted to a very poor yield of product (entry 8). On the grounds of both toxicity and expense, we were not keen to use such quantities of a crown ether and therefore we tested tetra(ethylene glycol) dimethyl ether (tetraglyme) as an alternative additive. Although these open-chain analogues of crown ethers are understandably less effective, their relative cheapness and ease of removal offer significant advantages.[17] In line with this, addition of 2.2 equivalents of tetraglyme gave a 9:1 ratio in favour of the desired product **23** (entry 9), improved to an essentially quantitative yield when this was increased to 5 equivalents (entry 10).

Having established conditions for the seemingly quantitative generation of the deep purple dianion **9**, we tested its reactivity

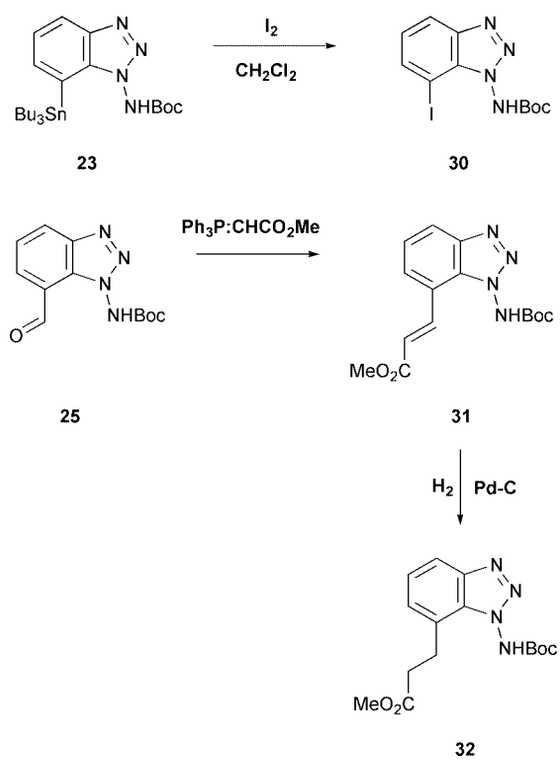
Table 2 Reactions of dianion **9** with electrophiles



8 9 23-30

Electrophile	Compound	E	Isolated yield (%) No $CeCl_3$	Isolated yield (%) With $CeCl_3$
Bu_3SnCl	**23**	Bu_3Sn	96	—
p-$MeOC_6H_4CHO$	**24**	*p*-$MeOC_6H_4CH(OH)$	79	95
DMF	**25**	CHO	67	95
$(MeO)_3B$	**26**	$[(MeO)_2B]$	[71]	—
$C_5H_{11}CHO$	**27**	$C_5H_{11}CH(OH)$	20	79
PrCH=CHCHO	**28**	PrCH=CHCH(OH)	75	87
	**29**		—	73
$C_6F_{13}I$	**30**	I	29	55
NIS	**30**	I	27	—
1,2-Diiodoethane	**30**	I	—	97

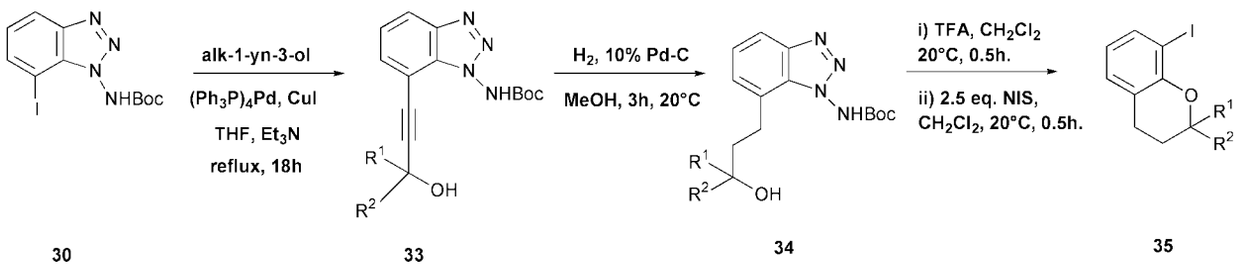
with a range of electrophiles. The results are presented in Table 2 and showed, initially, a rather disappointing outcome. While unambiguous electrophiles such as a benzaldehyde, DMF and trimethyl borate gave 70–80% yields, an enolizable aldehyde (hexanal) and various iodonium sources gave very poor returns, although (*E*)-hex-2-enal gave a good yield of the [1,2]-adduct, indicating at least that dianion **9**, under these conditions, is a hard nucleophile. As the poor yield obtained using hexanal as the electrophile was most likely due to dianion **9** acting as a base rather than a nucleophile, we reasoned that conversion to a more nucleophile cerium(III) species could improve matters, a phenomenon which has been exemplified many times,[18] although it was very uncertain if this would be effective in the case of dianion **9**. In the event, lithium–cerium exchange was effected by the combination of a solution of dianion **9** with a suspension of cerium(III) chloride at −78 °C in THF, followed by slow warming to 0 °C during 3 h. We were pleased to find that the modified species delivered significantly improved yields in all examples studied (Table 2). Enolization of a saturated aldehyde was evidently much reduced and an excellent 73% isolated yield was even obtained from cyclohex-2-enone. Trimethyl borate also reacted smoothly according to NMR analysis, although the final, presumed boronic acid was not isolated in a pure state. With modifications to the work-up procedure, it is likely that this will open the way for homologations of the product **26** using the Suzuki method. One limitation was the efficient incorporation of iodine: of a variety of electrophilic iodine sources tried, the best was iodoperfluorohexane which delivered only a 55% yield of the desired iodide **30**. It was only when we employed 1,2-diiodoethane as iodonium source and substituted the five equivalents of tetraglyme with a similar quantity of TMEDA that an essentially quantitative yield was obtained. It was also possible to prepare iodide **30** from the stannane **23** by a simple and highly efficient exchange using molecular iodine in dichloromethane. However, problems with removal of the tin residues from this two-step approach clearly rendered it far less attractive. Both these species could be useful in palladium-catalysed homologations. In contrast, the aldehyde derivative **25** represents a contrasting electrophilic intermediate and hence offers alternative synthetic possibilities. We have not yet explored this, beyond carrying out a Wittig homologation to the unsaturated ester **31** and then a hydrogenation to provide the propanoate **32** (Scheme 5).



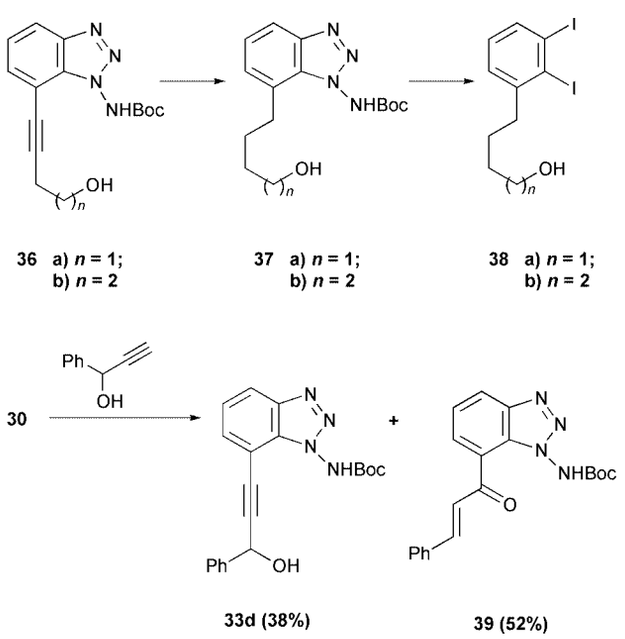
Scheme 5

In view of the now highly efficient and effectively three-step route to iodide **30**, we chose to focus on this intermediate and its suitability in Sonogashira couplings[19] with alk-1-ynes, as this appeared to offer a wide range of options and would allow us to pursue the original aim, as set out in Scheme 2. However, we were concerned that iodide **30** might not be an ideal participant in such couplings, as it is rather electron rich. This proved well founded as attempted couplings between iodide **30** and propargyl alcohol were unproductive at ambient temperature and it was only when we turned to a combination of 20 mol% each of $(Ph_3P)_4Pd$ and copper(I) iodide under reflux in THF that excellent yields were secured with a general series of propargylic alcohols (Table 3). The one exception was found when using 1-phenylprop-2-yn-1-ol when the major product was ketone **39**, presumably derived from Meyer–Shuster

Table 3 Chromane synthesis



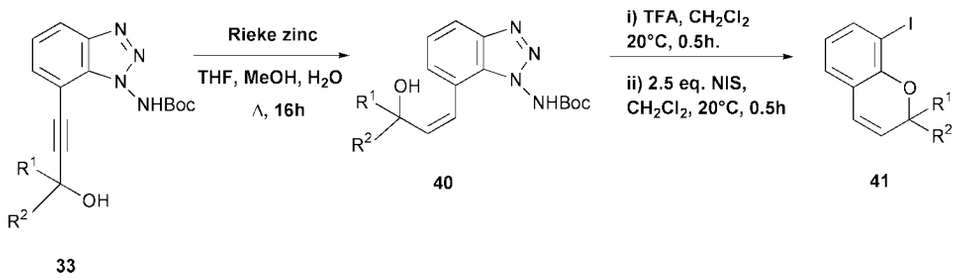
	Substituents		Isolated yields of alkynols 33 (%)	Isolated yields of saturated alcohols 34 (%)	Isolated yields of iodochromans 35 (%)
	R^1	R^2			
a	H	H	92	95	86
b	Et	H	91	96	85
c	Me	Me	87	95	90
d	Ph	H	38	—	—
e	*p*-$MeOC_6H_4$	H	81	0	—
f	CH_2OH	Me	72	92	78
	[See structure **36a**]		78 [**36a**]	95 [**37a**]	—
	[See structure **36b**]		76 [**36b**]	97 [**37b**]	—



rearrangement of the initial product **33d**. Oddly, the related *p*-methoxy derivative **33e**, which might be expected to be more prone to this rearrangement, was obtained in excellent yield. We assume that acid contamination from an unknown source was responsible; in view of the subsequent problems with this type of intermediate, this aspect was not pursued further. Compounds **33** could also be obtained, but in poorer yields (*ca*. 50–60%), by using a modified Castro–Stevens method[20] in which an isolated copper acetylide was reacted with iodide **30** in hot pyridine in the presence of $(Ph_3P)_4Pd$.[21] At ambient temperature in $CDCl_3$, the NMR spectra of intermediates **33** were very broadened, presumably because of rotamers, but were sufficiently sharpened at 55–60 °C to permit analysis. Subsequent hydrogenations to the corresponding saturated chromane precursors **34** proceeded smoothly using 10% Pd–C in methanol and one atmosphere of hydrogen (Table 3), except in the case of the aryl-substituted compound **33e**, when no recognizable products were obtained, presumably due to the sensitivity of the benzylic alcohol function. Finally, we were delighted to find that sequential *N*-deprotection and exposure of the resulting *N*-aminobenzotriazoles to *N*-iodosuccinimide, as previously described,[3] led to excellent overall yields of the iodochromanes **35**. This final two-step transformation could also conveniently be carried out without isolation of the intermediate free base. While the higher homologues **36** were both converted efficiently into the saturated species **37** and thence into the free amines, these both failed to cyclize in anything above trace yields and instead gave moderate yields of the diiodides **38**, which were only partly characterized by NMR and mass spectral data. This selectivity is further illustrated in the highly efficient cyclisation of the diol **34f** to the 2-hydroxymethylchromane **35f**. In this case, a tertiary alcohol competes successfully with a primary alcohol in the formation of a six- rather than a seven-membered ring. Clearly, the formation of seven and perhaps larger rings may be possible using this methodology, in cases with more conformationally restricted side chains. In the present cases, the reactions leading to chromanes are highly efficient in cases of primary, secondary and tertiary alcohols having aliphatic substituents but, as yet, fail with aryl substituents at the reduction stage. Efforts to resolve this are underway.

Finally, we investigated the prospects of partial reduction of the alkynols **33**, with a view to defining a novel approach to chromenes (Scheme 2). Using the unsubstituted alkynol **33a** as a test substrate, we found that Lindlar reduction was highly

Table 4 Chromene synthesis



	Substituents		Isolated yields of (*Z*)-alkenols 40 (%)	Isolated yields of iodochromenes 41 (%)
	R^1	R^2		
a	H	H	99[a]	75
b	Et	H	94	83
c	Me	Me	80	0
d	CH_2OH	Me	60	63
e	*p*-$MeOC_6H_4$	H	0	—

[a] Using a Lindlar reduction.

effective in producing the required (*Z*)-allylic alcohol **40a** (Table 4) when quinoline was used as the catalyst modifier.[22] Happily, the product delivered an encouraging 75% isolated yield of the parent iodochromene **41a** when treated sequentially with TFA and NIS under the established conditions, thus establishing the principle of this new approach at least. However, the Lindlar method was neither easily reproduced nor amenable to scale-up, despite many attempts and modifications. Similarly, with more substituted intermediates **33b–f**, such reductions were highly capricious. A search for alternatives led us to try reductions with titanocene dichloride and isobutylmagnesium chloride which has previously been used to obtain (*Z*)-allylic alcohols.[23] However, this was not successful; although the (*Z*)-alkene function was produced, loss of the Boc *tert*-butyl group also occurred. Subsequent attempts to obtain the free amine led to unrecognizable products. We then turned to the use of Rieke zinc[24] and were delighted to obtain excellent yields of the required allylic alcohols **40a–d** (Table 4). In contrast to the brief reaction times reported in the literature,[24] we found much lengthier periods were necessary to secure these conversions. Two factors were important: firstly, that all the initial potassium metal was completely reacted and secondly, that the acetylenic alcohol was not contaminated with traces of triphenylphosphine from the foregoing Sonogashira coupling. One limitation was that such a reduction of the aryl substituted propargylic alcohol **33e** led to a gross mixture of products, presumably due to the hydrogenolytic sensitivity of the benzylic C–O bond. Subsequent removal of the *N*-Boc group using TFA and exposure of the resulting free amines to *N*-iodosuccinimide then led smoothly to the iodochromenes **41a**,**b**,**d**, thus establishing that the second idea indicated in Scheme 2 is indeed viable. One limitation was that the sensitive tertiary allylic alcohol function in precursor **40c** underwent dehydration rather than simple deprotection; had this step provided the desired alcohol, we were confident that cyclisation would be successful, in view of the successful formation of chromane **35c** (Table 3). Finally, the diol derivative **34f** underwent cyclisation exclusively at the tertiary hydroxy function and none of the seven-membered ether derived from the adjacent primary hydroxy group was observed, as was the case with the related chromane formation (Table 3).

In summary, the efficient synthesis of the stannane **23** and iodide **30** opens up a new strategy for both chromane and chromene synthesis. It seems likely that the Sonogashira-based method illustrated herein can be augmented by related coupling reactions, all of which have the potential for the incorporation of delicate and enantiopure side chain arrays ready for cyclisation and which could avoid the potentially troublesome and somewhat limiting alkyne reduction step. It may also prove possible to exchange the Boc group prior to the coupling step and thereby obviate the requirement for exposure to acidic conditions necessary to free the amine function, which has resulted in some limitations to the present scheme. Further studies are also in progress aimed at extending this type of chemistry to more highly substituted examples.

Experimental

General details

Melting points were determined on a Kofler hot stage apparatus. Infra-red spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer using KBr discs for solid samples and thin films between NaCl plates in the cases of liquid samples. NMR spectra were recorded on a Bruker DPX 400 instrument operating at 400 MHz for ^1H spectra and 100 MHz for ^{13}C spectra. Unless otherwise stated, all such spectra were recorded at 300 K using dilute solutions in deuteriochloroform. Proton chemical shifts were determined relative to both tetramethylsilane (δ_H 0.00) and chloroform (δ 7.27) while carbon shifts were corrected to tetramethylsilane (δ_C 0.00) and the centre line of chloroform (δ_C 77.3). Coupling constants (*J*) are quoted in hertz (Hz) and multiplicities are expressed by the usual conventions; 'br' refers to a broadened resonance. Molecular weights and low resolution mass spectra were determined using a Fisons VG Platform II Quadrupole instrument using electrospray ionization (ES) unless otherwise stated. APcI = atmospheric pressure chemical ionization. High resolution data were obtained courtesy of the EPSRC Mass Spectrometery Service at University College, Swansea, using the ionization methods specified. Microanalyses were obtained using a Perkin-Elmer 240C Elemental Analyzer.

Unless otherwise stated, reactions were performed under an atmosphere of dry nitrogen. Solvents and reagents were purified by the usual methods;[25] all electrophiles were purified immediately prior to use. 'Petrol' refers to the fraction with bp 40–60 °C and 'ether' refers to diethyl ether. All organic solutions from work-ups were dried by brief exposure to dried magnesium sulfate. Column chromatography, referred to as 'CC', was carried out using Matrex Silica (35–70 μm) silica gel and the solvents specified. Where relevant, all compounds referred to below were racemates.

1-Aminobenzotriazole 20

Method A. Hydroxylamine-*O*-sulfonic acid (94.9 g, 840.2 mmol) was added portionwise to a stirred solution of benzotriazole **19** (50.0 g, 420.1 mmol) and potassium hydroxide (117.6 g, 2.1 mol) in water (500 ml) such that the temperature of the reaction mixture remained below 50 °C (*ca.* 1.0 g min^{-1}). After the addition was complete, the mixture was cooled to ambient temperature and stirring continued for a further 1 h. The resulting precipitate was removed by vacuum filtration and washed thoroughly with ether. The filtrate was separated and the aqueous layer extracted with ether (5 × 100 ml). The combined ether solutions were dried and evaporated to leave crude amine **20**. This was dissolved in a minimum of 2 M hydrochloric acid and the resulting solution kept at −2 °C overnight during which time 1-aminobenzotriazole hydrochloride crystallized and was removed by filtration. The solid was dried under vacuum and showed mp 131–134 °C and was >95% pure according to ^{1}H NMR data. The free amine was obtained by direct basification of the solid salt using 2 M aqueous sodium hydroxide followed by extraction with ether (3 × 100 ml). The combined extracts were dried and evaporated to leave the *amine* **20** (18.1 g, 32%) as a colourless solid, mp 84 °C [lit.[4] mp 84 °C].

Method B. The method was exactly as described in Method A except that dimethylformamide (250 ml) and water (12 ml) were used as solvent. The rate of addition was essentially the same; following removal and washing of the precipitate as described above, the filtrate was evaporated to dryness using a rotary evaporator attached to a rotary pump. The temperature of the water bath was kept below 50 °C; above this, rearrangement to the corresponding 2-amino isomer **21** became significant. The residue was purified *via* the hydrochloride salt, as in Method A, to give the amine **20** (38.8 g, 69%) which showed identical properties to the foregoing material.

Alternative purification of amine 20. The crude amine **20** isolated following the evaporation step in method B was absorbed onto silica gel (250 g), slurried in a large sinter funnel with petrol. The surface was covered with acid-washed sand and the silica eluted with petrol (1 l) with the aid of a water pump, followed by ether–petrol mixtures of the same volume, starting with 10% ether–petrol and increasing to neat ether. The amine was eluted in the fractions containing 70% ether up to neat ether. Evaporation of the combined fractions gave pure amine **20** (36.2 g, 64%), identical to the foregoing material.

1-[*N*,*N*-Bis(*tert*-butoxycarbonyl)amino]benzotriazole 22

A solution of di-*tert*-butyl dicarbonate (139.1 g, 637.8 mmol) in dry acetonitrile (100 ml) was added dropwise during 10 min to a stirred solution of 1-aminobenzotriazole **20** (38.8 g, 289.9 mmol) and 4-(dimethylamino)pyridine (DMAP; 0.707 g, 5.8 mmol) in dry acetonitrile (300 ml) maintained at 0 °C. The cooling bath was then removed and the resulting solution stirred for 1 h before the solvent was evaporated. The residue was dissolved in ether (300 ml) and the resulting solution washed successively with saturated aqueous sodium hydrogen carbonate (50 ml), water (50 ml) and brine (50 ml), then dried and evaporated to leave a beige gum. Crystallization from ether–petrol (1 : 1) gave the *bis-BOC derivative* **22** (89.9 g, 94%) as colourless crystals, mp 134–136 °C [Found: C, 57.55; H, 6.61; N, 16.91. $C_{16}H_{22}N_4O_4$ requires C, 57.46; H, 6.64; N, 16.76%], ν_{max}/cm^{-1} 1771, 1619, 1475, 1457, 1396, 1372, 1347, 1248, 1124, 1006 and 912; δ_H 1.37 (18H, s, 2 × Bu^t), 7.40–7.51 (2H, m, 5- and 7-H), 7.59 (1H, t, *J* 8.1, 6-H) and 8.10 (1H, d, *J* 8.1, 4-H); δ_C 28.1 (2 × $C(CH_3)_3$), 86.3 (2 × $C(CH_3)_3$), 108.6, 121.0, 125.0, 129.4 (all CH), 132.4, 144.5 (both C) and 148.7 (2 × CO), *m*/*z* (APcI) 335 (M^+ + H, 100%).

1-(*tert*-Butoxycarbonylamino)benzotriazole 8

a) From 1-[*N*,*N*-bis(*tert*-butoxycarbonyl)amino]benzotriazole 22. Aqueous 2 M sodium hydroxide (200 ml) was added slowly to a stirred solution of the bis-Boc aminobenzotriazole **22** (89.9 g, 272.5 mmol) in methanol (200 ml) maintained at 50 °C. After 2 h, the solution was cooled and evaporated. The residue was cooled in ice and carefully neutralised using ice-cold 2 M hydrochloric acid. The resulting solution was extracted with ether (5 × 100 ml) and the combined extracts washed with saturated aqueous sodium hydrogen carbonate (50 ml), water (50 ml) and brine (50 ml), then dried and evaporated. Crystallization of the residue from dichloromethane–petrol (1 : 1) gave the *mono-Boc derivative* **8** (60.2 g, 94%) as colourless crystals, mp 102–104 °C [Found: C, 56.47; H, 6.16; N, 24.06. $C_{11}H_{14}N_4O_2$ requires C, 56.38; H, 6.03; N, 23.93%], ν_{max}/cm^{-1} 3420, 2110, 1760, 1740 and 1630; δ_H 1.48 (9H, s, Bu^t), 7.41 (1H, t, *J* 6.8, 5-H), 7.50–7.71 (2H, m, 6- and 7-H), 8.03 (1H, t, *J* 8.0, 4-H) and 8.39 (1H, br s, NH); δ_C 28.4 ($C(CH_3)_3$), 83.9 ($C(CH_3)_3$), 109.4, 120.6, 124.9, 129.0 (all CH), 133.0, 144.6 (both C) and 153.8 (CO); *m*/*z* 235 (M^+ + H, 100%) and 179 (47).

b) One-pot procedure. A solution of di-*tert* butyl dicarbonate (139.1 g, 637.8 mmol) in dry acetonitrile (100 ml) was added during 10 min to a stirred solution of 1-aminobenzotriazole **20** (38.8 g, 289.9 mmol) and DMAP (0.707 g) in dry acetonitrile (300 ml) maintained at 0 °C. The cooling bath was removed and the solution stirred for 1 h, then heated to 50 °C and treated with 2 M aqueous sodium hydroxide (200 ml). The resulting mixture was stirred vigorously at this temperature for 1 h then cooled and evaporated. Subsequent work-up as described above gave the *mono-Boc derivative* **8** (64.4 g, 95%), identical to the foregoing sample.

Metallation and homologation of 1-(*tert*-butoxycarbonylamino)-benzotriazole 8

General procedure A. Butyllithium (2.2 equivalents of a 1.6 M solution in hexanes) was added dropwise to a stirred solution of dry tetraglyme (1.5 ml $mmol^{-1}$ of benzotriazole **8**) in dry tetrahydrofuran (10 ml $mmol^{-1}$ of **8**) cooled in a dry ice–acetone bath. After 0.5 h, a solution of 1-(*tert*-butoxycarbonylamino)benzotrizole **8** (1 equivalent) in dry tetrahydrofuran (10 ml $mmol^{-1}$ of **8**) was added dropwise. The resulting deep purple solution was stirred below −70 °C for 0.5 h before the addition of an electrophile (1.1 equivalents) dissolved in tetrahydrofuran (1 ml $mmol^{-1}$). The resulting solution was warmed to ambient temperature during 0.5 h then stirred for 1 h before quenching by the addition of saturated aqueous ammonium chloride (10 ml $mmol^{-1}$ of **8**) followed by acidification using 2 M hydrochloric acid. The resulting mixture was extracted with ether (3 × 30 ml $mmol^{-1}$). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate (10 ml $mmol^{-1}$), water (10 ml $mmol^{-1}$) and brine (10 ml $mmol^{-1}$), then dried and evaporated. CC of the residue (*ca.* 20 g silica per mmol) in petrol–ether (7 : 3), unless otherwise stated, separated the pure product.

General procedure B. Anhydrous cerium(III) chloride was prepared from the heptahydrate by drying in a vacuum oven at 140 °C and 0.1 mmHg for 4 days with regular turning and crushing of the sample. The dry salt (1.1 equivalents) was slurried in dry tetrahydrofuran (30 ml $mmol^{-1}$) for 16 h. In a separate flask, butyllithium (2.2 equivalents of a 1.6 M solution in hexanes) was added to a stirred solution of dry tetraglyme (5 equivalents) in dry tetrahydrofuran (10 ml $mmol^{-1}$) maintained below −70 °C using a dry ice–acetone bath. After 0.5 h, a solution of 1-(*tert*-butoxycarbonylamino)benzotriazole **8** (1 equivalent) in dry tetrahydrofuran (10 ml $mmol^{-1}$) was added dropwise. The resulting deep purple solution was stirred at the same temperature for 0.5 h. During this period, the cerium(III)

chloride suspension was cooled in a dry ice–acetone bath and titrated with butyllithium (1.6 M in hexanes) until a faint but permanent orange colour appeared; typically this required 0.1 ml mmol^{-1}. The purple dianion solution was then rapidly transferred *via* syringe into the cerium(III) chloride suspension. The resulting mixture was slowly warmed to 0 °C during 3 h then recooled to −78 °C and treated with a solution of an electrophile (1.1 equivalents) in tetrahydrofuran (1 ml mmol^{-1}). The mixture was then allowed to warm slowly to ambient temperature and stirred for 16 h before quenching with saturated aqueous ammonium chloride (10 ml mmol^{-1} of **8**), followed by work-up as described in general procedure A.

1-(*tert*-Butoxycarbonylamino)-7-tributylstannylbenzotriazole 23

By general procedure A, treatment of dianion **9** generated from benzotriazole **8** (0.234 g, 1.0 mmol) with tributyltin chloride (0.30 ml, 1.11 mmol) gave the *stannane* **23**, initially as a brown solid which, following crystallization from ether–petrol, gave pure material (0.501 g, 96%) as a colourless solid, mp 127–130 °C [Found: C, 51.51; H, 8.00; N, 10.36. $C_{23}H_{40}N_4O_2Sn$ requires C, 52.65; H, 7.69; N, 10.68%], ν_{max}/cm^{-1} 3180, 2960, 2919, 1749, 1425, 1335, 1195 and 1105; δ_H 0.88 (9H, t, *J* 7.4, 3 × Me), 1.19 (6H, app. t, *J* 7.4, 3 × CH_2), 1.29–1.39 (6H, m, 3 × CH_2), 1.45–1.82 (15H, m, 3 × CH_2Sn and Bu^t), 7.37 (1H, dd, *J* 7.5 and 7.5, 5-H), 7.56 (1H d, *J* 7.5, 6-H), 8.01 (1H, d, *J* 7.5, 4-H) and 8.13 (1H, br s, NH); δ_C 11.0 (CH_2), 14.1 (CH_3), 27.2 (CH_2), 28.5 (C(*C*H$_3$)$_3$), 29.4 (CH_2), 83.9 (*C*(CH$_3$)$_3$), 120.5 (CH), 121.7 (C), 124.8 (CH), 129.5 (C), 138.4 (CH), 143.1 (C) and 154.9 (CO); *m*/*z* 528 (20), 526 (23), 525 (M$^+$(Sn^{120}) + H, 100%), 523 (72), 522 (38), 469 (40), 467 (28), 465 (18) and 235 (28).

1-(*tert*-Butoxycarbonylamino)-7-[1′-hydroxy-1′-(4-methoxyphenyl)methyl]benzotriazole 24

By general procedure B, reaction between dianion **9** on a 1.0 mmol scale with *p*-anisaldehyde (0.12 ml, 1.1 mmol) gave the *alcohol* **24** (0.351 g, 95%) as colourless crystals, mp 153–154 °C (from ether–petrol) [Found: C, 61.35; H, 5.96; N, 15.18. $C_{19}H_{22}N_4O_4$ requires C, 61.61; H, 5.99; N, 15.13%], ν_{max}/cm^{-1} 3406, 2253, 1740, 1251, 1157, 911 and 738; δ_H 1.33–1.52 (9H, br s, Bu^t), 3.75 (3H, s, OMe), 6.26 (1H, s, C*H*OH), 6.79 (2H, d, *J* 8.7, 2 × ArH), 7.17 (2H, d, *J* 8.7, 2 × ArH), 7.35 (1H, t, *J* 7.5, 5-H), 7.47 (1H, d, *J* 7.5, 6-H), 7.95 (1H, d, *J* 7.5, 4-H) and 8.61 (1H, s, NH); δ_C 28.5 (C(*C*H$_3$)$_3$), 56.1 (OCH$_3$), 72.4 (CHOH), 84.2 (*C*(CH$_3$)$_3$), 114.5 (CH), 121.8 (C), 124.2 (CH), 126.1 (C), 127.2, 128.5 (both CH), 130.1 (C), 134.2 (CH), 146.1, 153.2 (both C) and 159.9 (CO); *m*/*z* 371 (M$^+$ + H, 100%) and 353 (16).

1-(*tert*-Butoxycarbonylamino)-7-formylbenzotriazole 25

By general procedure B, on a 1.0 mmol scale, condensation between dianion **9** and *N*,*N*-dimethylformamide (85 µl, 1.1 mmol) gave the *aldehyde* **25** (0.242 g, 92%) as a colourless solid, mp 94–95 °C (from ether–petrol) [Found: C, 54.90; H, 5.35; N, 21.18. $C_{12}H_{14}N_4O_3$ requires C, 54.94; H, 5.38; N, 21.37%]; ν_{max}/cm^{-1} 3257, 2981, 1748, 1700, 1596, 1496, 1394, 1370, 1257, 1159 and 1056; δ_H 1.49 (9H, br s, Bu^t), 7.61 (1H, dd, *J* 7.6 and 7.6, 5-H), 8.10 (1H, d, *J* 7.6, 6-H), 8.33 (1H, d, *J* 7.6, 4-H), 8.71 (1H, s, NH) and 10.20 (1H, s, CHO); δ_C 28.4 (C(*C*H$_3$)$_3$), 84.3 (*C*(CH$_3$)$_3$), 122.5, 124.9, 127.8 (all CH), 132.0, 136.2, 146.4 (all C), 154.2 and 189.8 (both CO); *m*/*z* 263 (M$^+$ + H, 100%) and 207 (52).

1-(*tert*-Butoxycarbonylamino)-7-(1′-hydroxyhexan-1′-yl)benzotriazole 27

Following general procedure B, condensation between dianion **9** (1 mmol) and hexanal (0.13 ml, 1.1 mmol) gave the *alcohol* **27** (0.264 g, 79%) as a colourless solid, mp 105–110 °C (from ether–petrol), ν_{max}/cm^{-1} 3400, 2931, 1737, 1458, 1371, 1254, 1158, 909 and 734; δ_H 0.94 (3H, t, *J* 5.2, 6′-CH_3), 1.18–1.34 (6H, m, 3 × CH_2), 1.37–1.57 (9H, br s, Bu^t), 1.60–1.75 (2H, m, 2′-CH_2), 3.65–4.00 (1H, br res, OH), 5.18 (1H, br t, *J* 5.2 C*H*OH), 7.15 (1H, t, *J* 7.1, 5-H), 7.43 (1H, d, *J* 7.1, 6-H), 7.67 (1H, d, *J* 7.1, 4-H) and 9.45–9.63 (1H, br s, NH); δ_C 14.4 (6′-CH_3), 23.0 (5′-CH_2), 25.8 (4′-CH_2), 28.4 (C(*C*H$_3$)$_3$), 31.9 (3′-CH_2), 38.3 (2′-CH_2), 69.7 (CHOH), 84.0 (*C*(CH$_3$)$_3$), 119.2, 124.9, 126.1 (all CH), 129.2, 129.8, 144.9 (all C) and 154.5 (CO); *m*/*z* 335 (M$^+$ + H, 100%) and 279 (13) [Found: M$^+$ + H, 335.2089. $C_{17}H_{27}N_4O_3$ requires *M*, 335.2083].

(*E*)-1-(*tert*-Butoxycarbonylamino)-7-(1′-hydroxyhex-2′-en-1′-yl)benzotriazole 28

By general procedure B, treatment of dianion **9** (1.0 mmol) with (*E*)-hex-2-enal (0.12 ml, 1.1 mmol) gave the *allylic alcohol* **28** (0.289 g, 87%) as a colourless solid, mp 138–144 °C (from ether–petrol) [Found: C, 61.27; H, 7.42; N, 16.88. $C_{17}H_{24}N_4O_3$ requires C, 61.41; H, 7.28; N, 16.86%], ν_{max}/cm^{-1} 3264, 2960, 2932, 2873, 1753, 1457, 1394, 1370, 1252, 1160, 1116, 1048, 969 and 907; 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, Bu^t), 1.94 (2H, q, *J* 7.4, 4′-CH_2), 3.25–3.51 (1H, br res, OH), 5.58 (1H, d, *J* 6.0, C*H*OH), 5.61 (1H, dt, *J* 15.0 and 7.4, 3′-H), 5.72 (1H, 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 (5′-CH_2), 28.1 (C(*C*H$_3$)$_3$), 34.4 (4′-CH_2), 70.5 (CHOH), 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 (CO); *m*/*z* 333 (M$^+$ + H, 100%) and 98 (92).

1-(*tert*-Butoxycarbonylamino)-7-(1′-hydroxycyclohex-2′-en-1′-yl)benzotriazole 29

By general procedure B, treatment of dianion **9** (1.0 mmol) with cyclohex-2-enone (0.106 ml, 1.1 mmol) gave the *allylic alcohol* **29** (0.24 g, 73%) as a colourless solid of indeterminate mp due to decomposition, ν_{max}/cm^{-1} 3216, 2976, 2934, 2869, 1755, 1480, 1370, 1255, 1158, 915 and 734; δ_H 1.45–1.62 (9H, br s, Bu^t), 1.65–1.72 (1H, br res, 5′-H_a), 1.78 (1H, dddd, *J* 11.5, 5.7, 5.7 and 2.0, 5′-H_b), 2.03–2.09 (2H, m), 2.12–2.30 (2H, m), 2.79–2.83 (1H, br res, OH), 5.84 (1H, br d, *J* 10, 2′-H), 6.20 (1H, dt, *J* 10.0 and 3.7, 3′-H), 7.30 (1H, t, *J* 8.1, 5-H), 7.39 (1H, d, *J* 8.1, 6-H), 7.95 (1H, dd, *J* 8.1 and 0.9, 4-H) and 9.42–9.51 (1H, br s, NH); δ_C 19.3, 25.1 (both CH_2), 28.5 (C(*C*H$_3$)$_3$), 38.3 (CH_2), 73.9 (COH), 83.7 (*C*(CH$_3$)$_3$), 120.5, 124.1, 127.2 (all CH; one C obscured), 130.7 (C), 131.1, 133.0 (both CH), 146.5 (C) and 154.1 (CO); *m*/*z* 331 (M$^+$ + H, 100%).

1-(*tert*-Butoxycarbonylamino)-7-iodobenzotriazole 30

By general procedure B, but using *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (5 equivalents) in place of tetraglyme, treatment of dianion **9** (1 mmol) with 1,2-diiodoethane (0.282 g, 1.1 mmol), added as a solution in tetrahydrofuran (10 ml) gave the *iodide* **30** (0.349 g, 97%) as a colourless solid, mp 142–144 °C (from petrol–ether) [Found: C, 36.97; H, 3.48; N, 15.85. $C_{11}H_{13}IN_4O_2$ requires C, 36.67; H, 3.64; N, 15.56%], ν_{max}/cm^{-1} 3295, 2990, 1762, 1735, 1582, 1485, 1370, 1275, 1250 and 1154; δ_H 1.22–1.58 (9H, br s, Bu^t), 7.05 (1H, t, *J* 7.8, 5-H), 7.86 (1H, d, *J* 7.8, 6-H), 7.95 (1H, d, *J* 7.8, 4-H) and 8.91–9.02 (1H, br s, NH); δ_C 28.7 (C(*C*H$_3$)$_3$), 71.0 (CI), 84.3 (*C*(CH$_3$)$_3$), 121.1, 126.7 (both CH), 132.5 (C), 139.9 (CH), 144.9 (C) and 153.3 (CO); *m*/*z* (APcI) 361 (M$^+$ + H, 100%).

(*E*)-1-(*tert*-Butoxycarbonylamino)-7-(2′-methoxycarbonylethen-1′-yl)benzotriazole 31

Methyl triphenylphosphorane (0.73 g, 2.20 mmol) in tetrahydrofuran (5 ml) was added carefully to a stirred solution of the aldehyde **25** (0.52 g, 2.0 mmol) in tetrahydrofuran (10 ml) at

ambient temperature. After 4 h, tlc analysis showed that all the aldehyde had reacted. Ether (30 ml) was added and the resulting suspension filtered through a pad of silica which was subsequently washed with ether (2 × 20 ml). The combined filtrates were evaporated and the residue purified by CC [petrol–ether (7:3)] to give the (*E*)-*unsaturated ester* **31** (0.55 g, 87%) as a colourless solid, mp 132–140 °C (decomp.) [Found: C, 56.75; H, 5.97; N, 17.72. $C_{15}H_{18}N_4O_4$ requires C, 56.58; H, 5.70; N, 17.61%], ν_{max}/cm^{-1} 3268, 2981, 2955, 1752, 1722, 1638, 1494, 1436, 1396, 1371, 1291, 1026, 913, 804 and 732; δ_H 1.41–1.60 (9H, br s, Bu^t), 3.82 (3H, s, OCH_3), 6.57 (1H, d, *J* 16.0, 2′-H), 7.41 (1H, dd, *J* 7.9 and 7.9, 5-H), 7.77 (1H, d, *J* 7.9, 6-H), 8.09 (1H, d, *J* 7.9, 4-H), 8.34 (1H, d, *J* 16.0, 1′-H) and 8.40–8.47 (1H, br s, NH); δ_C 28.4 (C(*C*H$_3$)$_3$), 52.3 (OCH_3), 84.6 (*C*(CH$_3$)$_3$), 119.7 (C), 121.4, 122.7, 125.2, 127.0 (all CH), 130.2 (C), 137.0 (CH), 145.4 (C), 153.3 and 167.1 (both CO); *m*/*z* 319 (M$^+$ + H, 100%).

1-(*tert*-Butoxycarbonylamino)-7-(2′-methoxycarbonylethyl)-benzotriazole 32

The foregoing unsaturated ester **31** (0.32 g, 1.0 mmol) was stirred in methanol (20 ml) with 10% palladium on carbon (0.05 g) under an atmosphere of hydrogen for 2 h then filtered through a plug of Celite. The solid was washed with methanol (2 × 10 ml) and dichloromethane (2 × 10 ml). The combined filtrates were evaporated and the residue crystallized from dichloromethane–petrol to give the *saturated ester* **32** (0.28 g, 89%) as a pale yellow solid, mp 144–145 °C, ν_{max}/cm^{-1} 3277, 3177, 2984, 2955, 2783, 1740, 1608, 1499, 1439, 1395, 1371, 1253, 1160, 1118, 1049, 914, 870, 803 and 754; δ_H 1.41–1.57 (9H, br s, Bu^t), 2.62 (2H, t, *J* 7.6, 2′-CH$_2$), 3.31 (2H, br t, *J* 7.6, 1′-CH$_2$), 3.60 (3H, s, OCH_3), 7.26 (2H, app d, *J* 7.9, 5- and 6-H), 7.83 (1H, dd, *J* 7.9 and 1.5, 4-H) and 9.87–9.92 (1H, br s, NH); δ_C 25.1 (CH$_2$), 28.3 (C(*C*H$_3$)$_3$), 35.2 (CH$_2$), 52.2 (OCH_3), 83.8 (*C*(CH$_3$)$_3$), 118.8 (CH), 124.1 (C), 125.1, 129.2 (both CH), 133.5, 145.1 (both C), 154.4 and 173.8 (both CO); *m*/*z* 321 (M$^+$ + H, 100%) [Found: M$^+$ + H, 321.1567. $C_{15}H_{21}N_4O_4$ requires *M*, 321.1563].

General conditions for Sonogashira couplings

To a stirred solution of the iodide **30** (*n* mmol) in degassed tetrahydrofuran (10 ml mmol^{-1}) containing triethylamine (3 ml mmol^{-1}) was added tetrakis(triphenylphosphine)palladium(0) (20 mol%) followed by an alk-1-ynol (1.5 equivalents). The mixture was further degassed by refluxing under nitrogen for 1 h before the addition of copper(I) iodide (20 mol%). Refluxing was continued for 18 h, then the mixture was cooled to ambient temperature and treated with water (10 ml mmol^{-1}). Stirring was continued for 4 h then the mixture was separated and the aqueous layer extracted with ether (3 × 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. The desired coupled acetylenic alcohols were then purified by CC followed by crystallization, unless otherwise stated.

1-(*tert*-Butoxycarbonylamino)-7-(3′-hydroxyprop-1′-yn-1′-yl)-benzotriazole 33a

By the general procedure, coupling between iodide **30** (0.36 g, 1.0 mmol) and propargyl alcohol (84 µl, 1.5 mmol) followed by CC [ether–petrol (1:1)] and crystallization from dichloromethane–petrol gave the *acetylenic alcohol* **33a** (0.265 g, 92%) as a brown, oily solid, mp 55–57 °C [Found: C, 58.07; H, 5.50; N, 19.57. $C_{14}H_{16}N_4O_3$ requires C, 58.31; H, 5.60; N, 19.44%], ν_{max}/cm^{-1} 3282, 2974, 2933, 2360, 1744, 1456, 1370, 1278, 1254 and 1159; δ_H (327 K) 1.36 (9H, br s, Bu^t), 4.55 (2H, s, 3′-CH$_2$), 7.21 (1H, t, *J* 8.0, 5-H), 7.42 (1H, d, *J* 8.0, 6-H), 7.91 (1H, d, *J* 8.0, 4-H) and 9.17 (1H, br s, NH); δ_C 26.7 (C(*C*H$_3$)$_3$), 50.2 (3′-CH$_2$), 77.2, 83.3, 93.3, 104.4 (all C), 120.0, 123.5, 130.9 (all CH), 131.3, 143.3 (both C) and 153.7 (CO); *m*/*z* 289 (M$^+$ + H, 100%) and 287 (65).

1-(*tert*-Butoxycarbonylamino)-7-(3′-hydroxypent-1′-yn-1′-yl)-benzotriazole 33b

By the general procedure, coupling between iodide **30** (0.36 g, 1.0 mmol) and pent-1-yn-3-ol (130 µl, 1.5 mmol) followed by CC [ether–petrol (1:1)] and crystallization from dichloromethane–petrol gave the *acetylenic alcohol* **33b** (0.289 g, 91%) as a pale orange solid, mp 139–143 °C [Found: C, 60.56; H, 6.11; N, 17.88. $C_{16}H_{20}N_4O_3$ requires C, 60.73; H, 6.38; N, 17.72%], ν_{max}/cm^{-1} 3397, 2962, 2926, 2110, 1724, 1667, 1435, 1258 and 1158; δ_H 0.90–1.05 (3 H, br res, 5′-CH$_3$), 1.15–1.29 (6H, br res), 1.31–1.58 (3H, br res), 1.68–1.88 (3H, br res), 4.40–4.76 (1H, br app d), 6.95–7.20 (1H, br app d), 7.29–7.41 (1H, br app d), 7.79–7.89 (1H, br app d) and 9.65–9.85 (1H, br app d, NH); δ_H (323 K) 1.01 (3H, br t, *J ca.* 6, 5′-CH$_3$), 1.15–1.51 (9H, br s, Bu^t), 1.78 (2H, br quintet, *J ca.* 6, 4′-CH$_2$), 4.51 (1H, br res, C*H*OH), 7.10 (1H, br t, *J ca.* 6, 5-H), 7.31 (1H, br d, *J ca.* 6, 6-H), 7.80 (1H, br d, *J ca.* 6, 4-H) and 9.27 (1H, br s, NH); δ_C (323 K) 9.9 (5′-CH$_3$), 28.3 (C(*C*H$_3$)$_3$), 30.8 (4′-CH$_2$), 64.4 (3′-CH), 78.7, 84.1, 97.1, 106.0 (all C), 121.0, 124.7, 132.3 (all CH), 132.5, 144.7 (both C) and 154.9 (CO); *m*/*z* 317 (M$^+$ + H, 100%).

1-(*tert*-Butoxycarbonylamino)-7-(3′-hydroxy-3′-methylbut-1′-yn-1′-yl)benzotriazole 33c

By the general procedure, coupling between iodide **30** (1.44 g, 4.0 mmol) and 2-methylbut-3-yn-2-ol (0.58 ml, 6.0 mmol) followed by CC [ether–petrol (1:1)] and crystallization from dichloromethane–petrol gave the *acetylenic alcohol* **33c** (1.10 g, 87%) as a yellow crystalline solid, mp 74–77 °C [Found: C, 61.04; H, 6.15; N, 17.46. $C_{16}H_{20}N_4O_3$ requires C, 60.73; H, 6.38; N, 17.72%], ν_{max}/cm^{-1} 3264, 2982, 2933, 2250, 1726, 1456, 1370, 1280, 1254, 1159, 1033, 913 and 733; δ_H 1.25–1.37 (6H, br res, 2 × CH$_3$), 1.37–1.75 (9H, br res, Bu^t), 4.32–4.44 (1H, br s, OH), 7.20–7.35 (1H, br res, 5-H), 7.41–7.49 (1H, br d, *J ca.* 8, 6-H), 7.89–7.99 (1H, br res, 4-H) and 9.05–9.15 (1H, br s, NH); δ_H (330 K) 1.36–1.49 (9H, br s, Bu^t), 1.70 (1H, br s, OH), 1.71 (6H, s, 2 × CH$_3$), 7.31 (1H, t, *J* 8.0, 5-H), 7.59 (1H, d, *J* 8.0, 6-H), 8.00 (1H, d, *J* 8.0, 4-H) and 8.44 (1H, br s, NH); δ_C (330 K) 28.3 (C(*C*H$_3$)$_3$), 31.4 (2 × CH$_3$), 65.8 (C), 84.5 (*C*(CH$_3$)$_3$), 106.9, 120.7 (both C), 121.1, 124.7, 126.3 (all CH), 132.6, 134.8, 144.7 (all C) and 154.7 (CO); *m*/*z* 317 (M$^+$ + H, 100%) and 261 (22).

(*E*)-1-(*tert*-Butoxycarbonylamino)-7-(3′-phenyl-1′-oxoprop-2′-en-1′-yl)benzotriazole 39 and 1-(*tert*-butoxycarbonylamino)-7-(3′-hydroxy-3′-phenylprop-1′-yn-1′-yl)benzotriazole 33d

By the general Sonogashira method, coupling between iodide **30** (1.44 g, 4.0 mmol) and 1-phenylprop-2-yn-1-ol (0.792 g, 6.0 mmol) resulted in the formation of two compounds which were separated by CC [ether–petrol (1:1)] to give i) the rearranged *enone* **39** (0.76 g, 52%) as a yellow crystalline solid, mp 138–140 °C (from CH_2Cl_2–petrol) [Found: C, 65.99; H, 5.63; N, 15.63. $C_{20}H_{20}N_4O_3$ requires C, 65.91; H, 5.54; N, 15.38%], 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 res, Bu^t), 7.50–7.56 (5H, m, 5 × ArH), 7.61 (1H, t, *J* 7.5, 5-H), 7.99 (1H, d, *J* 15.6, 2′-H), 8.18 (2H, m, 4- and 6-H), 8.21–8.30 (1H, br s, NH) and 8.92 (1H, d, *J* 15.6, 3′-H); δ_C 28.4 (C(*C*H$_3$)$_3$), 84.6 (*C*(CH$_3$)$_3$), 111.1 (CH), 128.4 (C), 128.5, 128.8, 129.1, 129.3, 133.5 (all CH), 133.7, 138.3 (both C), 139.2, 139.8 (both CH), 141.3 (C), 153.2 and 191.2 (both CO); *m*/*z* (APcI) 365 (M$^+$ + H, 100%), 309 (99) and 265 (40); and ii) the desired *acetylenic alcohol* **33d** (0.55 g, 38%) as a yellow crystalline solid, mp 78–82 °C (from CH_2Cl_2–petrol) [Found: C, 65.89; H, 5.74; N, 15.09%], ν_{max}/cm^{-1} 3254, 3062, 2982, 2933, 2196, 1749, 1602,

1493, 1455, 1391, 1370, 1253, 1157, 1019, 902, 800, 741 and 699; δ_H (330 K) 1.26–1.60 (9H, br s, Bu^t), 3.10–3.39 (1H, br s, OH), 5.82 (1H, s, 3′-H), 7.39 (2H, m, 2 × ArH), 7.46 (2H, m, 2 × ArH), 7.51 (2H, m, 2 × ArH), 7.74 (2H, m, 2 × ArH) and 8.15–8.22 (1H, br s, NH); δ_C (330 K) 28.4 (C(CH_3)$_3$), 65.5 (CH), 78.0, 81.6 (C), 84.6 (C(CH$_3$)$_3$), 109.9 (CH), 115.5, 118.0 (both C), 127.3, 128.8, 128.9, 129.0, 129.1 (all CH), 133.2, 140.7 (both C) and 153.1 (CO); *m*/*z* 365 (M^+ + H, 100%).

1-(*tert*-Butoxycarbonylamino)-7-[3′-hydroxy-3′-(4-methoxyphenyl)prop-1′-yn-1′-yl]benzotriazole 33e

By the general Sonogashira method, coupling between iodide **30** (1.44 g, 4.0 mmol) and 1-(4-methoxyphenyl)prop-2-yn-1-ol (0.97 g, 6.0 mmol) followed by CC [ether–petrol (1 : 1)] and crystallization from CH_2Cl_2–petrol gave the *acetylenic alcohol* **33e** (1.28 g, 81%) as an orange crystalline solid, mp 69–73 °C [Found: C, 64.22; H, 5.60; N, 14.02. $C_{21}H_{22}N_4O_4$requires C, 63.93; H 5.63; N, 14.21%]; ν_{max}/cm^{-1} 3268, 2974, 1747, 1610, 1512, 1251, 1158 and 1028; δ_H 1.37–1.50 (9H, br s, Bu^t), 1.78 (1H, br s, OH), 3.77 (3H, s, OCH_3), 5.79 (1H, s, 3′-H), 6.69–6.82 (2H, m, 2 × ArH), 7.33 (1H, br t, *J* 7.9, 5-H), 7.49 (2H, br d, *J ca.* 8, 2 × ArH), 7.57 (1H, d, *J* 7.9, 6-H), 8.02 (1H, d, *J* 7.9, 4-H) and 8.95–9.15 (1H, br s, NH); δ_H (323 K) 1.37–1.45 (9H, br s, Bu^t), 1.68 (1H, br s, OH), 3.81 (3H, s, OCH_3), 5.70 (1H, s, 3′-H), 6.93 (2H, d, *J* 8.9, 2 × ArH), 7.35 (1H, t, *J* 8.0, 5-H), 7.45 (2H, d, *J* 8.9, 2 × ArH), 7.59 (1H, d, *J* 8.0, 6-H), 8.04 (1H, d, *J* 8.0, 4-H) and 8.54 (1H, br s, NH); δ_C (330 K) 28.1 (C(CH_3)$_3$), 55.4 (OCH_3), 64.7 (CH), 70.2, 80.1 (C), 84.2 (C(CH$_3$)$_3$), 105.7 (C), 114.2, 121.1, 124.5 (all CH), 126.5 (C), 128.2 (CH), 128.6 (C), 132.2 (CH), 132.8 (C), 144.6 (C) and 160.0 (CO); *m*/*z* 395 (M^+ + H, 22%), 377 (100) and 279 (64).

1-(*tert*-Butoxycarbonylamino)-7-(3′,4′-dihydroxy-3′-methylbut-1′-yn-1′-yl)benzotriazole 33f

By the general procedure, coupling between iodide **30** (1.44 g, 4.0 mmol) and 2-methylbut-3-yne-1,2-diol (0.60 g, 6.0 mmol) followed by evaporation of the cooled reaction mixture gave a residue which was triturated with methanol (20 ml). The resulting mixture was filtered through Celite and the solid washed with methanol (2 × 10 ml). The combined filtrates were dried and evaporated and the residue crystallized from dichloromethane to give the *acetylenic diol* **33f** (0.96 g, 72%) as a colourless crystalline solid, mp 124–128 °C, ν_{max}/cm^{-1} 3248, 2976, 2933, 1742, 1430, 1366, 1251, 1158 and 1044; δ_H (333 K) 1.23–1.41 (9H, br s, Bu^t), 1.56 (3H s, 3′-CH_3), 3.66 (1H, d, *J* 11.1, 4′-H$_a$), 3.80 (1H, d, *J* 11.1, 4′-H$_b$), 7.26 (1H, t, *J* 8.3, 5-H), 7.53 (1H, d, *J* 8.3, 6-H) and 8.00 (1H, d, *J* 8.3, 4-H); δ_C (330 K) 25.5 (3′-CH_3), 28.3 (C(CH_3)$_3$), 69.8 (3′-C), 71.5 (4′-CH_2), 77.7 (C), 85.7 (C(CH$_3$)$_3$), 98.5, 116.4 (both C), 121.4, 124.8 (both CH), 126.1 (C), 132.6 (CH), 144.8 (C) and 154.3 (CO); *m*/*z* (APcI) 333 (M^+ + H, 100%) and 259 (20) [Found: M^+ + H, 333.1567. $C_{16}H_{21}N_4O_4$ requires *M*, 333.1563].

1-(*tert*-Butoxycarbonylamino)-7-(4′-hydroxybut-1′-yn-1′-yl)-benzotriazole 36a

Iodide **30** (0.36 g, 1.0 mmol) was coupled with but-3-yn-1-ol (0.11 ml, 1.5 mmol) using the general procedure, followed by CC [ether–petrol (1 : 1)] and crystallization from the same solvent combination, to give the *butynol* **36a** (0.24 g, 78%) as a colourless crystalline solid, mp 168–170 °C [Found: C, 59.25; H, 5.78. $C_{15}H_{18}N_4O_3$ requires C, 59.58; H, 6.00%], ν_{max}/cm^{-1} 3278, 2980, 2249, 1724, 1608, 1456, 1254 and 1159; δ_H (232 K) 1.19–1.39 (9H, br s, Bu^t), 2.70 (2H, t, *J* 6.0, 3′-CH_2), 3.89 (2H, t, *J* 6.0, 4′-CH_2), 7.21 (1H, t, *J* 8.0, 5-H), 7.69 (1H, d, *J* 8.0, 6-H), 7.92 (1H, d, *J* 8.0, 4-H) and 9.51 (1H, br s, NH); δ_C (323 K) 27.9 (C(CH_3)$_3$), 35.9, 66.4 (both CH_2), 82.7 (C(CH$_3$)$_3$), 124.5, 126.8, 133.0 (all CH) and 158.6 (CO) [other quaternaries not observed].

1-(*tert*-Butoxycarbonylamino)-7-(5′-hydroxypent-1′-yn-1′-yl)-benzotriazole 36b

Iodide **30** (0.36 g, 1.0 mmol) was coupled with pent-4-yn-1-ol (0.13 ml, 1.5 mmol) using the general procedure, followed by CC [ether–petrol (1 : 1)] and crystallization from the same solvent combination, to give the *pentynol* **36b** (0.24 g, 76%) as a colourless crystalline solid, mp 178–182 °C [Found: C, 60.88; H, 6.15; N, 17.88. $C_{16}H_{20}N_4O_3$ requires C, 60.73; H, 6.38; N, 17.72%], ν_{max}/cm^{-1} 3172, 2959, 2872, 1751, 1609, 1457, 1394 and 1160; δ_H (333 K; d$_6$-DMSO) 1.25–1.55 (9H br s, Bu^t), 1.56 (1H, br s, OH), 1.92 (2H, quintet, *J* 6.5, 4′-CH_2), 2.66 (2H, t, *J* 6.5, 3′-CH_2), 3.91 (2H, t, *J* 6.5, 5′-CH_2), 7.32 (1H, t, *J* 9.0, 5-H), 7.73 (1H, d, *J* 9.0, 6-H), 8.17 (1H, d, *J* 9.0, 4-H) and 8.50 (1H, s, NH); δ_C (323 K) 23.0 (CH_2), 28.4 (C(CH_3)$_3$), 30.3, 33.4 (both CH_2), 77.3, 84.0, 84.1 (all C), 118.2, 125.1 (both CH), 126.6 (C), 129.1 (CH), 131.3, 145.1 (both C) and 154.0 (CO).

General procedure for full reduction of the acetylenic alcohols

The acetylenic alcohol **33** (1 mmol) in methanol (20 ml) was added to 10% palladium on carbon (0.1 g) and the mixture stirred vigorously under an atmosphere of hydrogen for 8 h then filtered through Celite. The solid was washed with methanol (50 ml) and the combined filtrates evaporated.

General procedure for deprotection of 1-(*tert*-butoxycarbonylamino)benzotriazoles

The 1-(*tert*-butoxycarbonylamino)benzotriazole [**34** or **40**] (*n* mmol) was dissolved in dichloromethane (10 ml mmol^{-1}) containing trifluoroacetic acid (TFA) (2 ml mmol^{-1}) and the resulting solution stirred at ambient temperature until tlc analysis showed complete removal of the *N*-Boc group, typically 0.5–1 h. The solution was basified with 2 M aqueous sodium hydroxide (~10 ml mmol^{-1}), then the pH of the mixture was adjusted to ~5 using 2 M hydrochloric acid (~3 ml mmol^{-1}). The two-phase mixture was separated and the aqueous phase saturated with solid sodium chloride then extracted with dichloromethane (3 × 10 ml mmol^{-1}). The combined organic solutions were washed with brine (10 ml mmol^{-1}) then dried and evaporated. In most cases, the resulting 1-aminobenzotriazole was sufficiently pure that the subsequent benzyne formation and cyclisation were carried out immediately.

General procedure for benzyne generation and cyclisation

N-Iodosuccinimide (NIS) (2.5*n* mmol) was added in one portion to a stirred solution of the 1-aminobenzotriazole (*n* mmol) in dichloromethane (~30 ml mmol^{-1}) at ambient temperature and protected from light. Usually, a vigorous effervescence occurred soon after the addition. The resulting purple solution was stirred for 0.5 h then washed with saturated aqueous sodium thiosulfate (5 ml mmol^{-1}), water (5 ml mmol^{-1}) and brine (5 ml mmol^{-1}) then dried and evaporated. CC (petrol) of the residue then delivered the pure products. In some cases, the NIS was added directly to the dried and filtered dichloromethane solution obtained from the deprotection step, without isolation of the free amine. In such cases, a quantitative yield of the latter was assumed when calculating the quantity of NIS to be added.

1-(*tert*-Butoxycarbonylamino)-7-(3′-hydroxypropan-1′-yl)-benzotriazole 34a

The acetylenic alcohol **33a** (0.10 g, 0.34 mmol) was hydrogenated by the general procedure to give the *hydroxypropylbenzotriazole* **34a** (0.098 g, 96%) as a beige solid, mp 117–120 °C [Found: C, 57.36; H, 6.96; N, 19.38. $C_{14}H_{20}N_4O_3$ requires C, 57.50; H, 6.90; N, 19.17%], ν_{max}/cm^{-1} 3248, 2937, 2876, 1747, 1452, 1370, 1254, 1158 and 1058; δ_H (330 K) 1.21–1.59 (9H, br s, Bu^t), 1.97 (2H, br quintet, *J ca.* 7, 2′-CH_2), 3.01 (2H, br t, *J ca.*

7, 1′-CH_2), 3.45–3.56 (2H, br res, 3′-CH_2), 7.15–7.29 (2H, m, 5- and 6-H), 7.81 (1H, dd, *J* 6.5 and 2.9, 4-H) and 9.05–9.23 (1H br s, NH); δ_C (330 K) 26.0 (CH_2), 28.4 (C(CH_3)$_3$), 34.2, 61.7 (both CH_2), 84.0 (*C*(CH_3)$_3$), 118.6, 125.2 (both CH), 125.3 (C), 129.5 (CH), 145.6 (C) and 154.3 (CO); *m/z* 293 (M^+ + H, 100%) and 237 (45).

8-Iodochromane 35a

By the general deprotection procedure followed by direct treatment of the dichloromethane solution resulting from work-up with NIS, the foregoing hydroxypropylbenzotriazole **34a** (80 mg, 0.27 mmol) was converted into 8-*iodochromane* **35a** (61 mg, 86%), a yellow solid, mp 101–102 °C, ν_{max}/cm^{-1} 3062, 3026, 2984, 2933, 1495, 1450, 1371, 1226, 1146, 1017, 814, 738 and 699; δ_H 1.90–1.97 (2H, m, 3-CH_2), 2.71 (2H, app t, *J* 6.5, 4-CH_2), 4.18–4.22 (2H, m, 2-CH_2), 6.50 (1H, app t, *J* 7.6, 6-H), 6.92 (1H, dd, *J* 7.5 and 1.3, 5(7)-H) and 7.51 (1H, dd, *J* 8.3 and 1.2, 7(5)-H); δ_C 21.2, 24.2, 66.6 (all CH_2), 84.4 (8-CI), 120.7 (CH), 122.2 (C), 129.0, 136.0 (both CH) and 152.6 (C); *m/z* (EI) 260 (M^+, 81%), 127 (96) and 105 (100) [Found: M^+, 259.9695. C_9H_9IO requires *M*, 259.9700].

1-Amino-7-(3′-hydroxypentan-1′-yl)benzotriazole 34b

Hydrogenation of the acetylenic alcohol **33b** (0.26 g, 0.82 mmol) by the general procedure gave 1-(*tert*-butoxycarbonylamino)-7-(3′-hydroxypentan-1′-yl)benzotriazole **34b** (0.25 g, 96%) as an orange oil, δ_H 0.89 (3H, br t, *J ca.* 6, 5′-CH_3), 1.25–1.60 (11H, m, 4′-CH_2 and Bu^t), 1.72 (2H, br quintet, *J ca.* 6, 2′-CH_2), 2.95–3.15 (2H, br res, 1′-CH_2), 3.40–3.55 (1H, br res, C*H*OH), 7.19–7.26 (2H br res, 5- and 6-H), and 7.72–7.86 (1H, br res, 4-H). Without further purification or characterization, the sample was subjected to the general deprotection procedure to give the corresponding *aminoalcohol* (0.14 g, 84%) as an orange oil, ν_{max}/cm^{-1} 3344, 2933, 2876, 1640, 1603, 1504, 1456, 1370, 1252, 1168 and 1121; δ_H 0.91 (3H, t, *J* 7.4, 5′-CH_3), 1.51 (2H, quintet, *J* 7.4, 4′-CH_2), 1.86 (2H, m, 2′-CH_2), 2.45–2.52 (1H, br s, OH), 3.28 (2H, t, *J* 8.1, 1′-CH_2), 3.51–3.57 (1H, m, 3′-C*H*OH), 6.12 (2H, br s, NH_2), 7.11–7.23 (2H, m, 5- and 6-H) and 7.76–7.82 (1H, m, 4-H); δ_C 8.9 (5′-CH_3), 25.4, 29.2, 37.7 (all CH_2), 71.1 (3′-CH), 116.3, 123.4 (both CH), 125.6 (C), 127.0 (CH), 131.0 and 143.9 (both C); *m/z* 221 (M^+ + H, 100%) [Found: M^+ + H, 221.1404. $C_{11}H_{17}N_4O$ requires *M*, 221.1402].

2-Ethyl-8-iodochromane 35b

The foregoing 1-aminobenzotriazole, derived from benzotriazole **34b** (0.36 g, 1.63 mmol) was treated with NIS, as described in the general procedure, to give the 2-*ethyliodochromane* **35b** (0.40 g, 85%) as a yellow solid, mp 107–109 °C; ν_{max}/cm^{-1} 2955, 2923, 2848, 1638, 1449, 1373, 1237, 1108, 1072 and 757; δ_H 0.98 (3H, t, *J* 6.0, CH_3CH_2), 1.72–1.89 (3H, m, 3-H_a and CH_3CH_2), 2.01 (1H, dddd, *J* 13.6, 8.6, 5.4 and 2.6, 3-H_b), 2.73 (1H, dd, *J* 16.6, 5.5 and 5.4, 4-H_a), 2.85 (1H, ddd, *J* 16.6, 11.0 and 5.5, 4-H_b), 3.99 (1H, dddd, *J* 10.2, 7.7, 2.6 and 2.5, 2-H), 6.58 (1H, t, *J* 7.7, 6-H), 7.00 (1H, d, *J* 7.7, 7-H) and 7.56 (1H, d, *J* 7.7, 5-H); δ_C 10.4 (CH_3), 25.4, 27.5, 28.7 (all CH_2), 78.9 (2-CH), 86.4 (8-CI), 121.9 (CH), 123.2 (C), 130.0, 137.3 (both CH) and 152.3 (C); *m/z* (EI) 288 (M^+, 100%) and 233 (80) [Found: M^+, 288.0011. $C_{11}H_{13}IO$ requires *M*, 288.0013].

1-(*tert*-Butoxycarbonylamino)-7-(3′-hydroxy-3′-methylbutan-1′-yl)benzotriazole 34c

The acetylenic alcohol **33c** (0.54 g, 1.71 mmol), derived from 2-methylbut-3-yn-2-ol, was subjected to the general hydrogenation procedure to give the *3′-hydroxybutylbenzotriazole* **34c** (0.52 g, 95%) as an orange oil, ν_{max}/cm^{-1} 3288, 2973, 1748, 1459, 1370, 1276, 1254, 1159 and 773; δ_H 1.27–1.34 (6H, app br s, 2 × CH_3), 1.35–1.61 (9H, br s, Bu^t), 1.79–1.82 (2H, br res, 2′-CH_2), 3.06–3.15 (2H, br res, 1′-CH_2), 7.25–7.32 (2H, br res, 5- and 6-H), 7.82–7.90 (1H, br res, 4-H) and 9.34–9.56 (1H, br s, NH); δ_C 25.5 (2′-CH_2), 28.5 (C(CH_3)$_3$), 29.6 (2 × CH_3), 45.5 (1′-CH_2), 71.5 (3′-C), 83.9 (*C*(CH_3)$_3$), 118.4, 125.2 (both CH), 126.4 (C), 129.1 (CH), 131.2, 145.0 (C) and 154.3 (CO); *m/z* 321 (M^+ + H, 100%) [Found: M^+ + H, 321.1927. $C_{16}H_{25}N_4O_3$ requires *M*, 321.1927].

2,2-Dimethyl-8-iodochromane 35c

The foregoing *N*-Boc benzotriazole **34c** (0.30 g, 0.95 mmol) was deprotected using the general procedure to give an intermediate amino alcohol (0.19 g, 92%) as an orange oil, ν_{max}/cm^{-1} 3341, 2074, 1674, 1373 and 1166; δ_H 1.24 (6H, s, 2 × CH_3), 1.83–1.90 (2H, m, 2′-CH_2), 3.19–3.24 (2H, m, 1′-CH_2), 6.62–6.75 (2H, br s, NH_2), 7.11–7.32 (2H, m, 5- and 6-H) and 7.72 (1H, d, *J* 8.2, 4-H); δ_C 25.9 (2′-CH_2), 29.2 (2 × CH_3), 45.5 (1′-CH_2), 73.0 (3′-C), 116.8, 126.5 (both CH), 127.8 (C), 129.3 (CH), 130.9 and 143.3 (both C).

Without further characterization, the foregoing aminoalcohol (0.39 g, 1.78 mmol) was treated with NIS, as described in the general procedure, to give the *2,2-dimethyl-8-iodochromane* **35c** (0.45 g, 90%) as a yellow solid, mp 95–97 °C [Found: C, 45.93; H, 4.76. $C_{11}H_{13}IO$ requires C, 45.83; H, 4.55%], ν_{max}/cm^{-1} 3015, 2975, 2926, 2848, 1559, 1440, 1370, 1256, 1219, 1157 and 1120; δ_H 1.40 (6H, s, 2 × CH_3), 1.83 (2H, t, *J* 6.7, 3-CH_2), 2.79 (2H, t, *J* 6.7, 4-CH_2), 6.60 (1H, t, *J* 7.7, 6-H), 7.05 (1H, d, *J* 7.7, 7-H) and 7.61 (1H, d, *J* 7.7, 5-H); δ_C 23.2 (3-CH_2), 27.4 (2 × CH_3), 33.3 (4-CH_2), 76.4 (2-C), 86.9 (8-CI), 121.6 (CH), 122.3 (C), 130.0, 137.5 (both CH) and 153.5 (C); *m/z* (EI) 288 (M^+, 50%), 232 (53) and 127 (100) [Found: M^+, 288.0036. $C_{11}H_{13}IO$ requires *M*, 288.0013].

1-(*tert*-Butoxycarbonylamino)-7-(3′,4′-dihydroxy-3′-methylbutan-1′-yl)benzotriazole 34f

Benzotriazole **33f** (0.24 g, 0.72 mmol) was hydrogenated using the general procedure to give the *diol* **34f** (0.22 g, 92%) as a colourless solid, mp 132–135 °C [Found: C, 55.54; H, 6.94; N, 16.28. $C_{16}H_{24}N_4O_4$ requires C, 57.11; H, 7.19; N, 16.66%], ν_{max}/cm^{-1} 3350, 2979, 1740, 1440, 1376, 1255, 1159 and 773; δ_H (333 K) 1.30 (3H, s, 3′-CH_3), 1.50 (9H, s, Bu^t), 1.83–1.90 (2H, m, 2′-CH_2), 3.04–3.11 (2H, m, 1′-CH_2), 3.52 (1H, d, *J* 10.9, 4′-H_a), 3.60 (1H, d, *J* 10.9, 4′-H_b), 7.32 (2H, m, 5- and 5-H) and 7.89–7.96 (1H, m, 4-H); *m/z* 337 (M^+ + H, 100%) and 279 (57) [Found: M^+ + H, 337.1876. $C_{16}H_{25}N_4O_4$ requires *M*, 337.1876].

(8-Iodo-2-methylchroman-2-yl)methanol 35f

By the combined deprotection and cyclisation procedures in which the intermediate 1-aminobenzotriazole was not isolated, the foregoing diol **34f** (0.354 g, 1.05 mmol) was converted into the *8-iodochromanylmethanol* **35f** (0.25 g, 78%) as a beige oil, ν_{max}/cm^{-1} 3418, 2955, 2931, 2924, 1442, 1374, 1238, 1153, 1054 and 763; δ_H 1.37 (3H, s, 2-CH_3), 1.75 (1H, ddd, *J* 13.7, 6.2 and 4.2, 3-H_a), 1.97 (1H, ddd, *J* 13.7, 11.1 and 6.0, 3-H_b), 2.77 (1H, ddd, *J* 16.6, 6.2 and 6.0, 4-H_a), 2.86 (1H, ddd, *J* 16.6, 11.1 and 4.2, 4-H_b), 3.61 (1H, d, J_{AB} 9.7, 1′-H_a), 3.64 (1H, d, J_{AB} 9.7, 1′-H_b), 6.64 (1H, t, *J* 7.7, 6-H), 7.11 (1H, d, *J* 7.7, 7-H) and 7.64 (1H, d, *J* 7.7, 5-H); δ_C 21.1 (2-CH_3), 22.1, 28.3 (3- and 4-CH_2), 69.7 (CH_2OH), 79.0 (2-C), 86.8 (8-CI), 122.2 (CH), 122.9 (C), 130.0, 137.4 (both CH) and 152.4 (C); *m/z* (EI) 304 (M^+, 42%), 273 (84), 146 (36), 131 (61), 105 (93) and 77 (100) [Found: M^+, 303.9951. $C_{11}H_{13}IO_2$ requires *M*, 303.9962].

(*Z*)-1-(*tert*-Butoxycarbonylamino)-7-(3′-hydroxyprop-1′-en-1′-yl)benzotriazole 40a

Benzotriazole **33a** (0.10 g, 0.34 mmol), derived from propargylic alcohol, in methanol (1 ml) was added to a suspension of 10% palladium on charcoal (0.05 g) in methanol (5 ml) containing quinoline (10 μl). The resulting mixture was stirred vigorously under an atmosphere of hydrogen for 2 h, then the

methanol was evaporated and the resulting residue taken up in dichloromethane (10 ml). The resulting mixture was filtered through Celite and the solid washed with dichloromethane (20 ml). The combined filtrates were washed with 2 M hydrochloric acid (2 ml) then dried and evaporated to give the crude (*Z*)-*allylic alcohol* **40a** (0.10 g, ~100%), ν_{max}/cm^{-1} 3368, 1718, 1370, 1026 and 909; δ_H (323 K) 1.26–1.50 (9H, br s, Bu^t), 4.09 (2H, d, *J* 7.0, CH_2OH), 4.46 (1H, s, OH), 6.05 (1H, m, 2′-H), 6.81 (1H, br d, *J* 12.0, 1′-H), 7.13 (1H, d, *J* 8.0, 6-H), 7.27 (1H, t, *J* 8.0, 5-H), 7.83 (1H, d, *J* 8.0, 4-H) and 9.48 (1H, s, NH); δ_C (232 K) 26.2 (C(CH_3)$_3$), 61.6 (CH_2), 83.6 (*C*(CH_3)$_3$), 119.4 (CH), 120.6 (C), 124.9, 125.2, 129.6 (all CH), 130.5 (C), 134.4 (CH), 144.7 (C) and 154.5 (CO).

8-Iodochromene 41a

Deprotection and cyclisation, using TFA and NIS respectively, of the foregoing (*Z*)-allylic alcohol **40a** (100 mg, 0.34 mmol) according to the general procedures gave the *8-iodochromene* **41a** (70 mg, 75% overall) as a brown oil, ν_{max}/cm^{-1} 3048, 2960, 2926, 2848, 1441, 1224, 1170, 1072, 1014, 929, 889, 790 and 688; δ_H 4.97 (2H, dd, *J* 3.5 and 1.9, 2-CH_2), 5.79 (1H, dt, *J* 9.8 and 3.5, 3-H), 6.37 (1H, dt, *J* 9.8 and 1.9, 4-H), 6.65 (1H, t, *J* 7.8, 6-H), 6.92 (1H, dd, *J* 7.8 and 1.3, 5-H) and 7.56 (1H, dd, *J* 7.8 and 1.3, 7-H); δ_C 67.0 (2-CH_2), 84.2 (8-CI), 122.9 (CH), 123.3 (C), 123.4, 124.7, 127.1, 138.9 (all CH) and 153.7 (C); *m*/*z* (EI) 258 (M$^+$, 54%), 127 (97) and 89 (100) [Found (EI): M$^+$, 257.9543. C_9H_7IO requires *M*, 257.9543].

Formation and use of Rieke zinc[24]

Clean potassium (0.078 g, 2 mmol) was added to a still suspension of anhydrous zinc chloride (0.276 g, 2 mmol) in dry tetrahydrofuran (20 ml). After the initial reaction subsided, the mixture was stirred slowly then gradually heated to reflux. The resulting jet-black suspension was refluxed for 2 h then a solution of a propargyl alcohol (1 mmol) in methanol (15 ml) was added dropwise, followed by water (3 ml). Refluxing was continued, with protection from light, for 16 h, then the suspension was cooled to ambient temperature and filtered through Celite. The reaction vessel and solids were rinsed with ether (30 ml) and the combined filtrates separated. The aqueous layer was acidified with 2 M hydrochloric acid and saturated with solid sodium chloride before being extracted with ether (2 × 20 ml). The combined organic solutions were washed with brine (30 ml) then dried and evaporated to give the (*Z*)-allylic alcohol, sufficiently pure for use in the final deprotection–cyclisation steps.

(*Z*)-1-(*tert*-Butoxycarbonylamino)-7-(3′-hydroxypent-1′-en-1′-yl)benzotriazole 40b

Reduction of the acetylenic alcohol **33b** (0.316 g, 1.0 mmol) using Rieke zinc by the general procedure gave the (*Z*)-*allylic alcohol* **40b** (0.305 g, 94%) as a yellow oil, ν_{max}/cm^{-1} 3380, 1725, 1380, 1029 and 910; δ_H (333 K) 0.85 (3H, t, *J* 6.4, 5′-CH_3), 1.42–1.54 (9H, br s, Bu^t), 1.55–1.60 (2H, m, 4′-CH_2), 4.03 (1H, m, 3′-C*H*OH), 4.42–4.49 (1H, br s, OH), 5.89 (1H, dd, *J* 11.2 and 9.5, 2′-H), 6.81 (1H, br d, *J* 11.2, 1′-H), 7.24 (1H d, *J* 7.1, 6-H), 7.32 (1H, t, *J* 7.1, 5-H) and 7.89 (1H, d, *J* 7.1, 4-H); δ_C (330 K) 10.0 (5′-CH_3), 28.6 (C(*C*H_3)$_3$), 30.1 (4′-CH_2), 69.6 (3′-CH), 83.6 (*C*(CH_3)$_3$), 119.6 (CH), 120.8 (C), 124.9, 128.4, 129.5 (all CH), 130.7 (C), 138.0 (CH), 144.9 (C) and 154.5 (CO); *m*/*z* 333 (M$^+$ + H, 100%) and 259 (20) [Found: M$^+$ + H, 315.1459. $C_{16}H_{19}N_4O_3$ requires *M*, 315.1457].

2-Ethyl-8-iodochromene 41b

By the combined deprotection–cyclisation procedure, sequential treatment of the foregoing *N*-Boc-aminobenzotriazole **40b** (0.132 g, 0.42 mmol) with TFA and NIS gave the *2-ethyl-8-iodochromene* **41b** (100 mg, 83% overall) as a yellow oil, ν_{max}/cm^{-1} 2962, 2926, 2869, 1588, 1437, 1380, 1223, 1122, 1058, 901, 865 and 786; δ_H 1.19 (3H, t, *J* 9.6, 2′-CH_3), 1.53–1.62 (2H, m, 1′-CH_2), 4.82 (1H, br td, *J* 8.1 and 3.5, 2-H), 5.63 (1H, dd, *J* 9.7 and 3.5, 3-H), 6.24 (1H, dd, *J* 9.7 and 1.5, 4-H), 6.54 (1H, t, *J* 7.7, 6-H), 6.84 (1H, dd, *J* 7.7, 5-H) and 7.45 (1H, dd, *J* 7.7, 7-H); δ_C 8.6 (2′-CH_3), 27.5 (1′-CH_2), 59.8 (2-CH), 83.6 (8-CI), 121.6, 122.5 (CH), 124.2 (C), 124.9, 127.2, 137.0 (all CH) and 153.0 (C) [Found: M$^+$ + H, 286.9932. $C_{11}H_{12}IO$ requires *M*, 286.9935].

(*Z*)-1-(*tert*-Butoxycarbonylamino)-7-(3′-hydroxy-3′-methylbut-1′-en-1′-yl)benzotriazole 40c

Benzotriazole **33c** (0.316 g, 1.0 mmol), derived from 2-methylbut-3-yn-2-ol, was reduced using Rieke zinc according to the general procedure to give the corresponding (*Z*)-*allylic alcohol* **40c** (0.254 g, 80%) as an oil, ν_{max}/cm^{-1} 3342, 2976, 2912, 1738, 1573 and 1152; δ_H (330 K) 1.28 (6H, s, 2 × CH_3), 1.54 (9H, s, Bu^t), 5.98 (1H, d, *J* 12.4, 2′-H), 6.57 (1H, d, *J* 12.4, 1′-H), 7.29–7.35 (2H, m, 5- and 6-H), 7.89 (1H, dd, *J* 6.4 and 2.1, 4-H) and 8.99 (1H, s, NH); *m*/*z* 319 (M$^+$ + H, 100%).

(8-Iodo-2-methylchromen-2-yl)methanol 41d

Benzotriazole **33f** (0.33 g, 1.0 mmol), derived from 2-methylbut-3-yne-1,2-diol, was reduced using Rieke zinc according to the general procedure to give the corresponding (*Z*)-*allylic alcohol* **40d** (0.20 g, 60%) as an oil, ν_{max}/cm^{-1} 3376, 2962, 2920, 2855, 1732, 1459, 1370, 1257, 1159, 1051 and 650; δ_H (330 K) 1.27–1.34 (9H, br s, Bu^t), 1.40–1.48 (3H, br s, 3′-CH_3), 3.30 (1H, br d, *J* 10.7, 4′-H_a), 3.39 (1H, br d, *J* 10.7, 4′-H_b), 5.82 (1H, br d, *J* 12.3, 2′-H), 6.57 (1H, br d, *J* 12.3, 1′-H), 7.30–7.35 (2H, m, 5- and 6-H), 7.66–7.69 (1H, br res, 4-H) and 9.51–9.55 (1H, br s, NH).

A sample of the foregoing allylic alcohol **40d** (0.158 g, 0.24 mmol) was immediately subjected to the combined deprotection–cyclisation procedure by sequential treatment with TFA and NIS to give the *iodochromen-2-ylmethanol* **41d** (0.091 g, 63%) as a yellow oil, ν_{max}/cm^{-1} 3259, 2955, 2855, 1459, 1430, 1258, 1087, 1051 and 793; δ_H 1.34 (3H, s, 2-CH_3), 3.60 (2H, s, 2-CH_2OH), 5.51 (1H, d, *J* 9.8, 3-H), 6.30 (1H, d, *J* 9.8, 4-H), 6.59 (1H, t, *J* 7.6, 6-H), 6.92 (1H, dd, *J* 7.6, and 1.3, 5-H) and 7.48 (1H, dd, *J* 7.6 and 1.3, 7-H); δ_C 21.4 (2-CH_3), 59.0 (2-CH_2OH), 79.6 (2-C), 87.2 (8-CI), 120.1 (CH), 122.3 (C), 125.2, 126.2, 128.4, 137.1 (all CH) and 152.3 (C) [Found (EI): M$^+$, 301.9807. $C_{11}H_{11}IO_2$ requires *M*, 301.9806].

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