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A NEW TACTIC FOR TOCOPHEROL SYNTHESIS USING INTRAMOLECULAR BENZYNE TRAPPING BY AN ALCOHOL

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Abstract – A formal total synthesis of (*S*)-α-tocopherol, the major component of natural Vitamin E has been achieved using intramolecular benzyne trapping as a key step to form the chroman ring. The synthesis also features an efficient new method for benzotriazole *N*-amination using an oxaziridine; chiral, non-racemic intermediates are generated using asymmetric dihydroxylation.

This paper is dedicated to Professor Lutz Tietze on his 75th birthday, with all best wishes.

INTRODUCTION

α-Tocopherol **1** is the major component of naturally occurring Vitamin E, the remaining components of which generally consist of less methylated analogues and examples containing alkenes in their side chains.[1]

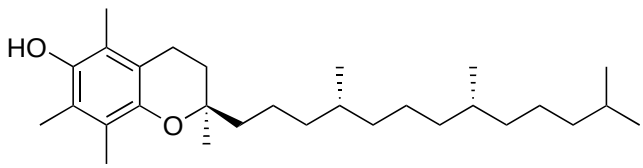

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Figure 1. a-Tocopherol, the major component of the natural Vitamin E mixture

The acetate derived from tocopherol is manufactured on a multi-ton scale by coupling trimethylhydroquinone and isophytol followed by acetylation and is used primarily as an anti-oxidant in a very wide variety of foods, pharmaceuticals, cosmetics, indeed almost any product which can suffer from the deleterious effects of oxidation upon prolonged storage.[2] More recent investigations

have revealed that tocopherol is distinguished by its ability to inhibit oxytosis, 5-lipoxygenase and phospholipase A_2 along with various kinases as well as being capable of activating protein phosphatase 2A and of gene regulation.[3] It has been strongly suggested that vitamin E should be studied much more seriously, in view of these discoveries.[3c] The anti-oxidant activity usually involves generation of a phenoxide radical followed by quinone formation and concomitant opening of the chroman ring.

Such anti-oxidant activity is not confined to tocopherol in this area: the analogous, commercially available acid, trolox **2**, also obtained from trimethylhydroquinone but together with methacrylic acid and formaldehyde, displays similar anti-oxidant properties and is differentiated from the very lipophilic vitamin E components by reason of its highly polar carboxylic acid group.[4] Contrasting applications as a preservative as well as a precursor to the tocopherols mark this compound out as an important member of this series, especially at it can be readily resolved.

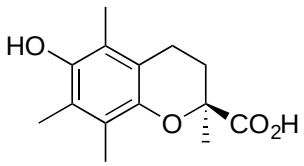

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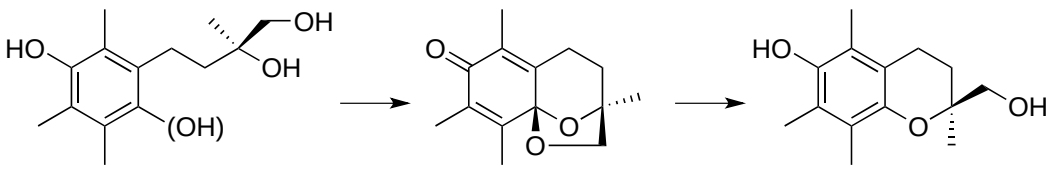
Figure 2. Trolox, a non-natural but powerful anti-oxidant

Synthetic activity in this area has employed many of the known methods for the asymmetric formation of C-O bonds. Once achieved, many earlier syntheses utilised the 'Cohen' approach outlined in Scheme 1.[5] Thus, a phenol or hydroquinone **3** carrying a suitably functionalised side chain, either protected or unprotected as shown, is oxidized to the corresponding quinone level and cyclised by mild acid treatment to the acetal **4**, subsequent reduction of which then leads to the target chroman-2-methanol **5**. There are many versions of this strategy, in which the order of events may be altered or an intermediate related to acetal **4** not isolated. Clearly, there are then many possibilities for the elaboration of a suitable side chain.[6]



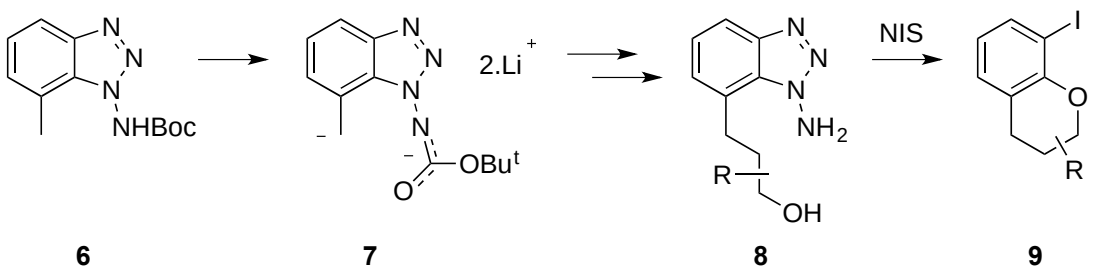
3 **4** **5**

Scheme 1. The 'Cohen' approach

Unsurprisingly, the Sharpless epoxidation[7] and AD-mix methods[8] have both been employed in the asymmetric synthesis of tocopherol. More modern approaches have usually focussed instead on formation of the chroman C-O bond from similar chiral, non-racemic precursors, often by intramolecular attack of the phenol group onto an activated intermediate derived from diols **3** or by a similar attack but onto an allylic alcohol or related structure, activated by a chiral catalyst, which is often palladium-based[9,10] but can also be a gold[11] or ruthenium species.[12] Various enzymatic resolutions and related methods have also proven useful in preparing enantiomerically enriched samples of the tocopherols,[13] which have also been obtained using a biomimetic approach.[14]

RESULTS AND DISCUSSIONS

The setting for our work in this area was the discovery that lateral deprotonation of the 1-aminobenzotriazole derivative **6** provides a quantitative conversion into the dianion **7**, which could then be reacted with a range of electrophiles to give generally excellent yields of a range of analogues.[15] In the light of the classic work by Rees' group,[16] this then provided an approach to 3-substituted benzynes, following *N*-deprotection and amine oxidation. One particular finding was that such benzynes could be effectively trapped in an intramolecular fashion by a pendant hydroxyl group (*cf.* **8**) to give iodo-chromans **9**, as well as other bicyclic derivatives (Scheme 2).[17]



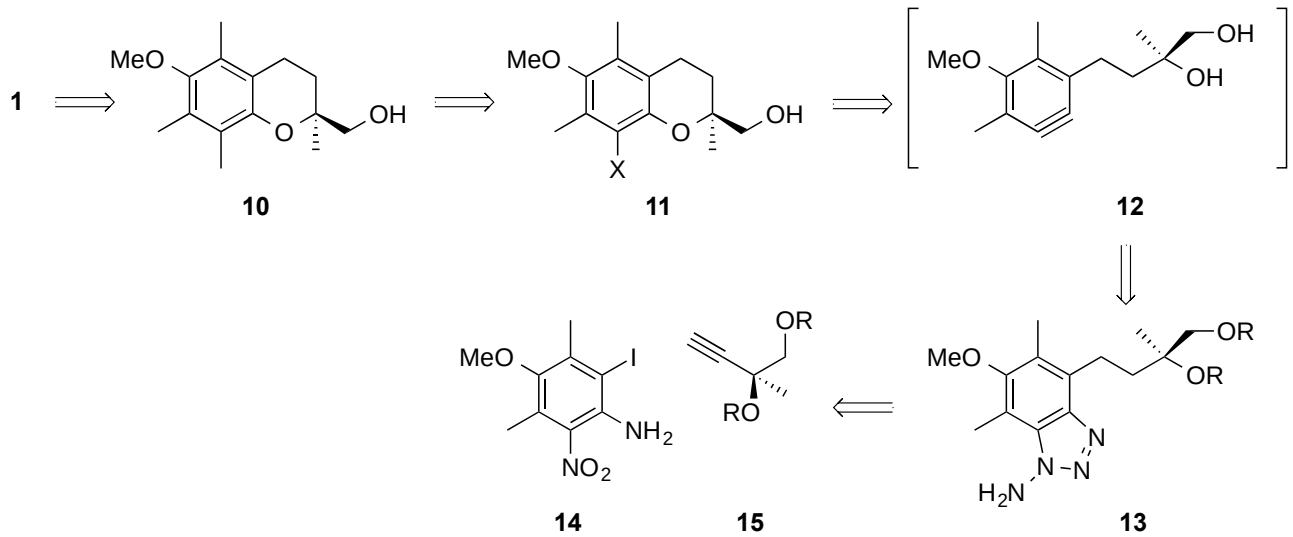
6 **7** **8** **9**

Scheme 2. Lateral metallation - benzyne trapping by an alcohol as an appropach to chromans

In general, alcohols have not been used in this way previously,[18] probably because benzyne generation was achieved from a halobenzene or a 1,2-dihalobenzene using halogen-metal exchange, which inevitably meant that the hydroxyl group would be deprotonated; it seems that such alkoxides, being 'hard' nucleophiles, are incompatible with the much softer benzynes. In the final oxidation step of the present method (Scheme 2), the alcohol is not ionized: the original Rees methods used either lead(IV) acetate or *N*-bromosuccinimide for this purpose; we found that *N*-iodosuccinimide (NIS) gave enhanced yields.[17] Of course, a potential bonus of this methodology is the incorporation of the iodine atom, which lends itself to additional homologation by a plethora of coupling and other reactions.

Hence, this method, overall, could be regarded a having some generality for the synthesis of 1,2,3,4-tetrasubstituted benzenes.

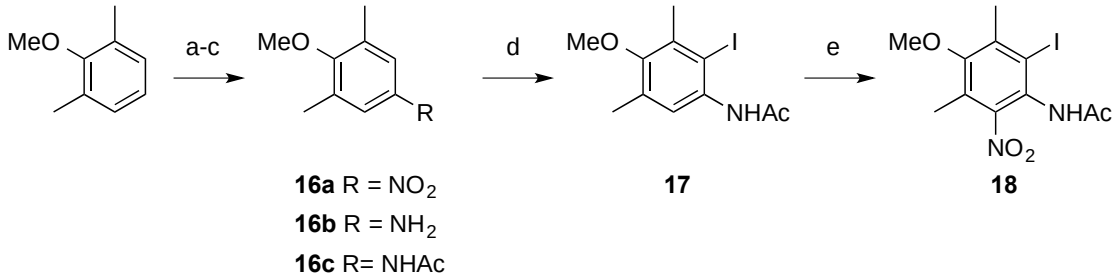
We wished to demonstrate that it was possible to apply this methodology to the synthesis of the tocopherol precursor alcohol **10**, with the particular aim of demonstrating that such a benzyne-based approach could be successfully used to synthesise a more highly substituted target. In the light of the foregoing results, the structure of alcohol **10** leads back to two, seemingly readily available, starting materials. (Scheme 3). Trapping of the key benzyne **12** was expected to be regiospecific in favour of chroman formation[17] and also result in incorporation of a halogen atom (X = Br or I) into the chroman **11**, which should allow addition of the final methyl group. The key benzyne **12** could then be generated from 1-aminobenzotriazole **13**, or its regioisomer, itself a product of a Sonogashira coupling between the fully-substituted benzene **14** and the alkyne-diol **15**, followed by a double hydrogenation of both the nitro and alkyne functions and triazole formation. We chose not to use our dianion methodology (Scheme 2), as trapping of such an intermediate (*cf.* dianion **7**) with saturated alkyl halides or epoxides was not generally very efficient and it was also likely to be a synthetic challenge to form a single regioisomer of a suitably substituted aminobenzotriazole.[15] In addition, other model reactions suggested that there would be a lack of regioselectivity in metallations of more highly substituted *N*-Boc-aminobenzotriazoles. The need for and the nature of the protecting groups in the alkyne diols **15** and subsequent derivatives were also far from clear.



Scheme 3. Retrosynthetic analysis for a possible benzyne-based appropach to chroman-2-methanol **10**

Synthesis of the fully-substituted benzene **18** began with an efficient nitration[19] of commercial 2,6-dimethylanisole, given that the temperature was always kept below 70 °C (see Experimental), followed by reduction of the resulting 4-nitro derivative **16a** to the corresponding aniline **16b** using transfer hydrogenation[20] and acetylation to give acetanilide **16c** in excellent overall yields (Scheme 4).

Subsequent iodination using *N*-iodosuccinimide in acetic acid[21] worked well and the sequence was completed by a slow but efficient nitration of the resulting iodide **17** to install all the required functionality. Any variation in the order of this sequence gave (much) lower returns, as expected.



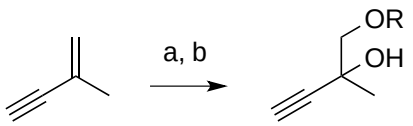
16a R = NO_2
16b R = NH_2
16c R= NHAc

17

18

Scheme 4. Reagents and conditions: a) 70% HNO_3, HOAc, 0-65 °C (61%); b) 10% Pd-C, cyclohexene, EtOH, 80 °C, ~14 h (91%); c) AcCl, Et_3N, THF, 0-20 °C,14 h (89%); d) NIS, HOAc, reflux, 1.5 h (70%); e) 70% HNO_3, HOAc, 65 °C, 5 h (76%).

The second component, the alkyne-diol **20a** was obtained from enyne **19**, readily obtained by acid-catalysed dehydration of the acetylene-acetone adduct,[22] by asymmetric dihydroxylation using AD-mix β.[22] While we were unable to achieve useful separations of the diol enantiomers using a variety of GC and HPLC methods, the derived benzoate **20b** proved readily separable by GC; unhappily, the enantiomeric enrichment was below 10% (Scheme 5). This is perhaps not too surprising, as terminal alkenes are often not good substrates for this reaction and an alkyne group is hardly a sterically dominant substituent. However, having secured a supply of the diol **20a**, we chose to continue with this essentially racemic material, to hopefully establish suitable conditions to enable completion of the projected synthesis.



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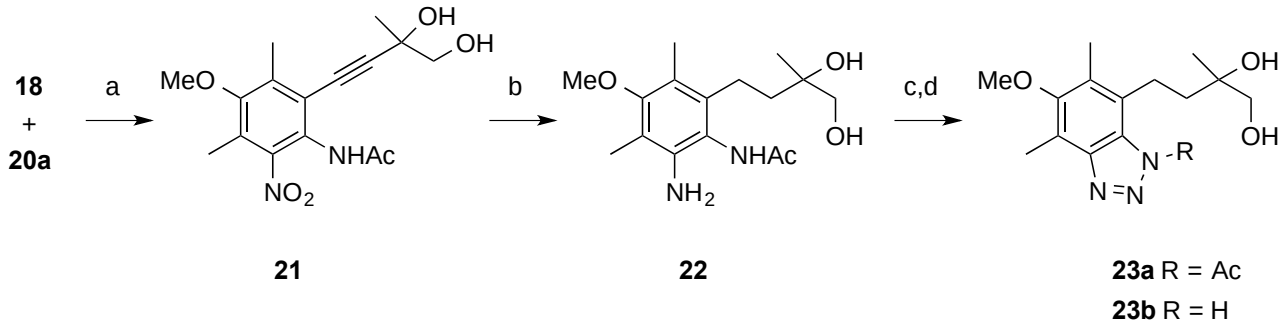
20a R = H [< 10% ee]
20b R = Bz

Scheme 5. Reagents and conditions: a) AD-mix-b, $MeSO_2NH_2$, ^tBuOH-H_2O (1:1), rt, 24 h (67%); b) BzCl, Et_3N, CH_2Cl_2, rt 14 h (71%).

The first of these steps was Sonogashira coupling between the iodo-anisole **18** and the alkyne-diol **20a**. This proved to be quite slow and required relatively large amounts of the catalysts to achieve even this rate of reaction, despite the activating effect of the nitro group, which we chose to retain for this very reason, and, to a lesser extent, the *N*-acetyl group. Happily, after a 24 h reflux in THF, a 77% isolated yield of the desired coupled product **21** was obtained (Scheme 6). Similarly, some experimentation

was required to establish optimised conditions for the simultaneous reduction of both the nitro and alkyne groups: eventually, it was found that prolonged exposure to Pearlman's catalyst (20% palladium hydroxide on carbon) at ambient temperature secured an essentially quantitative yield of the desired aniline **22**. Under more vigorous conditions, especially when a reduction was heated, we also noticed the formation of a by-product, which remained unidentified at this stage.

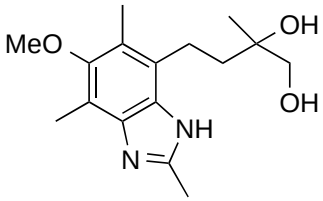


Scheme 6. Reagents and conditions: a) $Pd(Ph_3P)_4$ (20 mol%), Et_3N, **18** (1 eq.), **20a** (2 eq.), THF, CuI (20 mol%), reflux, 24 h (77%); b) 20% $Pd(OH)_2$-C, MeOH, H_2 (1 atm.), 48 h, rt, (99%); c) MeOH, rt, aq $NaNO_2$ (3 eq.), 5M HCl, 0 ^oC, 0.5 h (73%); d) K_2CO_3, aq MeOH, rt, 4 h (99%) .

The same unidentified by-product was again evident in initial attempts to form the triazole ring by diazotization of aniline **22**; eventually, its formation was much reduced by using three equivalents of sodium nitrite to carry out the diazotization-cyclisation step, which then delivered >70% yields of the benzotriazole **23a** from which the acetyl group was readily removed by mild, base-catalysed hydrolysis to give the free benzotriazole **23b**. The excellent yield was only realised when a non-aqueous work-up was used, due to the water solubility of this polar product. Unexpectedly, its NMR spectra, when obtained for a solution in CD_3OD, showed the presence of essentially a single tautomer, whereas in $CDCl_3$, two forms were observed, in a 2:1 ratio. Possibly, the tautomer shown, **23b**, may be favoured by hydrogen bonding between the new amino group and the pendant hydroxyls. A small amount of the by-product was also isolated during this stage: a small sample showed that it did not contain a carbonyl group (IR), but did have a ^{13}C resonance for a quaternary carbon at ~ 155 ppm, together with five methyl singlets in its ^1H NMR spectrum, but in slightly differing positions than related derivatives **21-23a** (Scheme 6). MS data (APCI) indicated its formation by loss of water: a probable molecular ion at m/z 293 (M + H) contrasted with that for the *N*-acetyl benzotriazole **23a** at m/z 311 (M + H).

We deduced that this was the benzimidazole **24**, formed by intramolecular cyclization of the *N*-acetyl benzotriazole **23a**, either when more vigorous hydrogenation conditions were used or when diazotization was relatively slow, allowing such an (acid-catalysed) cyclisation to compete with

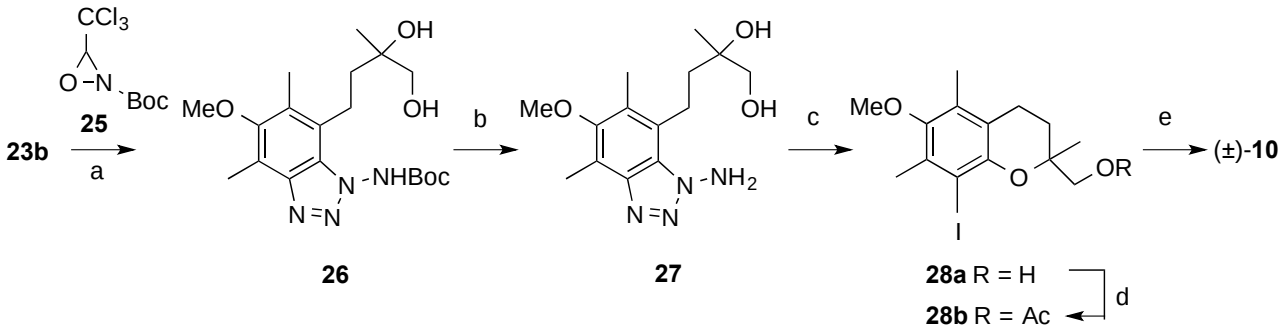
benzotriazole formation (Figure 3). Hence, relatively mild conditions or excess reagents were essential to secure high yields from these two steps [b) and c), Scheme 6].



24

Figure 3. The benzimidazole by-product .

The next step was electrophilic *N*-amination.[23] In previous work,[15] we had optimised the original Campbell and Rees method,[24] which used hydroxylamine-*O*-sulfonic acid as the source of an electrophilic amino group. However, the relatively delicate nature of benzotriazole **23b** meant that the method failed in this case. Fortunately, a mild alternative was the series of *N*-alkoxycarbonyl-oxaziridines, which can deliver an alkoxycarbonylamino group to a free amine function, thereby forming an N-N bond.[25,26] A range of such derivatives have been assessed, all of which carry electron-withdrawing groups; one of the best appeared to be the chloral derivative **25**.[27] We were delighted to find that simply stirring this compound with the benzotriazole **23b** in dichloromethane at ambient temperature delivered an essentially quantitative yield of the desired aminated product **26** (Scheme 7).

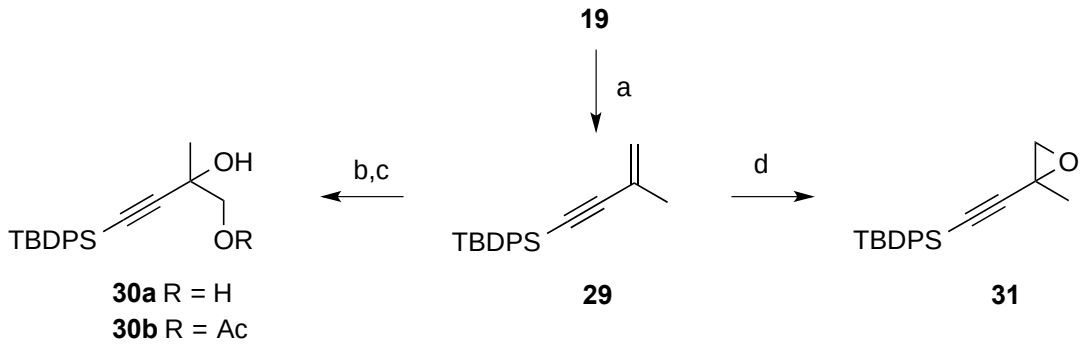


Scheme 7. a) CH_2Cl_2, rt, 18 h (94%); b) 20% TFA, CH_2Cl_2, rt, 0.75 h; c) K_2CO_3, CH_2Cl_2, filter, add NIS (2.5 eq.) rt, 1 h (63% **28a**; two steps); d) AcCl, pyridine, DMAP (cat.), rt, 14 h (75%); e) **28a**, Me_4Sn, $(dba)_3Pd_2.CHCl_3$, Ph_3P, CuI, Et_2NH, NMP, 100 °C, 24 h (59%).

Rather than risk difficulties with the isolation of the doubtless polar free amine **27**, we chose to deprotect using trifluoroacetic acid and, after basification, treat the residue directly with *N*-iodosuccinimide. We were delighted to then isolate the desired iodo-chroman **28a**, in 63% yield for the two steps, which was converted into the corresponding acetate **28b**, simply to more clearly observe the AB-system due to the new CH_2OR group, which overlapped with the methoxyl resonance in the initial

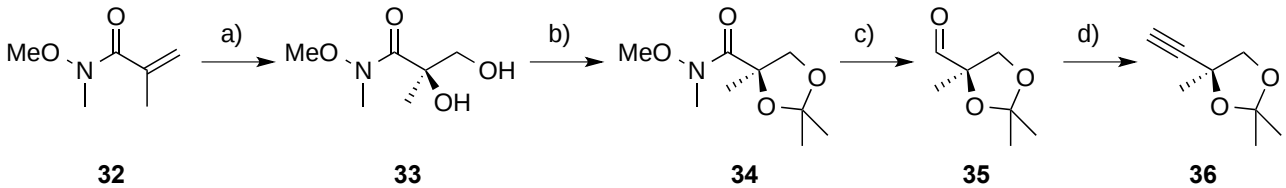
product **28a** (Scheme 7). A modified Stille methylation, with the addition of copper(I) iodide,[28] was then used to complete the sequence, giving a 59% yield of the target chroman, (±)-**10**.

A final problem was therefore to find a method suitable for obtaining the alkyne-diol **20a**, or a related protected form, in optically enriched form. We thought to add considerable bulk to the alkyne group in diol **19** in the form of a large silicon group. However, exposure of such a derivative **29** to AD-mix-β once again failed to give significant chiral induction: HPLC analysis of the derived acetate **30b** showed a ee of only 12.7% (Scheme 8). Hydrolytic kinetic resolution[29] of the derived epoxy-alkyne **31** also failed to give significant chiral induction.



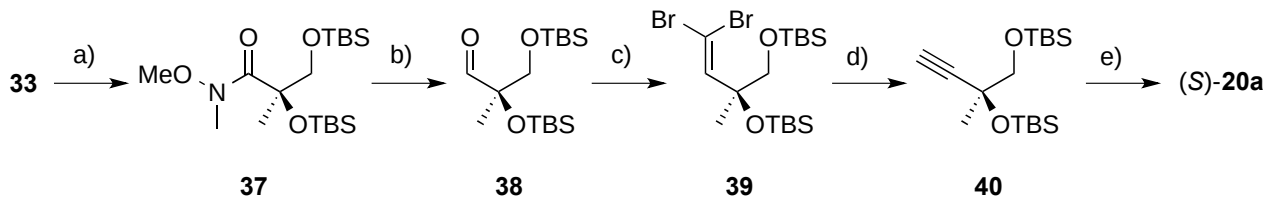
Scheme 8. a) BuLi, THF, ice bath, *t*-BuPh$_2$SiCl, 2 h (86%); b) AD-mix-b (Scheme 5), 70%; c) Ac$_2$O, pyridine, rt, 18 h (90%); d) *m*-CPBA, CH$_2$Cl$_2$, rt, 2 h (95%).

We therefore turned to the known if chemically more distant chiral, non-racemic diol **33**.[30] This time, AD-mix-α was used to obtain the required diol **33** with chemical and optical yields both of 91%, in agreement with the initial report of its synthesis (Scheme 9). Protection as the corresponding dioxolane **34** and selective Dibal-H reduction then proceeded smoothly to give the aldehyde **35**, which was converted into the alkyne **36** by addition of a trichloromethyl group to the aldehyde, acetylation, elimination of HCl using zinc and further HCl elimination from the resulting dichloroalkene using butyl lithium.[31] The method was readily scalable and routinely gave overall yields of around 60%. Alternatives based on Wittig chemistry (Seyferth-Gilbert or Ohira-Bestmann methods) were either low yielding or unsuccessful.



Scheme 9. a) AD-mix-a (ref. 30), (91%) (91% ee); b) 2,2-dimethoxypropane, *p*-TSA, toluene, reflux, 2 h (87%); c) Dibal-H, THF, ice bath, 1 h (100%); d) i) Cl$_3$CCO$_2$Na, Cl$_3$CCO$_2$H, DMF, ice bath, 4 h, no cooling, then ice bath, add Ac$_2$O, rt, 1 h, add HOAc then Zn, 60 ^{o}C, 1 h (57%), ii) BuLi, THF -30 ^{o}C - rt, 1 h (99%).

Sadly, attempts to use the dioxolane alkyne **36** in the Sonogashira coupling with iodo-anisole **18** (see Scheme 6) were only partly successful as, unexpectedly, around half the product was simply the deiodinated arene. Attempts to hydrolyse the dioxolane group were also not viable in our hands, using Brønsted or Lewis acid-based methods, due to the extreme sensitivity of the diol **20a** to dehydration. Basic deprotection conditions were therefore required and so silyl protection was next investigated. Silylation of the dihydroxyamide **33** was slow but uneventful while Dibal-H reduction of the resulting *bis*-silyl derivative **37** was insufficiently selective, giving the expected aldehyde **38** along with the corresponding alcohol and desilylation at the tertiary site (Scheme 10). By contrast, low temperature reduction using ethereal $LiAlH_4$ was completely selective and gave an 88% isolated yield, lowered no doubt by the high volatility of the aldehyde **38**. Corey-Fuchs homologation[32] then delivered the alkyne **40** by way of the dibromoalkene **39** and thence the (*S*)-alkyne-diol **20a**.



Scheme 10. a) *t*-$BuMe_2SiCl$, imidazole, DMF, 35 °C, 18 h (94%); b) $LiAlH_4$, Et_2O, -78 °C, 40 min., aq. NaOH work-up (88%); c) Ph_3P, CBr_4, CH_2Cl_2, rt, 4 h (74%); d) BuLi, THF, - 30 °C, rt 1 h (59%); e) TBAF, THF, rt 2 h (82%).

Using the same method as above (Scheme 6), the (*S*)-alkyne-diol **20a** was successfully coupled to the iodo-anisole **18** to give the expected (*S*)-(+)-alkynyl anisole **21** (Figure 4). We were also able to hydrolyse the acetyl group in iodo-anisole **18** to give the corresponding aniline **14**; this too coupled well with the (*S*)-alkyne-diol **20a** leading to the homologated aniline (*S*)-(+)-**41**, thereby completing a formal asymmetric synthesis of tocopherol **1**.

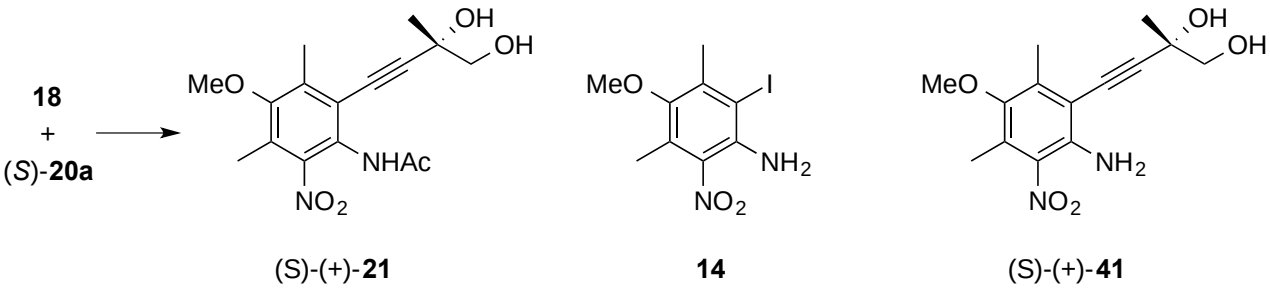
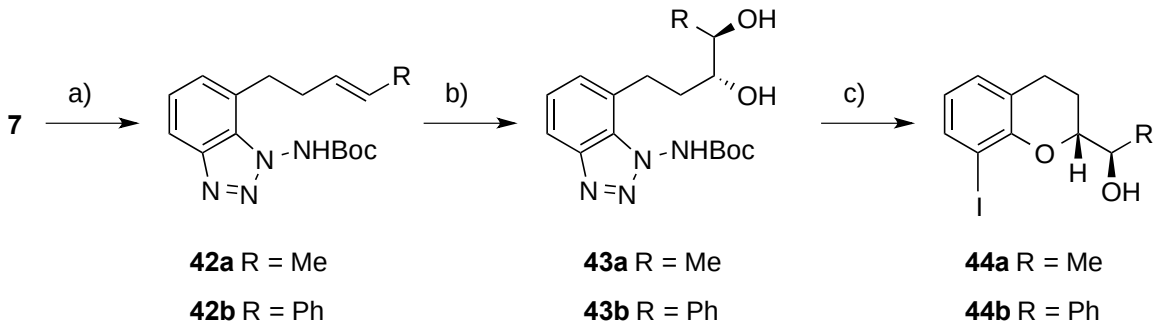


Figure 4. Chiral, non-racemic derivatives.

In any synthetic scheme that encounters problems; simply altering the order of steps can often obviate these. As a small caveat to the foregoing synthesis, we have shown that this might be possible in this

case, by first incorporating an alkene into a suitable benzotriazole and then carrying out the asymmetric dihydroxylation step (Scheme 11).



Scheme 11. a) crotyl chloride (**43a**) or cinnamyl bromide (**43b**), ref. 15, (97% and 78%); b) Scheme 5, AD-mix-b, 65% and 82%; c) As Scheme 7, steps b and c, (68% and 57%).

Thus, alkylation of the dianion **7** (Scheme 2)[15] derived from 1-aminobenzotriazole, by both (*E*)-crotyl and (*E*)-cinnamyl halides gave excellent yields of the unsaturated homologues **42a,b**. Asymmetric dihydroxylation then worked well with both substrates to give the diols **43a,b**, the optical purities of which were 76% and 82% respectively according to hplc analysis (see **30b** in Experimental). Both then underwent sequential deprotection and regiospecific cyclisation, as described above, to provide reasonable but unoptimised yields of the iodochromans **44a,b**. Hence, this alternative approach may have some potential in this and related areas for the elaboration of a wide variety of substituted chromans.

We have thus reached our goal of synthesising a tocopherol precursor using intramolecular benzyne trapping by an alcohol group. Clearly, the approach overall is quite lengthy but does demonstrate the viability of this key step and could probably be shortened in a number of ways. Additionally, the use of the oxaziridine **25** should be of considerable use in this and related areas in future, when *N*-amination is required. The final feature of note in this synthesis is the incorporation of an iodine atom at a late stage, which suggests that this chemistry could be useful for the synthesis of radio-labelled products, for example using iodine 131, which has a half-life of around eight days.

EXPERIMENTAL

Infrared spectra were recorded using a Perkin Elmer 1600 series FTIR instrument as thin films or KBr disks. ^{1}H NMR spectra were all recorded for dilute solutions in deuteriochloroform, unless otherwise stated, using a Bruker AM 400 MHz instrument with chloroform as internal reference (δ = 7.27). ^{13}C NMR spectra were all recorded in deuteriochloroform using a Bruker AM 400 MHz instrument, operating at 100 MHz with chloroform as internal reference (δ = 77.30). Low resolution mass spectra

were obtained using a Fisons VG Platform II instrument and high resolution spectra were measured by the EPSRC Service, Swansea University. All extracts were dried over dried magnesium sulfate. Column chromatography was performed using Silica 60A, particle size 35-70 micron, from Fisher Scientific.

2,6-Dimethyl-4-nitroanisole (16a): To an ice-cold, stirred solution of 2,6-dimethylanisole **15** (40.00 g, 294 mmol) in glacial acetic acid (60 mL) was added dropwise 70% nitric acid (60 mL). After the addition was complete and gas evolution began to subside, the solution was slowly heated to 65 ºC resulting in the formation of a pale yellow solution. [**CAUTION: It is essential to keep the reaction temperature below 70 ºC at all times as, above this, the mixture on occasions detonated with extreme violence; protection by a blast screen in recommended in any event].** The solution was then allowed to cool to ambient temperature and diluted with water (300 mL). Nitrogen was bubbled through the resulting deep brown solution for *ca.* 0.5 h to remove most of the nitrogen oxides present. The resulting yellow precipitate was separated by vacuum filtration and washed with copious water then crystallised from ethanol to give the *nitroanisole* **16a** (32.6 g, 61%), mp 91.5-93.5 ºC (lit.[18] mp 89-91 ºC); ^{1}H NMR δ 2.28 (s, 6H, 2 x Me), 3.71 (s, 3H, OMe), 7.83 (s, 2H, ArH); ^{13}C NMR δ 16.8 (2 x Me), 60.3 (OMe), 124.6 (2 x ArCH), 132.7 (2 x ArC), 143.8 (ArC), 162.8 (ArC); *m/z* (APCI) 152 (M-29, 100%).

4-Amino-2,6-dimethylanisole (16b): To a suspension of 10% Pd-C (0.65 g) in ethanol (130 mL) at rt was added portionwise the foregoing nitroanisole **16a** (10.00 g, 55 mmol) followed by cyclohexene (32 mL, 330 mmol). The mixture was then heated under reflux for 14 h, cooled to rt and filtered through celite. The filter cake was washed with ethanol and the combined filtrates evaporated to leave the sensitive *aniline* **16b** (7.56 g, 91%) as a brown solid which was sufficiently pure for further use and which showed mp 62-63 ºC (lit.[33] mp 60-61 ºC), IR (KBr) 3772, 3612, 3397, 1605, 1487, 1340, 1219, 1150, 1016 cm^{-1}; ^{1}H NMR δ 2.24 (s, 6H, 2 x Me), 3.47-3.51 (br s, 2H, NH_2), 3.69 (s, 3H, OMe), 6.39 (2, 2H, 2 x ArH); ^{13}C NMR δ 16.5 (2 x Me), 60.4 (OMe), 115.7 (2 x ArCH), 131.9 (2 x ArC), 142.5 (ArC), 150.0 (ArC); *m/z* (APCI) 152 (M + 1, 100%).

4-Acetamido-2,6-dimethylanisole (16c): A stirred solution of the foregoing aniline **16b** (7.60 g, 50 mmol) in dry THF (100 mL) containing triethylamine (7.4 mL, 53.2 mmol) was cooled in an ice-bath before the addition of acetyl chloride (4.0 mL, 54.1 mmol). The resulting solution was stirred overnight without further cooling then quenched by the sequential addition of saturated aqueous ammonium chloride (47 mL) and 2M hydrochloric acid (47 mL). The resulting mixture was extracted with ether (3 x 75 mL) and the combined extracts washed with water (75 mL) and brine (75 mL) then dried and evaporated. Crystallisation of the residue from ethanol left the *acetamide* **16c** (8.60 g, 89%); mp 136-137 ºC [lit.[34] mp 136-138 ºC]; IR (KBr) 3315, 1659, 1612, 1558, 1462, 1221, 1038, 1010 cm^{-1};

^{1}H NMR δ 2.10 (s, 3H, Ac), 2.22 (s, 6H, 2 x Me), 3.64 (s, 3H, OMe), 6.94 (br s, 1H, NH), 7.08 (s, 2H, 2 x ArH); ^{13}C NMR δ 16.5 (2 x Me), 24.8 (MeCO), 60.2 (OMe), 121.1 (2 x ArCH), 131.7 (2 x ArC), 133.8 (ArC), 153.9 (ArC), 168.9 (C=O); *m/z* (APCI) 194 (M^+, 100%).

4-Acetamido-2,6-dimethyl-5-iodoanisole (17): A suspension of the foregoing acetamide **16c** (7.4 g, 38.1 mmol) and *N*-iodosuccinimide (12.9 g, 57.2 mmol) in glacial acetic acid (120 mL) was heated to reflux for 1.5 h. The resulting purple solution was cooled to rt and neutralised with 2M aqueous sodium hydroxide to give a suspension which was vacuum filtered. The solid was washed with water then crystallised from ethyl acetate to give the *iodo-anisole* **17** (8.5 g, 70%); mp 189-191 ºC; IR (KBr) 3272, 1651, 1527, 1461, 1377, 1228, 1160, 1006 cm^{-1}; ^{1}H NMR δ 2.08 (s, 3H, Ac), 2.12 (s, 3H, Me), 2.28 (s, 3H, Me), 3.52 (s, 3H, OMe), 7.15-7.25 (br s, 1H, NH), 7.61 (s, 1H, 3-H); ^{13}C NMR δ 16.4 (Me), 22.9 (Me), 24.8 (Me), 60.4 (OMe), 96.4 (C-I), 123.0 (3-CH), 131.7 (ArC), 134.4 (ArC), 135.1 (ArC), 153.9 (ArC), 168.5 (C=O); *m/z* (APCI) 320 (M^+ + H, 100%). Anal. Calcd for $C_{11}H_{14}INO_2$: C, 41.38; H, 4.42; N, 4.39. Found: C, 41.60; H, 4.35; N, 4.36.

4-Acetamido-2,6-dimethyl-5-iodo-3-nitroanisole (18): The foregoing iodo-anisole **17** (1.00 g, 3.1 mmol) was stirred in glacial acetic acid (10 mL) at rt as 70% nitric acid (2.0 mL) was added dropwise. The resulting solution was then stirred at 65 ºC for 5 h, cooled to rt, diluted with water (18 mL) and the resulting precipitate collected by filtration and crystallised from aqueous ethanol to give the *nitro-iodide* **18** (0.85 g, 76%); mp 226-227 ºC; IR (KBr) 3617, 3212, 1667, 1519, 1455, 1376, 1272, 1221, 1039, 989 cm^{-1}; ^{1}H NMR δ 2.17 (s, 3H, Ac), 2.22 (s, 3H, Me), 2.49 (s, 3H, Me), 3.72 (s, 3H, OMe), 7.06-7.17 (br s, 1H, NH); ^{13}C NMR δ 12.2 (Me), 23.7 (Me), 23.9 (Me), 61.0 (OMe), 106.3 (CI), 125.2 (ArC), 126.3 (ArC), 127.3 (ArC), 139.9 (ArC), 156.2 (ArC), 169.3 (C=O); *m/z* (APCI) 365 (M^+ + H, 100%). Anal. Calcd for $C_{11}H_{13}IN_2O_4$: C, 36.28; H, 3.60; N, 7.69. Found: C, 36.43; H, 3.81; N, 7.56.

2-Methyl-1-buten-3-yne (19): 2-Methylbut-3-yn-2-ol (50 g) and *p*-toluenesulfonic acid (50 g) were stirred together and heated to 90 ºC under a distillation apparatus. After 3 h, the distillate was redistilled (bath temp. 50 ºC) to give the *enyne* **19** (11.4 g, 29%); bp 34 ºC; IR (film) 3300, 3100, 1614, 1455, 1374, 1266, 1214, 1171, 1013, 961, 904 cm^{-1}; ^{1}H NMR δ 1.71 (s, 3H, Me), 2.71 (s, 1H, 4-H), 5.11 (app. s, 1H, 1-H_a), 5.21 (app. s, 1H, 1-H_b).[21]

3,4-Dihydroxy-3-methyl-1-butyne (20a): AD-mix-β (63.70 g) was added to a stirred mixture of *t*-butanol (225 mL) and water (225 mL) followed by methanesulfonamide (4.30 g). Once the mixture became clear, the foregoing enyne **19** (3.00 g, 45.5 mmol) was added and the resulting mixture stirred at rt for 24 h. Sodium sulfite (68 g) was then added and stirring continued for 1 h. The mixture was then extracted with dichloromethane (4 x 100 mL) and the combined extracts washed with 2M aqueous potassium hydroxide (2 x 50 mL) then dried and evaporated. Column chromatography over silica gel eluted with ether-hexanes (2:1) then separated the *diol* **20a** (3.1 g, 67%) as a pale yellow oil.

IR (film) 3430, 2113, 1622, 1511, 1376, 1244, 1060, 953, 891 cm^{-1}; ^1H NMR δ 1.37 (s, 3H, Me), 2.39 (s, 1H, 1-H), 3.44 (d, *J* = 7.6 Hz, 1H, 4-H_a), 3.60 (d, *J* = 7.6 Hz, 1H, 4-H_b); ^{13}C NMR δ 25.6 (Me), 68.6 (3-C), 70.7 (4-CH_2), 72.6 (1-CH), 86.3 (2-C); *m/z* (APCI) 100 (M^+, 100%).

(±)-2-Hydroxy-2-methyl-3-butyn-1-yl benzoate (20b): Benzoyl chloride (26 μL, 0.22 mmol) was added to a stirred solution of the diol **20a** (20 mg, 0.2 mmol) in dry dichloromethane containing triethylamine (30 μL, 0.22 mmol). After stirring overnight at rt, the solution was diluted with dichloromethane (5 mL) and washed with water (3 mL), 1M hydrochloric acid (2 mL) and brine then dried and evaporated. Short-column chromatography (SiO_2; petrol-ether 4:1) separated the *benzoate* **20b** (29 mg, 71%) as a colourless oil; IR (film) 3456, 3284, 2360, 1722, 1452, 1371, 1274, 1116, 710; ^1H NMR δ 1.53 (s, 3H, 2-Me), 2.43 (s, 1H, 4-H), 2.92 (br s, 1H, OH), 4.23 (d, *J* = 11.1 Hz, 1H, 1-H_a), 4.36 (d, *J* = 11.1 Hz, 1H, 1-H_b), 7.36 (t, *J* = 7.6 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 1H), 8.00 (dd, *J* = 7.6, 1.0 Hz, 2H); ^{13}C NMR δ 26.4 (Me), 67.3 (CH2), 71.6 (2-C), 73.1 (4-CH), 85.1 (3-C), 128.9 (2 x ArCH), 130.0 (ArC), 130.2 ArCH), 133.7 (2 x ArCH), 166.8 (C=O); *m/z* (APCI) 205 (M+H, 100%).

GC analysis using a chiral CDX-β column at 150 °C (detector: 300 °C; injection: 250 °C]; column head pressure: 20 psi, R_t ~ 14.2 min. showed < 10% ee against a racemic sample.

Sonogashira coupling; General Procedure:[35] The aryl iodide (3.5 mmol) was stirred in degassed THF (40 mL) then triethylamine (14 mL) and tetrakis(triphenylphosphine)palladium(0) (0.80 g, 0.7 mmol) was added followed by the 1-alkyne (7.0 mmol). The resulting solution was degassed again by passage of dry nitrogen for 40 minutes before copper(I) iodide (133 mg, 0.7 mmol) was added and the mixture stirred at reflux for 24 h then cooled to rt and the bulk of the THF evaporated. The residue was diluted with water (35 mL) and extracted with dichloromethane (3 x 50 mL). The combined extracts were dried and evaporated and the product(s) separated by column chromatography over silica gel, typically using 5% MeOH-$CHCl_3$ as elutant.

(±)-4-Acetamido-2,6-dimethyl-5-[3',4'-dihydroxy-3'-methylbut-1'-yn-1'-yl]-3-nitroanisole (21): Following the general Sonogashira procedure, the nitro-iodide **18** (1.30 g, 3.5 mmol) was coupled with the diol **20a** (0.70 g, 7.0 mmol) using $(Ph_3P)_4Pd$ (0.80 g, 0.7 mmol) to give the *alkyne-diol* **21** (1.00 g, 86%) as a pale yellow, amorphous solid, mp 178-182 °C (MeOH); IR 3822, 3580, 3280, 1667, 1504 cm^{-1}; ^1H NMR δ 1.46 (s, 3H, 3'-Me), 2.13 (s, 3H, Ac), 2.23 (s, 3H, ArMe), 2.36 (s, 3H, ArMe), 3.04 (br s, 2H, 2 x OH), 3.43-3.50 (m, 2H, 4'-CH_2), 3.65 (S, 3H, OMe), 7.54 (BR S, 1H, NH); ^{13}C NMR (CD_3OD) δ 12.1 (Me), 15.5 (Me), 23.0 (Me), 26.6 (Me), 61.4 (OMe), 70.2 (CH_2), 71.4 (C), 78.7 (C), 103.9 (1'-C), 124.3 (ArC), 126.2 (ArC), 127.7 (ArC), 128.3 (ArC), 138.6 (ArC), 157.8 (ArC), 173.4 (C=O); *m/z* (APCI) 319 (M^+-OH, 100%). HR-MS (FAB). Calcd for $C_{16}H_{21}N_2O_6$ (M+H): 337.1396. Found: *m/z* 337.1400.

(±)-4-Acetamido-3-amino-2,6-dimethyl-5-[3',4'-dihydroxy-3'-methylbut-1'-yl]anisole (22): The alkyne-diol **21** (0.22 g, 0.66 mmol) was added to a suspension of 20% palladium hydroxide on carbon (Pearlman's catalyst) (44 mg) in methanol (40 mL) and the mixture stirred under an atmosphere of hydrogen for 48 h then filtered through celite. The solid was washed with warm methanol and the combined filtrates evaporated to leave the *aniline* **22** (0.202 g, 99%) as a pale yellow gum; IR (film) 3418, 1641, 1461, 1121 cm^{-1}; ^1H NMR δ 1.09 (s, 3H, 3'-Me), 1.42 (t, *J ca.* 8.6 Hz, 2'-CH_2), 1.68-1.73 (m, 2H, NH_2), 1.95 (s, 3H, Me), 2.04 (s, 3H, Me), 2.08 (s, 3H, Me), 2.45 (t, *J ca.* 8.6 Hz, 1'-CH_2), 2.79 (br s, §1H, OH), 2.93 (br s, 1H, OH), 3.30-3.36 (m, 2H, 4-CH_2), 3.49 s, 3H, OMe), 7.89 (s, 1H, NHCO); ^{13}C NMR (CD_3OD) δ 11.0 (Me), 12.3 (Me), 23.2 (Me), 24.1 (Me), 24.7 (CH_2), 39.5 (CH_2), 60.9 (OMe), 70.6 (CH_2OH), 74.1 (3'-C), 115.6 (ArC), 119.3 (ArC), 119.8 (ArC), 139.0 (ArC), 142.8 (ArC), 158.0 (ArC), 174.0 (C=O); *m/z* (APCI) 311 (M^++H, 100%). HR-MS (FAB). Calcd for $C_{16}H_{27}N_2O_4$ (M+H): 311.1965. Found: *m/z* 311.1963.

(±)-1-Acetyl-7-(3',4'-dihydroxy-3'-methylbutan-1'-yl)-4,6-dimethyl-5-methoxybenzotriazole (23a): To a solution of the foregoing aniline **22** (0.34 g, 1.1 mmol) in methanol (3 mL) at rt was added a solution of sodium nitrite (0.22 g, 3.3 mmol) in water (0.6 mL). The resulting solution was added slowly to a stirred solution of 10M hydrochloric acid (1.0 mL) in water (1.2 mL) maintained at 0 °C. Stirring at this temperature was continued for 0.5 h then water (12 mL) was added and the mixture extracted with dichloromethane (3 x 20 mL). The combined extracts were dried and evaporated to leave the *N-acetyl-benzotriazole* **23a** (0.266 g, 73%) as a colourless solid, mp 99-102 °C ($CHCl_3$-petrol); IR (KBr) 3270, 1745, 1459, 1366, 1309, 1266, 1130, 1094 cm^{-1}; ^1H NMR δ 1.24 (s, 3H, 3'-Me), 1.72 (t, *J* = 8.8 Hz, 2H, 2'-CH_2), 2.38 (s, 3H, Ac), 2.49-2.54 (br res., 2H, 2 x OH), 2.66 (s, 3H, ArMe), 2.96 (s, 3H, ArMe), 2.99-3.15 (m, 2H, 1'-CH_2), 3.41 (dd, *J* = 11.3, 5.9 Hz, 1H, 4'-H_a), 3.54 (dd, *J* = 11.3, 5.9 Hz, 1H, 4'-H_b), 3.70 (s, 3H, OMe); ^{13}C NMR δ 9.6 (Me), 12.0 (Me), 22.1 (Me), 24.3 (Me), 24.9 (2'-CH_2), 37.3 (1'-CH_2), 59.5 (OMe), 68.2 (4'-CH_2), 71.8 (3'-C), 118.9 (ArC), 123.4 (ArC), 126.8 (ArC), 133.6 (ArC), 145.4 (ArC), 154.4 (ArC), 169.9 (C=O); *m/z* (APCI) 322 (M^++H, 100%). HR-MS (FAB). Calcd for $C_{16}H_{24}N_3O_4$ (M+H): 322.1761. Found: *m/z* 322.1763.

(±)-7-(3',4'-Dihydroxy-3'-methylbut-1'-yl)-4,6-dimethyl-5-methoxybenzotriazole (23b): Potassium carbonate (0.14 g, 1.00 mmol) and water (0.5 mL) were added to a stirred solution of the foregoing *N*-acetyl-benzotriazole **23a** (0.10 g, 0.32 mmol) in methanol (2 mL) at rt and the hydrolysis followed by tlc. Upon completion (*ca.* 4 h), the bulk of the methanol was evaporated and the residue taken up into dichloromethane (20 mL), which was then dried, filtered and evaporated. The solid residue was washed with methanol and the combined filtrates evaporated to leave the *benzotriazole* **23b** (0.09 g, 99%) as a colourless solid, mp 250-252 °C (MeOH); IR (KBr) 3376, 1621, 1434, 1140, 1071, 998, 880 cm^{-1}; ^1H NMR (CD_3OD) δ 1.17 (s, 3H, 3'-Me), 1.64-1.73 (m, 2H, 2'-CH_2), 2.23 (s, 3H,

Ac), 2.45 (s, 3H, ArMe), 2.97-3.03 (m, 2H, 1'-CH_2), 3.36 (d, J = 11.3 Hz, 1H, 4'-H_a), 3.41 (d, J = 11.3 Hz, 1H, 4'-H_b), 3.62 (s, 3H, OMe); ^{13}C NMR (CD_3OD) δ 11.8 (Me), 12.6 (Me), 24.4 (Me), 24.6 (2'-CH_2), 39.6 (1'-CH_2), 61.3 (OMe), 70.3 (4'-CH_2), 74.4 (3'-C), 115.3 (ArC), 124.6 (ArC), 127.8 (ArC), 142.7 (ArC), 145.0 (ArC), 153.9 (ArC); *m/z* (APCI) 280 (M^++H, 100%). HR-MS (FAB). Calcd for $C_{14}H_{22}N_3O_3$ (M+H): 280.1656. Found: *m/z* 280.1652.

(±)-1-(*tert*-Butylcarbonylamino)-7-(3',4'-dihydroxy-3'-methylbut-1'-yl)-4,6-dimethyl-5-methoxybenzotriazole (26): To a stirred solution of the foregoing benzotriazole **23b** (0.28 g, 1 mmol) in dry dichloromethane (8 mL) at rt was added the *N*-Boc-oxaziridine **25** (0.53 g, 2.0 mmol)[27] and the resulting solution stirred overnight. The solvent was then evaporated and the residue separated by column chromatography (5% MeOH-$CHCl_3$) to give the *N-Boc-amino-benzotriazole* **26** (0.40 g, 94%) as a yellow oil; IR (film) 3274, 1739, 1452, 1362, 1248, 1158, 1110, 1050, 906, 834, 732 cm^{-1}; ^{1}H NMR δ 1.23 (s, 3H, 3'-Me), 1.32-1.75 (br s, 9H, Boc), 1.78 (t, J = 8.6 Hz, 2H, 2'-CH_2), 2.30 (s, 3H, ArMe), 2.56 (s, 3H, ArMe), 2.99-3.02 (m, 2H, 1'-CH_2), 3.54 (d, J = 11.3 Hz, 1H, 4'-H_a), 3.65 (d, J = 11.3 Hz, 1H, 4'-H_b), 3.69 (s, 3H, OMe); ^{13}C NMR δ 7.9 (Me), 10.9 (Me), 21.9 (Me), 24.9 (2'-CH_2), 27.1 (3 x Me), 37.1 (1'-CH_2), 59.5 (4'-CH_2), 59.6 (OMe), 72.1 (3'-C), 82.4 ($\underline{C}Me_3$),109.0 (ArC), 124.9 (ArC), 126.0 (ArC), 129.5 (ArC), 139.4 (ArC), 152.7 (ArC), 156.7 (C=O); *m/z* (APCI) 395 (M^++H, 100%). HR-MS (FAB). Calcd for $C_{19}H_{31}N_4O_5$ (M+H): 395.2289. Found: *m/z* 395.2295.

(±)-8-Iodo-6-methoxy-2,5,7-trimethylchroman-2-methanol (28a): The *N*-Boc-amino-benzotriazole **26** (0.22 g, 0.56 mmol) was dissolved in a stirred solution of trifluoroacetic acid (1.1 mL) in dichloromethane (5 mL) at rt. The deprotection was followed by tlc and when complete (*ca.* 0.75 h), the volatiles were evaporated, finally under high vacuum. The residue was then dissolved in dichloromethane (5 mL) and stirred with anhydrous potassium carbonate (1.0 g) for 0.25 h and filtered. The solid was washed with warm dichloromethane and the combined filtrates concentrated to a volume of *ca.* 5 mL and protected from light before *N*-iodosuccinimide (0.38 g, 1.7 mmol) was added in one portion. The resulting purple solution was stirred at rt for a further 1 h then diluted with dichloromethane (15 mL) and the solution washed with saturated aqueous sodium thiosulfate (5 mL) and then dried and evaporated. Silica gel column chromatography (petrol-EtOAc, 2:1) separated the *iodochroman* **28a** (0.129 g, 63%) as a yellow semi-solid; IR (film) 3390, 1450, 1390, 1219, 1058, 882 cm^{-1}; ^{1}H NMR δ 1.21 (s, 3H, 2-Me), 1.67 (ddd, J = 13.6, 6.0, 4.8, 3-H_a), 1.80-1.90 (m, 1H, 3-H_b), 2.08 (s, 3H, ArMe), 2.35 (s, 3H, ArMe), 2.56-2.60 (m, 2H, 4-CH_2), 3.57 (m, 5H, $C\underline{H}_2OH$ and OMe); ^{13}C NMR δ 11.0 (2-Me), 19.2 (ArMe), 19.4 (3-CH_2), 20.9 (ArMe), 26.9 (4-CH_2), 59.5 (OMe), 68.2 (CH_2OH), 77.2 (2-C), 90.0 (C-I), 117.8 (ArC), 128.4 (ArC), 132.3 (ArC), 146.8 (ArC), 149.1 (ArC); *m/z* (APCI) 345 (M^+-OH, 100%). HR-MS (NH_4-CI). Calcd for $C_{14}H_{23}INO_3$ (M+NH_4): 380.0717. Found: *m/z* 380.0714.

(±)-2-Acetoxymethyl-8-iodo-6-methoxy-2,5,7-trimethylchroman (28b): Iodochroman **28a** (30 mg, 0.08 mmol) was stirred in dry pyridine (1.5 mL) containing acetyl chloride (0.02 mL, 0.24 mmol) and 4-dimethylaminopyridine (2 mg) overnight at rt. The solution was then diluted with dichloromethane (5 mL) and washed with water (2 x 2 mL), saturated aqueous copper sulphate (2 mL) and saturated aqueous potassium carbonate (2 mL) then dried and evaporated. Silica gel column chromatography (ether-hexane 1:3) separated the *acetoxy-chroman* **28b** (23 mg, 75%) as a yellow oil; IR (film) 1744, 1450, 1390, 1260, 1057, 800 cm^{-1}; ^1H NMR δ 1.28 (s, 3H, 2-Me), 1.72-1.88 (m, 2H, 3-CH_2), 2.05 (s, 3H, ArMe), 2.06 (s, 3H, ArMe), 2.34 (s, 3H, Ac), 2.53 (app. t, *J* = 6.9 Hz, 2H, 4-CH_2), 3.56 (s, 3H, OMe), 4.02 (d, *J* = 11.3 Hz, 1H, 1'-H_a), 4.09 (d, *J* = 11.3 Hz, 1H, 1'-H_b); ^{13}C NMR δ 11.0 (2-Me), 19.4 (ArMe), 20.0 (ArMe), 20.1 (3-CH_2), 20.9 (MeCO), 28.7 (4-CH_2), 59.5 (OMe), 67.2 (CH_2OH), 74.3 (2-C), 89.1 (C-I), 117.2 (ArC), 128.3 (ArC), 133.0 (ArC), 147.1 (ArC), 149.0 (ArC), 169.9 (C=O); *m/z* (APCI) 277 (M^+-I, 100%). HR-MS (EI). Calcd for $C_{16}H_{21}IO_4$ (M^+): 404.0485. Found: *m/z* 404.0483.

(±)-6-Methoxy-2,5,7,8-tetramethylchroman-2-methanol (10): To a solution of the iodochroman **28a** (0.153 g, 0.75 mmol) in 1-methyl-2-pyrrolidinone (NMP; 3 mL) at rt was added triphenylphosphine (40 mg), *tris*-(dibenzylideneacetone)dipalladium(0).$CHCl_3$ (50 mg) and copper(I) iodide (15 mg). The stirred mixture was then degassed for 0.5 h before the addition of diethylamine (0.5 mL) and tetramethyltin (0.75 g, 4.5 mmol) in NMP (1 mL) and then heated at 100 °C for 24 h. The cooled suspension was then diluted with 10% aqueous sodium sulfite (40 mL) and extracted with ether (3 x 25 mL). The combined extracts were washed with 10% aqueous potassium fluoride (15 mL) then dried and evaporated. Column chromatography (SiO_2; petrol-EtOAc 2:1) of the residue separated the *chroman-methanol* (±)-**10** (0.111 g, 59%) as a thick, colourless oil, which slowly solidified, mp 49-52 °C; IR 3310, 1450, 1233, 1040 cm^{-1}; ^1H NMR δ 1.23 (s, 3H, 2-Me), 1.74 (ddd, *J* = 13.6, 6.1, 4.8, 3-H_a), 1.80-1.90 (m, 1H, 3-H_b), 2.08 (s, 3H, ArMe), 2.16 (s, 3H, ArMe), 2.30 (s, 3H, ArMe), 2.56-2.67 (m, 2H, 4-CH_2), 3.54 (2 x d (partly obscured), J_{AB} = 11.1 Hz, CH_2OH), 3.56 (s, 3H, OMe); ^{13}C NMR δ 11.2 (Me), 11.4 (Me), 12.4 (Me), 19.9 (Me), 20.3 (Me), 27.4 (4-CH_2), 60.0 (OMe), 68.8 (CH_2OH), 75.2 (2-C), 117.3 (ArC), 122.4 (ArC), 125.1 (ArC), 128.0 (C), 146.9 (ArC), 149.3 (ArC); *m/z* (APCI) 251 (M^++ H, 100%). HR-MS (FAB). Calcd for $C_{15}H_{22}O_3$ (M^+): 250.1569. Found: *m/z* 250.1567. The spectroscopic data were identical to those recorded previously for a while solid, no mp quoted.[2d]

4-(*tert*-Butyldiphenylsilyl)-2-hydroxy-2-methylbut-3-yn-1-yl acetate (30b): *i) 4-(tert-Butyldiphenylsilyl)-2-methyl-1-buten-3-yne (29):* Butyl lithium (24 mL of a 2.5M solution in hexanes, 60 mmol) was added dropwise to a stirred solution of 2-methyl-1-buten-3-yne **19** (4.00 g, 60 mmol) in dry THF (45 mL), cooled in an ice bath. After 0.25 h, *t*-butylchlorodiphenylsilane (14.0 g, 60 mmol) was added dropwise and stirring continued for 2 h before the bulk of the THF was evaporated. The

residue was partitioned between ether (10 mL) and water (10 mL) and the separated aqueous layer extracted with ether (3 x 10 mL). The combined ether solutions were dried, filtered through a pad of silica gel and evaporated to leave the *silane* **29** (17.7 g, 86%) as a light yellow oil of sufficient purity for use in the next step, which showed IR (film) 3428, 2154, 1682, 1589 cm^{-1}; ^1H NMR δ 0.99 (s, 9H, t-Bu), 1.92 (s, 2H, 2-Me), 5.27 (d, *J* = 1.7 Hz, 1-H_a), 5.41 (d, *J* = 1.7 Hz, 1-H_b), 7.27-7.33 (m, 6H), 7.63-7.67 (m, 4H); ^{13}C NMR δ 19.1 (CMe_3), 25.4 (2-Me), 26.6 (3 x Me), 88.5 (4-C), 109.0 (3-C), 123.3 (1-CH_2), 127.8, 129.7, 134.8, 135.2 (2-C), 135.6 (2 x ArC); *m/z* (APCI) 305 (M+H), 100%). ii) *4-(tert-Butyldiphenylsilyl)-2-methylbut-3-yne-1,2-diol (30a):* Using exactly the same method as for the dihydroxylation of enyne **19**, reaction of the foregoing silylated enyne (0.58 g, 1.7 mmol) with AD-mix-β (2.40 g) gave the *silyl diol* **30a** (0.44 g, 70%); IR (film) 3426, 2359, 1635, 1428, 1110, 908, 700 cm^{-1}; ^1H NMR δ 1.01 (s, 9H), 1.51 (s, 3H, 2-Me), 3.56 (d, *J* = 11.0 Hz, 1-H_a), 3.70 (d, *J* = 11.0 Hz, 1-H_b), 7.29-7.35 (m, 6H), 7.68 (d, *J* = 7.1 Hz, 4H); ^{13}C NMR δ 18.5 (CMe_3), 24.1 (2-Me), 27.0 (3 x Me), 58.9 (2-C), 70.7 (CH_2), 84.1 (4-C), 111.6 (3-C), 127.8 (ArCH), 129.7 (ArCH), 132.9 (ArC), 135.5 (ArCH). iii) *4-(tert-Butyldiphenylsilyl)-2-hydroxy-2-methylbut-3-yn-1-yl acetate (30b):* Acetic anhydride (2 drops) was added to a solution of the silyl diol **30a** (20 mg) in pyridine (0.5 mL) and the resulting solution stirred at rt for 18 h and then diluted with water (1 mL) and extracted with ether (3 x 3 mL). The combined extracts were dried and evaporated and the residue separated by column chromatography (EtOAc-petrol 4:1) to give the *acetate* **30b** (19 mg, 90%) as a colourless oil, ee = 12.7%; IR 3438, 2173, 1745, 1650, 1471, 1372, 1237, 1110, 1048, 968, 921 cm^{-1}; ^1H NMR δ 1.00 (s, 9H), 1.55 (s, 3H, 2-Me), 2.06 (s, 3H, MeCO), 2.54 (br s, 1H, OH), 4.02 (d, *J* = 11.1 Hz, 1-H_a), 4.28 (d, *J* = 11.1 Hz, 1-H_b), 7.29-7.37 (m, 6H), 7.69 (d, *J* = 6.4 Hz, 4H); ^{13}C NMR δ 18.5 (CMe_3), 25.3 (3 x Me), 26.0 (2-Me), 27.0 (MeCO), 67.2 (2-C), 71.1 (CH_2), 84.2 (4-C), 110.6 (3-C), 127.8 (ArCH), 129.7 (ArCH), 132.8 (ArC), 135.5 (ArCH).

Chiral hplc analysis using an 5μ OD column at 0.8 mL min^{-1} flow of 0.7% IPA in hexanes, detector set at 254 nm, gave a retention time of ~ 25 min.

2-(*tert*-Butyldiphenylsilyl)ethyn-1-yl-2-methyloxirane (31): To a well-stirred solution of the silyl butenyne **29** (0.60 g, 1.73 mmol) in dichloromethane (9 mL) was added *m*-chloroperoxybenzoic acid (0.60 g, 3.46 mmol). The resulting suspension was stirred for 2 h at rt before saturated aqueous sodium bicarbonate (10 mL) was added and the mixture extracted with ether (3 x 15 mL). The combined extracts were dried and evaporated and the residue separated by column chromatography (ether-hexane 9:1) to give the *oxirane* **31** (0.59 g, 95%) as a yellow oil; IR (film) 3429, 2156, 1589, 1471, 1428, 1362, 1193, 1111, 1009, 907, 820 cm^{-1}; ^1H NMR δ 0.99 (s, 9H), 1.57 (s, 3H, 2-Me), 2.71 (d, J = 5.6 Hz, 3-H_a), 3.03 (d, J= 5.6 Hz, 3-H_b), 7.26-7.35 (m, 6H), 7.62-7.69 (m, 4H); ^{13}C NMR δ 19.0 (CMe_3), 23.3

(2-Me), 27.0 (3 x Me), 48.0 (2-C), 56.1 (CH_2), 83.2 (4-C), 109.2 (3-C), 128.2 (ArCH), 130.5 (ArC), 132.9 (ArC), 135.2 (ArCH), 136.0 (ArCH); *m/z* (APCI) 321 (M^+ + H, 100%).

(+)-(*R*)-2,3-Dihydroxy-2,*N*-dimethyl-*N*-methoxy propanamide (33): AD-mix-α directed dihydroxylation of the Weinreb amide derivative **32** (6.10 g, 47.1 mmol) of methacrylic acid as described previously[30] gave the expected *dihydroxyamide* **33** (7.00 g, 91%), which showed $[\alpha]_D^{26}$ = + 4.3 (*c* 2.0 g/100 mL MeOH) [lit.[30] $[a]_D^{25}$ = + 4.7 (*c* 1.80 g/100 mL MeOH)] and otherwise identical spectroscopic and analytical data.

(*R*)-*N*-Methoxy-*N*-methyl-2,2,4-trimethyl-1,3-dioxolane-4-carboxamide (34): A solution of the dihydroxyamide **33** (3.25 g, 19.9 mmol), 2,2-dimethoxypropane (12.3 mL, 99.5 mmol) and *p*-toluenesulfonic acid monohydrate (76 mg) in toluene (60 mL) was heated under reflux for 2 h then cooled and evaporated. Silica gel column chromatography (EtOAc-petrol 1:1) separated the *dioxolane* **34** (3.60 g, 87%) as a colourless oil: IR 1658, 1456, 1372, 1247, 1211 cm^{-1}; ^1H NMR δ 1.16 (s, 3H, 5-Me), 1.25 (s, 3H, 2-Me), 1.31 (s, 3H, 2-Me), 3.10 (br. s, 3H, NMe), 3.53 (s, 3H, OMe), 3.56 (d, *J* = 8.3 Hz, 4-H_a), 4.37 (d, *J* = 8.3 Hz, 4-H_b); ^{13}C NMR δ 23.4 (5-Me), 26.1 (2-Me), 27.3 (2-Me), 60.7 ~(NMe), 61.1 (OMe), 73.0 (4-CH_2), 77.7 (5-C), 110.7 (2-C), 171.7 (C=O); *m/z* (APCI) 204 (M+H, 100%).

(*S*)-4-Ethynyl-2,2,4-trimethyl-1,3-dioxolane (36): i) (*R*)-*2,2,4-Trimethyl-1,3-dioxolane-4-carboxaldehyde (**35**):* Dibal-H (53.2 mL of a 1M solution in THF, 53.2 mmol) was added dropwise to a stirred solution of the acetal **34** (3.60 g, 17.7 mmol) in THF cooled in an ice-water bath. After 1 h at this temperature, the reaction mixture was poured into 5% hydrochloric acid in ethanol (50 mL) and the resulting mixture partitioned between brine (20 mL) and ether (100 ml). The separated organic solution was washed with water (15 mL) then dried and evaporated to leave the *aldehyde* **35** (2.80 g, 100%); IR (film) 3424, 1725, 1458, 1373 cm^{-1}; ^1H NMR δ 1.29 (s, 3H, Me), 1.39 (br s, 6H, 2 x Me), 3.66 (s, 2H, 4-CH_2), 9.59 (s, 1H, CHO); ^{13}C NMR δ 18.2 (Me), 25.4 (Me), 25.8 (Me), 69.8 (4-CH_2), 76.3 (C), 83.6 (C), 201.4 (C=O); *m/z* (APCI) 145 (M + H, 100%), which was used immediately in the next step. ii) (*S*)-*4-(2,2-Dichloroethen-1-yl)-2,2,4-trimethyl-1,3-dioxolane:* Sodium trichloroacetate (4.70 g, 25.4 mmol) was added in portions to a stirred solution of the foregoing aldehyde **35** (2.27 g, 15.9 mmol) and trichloroacetic acid (4.20 g, 25.4 mmol) in DMF (12 mL); an ice-water bath was used to maintain the temperature below 35 °C during the addition. The mixture was then stirred without further cooling for 4 h as CO_2 was continually evolved before cooling to 5 °C and the addition of acetic anhydride (3.0 mL, 31.8 mmol), which caused increased CO_2 evolution. After a further 1 h at rt, the mixture was diluted with acetic acid (15 mL) and cooled in an ice-water bath. Zinc powder (2.10 g, 31.8 mmol) was then added in one portion and the mixture heated to 60 °C for 1 h. After cooling to rt, water (10 mL) was added and the mixture extracted with hexanes (3 x 30 mL). The combined extracts were washed with water (10 mL) and brine (10 mL) then dried and evaporated to leave the crude

dichloroalkene (1.89 g, 57%) as a pale yellow oil; IR (film) 1613, 1451, 1372, 1210, 1111, 991, 883, 810 cm^{-1}; ^1H NMR δ 1.30 (s, 3H, Me), 1.36 (s. 3H, Me), 1.42 (s, 3H, Me), 3.88 (d, *J* = 8.6 Hz, 4-H_a), 4.09 (d, *J* = 8.6 Hz, 4-H_b), 6.20 (s, 1H, :CH); ^{13}C NMR δ 24.3 (Me), 26.0 (Me), 27.2 (Me), 73.9 (4-CH_2), 80.5 (C), 109.5 (C), 120.2 (:C), 136.0 (:CH). iii) *(S)-4-Ethynyl-2,2,4-trimethyl-1,3-dioxolane (**36**):* To a stirred solution of the foregoing dichloroalkene (1.64 g, 7.8 mmol) in THF (10 mL) maintained at -30 °C was added dropwise butyl lithium (9.4 mL of a 2.5M solution in hexanes, 23.5 mmol). The resulting solution was stirred for 1 h without further cooling then quenched by the addition of saturated aqueous ammonium chloride (10 mL) and diluted with ether (30 mL). The separated aqueous phase was extracted with ether (3 x 30 mL) and the combined organic solutions washed with water (10 mL) and brine (10 mL) then dried, filtered through a pad of silica gel and the filtrate and washings evaporated to leave the *alkyne* **36** (1.10 g, 99%) as a pale yellow oil; IR (film) 3430, 2140, 1460, 1369, 1270, 1200 cm^{-1}; ^1H NMR δ 1.28 (s, 3H, 5-Me), 1.39 (s, 3H, Me), 1.43 (s, 3H, 2-Me), 2.35 (s, 1H, 2'-H), 3.65 (d, *J* = 8.2 Hz, 4-H_a), 4.05 (d, *J* = 8.2 Hz, 4-H_b); *m/z* (APCI) 141 (M + H, 100%).

(+)-(*R*)-2,3-Di-(*tert*-butyldimethylsilyloxy)-2,*N*-dimethyl-*N*-methoxy propanamide (37): *t*-Butyldimethylsilyl chloride (23.0 g, 152 mmol) was added to a stirred solution of the dihydroxyamide **33** (10.30 g, 63.3 mmol) and imidazole (21.50 g, 316.5 mmol) in dry DMF (40 mL), which was then stirred at 35 °C for 18 h before being cooled to rt, diluted with water (10 mL) and extracted with dichloromethane (3 x 50 mL). The combined extracts were washed with water (20 mL) and brine (20 mL) and then dried and evaporated. Silica gel column chromatography (EtOAc-petrol 95:5) then separated the *bis-silyl ether* **37** (23.2 g, 94%) as a colourless oil; $[\alpha]_D^{26}$ = + 3.2 (*c* 2.0 g/100 mL $CHCl_3$); IR (film) 1670, 1472, 1387, 1361, 1251, 1214, 1033, 778, 723 cm^{-1}; ^1H NMR δ 0.00 (s, 3H), 0.01 (s, 3H), 0.08 (s, 3H), 0.11 (s, 3H), 0.83 (s, 9H), 0.84 (s, 9H),

(*R*)-2,3-Di-(*tert*-butyldimethylsilyloxy)-2-methylpropanal (38): Lithium aluminium hydride (80 mL of a 1M solution in ether, 77.7 mmol) was added dropwise to a stirred solution of the *bis*-silyl ether **37** (10.1 g, 25.9 mmol) in ether (260 mL) maintained at – 78 °C. Stirring was continued at this temperature for 40 mins. and then an aqueous solution of 2M sodium hydroxide (40 mL) was slowly added. After warming to rt, the resulting mixture was separated and the aqueous layer extracted with ether (3 x 100 mL). The combined organic solutions were dried and carefully evaporated to leave the *aldehyde* **38** (7.50 g, 88%) as a pale yellow oil, which was sufficiently pure for the next step and which showed: IR (film) 2858, 1740, 1472, 1388, 1362, 1255, 1156, 1108 cm^{-1}; ^1H NMR δ -0.08 (s, 3H, MeSi), -0.06 (s, 3H, MeSi), 0.01 (s, 3H, MeSi), 0.02 (s, 3H, MeSi), 0.80 (s, 9H), 0.82 (s, 9H), 1.12 (s, 3H, 3-Me), 3.51-3.55 (m, 2H), 9.51 (s, 1H, CHO); ^{13}C NMR δ -5.8 (MeSi), -5.7 (MeSi), -3.6 (MeSi), -

3.2 (MeSi), 15.2 (2-Me), 18.1 (CSi), 18.2 (CSi), 25.7 (6 x Me), 68.4 (3-CH_2), 80.7 (2-C), 204.6 (CHO); *m/z* (APCI) 333 (M + H, 100%).

(+)-(*S*)-1,1-Dibromo-3,4-di-(*tert*-butyldimethylsilyloxy)-3-methylbut-1-ene (39): Triphenylphosphine (44.0 g, 167.7 mmol) was added to a stirred solution of carbon tetrabromide (27.8 g, 83.3 mmol) in dichloromethane (200 mL) followed by the foregoing aldehyde **38** (13.9 g, 41.9 mmol). The resulting solution was stirred at rt for 4 h then washed with water (30 mL), the solvent evaporated and the residue separated by silica gel column chromatography (pentane-ether 9:1) to give the *dibromoalkene* **39** (15.2 g, 74%) as a colourless oil; $[\alpha]_D^{25}$ = + 2.7 (*c* 1.9 g/100 mL $CHCl_3$); IR (film) 1607, 1472, 1388, 1361, 1255, 1108, 1036, 938, 836 cm^{-1}; ^1H NMR δ -0.01 (s, 3H, MeSi), 0.00 (s, 3H, MeSi), 0.04 (s, 3H, MeSi), 0.05 (s, 3H, MeSi), 0.81 (s, 9H), 0.84 (s, 9H), 1.38 (s, 3H, 3-Me), 3.42 (d, *J* = 9.1 Hz, 4-H_a), 3.52 (d, *J* = 9.1 Hz, 4-H_b), 6.64 (s, 1H, 2-H); ^{13}C NMR δ -5.6 (MeSi), -3.0 (MeSi), -2.3 (MeSi), -2.2 (MeSi), 18.2 (CSi), 18.3 (CSi), 22.6 (3-Me), 25.8 (3 x Me), 25.9 (3 x Me), 69.7 (4-CH_2), 87.3 (3-C), 143.5 (2-CH), 204.5 (1-C); *m/z* (APCI) 279 (M – TBS, Me and Br +H).

(+)-(*S*)-3,4-Di-(*tert*-butyldimethylsilyloxy)-3-methylbut-1-yne (40): To a stirred solution of the dibromoalkene **39** (5.25 g, 10.8 mmol) in THF (175 mL) maintained at -30 °C was slowly added butyl lithium (13 mL of a 2.5M solution in hexanes, 32.5 mmol) and the resulting solution stirred without additional cooling for 1 h then treated with saturated aqueous ammonium chloride (10 mL) and ether (50 mL). The separated aqueous layer was extracted with ether (3 x 50 mL) and the combined organic solutions washed with water (20 mL) and brine (20 mL) then dried and evaporated. Silica gel column chromatography then separated the *alkyne* **40** (2.60 g, 59%) as a colourless oil; $[\alpha]_D^{26}$ = + 3.5 (*c* 1.0 g/100 mL $CHCl_3$); IR (film) 3311, 1472, 1389, 1361, 1254, 1190, 1119, 1032, 939, 836, 777 cm^{-1}; ^1H NMR δ 0.00 (s, 3H, MeSi), 0.01 (s, 3H, MeSi), 0.10 (s, 3H, MeSi), 0.11 (s, 3H, MeSi), 0.80 (s, 9H), 0.84 (s, 9H), 1.36 (s, 3H, 3-Me), 2.32 (s, 1H, 1-H), 3.35 (d, *J* = 9.5 Hz, 4-H_a), 3.47 (d, *J* = 9.5 Hz, 4-H_b); ^{13}C NMR δ -5.3 (MeSi), -5.2 (MeSi), -3.0 (MeSi), -2.9 (MeSi), 18.0 (CSi), 18.3 (CSi), 25.7 (3 x Me), 25.9 (3 x Me), 27.4 (3-Me), 69.9 (2-C), 71.6 (4-CH_2), 72.3 (1-CH), 87.2 (2-C); *m/z* (APCI) 329 (M + H, 100%). HR-MS (APCI). Calcd for $C_{17}H_{37}O_2Si_2$ (M^+): 329.2332. Found: *m/z* 329.2337.

(-)-(*S*)-3,4-Dihydroxy-3-methyl-1-butyne ((*S*)-(-)-20a): Tetrabutylammonium fluoride (7.6 mL of a 1M solution in THF) was added dropwise to a stirred solution of the foregoing alkyne **40** (1.00 g, 3.0 mmol) at rt. After 2 h, the solvent was evaporated and the residue separated by silica gel column chromatography (petrol-EtOAc 95:5) to give the *(S)-diol* **20a** (0.25 g, 82%) as a pale yellow oil, $[\alpha]_D^{26}$ = -0.7 (*c* 20.0 g/100 mL $CHCl_3$); all other spectroscopic and analytic data were identical to the racemate **(±)-20a** described above.

(+)-(*S*)-4-Acetamido-2,6-dimethyl-5-[3',4'-dihydroxy-3'-methylbut-1'-yn-1'-yl]-3-nitroanisole (21): Following the general Sonogashira procedure, the nitro-iodide **18** (0.364 g, 1.0 mmol) was

coupled with the (*S*)-diol **20a** (0.20 g, 2.0 mmol) using $(Ph_3P)_4Pd$ (0.578 g, 0.5 mmol), copper(I) iodide (0.095 g) and triethylamine (3.6 mL, 26 mmol) to give the (*S*)-(+)-*alkyne-diol* **21** (0.26 g, 77%) as a pale yellow solid, mp 173-174.5 °C (MeOH); $[\alpha]_D^{26}$ = +3.5 (*c* 1.9 g/100 mL MeOH); all other spectroscopic and analytic data were identical to the racemate **(±)-21** described above.

4-Amino-2,6-dimethyl-5-iodo-3-nitroanisole (14): The nitro-iodide **18** (0.32 g, 0.88 mmol) was dissolved in methanol (5 mL) before concentrated sulfuric acid (0.18 mL) was added. The resulting solution was heated to reflux for 16 h, then cooled and poured onto ice (~20 g) and the mixture basified using potassium carbonate. The product was extracted into dichloromethane (3 x 10 mL) and the combined extracts dried and evaporated. Silica gel column chromatography then separated the *nitroanisole* **14** (0.18 g, 64%) as a bright yellow solid, mp 214-215 °C; IR (KBr) 3375, 1602, 1455, 1259, 1047, 799, 650 cm^{-1}; ^1H NMR δ 2.24 (s, 3H), 2.40 (s, 3H), 3.58 (s, 3H, OMe), 5.25 (br s, 2H, NH_2); *m/z* (EI) 322 (M, 100%). Anal. Calcd for $C_9H_{11}IN_2O_3$: C, 33.56; H, 3.44; N, 8.70. Found: C, 33.78; H, 3.51; N, 8.55.

(+)-(*S*)-4-Amino-2,6-dimethyl-5-[3',4'-dihydroxy-3'-methylbut-1'-yn-1'-yl]-3-nitroanisole (41): By the general Sonogashira procedure, coupling between the nitroanisole **14** (0.18 g, 0.55 mmol) and the (*S*)-(+)-diol **21** (0.11 g, 1.1 mmol) using $(Ph_3P)_4Pd$ (0.324 g, 0.28 mmol), copper(I) iodide (0.053 g) and triethylamine (2.0 mL, 14.3 mmol) in THF (6 mL) gave the *unprotected* (*S*)-*alkyne-diol* **41** (0.127 g, 79%) as a yellow solid, mp 163-164 °C; $[\alpha]_D^{25}$ = +6.8 (*c* 1.7 g/100 mL MeOH); IR 3377, 2221, 1603, 1509, 1452, 1376, 1330, 1260, 1198, 1153, 1116, 1054, 998, 912, 873, 767, 733 cm^{-1}; ^1H NMR δ 1.50 (s, 3H, 3'-Me), 2.26 (s, 3H, ArMe), 2.28 (s, 3H, ArMe), 3.05 (br res, 2H, 2 x OH), 3.55 (s, 3H, OMe), 3.56 (d, *J* = 11.0 Hz, 4'-H_a), 3.69 (d, *J* = 11.0 Hz, 4'-H_b), 5.62 (br res, 2H, NH_2); ^{13}C NMR δ 13.9 (Me), 15.8 (Me), 25.9 (Me), 60.9 (OMe), 69.7 (CH_2), 71.2 (C), 78.5 (C), 102.5 (C), 108.8 (C), 128.9 (C), 134.8 (C), 140.2 (C), 141.0 (C), 148.1 (C); *m/z* (APCI 277 (M – OH, 100%). HR-MS (APCI). Calcd for $C_{14}H_{17}N_2O_4$ (M^+ - OH): 277.1188. Found: *m/z* 277.1197.

(*E*)-1-(*tert*-Butyloxycarbonylamino)-7-(3'-penten-1'-yl)benzotriazole (42a): Following the previously reported procedure for metalation and homologation,[15] treatment of the dianion **7** derived from 1-(*tert*-butyloxycarbonylamino)-7-methylbenzotriazole **6** (0.30 g, 1.2 mmol) using BuLi-TMEDA with crotyl chloride (0.13 mL, 1.32 mmol) gave the *(E)-pentene* **42a** (0.35 g, 97%) as a thick yellow oil; IR (film) 3166, 1750, 1606, 1455, 1394, 1370, 1252, 1160, 1050, 966, 910, 749 cm^{-1}; ^1H NMR δ 1.30-1.53 (br res, 9H, *t*-Bu), 1.54-1.58 (m, 3H, 5'-Me), 2.24-2.38 (m, 2H, 2'-CH_2), 2.94 (t, *J* = 8.3 Hz, 1'-CH_2), 5.39-5.41 (m, 2H, 3'- and 4'-H), 7.20-7.23 (m, 2H), 7.75-7.79 (m, 1H), 8.59 (br s, 1H, NH); ^{13}C NMR δ 11.9 (5'-Me), 27.0 (3 x Me), 29.3 (CH_2), 32.7 (CH_2), 82.7 (C), 117.0 (ArCH), 123.7 (ArCH), 124.3 (:CH), 125.2 (:CH), 127.9 (ArCH), 129.8 (7-C), 143.7 (C-N), 152.5 (C-N), 157.2

(C=O); *m/z* (APCI) 302 (M^+, 100%). HR-MS (FAB). Calcd for $C_{16}H_{23}N_4O_2$ (M^+ + H): 303.1816. Found: *m/z* 303.1816.

(*3'R*, *4'R*)-1-(*tert*-Butyloxycarbonylamino)-7-(3',4'-dihydroxypent-1'-yl)benzotriazole (43a): Following the procedure detailed above for the preparation of diol **20a**, reaction of the foregoing pentene **42a** (0.273 g, 0.9 mmol) with AD-mix-β (1.26 g) at rt for 42 h gave the *diol* **43a** (0.196 g, 65%) as a thick, pale yellow oil; IR (film) 3252, 1749, 1508, 1456, 1370, 1254, 1159, 912, 733 cm^{-1}; ^1H NMR (rotameric) δ 1.08 (d, *J* = 6.3 Hz, 3H, 5'-Me), 1.22-1.52 (br s, 9H, 3 x Me), 1.71-1.80 (m, 2H), 2.75 (br s, 1H, OH), 3.00-3.13 (m, 2H), 3.13 (br s, 1H, OH), 3.35-3.48 (m, 1H, 3'-H), 3.56 (qd, *J* = 6.3, 6.0 Hz, 1H, 4'-H), 7.22-7.25 (m, 2H), 7.81-7.85 (m, 1H), 9.16 (br s, 1H, NH); ^{13}C NMR δ 18.5 (5'-Me), 26.9 (3 x Me), 33.8 (2'-CH_2), 42.2 (1'-CH_2), 69.4 (CH), 73.8 (CH), 82.4 (C), 117.0 (CH), 123.6 (CH), 124.2 (7-C), 127.8 (CH), 129.8 (C-N), 143.7 (C-N), 152.9 (C=O); *m/z* (APCI) 336 (M^+, 100%). HR-MS (FAB). Calcd for $C_{16}H_{25}N_4O_4$ (M^+ + H): 337.1868. Found: *m/z* 337.1868. [ee: ~ 76%]

(-)-(*1'R*, *2R*)-2-(1-Hydroxyethyl)-8-iodochroman (44a): Using the same procedure for benzyne generation and trapping that gave the iodochroman **28a**, treatment of the foregoing diol **43a** (0.074 g, 0.22 mmol) with trifluoroacetic acid (0.44 mL) and *N*-iodosuccinimide (0.124 g, 0.55 mmol) gave the *iodochroman* **44a** (0.046 g, 68%) as a thick, yellow oil; $[\alpha]_D^{29}$ = - 7.4 (*c* 6.25 g/100 mL $CHCl_3$); IR (film) 3367, 1454, 1261 cm^{-1}; ^1H NMR δ 1.26 (d, *J* = 6.0 Hz, 3H, '-Me), 1.45-1.61 (br res, 1H, OH), 1.67-1.78 (m, 1H, 3-H_a), 1.93-1.98 (m, 1H, 3-H_b), 2.67 (ddd, *J* = 16.3, 5.4, 2.7 Hz, 1H, 4-H_a), 2.77 (ddd, *J* = 16.3, 12.1, 5.9 Hz, 1H, 4-H_b), 3.78-3.84 (m, 2H, 2- and 1'-H), 6.56 (t, *J* = 7.7 Hz, 1H, 6-H), 7.02 (d, *J* = 7.7 Hz, 1H, 7-H), 7.49 (d, *J* = 7.7 Hz, 1H, 5-H); ^{13}C NMR δ 18.5 (Me), 23.9 (CH_2), 24.8 (CH_2), 70.0 (CH), 81.6 (CH), 85.8 (C-I), 122.2 (CH), 123.1 (4a-C), 130.3 (CH), 136.9 (CH), 142.9 (8a-C); *m/z* (APCI) 286 (M^+-H_2O, 100%). HR-MS (NH_4-CI). Calcd for $C_{11}H_{17}INO_2$ (M^+ + NH_4): 322.0298. Found: *m/z* 322.0296.

(*E*)-1-(*tert*-Butyloxycarbonylamino)-7-(4'-phenyl-3'-buten-1'-yl)benzotriazole (42b): Following the previously reported procedure for metalation and homologation,[15] treatment of the dianion **7** derived from 1-(*tert*-butyloxycarbonylamino)-7-methyl)benzotriazole **6** (0.918 g, 3.7 mmol) using BuLi-TMEDA with cinnamyl bromide (0.87 g, 4.4 mmol) gave the *(E)-butene* **42b** (1.05 g, 78%) as a colourless oil; IR (film) 3458, 1745, 1494, 1453, 1368, 1253, 1157, 966, 750 cm^{-1}; ^1H NMR δ 1.35 (br res, 9H, *t*-Bu), 2.41 (td, *J* = 7.1, 6.7 Hz, 2H, 2'-CH_2), 3.00 (t, *J* = 7.1 Hz, 1'-CH_2), 6.10 (dt, *J* = 15.9, 6.7 Hz, 1H, 3'-H), 6.28 (d, *J* = 15.9 Hz, 1H, 4'-H), 7.03-7.21 (m, 7H), 7.66-7.72 (br res, 1H, ArH), 9.32 (br s, 1H, NH); ^{13}C NMR δ 28.1 (3 x Me), 30.1 (2'-CH_2), 34.0 (1'-CH_2), 83.6 (C), 118.1 (CH), 124.7 (ArC), 125.0 (CH), 126.0 (CH), 127.2 (CH), 128.5 (CH), 129.0 (CH), 137.4 (C), 144.7 (C-N), 153.9 (C-N), 154.1 (C=O); *m/z* (APCI) 365 (M^+ + H, 100%). HR-MS (FAB). Calcd for $C_{21}H_{25}N_4O_2$ (M^+ + H): 365.1972. Found: *m/z* 365,1972.

(*3'R, 4'R*)-1-(*tert*-Butyloxycarbonylamino)-7-(3',4'-dihydroxy-4'-phenylbutan-1'-yl)benzotriazole (43b): Following the procedure detailed above for the preparation of diol **20a**, reaction of the foregoing butene **42b** (0.737 g, 2.0 mmol) with AD-mix-β (2.80 g) at rt for 40 h gave the *diol* **43b** (0.65 g, 82%) as a thick, pale yellow oil; IR (film) 3498, 1735, 1453, 1368, 1253, 1157 cm^{-1}; ^1H NMR (rotameric) δ 1.22-1.35 (br s, 9H, 3 x Me), 1.46-1.51 (br s, 1H, OH), 1.54-1.63 (br s, 1H, OH), 2.80-2.86 (m, 2'-H_a), 2.96-3.01 (m, 1H, 2'-H_b), 3.53-3.57 (m, 1H, 3'-H), 3.80-3.86 (m, 2H, 1'-CH_2), 4.30 (d, *J* = 6.6 Hz, 1H, 4'-H), 6.95 (d, *J* = 7.0 Hz, ArH), 7.05-7.19 (m, 6H), 7.60 (d, *J* = 7.0 Hz, 1H, ArH), 9.70 (br s, 1H, NH); ^{13}C NMR δ 25.7 (2'-CH_2), 27.1 (3 x Me), 33.4 (1'-CH_2), 74.5 (CH), 77.2 (CH), 82.6 (C), 116.9 (CH), 124.8 (CH), 126.0 (C), 126.7 (CH), 127.2 (CH), 127.8 (CH), 128.5 (CH), 130.8 (C), 142.0 (C-N), 144.4 (C-N), 154.7 (C=O); *m/z* (APCI) 399 (M^+ + H, 100%). HR-MS (FAB). Calcd for $C_{21}H_{27}N_4O_4$ (M^+ + H): 399.2027. Found: *m/z* 399.2025. [ee: ~ 82%].

***(-)*-(*1'R, 2R*)-2-(1-Hydroxy-1-phenylmethyl)-8-iodochroman (44b):** Using the same procedure for benzyne generation and trapping that gave the iodochroman **28a**, treatment of the foregoing diol **43b** (0.628 g, 1.60 mmol) with trifluoroacetic acid (6.3 mL) and *N*-iodosuccinimide (0.90 g, 4.0 mmol) gave the *iodochroman* **44b** (0.334 g, 57%) as a thick, yellow oil; $[\alpha]_D^{26}$ = -19.7 (*c* 3.00 g/100 mL $CHCl_3$); IR (film) 3564, 1562, 1494; 1448, 1237, 1194, 1093, 1045, 905, 887, 761, 701 cm^{-1}; ^1H NMR δ 1.53-1.70 (m, 2H, 3-CH_2), 2.60-2.65 (m, 2H, 4-CH_2), 3.12 (br s, 1H, OH), 4.01 (ddd, *J* = 10.5, 7.8, 2.7 Hz, 1H, 2-H), 4.65 (d, *J* = 7.8 Hz, 1H, 1'-H), 6.54 (t, *J* = 7.6 Hz, 1H, ArH), 6.91 (d, *J* = 7.6 Hz, 1H, ArH), 7.24-7.39 (m, 5H), 7.49 (d, *J* = 7.6 Hz, 1H, ArH); ^{13}C NMR δ 23.5 (3-CH_2), 24.7 (4-CH_2), 77.5 (2-CH), 81.4 (1'-CH), 85.8 (C-I), 122.4 (CH), 123.2 (4a-C), 127.4 (CH), 128.5 (CH), 128.6 (CH), 129.7 (CH), 137.0 (CH), 139.0 (C), 152.4 (C); *m/z* (APCI) 366 (M^+, 100%). HR-MS (NH_4-CI). Calcd for $C_{16}H_{19}INO_2$ (M^+ + NH_4): 384.0455. Found: *m/z* 384.0458.

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