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A synthesis of α-tocopherol featuring benzyne trapping by an alcohol

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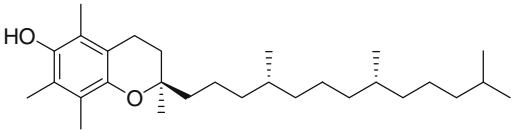
This Letter is dedicated to the memory of Professor Charles W. Rees of Imperial College, London

ABSTRACT

A formal total synthesis of α-tocopherol, the main component of Vitamin E, has been achieved in which a central step is the intramolecular trapping of a highly substituted benzyne by an alcohol group to establish the pyran ring.

α-Tocopherol **1** is the major component of the naturally occurring 'Vitamin E' mixture, which is generally composed of a mixture of less methylated tocopherols along with the four tocotrienols having alkenes in the side-chain but the same methylation pattern around the aryl ring.[1]



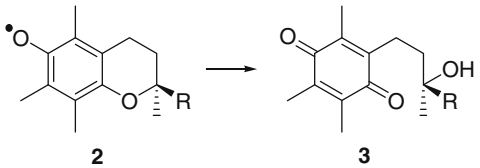
1

α-Tocopherol acetate is produced on a multi-ton industrial scale as a complete racemate by an acid-catalysed coupling between trimethylhydroquinone and phytol or isophytol followed by acetylation,[2,3] and is added to a wide variety of foods, pharmaceuticals and cosmetics where it functions as an anti-oxidant, often by the mechanism summarised in Scheme 1, wherein a phenoxide radical **2** is initially generated, which then undergoes ring opening and trapping by water to give a quinone **3**.[4]

The industrial syntheses contrast somewhat with various smaller-scale approaches that have been reported in recent times, many of which are based on an early synthesis by Cohen et al.[5] The essence of this strategy (Scheme 2) is disconnection of the phytyl chain to give the alcohol **4**, which is prepared by reduction of the ketone function in the acetal **5**, derived from the quinone **6**. The variations in many such syntheses are then in exactly how the quinone **6** or a similar intermediate is prepared.

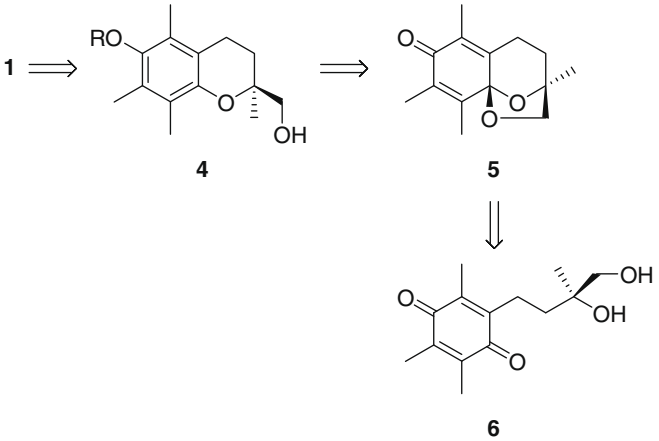
In order to introduce asymmetry into this method, more recent applications have included precursor synthesis using Sharpless asymmetric epoxidation,[6] asymmetric dihydroxylation[7] and various asymmetric palladium-catalysed C–O bond formations (asymmetric allylic alkylation and relatives).[8] A neat application of Grubbs olefin cross-metathesis has also contributed to methodology in the area,[9] while a highly diastereoselective biomimetic approach indicates how the chroman ring might be synthesised in Nature.[10]

In our exploration of new ways to prepare substituted benzynes, we have defined new metallation strategies that are highly suited to the elaboration of the amino-benzotriazole benzyne



2 **3**

Scheme 1.



4 **5** **6**

Scheme 2.

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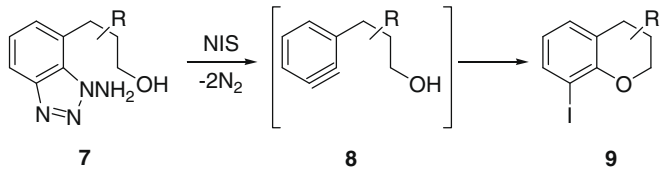
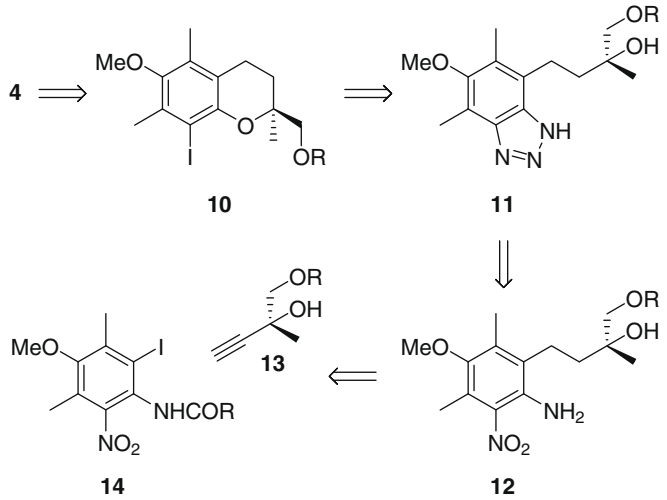


Scheme 3.

precursors **7** (Scheme 3). As the subsequent benzyne generation can be carried out under neutral conditions using, for example, *N*-iodosuccinimide to carry out the necessary amine oxidation, the resulting benzynes **8** are trapped by the pendant neutral alcohol groups to give excellent yields of the related chromans **9**. A bonus is the incorporation of an additional iodine atom, which offers many opportunities for further elaboration of the initial products.[11] Similarly, phenols can be used as traps to provide access to xanthenes,[12] all of which is in direct contrast to the more commonly encountered highly basic methods for benzyne generation wherein any free hydroxy groups are inevitably present as the corresponding alkoxides. These latter 'hard' species are evidently incompatible with the much softer benzynes, in terms of efficient reactivity.[13]

Although this methodology makes some contribution to the synthesis of substituted benzynes, it still fails to provide access to very highly substituted examples. Therefore, we were interested to test the general idea of using highly substituted benzynes, generated from 1-aminobenzotriazoles, in target synthesis in order to demonstrate the potential of this method in general. For this, α-tocopherol appeared to be a highly suitable target; herein, we report in preliminary form, the successful outcome of this idea, together with some of the pitfalls encountered along the way.

We initially aimed to extend our metallation methodology[11] to this target, but were thwarted by a lack of regioselectivity in such reactions involving the necessary highly substituted intermediates. We therefore turned to more conventional methods to prepare the required precursors; the basic strategy is outlined in Scheme 4. In common with many previous syntheses, we reduced the problem to one of preparing the chroman-2-methanol **4** (Scheme 2) and therefore anticipated the iodide **10** as being the initial benzyne product. This naturally led back to the benzotriazoles **11**, and thence to the amino-nitrobenzenes **12** or a regioisomer thereof. Retention of the nitro group should then be useful in facilitating a Sonogashira coupling between the alkyne-1,2-diol **13** and the worryingly crowded, fully substituted iodobenzene **14**. Previous



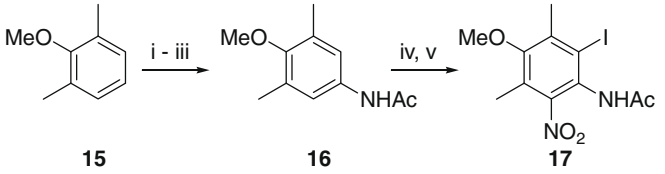
Scheme 4.

studies had established that benzynes generated in this way are not trapped by δ-hydroxy groups, which would give rise to seven-membered rings. Therefore, it was anticipated that the alkyne-diol **13** probably would not require any protection (i.e., R = H), as trapping would be highly favoured towards six-membered chroman formation, even though the reacting alcohol group would be tertiary.[14] We reasoned that both such precursors should be reasonably readily available, and that the alkyne-diol **13** should be obtainable in optically pure form.

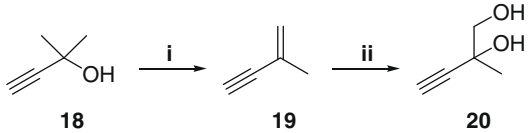
Our synthesis began with known literature methods (Scheme 5). Nitration[15] of commercially available 2,6-dimethylanisole **15** gave a reasonable return of the expected crystalline *p*-nitro derivative, in a reaction which could be carried out on a large scale.[16] Transfer hydrogenation[17] of the nitro group using cyclohexene as the source of hydrogen then gave a sensitive aniline which was immediately acetylated to give a good overall yield of the acetanilide **16**. This activated intermediate was then mono-iodinated using *N*-iodosuccinimide in hot glacial acetic acid[18] and the final substituent, a second nitro group, introduced by a relatively slow nitration using concentrated nitric acid in warm acetic acid, to give the fully substituted aryl intermediate **17**.

The other component of the projected Sonogashira coupling, the alkyne-diol **20**, which we anticipated from previous work,[19] could be readily obtained in a highly enantiomerically enriched form from the cheap acetylide-acetone adduct **18** by sequential dehydration[20] and asymmetric dihydroxylation (AD)[21] (Scheme 6). This proved to be an erroneous assumption: while chemical yields were acceptable, the final diol **20** was obtained in almost racemic form, according to GC analysis of the corresponding mono-benzoate. It appears that our previous optimism[19] with regard to the levels of enantiomeric enrichment of this compound was based on a somewhat over-enthusiastic interpretation of its HPLC analysis. However, having secured decent amounts of the *racemic* alkyne-diol **20**, we chose to continue with the projected synthesis, in order to establish suitable conditions for basic bond formation. The problem of obtaining the chiral, non-racemic alkyne diol was left until later.

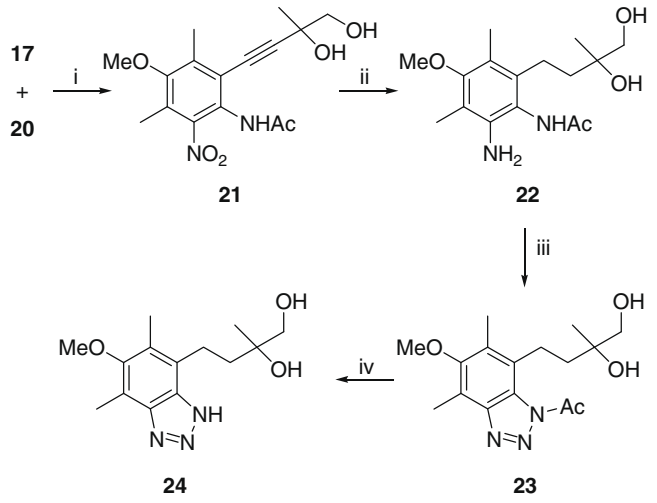
After a number of trials, we established that the pivotal Sonogashira coupling was, as anticipated, relatively difficult but that good yields of the aryl alkyne **21** could be obtained by carrying out the reaction in refluxing tetrahydrofuran for 24 h. Steric hindrance no doubt played a part in this and the subsequent one-pot reductions of both the nitro and alkyne groups. Again after a number of trials, we found that prolonged exposure to an atmosphere of hydrogen and 20% palladium hydroxide on carbon (Pearlman's catalyst) in methanol at ambient temperature secured an



Scheme 5. Reagents and conditions: (i) concd HNO_3, HOAc, 0–65 °C (~65%); (ii) 10% Pd–C, EtOH, cyclohexene, 80 °C (91%); (iii) AcCl, Et_3N, THF, 0–20 °C, 16 h (89%); (iv) NIS, HOAc, reflux, 1.5 h (70%); (v) concd HNO_3, HOAc, 65 °C, 5 h (52%).



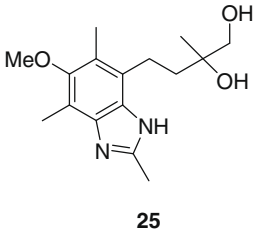
Scheme 6. Reagents and conditions: (i) Distill from *p*-toluenesulfonic acid (~35%); (ii) AD mix β, $MeSO_2NH_2$, 1:1 *t*BuOH–H_2O, 24 h, 20 °C (67%; ee ~5%).



Scheme 7. Reagents and conditions: (i) $Pd(PPh_3)_4$ (20 mol %), Et_3N, **17** (1 equiv), **20** (2 equiv), THF, degas, add CuI (20 mol %), reflux, 24 h (77%); (ii) 20% $Pd(OH)_2$–C, MeOH, H_2 (1 atm), 48 h, 20 °C (99%); (iii) **22** in MeOH, 20 °C; add aq $NaNO_2$ (3 equiv) then add the solution to 5 M HCl at 0 °C, 0.5 h (73%); (iv) K_2CO_3, aq MeOH, 20 °C, 4 h (99%).

excellent yield of the desired alkylated aryl diol **22** (Scheme 7). Analysis of the intermediates during these hydrogenations clearly showed that alkyne reduction was the slow step; the nitro group was rapidly reduced under most conditions examined.

Diazotisation then delivered the acetylated benzotriazole **23**, which was readily hydrolysed to give the 'free' benzotriazole **24** in excellent yield and as a mixture of tautomers (only one shown). While these were irrelevant to the later benzyne formation, their existence did rather complicate spectroscopic analysis of these and the following intermediates. It was found important to use an excess of sodium nitrite during the diazotisation reaction, in order to lessen competitive formation of the benzimidazole **25** (and its tautomer), which proved to be the major reason for loss of material at this stage. Presumably, higher concentrations of nitrous acid accelerated the diazotisation reaction at the expense of the undesired ring closure. Not surprisingly, in view of this relatively facile cyclisation, formation of compound **25** and the corresponding alkyne was also the reason why more forcing conditions (e.g., heat, use of acidic conditions) could not be employed in the foregoing hydrogenation steps (Scheme 7). Attempts to hydrolyse the rather stable benzimidazole were unsuccessful, as were attempts to alter the order of reaction, that is, hydrolyse the acetanilide **22** before diazotisation of the resulting diamine.



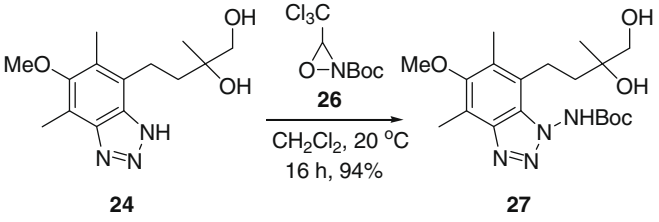
It was now necessary to introduce an *N*-amino function into the advanced intermediate **24**, for which purpose we required a reagent capable of electrophilic amination. In our previous studies,[11,12] we had optimised the use of hydroxylamine-*O*-sulfonic acid[22] for the preparation of the parent 1-aminobenzotriazole from benzotriazole. However, while suitable for large-scale runs on simple substrates, we were doubtful that it would be possible to isolate the desired amino-diol, a highly polar material, from a polar (DMF as solvent) and highly contaminated reaction mixture, following an aqueous work-up.

We therefore examined alternatives and were delighted to find that the oxaziridine **26**,[23] established by Vidal and Collet as a generally useful source of electrophilic nitrogen capable of effecting N-aminations, delivered an NHBoc moiety to the benzotriazole **24** under the simplest of conditions in essentially quantitative yield (Scheme 8). Unexpectedly, the product **27** was isolated as essentially a single regioisomer, of still unknown structure. In view of the similar levels of steric hindrance which would be experienced by the new NHBoc group, we speculate that the product is indeed compound **27**, due to hydrogen bonding between the incoming reagent **26** and the diol functionality of the substrate **24**.

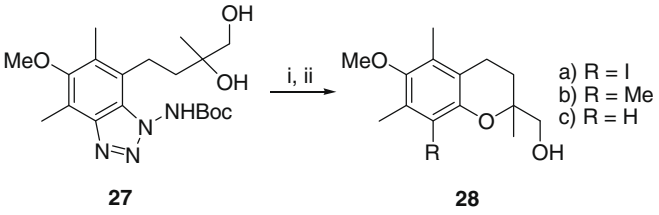
In any event, this was irrelevant to the final benzyne generation, for which we employed our previously reported tactic[12] of deprotection of the *N*-Boc derivative **27** using trifluoroacetic acid, followed by basification and exposure to *N*-iodosuccinimide (Scheme 9). After careful chromatography, it was possible to separate the desired iodochroman **28a** in excess of 50% yield. No other cyclised products were detected.

Finally, a modified Stille-type coupling reaction[24] employing copper(I) iodide as an additional catalyst with tetramethyltin as the methyl source delivered the target α-tocopherol precursor **28b**, but only after very careful chromatography, required to separate this from both starting material **28a** and deiodinated material **28c**. Comparisons of spectroscopic and analytical data with those previously reported confirmed the structural assignment.[7] Mixtures of both products **28b** and **28c** could also be obtained by low-temperature halogen-lithium exchange in tetrahydrofuran to give a presumed dianionic intermediate, followed by treatment with iodomethane; overall conversions were, however, poorer than those obtained from the coupling method.

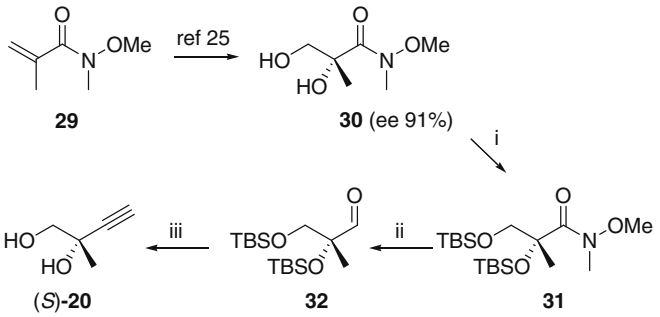
To complete an asymmetric synthesis of compound **28b**, we returned to the problem of obtaining an optically enriched source of the alkyne diol **20**, following our failure to use a direct AD reaction for this purpose (Scheme 6). Of a number of options examined, a successful method turned out to be a less direct but known version of the same reaction: asymmetric dihydroxylation of the Weinreb amide **29** derived from methacrylic acid is known to give the dihydroxy amide **30** with an ee value of 93%.[25] In our hands, this



Scheme 8.



Scheme 9. Reagents and conditions: (i) 20% TFA–CH_2Cl_2, 20 °C, 0.75 h; high vacuum; K_2CO_3, CH_2Cl_2, filter, add NIS (2.5 equiv), 20 °C, 1 h (54%; R = I); (ii) Me_4Sn, $(dba)_3Pd_2{\cdot}CHCl_3$, PPh_3, CuI, Et_2NH, NMP, 100 °C, 24 h (67%).



Scheme 10. Reagents and conditions: (i) TBSCl (2.2 equiv), imidazole (3.3 equiv), DMF, 35 °C, 16 h (94%); (ii) $LiAlH_4$, Et_2O, −78 °C, 40 min, then aq 2 M NaOH (88%); (iii) (a) PPh_3, CBr_4, CH_2Cl_2, 20 °C, 4 h (74%), (b) BuLi, THF, −30 °C, then warm to 0 °C, 1 h (59%), (c) 1 M TBAF, THF, 20 °C, 2 h (82%).

reaction gave the reported excellent yields of the dihydroxy amide **30**, with 91% ee, according to GC analysis (Scheme 10).[26]

Subsequent manipulation through to the desired alkyne diol followed a relatively standard pathway (Scheme 10): bis-silylation worked well to give the expected derivative **31**, which we found was best reduced to the aldehyde **32** using lithium aluminium hydride at low temperature, rather than the more usual DIBAL, which also gave substantial quantities of the corresponding alcohol and mono-desilylated aldehyde. Corey-Fuchs homologation and desilylation finally gave the desired (*S*)-alkyne-diol, (*S*)-**20**, in acceptable yield. As this compound would be expected to react in exactly the same manner as the racemate **20**, we had therefore formally completed an asymmetric synthesis of the target α-tocopherol precursor **4**.

Hence, overall, this synthesis clearly demonstrates that highly substituted benzynes can indeed be generated from 1-aminobenzotriazoles and trapped efficiently by alcohols. The length of this present route is not especially attractive, however, and our current efforts are directed towards developing new chemistry which will hopefully result in much shorter preparations of such benzyne precursors in general.

Acknowledgements

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26. CDX-β column; temperatures: oven 100 °C; detector 300 °C; injection port 200 °C; helium flow at column head pressure of 20 psi; retention time of (*R*)-isomer: 29 min. Ees determined against a racemic sample.