Intramolecular Benzyne Trapping in Synthesis of a Vitamin E Precursor

A thesis submitted to Cardiff University

By

Qing Xu

BSc (Hons.)

In candidature of

Doctor of Philosophy

November 2004

School of Chemistry

Cardiff University

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Acknowledgements

I would like to acknowledge and thank the following people for the following reasons.

For his supervision and constant encouragement throughout the course of my PhD I would like to thank Prof. D. W. Knight.

For financial support I would like to thank my parents and Prof. D. W. Knight as well as an ORS award.

For NMR analysis, GC analysis, HPLC analysis and the accurate mass spectroscopic data, I would like to thank Mr. Rob Jenkins.

For proof reading I would like to thank Dr. Nigel Bainbridge and Dr. Charlie Haskins, with special thanks to Prof. D. W. Knight.

For friendship, intellectual and moral support I would to thanks: my parents G. L. Xu and R. Z. Wang, Nigel, W. F. Tan, Charlie, Ying Fa, Simon, Sian, Ian, Tony, Emily, Mel, Charlie boy and Tai.

This thesis is dedicated to my parents Guolin Xu and Ruizhi Wang.

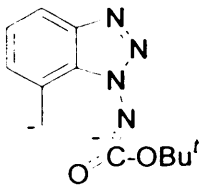
Abstract

Intramolecular benzyne trapping by alcohols have been applied to the synthesis of a series of racemic chromans. The theme of this project was to utilise this technique in the synthesis of the precursor, (*R*)-8-iodo-6-methoxy-2,5,7-trimethyl chroman-2-methanol, to the natural product Vitamin E.

The racemic form of the above compound has been synthesised in 12 linear steps from the commercially available 2,6-dimethyl-4-nitroanisole. Attempts to synthesize the enantiomerically enriched side chain (-)-(*S*)-3,4-dihydroxy-3-methyl-1-butyne have also taken place; and was achieved in seven linear steps.

Methylation of 8-iodo-6-methoxy-2,5,7-trimethyl chroman-2-methanol on its 8 position was carried out by Stille coupling reaction; the best result was a 25% conversion to the product.

In addition, a series non-racemic chromans have also been synthesised. The benzyne precursors were prepared by condensation between the dianion **391** and allylic halides, and the chirality introduced by AD-mix reactions of the resulting alkenes.



391

Abbreviations

AD-mix	Asymmetric dihydroxylation
Ac	Acetate
Boc	*t*-Butoxycarbonyl
BuLi	Butyl lithium
Bn	Benzyl
Conc.	Concentrated
CAN	Ammonium nitrate
CM	Cross metathesis
Cy	Cyclohexane
DA	Diels-Alder
DCM	Dichloromethane
$(DHQD)_2PHAL$	Dihydroquinidine phthalazine
DIBAL	diisobutylaluminium hydride
DMAP	4-*N*,*N*-Dimethylaminopyridine
D-(-)-DET	D-(-)-Diethyl tartrate
DMF	Dimethylformamide
DMP	2,2-Dimethoxypropane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	Dimethylsulfoxide
DTBS	di-*tert*-Butylsilyl
ee.	Enantiomeric excess
eq.	Equivalence
GC	Gas chromatography
HKR	Hydrolytic kinetic resolution
HOMO	Highest occupied molecular orbital
HOSA	Hydroxylamine-O-sulphonic acid
HPLC	High performance liquid chromatography
LDA	Lithium diisopropylamide
m-CPBA	*meta*-Chloroperoxybenzoic acid
MIPE	Methyl isopropenyl ether
Moc	Methoxycarbonyl
MOM	Methoxymethyl
Me	Methyl
n-Bu	Normal butyl
^{n}Hex	Hexane
NIS	*N*-iodosuccinimide
NMP	Methylpyrrolidinone
P	para
Pd-C	Palladium on carbon
$Pd^0_2(dba)_3$	tris-(Dibenzylidene-acetone) dipalladium (0)
PPTS	Pyridinium *p*-toluene sulfonate
pyr.	pyridine
t-Butyl	*tert*-Butyl
TFA	Trifluoroacetic acid
TBAF	*tetra-n*-Butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl

THF	Tetrahydrofuran
t.l.c.	Thin layer chromatography
TMEDA	*N*,*N*,*N*,*N*-tetramethylethylenediamine
TMS	Tetramethylsilane
TsOH	*para*-Toluenesulfonic acid
Triflate (Tf)	Trifluoromethanesulfonate

CONTENTS

Chapter 1 – Introduction

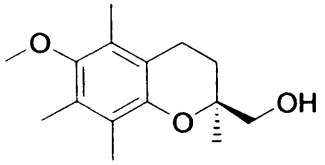
Chapter 2 – Towards the Total Synthesis of Vitamin E Precursor

Chapter One

Introduction

1.1 Review of Dr P.B. Little's Thesis—'Novel Benzyne Chemistry':

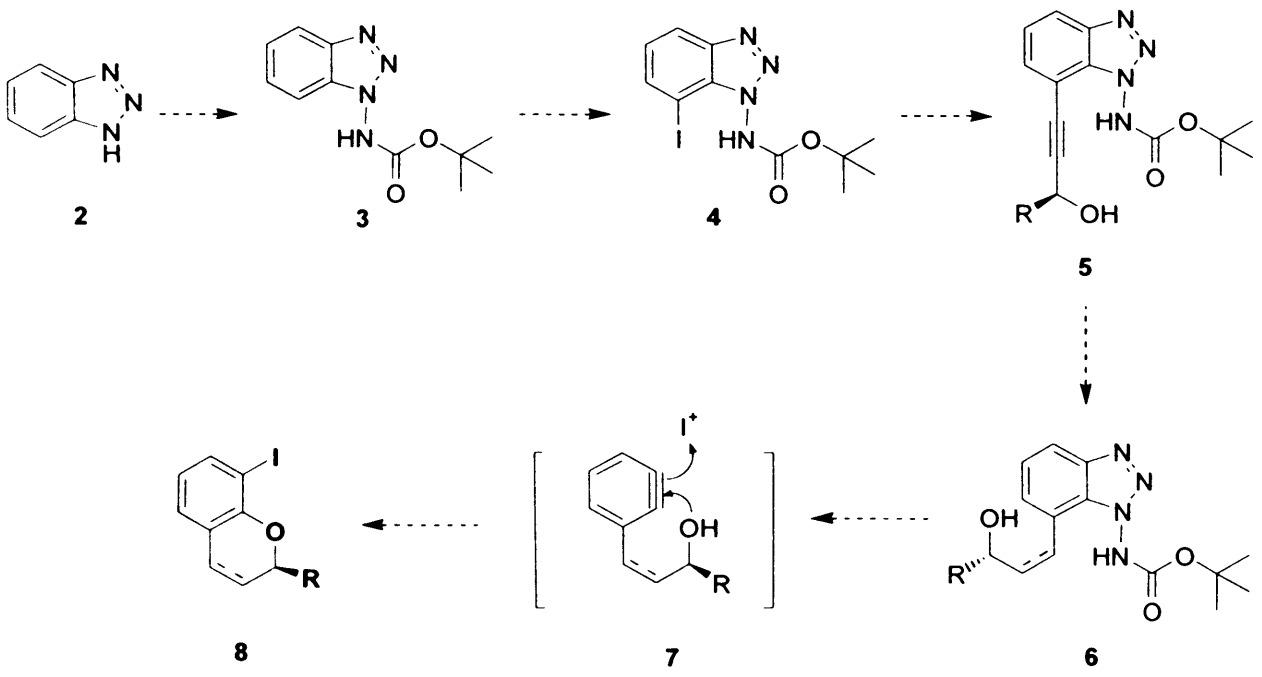
The current project follows on from and develops further the themes in Dr Paul B. Little's PhD thesis entitled 'Novel Benzyne Chemistry'.* In this, he had developed a new synthetic route which could possibly be applied to a synthesis of the precursor **1** to the natural product Vitamin E and also to the syntheses of other optically active chromans, using intramolecular benzyne trapping by alcohols as the key step.



(*S*)-1

One overall strategy, which was eventually established in Little's work for synthesising chromans and chromenes by intramolecular benzyne cyclisation, is outlined in Scheme 1. The commercially available benzotriazole **2** could be aminated to an amine, followed by protection to form the *N*-Boc derivative **3**. It was hoped that precursor **3** would undergo a regioselective lithiation, which would allow the introduction of an iodine into the 7-position of this molecule, to give the iodide **4**. Acetylenic alcohols **5** could then be formed by a Sonogashira coupling reaction. Reduction of the triple bond could either give a (*Z*)-allylic alcohol **6**, for chromene synthesis, or a fully saturated side chain for chroman synthesis. After the reduction, deprotection followed by benzyne formation, using the *N*-iodosuccinimide (NIS) technology devised by Birkett,[1] should complete the required chroman / chromene **8** syntheses. The realisation of these ideas are described in more detail below to set the scene for the present project, which is aimed at applying this type of chemistry to a new synthesis of Vitamin E as indicated above.

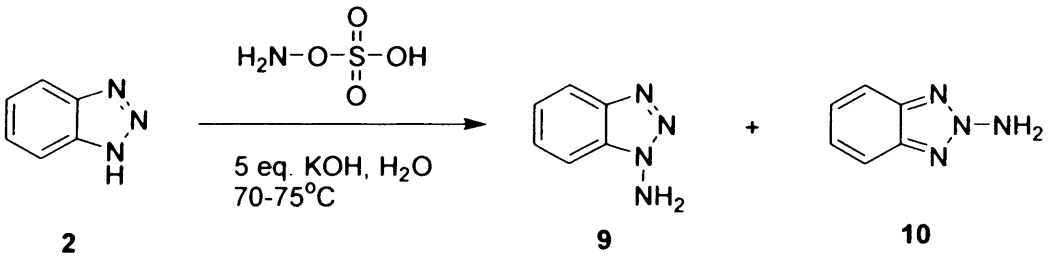
*P.B.Little, PhD dissertation, Cardiff University, 1999.



Scheme 1

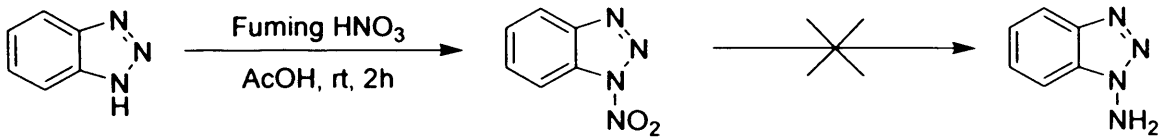
1.1.1 Synthesis of 1-aminobenzotriazole

Direct amination of the commercially available benzotriazole **2** was carried out using hydroxylamine-*O*-sulphonic acid as the aminating reagent, according to a literature method (Scheme 2).[2] Alternative solvent systems as well as temperatures were tried by Little. As a result, amination at room temperature in dimethylformamide containing 5% water, as well as potassium hydroxide as base, was found to be a superior way to prepare 1-aminobenzotriazole **9** in a reasonable yield (69%). In this way, the desired 1-aminobenzotriazole **9** was the sole product. The conversion was improved (82%) when the reaction was heated to 75-85°C under these conditions, but a 4:1 mixture of 1-aminobenzotriazole **9** and 2-aminobenzotriazole **10** was obtained due to the increased stability of isomer **10** at this higher temperature.[2] Separation of the two isomers proved not to be a simple matter.



Scheme 2

A two-step method was also attempted for large scale production of the required 1-aminobenzotriazole **9** (Scheme 3).

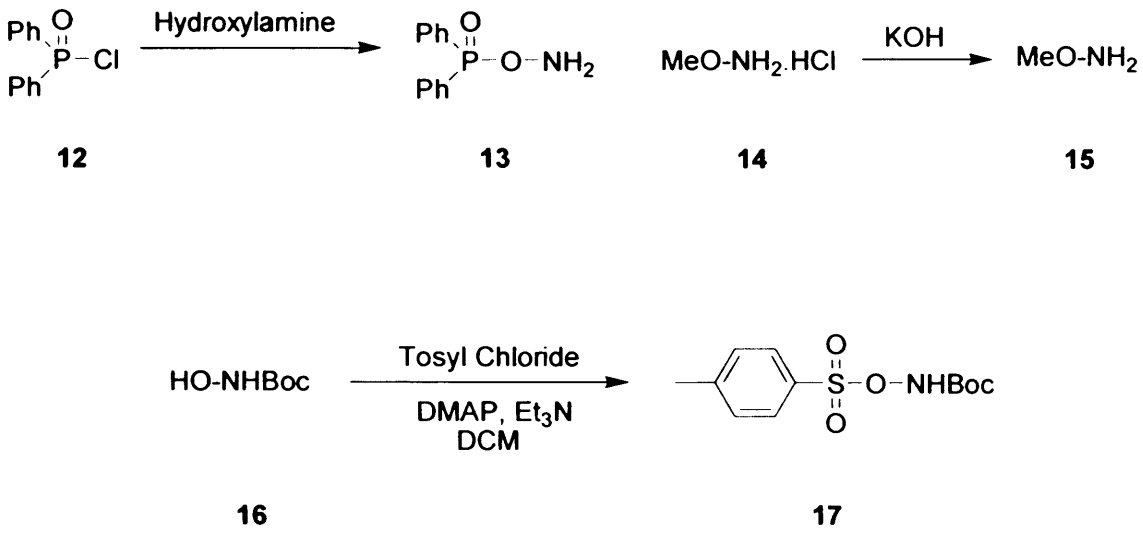


2 **11** **9**

Scheme 3

Nitration of benzotriazole **2** with fuming nitric acid in acetic acid gave 1-nitrobenzotriazole **11** in excellent yield (>90%), using the method developed by Fernandes and Habraken[3] (Scheme 3), but the attempted conversion into 1-aminobenzotriazole **9** under palladium-catalysed hydrogenations and other reducing conditions failed to give the desired product.

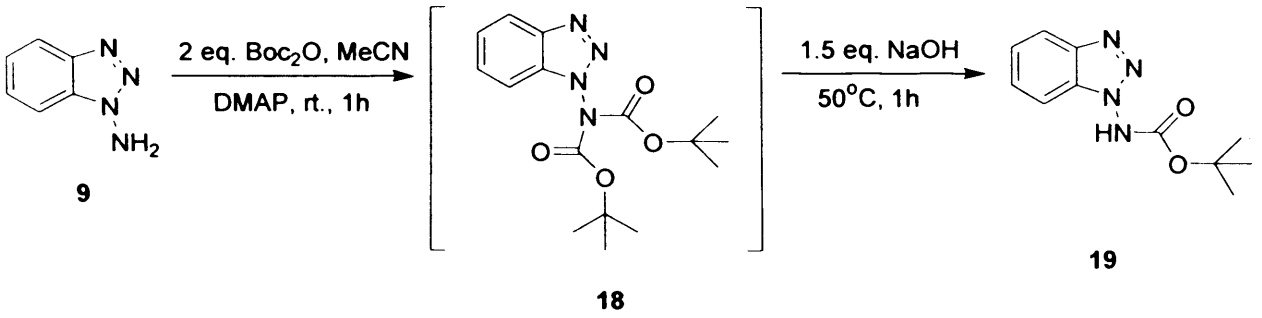
Due to the desire to find a more efficient and cleaner aminating reagent than hydroxylamine-*O*-sulphonic acid, three other hydroxylamine-based electrophilic aminating reagents with different leaving groups, namely diphenylphosphinoxy-**13**, methoxy-**15** and tosyloxy-**17**, were prepared from their commercially available precursors[4] (Scheme 4) but none of these reagents aminated the benzotriazole **2**.



Scheme 4

1.1.2 Protection of 1-aminobenzotriazole

Since the formation of 1-aminobenzotriazole **9** could be readily scaled up, to give a sufficient amount by the one-step procedure, the amino group was then protected to generate a suitable metallation directing group, as well as to remove any chance of premature oxidation to a benzyne. *t*-Butoxycarbonyl (Boc) was chosen as the protecting group; the *mono*-protected 1-aminobenzotriazole **19** was prepared by a one-pot, two-step procedure, in 95% yield (Scheme 5).

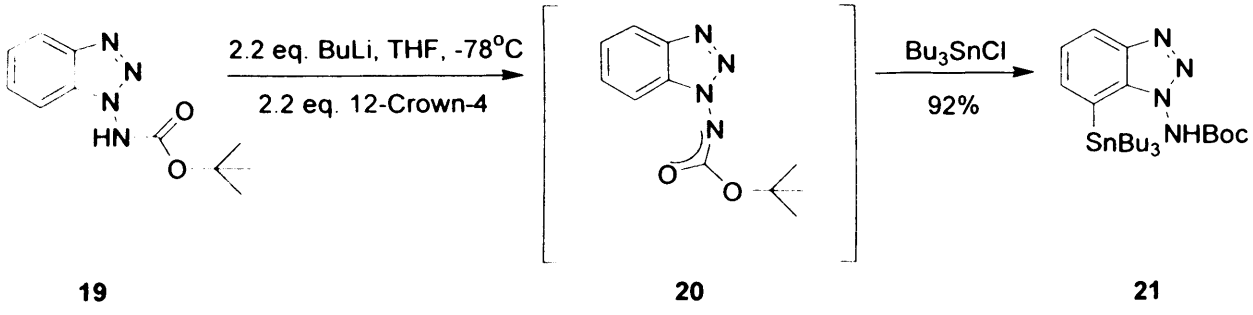


Scheme 5

1-Aminobenzotriazole **9** was reacted with two equivalent of di-*tert*-butoxycarbonyl dicarbonate in acetonitrile, containing a catalytic amount of 4-*N*,*N*-dimethylaminopyridine (DMAP). This led to the formation of *N*,*N*-*bis*-*tert*-butoxycarbonyl aminobenzotriazole **18**. Sodium hydroxide was then added and after heating the reaction mixture to 50°C, one of the Boc groups was selectively removed. It was found that using one equivalent of di-*tert*-butoxycarbonyl dicarbonate led only to an equal mixture of *bis*-protected aminobenzotriazole **18** and starting material **9**. This showed that the *mono*-protected amine **19** is of similar reactivity to the unprotected amine **9**. This was the first indication of the perhaps surprisingly high nucleophilicity of the acylated amine **19**, presumably due to the α-effect.

1.1.3 Lateral lithiation

After setting up the two-step methodology for obtaining the *mono*-protected amine **19**, the next step on the route to substituted benzyne precursors was a lithiation with subsequent condensation with electrophiles (Scheme 6).

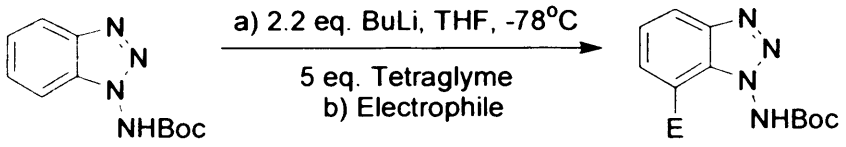


Scheme 6

As a model reaction, tributyltin chloride was chosen as the electrophile due to it being, as claimed by Little, an excellent electrophile, when combined with the ability of aryl stannanes

to participate in palladium-catalysed cross couplings. After a series of optimisations, Little found that stirring the aminobenzotriazole **19** in a solution of *n*-butyl lithium and 12-crown-4[5] in tetrahydrofuran at -78°C for half an hour, followed by the addition of tributyltin chloride, gave an excellent yield (92%) of the stannane **21**. Meanwhile, other conditions such as using *N,N,N,N*-tetramethylethylene-1,2-diamine (TMEDA)[6] as a chelating agent, with THF or diethyl ether as the solvent, as well as using *tert*-butyl lithium, potassium *tert*-butoxide and lithium diisopropylamide as the base only resulted in partial conversions (~60% or less). Use of a catalytic amount (20%) of the ligand, 12-crown-4, also only gave a poor conversion (23%). On the other hand, a stoichiometric amount of tetraethylene glycol dimethyl ether (tetraglyme),[7] which can be regarded as a ring opened homologue of 12-crown-4, and is cheaper and less toxic, worked as effectively as its cyclic counterpart. However, when 5 equivalents of tetraglyme were used, the yield was increased to 94%.

Since Little proved that the dianion **20** could be completely formed and could be reproducibly condensed with tributyltin chloride in excellent yield, a range of electrophiles were condensed with this intermediate, using the tetraglyme protocol (Table 1).



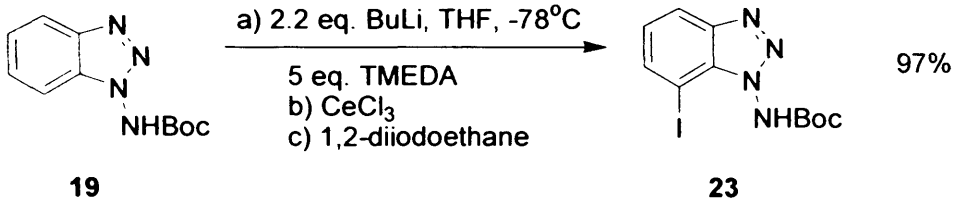
19 **22**

	Electrophile	**E**	**% Isolated Yield**
1.	Bu_3SnCl	$SnBu_3$	96
2.	D_2O	D	89
3.	*p*-$MeOC_6H_4CHO$	*p*-$MeOC_6H_4CH(OH)$	79
4.	DMF	CHO	67
5.	*n*-$C_5H_{11}CHO$	*n*-$C_5H_{11}CH(OH)$	20
6.	NIS	I	27
7.	Iodoperfluorohexane	I	29
8.	*n*-PrCH=CHCHO	*n*-PrCH=CHCH(OH)	75

Table 1

Little found that the dianion **20** reacted efficiently with non-enolizable electrophiles, such as deuterium oxide (entry 2) and *para*-anisaldehyde (entry 3), while the yield was poor when it was condensed with the alkyl aldehyde hexanal, an enolizable electrophile (entry 5). It was reasoned that the nucleophilicity of the dianion was lower than its basicity and that the dianion was deprotonating the enolizable electrophiles in preference to nucleophilic attack.

For his additional objective of forming the 7-iodoaminobenzotriazole (E=I), the use of *N*-iodosuccinimide (NIS) and iodoperfluorohexane resulted in only 27 and 29% yields respectively of the 7-iodo derivative **23**. An alternative iodination method, which involved a lithium / cerium exchange[8] was therefore used (Scheme 7).



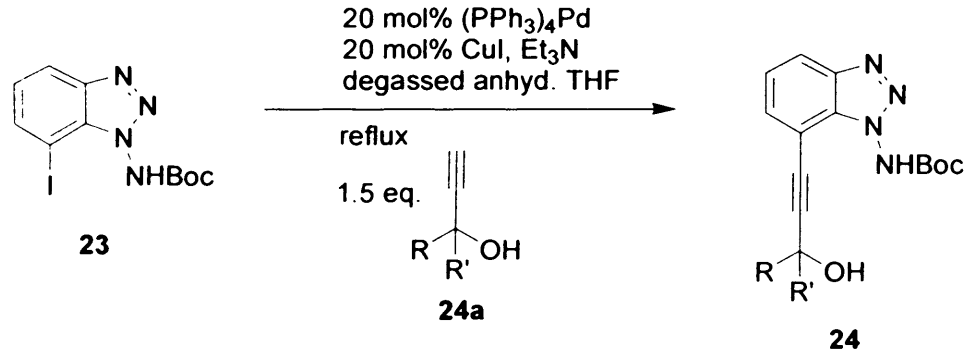
19 **23**

Scheme 7

The exchange was made by transferring the dianion **20** solution, which was produced in the normal way, to a slurry of cerium(III) chloride in tetrahydrofuran *via* canula at -78°C. Electrophiles such as *para*-anisaldehyde (entry 3), dimethylformamide (entry 4), hexanal (entry 5), *trans*-2-hexenal (entry 8) as well as iodoperfluorohexane were applied again and all of the yields were improved, to 95%, 95%, 79%, 87% and 55% respectively. These results amply demonstrated the increased nucleophilicity of the cerium species, however, the original reason for employing cerium was to reduce the basicity of the dianion towards enolizable electrophiles. The iodination yield using iodoperfluorohexane was also increased, from 29% to 55%. Eventually, he found that the use of 1,2-diiodoethane delivered an outstanding 97% yield of iodide **23,** treating the initial dianion with five equivalents of tetramethylethylenediamine (TMEDA).

1.1.4 The Sonogashira Coupling

As described above, a number of benzyne precursors **22** including iodide **23** had been produced. The next phase of Little's project was the introduction of tethered nucleophiles for the projected intramolecular benzyne trapping. Due to the desire to incorporate asymmetry into the synthesis in order to produce chiral chomans and chromenes, Sonogashira cross coupling was examined as this strategy would give the opportunity for diversity in the synthetic route, and allow the easy introduction of the desired stereogenic centres (see structure **5**, Scheme 1). After a series of modifications to the cross coupling using propargylic alcohols, Little found that using a catalytic amount of *tetrakis*-triphenylphosphinepalladium(0), copper(I) iodide and triethylamine in tetrahydrofuran[9] under reflux gaves a range of acetylenes **24** in moderate to good yields (Table 2).



23 **24a** **24**

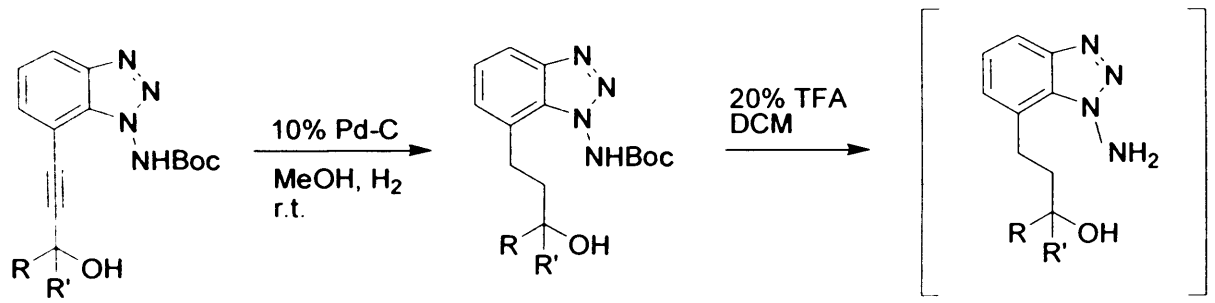
	R	R'	Yield (%)
1	H	H	92
2	Et	H	91
3	Me	Me	87
4	Ph	H	38
5	*p*-MeOC$_6$H$_4$	H	81
6	CH$_2$OH	Me	72

Table 2

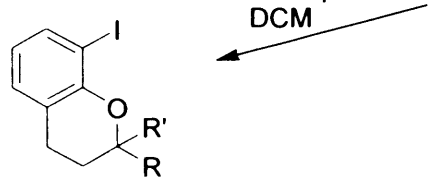
1.1.5 Reduction / Deprotection / Cyclization

The incorporated tethers were then reduced. Palladium-catalysed hydrogenation in methanol delivered the saturated alcohols **25** (Table 3). The last remaining transformations were a deprotection followed by benzyne formation. A two-pot sequential reaction was developed to avoid isolation and purification of the reactive and rather polar free amines **26**.

After the removal of the *tert*-butoxycarbonyl protecting group, by treatment with a 20% solution of trifluoroacetic acid (TFA) in dichloromethane over half an hour, the reaction mixture was basified to liberate the free amine **26**. Benzyne generation and cyclisation, triggered by *N*-iodosuccinimide (NIS), formed chromanes **27**, in satisfactory yields.



24 **25** **26**



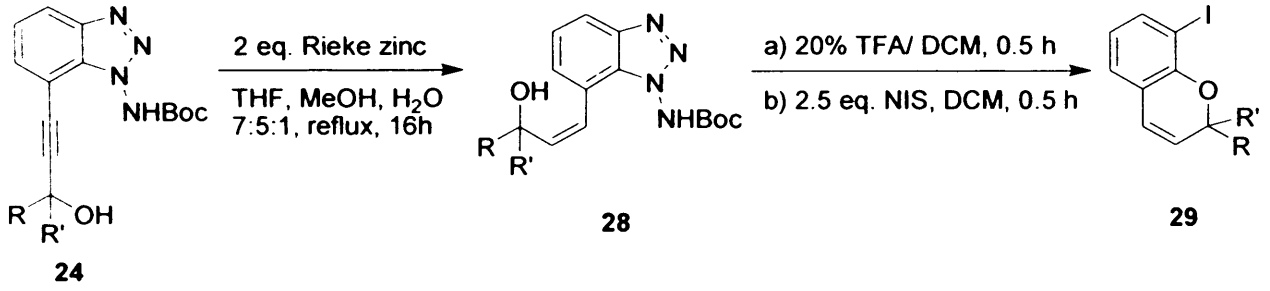
27

	R	R'	25(%)	27(%)
1.	H	H	95	86
2.	Et	H	94	85
3.	Me	Me	95	90
4.	Me	CH_2OH	72	78
5.	*p*-$MeOC_6H_4$	H	0	~

Table 3

1.1.6 Partial reduction: towards chromenes

It was felt that the partial reduction of acetylenes **24** to (*Z*)-allylic alcohols **28**, followed by deprotection and cyclisation could, in a similar fashion, give their unsaturated anologues. After a lengthy search for optimised conditions for this partial reduction, Little found a reproducible protocol using Rieke zinc,[10] which is a highly divided zinc metal that acts as a selective reducing agent in a tetrahydrofuran, methanol and water solvent mixture. Rieke zinc was generated *in situ* by the reduction of zinc(II) chloride with potassium metal in hot tetrahydrofuran. As a result, a range of chromenes **29** have been synthesised by this method, with the exception of the aryl substituted alcohol which gave unrecognisable products (entry 4) (Table 4).



24 **28** **29**

	R	R'	28(%)	29(%)
1.	Et	H	94	83
2.	Me	Me	80	0
3.	CH_2OH	Me	60	63
4.	*p*-$MeOC_6H_4$	H	0	~

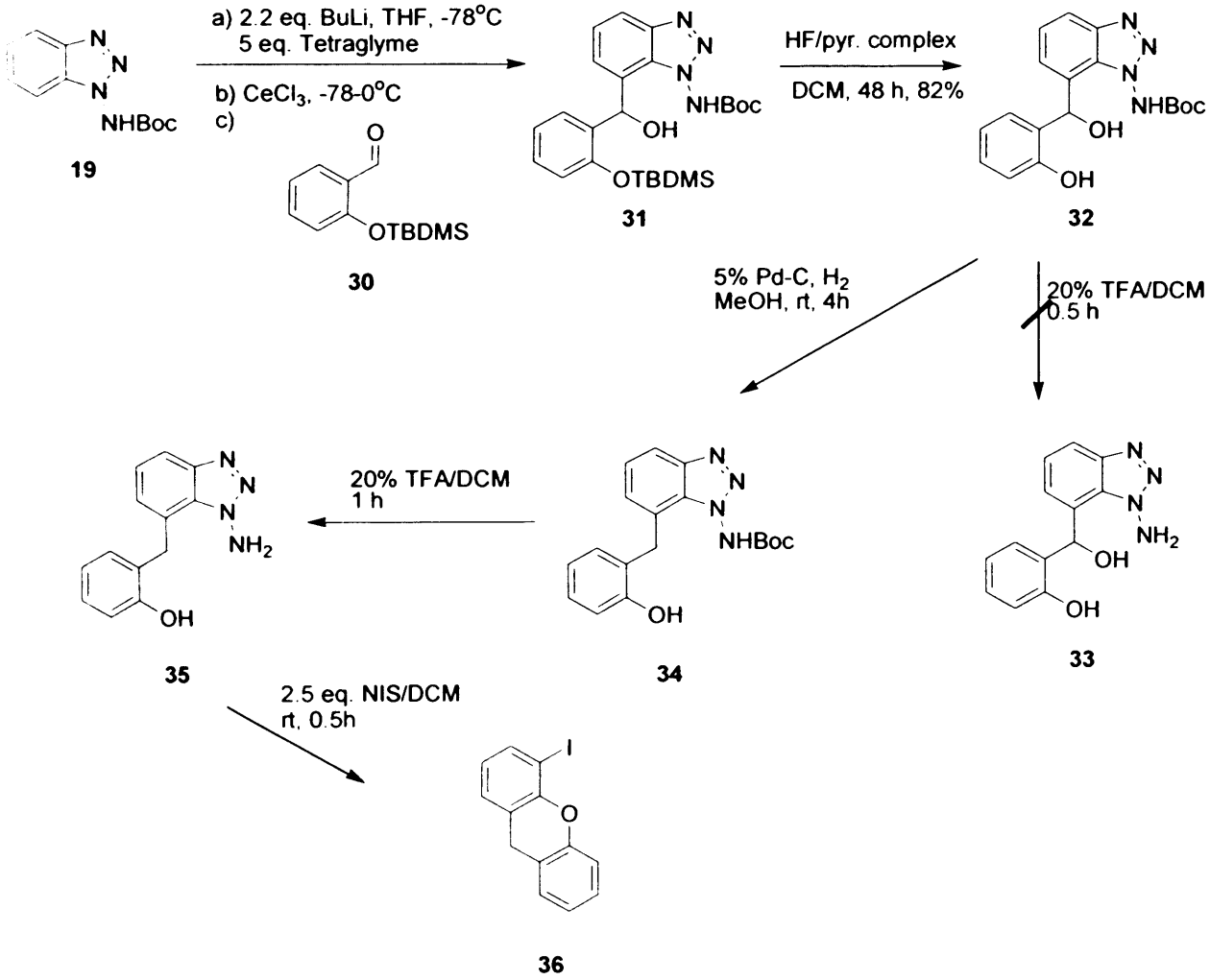
Table 4

Little also mentioned but did not investigate the idea that the chromene **29** might be functionalised by derivatisation of its double bond. Possibilities include dihydroxylation, epoxidation, hydroboration, Heck type reactions *etc*.

1.1.7 Phenols as efficient traps in the benzyne cyclisation

Due to the fact that aromatic substituents are present in the majority of chroman natural products, and that there was a gap with respect to this area in the literature,[11] Little began to focus on the efficient intramolecular trapping of a benzyne by a tethered phenol (Scheme 8).

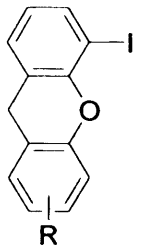
Condensing the dianion derived from benzotriazole **19** with protected salicylaldehyde **30** formed alcohol **31** in 82% yield; the silyl ether was then cleaved with hydrogen fluoride / pyridine complex in dichloromethane to give the free phenol **32**. Unfortunately, deprotection of the Boc group using the routine method as well as under other mildly Lewis acidic conditions[12] failed. It was reasoned that the acidic lability of the *bis*-benzylic alcohol was to blame for this result and the solution was to remove this functionality.



Scheme 8

Dehydroxylation of the *bis*-benzylic alcohol by palladium-catalysed hydrogenolysis formed the phenol **34**. Carbamate cleavage by trifluoroacetic acid as usual then gave the free amine **35**, which underwent the benzyne cyclisation after treatment with *N*-iodosuccinimide and afforded a single product—the iodoxanthene **36**.

Methoxy-substituted iodoxanthenes **37** (Scheme 9) have also been synthesised using a similar method. The protecting group was changed from *t*-butyldimethylsilyl (TBDMS) to benzyl (Bn), in order to achieve simultaneous deprotection and dehydroxylation under the hydrogenolysis conditions.

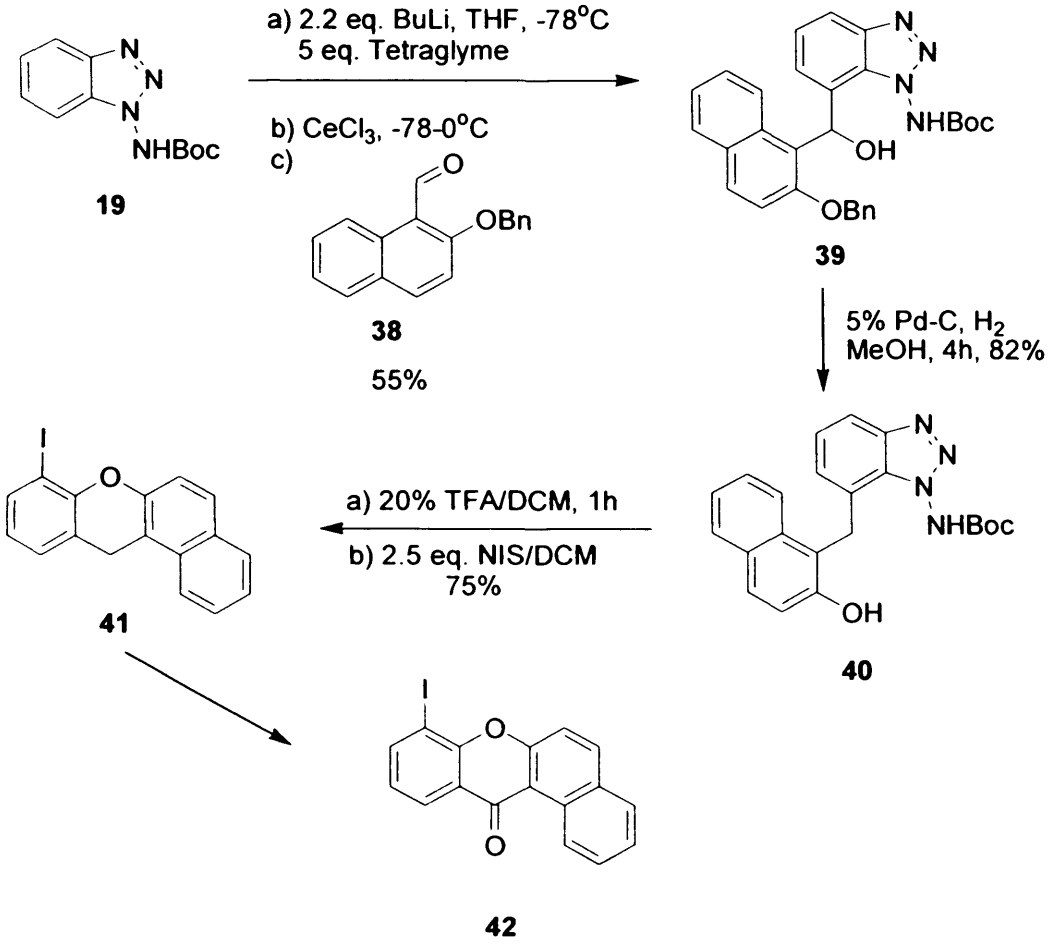


37

R_1=3-MeO, 81%;
R_2=5-MeO, 81%.

Scheme 9

The same methodology has been successfully extended by Little to synthesise a fused-four ring— benzoxanthene **41** (Scheme 10). Surprisingly, when the benzoxanthene **41** remained in the reaction mixture with *N*-iodosuccinimide for longer than half an hour, a further oxidation reaction occurred and the benzoxanthone **42** was formed. It was reasoned that the *N*-iodosuccinimide is known to be a mild oxidising agent and this, combined with the sensitive nature of the bis-benzylic methylene group, probably explains this result.

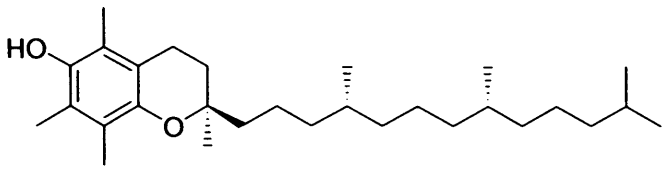


Scheme 10

1.1.8 An attempted synthesis of tocopherol

On the basis of Little's investigations on the scope and limitations of the intramolecular benzyne cyclisation, a series of chromans and chromenes were synthesised although, while most of these were racemic, the non-racemic compounds were not proven to be optically pure. More importantly, this methodology needed to be applied on a formal natural product synthesis, to explore its potential value and gain our long-term aim of showing the utility of this type of chemistry when applied to highly substituted benzynes.

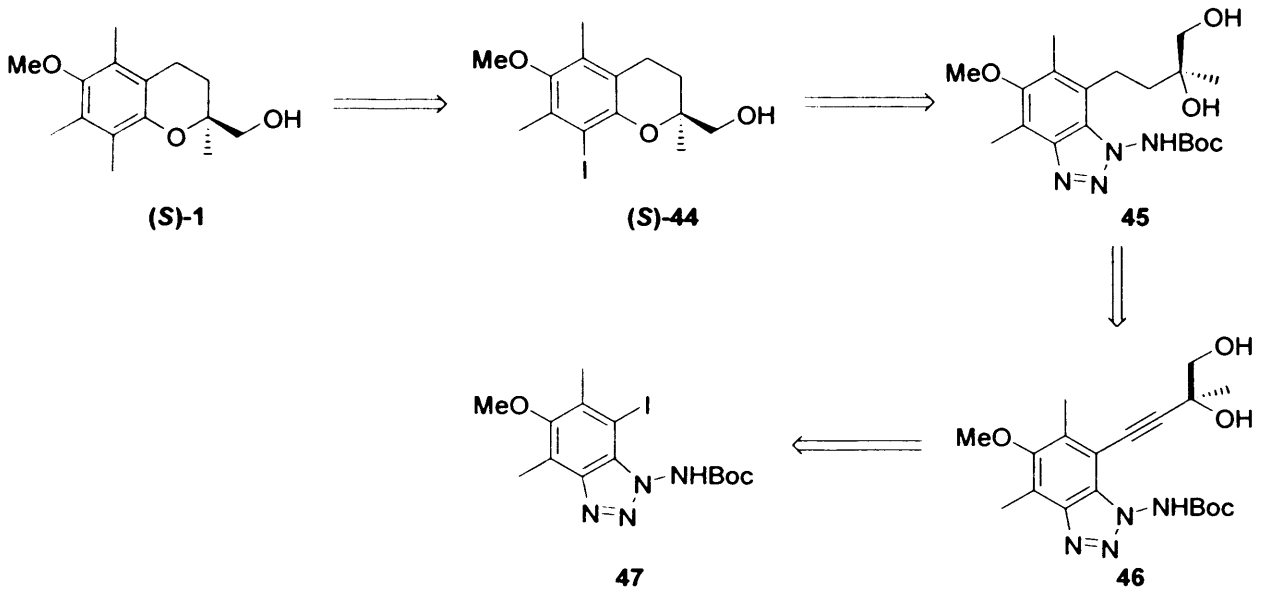
There are a wide range of natural products containing the chroman core. Among these vitamin E (α-tocopherol) **43** was chosen due to the juxta-positioning of the aliphatic and aromatic sections of the molecule. The disconnection which Little developed would separate these two sections.



43

Scheme 11

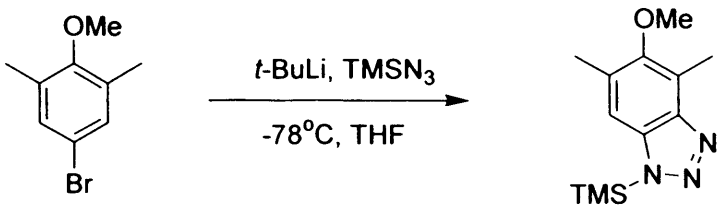
Little has laid out the initial retrosynthesis as follow (Scheme 12).



Scheme 12

Starting from chroman **1**, the methyl group in the 8-position could be retrosynthetically converted to the iodide **44**, which would be synthesised from the Sonogashira product, the acetylene **46**, *via* the saturated diol **45**. According to this, the iodide **47** was the key compound to be prepared.

Little initially attempted to apply a 3 + 2 cycloaddition between benzyne and trimethylsilyl azide to prepare benzotriazole **49** (Scheme 13), the iodide **47** then could be achieved in a few steps.

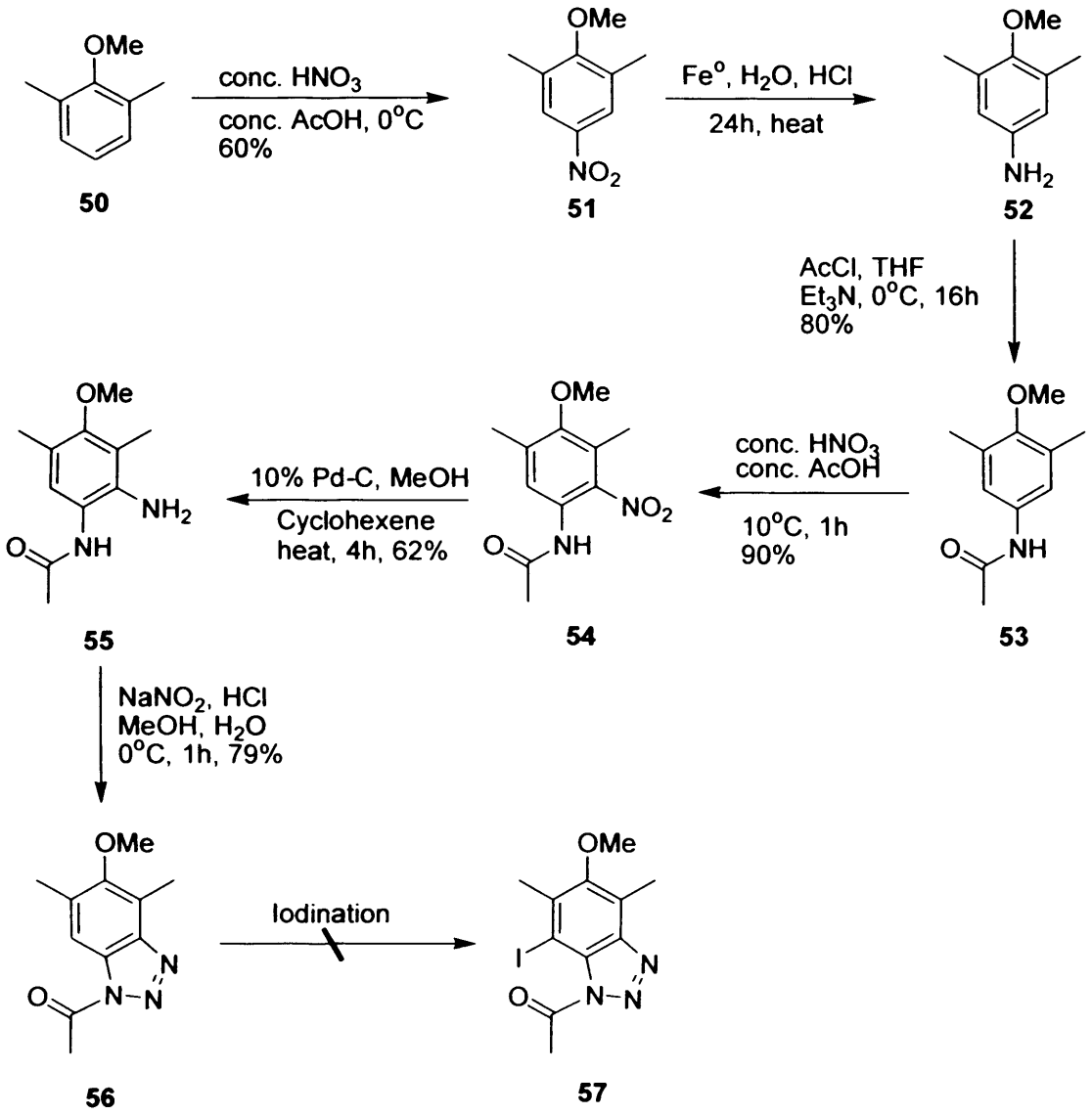


48 **49**

Scheme 13

Commercially available 4-bromo-2,6-dimethylanisole **48**, a classical benzyne precursor, was treated with trimethylsilyl azide under basic condition at -78°C. The cycloaddition was not selective and multiple products (approximately 12) were formed.

After giving up the above method, Little began to focus on a five-step route[13] to the synthesis of acetamide **55** (Scheme 14), which would hopefully be converted into the iodide **47** by diazotization and then iodination. Nitration of anisole **50** in concentrated acids gave nitro anisole **51**, which was then reduced using a classic iron powder reduction method in the presence of a catalytic amount of hydrochloric acid to give the aniline **52**. Protection by a standard triethylamine / acetyl chloride protocol afforded amide **53**, which was followed by a second nitration which delivered *o*-nitroamide **54** in 90% yield. The acetamide **55** was then prepared *via* a transfer hydrogenation from cyclohexene before being subjected to the standard diazotisation condition to give 1-acetylbenzotriazole **56**.



Scheme 14

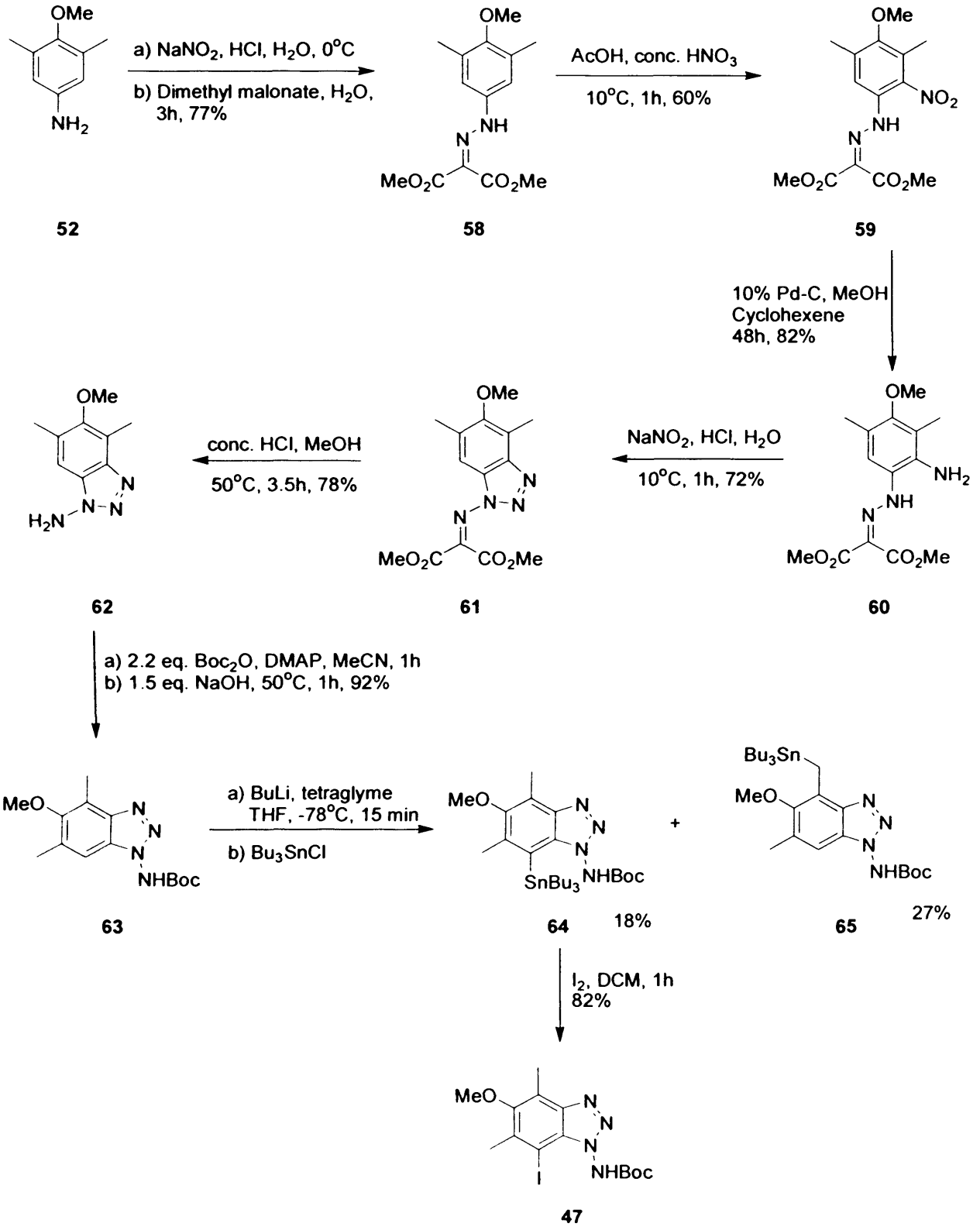
But this route failed at the iodination step: no reaction occurred with *N*-iodosuccinimide and catalytic amounts of *p*-toluenesulphonic acid;[14] tetrabutylammonium iodide in acetonitrile with two equivalents of ceric ammonium nitrate[15] caused non-selective and multiple iodinations; stirring 1-acetylbenzotriazole **56** with molecular iodine, periodic acid and sulphuric acid[16] in acetic acid was also problematic.

Therefore Little decided to follow a modified Campbell and Rees route to the 1-aminobenzotriazole,[1a] a classical way which was developed in 1969. In this case, 4-amino-2,6-dimethylanisole **52** was the starting point for this route (Scheme 15).

Diazotization of amine **52** under standard conditions, followed by a nucleophilic addition of dimethyl malonate led to the hydrazone **58**. Nitration of this hydrazone **58** gave *o*-nitrohydrazone **59** which was reduced to the diamine derivative **60** by transfer hydrogenation from cyclohexene. Again, a standard diazotisation afforded the protected benzotriazole **61**. At this point, the direct iodination procedures, which were described earlier were applied again, this time on benzotriazole **61**; again, no useful reactions occurred.

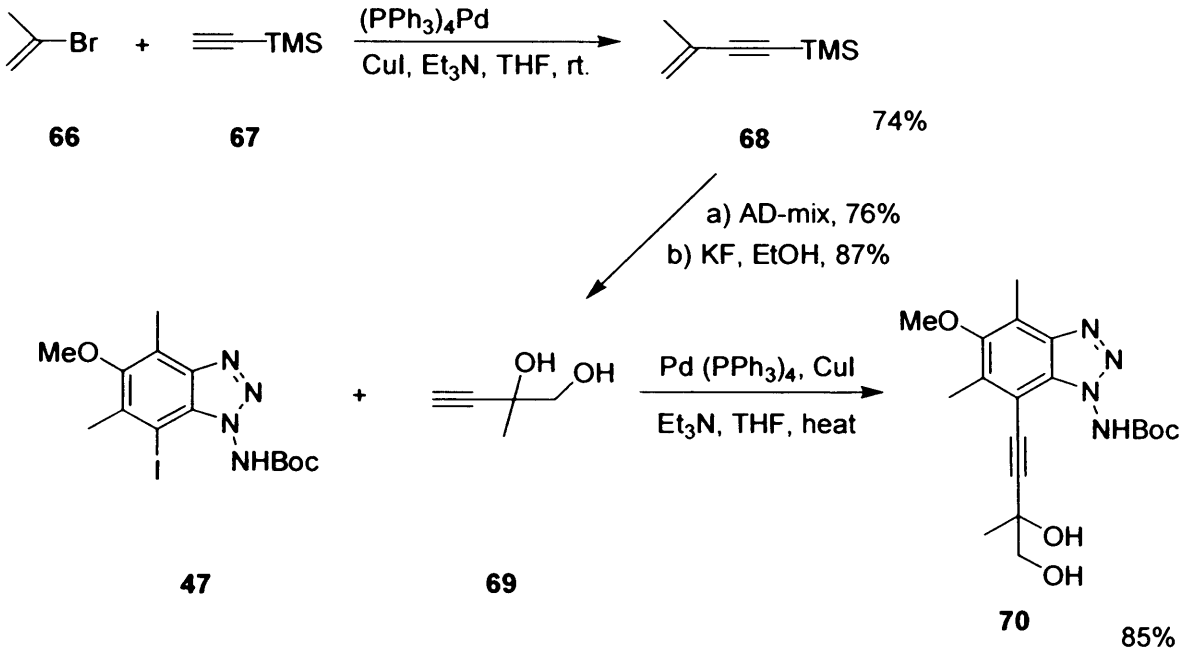
At this stage, Little returned to the lithiation protocol, which had been developed for the unsubstituted aminobenzotriazoles, to form the iodide **47**. Deprotection of benzotriazole **61** in acidic conditions gave the free 1-aminobenzotriazole **62**, and was followed by the one-pot protection procedure to give *mono*-carbamate **63**. After forming the dianion intermediate by the standard procedure from *mono*-carbamate **63**, 1,2-diiodoethane was added as the electrophile, but multiple addition products were formed. Little then used a better electrophile, tributyltin chloride, to trap the presumed lithium dianion. As a result, two substituted products were found: the desired stannane **64**, in a poor 18% yield, along with stannane **65** in 27% yield.

Despite this, the iodination was still performed by treating the stannane **64** with molecular iodine in dichloromethane at room temperature. The key iodide **47** was then obtained but obviously in an unacceptably low overall yield. However, sufficient material was isolated to allow a further preliminary study.



Scheme 15

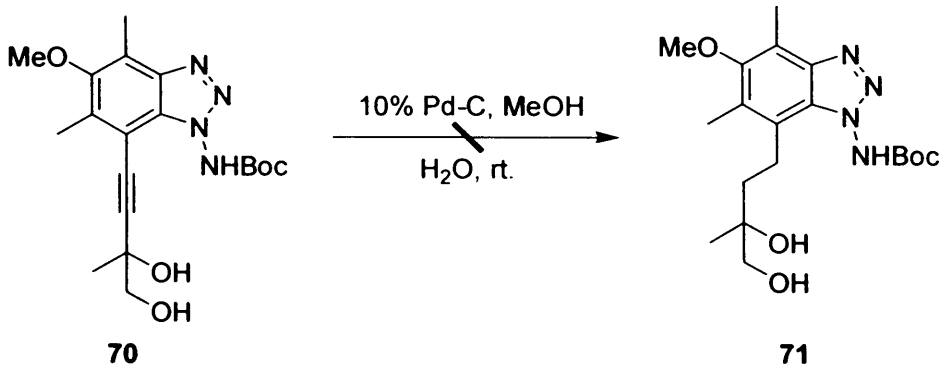
Therefore, Little's next step was to attempt a Sonogashira coupling of the key iodide **47** with diol **69** (Scheme 16).



Scheme 16

The enyne **68** was produced by Sonogashira coupling between 2-bromopropene **66** and trimethylsilylacetylene **67** at room temperature. AD-mix reaction of enyne **68** followed by deprotection afforded diol **69**. Analytical methods such as Mosher's ester and chiral GC 'failed to give clear results and therefore enantiomeric mixtures cannot be ruled out', Little stated. The key Sonogashira coupling of iodide **47** with diol **69** under reflux as mentioned above, gave the diol **70** in 85% isolated yield.

It now only required a hydrogenation to saturate the aliphatic chain, followed by deprotection / cyclisation, to achieve the target. Unfortunately, the attempted hydrogenation, using the method employed previously, did not return any product, possibly due to the very small scale (Scheme 17).



70 **71**

Scheme 17

Overall, it can be stated that Little made substantial progress in the area of synthesising *ortho*-substituted benzyne precursors, as well as in the benzyne cyclisation chemistry using oxygen nucleophiles. He has also opened a new entry towards the natural product Vitamin E (α-tocopherol) synthesis. Against the background of Little's research, the current project was aimed at developing this new route towards the optically pure Vitamin E precursor **1**.

1.2 A General Introduction to Benzyne

Benzyne **72** is considered to be one of the classic reactive intermediates in organic chemistry. This highly unstable, neutral species can be derived formally by the removal of two adjacent hydrogen atoms from an aromatic ring.

72

1.2.1 Structure and reactivity

The first proof of benzyne came from Roberts[17] in 1953. His experiments on the conversion of ^{14}C-labeled chlorobenzene with potassium amide into aniline gave strong support to the intermediacy of *o*-benzyne in this and related reactions. Additional direct evidence for the existence of benzyne was provided by the observation of its infrared spectrum, solid-state ^{13}C dipolar NMR spectrum, ^{1}H and ^{13}C NMR in a molecular cage and by ultraviolet

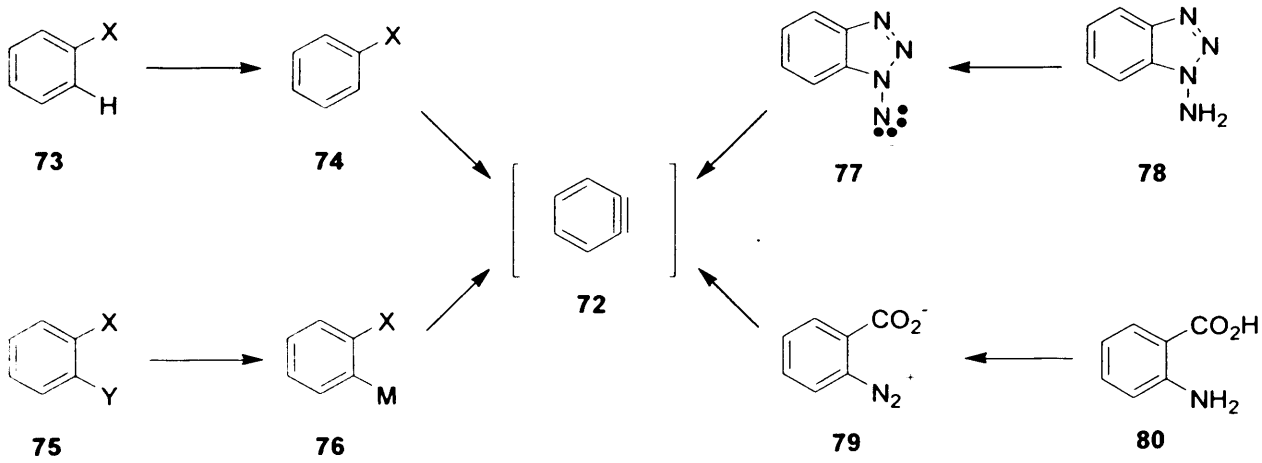
photoelectron spectroscopy.[18] Benzyne has been the subject of extensive high-level theoretical studies.

The experimental findings and theoretical calculations agree in concluding that benzyne has the general structure depicted above, in which a degree of triple bonding with some diradical character exists between two adjacent carbons.

Even at low temperatures, benzyne is extraordinarily reactive. The reactions of this compound can be divided into three groups: pericyclic reactions, nucleophilic additions and transition metal-catalysed reactions.

1.2.2 Generation of benzyne

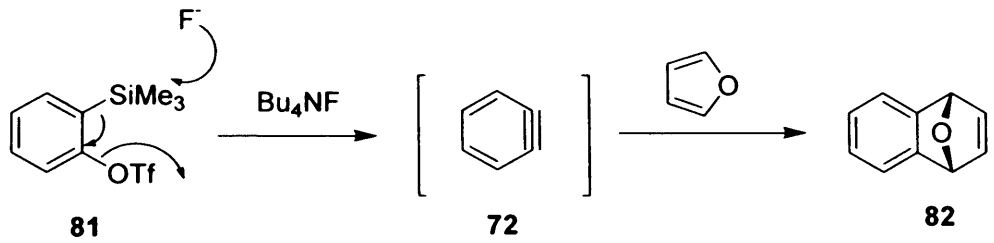
Benzyne is an important reactive intermediate and many studies on its generation have been undertaken. Due to their extreme reactivity, benzynes must be trapped *in situ*. The generation methods most widely used are summarised in Scheme 18.[18]



Scheme 18

A halide **73** can be treated with a strong base, such as butyl lithium or sodamide, to remove the *o*-aromatic proton and generate benzyne *via* an anion. The use of strong bases which may act as nucleophiles can be avoided by treatment of *o*-dihalosubstituted benzenes **75** with a metal (lithium or magnesium) to generate an *o*-metallohalobenzene **76**, which rapidly collapses to benzyne by elimination.

A more recent and milder method features a very similar mechanism to the metal-halogen exchange method and is instigated by fluoride attack onto a silylbenzene **81**, having also an excellent leaving group (triflate) in the *ortho*-position (Scheme 19).[18]



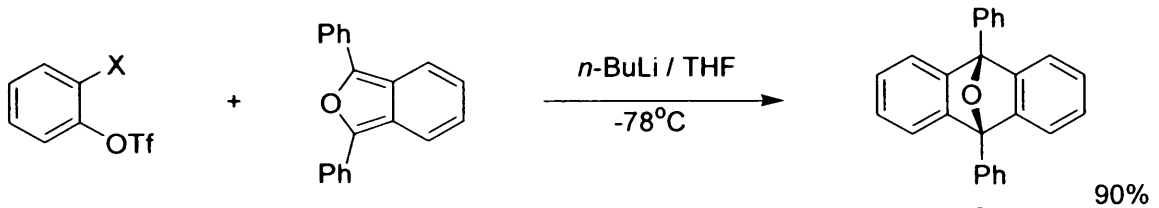
81 **72** **82**

Scheme 19

In contrast, another classical approach operates under mildly acidic conditions by diazotisation of anthranilic acid **80**. Neutralising the diazonium salt with NaOH gives a zwitterion **79** with the negative charge on the carboxylate. The loss of nitrogen and carbon dioxide delivers benzyne **72**.

Alternatively, oxidation of aminobenzotriazole **78** usually produces good yields, but has the disadvantage of requiring an oxidant such as lead tetraacetate in the reaction mixture.

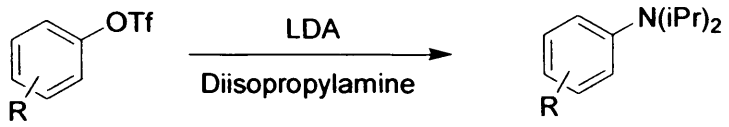
Recent typical and improved examples of the different methods outlined above, in addition to novel methods, are introduced below.



83 **84** **85**

Scheme 20

Metal-halogen exchange of *o*-halotriflates **83** with *n*-BuLi at -78°C produces arynes (Scheme 20).[18]

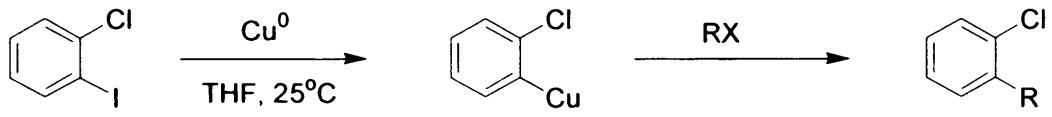


86 **87**

Scheme 21

Aryl triflates **86** react with lithium diisopropylamine (LDA) in diisopropylamine to give the corresponding amines **87**, which must proceed by a benzyne mechanism (Scheme 21).[18]

Whereas *o*-halolithium or magnesium arenes readily undergo elimination to benzynes, *o*-fluoro and *o*-chloro-copper reagents **89** do not, and can therefore be used in nucleophilic displacements (Scheme 22).[18]

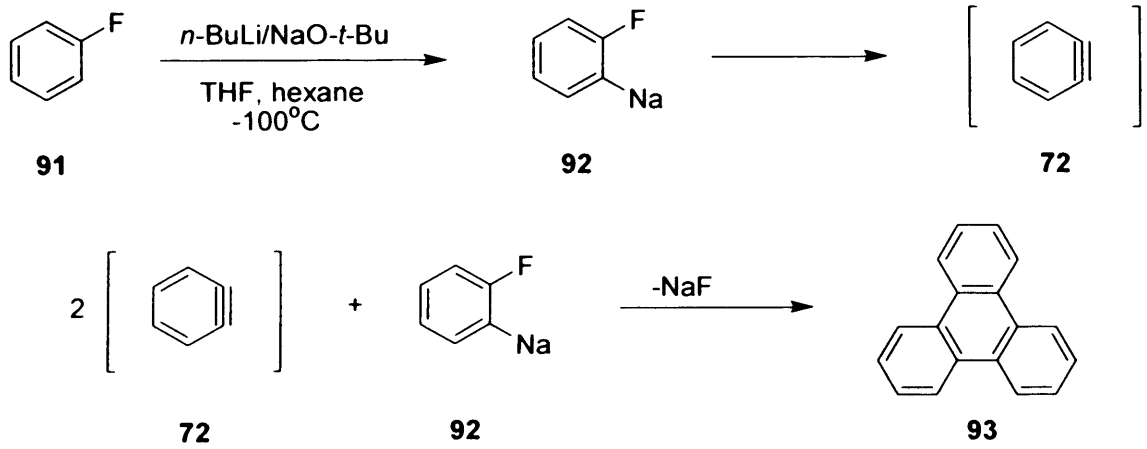


88 **89** **90**

R= Me, Et, PhCO, MeCO

Scheme 22

An efficient triphenylene synthesis involves *o*-sodiofluorobenzene **92** as an intermediate. Its fast decomposition gives rise to a high benzyne concentration and hence a high yield of triphenylene **93** (Scheme 23).[18]

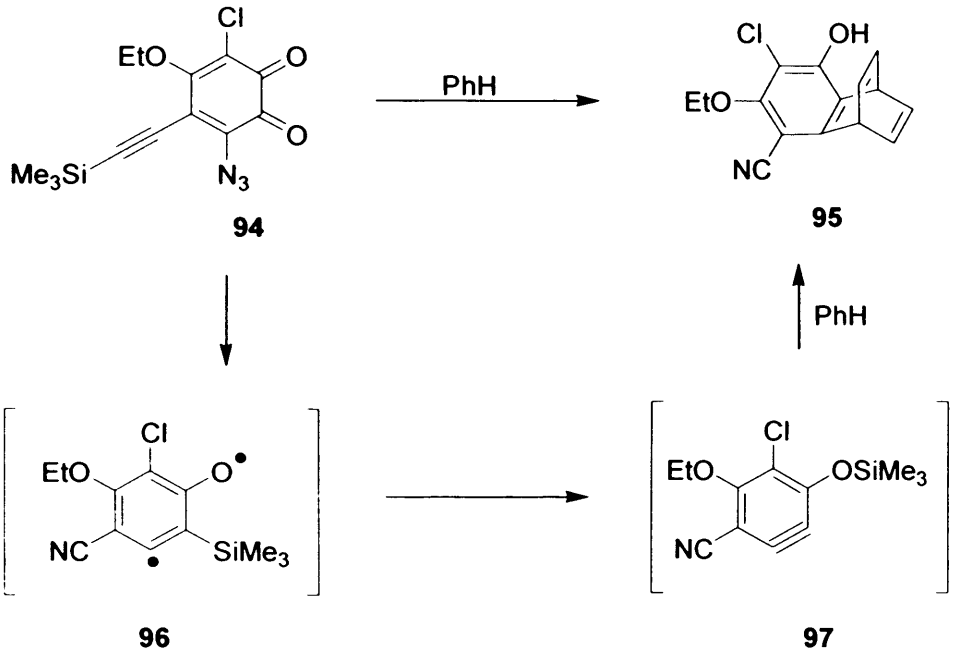


91 **92** **72**

72 **92** **93**

Scheme 23

A remarkable generation of a benzyne intermediate has been proposed in the thermal decomposition of azidoquinone **94** in benzene which provides cycloadduct **95** by reaction with the solvent (Scheme 24).[18,19]

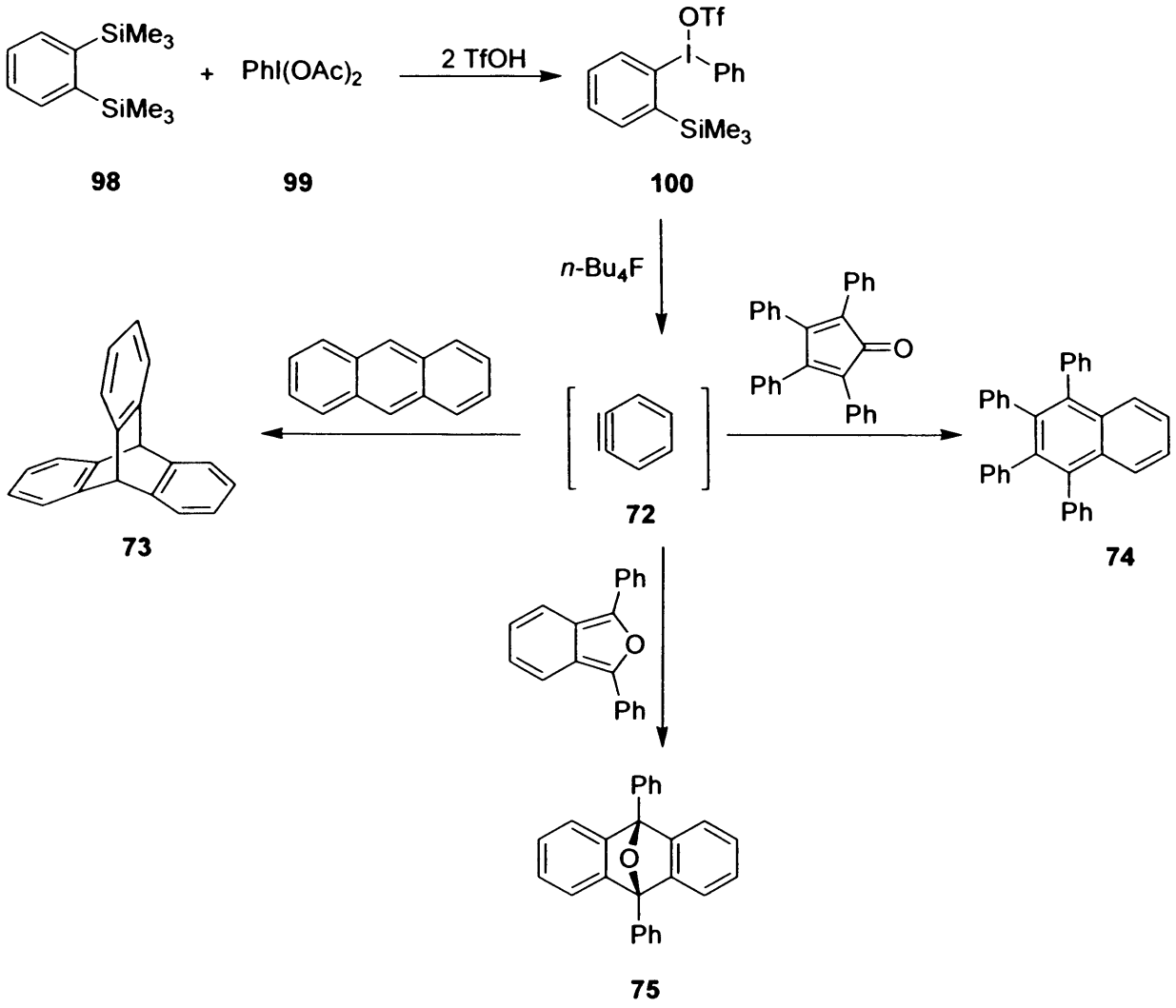


Scheme 24

This unusual transformation is considered to proceed *via* the diradical intermediate **96**, which suffers a trimethylsilyl shift from carbon to oxygen to give the benzyne **97**. This then undergoes a Diels-Alder cycloaddition to the solvent resulting in adduct **95**.

(Phenyl)[*o*-(trimethylsilyl)phenyl]iodonium triflate **100** readily prepared from *o*-bis(trimethylsilyl)benzene **98** and $PhI(OAc)_2$ **99**, was reported to be a new and efficient precursor of benzyne by Kitamura in 1995. Mild and neutral conditions provide adducts with typical agents.[18]

One limitation to many of these methods is the difficulty in synthesising substituted homologues.



Scheme 25

1.2.3 Reactions of benzyne

The above chemistry demonstrates the wide range of conditions under which a benzyne can be formed, and now some example reactions of benzynes in synthetic organic chemistry are to be dicussed. As was described in section **1.2.1**, the reactions of benzyne can be divided into pericyclic reactions, nucleophilic additions and transition metal-catalysed reactions. Benzyne is well set up to act as a dienophile which, together with the strained nature of the triple bond, allows benzyne to undergo a wide range of facile cycloadditions.

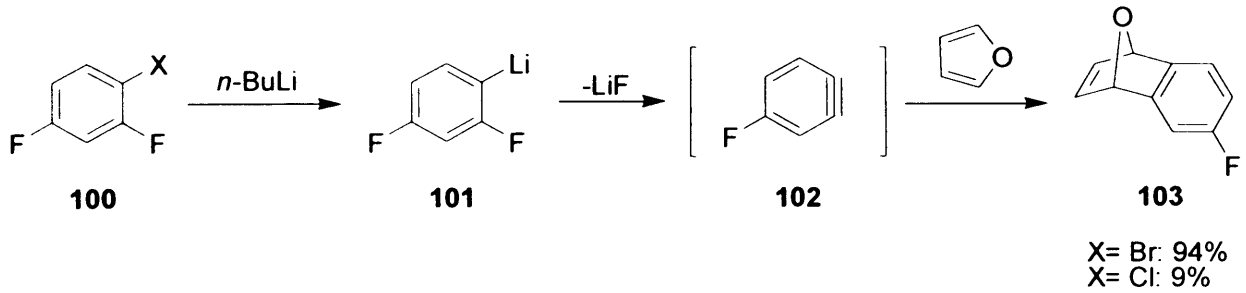
1.2.3.1 Pericyclic reactions of arynes

The pericyclic reactions can be divided into several categories such as Diels-Alder reactions occurring in an inter- or intramolecular mode; [2+2] cycloadditions; [1,3]-dipolar cycloadditions; [1,4]-dipolar cycloadditions and ene reactions.[18]

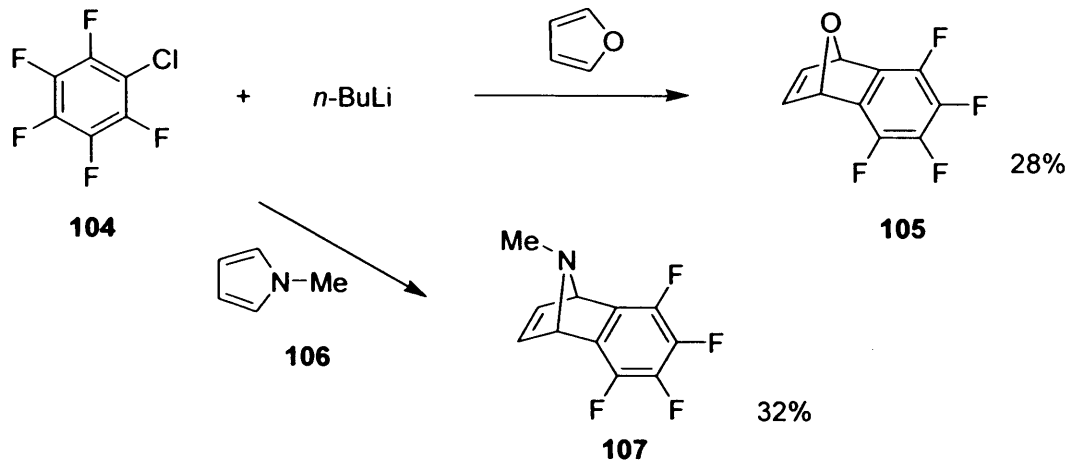
A) Diels-Alder cycloadditions

One of the main applications of benzyne is in the Diels-Alder cycloaddition reaction; this has been used both as a means of detecting benzynes and as a synthetic tool. Due to the highly dienophilic character of benzynes, the reaction is observed with a wide range of dienes.

Aromatic five-membered heterocycles react efficiently with benzynes to give the [4+2] cycloadducts. Furan and its derivatives have been widely used to intercept benzynes, and their adducts are useful as intermediates in the synthesis of naphthalenes, because the endoxide bridge can be readily cleaved by acids. One very recent example was reported by Caster.[20] A series of fluorinated benzonorbornadienes were synthesised in high yields and selectivities by trapping the benzyne intermediates **102** with furan or *N*-methylpyrrole **106** (Scheme 26 & 26a).

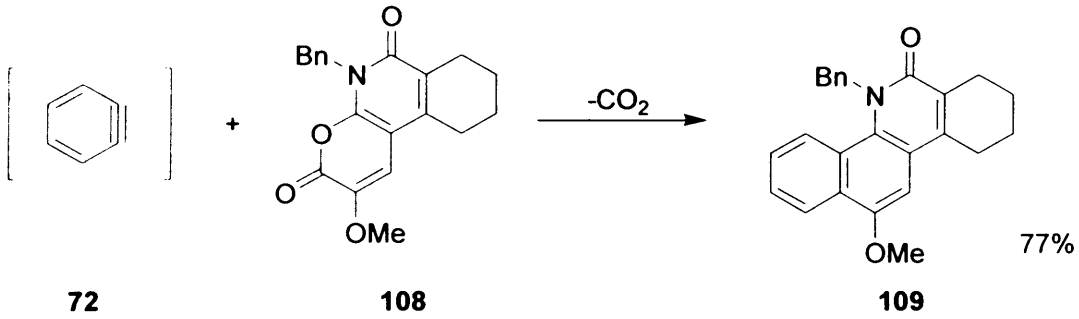


Scheme 26



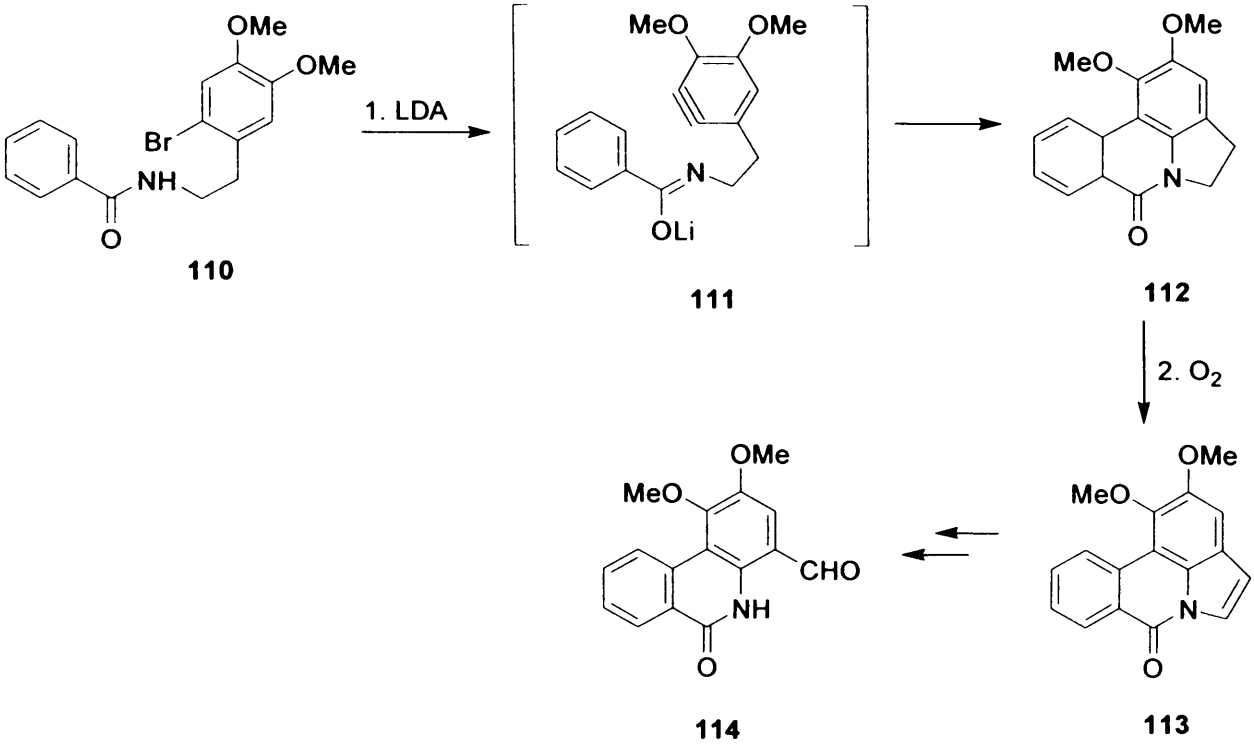
Scheme 26a

In addition to the cycloadditions with various heterocyclic compounds, the reaction of benzyne with heterodienes has also proved to be a powerful tool in natural product synthesis. A new approach to the polycyclic framework of dynemicin A **109** was reported recently.[21] The key step was the intermolecular Diels-Alder cycloaddition of pyrone **108** with benzyne **72** followed by CO_2 extrusion (Scheme 27).



Scheme 27

As a complementary strategy to the intermolecular benzyne cycloaddition, the intramolecular cycloaddition approach has also been developed with the aim of preparing various alkaloids. For instance, treatment of amide **110** with LDA in THF achieved benzyne formation and intramolecular cyclization to afford the tetracyclic amide **112** in good yield. Mild oxidation followed by ring cleavage of lycorines **113** led to the phenanthridines **114** (Scheme 28).[22]

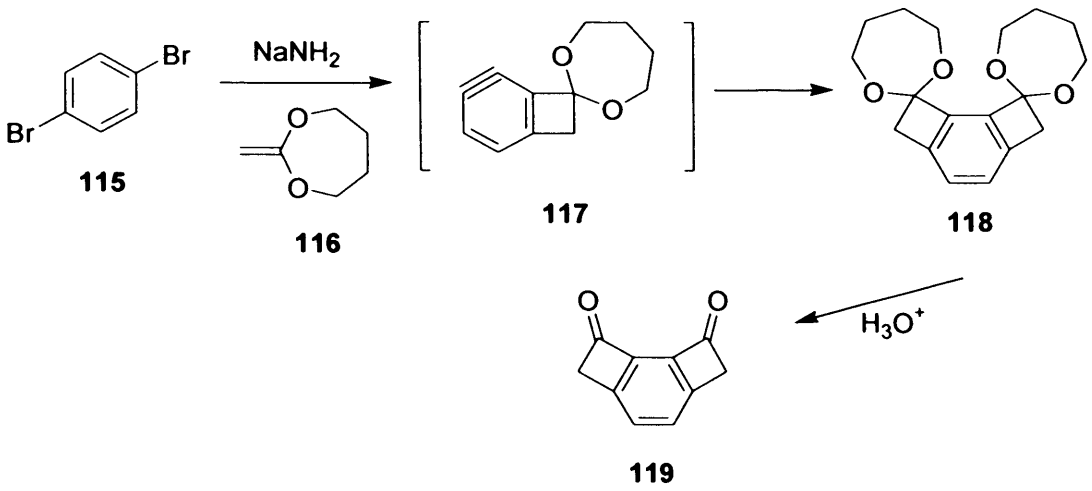


Scheme 28

B) [2+2] Cycloadditions

Benzynes are also well known to undergo [2+2] cycloadditions. They react with a wide range of olefins to give the [2+2] cycloadducts, benzocyclobutenes. Due to the electrophilic nature of benzyne, the reactions proceeds best with alkenes that bear electron-donating substituents and this reaction offers a simple and direct route to useful synthetic intermediates.

Treatment of 1,4-dibromobenzene **115** with $NaNH_2$ in the presence of 2-methylene-1,3-dioxepane **116** leads to benzo-*bis*-cyclobutenone derivative **118**, a precursor of tricyclo dione **119** (Scheme 29).[23]



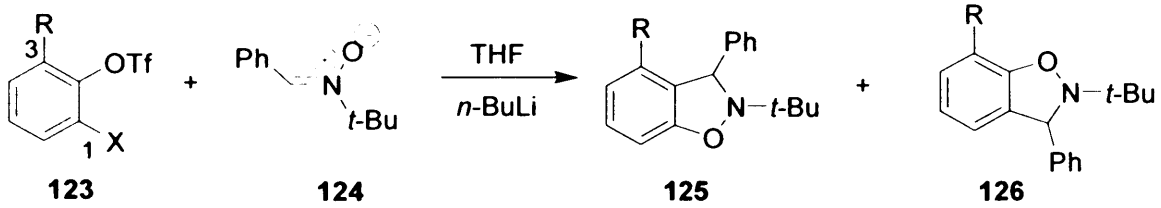
115 116 117 118 119

Scheme 29

C) [1,3]-Dipolar Cycloaddtions

Another well exemplified reaction of benzyne is the [1,3]-dipolar cycloaddition with a wide variety of stable [1,3]-dipolar compounds.

In 1993, Suzuki *et al.*[24] studied the regiochemistry of cycloadditions of unsymmetrical benzynes with nitrones **124**. They showed the effect of the C(3)-substituent of the benzyne on the regioselectivity of the benzyne-nitrone cycloaddition (Scheme 30).

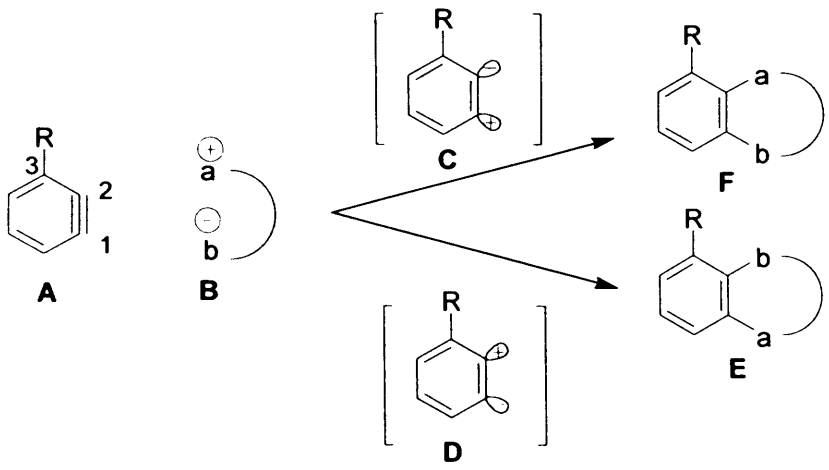


123 **124** **125** **126**

1. X = I, R = OMOM	91%	0%
2. X = Br, R = Me	23%	63%
3. X = Br, R = *t*-Bu	76%	14%

Scheme 30

The regioselectivity of such cycloaddition was explained in a general form as shown below (Scheme 31). If the C(3) substituent R was an electron-withdrawing group, *e.g.*, the OMOM in entry 1, the contribution of C would be dominant so that a dipole B would react in a way that leads to the formation of adduct F. An electron-donating group, *e.g.*, when R = Me in entry 2, would behave in the opposite manner.



Scheme 31

However, the steric factor also influences the regioselectivity. In the case of R = *t*-Bu (entry 3), adduct **125** was the major product. These observations could be rationalized as follows (Scheme 32).

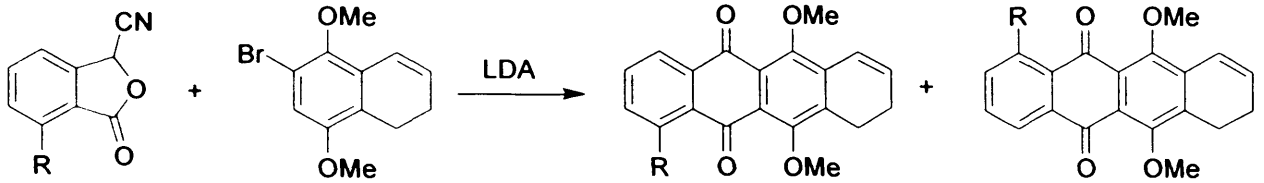
Scheme 32

The reaction process was governed by the direction of the nucleophilic attack of the oxygen terminus with high electron density. In the type **D** case the attack of the oxygen occurs at C(2) while the steric interaction discourages this C-O bond formation. Thus, the two factors, electronic and steric, work against each other in terms of the regioselectivity. Note that the type **C** is free from steric hindrance.

D) [1,4]-Dipolar Cycloadditions

A [1,4]-dipolar benzyne cycloaddition has been applied to the preparation of an important intermediate in the synthesis of daunomycinone.[25] Cycloaddition of lithiated 2-cyanophthalide **127** with the benzyne intermediate generated from bromo-dimethoxynaphthalene **128** gave tetracyclic olefin **129** and **130** in moderate to good yields

(Scheme 33). During this key reaction, cyanophthalides functioned as 1,4-dipoles and the benzyne behaved as a 1,2-dipole.



127 **128** **129** **130**

R = H: 73%, R = OMe: 66%

Scheme 33

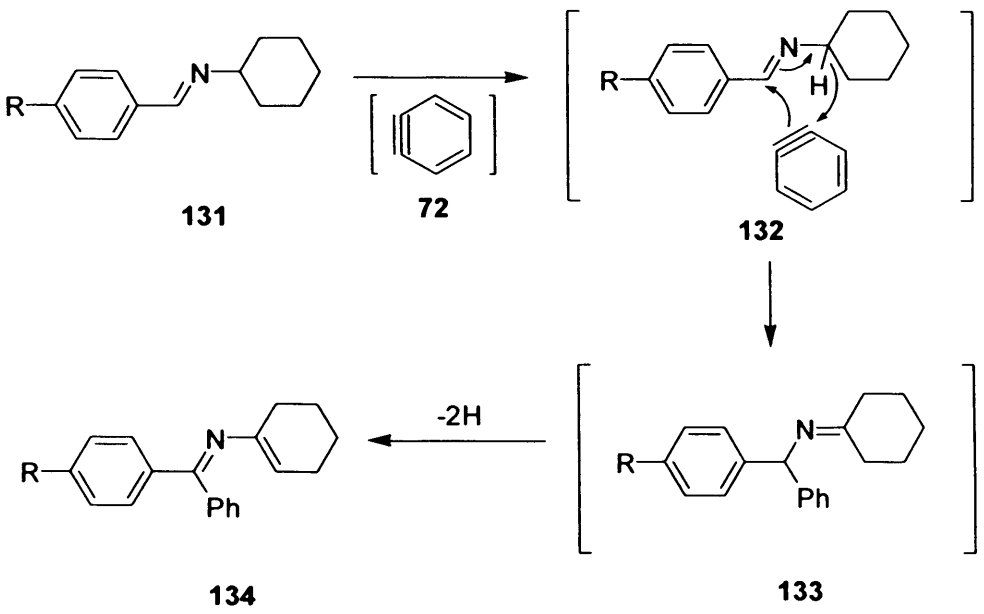
E) Ene Reactions

The ene reactions of benzyne with olefins and imines have been used essentially to detect benzyne. Benzyne **72** will react with *trans* double bonds which have an allylic hydrogen atom (such as imine **131**) to give ene adducts (such as **134**) (Scheme 34).[26] However this type of reaction has not been extensively employed for synthesis.

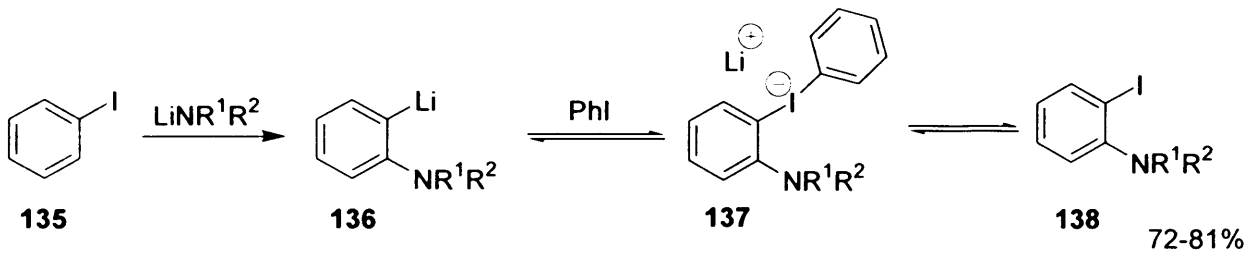
1.2.3.2 Nucleophilic additions to benzynes

Benzyne **72** has the ability to act as an electrophile to a wide range of nucleophiles. From a synthetic point of view, the most interesting species are probably nitrogen-bearing nucleophiles and carbanions (Scheme 34).

The reaction of benzyne with primary and secondary amines provides a convenient route to different anilines. Various precursors of benzyne have been involved in this kind of reaction, but one of the most recent examples is the synthesis of iodoanilines **138** from iodobenzene **135**, which was reported by Durst *et al.* (Scheme 35).[27]



Scheme 34



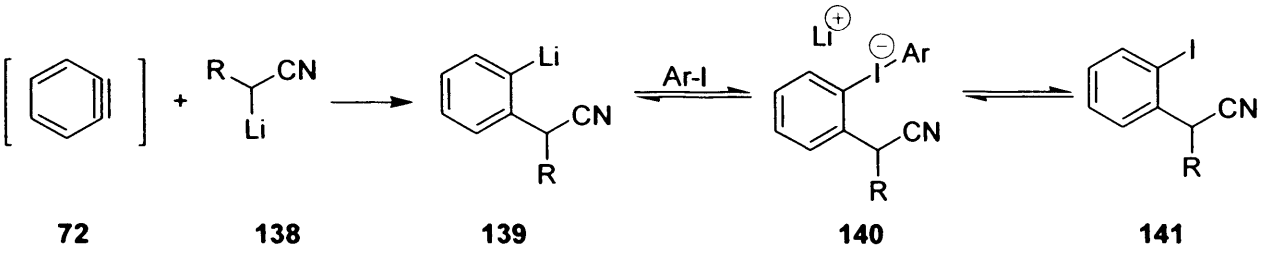
$R^1 = R^2 = i\text{-Pr}$
$R^1 = R^2 = \text{-C(Me)}_2\text{-(CH}_2)_3\text{-C(Me)}_2\text{-}$

Scheme 35

The lithio derivatives **136**, formed by the trapping of benzyne with lithium amine, combine rapidly with unreacted iodobenzene **135** to give the ate complexes **137**, which are unreactive towards typical electrophiles but are in equilibrium with their components.

The addition of carbon nucleophiles to benzyne intermediates could be divided into two types. One is the addition of lithioacetonitrile derivatives and the other is of lithio enolates.

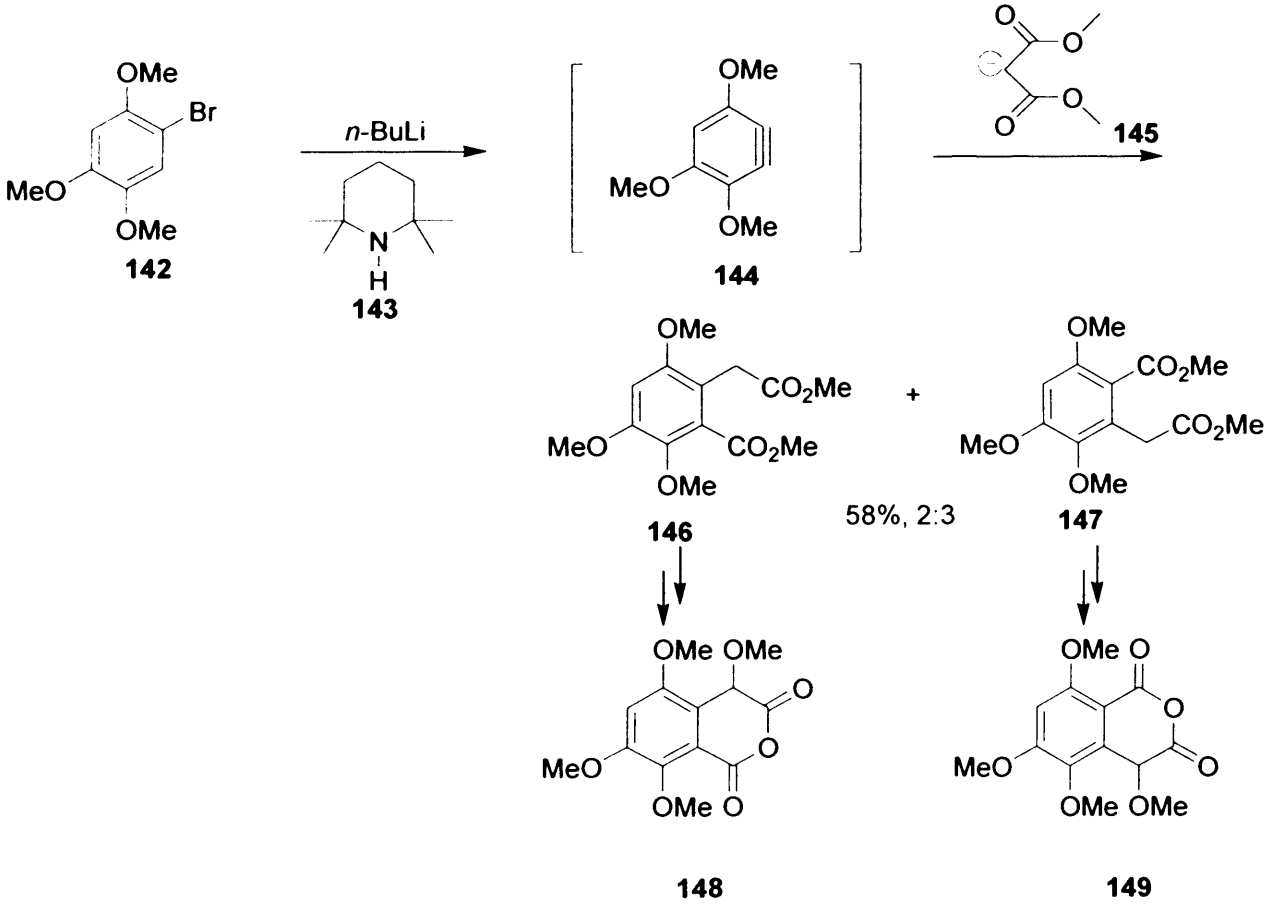
The reaction of benzyne **72** with α-lithionitrile **138** in the presence of iodobenzene gave 2-iodobenzyl cyanides **141** as the major products. Again, this presumably takes place *via* the iodine-ate complexes **140** (Scheme 36).[28]



72 **138** **139** **140** **141**

Scheme 36

Very recently, Kita *et al.*[29] reported the total synthesis of a potent antitumour antibiotic, fredericamycin A, which involved the addition of the malonate anion **145** to a substituted benzyne **144** (Scheme 37). Reaction of bromo benzene **142** with lithium tetramethylpiperidide and dimethyl malonate anion **145** afforded a regioisomeric mixture (2:3) of the homophthalates **146** and **147** through a non-regioselective addition of the lithiomalonate to the benzyne intermediate. Each regioisomer was readily separated by column chromatography to give the pure products.



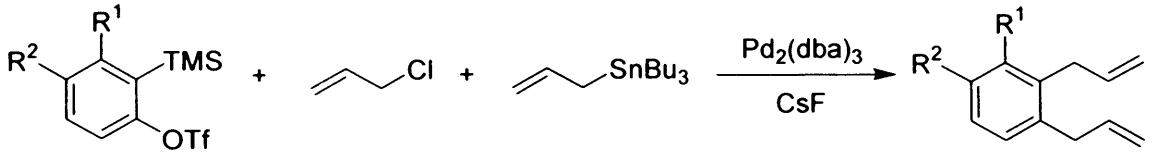
Scheme 37

1.2.3.3 Transition metal-catalysed reactions of benzynes

Benzynes participate in a number of synthetically useful metal-catalysed transformations, but the synthetic applications of metal-benzyne complexes are still limited owing to the lack of a general and mild method for their generation and the need for stoichiometric amounts of metal.[18]

Very recently, Yamamoto *et al.*[30] found that benzyne was very reactive as a carbo-palladation partner to π-allylpalladium chloride. 1,2-Diallylated derivatives of benzene **153** were prepared by the reaction of benzyne **150** with a *bis*-π-allylpalladium complex generated from allyl chloride **151** and allyltributylstannane **152** (Scheme 38).

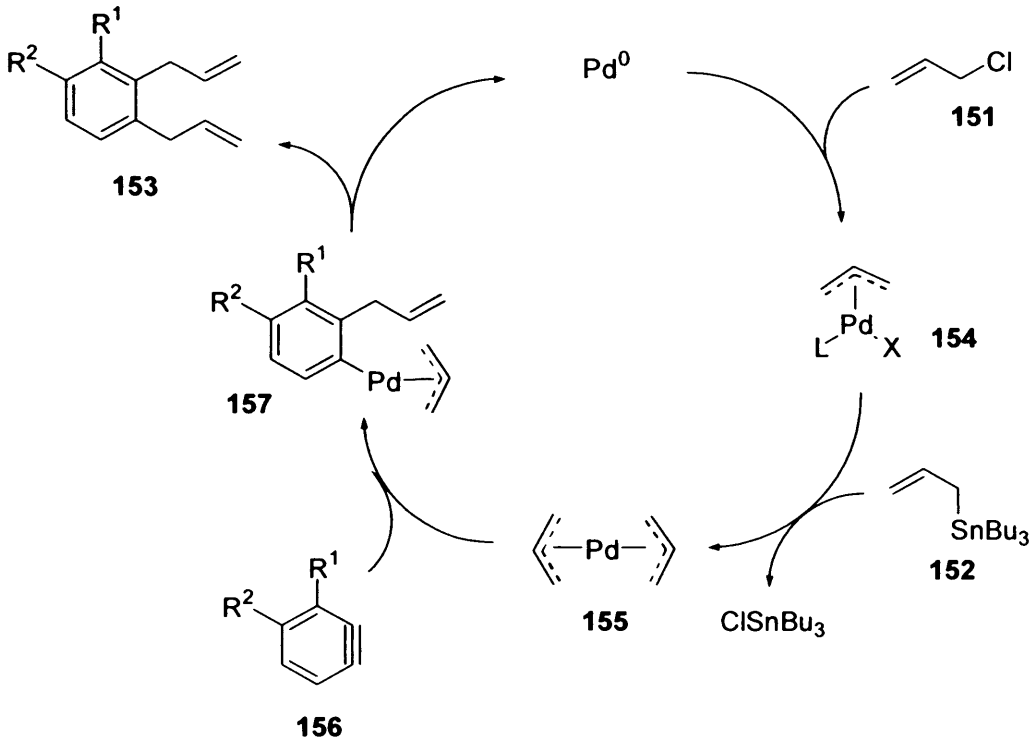
A mechanism for this intermolecular benzyne-alkene insertion reaction is shown below (Scheme 39). Insertion of Pd(0) to allyl chloride **151** gives the π-allyl palladium complex **154**, which can be converted to *bis*-π-allyl palladium **155** by reaction with allytributylstannane **152**. Subsequent addition of the two allyl groups of *bis*-π-allyl palladium **155** to the triple bond of benzyne **156** gives the 1,2-diallylated benzene **153** and regenerates the Pd(0) species.



150 **151** **152** **153**

$R^1 = R^2 = H$: 76% $R^1 = H$; $R^2 = Me$: 67%
$R^1 = OMe$; $R^2 = H$: 81% $R^1 = H$; $R^2 = Cl$: 40%

Scheme 38



Scheme 39

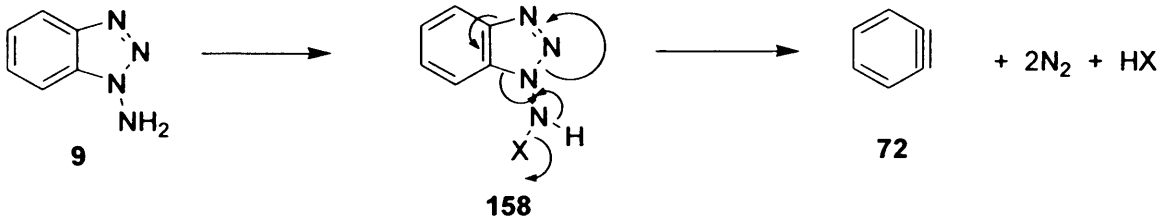
1.3 Towards the Total Synthesis of Vitamin E Precursor Using Intramolecular Benzyne Trapping By Alcohol

1.3.1 The use of 1-aminobenzotriazole as a benzyne precursor

As it was described in section **1.2.2**, the classical methods for benzyne generation, such as elimination of hydrogen halide from halobenzenes and halogen-metal exchange, are generally under strongly basic conditions. Alternatives which avoid strongly basic conditions include the use of another classical benzyne precursor, anthranilic acid **80**, together with a variety of heteroaromatic systems, such as 1-aminobenzotriazole **9**. As has recently been succinctly emphasised: 'An important drawback of the aryne routes starting with bidentate or cyclic precursors can be the effort needed to prepare the precursor itself, especially for substituted arynes. However, these have the advantage that the arynic bond can be generated without positional ambiguity.'[31] Certainly, a number of relatively complex benzyne precursors have been prepared, most often from bromobenzenes; few has been reported on the synthesis of fully substituted 1-aminobenzotriazole, beyond the original studies by

Campbell and Rees,[2] and a few more recent, usually symmetrical examples and higher homologues, together with a benzene fused to two aminotriazole rings, which effectively acts as a *bis*-benzyne precursor although, presumably, the process occurs in a stepwise fashion.[31]

The use of 1-aminobenzotriazole **9** as a benzyne precursor was highlighted by Campbell and Rees[1a] who demonstrated the ease of formation of the parent benzyne **72** by oxidation to the intermediates **158**, which rapidly disintegrate presumably by the spectacular cascade shown (Scheme 40).

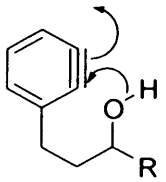


Scheme 40

Two of the best methods identified for achieving this rely on direct oxidation by lead(IV) acetate, in which case X = OAc, or using N-bromosuccinimide, when X = Br.

1.3.2 Hydroxyl group acting as intramolecular traps for benzyne

The extremely mild conditions associated with the oxidation methods stand in stark contrast to the alternatives outlined above which employ various strong base-induced eliminations from halo- or dihalo- benzenes. It occurred to us that these oxidative conditions might be compatible with hydroxyl groups and perhaps enable these to act as intramolecular traps for the benzynes so generated, as indicated in formula **159**.



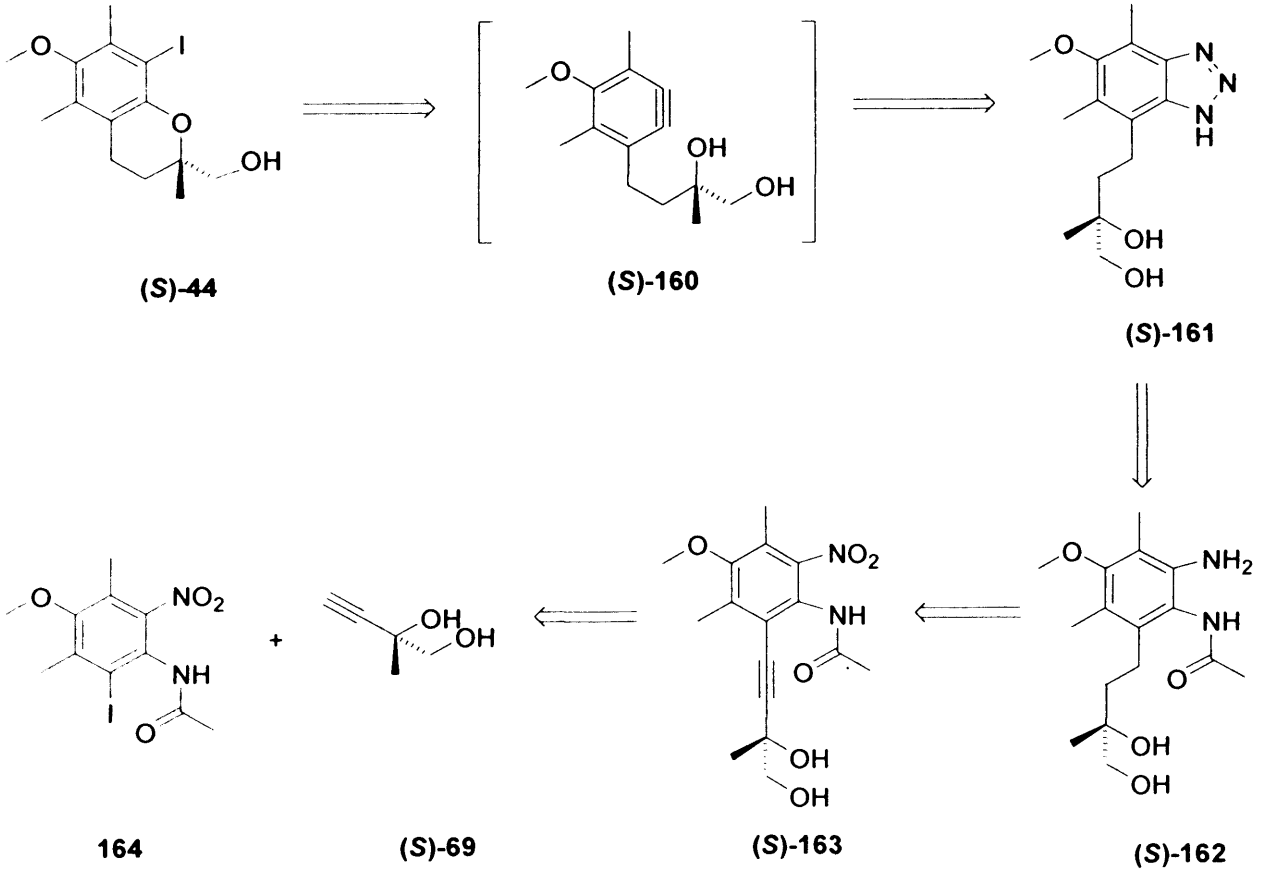
159

In great constrast to related intramolecular cyclisations using amino- and enolate nucleophiles, such trapping by hydroxyl functions was virtually unknown and then using

only very simple types of alcohol.[31] Arynes are soft electrophiles, but alkoxides are hard nucleophiles, the latter inevitably formed in base-induced aryne formation, would be expected to be less reactive partners. While intermolecular trapping of benzynes by phenols was well precedented, related intramolecular reactions were almost unknown until recently.[31]

1.3.3 Novel strategy towards the vitamin E precursor based on the intramolecular trapping by –OH of benzyne

Little's routes towards the Vitamin E precursor **1** (described in the first section) have foundered due to the following reasons: the lateral deprotonation with base was not regioselective and resulted in the generation of similar amounts of stannanes **64** and **65**, both in poor yields; and diol **70** could not be reduced to its saturated homologue diol **71**. Therefore, a new route was developed during the present project, which avoided metallation chemistry and hydrogenation of the diol **70**. The retrosynthetic route is show in Scheme 41.



Scheme 41

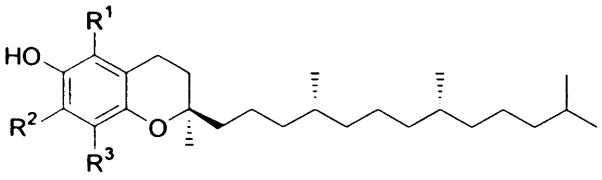
The chroman **(*S*)-44** would be produced from iodocyclisation of the benzyne intermediate **(*S*)-160**, which could be synthesised from the benzyne precursor, benzotriazole **(*S*)-161**. The benzotriazole **(*S*)-161** may be made by diazotisation of amide **(*S*)-162** followed by cyclisation, according to Little's method (Scheme 14). Amide **(*S*)-162** could in turn be formed by hydrogenation of acetylene **(*S*)-163**. Presumably, this hydrogenation is more promising since acetylene **(*S*)-163** is less steric hindered than diol **70**. Then it was hoped that Sonogashira coupling of iodide **164** with optically pure diol **(*S*)-69**, using the protocol developed by Little, would give the acetylene **(*S*)-163**. At this point, the electron-withdrawing nitro group on the position *para* to iodine may activate the reaction and make the coupling more facile. If successful, this would prove to be an improvement on the previous route to this highly important natural product. Another important issue requiring attention was also the realisation of an asymmetric synthesis of the diol **69**.

1.4 An Introduction to Vitamin E

Vitamin E was discovered 80 years ago and is best known as an important food supplement in the nutrition of humans and animals.

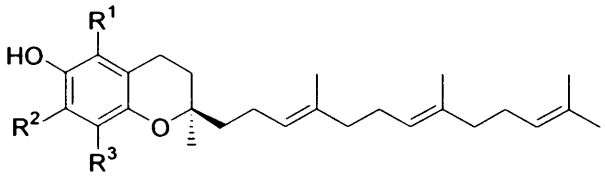
1.4.1 The structure

Vitamin E occurs naturally in eight main forms: α, β, γ, and δ-tocopherols **165** and the four corresponding tocotrienols **166**[32] (Scheme 42). The α, β, γ, and δ-homologues vary by the methylation patterns of the common chromanol moiety. Tocotrienols differ from tocopherols by possessing three double bonds rather than a saturated side chain. α-Tocopherol shows the highest Vitamin E activity in both animals and humans and is the predominant tocopherol in tissue.[33]



Tocopherols

165



Tocotrienols

166

α R^1=Me R^2=Me R^3=Me
β R^1=Me R^2=H R^3=Me
γ R^1=H R^2=Me R^3=Me
δ R^1=H R^2=H R^3=Me

Scheme 42

1.4.2 Food sources

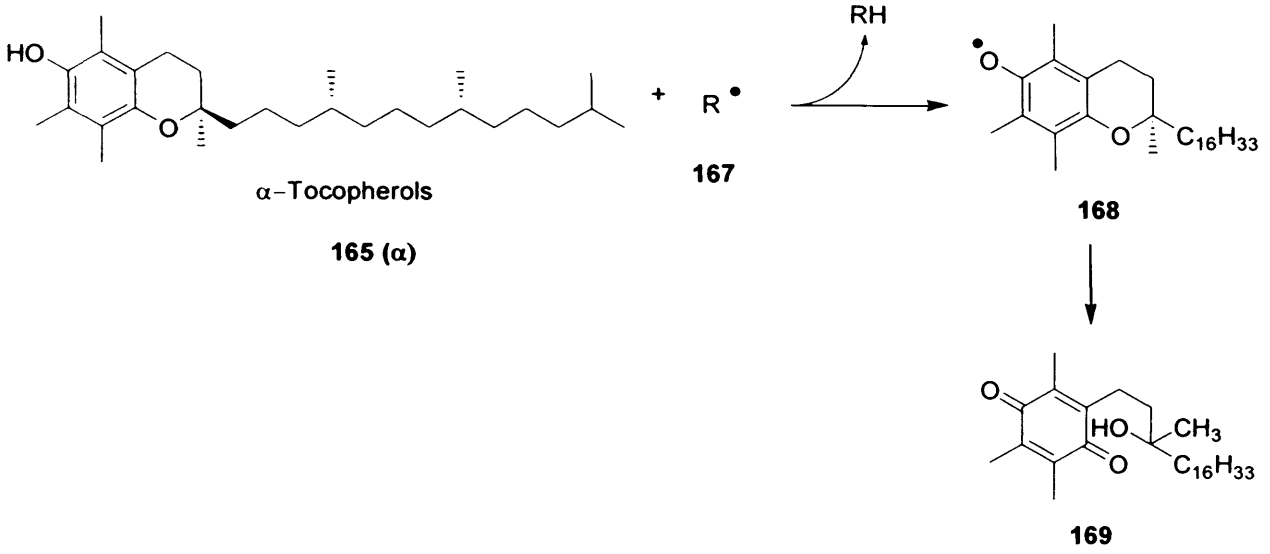
The tocopherols occur in a variety of plant life such as nuts, seeds, oils, fruits, vegetables, and grasses. The tocopherols are interconvertible in plants and during germination and growth: the α-form is synthesized from other tocopherols by transmethylation. Tocopherol content of foods depends upon the stage of life cycle, agronomic and genetic factors, season, weather, harvesting methods, processing procedures, storage environment and time periods of storage. The feeding of vitamin E to cattle, pigs and poultry results in increased levels of the vitamin in meat, milk and eggs and, if given in sufficient quantity, is effective in preventing oxidative rancidity and resultant off-flavours in these foods.[33]

1.4.3 Biochemical function

Vitamin E is primarily concerned with the protection of cellular membranes from damage resulting from both endogenous and exogenous sources of free radicals.[33] Free radicals in biological systems can be formed through homolytic cleavage of covalent bonds in organic compounds, in which each fragment retains one electron of the original bonding pair. Radicals can also be produced from the capture of an electron by a molecule.

The principle role of vitamin E as an antioxidant is to neutralize free radicals. Quenching of a free radical **167** by vitamin E results in the formation of a tocopherol semiquinone radical

168 which rapidly degrades to non-radical products. For example, α-tocopherol can donate a phenolic hydrogen atom to a free radical, thereby resolving the unpaired electron of the radical and oxidizing the tocopherol to its quinone form **169** (Scheme 43).



Scheme 43

In addition to its antioxidant functions, vitamin E is now known to act through other mechanisms, having direct effects on inflammation, blood cell regulation, connective tissue growth and genetic control of cell division.[34]

1.4.4 Vitamin E deficiency

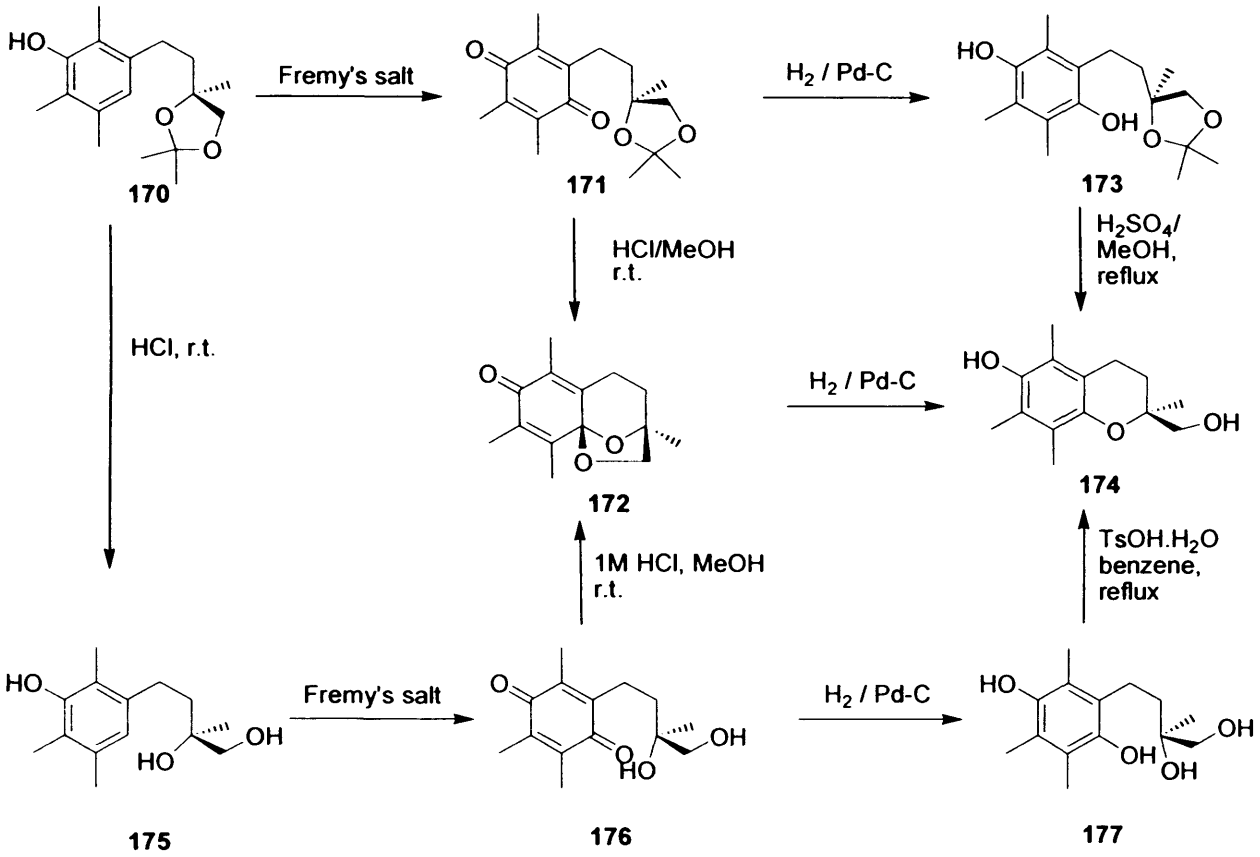
Vitamin E deficiency is defined as a low blood tocopherol level or evidence of *in vitro* haemolysis of erythrocytes exposed to hydrogen peroxide or other oxidants.[33] Dietary deficiency of vitamin E may be associated with disorders of the vertebrate reproductive system, skeletal muscle, nervous system, cardiovascular system, haematopoietic tissue and liver. In addition, a recent study by Finnish scientists shows that the long-term use of a moderate-dose vitamin E supplement substantially reduced prostate cancer incidence and deaths in male smokers.[35]

Although many scientific questions remain with regard to the role of vitamin E in human and animal physiology, the research to date shows a great deal of promise. It was concluded

eighty years after the discovery of vitamin E: "it is time to take it more seriously and undertake the research needed to determine what makes it a real vitamin."[35]

1.5 Previous Routes Towards the Total Synthesis of Vitamin E

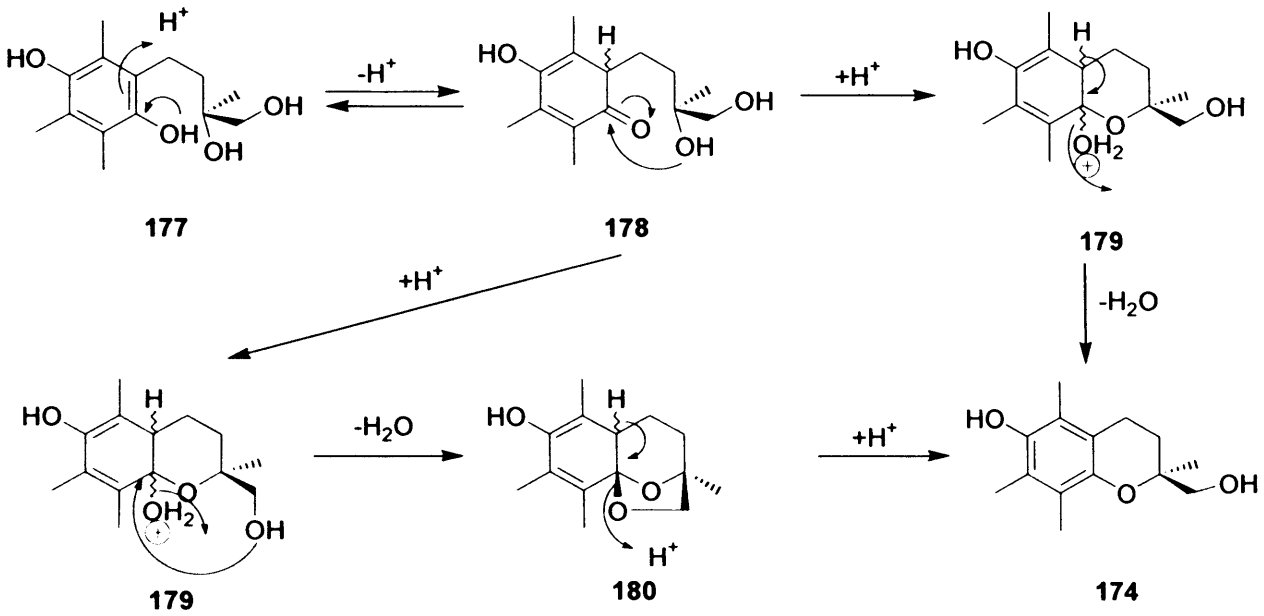
During the past 50 years, Vitamin E has received increasing attention with regard to the total synthesis of the major naturally occurring form, α-tocopherol **165(α)**. In 1979, Cohen and co-workers[36] developed new strategies towards α-tocopherol **165(α)** by formation of substituted heterocyclic rings from *p*-benzoquinone as key intermediates (Scheme 44). (*S*)-Phenol **170** was synthesised *via* a seven-step sequence starting from (*S*)-2-methyl-5-oxotetrahydro-2-furoic acid, which was prepared from its racemic form by resolution with cinchonine. Oxidation of (*S*)-phenol **170** with excess Fremy's salt (dipotassium nitrosodisulfonate) furnished the (*S*)-*p*-benzoquinone **171**. Treatment of this quinone with aqueous methanolic HCl afforded the bridged tricyclic monoketal **172**. Selective scission of the oxymethylene bridge with hydrogen-palladium on carbon led to the desired (*S*)-chroman-2-methanol **174**. Chromanol **174** was also accessible from alternative sequences not involving ketal **172**. The hydroquinone acetonide **173**, obtained by catalytic hydrogenation of **171**, yielded chromanol **174** when exposed to refluxing, dilute methanolic H_2SO_4.



Scheme 44

Alternatively, hydrolysis of (*S*)-phenol **170** gave the phenol diol **175** which was oxidized to the quinone **176** using Fremy's salt. Catalytic hydrogenation under neutral conditions produced the air-sensitive hydroquinone diol 177. Upon treatment with *p*-toluenesulfonic acid in refluxing benzene, diol 177 was transformed into chromanol **174**, in a similar manner. The proposed mechanism for the key cyclisations of diol 177 is shown below (Scheme 45).

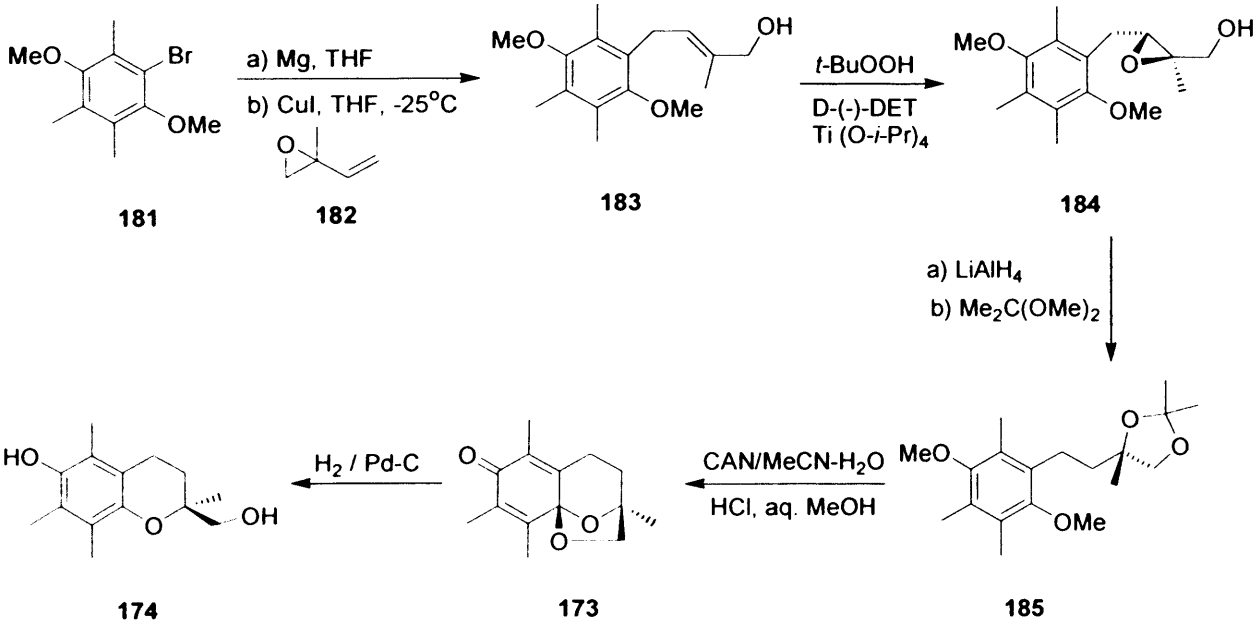
Acid-induced tautomerisation of the hydroquinone moiety 177 could give the keto-tautomer **178**. The subsequent attack of the tertiary hydroxyl and rearomatization with loss of a water molecule should generate the observed chromanol **174**. The intermediate **179** could also be attacked by the primary hydroxyl group to form tricyclic ketal intermediate **180**, which again rearomatizes to give the observed product **174**.



Scheme 45

Cohen's cyclodehydration method as well as the selective hydrogenation method (Scheme 44 from **172** to **174**) to achieve the chroman moiety were so crucial that they have been applied in the following vitamin E syntheses which were developed later.

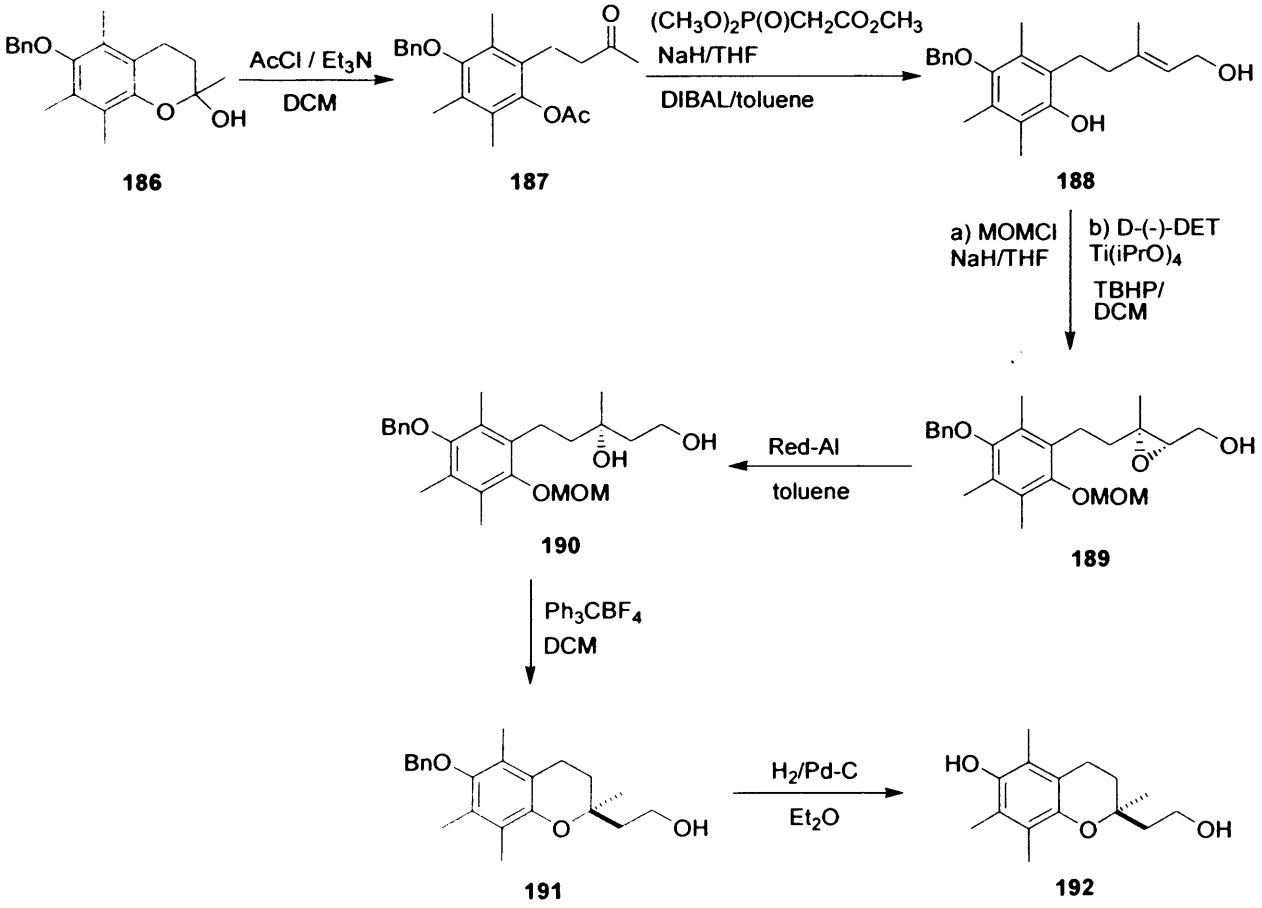
In 1985, Kunihiko[37] and co-workers reported the synthesis of (*S*)-chromanmethanol **174** by utilizing the asymmetric epoxidation of (*E*)-allylic alcohol **183**, which was made from an aromatic Grignard reagent (Scheme 46).



Scheme 46

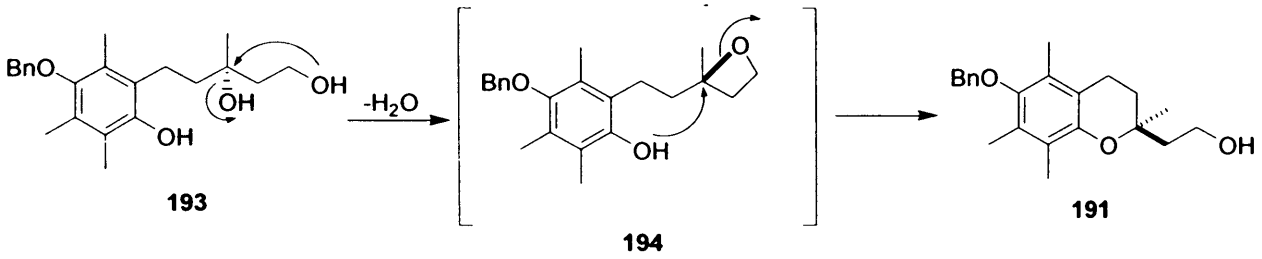
Treating bromide **181** with magnesium in THF followed by reaction with the isoprene oxide **182** and CuI at low temperature afforded the (*E*)-allylic alcohol **183**. Sharpless asymmetric epoxidation gave the (2*R*,3*R*)-epoxy-alcohol **184**. Reductive opening of the epoxide using lithium aluminium hydride, followed by protection of the diol product provided the acetonide **185**. The aromatic ring was then oxidised with ceric ammonium nitrate (CAN). Subsequent acetonide deprotection with acid and dehydration afforded tricyclic monoketal **173**. Reductive transformation using the method described previously (Scheme 45) gave chromanol **174** in a respectable yield (62%) from the monoketal **173**.

Ten years later, an approach to (*S*)-chromanethanol **192**, *via* deprotection and cyclisation of MOM protected diol **190** to benzylchromanethanol **191** in one step, was reported (Scheme 47).[38]



Scheme 47

Acetylation of the hemiacetal **186** gave the acetate **187**, which then underwent Wittig reaction with trimethyl phosphonoacetate followed by reduction with DIBAL to afford the (*E*)-allylic alcohol **188**. Chemoselective protection using MOMCl with subsequent Sharpless asymmetric epoxidation afforded the optically active epoxy-alcohol **189**. The ensuing reduction with Red-Al gave the diol **190**, then cyclisation by treatment with Ph_3CBF_4 gave the (*S*)-chromanethanol **191**, with retention of absolute configuration, supposedly by double inversion (Scheme 48). Finally, deprotection of the benzyl group of **191** by palladium-catalysed hydrogenolysis gave the (*S*)-chromanethanol **192**.



193 **194** **191**

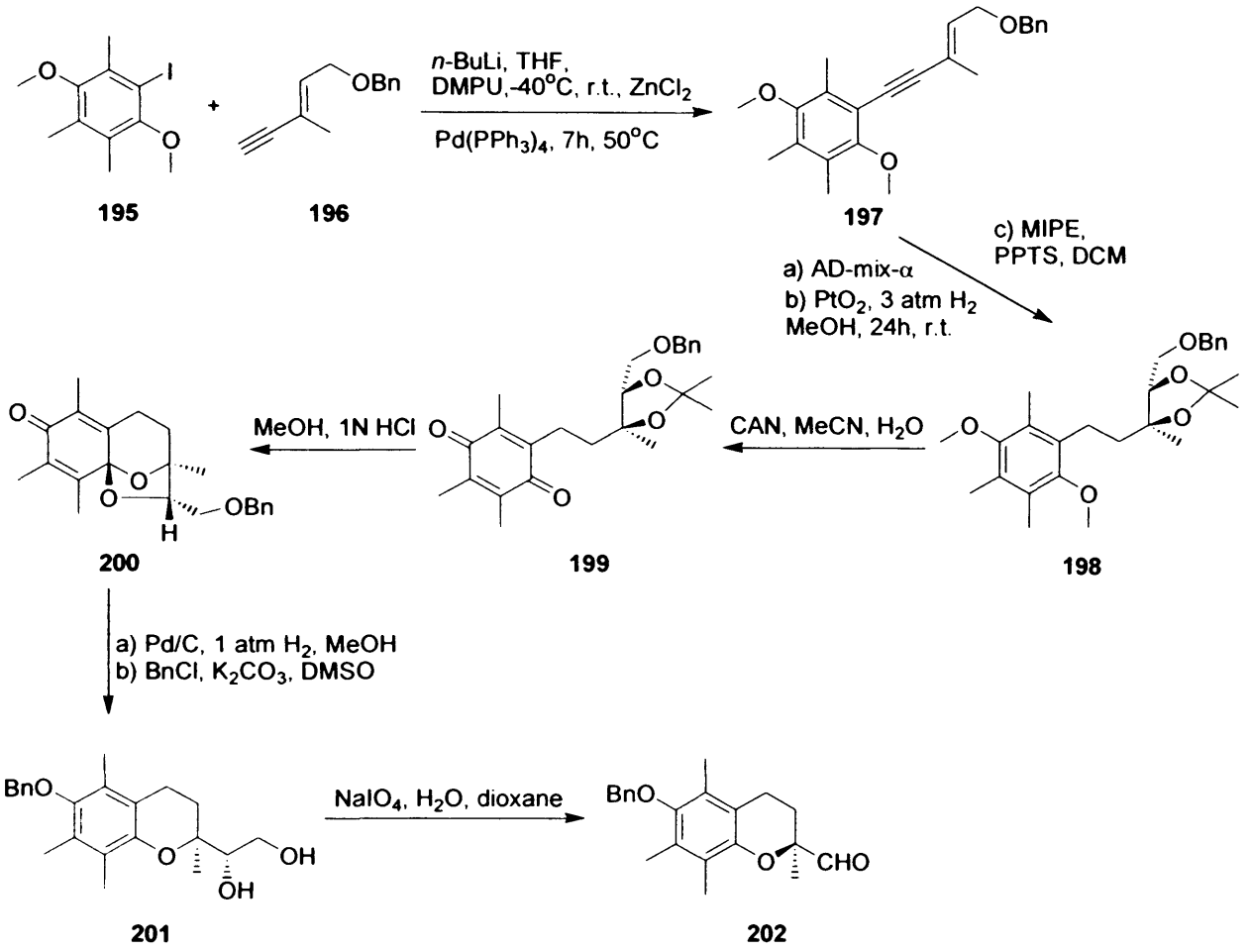
Scheme 48

The double inversion (net retention) mechanism shown above has already been reported by Cohen *et al.*[36] It involves formation of the (*R*)-oxetane **194** followed by an intramolecular, backside attack on the oxetane ring by the phenolic hydroxyl group.

A more recent synthetic route was reported by Tietze *et al.*,[39] whose approach to vitamin E is laid out below (Scheme 49). Catalytic asymmetric dihydroxylation (AD-mix reaction) has been applied to obtain the vitamin E precursor **202** with high enantiomeric excess (ee.).

A coupling reaction between iodine **195** and enyne **196** using Negishi's procedure[40] gave enyne **197**. A subsequent AD-mix-α reaction on the double bond of the side chain afforded optically active diol; reduction of the triple bond with Adams' catalyst followed by acetalisation with methyl isopropenyl ether (MIPE) then produced acetonide **198**. Oxidative demethylation with CAN generated the quinone **199**, which was cyclised to acetal **200** under acidic conditions. The following hydrogenation led to rearomatisation and deprotection of the

benzyl ether; selective benzylation[41] of the phenol with benzyl chloride gave diol **201** and subsequent oxidative cleavage of the diol accomplished the synthesis of aldehyde **202**.



Scheme 49

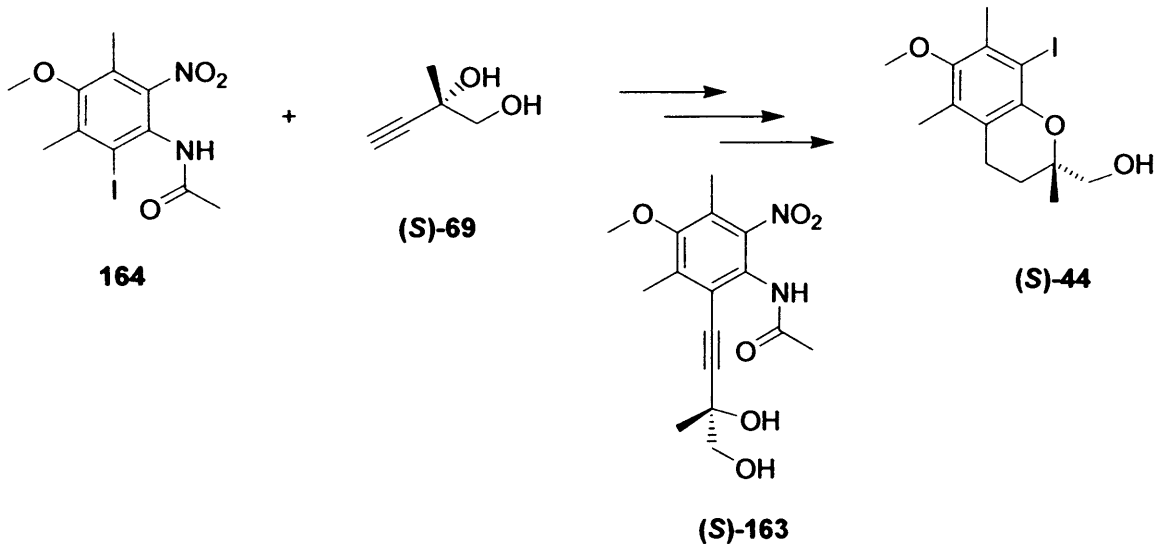
In summary, the chroman moiety of vitamin E precursor has been synthesised *via* a variety of routes. To the best of our knowledge, most of the previous methods applied Cohen's[36] procedure with quinone and hydroquinone cyclisations to achieve the chroman skeleton. This thesis will introduce a novel approach towards vitamin E in which the chroman core is successfully generated by intramolecular cyclisation of a hydroxy group onto a benzyne.

Chapter Two

Towards the Total Synthesis of Vitamin E Precursor

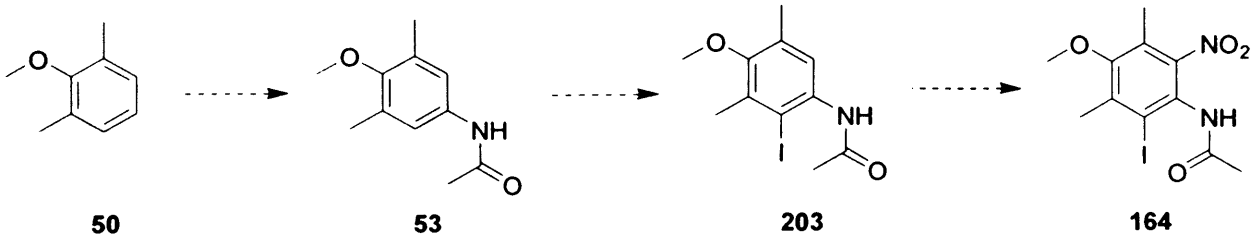
2.1 Introduction

On the basis of Dr Little's study on benzyne chemistry and his initial but unsuccessful approaches towards a vitamin E precursor, the current project is aimed at exploring a new route towards this crucial natural product, by using our well-developed intramolecular benzyne trapping technology. The retrosynthesis of this new route was laid out in Scheme 20 (Chapter 1), and was followed by an analysis of the retrosynthesis. According to this method, the synthesis was divided into three parts: 1) synthesis of the fully substituted aryl iodide **164**; 2) synthesis of the necessary alkyne-diol **69** as a single enantiomer; 3) synthesis of chroman **(*S*)-44**, which has the ***R*** α-tocopherol **43** stereochemistry. Due to sequence rules (Cahn-Ingold-Prelog) the ***R*** and ***S*** descriptors change; the stereochemistry does not.



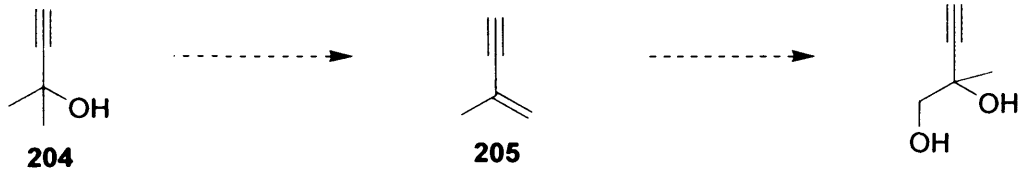
Scheme 50

According to Little's work, amide **53** was prepared from commercially available 2,6-dimethylanisole **50** by classical methods (Scheme 14, Chapter 1).[42] Presumably, the subsequent iodination and nitration on the two free positions of the benzene ring should readily give us the key aryl iodide **164** (Scheme 51).



Scheme 51

For the second part of this approach, it was thought that our necessary alkyn-diol **69** could be made from the ynol **204**. Dehydration of this tertiary alcohol by Carothers's method[43] gives enyne **205**. Applying asymmetric dihydroxylation (AD-mix reaction) to the enyne **205** should give the alkyne diol **69** (Scheme 52). Due to the small steric bulk of the flat triple bond on the enyne **205**, it could be difficult to obtain the alkyne diol **69** in high enantiomeric excess (ee.) under the AD-mix conditions. But considering that this is a quick way to access the required compound, we still decided to apply this popular method during the first stage.



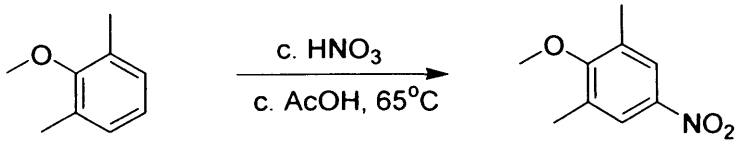
204 **205** **rac-69?**

Scheme 52

The last part of our total synthesis, which probably would be more difficult than the above two parts, starts with a Sonogashira coupling of the key iodide **164** and the alkyne diol **69**, to give acetylene **163**. Our initial retrosynthetic analysis from this point is laid out in Chapter 1 [Scheme 41, p.36].

2.2 The Synthesis of Iodide 164

To build our key iodide **164** from the commercially available 2,6-dimethylanisole **50**, the first step was a nitration using concentrated nitric acid and glacial acetic acid[44] (Scheme 53).



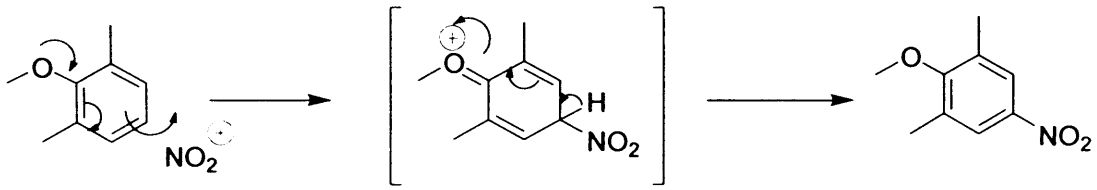
50 **51**

Scheme 53

The anisole **50** is stirred in acetic acid at 0°C before the nitric acid is dripped in very slowly (**Caution:** Towards the end of the nitric acid addition, the temperature of the reaction increases rapidly and large volumes of nitrogen oxides are evolved. This reaction must be undertaken in an efficient fume hood, preferably with the sash pulled down. Upon cooling,

the reaction mixture becomes immobile.) Once the addition of nitric acid was complete, the reaction mixture was slowly heated to just over 65°C (on a large scale, it has the risk of explosion if heated much above 70 °C) before being allowed to cool to ambient temperature over the course of 2 hours. By addition of water to the reaction mixture, a complete precipitation of the yellow *p*-nitroanisole **51** occurs. The product is collected by filtration and recrystallised from methanol to give product as bright yellow crystals in around 60% yield, which had a melting point agreeing with the literature.

The mechanism of this electrophilic aromatic substitution can be explained as follows (Scheme 54). The lone pair of electrons on the oxygen contribute to a high-energy 'highest occupied molecular orbital' (HOMO) and these electrons are fed through the benzene ring to emerge at the *para* position to attack the nitronium cation.

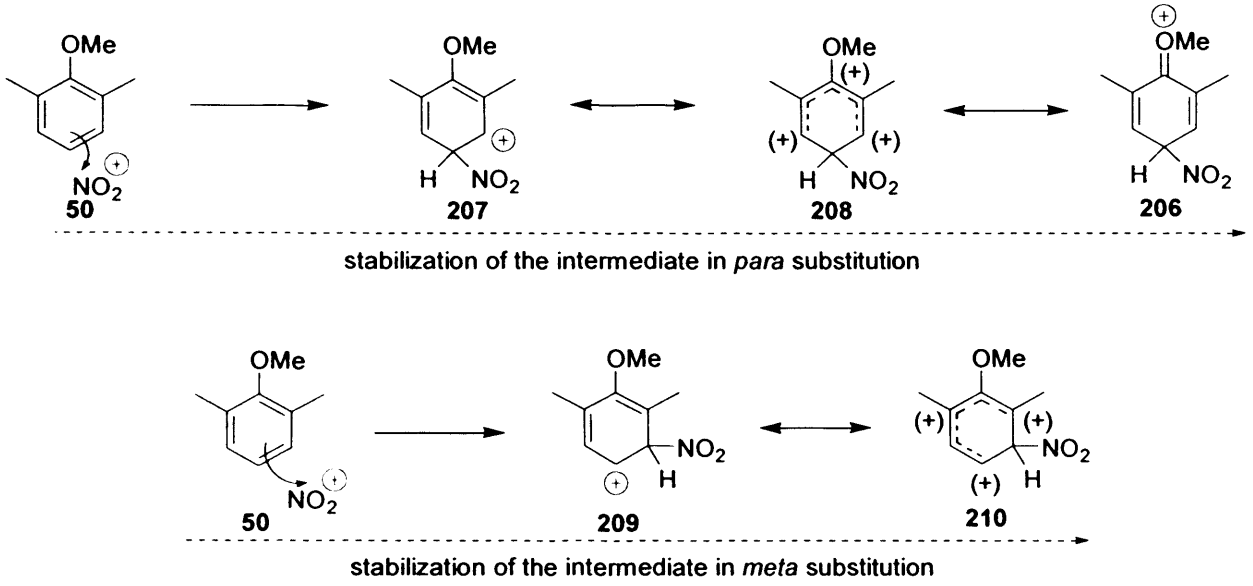


50 **206** **51**

Scheme 54

The methoxy group, being electron-releasing as a result of this strong resonance effect, is said to be an *ortho*, *para*-directing group towards electrophiles, while the two methyl groups are moderately electron-donating by the inductive effect and are also activating and hence *ortho*- and *para*-directing. As a result, the more powerful activating group- the methoxy group- has the dominant influence and gives *p*-nitroanisole **51** as the major product, even though the directing effects of the three groups are opposite to each other.

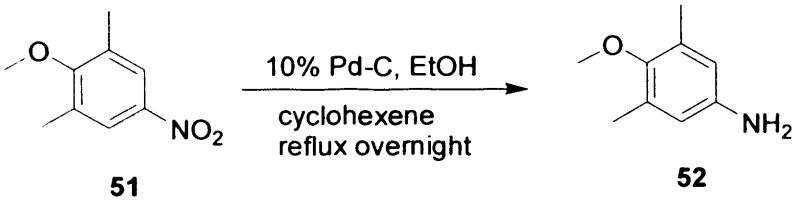
From another point of view, formation of the *para*-substituted nitroanisole **51** can also be explained by analysing the reaction intermediate. For this reaction, the following intermediates are possible, depending on whether the electrophile attacks *meta* or *para* to the methoxy group (Scheme 55).



Scheme 55

Each intermediate is stabilized by delocalisation of the positive charge over three carbon atoms in the ring. If the electrophile attacks *para* to the electron-donating methoxy group, the positive charge is further delocalised directly onto the oxygen, but the intermediate in *meta* substitution does not enjoy this extra stabilization. Therefore, the extra stabilization in the intermediate in *para* substitution means that the transition state is lower in energy than that in *meta* substitution.

The nitration product was subsequently reduced to the amine **52**, smoothly by a transfer hydrogenation from cyclohexene (Scheme 56).[45]

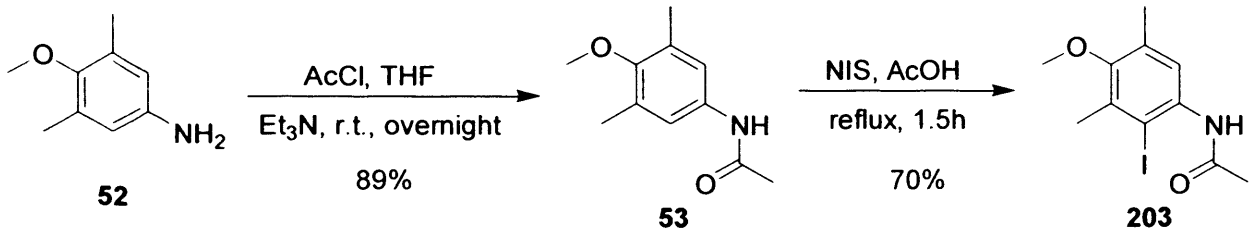


Scheme 56

p-Nitroanisole **51** was refluxed in ethanol with a large excess of cyclohexene in the presence of a catalytic amount 10% palladium on carbon. The reaction can be followed easily by t.l.c.. A brown solid amine **52** was obtained in a high 91% yield after filtration and evaporation of the solvent. The reaction occurs by transfer of hydrogen from cyclohexene to the nitro group *via* the palladium-carbon catalyst, with the formation of benzene. The process therefore

involves donor dehydrogenation and acceptor hydrogenation by the catalyst. According to proton NMR of the crude product, it was sufficiently pure for the following reaction. This was a much more convenient method than tin-HCl or Zn-HCl reduction.

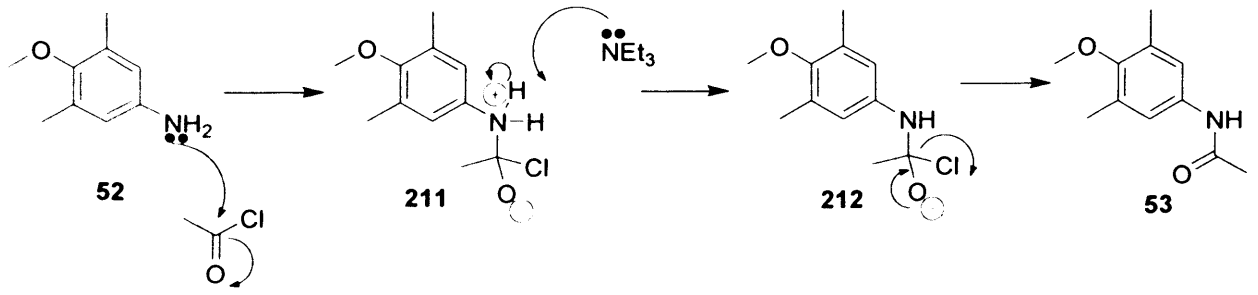
The relatively unstable free amine **52** was then protected as its acetamide **53**, which is much less nucleophilic, to prevent it interfering in the following steps. Subsequently, iodination using *N*-iodosuccinimide (NIS) in glacial acetic acid formed iodide **203** (Scheme 57).



Scheme 57

Amine **52** was derivatised by a standard triethylamine/acetyl chloride protocol, to give the acetamide **53** as colourless crystals in 89% yield, after recrystallisation from ethanol. This was a modification and compares to Little's report of orange crystals in 80% yield. The mechanism of this nucleophilic substitution is laid out below (Scheme 58).

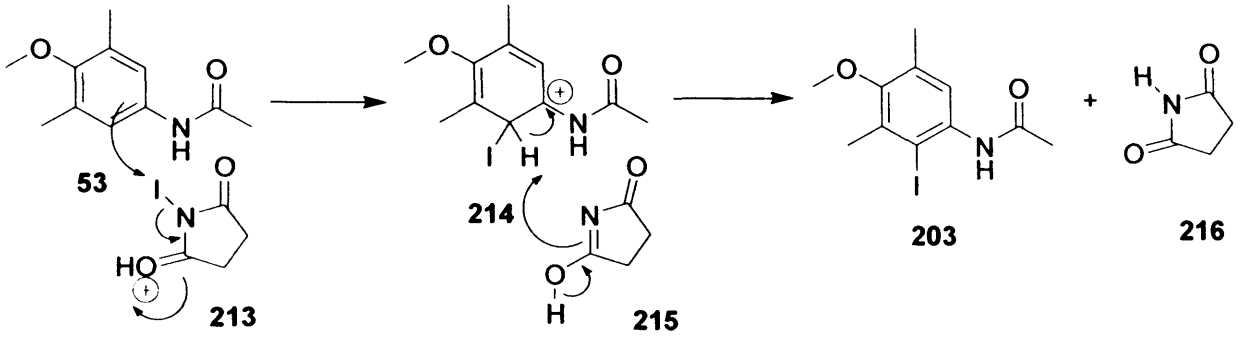
The first step of the reaction is addition of the nucleophilic amine to the electrophilic acyl chloride. Triethylamine removes the proton from the amine as it attacks the carbonyl group. The tetrahedral intermediate **212** is unstable. It collapses by an elimination reaction and loses chloride ion and forms the amide **53**.



Scheme 58

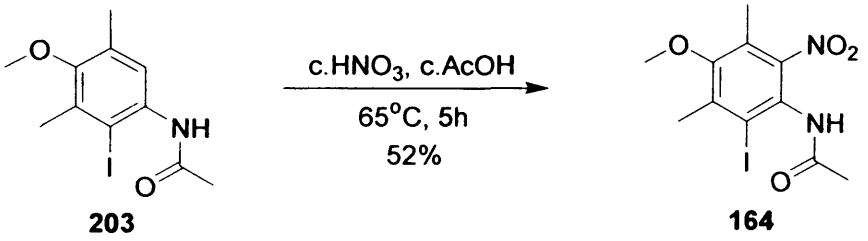
Acetamide **53** then underwent iodination with NIS by heating under reflux in glacial acetic acid (Scheme 59) and afforded the iodoanisole **203** in 70% yield after recrystallisation. This

is again an electrophilic aromatic substitution in which NIS provides iodonium cations for the reaction. As the acetamide **53** is symmetrical, there is only one possible product, unless a double iodination occurs. This did not appear to happen presumably because of the deactivating effect of the new iodine atom.



Scheme 59

Nitration of the remaining free position in iodoanisole **203** provided the key aryl iodide **164** as pale yellow crystals (52%).



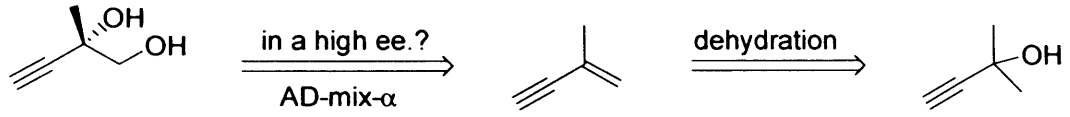
Scheme 60

The reaction took much longer (5 hours), compared to the previous nitration of 2,6-dimethylanisole **50**, which went to completion in less than 2 hours. This may be caused by the steric hindrance from the adjacent methyl and acetyl groups of the substitution position on the benzene ring.

The idea was then to introduce the necessary side chain using a Sonogashira coupling, and so the powerful electron-withdrawing nitro group was retained to assist this reaction.

2.3 The Preparation of 3,4-Dihydroxy-3-methyl-1-butyne 69

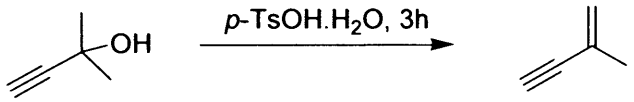
The retrosynthetic analysis (Scheme 61) shows that the diol **69** could be obtained by an asymmetric dihydroxylation reaction (AD-mix reaction) on the butenyne **205**, which should be readily prepared by a dehydration reaction of ynol **204**.



(S)-69 **205** **204**

Scheme 61

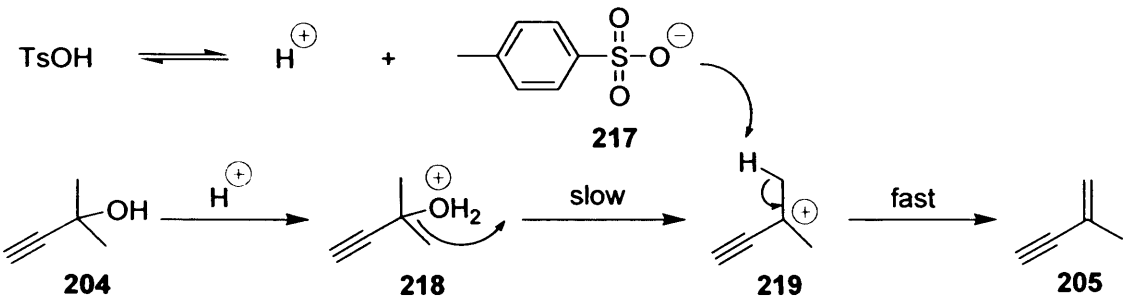
Following the above procedure, butenyne **205** was made from ynol **204** by refluxing with acid (Scheme 62).[43]



204 29% **205**

Scheme 62

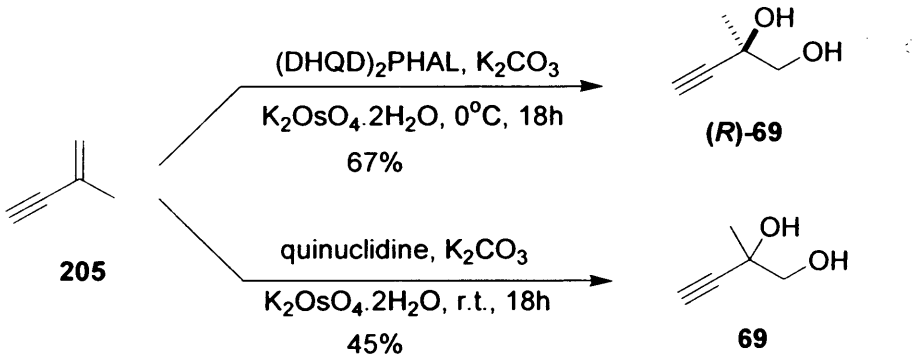
Dehydration of the ynol **204** occurred under reflux with an equal weight of *p*-toluenesulfonic acid monohydrate. The highly volatile product, the butenyne **205** (b.p. 34 °C), was distilled into a receiving flask as it was formed, along with a small amount of water by-product and the starting material. The crude product was purified by redistillation at 50°C to afford the pure butenyne **205** as a colourless liquid. Although the yield was poor (29%), by reacting at a scale of 50 g of starting material, the reaction gave a sufficient amount of substrate. The starting ynol **204** is a very cheap adduct formed from ethyne and acetone. The mechanism of this dehydration is believed to follow an E1 elimination procedure, during which the unimolecular loss of water from the protonated cation **218** was the rate-determining step (Scheme 63).



Scheme 63

As a weak nucleophile, counterion **217** of the toluenesulfonic acid does not attack the carbon of the carbocation **219**, but only removes its proton and forms butenyne **205** as the product.

AD-mix-β reaction on butenyne **205** afforded the non-racemic diol **(*R*)-69** smoothly in a reasonable yield (Scheme 64). (Since the AD-mix-β reagent was readily available in our laboratory, it was used in the experiment.)

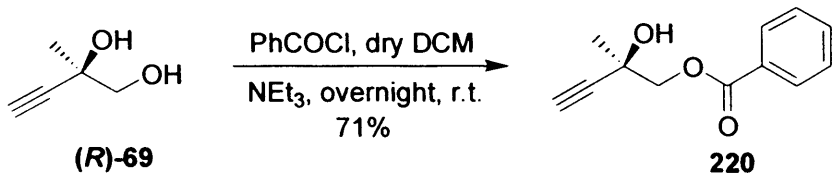


Scheme 64

The typical protocol for dihydroxylation to make racemic diol **69** was also applied, by using quinuclidine as the ligand instead of $(DHQD)_2PHAL$. The same product (according to NMR) was achieved, albeit in lower yield (45%). The racemic diol would be necessary in determining the optical purity of the asymmetrical dihydroxylation (AD) product.

Determination of the enantiomeric excess (ee) of the non-racemic diol **(*R*)-69** from the AD-mix reaction, using chiral high performance liquid chromatography (HPLC) or gas chromatography (GC), failed to give clear separation of the enantiomers. Presumably, this was due to the high polarity and small size of the diol **(*R*)-69**. Therefore, the compound was

selectively protected by a benzoyl group to afford a larger molecule, the benzoate **220** with lower polarity (Scheme 65).



(*R*)-69 **220**

Scheme 65

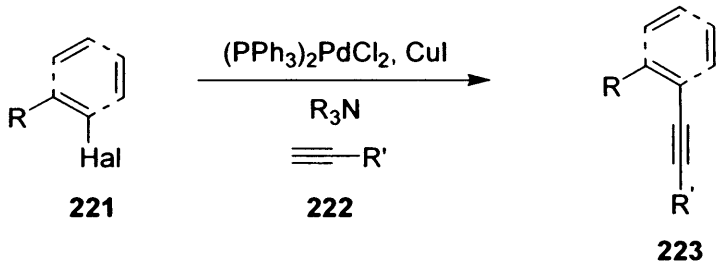
The esterification proceeded by stirring the diol **(*R*)-69** with benzoyl chloride and triethylamine (NEt_3) in dry dichloromethane. The expected product was obtained in a 71% yield. As a result, GC analysis of the benzoate **220** showed a poor ee of 5.6% (CDX-β column; temp.: oven- 150°C, detector- 300°C, injection- 250°C; column head pressure- 20 PSI, retention time: 14.2 min.).

We realised that it would be difficult to achieve the optically pure product due to the structure of butenyne **205**. Since the terminal triple bond is among the sterically least demanding functional groups, and as terminal double bonds are also known to not perform well in AD reactions, the enantioselectivity was therefore poor. But considering that the two steps are both simple reactions and are readily scaled up to multigram scale if required, we decided to temporarily follow this method to prepare our necessary side chain diol **69**. If the following study proved our synthetic route towards vitamin E is efficient, a new way of making the optically active diol **(*S*)-69** could probably be developed.

Until now, a large amount of the side chain diol **69** has been made, although in a poor ee. We were now ready to start part three of our total synthesis, which begins with the cross coupling of the two moieties, the iodide **164** and diol **69**. The problem of the low ee of the latter would have to be addressed later, given that the subsequent steps could be made to work.

2.4 The Sonogashira Coupling

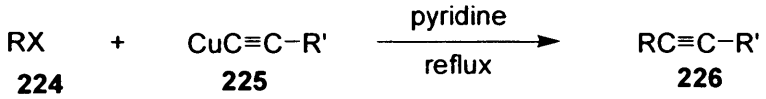
The Pd-Cu catalysed cross-coupling reaction of terminal acetylenes with sp^2-C halides was developed by Sonogashira three decades ago.[46] He showed that a terminal acetylene **222** could be coupled directly with vinyl or aryl halides **221** in the presence of *bis*-triphenylphosphine palladium(0) dichloride and copper(I) iodide under mild basic conditions, to form either enynes or aryl acetylenes **223** (Scheme 66).



221 **222** **223**

Scheme 66

The reaction could be considered to be an application of Pd-catalysis to the classic Stephens-Castro reaction (Scheme 67).[47]



224 **225** **226**

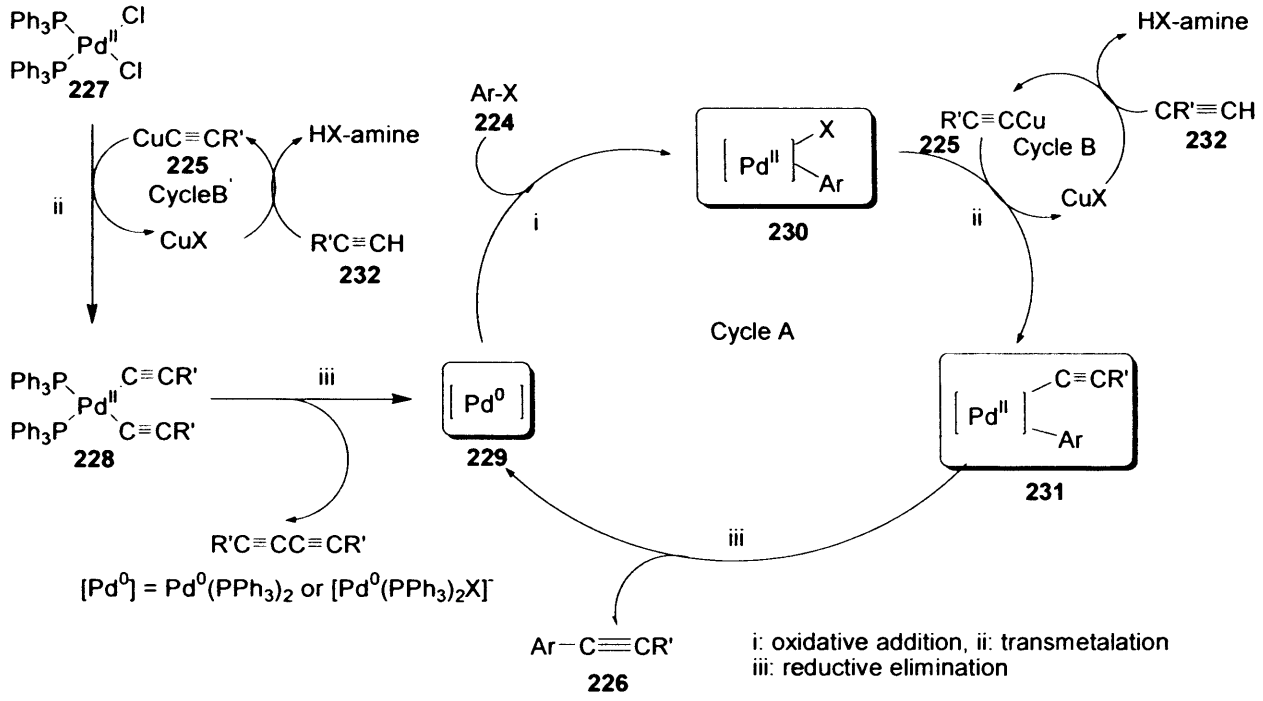
R = Aryl, Alkenyl

Scheme 67

Coupling of copper(I) acetylides **225** with aryl or alkenyl halides **224** under reflux with base gave aryl or alkenyl acetylenes **226**.

Based on the above reaction, the Sonogashira coupling has been developed by combining a copper(I)-catalysed alkynylation of Pd complexes (cycle B and B', Scheme 68) and a Pd-catalysed cross coupling of sp^2-C halides with terminal acetylenes (cycle A).[48] This protocol is based on the discovery of CuI-catalysed transmetalation with amine (cycle B and B'), and is constructed by a combination of three catalytic cycles (A, B, and B'). Although the reaction certainly follows the normal 'oxidative addition-reductive elimination' process common to many Pd-catalysed C-C bond-forming reactions, the exact mechanism for the

reaction is not known. In particular, the structure of the catalytically active species and the role of the CuI catalyst remain obscure.

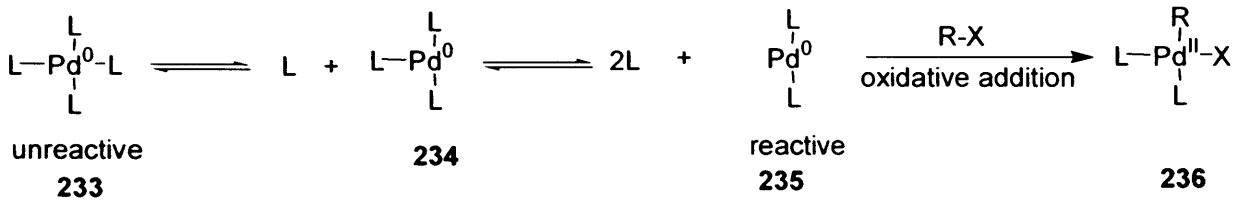


Scheme 68

The process may be considered to involve Pd^0 species [Pd^0] **229**, neutral $Pd^0(PPh_3)_2$ or anionic $[Pd^0(PPh_3)_2X]^-$, which is generated from the Pd(II) pre-catalyst **227** to give the Pd(II) intermediate **230** by the oxidative addition of the sp^2-C halide. Subsequent reaction with a terminal acetylene, possibly *via* a transient copper acetylide species (Cycle B), leads to the alkynylpalladium (II) derivative **5** which proceeds to give the required coupled product and regenerates the active Pd species 231.

As a palladium source, $(PPh_3)_2PdCl_2$ **227** commonly is used in Sonogashira couplings, where a catalytically active, coordinatively unsaturated complex **229** is produced by reductive elimination of a Pd-acetylide complex, which is generated from $(PPh_3)_2PdCl_2$ **227** and a terminal acetylene (Scheme 68). In many cases, $Pd(OAc)_2$ or $(CH_3CN)_2PdCl_2$, two equivalents of a tertiary phosphine, L, and a terminal acetylene are used to reduce the Pd(II) complexes *in situ* to the catalytically active complexes **229**.[48] $Pd^0(PPh_3)_4$, which generates

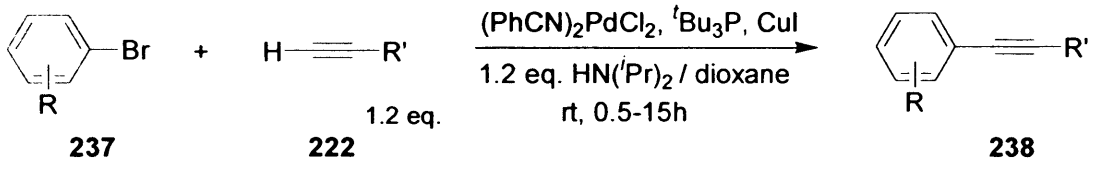
active catalytic species, $Pd^0(PPh_3)_2$, after the loss of excess triphenylphosphine (Scheme 69) is also useful (L = PPh_3).



Scheme 69

tris-(Dibenzylidene-acetone)dipalladium(0), $Pd^0_2(dba)_3$, in the presence of phosphine ligands (L), is also a useful Pd^0 source, where the dba ligand should easily be displaced to afford the active species, PdL_2 **235**, in nearly quantitative amounts.

Recently, a room temperature Pd-catalysed reaction for less reactive aryl bromides was reported (Scheme 70).[49]



R = COMe, H, Me, OMe, NMe_2
R' = Ph, ^{n}Hex, $CMe_2(OH)$, TMS

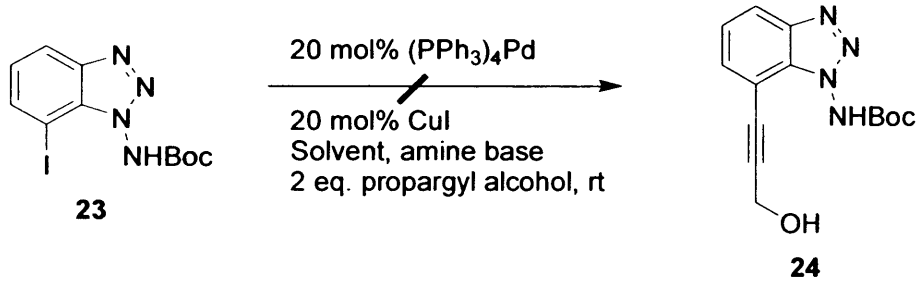
Scheme 70

Aryl bromides **237** coupled with an equimolar amount of a terminal acetylene **222** at room temperature in quantitative yield. The reaction proceeds in $^iPr_2NH$-dioxane in the presence of $(PhCN)_2PdCl_2$(3%), CuI(2%), and $^tBu_3P$(6%) within 0.5-15h. Other phosphines such as PPh_3, P(*o*-tolyl)$_3$, dppf or PCy_3 are ineffective. This effect can be explained by the acceleration of the oxidative addition step (i) (Scheme 68) through coordination of a bulky electron-rich phosphine to the palladium center.

In general, the Pd-Cu-catalysed cross-coupling of terminal acetylenes with sp^2-C halides is a useful method for the synthesis of conjugated acetylenes. Since it was discovered, a vast number of modifications have been employed to improve reaction rates and yields. The

major modifications include the choice of palladium catalyst, ligand, solvent system, temperature and amine base. There appears to be a seemingly endless number of combinations that may be used to achieve the best results for a particular system.[42]

With regards to the system under investigation, a Sonogashira coupling between aryl iodide and propargyl alcohol, Dr Little endeavoured to develop an efficient procedure. The initial attempt was to react iodide **23** with propargyl alcohol at ambient temperature, using 20 mol% of both $Pd^0(PPh_3)_4$ catalyst and copper(I) iodide (Scheme 71).



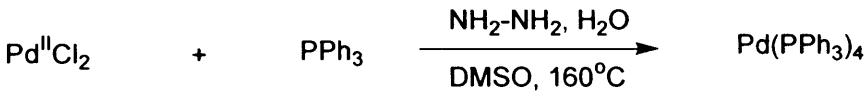
23 **24**

Scheme 71

Both diethylamine ($HNEt_2$) and triethylamine (NEt_3) were employed with and without various quantities of tetrahydrofuran or dimethylformamide. In all cases, the reactions failed and starting materials were returned. At last, Little applied more vigorous conditions by heating the mixture under reflux with NEt_3 as the base, in oxygen free, anhydrous tetrahydrofuran. As a result, the reaction was complete in 18 hours and the alcohol **24** was formed almost in a quantitative yield (92%) (See Table 2, section 1.1.4, Chapter 1).

With the result of Little's study of Sonogashira couplings on his compounds, we planned to use an efficient procedure for coupling our iodide **164** and diol **69**. Since the diol **24a** was successfully coupled with the iodide **23** by Little (entry 6, Table 2, Chapter 1) in a reasonable yield (72%), we also used the same base, catalyst and solvent as used in Little's procedure. Initially, we tried our reaction in mild conditions, because our iodide **164** should be more active than Little's for the reaction. Its strong electron-withdrawing nitro group in the *meta* position should help the initial oxidative addition of the palladium(0) complex.

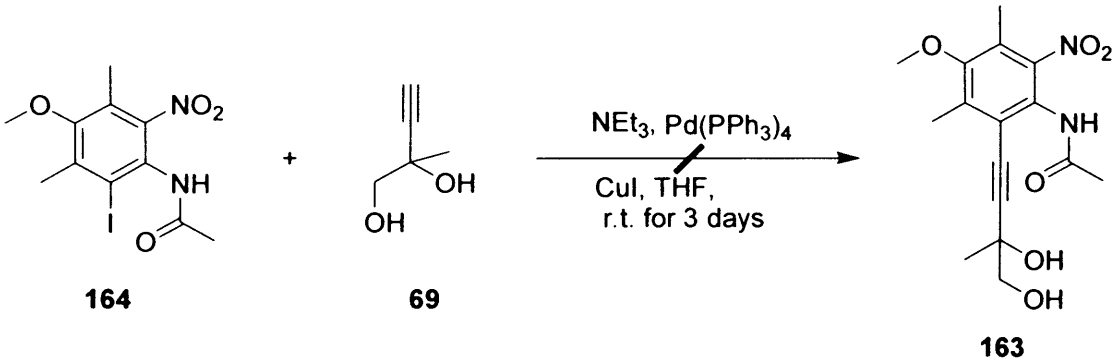
Before our first attempt at the reaction could take place, preparation of the catalyst $Pd^0(PPh_3)_4$ was required (Scheme 72).*



Scheme 72

A suspension of palladium(II) chloride and triphenylphosphine (5 equivalents) in dimethysulfoxide (DMSO) was heated under nitrogen until it became a clear solution (~160°C). The heat was removed before a solution of hydrazine (NH_2-NH_2) in water (55%) was added. Bright yellow crystals precipitated when the solution was cooled to room temperature. The fine crystals were collected by quick filtration and washed with water. Due to the air sensitivity of $Pd^0(PPh_3)_4$, it was found to be more efficient to store it in water or DMSO under nitrogen. As $Pd^0(PPh_3)_4$ is not water/ DMSO soluble at low temperature, the liquid layer could 'seal' the crystals, and protect them from attack by oxygen. Before use, the crystals were taken out by a pipette and dried by filtration. The water/ DMSO still attached to the crystals could be removed by squeezing the crystals between two layers of filter paper.

After the palladium catalyst $Pd^0(PPh_3)_4$ was prepared, the iodide **164** and diol **69** were stirred at room temperature in dried and degassed tetrahydrofuran containing triethylamine and copper iodide (Scheme 73).



Scheme 73

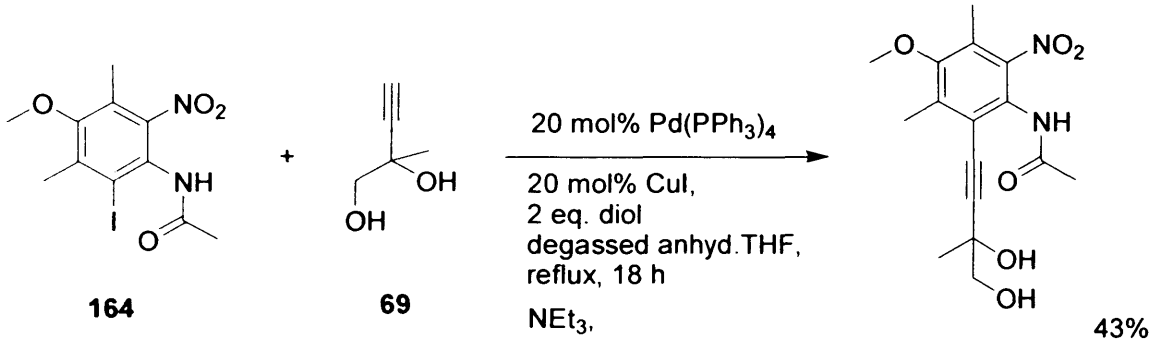
The proton NMR showed that no reaction occurred after 3 days. We then used forcing

* Wen Fei Tan, PhD dissertation, Lan Zhou University, 2001 (written in Chinese).

conditions by heating the reaction mixture under reflux with a stronger base diethylamine for 6 hours. This reaction also failed. Therefore, we decided to repeat Little's procedure, we hoped it would be successful. After the reaction was heated under reflux overnight using neat triethylamine, some coupling product appeared, according to ^{1}H NMR spectroscopic analysis, however the majority of the iodide **164** remained unreacted. The result was disappointing, but it also gave us some hope. The reaction time was then prolonged by 50 hours and the process was followed by t.l.c. and proton NMR. It showed that the coupling reaction stopped after 25 hours reflux, despite the fact that extra amounts of base (triethylamine) and catalysts $Pd^0(PPh_3)_4$, Cu(I) were added from this point. Proton NMR of the crude product shows unreacted iodide **164** but no sign of diol **69**, which was in 1.5 equivalents to the iodide **164**. It was reasoned that the diol **69** had been consumed by the palladium(II) complex, which was formed *in situ* from $Pd^0(PPh_3)_4$), to afford the unwanted oxidised dimer **239**. This process was probably similar to cycle B' of Scheme 68.

239

To solve this problem, two equivalents of the diol **69** were used. We were pleased to find that the reaction went to completion after 18 hours, without the need to add extra catalysts and base.



164 **69** **163** 43%

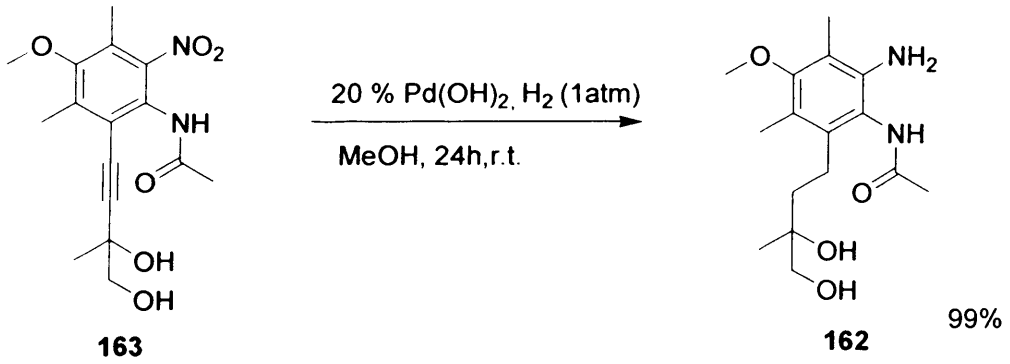
Scheme 74

The crude solid was then purified by column chromatography using methanol / chloroform as the solvents followed by crystallisation from methanol in the fridge overnight. The pure

product, the acetylenic alcohol **163**, was obtained as pale yellow crystals in a moderate 43% yield. In the ^1H NMR spectrum of the product, peaks for the methyl groups had shifted compared to the starting materials, and the integrations for all the five methyl groups and the CH_2 group were correct. The structure was confirmed by all the other usual criteria.

2.5 Reduction

To complete our chroman synthesis, we needed to saturate the newly incorporated tether as well as to reduce the nitro group to an amine. When a simple hydrogenation was attempted, following Little's method using 10% palladium on carbon in methanol under hydrogen (Table 3, Chapter 1), no reduction on the triple bond occurred even after stirring for 48 hours at room temperature. This was confirmed, as ^1H NMR analysis showed no shift for the five methyl groups. A broad single peak appeared at 1.8 ppm. with reasonable integration, suggesting that the NH_2 was probably formed from the nitro group. A more vigorous condition of heating the mixture under refluxing with excess of cyclohexene was then tried, but this delivered the same product. The result proves that transfer hydrogenation by cyclohexene selectively reduces the nitro group without affecting the alkyne. After this failure of the reaction at both ambient and high temperature with palladium on carbon, we decided to modify the reduction by altering the catalyst. Palladium hydroxide (Pearlman's catalyst) on carbon is known to be a more powerful catalyst than palladium on carbon. Indeed, our reaction went to completion and gave the saturated amine **162** after 24 hours of stirring under hydrogen (Scheme 75).



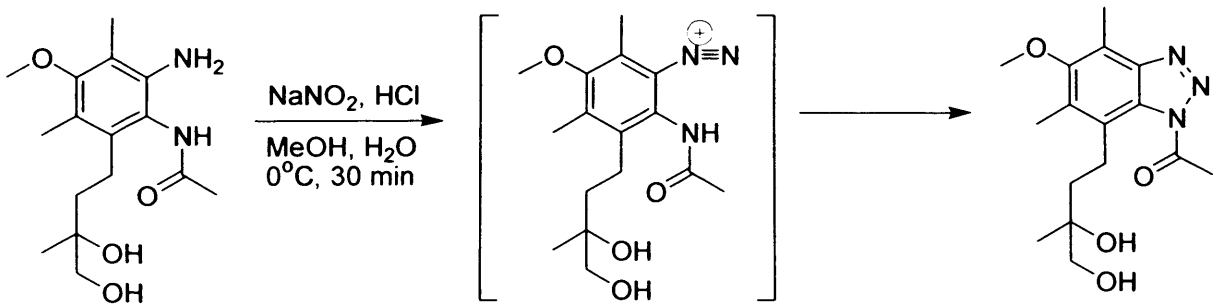
163 **162**

Scheme 75

The reaction mixture was filtered through celite during the work-up. The residue was washed with warm methanol to dissolve the product which adhered to the catalyst. Evaporation of the filtrates gave the amine **162** in an excellent yield (99%), as a pale yellow gum. Evidence for the structure was that all the methyl groups in the ^{1}H NMR spectra showed a move upfield. Two new triplets with the same coupling constant (~8.6 Hz) represented the newly formed CH_2 groups. The successful hydrogenation initially proceeded in a small scale, from 111 mg of starting material. For a larger scale of 395 mg, a much longer reaction time was needed (~48 h) to fully hydrogenate the triple bond. ^{1}H NMR evidence suggested that traces of the corresponding double bond were present. Since there was only a small amount of this by-product and it should not affect the following reactions, we carried on to the next step without further purification.

2.6 Diazotisation and Cyclisation

The reduced amine **162** was subjected to standard diazotization conditions, to form a diazonium salt **240**; subsequent intramolecular cyclisation should afford the benzotriazole **241** (Scheme 76).



162 **240** **241**

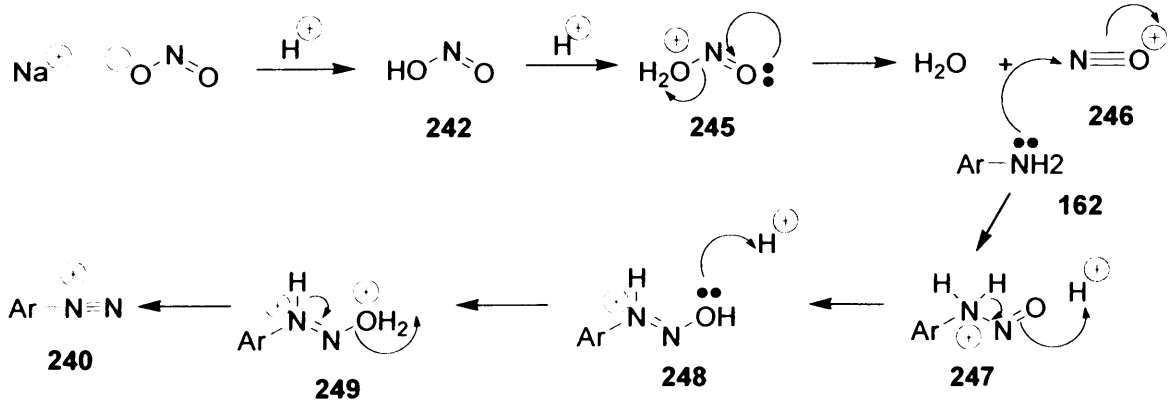
Scheme 76

An aqueous sodium nitrite solution (1.3 equivalents) was added to a stirred solution of amine **162** in methanol at ambient temperature. The mixture was then transferred dropwise to a separate flask containing 10 M hydrochloric acid (~10 eq.) at 0 °C. Stirring at 0 °C was continued for 0.5 h before water was added. The suspension was then extracted with

dichloromethane before being dried and evaporated to give the benzotriazole **241** in a moderate yield (50%).

^{1}H NMR analysis shows that the broad peak (at 1.71 ppm.) which represented NH_2 for the amine **162** has disappeared, and the pattern for CH_2 and CH_3 groups had also changed (Figure 1). The peak for CH_2 attached to the aromatic ring (2.99-3.15 ppm.) turned into a multiplet, rather than the previous triplet. This is believed to be caused by the geminal effect of the two hydrogen atoms on the same carbon. This effect was also observed in the 4'-CH_2 peak: two double-doublets (3.41 and 3.54 ppm.) represent the two hydrogens, both of which coupled with the OH group next to them, as well as coupling with each other. The shifts of all five methyl groups (singlets) were also evidence of the reaction. Due to a shortage of other evidence about changes of coupling constants, the main method for identifying the products in this project was by comparing the chemical shifts of the methyl groups of the products with that of the starting materials in the ^{1}H NMR spectra.

The first step of the diazotization reaction involves the formation of the weak acid, nitrous acid **242**, from sodium nitrite and the strong acid HCl. Nitrous acid **242** is itself protonated and then loss of water creates the reactive electrophile NO^+ **246** (Scheme 77). The NO^+ cation **246** then attacks the lone pair of the amine group and dehydration follows after a series of proton transfers.



Scheme 77

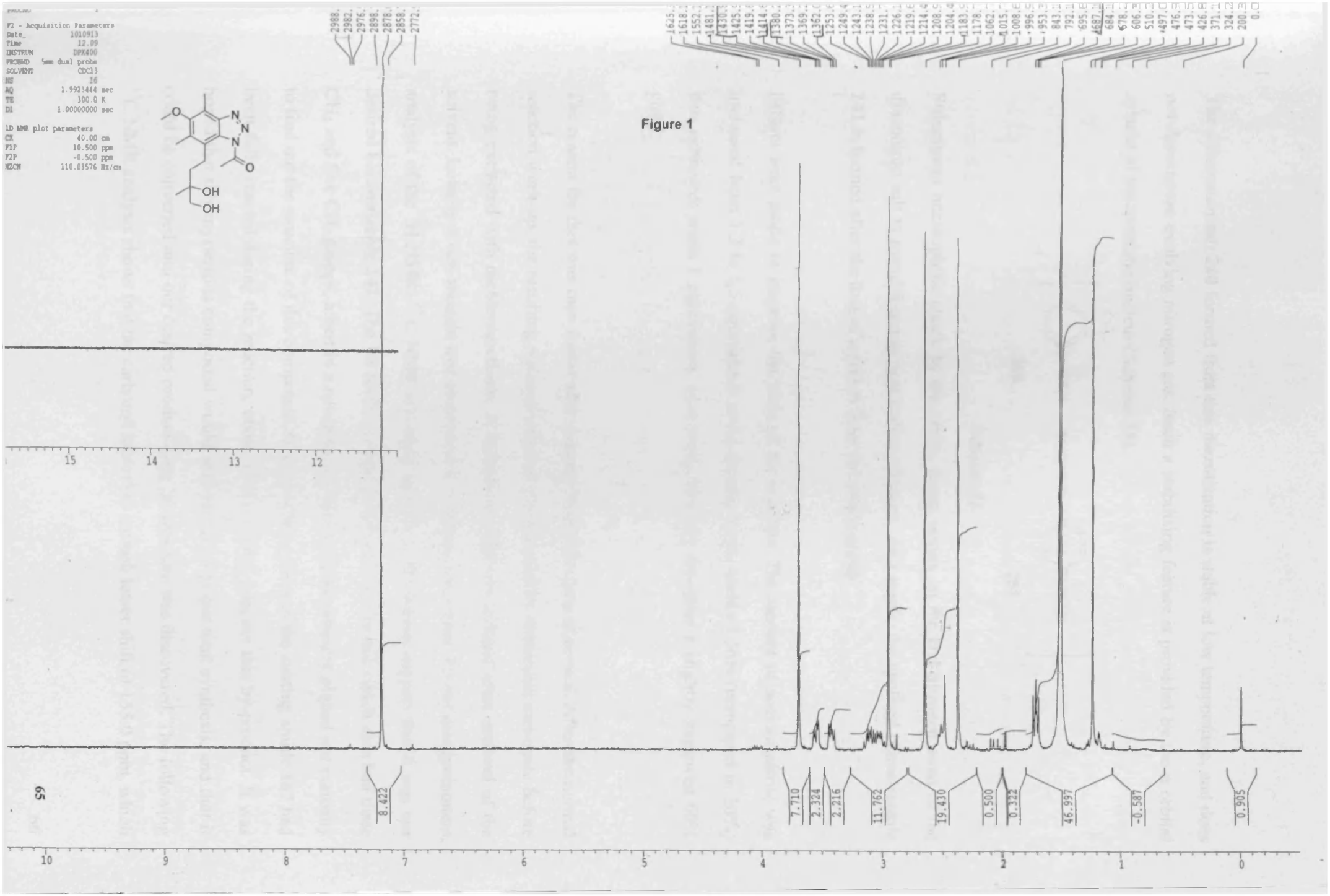
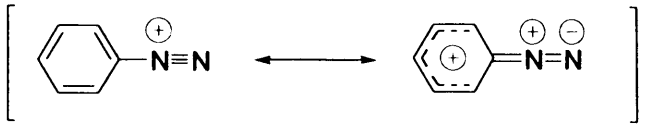

F2 - Acquisition Parameters
Date_ 1010913
Time 12.09
INSTRUM DPX400
PROBHD 5mm dual probe
SOLVENT CDCl3
NS 16
AQ 1.9923444 sec
TE 300.0 K
D1 1.00000000 sec
1D NMR plot parameters
CX 40.00 cm
F1P 10.500 ppm
F2P -0.500 ppm
HZCM 110.03576 Hz/cm
OH
OH
8.422
7.710
2.324
2.216
11.762
19.430
0.500
0.322
46.997
-0.587
0.905

Figure 1

The diazonium salt **240** formed from this diazotization is stable at low temperature, and does not decompose evolving nitrogen gas. Such a stabilising feature is provided by the π orbital system of the aromatic nucleus (Scheme 78).



250 **251**

Scheme 78

Subsequent nucleophilic attack by the amide group occurs on the end nitrogen atom of the diazonium salt to avoid forming pentavalent nitrogen. As a result, the cyclised benzotriazole **241** is formed after the loss of a proton from the amide group.

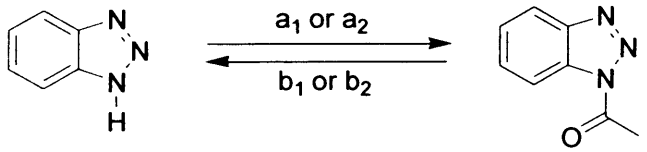
Efforts were made to improve the yield of the reaction. The amount of sodium nitrite was increased from 1.3 to 1.5 equivalents and a slightly better yield of 56% (compared to 50%) was achieved; when 2 equivalents were used, this only delivered a slightly improved 60% yield.

The reason for this was then found after a major by-product was observed. After the normal reaction work-up, the resulting aqueous solution was basified by potassium carbonate before being extracted with dichloromethane. A colourless solid was isolated after removal of the solvent. Initially it was thought that more product had been recovered. To our disappointment, analysis of the ^{1}H NMR, ^{13}C NMR and mass spectra or IR did not support that it was our desired benzotriazole **241**. The ^{1}H NMR spectrum showed a compound which also had three CH_2 and five CH_3 groups, albeit in a new pattern. This evidence strongly piqued our curiosity to find out the structure of this compound. It seemed that although the starting amide **162** had been fully reacted during the reaction, about 40% of it had become this by-product. It was hoped that this mysterious compound would also be useful to our total synthesis, and that it could be converted into our desired product once its structure was discovered. The following ^{13}C NMR analysis shows that the carbonyl moved to a much lower shift of 155.0 ppm. which

seemed abnormal. The infrared spectrum showed no signal for a carbonyl stretch but a weak absorption appeared at 1448 cm^{-1}. Mass spectra (APcI) showed a peak of 293 mass units, which is different from the main product molecular weight of 322, and the starting material amide **162** value of m/z 311.

To further test the existence of any acetyl group, the unknown compound was treated with excess amounts of potassium carbonate in aqueous methanol at room temperature. No reaction occurred after 4 hours and the starting material was recovered. The same result was achieved using the stronger base potassium hydroxide. The compound also survived the more vigorous condition of refluxing in methanol for 2 hours with potassium hydroxide.

We then applied the above procedures on the similar acetyl benzotriazole **252**, assuming it would show similar reactivity (Scheme 79); this was prepared from commercially available benzotriazole **2** using Katritzky's method.[50] As a result, the acetyl group of compound **252** was hydrolysed smoothly at room temperature with K_2CO_3 or KOH after 2.5 hours. This proved the efficiency of our hydrolysis method for the analogous benzotriazole **(*R*)-161**.

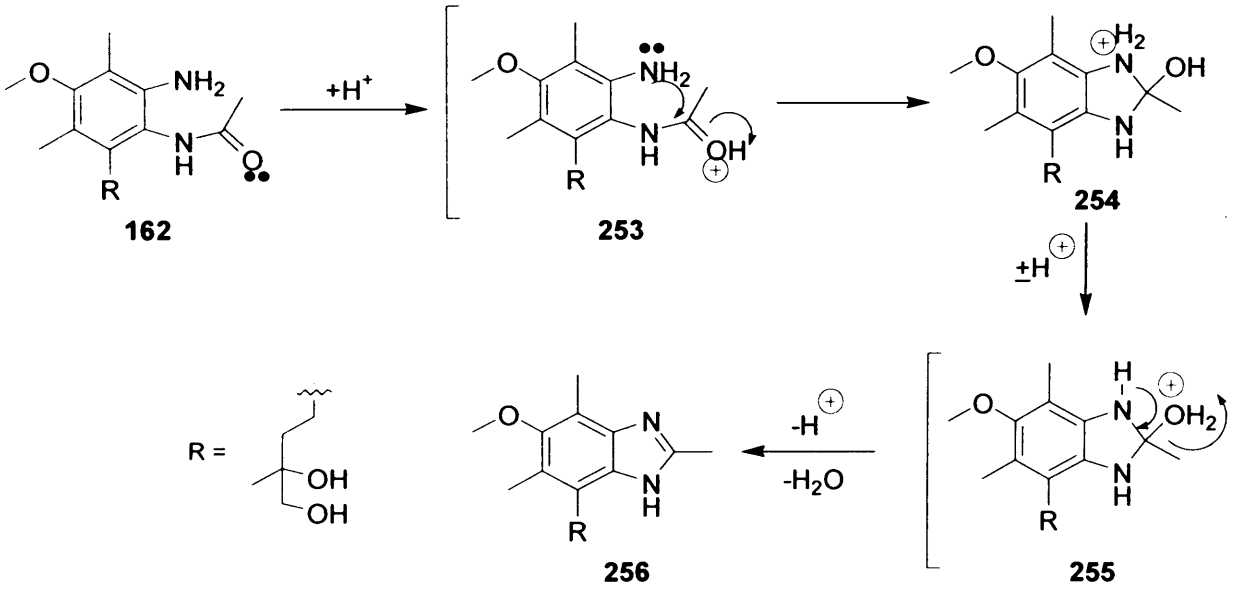


2 **252**

a_1. CH_3COCl, 80°C, 3h
a_2. CH_3COCl, dry DCM, NEt_3, reflux, 4h.
b_1. K_2CO_3, MeOH, H_2O, r.t., 2.5h
b_2. KOH, MeOH, H_2O, r.t., 2.5h
Scheme 79

Benzotriazole **2** was refluxed in acetyl chloride for 3 hours before the volatiles were evaporated.[50] The residue was crystallised from methanol and the acetyl benzotriazole **252** was obtained as colourless crystals in poor yield (11%). A better yield (60%) was obtained by refluxing equal amounts of the benzotriazole **2** and acetyl chloride in dry dichloromethane with triethylamine. Hydrolysis of the product with K_2CO_3 or KOH in aqueous methanol returned the benzotriazole in moderate yields (45%, 42% respectively).

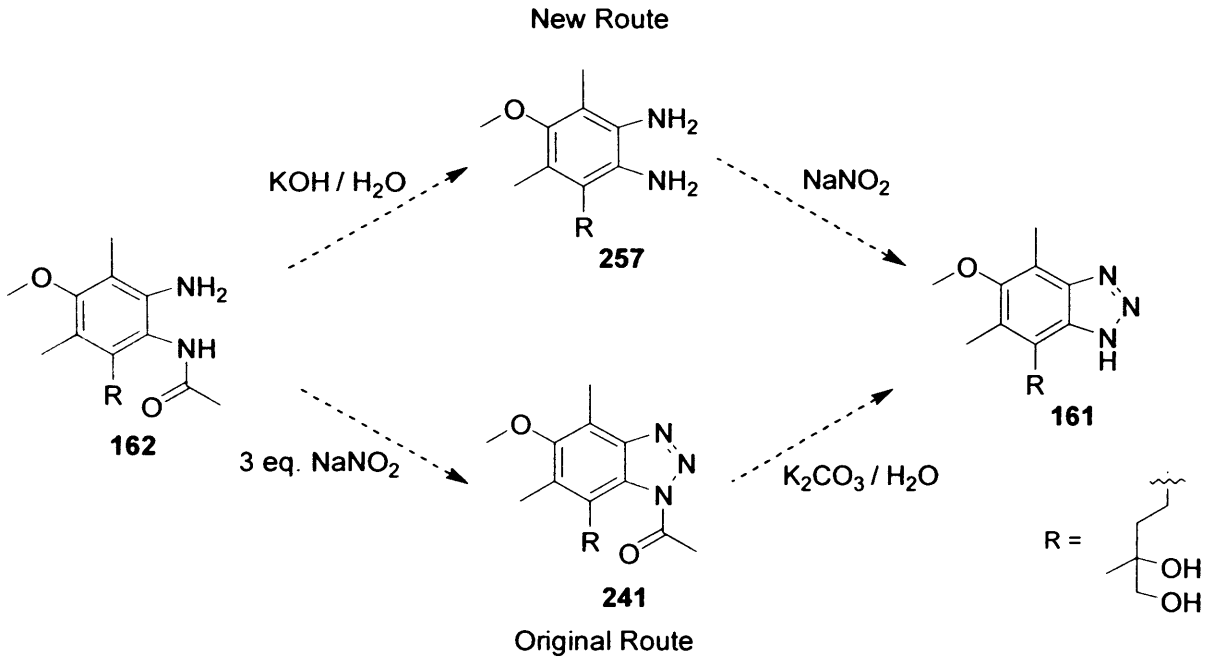
Through the above spectroscopic analyses and the test reactions, we can draw the conclusion that the unknown by-product does not contain a carbonyl group. Since the ^{1}H NMR spectra still shows five methyl groups, and a quaternary carbon peak appears at 155.0 ppm. after analysis of the ^{13}C NMR, we realised that the carbonyl had probably been attacked by a nucleophile under the acidic condition during the diazotization reaction. The only nucleophile we could think of during the reaction was the free amine on the benzene ring. We therefore found that a nucleophilic addition could occur between the amine and the carbonyl group under the acidic condition to form a stable five-membered ring – a benzimidazole **256** (Scheme 80). Indeed, the molecular weight of this final product is 292, which corresponds to the mass spectra ion at m/z 293 ($M+H^{+}$).



Scheme 80

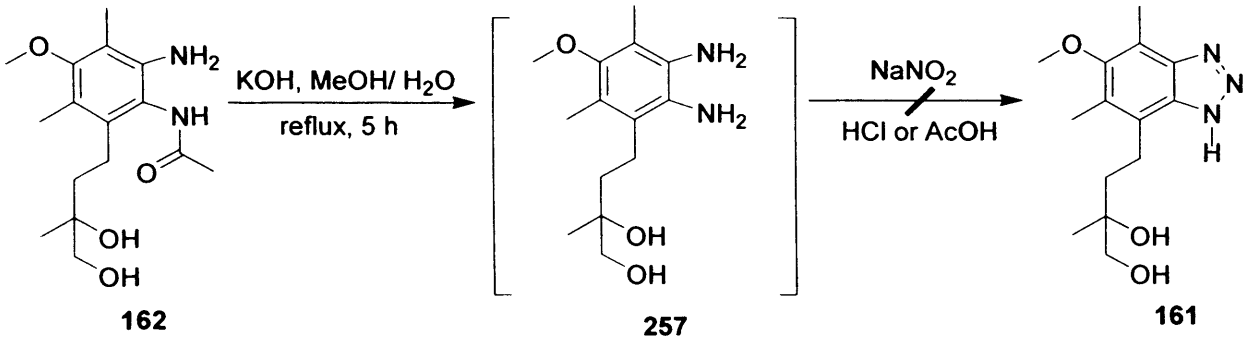
Protonation of the carbonyl group by hydrochloric acid would give the cation **253** which is much more electrophilic. Attack of the free amine followed by proton transfers forms cation **255**, which then loses a water molecule to give the benzimidiazole **256** as the by-product. Due to the high stability of the imidazole ring in benzimidazole **256** towards hydrogenation[51] for converting it back to an amine, and the relatively small amount we had in hand, we decided to stop our research on this aspect.

After discovering that the side reaction affected the yield of the diazotization, we made two plans to try to solve this problem. One plan was to hydrolyse the amide **162** to form a diamine **257** before diazotization (Scheme 81). If successful, this would avoid the formation of benzimidazole **256** and also deliver our desired benzyne precursor **161**. The other plan was to follow the original route but use three equivalents of sodium nitrite for the diazotization, with the aim of producing a greater excess of the reactive electrophile NO^+ to attack the amine, before the side reaction happens, and then deprotect the acetyl group using the known method (Scheme 79) to form the precursor **161**.



Scheme 81

Amide **162** was refluxed in aqueous methanol with potassium hydroxide (2 equivalents) for 2 hours. The ^1H NMR spectra of the crude product showed a mixture with a 2 : 3 ratio of the product diamine **257** and the starting material. Repeating the reaction with a large excess of KOH (30 equivalents) and refluxing for 4 hours also delivered a mixture but with an increased ratio of 2 : 1 (product / starting material). During the reaction work-up, it proved difficult to separate the product due to the high polarity of the diamine **257**, which makes it water soluble. Therefore, we used a one-pot reaction, trying to form the benzotriazole **161**, which should be less polar.



Scheme 82

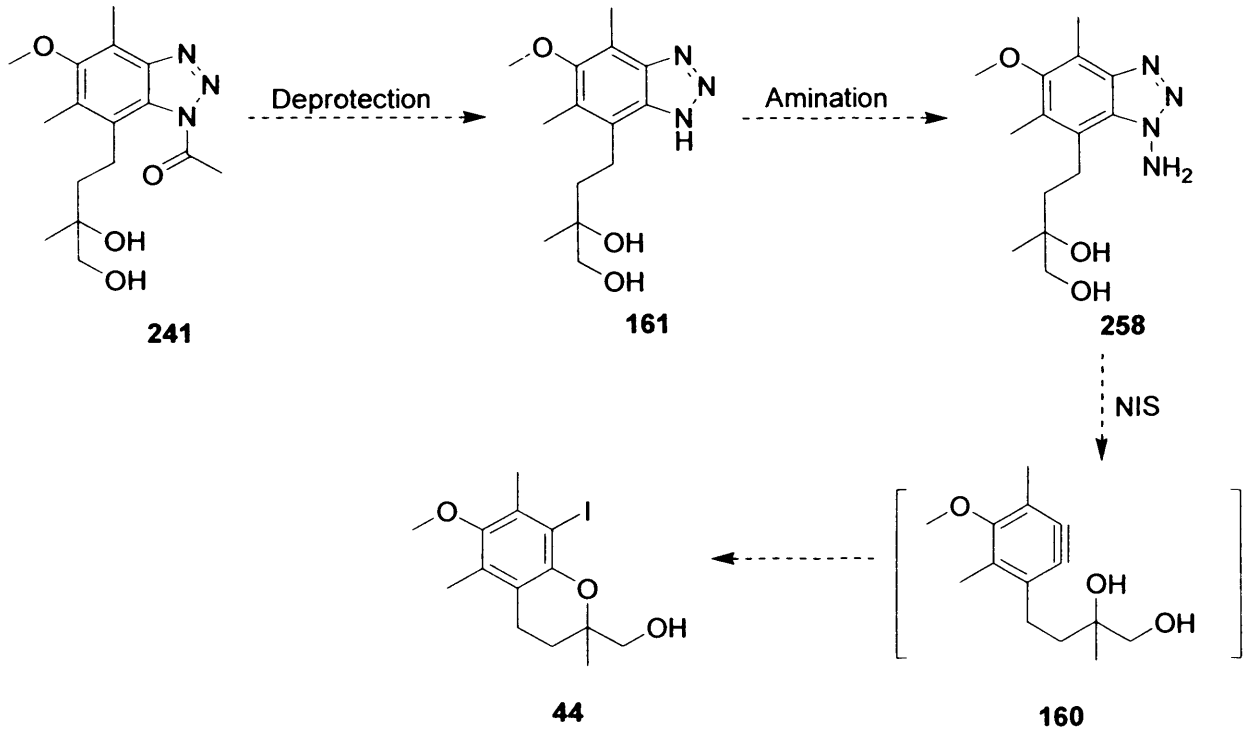
After heating the reaction mixture under reflux for 5 hours, tlc analysis showed that the starting material had disappeared. The methanol was removed by evaporation before a small amount of water was added. The solution was then acidified with 2M HCl, before being treated with $NaNO_2$ and 10M HCl, followed by stirring at 0 °C for 40 minutes. Unfortunately, an unrecognisable mixture of products was formed according to ^1H NMR analysis. We then altered the conditions of diazotization by following a literature method for cyclisation of diamines,[52] which uses glacial acetic acid and a temperature of 80°C, after stirring at low temperature for 30 minutes. But this method also delivered unknown compounds. The above results were disappointing, after all the efforts we made. The failure of this reaction was probably caused by the high polarity of the diamine **257** which contains two amines and two hydroxyl groups. Purifying the diamine **257** before diazotization might make the reaction proceed. But we left this sequence at this stage in search of a more efficient route.

Back to our original route, since we had already achieved a reasonable yield from the diazotization, we hoped that a useful modification could be made by simply adding more of the reagent $NaNO_2$. Indeed, an improved 73% yield was achieved by repeating the diazotization of amide **162** with 3 equivalents of $NaNO_2$. Only trace amounts of the by-product benzimidazole were found after the aqueous layer was basified. Now we could follow our original route, to carry the synthesis towards the vitamin E precursor **44**.

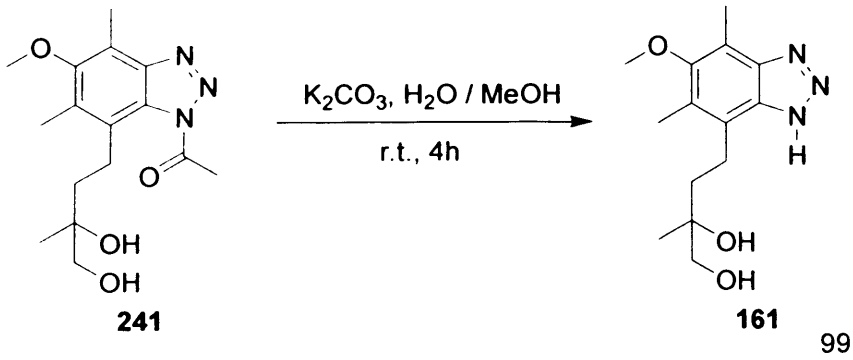
2.7 Deprotection of the Acetyl Group

After the amino-benzotriazole **241** was obtained in a good yield, it was our plan to then deprotect the acetyl group and give the *NH*-benzotriazole **161**. Hopefully, the following electrophilic amination on the NH group would form the benzyne precursor- the free amine- **258** (Scheme 83), which would form the benzyne intermediate with *N*-iodosuccinimide, and which would then be trapped by the alcohol to give the chromane **44**.

Hydrolysis of the amino-benzotriazole **241** was performed with K_2CO_3 at room temperature (Scheme 84).



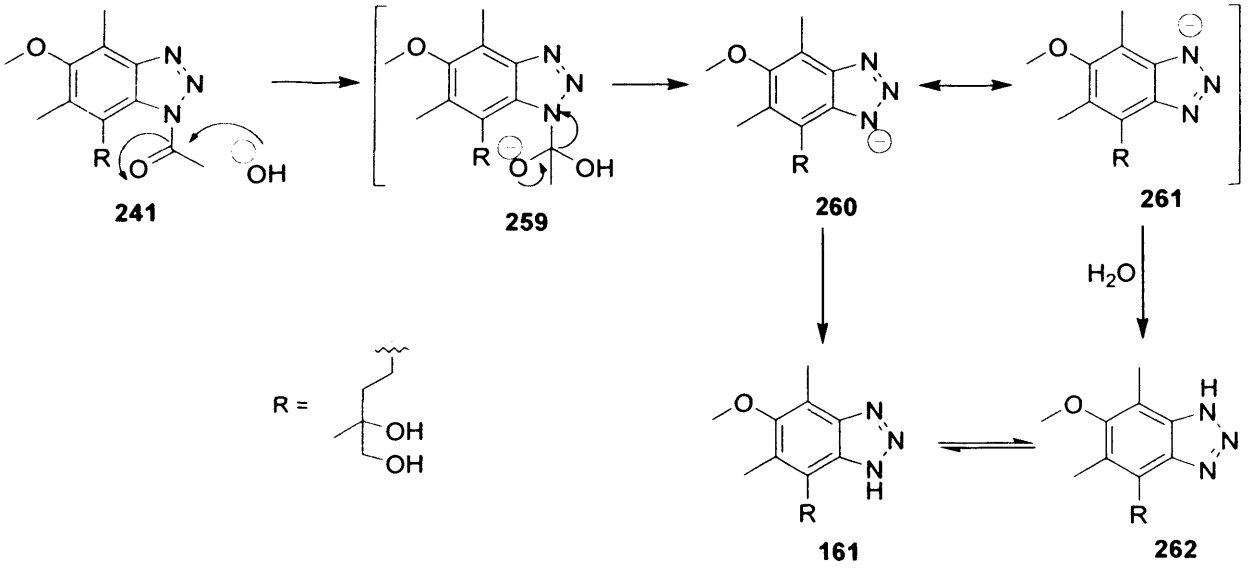
Scheme 83



Scheme 84

Amino-benzotriazole **241** was stirred in methanol at ambient temperature and K_2CO_3 was added along with water. The reaction was tested by tlc before the solvent was removed. Initially, the reaction was worked-up by treating the residue with water, followed by extraction with dichloromethane; a 77% yield of the product was obtained. Since the fact that *NH*-benzotriazole **161** is a highly polar compound and is water soluble, part of the product could have been lost during the aqueous work-up. Therefore, the procedure was altered by treating the evaporation residue with dichloromethane directly, before being dried and filtered, to avoid adding water. The filtered solid was washed with warm dichloromethane and a higher yield of 83% was achieved. At last, it was found that washing the solid residue with distilled methanol could give an excellent yield of 99%. The resulting ^1H NMR spectrum (run in CD_3OD) from this modified work-up shows a pure product, which was ready for the next step.

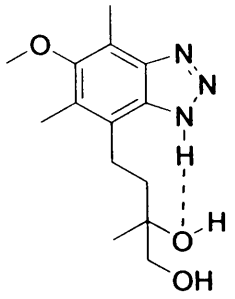
The mechanism of this reaction is believed to follow the typical process of hydrolysis of amide under basic condition (Scheme 85).



Scheme 85

Attack of the hydroxide anion on the amide carbonyl group forms a tetrahedral intermediate **259**. Benzotriazole is then lost as the leaving group to give the anion **260** which is stablised by electron delocalisation in the ring system. Therefore, the *NH*-benzotriazole **161** was

formed with its tautomer **262**. The *NH*-benzotriazole **161** should be the favoured product because a hydrogen bond between the NH and the OH could form to stablise the structure (Scheme 86).



161

Scheme 86

There was actually no need to separate these two isomers, even if this were possible, since they could both deliver the desired benzyne intermediate through the same method. Interestingly, the mixture of the two tautomers can only be observed from ^{1}H NMR spectra run in deuterated chloroform ($CDCl_3$), the spectra show a mixture of the two compounds in a 2 : 1 ratio. In the case of running the sample in deuterated methanol, in which the products are more soluble, the spectra show only a single tautomeric form. This may be because of the much higher solubility helps to form stronger hydrogen bonds.

2.8 Electrophilic Amination of the *NH*-Benzotriazole 161

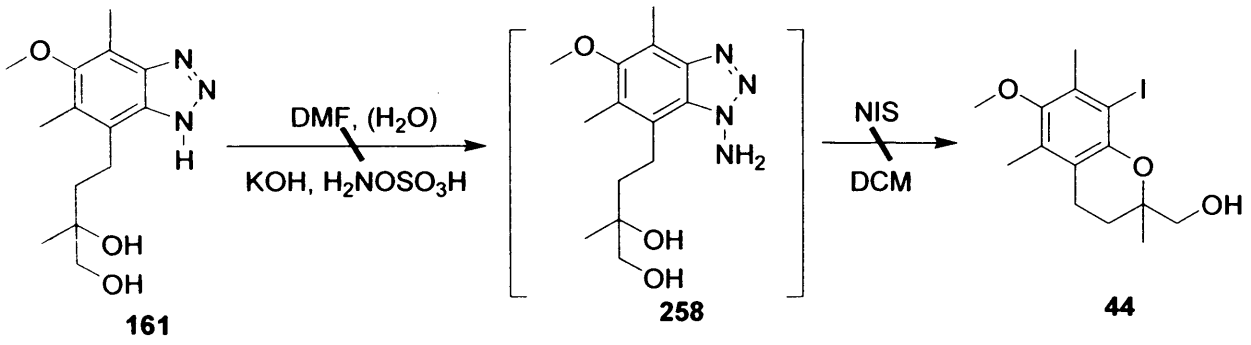
2.8.1 Using hydroxylamine-*O*-sulphonic acid

We had now synthesised the *NH*-benzotriazole **161** (with its tautomer) in a satisfying yield, and so the next phase of our project required the introduction of an amine group onto the amine (*NH*) of the benzotriazole, to obtain the key benzyne precursor.

Electrophilic amination is an important synthetic reaction in which an electron-poor nitrogen carried by the reagent is transferred to a nucleophilic centre of the substrate to form a Nu-N bond in the product. From the work of Campbell and Rees,[2] hydroxylamine-*O*-sulphonic acid was employed as the aminating reagent in a direct electrophilic amination of benzotriazole **2**

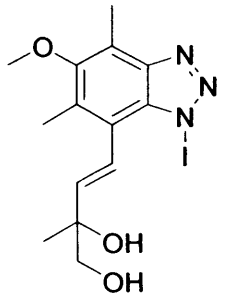
(Scheme 2, Chapter 1). To avoid formation of the unwanted by-product, 2-aminobenzotriazole **10**, Little modified the condition and achieved a moderate yield of 69% (Section 1.1.1).

To follow Little's established amination method, we planned a one-pot procedure of amination and benzyne cyclisation towards iodo-chroman **44**. This is due to the even higher polarity of the desired amination product, the amino diol **258** than its precursor, making it more water soluble and therefore difficult to isolate by a normal work-up. If successful, the direct amination and the concomitant benzyne cyclisation triggered by *N*-iodosuccinimide (NIS) would afford our final product in only a single step (Scheme 87).



Scheme 87

Hydroxylamine-*O*-sulphonic acid[1a,2] (HOSA) (5 eq.) was added to a solution of *NH*-benzotriazole **161** and KOH (10 eq.) in dimethylformamide (DMF) containing water (5%). The resulting solution was stirred for a further 10 minutes before being placed in a water bath at 45-50°C. This was to ensure the reaction temperature remained below 50°C and prevent the formation of the 2-isomer. After 30 minutes, the DMF was removed by rotary evaporation and high vacuum. The residue was treated with dichloromethane and stirred vigorously before NIS was added. The resulting solution turned a pink colour and stirring was continued for 2 hours. The crude product was obtained after a normal aqueous work-up. Unfortunately, ^{1}H NMR analysis presented an unrecognisable set of resonances which showed no sign of the cyclised iodo-chroman **44**. Further analysis by mass spectrometry showed a base peak of m/z 404. We thus deduced that the iodo-diol **263** (m.w. 403) could have been formed.



263

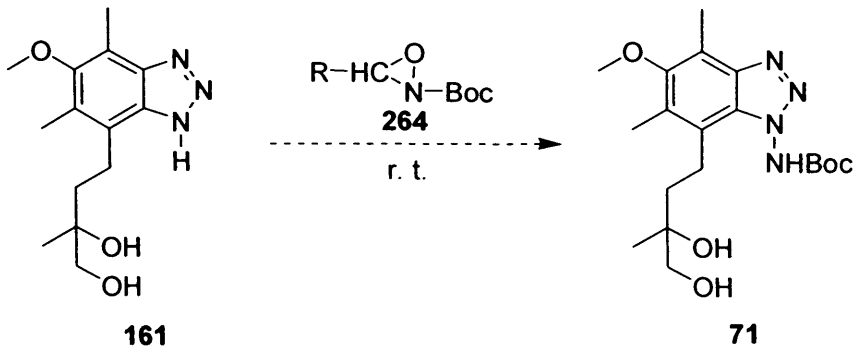
If the above by-product did form, the *N*-amination must have failed and the NH group of the starting material was iodinated by NIS. Formation of the double bond on the side chain could also be caused by NIS, due to its oxidative property. We thus avoided the aqueous condition by carrying out the amination without water. But the same result was obtained, even with a prolonged reaction time.

Since our attempts at direct amination were unsuccessful, probably because of the steric hindrance from the side chain, or the rather polar nature of the desired product, our following work was to develop an alternative aminating procedure.

2.8.2 Using oxaziridine

2.8.2.1 A brief review of oxaziridines

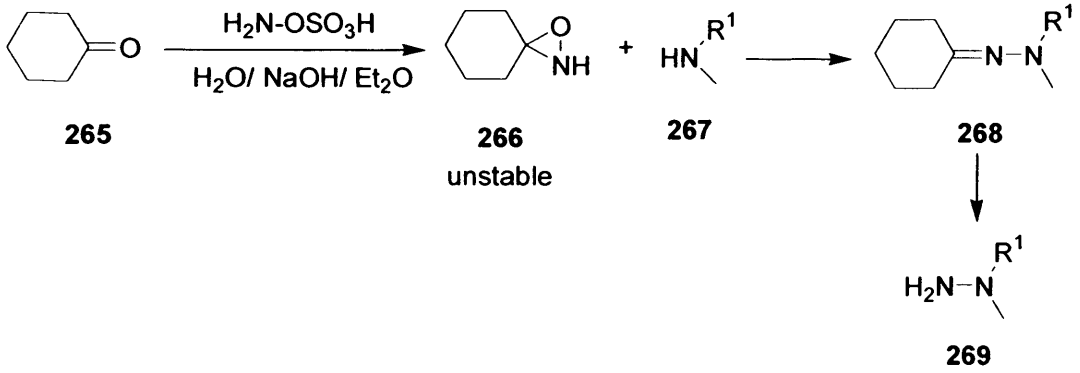
Oxaziridines have the ability to readily deliver their *N*-alkoxycarbonyl amino (such as *N*-Boc) fragment to amines to give, under mild conditions, their amination products in *N*-protected form.[53] Presumably, utilising this method on our compound could afford a stable *NH*-Boc protected amine **71** (Scheme 88). If successful, we could then follow Little's one-pot procedure of Boc-deprotection (to give amino-diol **258** *in situ*) and subsequent benzyne cyclisation, to achieve our final product chroman **44**.



161 71

Scheme 88

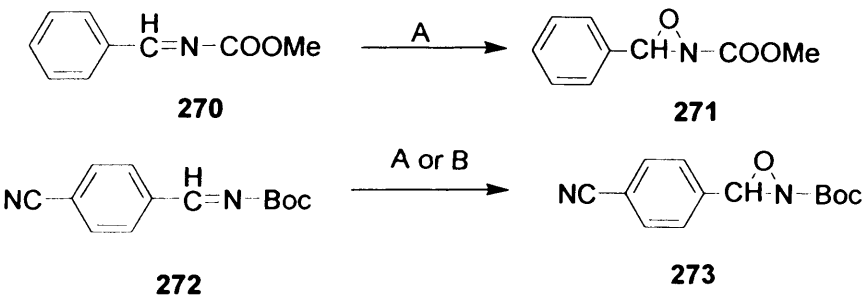
The amination of nucleophiles by oxaziridines such as **266**, derived from dialkylketones **265**, was first reported by Schmitz and coworkers in 1964 (Scheme 89).[54]



265 266 unstable 267 268 269

Scheme 89

Owing to their instability, Schmitz oxaziridines are prepared *in situ* in dilute diethyl ether solutions and this circumstance somewhat restricts their utilization in organic synthesis. Three decades later, Vidal[55] focused on the design of oxaziridines stable enough to be isolated and which can deliver an *N*-protected group, rather than a free amino group. This objective was met by means of the 3-aryl-*N*-alkyloxycarbonyl oxaziridines **271** and **273** (Scheme 90).

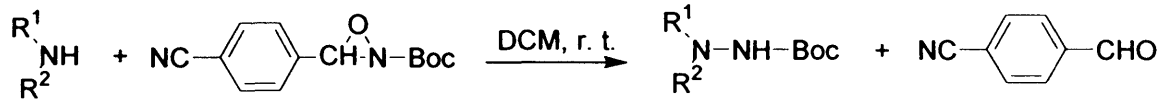


270 271 272 273

A. oxone, K_2CO_3, H_2O/ $CHCl_3$, 0-4°C;
B. BuLi, MCPBA, hexane/ DCM, -78°C

Scheme 90

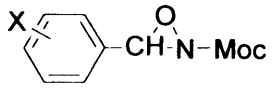
These reagents are crystalline solids, which transfer their *N*-methoxycarbonyl (*N*-Moc) and *N-tert*-butoxycarbonyl (*N*-Boc) fragments respectively, under mild conditions, to nucleophiles such as primary and secondary amines (Scheme 91). Meanwhile, aminations of amino acids, enolates, sulfides and phosphines by this methodology were also shown to be possible.



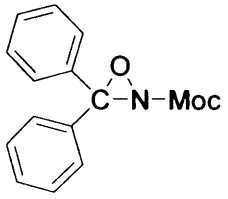
274 **274** **275** **276**

Scheme 91

Vidal[53] then extended the investigations to include a number of new 3-aryl-*N*-protected oxaziridines, including the *N*-Moc derivatives **277 (a-h)** and **278** and their *N*-Boc analogues **279 (a-d)**.

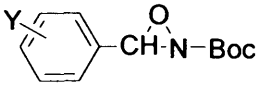


277



278

X = a: 4-CH_3; b: 4-F; c: 4-Cl; d: 4-CF_3; e: 4-CN; f: 2-Cl; g: 3-Cl; h: 2,4-di-Cl.



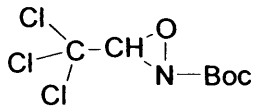
279

Y = a: 4-CN; b: 2,4-di-Cl; c: 3,4-di-Cl; d: 2,3,5-tri-Cl.

Scheme 92

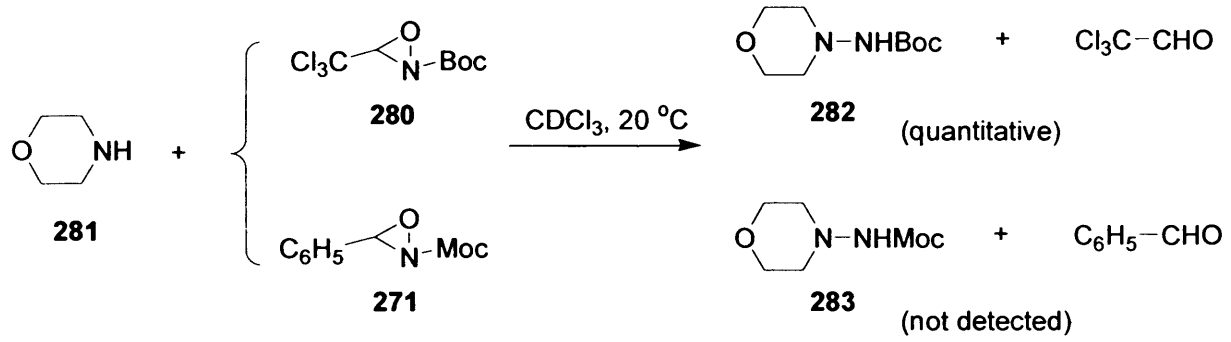
It was found that these new oxaziridines behave similarly to their analogues **271** and **273** shown in Scheme 90. The main difference between them was the rate of transfer of the N-CO_2R fragment. In reactions with secondary amines, the presence of electron-withdrawing substituents on the phenyl ring speeds up the amination reaction significantly. For example, the fastest amination is obtained using the 2,3,5-trichlorophenyl derivative **279(d)** in the Boc series. Due to this fact, Vidal continued to explore alternative structures of the same family that would also fulfil this reaction.[56]

The improvement was then made by an efficient synthesis of oxaziridine **280**, a congener of **271** and **273**, in which the 3-aryl group is replaced by a 3-trichloromethyl group.



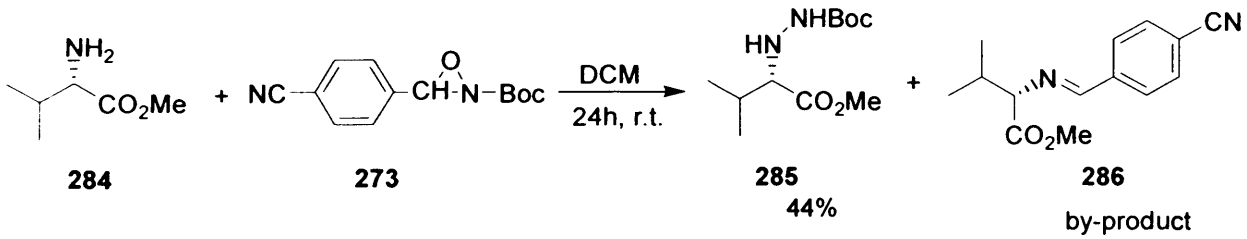
280

This new oxaziridine proved to deliver its N-Boc fragment to nucleophiles at a much faster rate than its substituted 3-aryl analogues. When morpholine **281** was reacted with a 1:1 mixture of oxaziridines **280** and **271** (0.5 mmol each), only hydrazine **282** and chloral were formed (Scheme 93).



Scheme 93

Although the amination properties of oxaziridine **280** were essentially the same as those of **273**, it was found in most cases the yields were slightly better when using oxaziridine **280**. A typical example was amino acid **284**, which reacts slowly with the 3-aryl oxaziridine **273** to give the N_{β}-Boc-hydrazine ester **285** in 44% yield,[53] the main side product being imine **286**, formed from the released 4-cyanobenzaldehyde and amino acid **284** (Scheme 94).



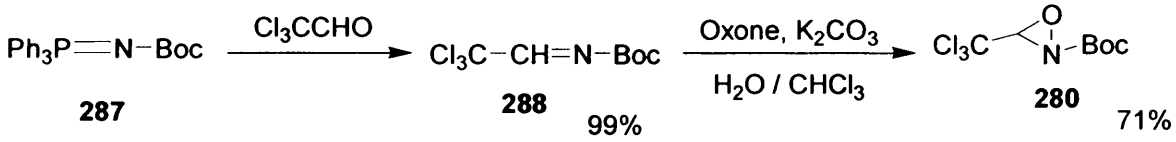
Scheme 94

The reaction of oxaziridine **280** with the amino acid **284** was much easier. The reaction was complete within 3 hours at 0 °C, giving hydrazine ester **285** in 56% yield. In this case, the amination was faster than the side-reaction with the released chloral.

2.8.2.2 Preparation of *t*-butyl 3-trichloromethyl-2-oxaziridinecarboxylate 280

Since an optimised oxaziridine has been developed by Vidal, we decided to follow his procedures for the synthesis of the oxaziridine **280**, hopefully for making our desired *NH*-Boc protected amine **71**.

The synthesis of oxaziridine **280** was achieved by oxone oxidation of imine **288**, which could be prepared from the aza-Wittig reaction of the *N*-Boc iminophosphorane **287** with chloral (Scheme 95).



287 **288** 99% **280** 71%

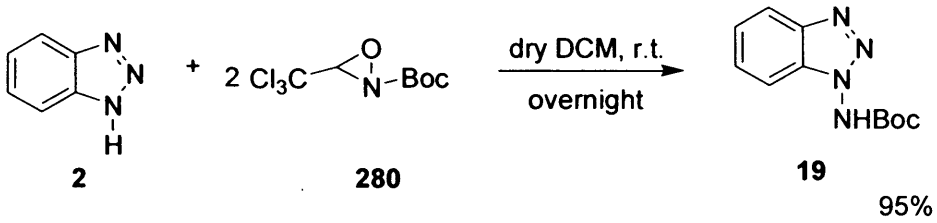
Scheme 95

A mixture of freshly distilled, anhydrous chloral and the iminophosphorane **287** in dry toluene was refluxed for 3 hours under nitrogen. After evaporation of the solvent, by-product Ph_3PO was precipitated by the addition of dry hexane and filtered off. After evaporation of the filtrate, the imine **288** was then obtained as a yellow oil in an excellent yield (99%).

The following oxone oxidation was carried out on the crude imine **288**. A solution of oxone in chilled water was added at 0°C to a vigorously stirred mixture of imine **288** in chloroform, potassium carbonate and water. The aqueous phase was discarded every hour and replaced by a freshly chilled K_2CO_3 -oxone solution until the oxidation of imine **288** was complete. A total of 8 such cycles was needed. This is due to the relatively fast decomposition of oxone in basic aqueous solutions.[57] The reaction was worked up by washing the organic phase with water, before drying and evaporating. The bath temperature of the evaporator was kept below 30°C. Column chromatography of the crude product using dichloromethane as the eluant gave oxaziridine **280** in 71% yield, as a foul-smelling, volatile oil which was stable, if stored in the dark below 0°C, for a number of months.

2.8.2.3 Amination of *NH*-Benzotriazole Using Oxaziridine 280

Before employing the oxaziridine **280** on our vitamin E precursor *NH*-benzotriazole **161**, it was felt necessary to explore suitable reaction conditions through a series of test reactions on a model compound – the commercially available benzotriazole **2**. Firstly, the reaction was undertaken with slight excess of oxaziridine **280** (1.1 equivalents) in dry dichloromethane.

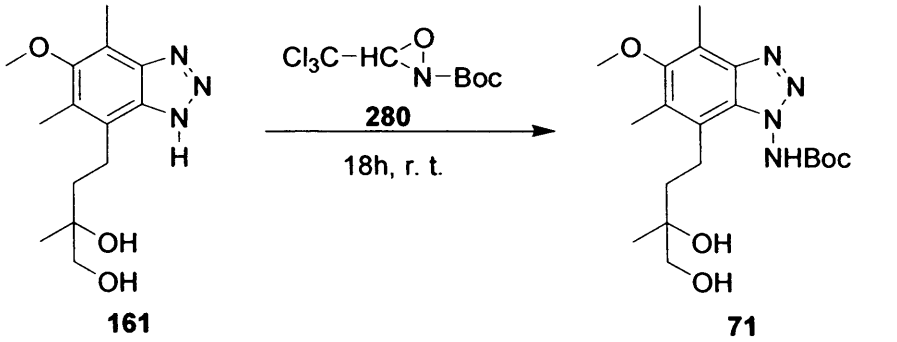


2 **280** **19** 95%

Scheme 96

After stirring the solution at ambient temperature overnight, it successfully delivered the *NH*-Boc benzotriazole **19** albeit in moderate yield (65%). We then tried to improve this yield by adding bases, in order to deprotonate the N-H group to form a more powerfully nucleophilic anion to attack the oxaziridine **280** or, alternatively, using a greater excess of the oxaziridine **280** without base. Thus, three trial reactions proceeded simultaneously: the first one was using triethylamine (1.5 eq.) with oxaziridine **280** (1.2 eq.), the second with a catalytic amount of *N, N*-dimethylaminopyridine (DMAP) and the last one adding two equivalents of the oxaziridine **280**. All of these used dry dichloromethane as the solvent. As a result, the first two conditions only gave us unrecognisable mixtures as the product, while the third one significantly improved the amination to an excellent 95% yield.

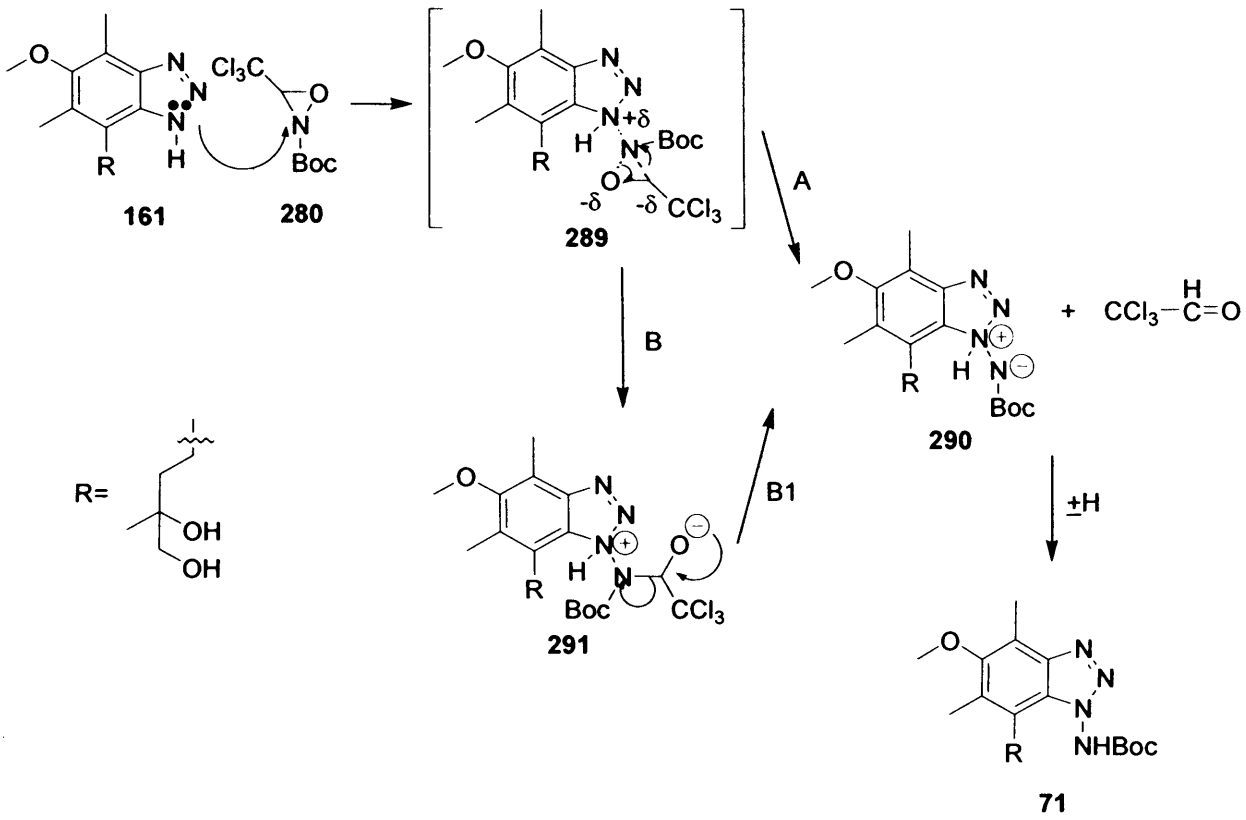
Thus encouraged, these optimised conditions were applied to the key *NH*-benzotriazole **161** (Scheme 97).



Scheme 97

The same good result was obtained after stirring the solution of *NH*-benzotriazole **161** and oxaziridine **280** (2 eq.) in dry dichloromethane overnight. An analytical sample was isolated by column chromatography using a 5% solution of methanol in chloroform as the eluant. An excellent 94% yield was attained and the product was a yellow oil. ^{1}H NMR spectra showed a broad single resonance between 1.32-1.75 ppm. with the integration of 9 protons, which represents the Boc group. The line broadening of this peak could be due to slow rotation of the Boc group, which was caused by its enclosed side chain. ^{13}C NMR spectra showed a peak at 156.7 ppm.; a strong absorbance appeared at 1739 cm^{-1} in infrared spectra -both of these support the incorporation of the carbonyl group. High resolution mass spectra (HRMS) analysis found a molecular weight of 395.2295; the calculated mass $[M+H]^{+}$ is 395.2289.

Two mechanisms can be postulated to account for the course of this reaction (Scheme 98). Attack of the *NH*-benzotriazole **161** at the oxaziridine nitrogen leads to a symmetrical transition state **289**, with a negative charge developing both on the oxaziridine carbon and oxygen atoms. This transition state can fragment either in a concerted way (path A) to yield ylide **290**, followed by fast proton transfers to the *NH*-Boc-benzotriazole **71**, or *via* a betaine intermediate **291** (path B). This betaine can then fragment to the amination product (path B1).

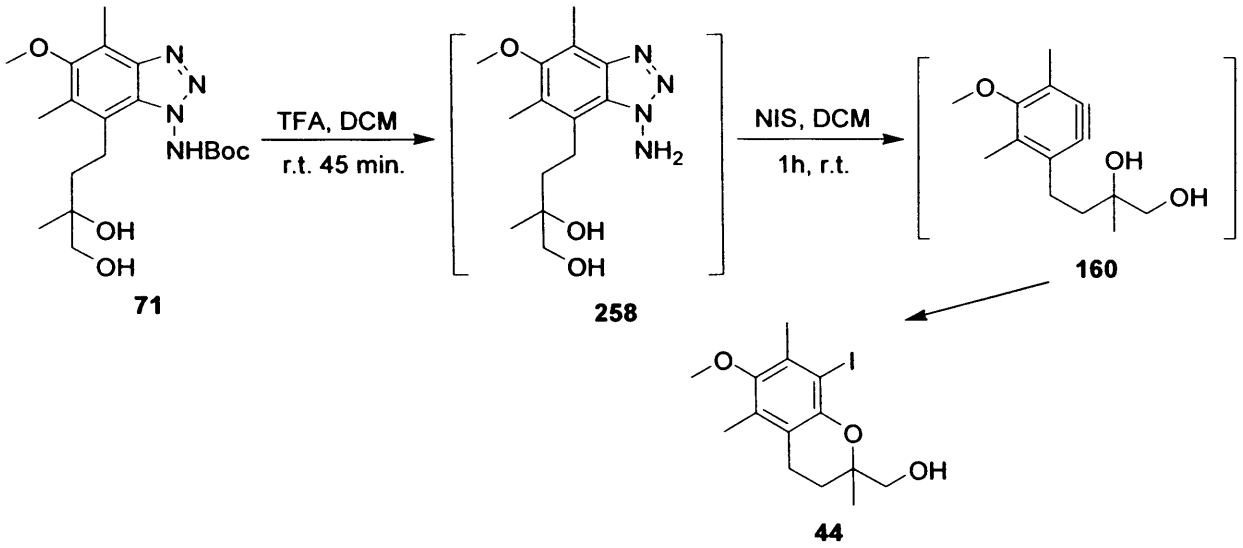


Scheme 98

2.9 Deprotection and Benzyne Cyclisation

Since *NH*-Boc-benzotriazole **71** has been synthesised efficiently, the last remaining transformations were a deprotection followed by benzyne formation. Utilizing the two-pot, sequential reaction protocol that Little had developed, the protected aminobenzotriazole **71** could be converted into the iodo-chroman **44** without isolating the actual cyclisation precursor **258** (Scheme 99).

Removal of the *tert*-butoxycarbonyl protecting group was achieved by reaction with a 20% solution of trifluoroacetic acid in dichloromethane. The reaction progress was followed by tlc analysis. After 45 minutes stirring at room temperature, the solvent was removed and the residue was put under high vacuum to remove residual trifluoroacetic acid (TFA).



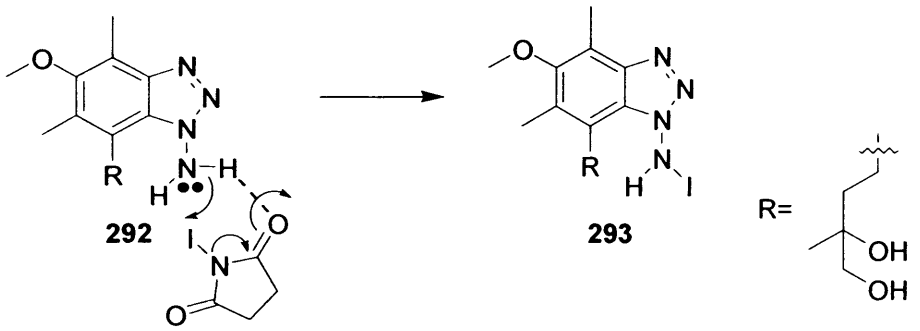
Scheme 99

The remaining product was treated with dichloromethane before basifying by the addition of 2M aqueous sodium hydroxide to liberate the free amine. The organic layer was then separated and salt was added to the aqueous layer, before extraction with further dichloromethane. This work-up procedure was a modification of Little's, owing to the higher polarity of the desired amino-diol **258** relative to Little's amine **26** (section 1.1.5, Chapter 1). The solution was then dried, filtered and concentrated before *N*-iodosuccinimide (NIS) was added. The resulting solution turned to deep purple, indicating that iodine was being produced. The reaction was stirred for 1 hour before a simple work up. Flash column chromatography isolated the racemic iodo-chroman **44** as a yellow gum in a poor yield of 14%. Mass spectrometric analysis showed a peak at m/z 345, which corresponded to [M^+ - OH]. ^{13}C NMR analysis showed the aromatic carbon C-I at the right position 90.0 ppm.; the resonances due to the CH_2 and CH_3 groups on ^1H NMR spectra has also changed dramatically. Thereby, we had the confidence that the benzyne cyclisation was successful and had formed the desired chroman **44**.

The problem of this low yield could reside in the small reaction scale (< 100 mg) as well as the highly polar nature of the amino-diol **258**, which was soluble in the aqueous NaOH during the deprotection work up. Thus, the aqueous basifying conditions were avoided by

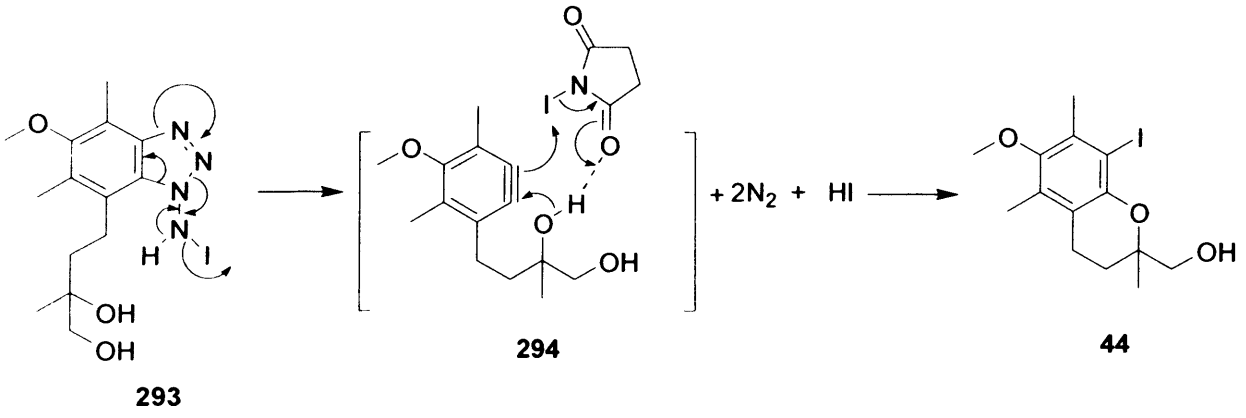
adding solid potassium carbonate, after which the solid was filtered off and washed with warm dichloromethane. The overall yield was then measured at 21% from *NH*-benzotriazole **161** to iodo-chroman **44**, which was a slight increase from the 14% obtained from the first one-pot deprotection-cyclisation step.

At present, a detailed mechanistic rationale is not clear; the generation of benzyne perhaps begins with iodination of the amine **258**. This could be depicted as proceeding *via* a hydrogen-bonded species **292** to form the iodo-amine **293** (Scheme 100).



Scheme 100

Decomposition of this iodo-amine intermediate **293** gives benzyne **160** and two moles of nitrogen gas (Scheme 101). Then perhaps a similar hydrogen-bonded association between the reactants, as depicted in formula **294**, plays a key role in activating the key nucleophilic attack: the subsequent trapping by iodine and also proton transfer to succinimide in a concerted but non-synchronous manner as indicated could occur.[31]



Scheme 101

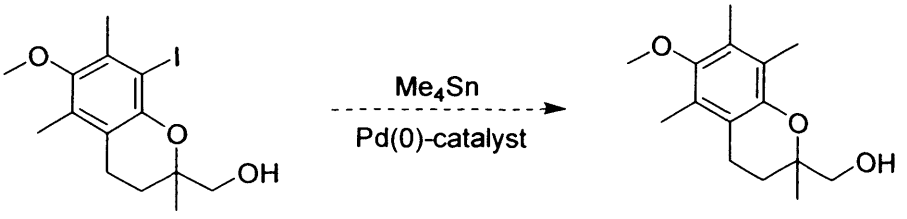
The ^{1}H NMR spectrum of the iodo-chroman **44** showed a different pattern compared to its precursor *NH*-Boc-benzotriazole **71**. One of the major changes is in the 3-CH_2 group: one of its protons shows a double, double, doublet (ddd) at 1.67 ppm, and the other one shows a multiplet (1.80-1.90 ppm) resonance. Another multiplet was also observed at 2.59-2.74 ppm representing the 4-CH_2. Comparing to the literature's data[39] for the analogous chroman diol **201** (Chapter 1, section 1.5), we now had more confidence of the structure of our cyclised compound. For the chroman **201** that Tietze had made, the 3-CH_2 appeared at 1.73-1.85 and 1.98-2.15 ppm as two multiplets, and the 4-CH_2 also appeared as multiplets, at a similar shift to ours (2.56-2.60 ppm). As for the other groups, there are four methyls on the chroman diol **201** which correspond to our iodo-chroman **44** and they also have very similar chemical shifts indeed. The two methyls on the benzene ring for the former resonate at 2.10 and 2.23 ppm, and for the later at 2.08 and 2.35 ppm; the methyl groups on the chroman ring for the two compounds resonate at 1.24 and 1.21 ppm respectively. HRMS showed $[M+NH_4]^+$ of 380.0714; the corresponding calculated mass is 380.0717.

The iodine atom brings to the chroman **44** an important potential utility on biochemistry. Replacing this iodine with isotope I^{125} or I^{131} would give radioactive labelled vitamin E derivatives. This modification could possibly be used for detection, such as for localization and imaging studies, and molecular structure and function studies of vitamin E in human and animal cells.

2.10 Methylation of Iodo-Chroman 44

As the iodo-chroman **44** has been synthesised successfully, the feasibility of our benzyne methodology as a viable approach towards the vitamin E precursor had nearly been proven. The incorporated iodine atom offered possibilities for further elaboration of the cyclised product. Our iodide was expected to show enhanced reactivities and hence represent even more attractive intermediates. Some of these possibilities such as Stille coupling, Sonogashira coupling and Heck reactions were illustrated by previous PhD students in our group[31] and it may even be possible to effect halogen-metal exchange and also useful radical trapping reactions.

In our case of synthesising the vitamin E precursor, a methylation on the iodide was undertaken to effectively complete the total synthesis of this highly important natural product. It was felt that the palladium-catalysed Stille cross-coupling with tetramethyltin and base could generate our desired final compound **1** (Scheme 102).



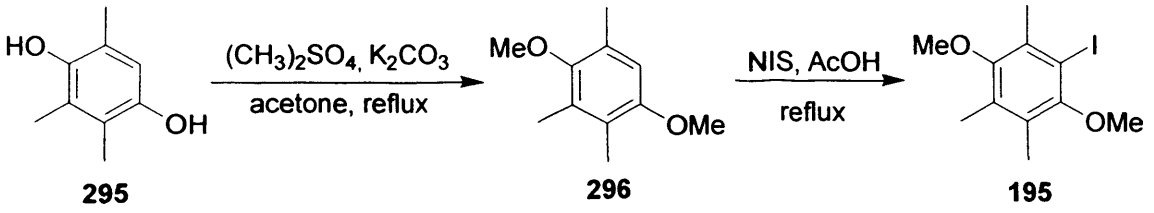
44 **1**

Scheme 102

2.10.1 Synthesis of model compound- iodo dimethoxy benzene 195

Before utilising the cross-coupling on the iodo- chroman **44**, it was felt necessary to find the best conditions by a series of test reactions on an accessible model compound. Thus we planned to synthesise an analogue of the chroman **44**, the dimethoxy-iodo benzene **195** (Scheme 103). We assumed that it would provide a very similar environment to the central iodo-chroman **44**, as it also contained two electron donating oxygen atoms, as well as the iodine, at the corresponding positions on the benzene ring.

Starting with the commercially available phenol **295**, the dimethoxybenzene **296** was obtained by *bis*-*o*-methylation on oxygen[58] using dimethyl sulphate and anhydrous potassium carbonate in dry acetone (Scheme 103).



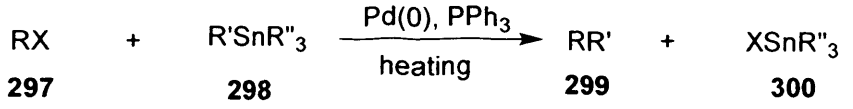
295 **296** **195**

Scheme 103

The reaction was stirred overnight under reflux, before an aqueous work-up with 2M potassium hydroxide and ammonia. Dimethoxybenzene **296** was obtained as a colourless solid in a good 94% yield. ^{1}H NMR data suggested that the crude product was pure enough for the next step. Iodination employed the same procedure as had been used to prepare the iodine **164**, utilising *N*-iodosuccinimide in acetic acid. The crude product was recrystallised from a mixture of 1: 1 diethyl ether/hexane and the iodo-dimethoxybenzene **195** was obtained in a moderate 40 % yield.

2.10.2 Stille cross-coupling reaction

Once we had produced enough of the model compound, we tried our hand at the Stille reaction. The palladium-catalyzed coupling of unsaturated halides or sulfonates with organostannanes is commonly referred to as the Stille reaction (Scheme 104).[59]

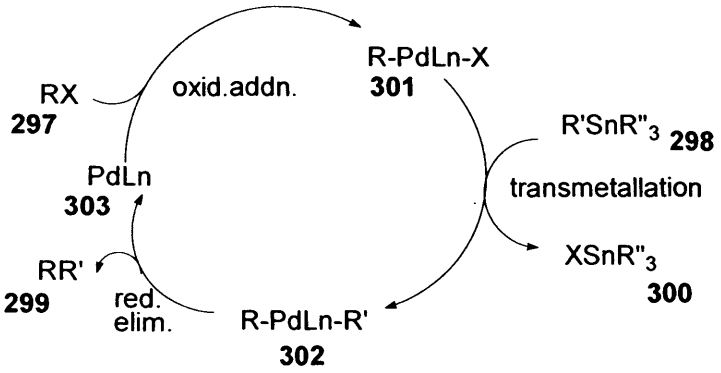


297 **298** **299** **300**

R, R'= aryl, vinyl, allyl X = Br, I, OTf

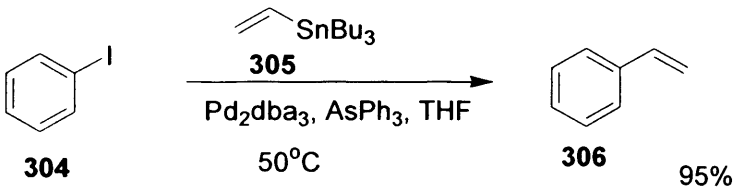
Scheme 104

The currently accepted mechanism for the Stille coupling involves three basic steps, which are oxidative addition, transmetallation and reductive elimination, as shown in Scheme 105. Some evidence suggests that the transmetallation is the rate-determining step in most couplings of synthetic interest,[59,60] and yet little is known about the mechanism of this step.



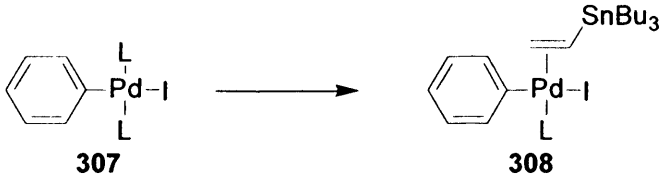
Scheme 105

In 1991, which was five years after the reaction was discovered by Stille,[61] Farina[59] and co-workers reported an improvement over the typical Stille conditions. Large rate enhancements, typically 10^2-10^3 over triphenylphosphine-based catalysts, were observed when tri-2-furylphosphine (TFP) and triphenylarsine ($AsPh_3$) were used as the palladium ligands. According to his study on the coupling between iodobenzene **304** and vinyltributyltin **305** (Scheme 106) in the presence of 17 ligands, Farina found that $AsPh_3$ provided the highest yield (95%) and the reaction went 1100 times faster than when using PPh_3 as the ligand.



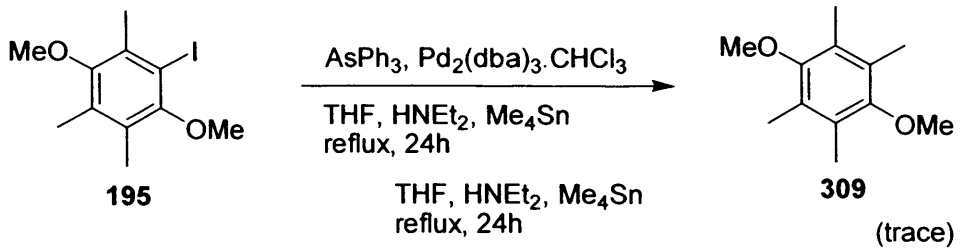
Scheme 106

This was probably because the bond between Pd(II) and $AsPh_3$ is weaker than the one between Pd(II) and PPh_3, which makes the ligand dissociate from the complex **307** much more readily, allowing formation of the key transmetalation intermediate, in this case, a π-complex between the Pd(II) and the olefinic stannane **308** (Scheme 107).[59]



Scheme 107

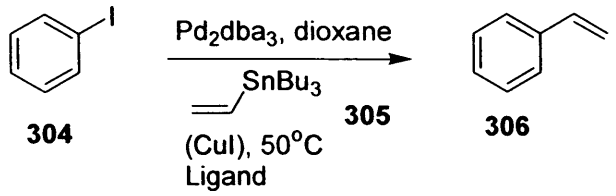
Thus, we decided to utilise Farina's procedure for the coupling between our model compound dimethoxy benzene **195** and tetramethyltin (Scheme 108).



Scheme 108

Using *tris*(dibenzylidene-acetone)dipalladium(0)·chloroform ($Pd_2dba_3 \cdot CHCl_3$) as the palladium source and triphenylarsine ($AsPh_3$) as the ligand, the reaction mixture was refluxed with tetramethyltin (Me_4Sn) in tetrahydrofuran for 24 hours. Unfortunately, only traces of the product **309** were formed according to analysis of the ^1H NMR spectra. The reaction was then repeated but using a highly dipolar solvent, *N*-methylpyrrolidinone (NMP) and the reaction temperature was also increased from ~80 to 100 °C. But the result was still poor; a 30% conversion was observed according to the ^1H NMR data. Due to the similar polarity of the methylated product and the starting material, separation by column chromatography proved to be difficult. It seems to us that in our case, $AsPh_3$ does not work as efficiently as in Farina's reaction shown in Scheme 106. Presumably this was due to the fact that our transmetalation step with Me_4Sn follows a different pathway from Scheme 107, in which the π-complex intermediate **308** was formed by ligand dissociation. The weak bond between $AsPh_3$ and Pd(II), in our reaction, could have provided insufficient stabilization for the Pd(0) intermediate, leading to catalyst decomposition with precipitation of metallic Pd.[59]

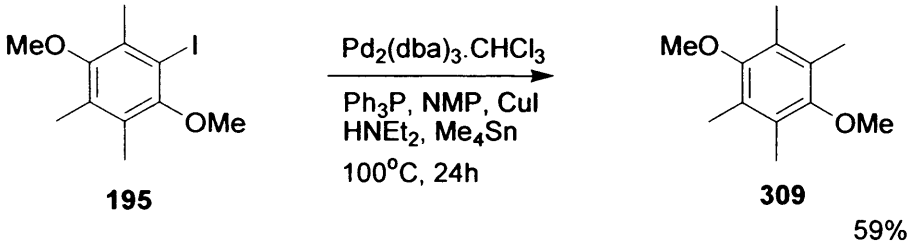
With regard to the reason above, we decided to replace the $AsPh_3$ ligand with the traditional PPh_3, which binds tighter to palladium[59] and therefore better stabilizes the Pd(0) species. A more recent report by Farina[62] shows that with PPh_3 as ligand, co-catalytic Cu(I) salts can give a >100-fold rate increase over the traditional Stille conditions. In the report, Farina examined the coupling between iodobenzene **304** and vinyltributyltin **305**, both in the presence and in the absence of copper(I) salts (Scheme 109).



Scheme 109

After exploring different ratios of Pd to PPh_3, and Cu to Pd, Farina found that it is the ratio between Cu and PPh_3 that affects the rates most. The best result was obtained with a ratio of 1:4:2 (Pd:L:Cu); the reaction rate was enhanced by ~120 times, compared to when CuI is absent, but the ratio of palladium to ligand remains the same.

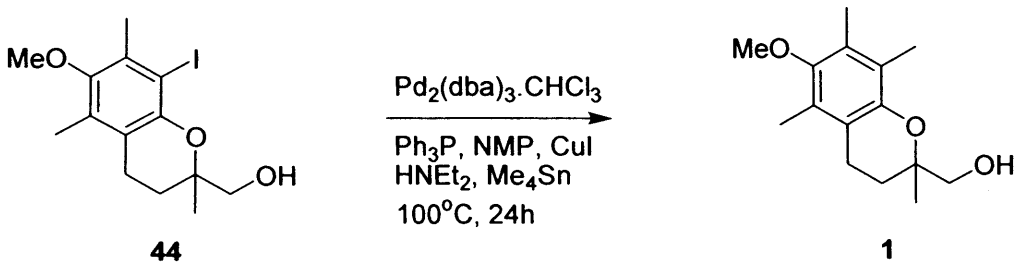
We were delighted to find that when applying the above procedure to our model reaction, dimethoxybenzene **309** was successfully generated from its iodo precursor **195** (Scheme 110).



Scheme 110

Iodobenzene **195** was dissolved in dry, degassed NMP before being treated with PPh_3, $Pd_2(dba)_3.CHCl_3$ and CuI (in the ratio of 1:4:2). The solution was degassed by being stirred at room temperature for 20 minutes under a flow of nitrogen; diethylamine and Me_4Sn were then added. The reaction mixture was heated at 100°C for 24 hours before being quenched by 10% aqueous sodium sulphite. The suspension was washed with 10% aqueous potassium fluoride before being extracted with diethyl ether. The crude product was purified by column chromatography and the symmetrical tetramethyl benzene **309** was obtained as a colourless solid in a reasonable yield (59%). None of the starting iodide **195** was observed; presumably it had all been reacted during the reaction.

Therefore we utilised the method on our key iodide chroman **44**, but it did not deliver the same result (Scheme 111).



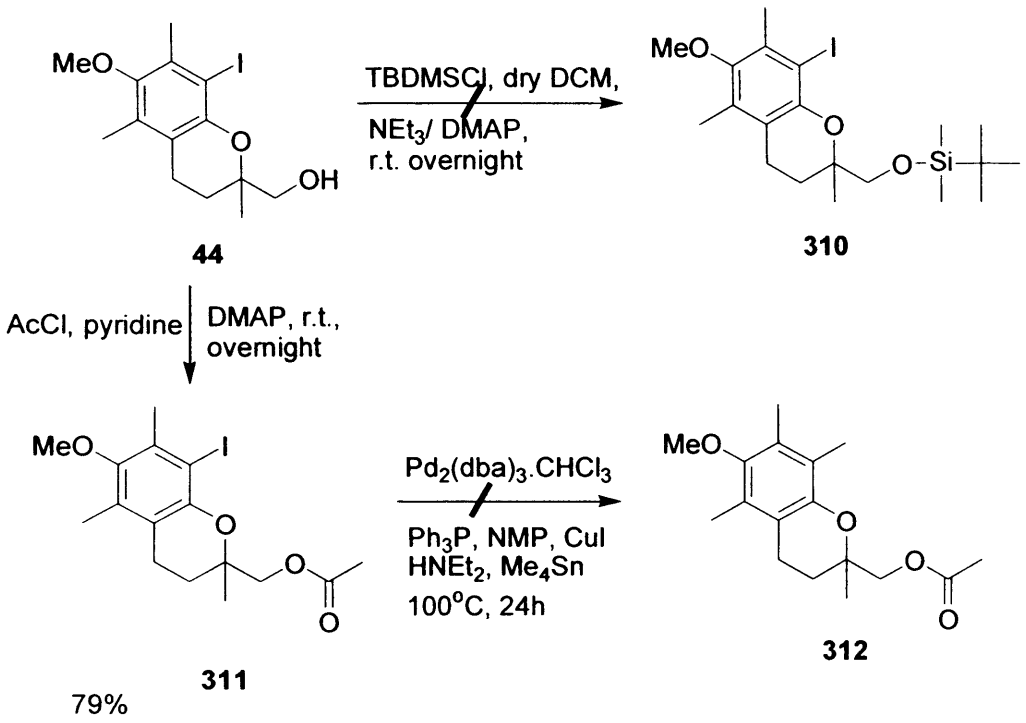
44 **1**

Scheme 111

After repeating the procedure above as shown in Scheme 110 and purifying the crude product by column chromatography, a mixture of the desired product **1** and the starting material was obtained in a ratio of 1:3, according to analysis of the ^{1}H NMR spectra. Mass spectra (APcI) showed the peak of 250, which represents the methylated product **1**.

It was felt that the nucleophilic free hydroxide group could have destroyed the catalytic cycle and thus stopped the reaction from going to completion. To prove this idea, the reaction on the model compound, iodobenzene **195** (Scheme 110) was repeated with one equivalent of butanol, to check if the same yield can be achieved. As a result, the conversion was not complete after the same reaction time. The ^{1}H NMR spectrum showed a 1:1 mixture of the starting material and the desired product, after column chromatography. Thus, it seems that the free OH group does affect the Stille reaction; we therefore decided to protect the alcohol before proceeding with the coupling. *tert*-Butyldimethylsilyl was our first choice as the protecting group as it should be easy both to put on and take off (Scheme 112).

To a solution of iodo-chroman **44** in dry dichloromethane at ambient temperature was added *tert*-butyldimethylsilyl chloride (TBDMSCl) and triethylamine. The reaction mixture was stirred at this temperature overnight. T.l.c. showed that no reaction had occurred. Then a more powerful base, 4-dimethylaminopyridine (DMAP), was added to the mixture, the reaction was stirred for further 24 hours; unfortunately, the product had still not formed and the starting material was recovered.



Scheme 112

Presumably a higher temperature is needed for the substitution to occur. But heating the reaction would have risked the destruction of the iodide; therefore we turned to protecting the alcohol with an acetyl group, which should proceed smoothly under mild conditions.

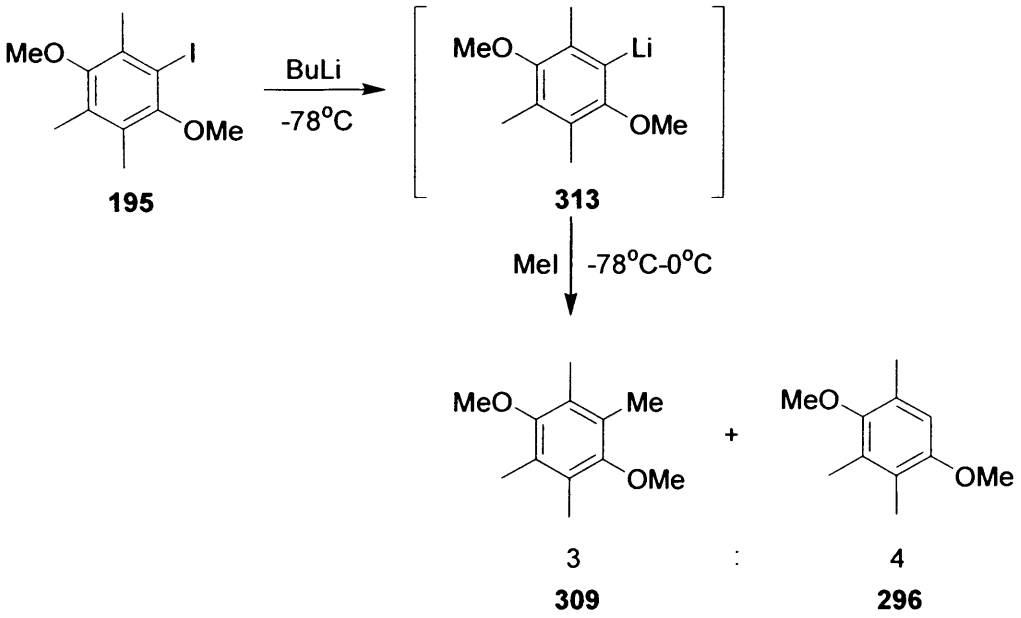
The iodo-chroman **44** was stirred with acetic anhydride and pyridine overnight at ambient temperature; the reaction occurred but did not go to completion, a mixture of product and starting material (3:2) being obtained. Changing the conditions by using acetyl chloride and a catalytic amount of DMAP, the desired acetyl chroman **311** was finally achieved in good yield (79%), after column chromatography. The $-OCH_2-$ group appeared as a pair of double doublets in the ^1H NMR spectrum, while before protection, the signal overlapped with the methoxy group and appeared as a multiplet.

Now, applying the well-developed Stille reaction procedure on the acetyl chroman **311**, it was disappointing to find that none of the desired product was formed (Scheme 112).

Due to the result above, we decided to return to our original method, in Scheme 111, but with 3 times the amount of the reagents and catalysts, including PPh_3, $Pd_2(dba)_3{\cdot}CHCl_3$, CuI, $HNEt_2$ and $SnMe_4$. Unfortunately, the reaction was not an improvement and delivered the same result of the partial conversion (25%).

2.10.3 Attempted methylation using methyl iodide by halogen-lithium exchange

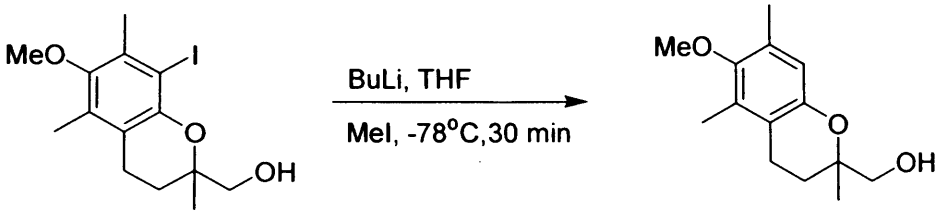
As the Stille reaction failed to give us a satisfactory result, we planned another procedure, using halogen-lithium exchange by *n*-butyllithium, followed by the addition of methyl iodide at low temperature, with the aim of delivering a better result. Again, a test reaction was performed first (Scheme 113).



Scheme 113

A solution of the iodobenzene **195** in dry tetrahydrofuran was cooled to -78°C before *n*-butyllithium (1.0 eq.) was added. After 15 minutes of stirring at this temperature, methyl iodide (1.5 eq.) was added. The solution was then gradually warmed to 0°C and stirred at this temperature for a further 5 hours. The reaction was quenched by addition of aqueous ammonium chloride, and the suspension was then extracted with diethyl ether. As a result, a 3:4 mixture of the desired product **309** and 1H-trimethylbenzene **296** was obtained according to ^1H NMR spectrum of the crude product. Presumably, the aryl anion **313** reacted with a

small amount of water, which was present, quicker than with the reagent itself. Since the desired product **309** has been formed by this method, we decided to apply it on our key iodo-chroman **44**, using more equivalents of the methyl iodide and butyllithium thereby trying to avoid the unwanted reaction (Scheme 114).



44 **314**

Scheme 114

After 7 equivalents of methyl iodide was added to a solution of iodo-chroman **44**, to which 2.5 equivalents of butyllithium had been added at -78°C, the solution was stirred for a further 30 minutes at this temperature. The reaction was then quenched by saturated aqueous ammonium chloride before being extracted by dichloromethane. Unfortunately, 8-H chroman **314** was the only product formed; the reaction was then repeated with distilled methyl iodide, but gave the same result.

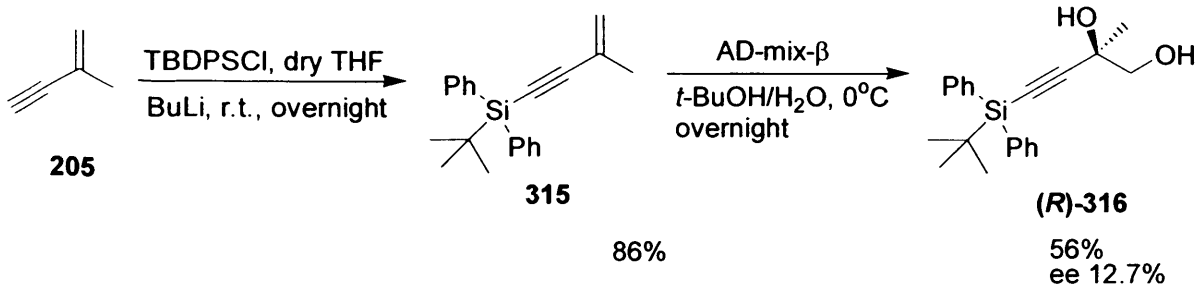
After all the above efforts were made, the best result came from the Stille reaction with a 25% conversion to the product. Time constraints and running out of material meant that we had to leave this subject and carry out the synthesis of the enantiomerically enriched side chain, the acetylene diol **69**.

2.11 Synthesis of Enantiomerically Enriched Diol 69

2.11.1 From the silylated enyne 315 by AD-mix reaction

Since the racemic form of the iodo-chroman **44** has been synthesised successfully, we turned our attention to making the enantiomerically enriched side chain diol **69**. If successful, we could use our methodology, in the synthesis of enantiomerically pure vitamin E. Our initial AD-mix reaction on the butenyne **205** (Scheme 64, section 2.3, p 52) delivered the diol **69** with a poor ee; probably this was because the small and flat olefin failed to align with the

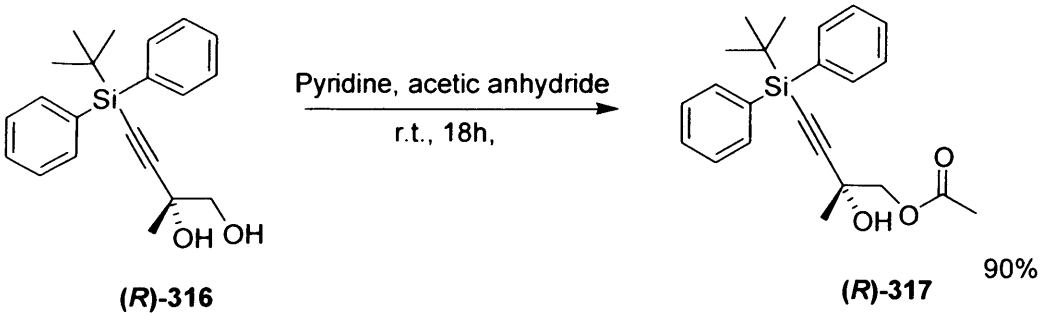
osmium-ligand complex in the desired manner, and therefore did not give enantioselectivity during the hydroxylation. We therefore decided to enlarge the molecule by putting a bulky protecting group- a *tert*-butyldiphenylsilyl (TBDPS)-onto the terminal alkyne. Again, the readily accessible AD-mix-β would be applied. As the C≡C–(TBDPS) group is much larger than the methyl group, presumably the reaction would form the silyl diol ***(R)*-316**. The selectivity of the reaction would also be tested, although the ***(S)*** enantiomer is actually needed for the final natural product (Scheme 115).



Scheme 115

To synthesise the silyl butenyne **315**, butyllithium was added dropwise to a solution of the butenyne **205** in dry tetrahydrofuran at 0°C. The solution was then added to *tert*-butylchlorodiphenylsilane (TBDPSCl) dropwise, before stirring at this temperature for 2 hours. A standard aqueous work-up gave the crude silyl butenyne **315** as a light yellow gum, which was suitable for the next step without further purification. Asymmetric *bis*-hydroxylation using the AD-mix-β reagent under the standard reaction conditions[63] afforded the silyl diol **(*R*)-316** in 56% yield.

The silyl diol **(*R*)-316** was then protected as its ester analogue to reduce the polarity. Again, this was for the purpose of a clear separation on chiral HPLC (Scheme 116).



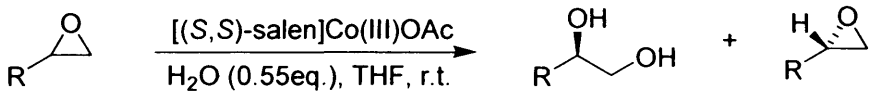
Scheme 116

The silyl diol **(*R*)-316** was treated with pyridine and acetic anhydride at room temperature. The solution was stirred overnight before a simple work up with aqueous copper sulphate. The crude product was purified by chromatography and the acetate **(*R*)-317** was obtained as a colourless oil in 90% yield.

Analysis of the enantiomeric excess by chiral HPLC on the acetate **(*R*)-317** showed a slightly improved ee. of 12.7% (column: OD; inj. vol: 10μ; flow: 0.8ml/min, solvent: 0.7% IPA/Hexane; λmax: 254nm; 25.8 min.), but this result was still far from our expectation and requirement. We realised that the problem could reside in the terminal alkene, which is also known to be disadvantageous, apart from the triple bond, towards the AD-mix reactions.[63] Therefore, we began to search for another asymmetric methodology which would be more suitable for the synthesis of our diol **(*R*)-69**.

2.11.2 By hydrolytic kinetic resolution (HKR) of terminal epoxide

Recently, there has been great interest in the applications of the hydrolytic kinetic resolution (HKR) of terminal epoxides using Jacobsen's salen Co(III)OAc catalysts.[64] This method is based on the enantioselective ring opening of a racemic terminal epoxide **318** by water, or other simple nucleophiles, in the presence of the chiral metal-ligand catalyst. This process provides direct access to both 1,2-diols **319** and the unreacted epoxide **320** in high enantiomeric excesses (ee) and chemical yields (Scheme 117).



318 **319** **320**

Scheme 117

It seemed that this could resolve our problem of making the diol **69** in a high ee, as long as the 1-alkene silane **315** could be oxidised to an epoxide; we could then employ the above method to achieve the mixture of our desired diol **(*R*)-69** and its epoxide counterpart, which should be readily separated by column chromatography.

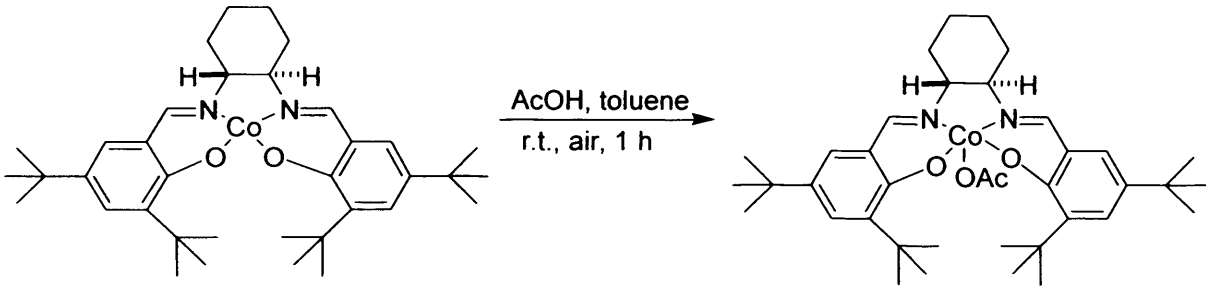
Epoxidation[65] of the silane **315** proceeded smoothly without affecting the triple bond and gave the epoxide **321** in good yield (95%) (Scheme 118). The reaction was carried out by adding *meta*-chloroperoxybenzoic acid (*m*-CPBA) to a stirred solution of the silane **315** in dichloromethane. The resulting suspension was stirred for 2 hours at room temperature before saturated aqueous sodium bicarbonate was added.

315 **321** 95%

Scheme 118

The resulting mixture was extracted with ether. The pure epoxide **321** was obtained as a yellow oil after purification of the crude product by chromatography.

Now there was only one thing left before we could carry out the HKR reaction- preparing the salen Co(III)OAc catalyst **323** (Scheme 119).



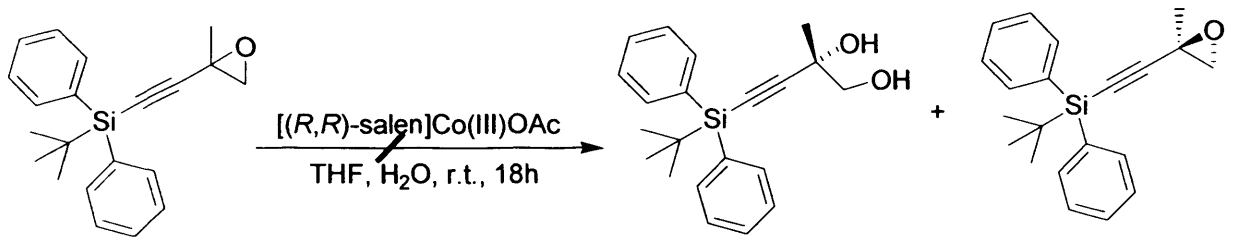
322 [(*R*,*R*)-Salen]Co(III)OAc

323

Scheme 119

Having obtained complex **322** from co-workers in our department, the orange solid was stirred, open to the air, with two equivalents of acetic acid in toluene.[64] The reaction progress was followed by tlc. After stirring for 1 hour at room temperature, the solution was evaporated and the brown residue was dried under vacuum. The pure activated catalyst [(*R*,*R*)-salen]Co(III)OAc **323** was then obtained.

We then tried our hand at this HKR reaction on our epoxide **321** (Scheme 120).[66]



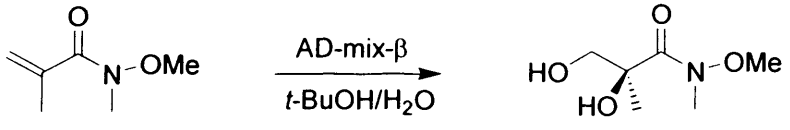
321 **(*S*)-316** **(*R*)-321**

Scheme 120

The epoxide **321** in dry THF was stirred at room temperature in the presence of the [(*R,R*)-salen]Co(III)OAc catalyst **323** (1.0 mol%) and H_2O (0.4 eq.). The solution was stirred overnight before the solvent was removed. The residue was purified by chromatography. Unfortunately, only a trace of the desired diol **(*S*)-316** was found according ^1H NMR analysis and the unreacted epoxide **321** was recovered. This suggested that this methodology might not be suitable for epoxides that contain tertiary carbon: no example of this kind of ring opening has been found in the literature.[64,66,67]

2.11.3 By asymmetric *bis*-hydroxylation (AD-mix) on *N*-Methoxy-*N*-methyl methacrylamide 324 and subsequent transformations

Since the attempts above failed to deliver the diol **(*R*)-69**, due to the disadvantages of the butenyne **205** because of its structure, the terminal double bond and the quaternary centre, as well as the triple bond. We had therefore to look for a brand new route to generate this chiral centre. After searching through the literature, we found that Alberto *et al.*[68] had reported the successful generation of (*S*)-propionamide **325** by an AD-mix reaction on the readily accessible methacrylamide **324** in a high ee (93%) (Scheme 121).

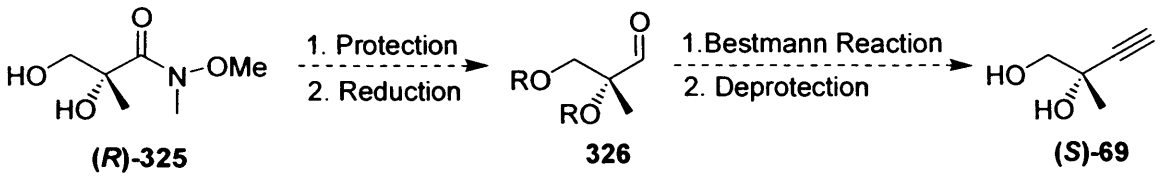


324 **(*S*)-325**

ee. 93%

Scheme 121

Considering that an aldehyde **326** could be generated from (***R***)-propionamide **325** in two simple steps, and a subsequent Wittig-type reaction[69] could deliver an acetylene, which should undergo a deprotection reaction to achieve diol (***S***)-**69** (Scheme 122), we decided to use this route.

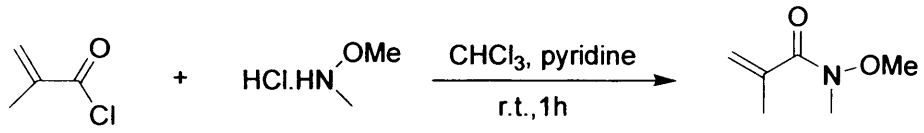


(*R*)-325 326 (*S*)-69

Scheme 122

2.11.3.1 Preparing methacrylamide 324

Therefore we started our new route by making the methacrylamide **324** on a large scale (Scheme 123).[70]



327 **328** **324** 99%

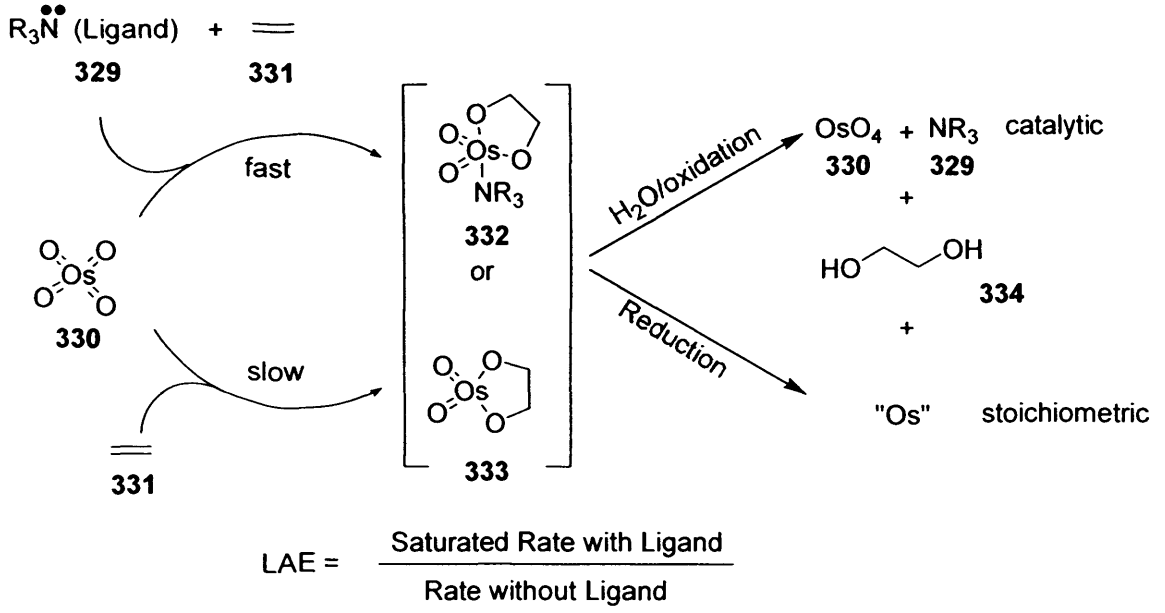
Scheme 123

A solution of methacryloyl chloride **327** and *N,O*-dimethylhydroxylamine hydrochloride **328** in chloroform was cooled to 0^0C before pyridine was added dropwise. The mixture was stirred at room temperature for one hour before the volatiles were evaporated. The residue was partitioned between brine and a 1:1 mixture of ether and dichloromethane. The separated organic layer was dried and evaporated carefully to afford the volatile amide **324**, which was then purified by chromatography. The pure product was then obtained as light yellow oil in an excellent 99% yield.

2.11.3.2 AD-mix reaction

Over the past few years, the osmium-catalysed asymmetric dihydroxylation reaction of substituted alkenes with the AD-mix-α and -β reagents has emerged as one of the most

powerful and practical methods for controlling relative and absolute stereochemistry, in secondary and tertiary alcohol derivatives.[71] The process of the AD reaction crucially depends on the ligand acceleration effect (LAE); this ensures that the reaction is funnelled through a pathway, which involves the chiral catalyst. The principle of ligand acceleration, for the AD reaction is illustrated below (Scheme 124).[63]

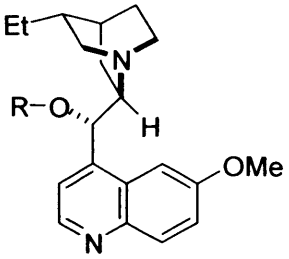


Scheme 124

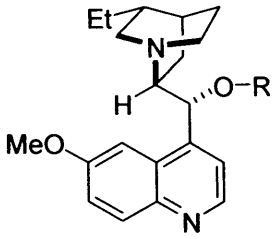
Employing relatively inexpensive reagents for the reoxidation of the osmium(VI) glycolate products **332** greatly enhances its synthetic utility; a great deal of work has been done on this subject.[63] In 1990, Minato[72] and co-workers demonstrated that potassium ferricyanide ($K_3Fe(CN)_6$) in the presence of K_2CO_3 provides a powerful system for the osmium-catalyzed dihydroxylation of olefins with the $K_3Fe(CN)_6$ acting as a reoxidant.

In an effort to induce enantioselectivity into the osmylation, chiral pyridine derivatives were introduced, but these ligands failed, due to their low affinity for OsO_4.[73] Consequently, quinuclidine derivatives, and cinchona alkaloids, **335** and **336** (R = Ac) (Scheme 125), were used instead of pyridines in later investigations, due to their intrinsically higher affinity for OsO_4.[63] Thereafter, the discovery of ligands with two independent cinchona alkaloid units (**335** or **336**), attached to a heterocyclic spacer, such as phthalazine **337**[74] or

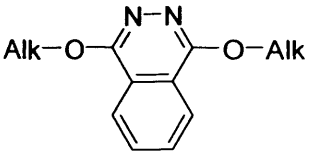
diphenylpyrimidine **338**[75] (Scheme 125), has led to a considerable increase in both the enantioselectivity and the scope of the reaction.[63]



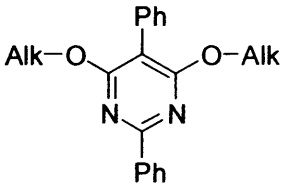
Dihydroquinidine (R=H)
DHQD
335



Dihydroquinine (R=H)
DHQ
336



Phthalazine (PHAL)
337

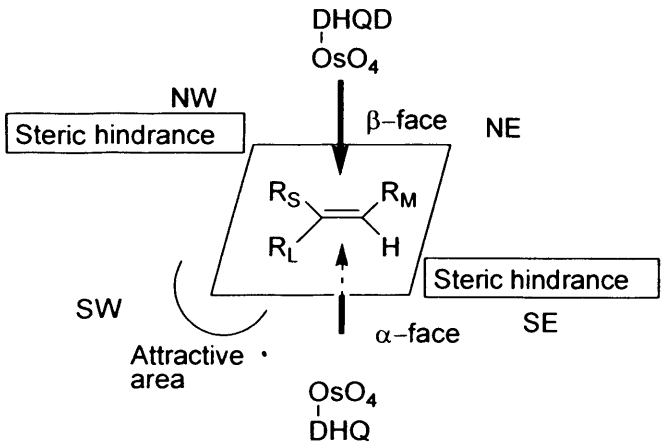


Diphenylpyrimidine (PYR)
338

Scheme 125

After studies on ligand structure-activity and on the origins of the enantioselectivity, Sharpless[76] demonstrated that the 'dimeric' cinchona alkaloid ligands provide a 'binding pocket', like an enzyme active site. Alkenes can only approach the osmium if they are correctly aligned in the chiral pocket; steric hindrance forces such an alignment.

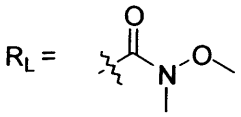
For predicting the enantiofacial selectivity in the reaction, a mnemonic device has been developed (Scheme 127).[77]



Scheme 127

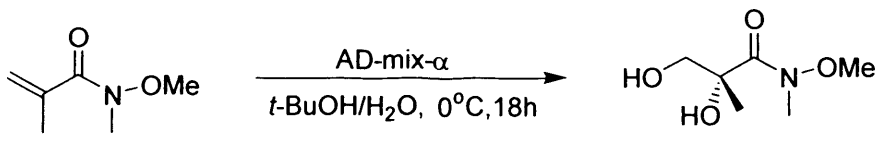
The special southwest (SW) quadrant is regarded as being an 'attractive' area, which is especially well-suited to accommodate flat, aromatic substituents, or 'large' aliphatic groups. On the other hand, the southeast (SE) quadrant and to a much lesser extent the northwest (NW) quadrant present steric barriers. The northeast (NE) quadrant is relatively open for olefin substituents of moderate size. As a result, an olefin positioned according to these constraints will be attacked either from the top face (i.e., the β-face), when using dihydroquinidine (DHQD) derivatives, or from the bottom face (i.e., the α-face), when applying dihydroquinine (DHQ) derived ligands.

Using the empirical mnemonic device to predict terminal olefins could be ambiguous,[71] since it may be difficult to judge which of the two substituents prefers the attractive, SW quadrant. Groups which are well suited for this quadrant have to be 'soft', large and/or flat. As for the methacrylamide **324** which gave a high ee[68] in the AD-mix reaction, presumably the R_L, shown below, could have favoured the SW quadrant due to its soft property, from the nitrogen atom and its relatively large bulk compared to the methyl counterpart.



Scheme 128

Following the general procedure for the AD-mix reaction,[63] methacrylamide **324** was *bis*-hydroxylated smoothly in good yield (91%) (Scheme 129).



324 **(*R*)-325**

t-BuOH/H_2O, 0°C,18h 91%, ee. 91%

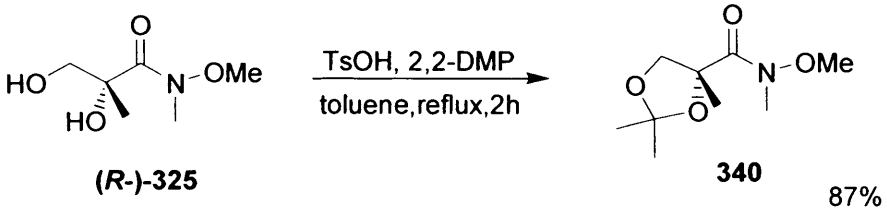
Scheme 129

A round-bottomed flask was charged with equal amounts of *tert*-butyl alcohol and water, AD-mix-α (containing $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2$-PHAL and $K_2OsO_2(OH)_4$) was also added. The suspension was stirred at room temperature until both phases became clear, then

the olefin **324** was added. The heterogeneous slurry was stirred vigorously at room temperature until tlc analysis indicates the absence of the starting olefin **324** (*ca.* 18h). The reaction was quenched by the addition of aqueous sodium sulfite, with stirring being continued for 30-60 min. The reaction mixture was extracted several times with dichloromethane. Purification of the crude product by chromatography gave the pure diol-amide **(*R*)-325** as a yellow oil. Determination of the ee. using gas chromatography (GC) (CDX-β column; temp.: oven- 100°C, detector- 300°C, injection- 200°C; column head pressure- 20 PSI, retention time: 29 min.) on the basis of the racemic counterpart of the product, which was made following the method in Scheme 64 (section 2.3, p.53), showed a 91% ee., compared to the literature value of 93%.[68]

2.11.3.3 Protection of diol-amide (*R*)-325 as an acetal and the following reduction to aldehyde 341

After the chiral centre was created with a satisfactory ee, the following work was to transform the diol-amide **(*R*)-325** into the diol **(*S*)-69**. As was planned above in Scheme 122, the diol-amide **(*R*)-325** was protected as an acetal **340** using 2,2-dimethoxypropane (DMP) (Scheme 130).[68] This protection was necessary for preventing the deprotonation of the diol group by the powerful hydride source which was to be used in the next step.

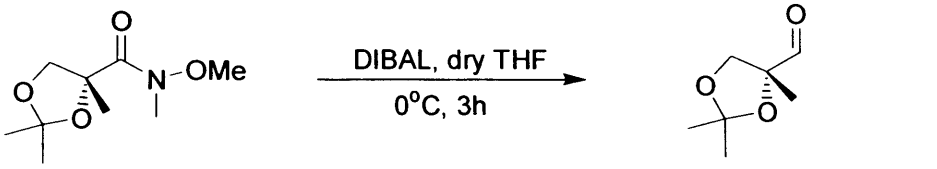


(*R*-)-325 **340** 87%

Scheme 130

A solution of the diol-amide **(*R*)-325**, 2,2-DMP and *p*-toluenesulphonic acid (TsOH) in toluene was heated under reflux (~105 °C) for 2 hours. The solution was cooled to room temperature and the solvent was removed. The residue was purified by column chromatography to give the pure acetal **340** as a pale yellow oil in good yield (87%).

The following reduction using diisobutylaluminium hydride (DIBAL) at low temperature smoothly delivered the aldehyde **341** in an excellent yield (Scheme 131).[70]



340 **341** ~100%

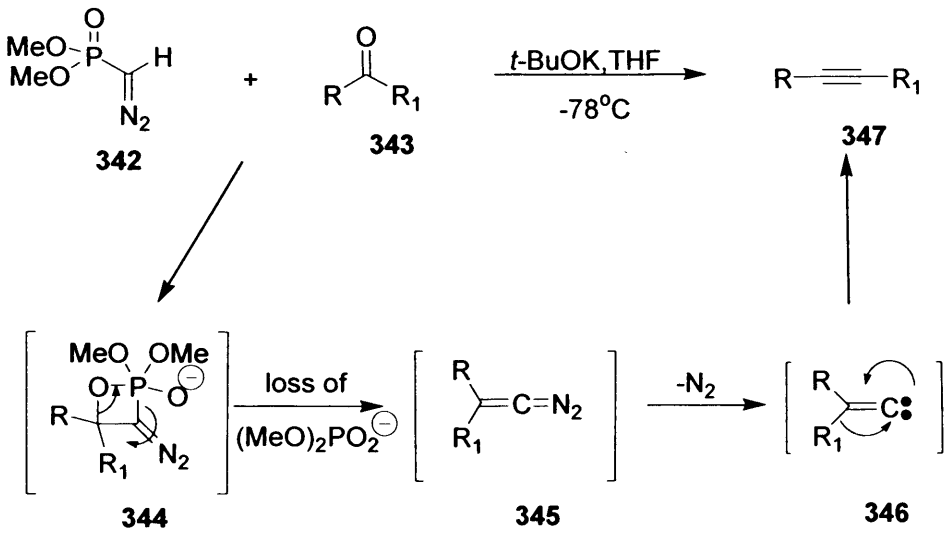
Scheme 131

A solution of the acetal **340**, in dry THF, was treated with DIBAL (3 eq.) at 0°C. After 1 hour stirring at this temperature, the reaction was quenched by being poured into a cold solution of 5% hydrochloric acid in ethanol, to form the aldehyde product **341**. The organic extract was washed with a small amount of water before being evaporated carefully, to give the crude aldehyde **341** as a yellow oil. Due to the likelihood that it might decompose during column chromatography, we decided to use the crude material in the next reaction, even though ^{1}H NMR analysis showed small amounts of impurities.

We had previously used five equivalents of DIBAL for the above reaction (Scheme 131); stirring for 30 minutes at 0°C only delivered trace amounts of unrecognisable product. We believed this was due to the excess amount of the DIBAL, which had over-reduced the amide **340** to the primary alcohol. The acid work-up could protonate the alcohol and form water soluble cation.

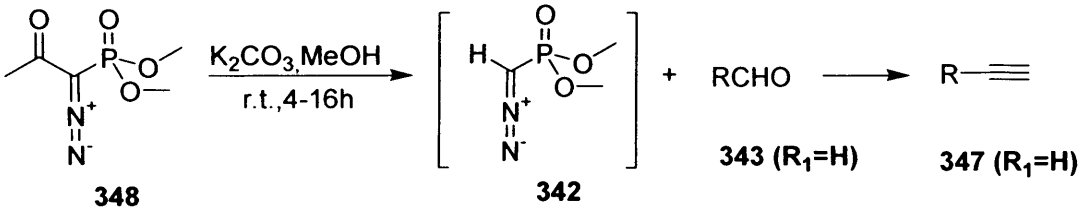
2.11.3.4 Preparation of dimethyl diazoketophosphonate 348 and the attempted transformation of aldehyde 341 to alkyne 352

Dimethyl (diazomethyl)phosphonate **342** (the Seyferth/Gilbert reagent) is a valuable reagent, useful for the efficient one-carbon homologation of aldehydes and ketones to alkynes.[69a] (Scheme 132).



Scheme 132

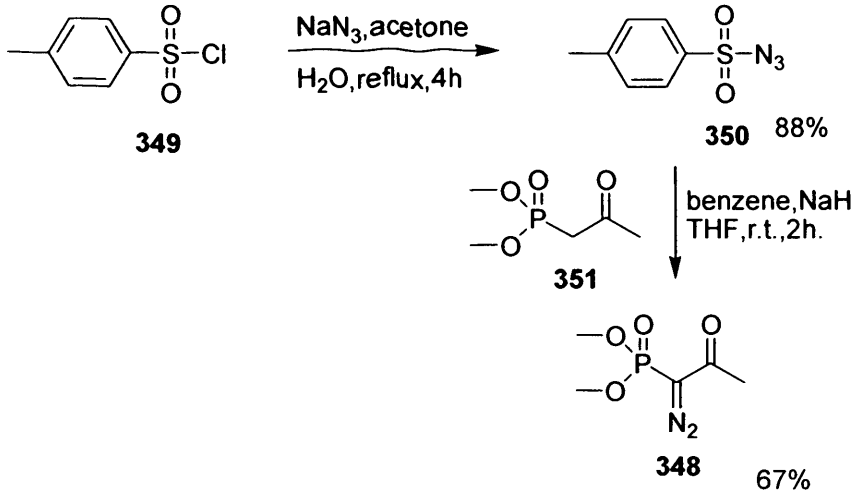
It is presumed that the mechanism is Wittig-like and involves initial formation of adduct **344**. Elimination of dimethyl phosphate leads, *via* the diazo intermediate **345**, to an alkylidene carbene **346**, which undergoes a 1,2-rearrangement to give the alkyne **347**. Since the Seyferth/Gilbert reagent **342** is unstable, it should be freshly prepared and isolated prior to its reactions with ketones **343**. The reactions normally proceed with strong bases at low temperatures.[69a] For the conversions of aldehydes into terminal alkynes (R_1 = H), the phosphonate **342** could be generated *in situ* from its stable and easily prepared precursor, the ketophosphonate **348**, and then the reactions can be carried out under mild conditions (Scheme 133).[69b]



Scheme 133

Applying the above method, we could make the corresponding acetylene from the aldehyde **341** in a single step, which should then, subject to acetal deprotection, form the key diol **(*S*)-69**.

Following the literature method,[69b] diazophosphonate **348** was prepared from the commercially available oxopropylphosphonate **351** in a single step by diazo transfer with tosyl azide (TsN_3) **350** (Scheme 134).

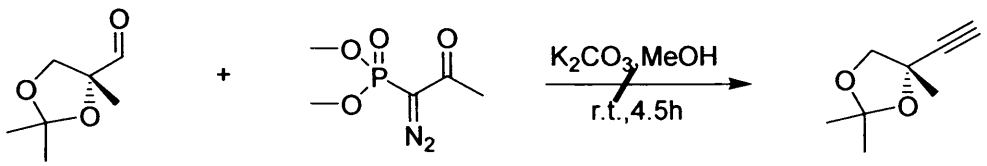


349 **350** 88% **351** **348** 67%

Scheme 134

Firstly, the reactive TsN_3 **350** was prepared from toluenesulfonyl chloride (TsCl) **349** with sodium azide, in an acetone / water solution, which were reacted under reflux. Then, a solution of the phosphonate **351**, in dry benzene, was added to a suspension of sodium hydride (NaH) in dry benzene / THF at 0-5°C, the resulting mixture was then stirred for one hour at this temperature before TsN_3 **350** in benzene was added. The reaction mixture was then warmed to room temperature and stirred for further two hours. The solution was then simply filtered and concentrated under reduced pressure before being purified by chromatography. The pure diazophosphonate **348** was obtained as a pale yellow oil in reasonable yield.

Finally, we could try our hand at this Wittig-type carbene rearrangement (Scheme 135). To a suspension of the crude aldehyde **341** and K_2CO_3 in dry MeOH was added diazophosphonate **348** (1.5 eq.).[69b] Stirring was continued at room temperature for 4.5 hours, during which time the yellow suspension turned to a clear solution. The solution was then diluted with diethyl ether and washed with 5% sodium bicarbonate ($NaHCO_3$).



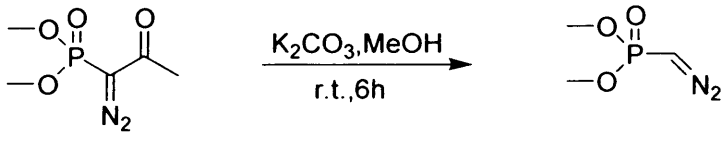
341 **348** **352**

Scheme 135

However, to our disappointment, neither the desired product nor the starting material were obtained after column chromatography. It was possible that the aldehyde **341** did not react with the reagents and had been destroyed during the aqueous base work up. Considering that the impurities from the crude aldehyde **341** could have damaged the reagent before the desired reaction occurred, we modified the conditions by adding two equivalents of the diazophosphonate **348**, and also prolonged stirring to 18 hours. Unfortunately, the same mysterious result was delivered.

Still blaming the impurities present in the aldehyde **341**, we therefore decided to purify the mixture by Kugelrohr distillation.[78] As a result, only a small amount of neat aldehyde **341** was obtained, as a colourless oil; the majority of the crude product turned from a yellow oil into a brown gum under heating. This was possibly because the reactive aldehyde **341** had polymerised at high temperature. Repeating the Wittig-type reaction with this pure aldehyde **341** gave only unrecognisable compounds. We therefore realised that the reason for this failure was possibly due to the steric hindrance from the quaternary carbon that is α to the carbonyl. But before we left this attractive method, we gave it one last try. The idea was to apply the original procedure in Scheme 132, using the freshly made Seyferth/Gilbert reagent **342** and a strong base, since this method has worked efficiently on bulkier ketones.

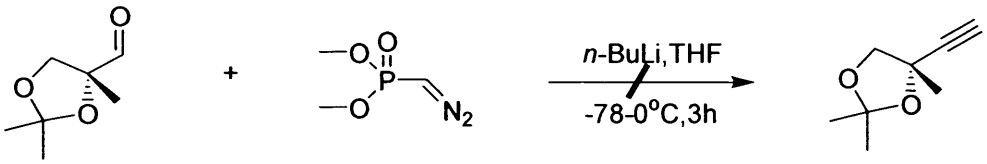
Consequently, using the same conditions as above (Scheme 135), the phosphonate **342** was prepared and isolated (Scheme 136).



348 **342**

Scheme 136

The reactions process was followed by tlc. After 6 hours, the solvent was removed and the resulting yellow oily residue was treated with dichloromethane. The suspension was filtered and the solid washed with further dichloromethane. Careful evaporation of the filtrate gave the phosphonate **342** as an orange-yellow oil, which was stirred in dry THF and cooled to -78°C.[69a] *n*-Butyllithium was added at this point and, after 6 minutes stirring, the aldehyde **341** in THF was added slowly to the cold solution. The reaction mixture was stirred for another 15 minutes before being gradually warmed to 0°C, and then stirred at this temperature for another three hours before the reaction was quenched with saturated aqueous ammonium chloride (Scheme 137).



341 **342** **352**

Scheme 137

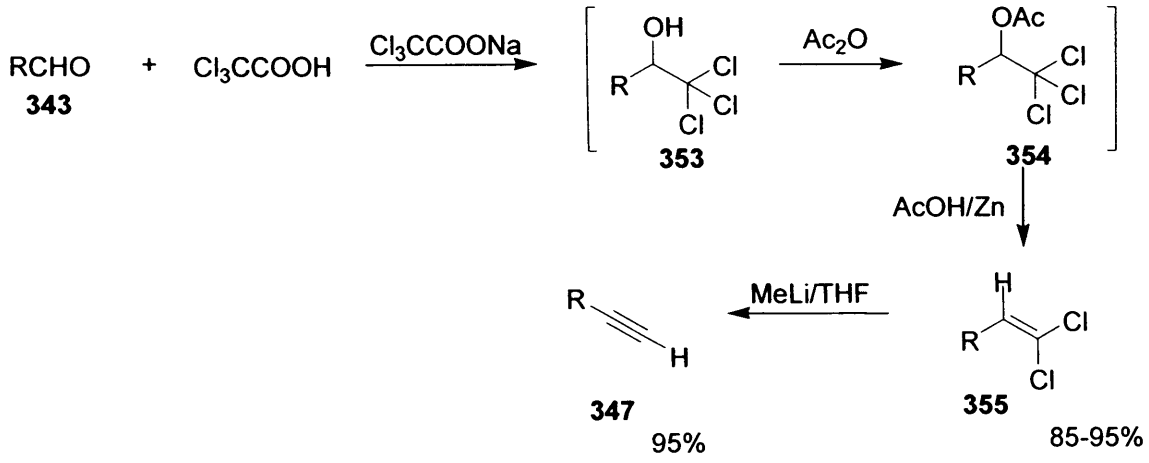
To our disappointment, we still found no product, according to ^{1}H NMR analysis. Therefore, we drew the conclusion that this method is not suitable for our aldehyde **341**.

The five-membered ring together with the methyl group at the α-position formed bulky hindrance and presumably prevented the attack of the phosphonate ion.

2.11.3.5 Synthesis of the acetylene 352 through the trichloro-intermediate 357 followed by eliminations

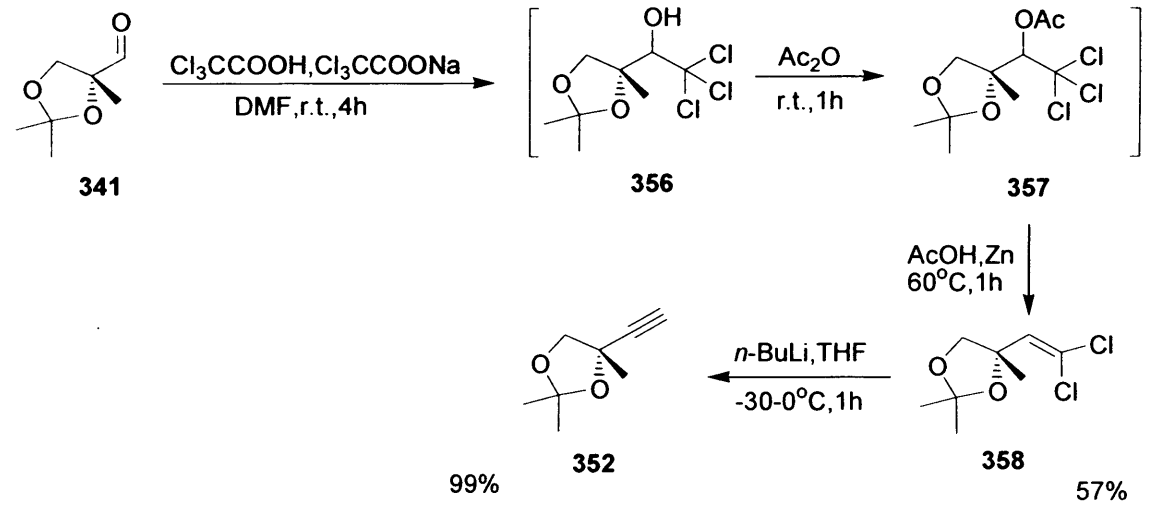
Having failed with the Wittig-type reaction, we were looking for a two-step method towards the synthesis of the acetylene **352**, possibly through a halo-olefin, which could be further eliminated to form the triple bond. By searching through the literature, we found a paper entitled 'A new and practical synthesis of vinyl dichloride *via* a non-Wittig-type approach'.[79] It reported the conversion of aldehydes **343** into vinyl dichlorides **355** by a three-step, one-pot reaction involving the formation of a trichlorocarbinol **353** by the treatment of aldehydes **343** with trichloroacetic acid and sodium trichloroacetate followed by *in situ* protection and

elimination to form the vinyl dichlorides **355** (Scheme 138). Further elimination by methyl lithium at low temperature gave the corresponding acetylenes **347** in good yields.



Scheme 138

On applying this procedure directly to our aldehyde **341**, the desired acetylene **352** was finally achieved (Scheme 139).



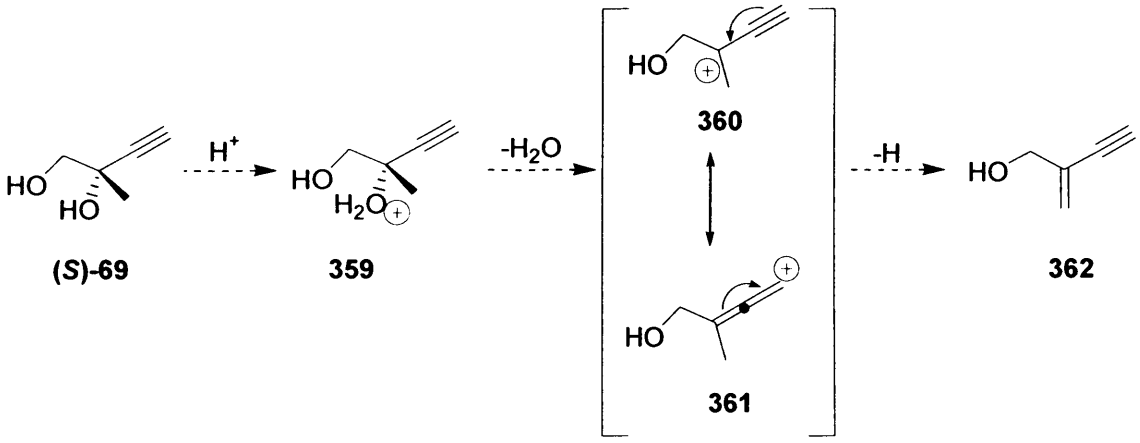
Scheme 139

Sodium trichloroacetate was added in portions to a stirred solution of trichloroacetic acid and the aldehyde **341** in *N,N*-dimethylformamide (DMF) at room temperature. The mixture was then stirred at room temperature for 4 hours, with continuous evolution of CO_2. The solution was cooled in an ice-bath and acetic anhydride was carefully added: strong CO_2 evolution was observed. The mixture was warmed to room temperature and stirred for an additional hour, then diluted with acetic acid and cooled again to 0°C. Zinc powder was added at this point in one portion. The solution was then gradually heated to 60°C and stirred for one hour,

before being cooled to room temperature. A standard aqueous work up gave the crude dichloro-alkene **358** in a 57% yield, which was pure enough for the further elimination according to ^{1}H NMR spectra. Treatment of the dichloro-alkene **358** with *n*-butyllithium (3 eq.), which was considered to be more efficient than methyl lithium, afforded a 99% yield of the crude acetylene **352**. Purification by silica chromatography failed due to the decomposition of the product. As the next step (deprotection) was not demanding in terms of reagent sensitivity to impurities, we decided to bring this crude material through to the final step.

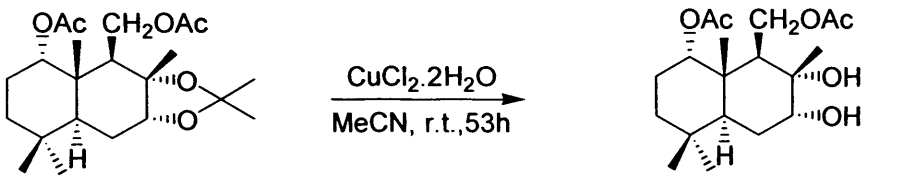
2.11.3.6 Reactions of acetal acetylene 352

The hydrolysis of acetal acetylene **352** was of concern to us, due to the fact that the expected diol product **(*S*)-69** could well be unstable under acidic conditions. The reactive tertiary alcohol group could be protonated by the acid and dehydration could follow. The resulting cation intermediate **360** would be stablised by the triple bond (Scheme 140).



Scheme 140

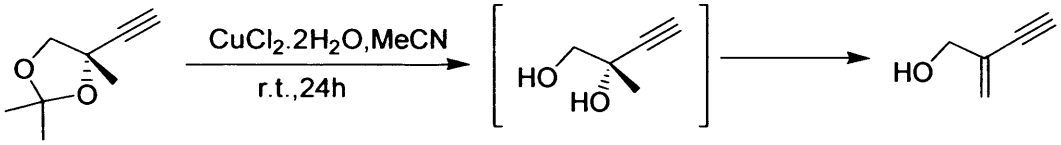
For this reason, the typical conditions, using strong acid and heat,[80] should be avoided. We were delighted to find a mild and clean deprotection method recently reported by Aranda[81] (Scheme 141).



363 **364** 85%

Scheme 141

The acetal **363** was hydrolysed slowly and selectively by using $CuCl_2 \cdot 2H_2O$ in acetonitrile at room temperature, in 85% yield, without affecting the acetyl functions as well as the reactive tertiary OH. Utilising this new method on our acetylene acetal **352**, we were disappointed to find that the unwanted dehydration occurred and the key chiral centre was simultaneously destroyed (Scheme **142**).

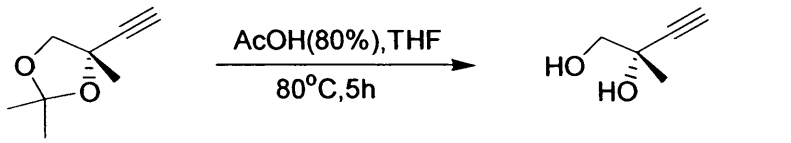


352 **(*S*)-69** **362**

Scheme 142

The acetal **352** was stirred in acetonitrile with $CuCl_2 \cdot 2H_2O$ for 24 hours then the blue solution was filtered through silica gel. ^1H NMR of the resulting residue showed a clean conversion to the olefin **362**, in which the resonance of a terminal double bond appeared at 5.7 ppm as a multiplet.

The failure of this method, with the salt $CuCl_2 \cdot 2H_2O$, prompted us to test the stability of the acetal **352** towards a typical deprotection method, using acetic acid. Following a literature procedure,[80] the acetal **352** was dissolved in an 80% acetic acid / THF mixture; the mixture was kept at 80°C for five hours. After a standard aqueous work up, we found a trace of the desired diol product **(*S*)-69** revealed in the ^1H NMR spectra (Scheme 143).

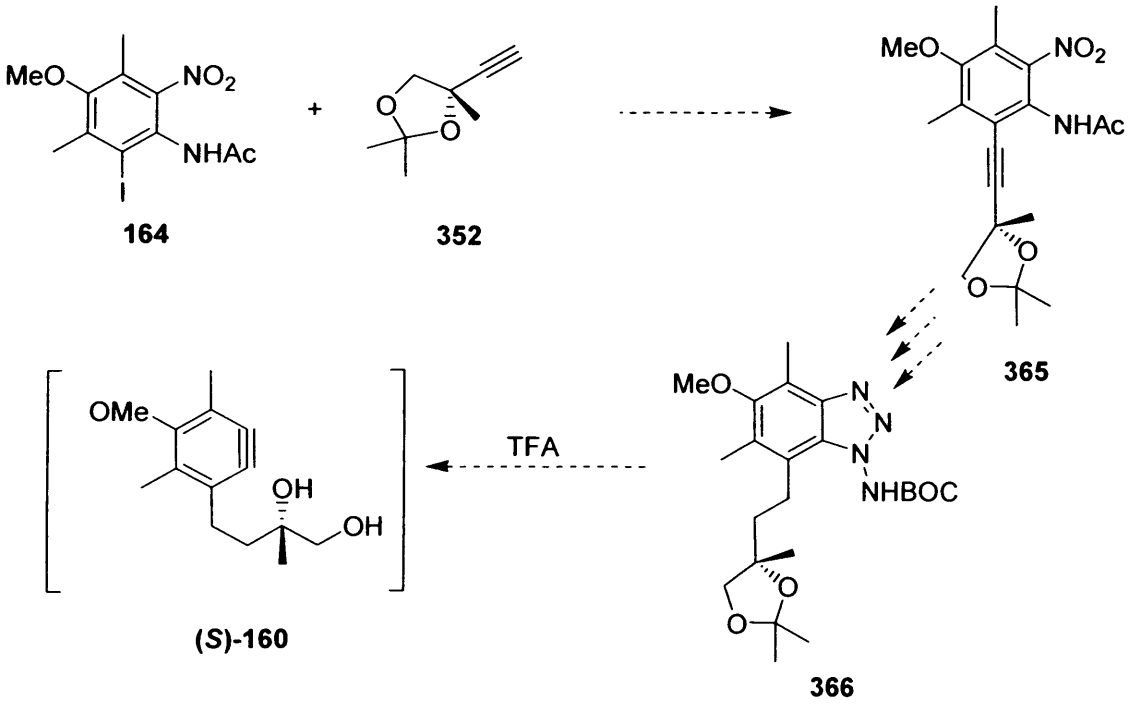


352 **(*S*)-69** (trace)

Scheme 143

There was no resonance for the elimination product olefin **362** or the starting material. This result was obviously still far from satisfactory. We now designed another plan of treating this chiral core.

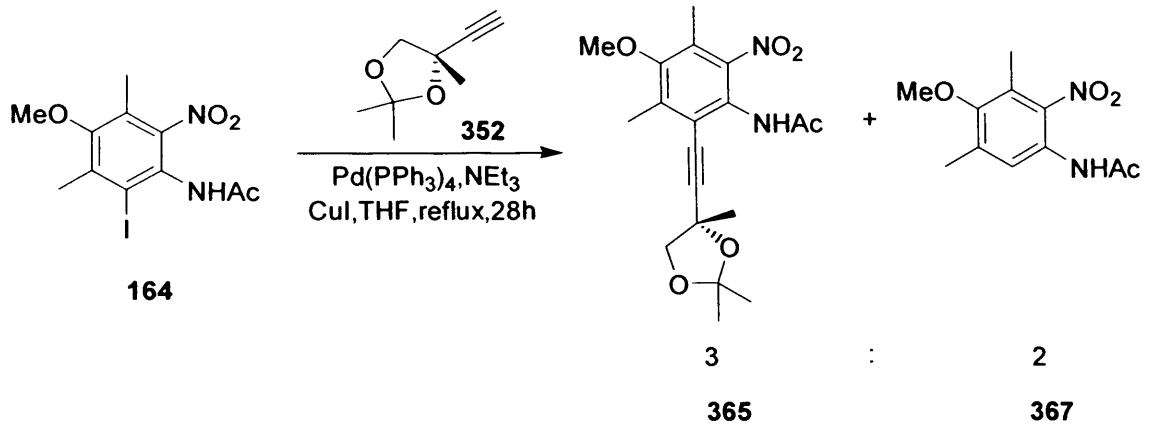
Considering that the unsaturated triple bond is a disadvantage towards the hydrolysis at this point, we decided to carry out the Sonogashira coupling of it with the iodide **164**. If this was successful, the coupled product could follow the same synthetic route as its diol analogue **163**, thus both the Boc and the acetal protecting group could be hydrolysed in a single step by TFA, before the benzyne cyclisation (Scheme 144). The key here is that the tertiary hydroxyl really should be significantly less sensitive, once the acetylene group has been reduced.



164 **352** **365** **(*S*)-160** **366**

Scheme 144

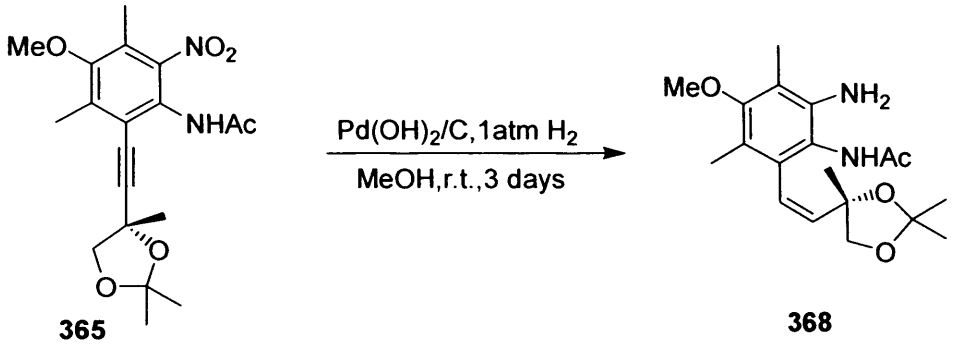
When we repeated the Sonogashira procedure, as in Scheme 74 (Section 2.4, p.60), but coupling with the acetal **352** instead of the diol **69**, the reaction did not give a good result (Scheme 145).



Scheme 145

Column chromatography of the crude material gave a 3:2 mixture of the coupled acetal **365** and the deiodinated benzene **367**, according to ^{1}H NMR analysis. The above two compounds were found to be difficult to separate due to their similar polarity. The calculated yield of the desired product was about 19%. The reason for the lower yield of this reaction, compared with the coupling with the diol **69**, might reside in the bulky five- membered ring structure of the acetal **352**.

We have further investigated the validity of this route by undertaking the hydrogenation of the above mixture. If the reductions were successful, we thought that the saturated acetal product should be separable from the other impurities, and allows us to further explore this subject. However, $Pd(OH)_2$-catalysed hydrogenation under one atmosphere of hydrogen formed the (*Z*)-alkene **368** after three days, and column chromatography failed to separate this product from the deiodinated impurity **367** (Scheme 146).

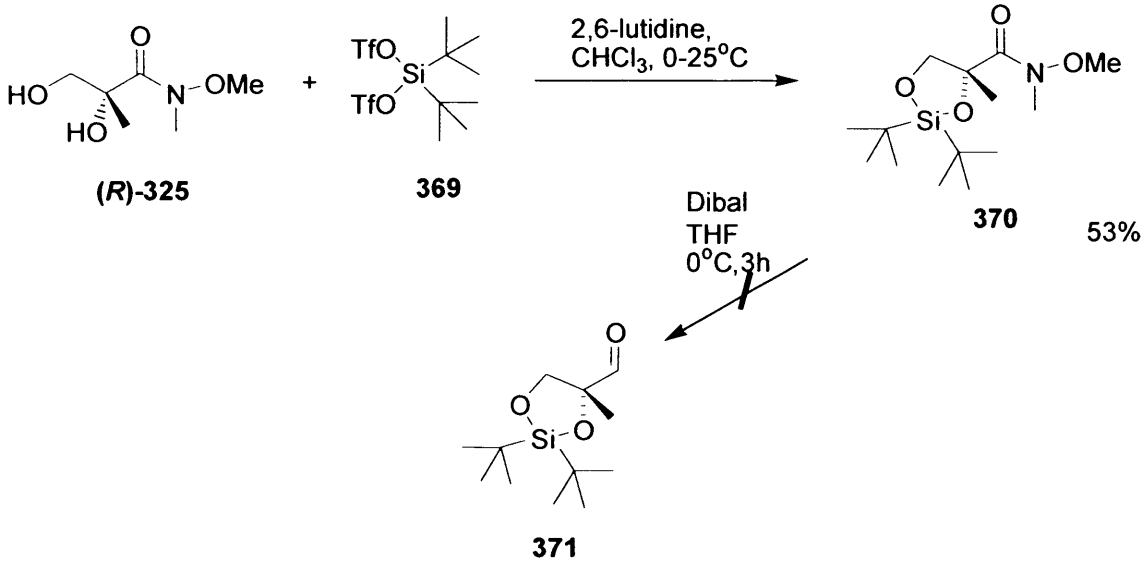


Scheme 146

It was believed that the steric hindrance from the five-membered dioxolane was again the reason for the poor reduction.

2.11.3.7 Protection by di-*tert*-butylsilyl (DTBS), benzyl (Bn) or *bis*-*tert*-butyldimethylsilyl (TBDMS)

Having made several attempts with the acetal **352**, which all failed, we began to think of other protecting groups that could be readily removed under milder conditions. Di-*tert*-butylsilyl (DTBS) protection of diols was thought of; ease of formation and the mild conditions for its deprotection, *tetra*-*n*-butylammonium fluoride (TBAF) at room temperature, favoured its use. Following a standard method,[82] methacrylamide diol **(*R*)-325** was protected as its di-*tert*-butylsilylene derivatives **370** using di-*tert*-butylsilyl ditriflate. Unfortunately, the following reduction reaction by DIBAL at low temperature failed to deliver any recognisable product, according to ^{1}H NMR analysis (Scheme 147).

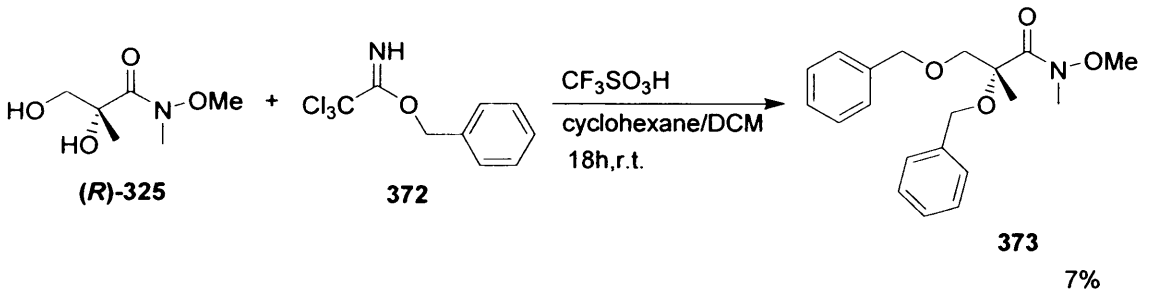


Scheme 147

The above two steps were performed as follows: to a solution of the diol **(*R*)-325** and 2,6-lutidine in chloroform at 0°C was added di-*tert* butylsilyl *bis*-(trifluoromethanesulfonate) **369**, the mixture was warmed to room temperature and stirred overnight. The crude product was purified by florisil column chromatography and the silyl ether **370** was obtained as a colourless oil (53 %). Subsequently, a solution of this oil in dry THF was treated with DIBAL (3 eq.) at 0°C; it was stirred at this temperature for three hours before an aqueous work up. To our disappointment, the ^{1}H NMR spectrum of this product showed no sign of any aldehyde proton, while a huge singlet peak appeared for the *tert*-butyl groups. The 1,2-diol derivative **370** was believed to have decomposed during the reaction. This suggested that, even at low temperature, it is more sensitive than its 1,3- and 1,4-diol counterparts towards basic conditions.[82]

Having experienced difficulties with the foregoing two functional groups, we planned another two protections: one was benzyl protection (Bn), which should be stable enough towards strong bases and could be removed by palladium-catalysed hydrogenolysis; the other

was *tert*-butyldimethylsilyl (TBDMS) protection, which was also thought to be more stable than DTBS, but which could be removed under the same conditions using TBAF. Following a literature method,[83] the benzyl protection was carried out with trichloroacetimidate **372** and triflic acid (Scheme 148).

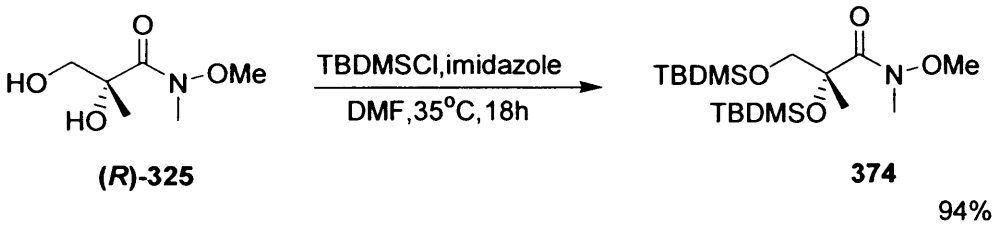


Scheme 148

A catalytic amount of triflic acid was added to a solution of diol **(*R*)-325** and benzyl trichloroacetimidate **372** (4 eq.) in cyclohexane/dichloromethane (2 : 1). The reaction was

stirred overnight at room temperature prior to a simple work up. Unfortunately, only a poor 7% yield of the product was achieved after chromatography. We believed that the majority of the starting material had decomposed in the strong acid.

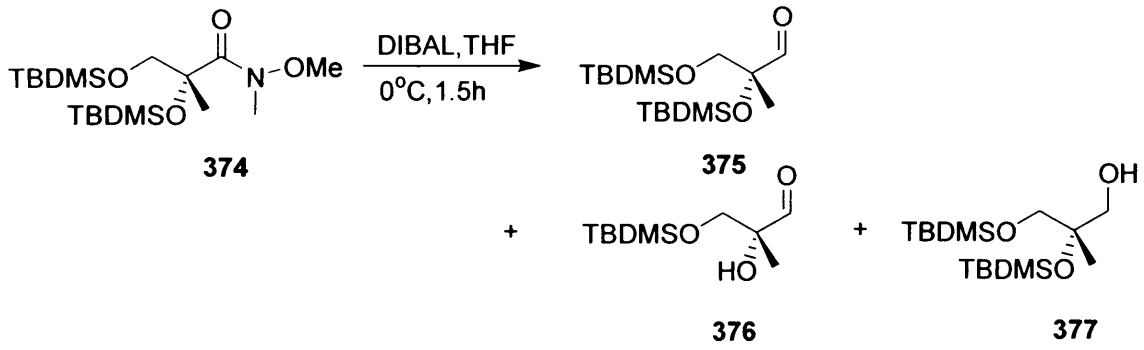
Meanwhile, the other protection gave us hope, as it went smoothly and lead to the *bis*-TBDMS derivative **374** in good yield (94%) (Scheme 149).[84]



Scheme 149

Diol **(*R*)-325** was treated with *t*-butyldimethylsilyl chloride (2.1 eq.) and imidiazole in *N*, *N*-dimethylformamide (DMF), the solution was heated to 35°C and stirred overnight. The protected product, the *bis*-silyl ether **374**, was finally obtained as a colourless oil, after a simple work up followed by chromatography.

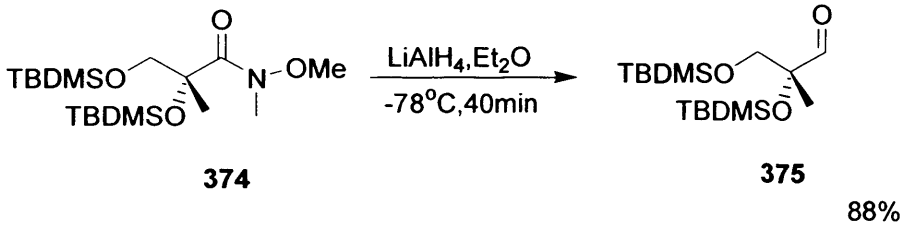
After repeating the usual reduction procedure using DIBAL, we were disappointed to discover that three products arose from the reaction, according to ^{1}H NMR spectra and tlc: the expected aldehyde **375**, the mono-protected aldehyde **376** and a trace of the over-reduced alcohol **377** (Scheme 150).



Scheme 150

Employing the above mixture in the trichloromethylation reaction, followed by elimination (as in Scheme 138, Section 2.11.3.5, p.109), delivered unrecognisable products after column chromatography.

After considering the failure of the reduction step using DIBAL, we thought that the problem arose from the acidic work up using an HCl / EtOH solution, as one of the TBDMS groups had been hydrolysed to form the mono-protected aldehyde **376**. Due to the fact that lithium aluminium hydride ($LiAlH_4$) reduction can use a basic work up, we decided to give it a try. (Scheme 151).



374 **375**

88%

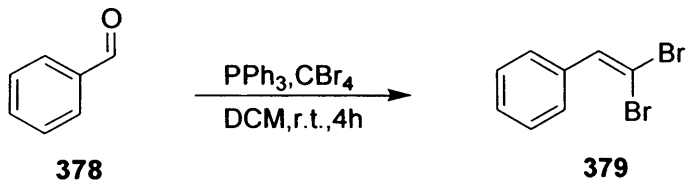
Scheme 151

The reaction was performed in dry ether with $LiAlH_4$ (3 eq.) at -78°C, and was followed by tlc. After approximately 40 minutes, it was quenched with 2M aqueous sodium hydroxide to destroy the excess $LiAlH_4$. The crude material was shown to be the neat aldehyde **375**; the ^1H NMR spectrum showed it be a single compound. It was therefore used in the next step without purification.

2.11.3.8 Synthesis of the key diol (*S*)-69

Since we had obtained the aldehyde **375** in an efficient manner, the next step was to transform it into an olefin. Although the trichloromethylation-elimination method had successfully delivered the vinyl dichloride **358** from the acetal derivative (Scheme 138), the yield (57%) was only moderate, as it took two steps. We thus planned to use a Wittig reaction, trying to obtain a dibromo-olefin in a single step, which should readily undergo elimination to form the acetylene. According to the literature method,[85] we first carried out a

test reaction using the commercially available benzaldehyde **378** as the starting material (Scheme 152).

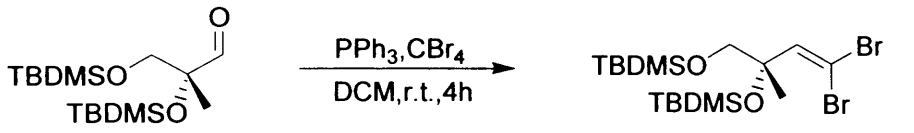


378 **379** 50%

Scheme 152

To an orange solution of triphenylphosphine (PPh_3) (2 eq.) and carbon tetrabromide (CBr_4) (1 eq.) in dry DCM was added benzaldehyde **378**. the solution was stirred overnight before being quenched with water. The solvent was removed and the residue was purified by stirring in hexane, filtering off triphenylphosphine oxide and careful evaporation. The pure dibromo-alkene **379** was obtained as a yellow oil but in a poor yield (9%). We then repeated the reaction with double the amounts of the reagents PPh_3 (4 eq.) and CBr_4 (2 eq.): the yield was thus increased to 50%.

Now we felt ready to apply the above method on aldehyde **375**. We were delighted to obtain the dibromo derivative **380** in an increased yield (74%) (Scheme 153).

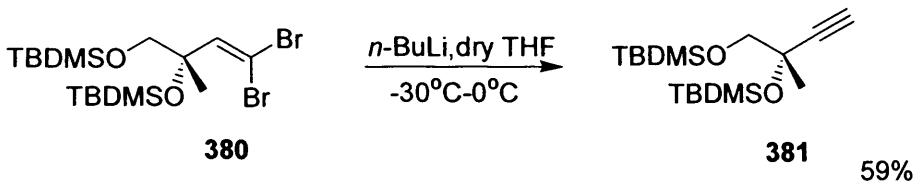


375 **380** 74%

Scheme 153

The increase in the yield probably results from the fact that a different work up was used from that in the above procedure. It was found that more product could be obtained by taking the crude residue obtained after evaporation directly onto column chromatography. When using the traditional hexane-workup, the oily dibromo product was found to be attached to the triphenylphosphine oxide (PPh_3O) by-product and was difficult to wash off with hexane, while silica column chromatography can allow isolation of the product more efficiently.

The dibromo-olefin **380** was treated with *n*-butyllithium; the subsequent elimination gave us the acetylene **381** (Scheme 154).

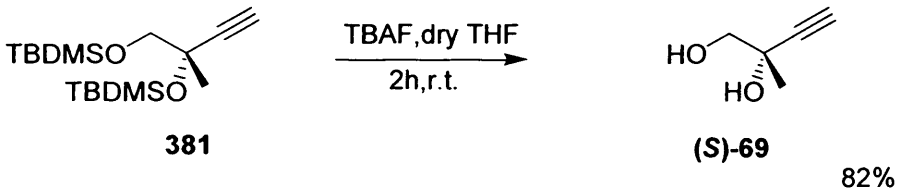


380 **381** 59%

Scheme 154

Due to the relatively low polarity and high volatility of the product, pentane was used as the eluent for column chromatography.

The final deprotection was also successful, using TBAF under mild conditions (Scheme 155).



381 **(*S*)-69** 82%

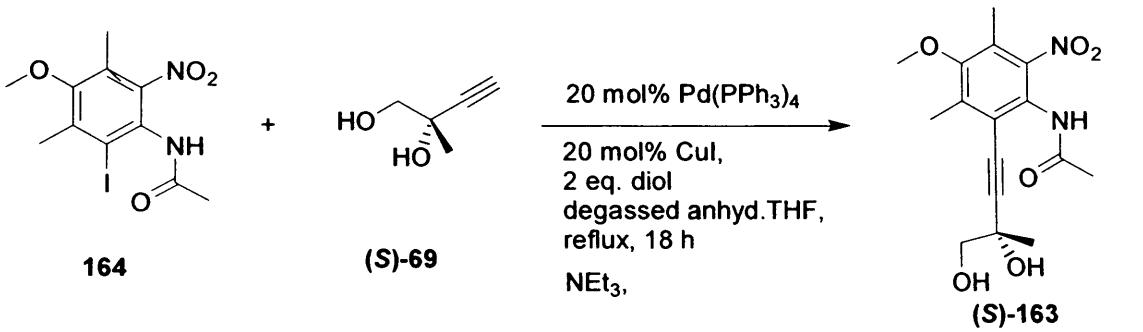
Scheme 155

A solution of acetylene **381** in THF was treated with TBAF (1M solution in THF), which was added dropwise at ambient temperature. The reaction was stirred for two hours before the solvent was removed. The product, diol **(*S*)-69**, survived silica gel chromatography in a pleasing yield (82%).

2.12 Towards (*S*)-Chromane 44

Until now, we have successfully synthesised the racemic form of the vitamin E precursor **44**, and we had prepared a large quantity of the chiral core diol **(*S*)-69** by the above methods. By these means, we have proven the validity of our benzyne methodology toward the synthesis of this highly important natural product. The following work was to repeat the previous schemes that used the racemic compound, but with chiral starting materials, starting with the Sonogashira coupling of iodide **164** with the diol **(*S*)-69**, to furnish the enantiomerically enriched diol **(*S*)-163**.

The Sonogashira coupling reaction was repeated and went smoothly as shown (Scheme 156).



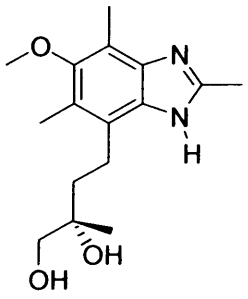
164 **(*S*)-69** **(*S*)-163**

77%

Scheme 156

Purification by column chromatography gave the acetylene diol **(*S*)-163** in a good yield. ^{1}H NMR spectra of this product revealed a small amount of triphenylphosphine impurity. The solvent system used (chloroform / methanol) on silica gel failed to separate this completely from our product. As for the high polarity of our diol product **(*S*)-163**, using a large ratio of ethyl acetate as the column eluent could affect the nucleophilic amide group. Crystallisation of the diol product usually caused significant loss of the compound, and it was thought that a small amount of triphenylphosphine impurity would not effect the next hydrogenation step. Therefore, the above product was taken into the following step.

After stirring the acetylene diol **(*S*)-163** with $Pd(OH)_2/C$ in methanol under hydrogen (1atm) for three days, it was disappointing to find that none of the desired product was formed; instead, we found the over-reacted benzimidiazole **(*S*)-256** again (Scheme 157).



(*S*)-256

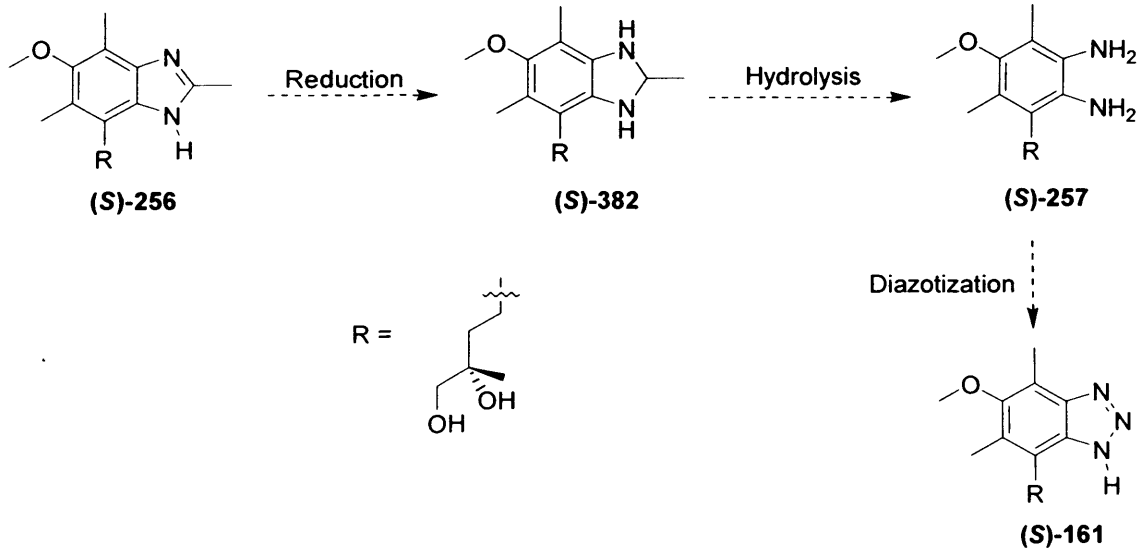
Scheme 157

This unpleasant by-product had been formed before in the diazotisation reaction, which was under acidic conditions (aq. HCl) (see section 2.6). This time, unexpectedly, the triphenylphosphine impurity was believed to act as a catalyst, and the methanol helped

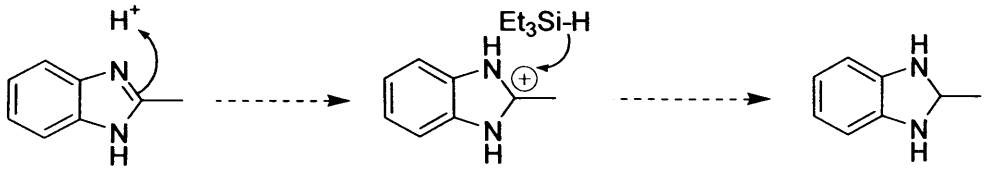
proton transfers to cause the loss of water, which was found during the work up. This was a large scale reaction and meant that we were running out of material. We therefore had to consider a way of performing the transformation using multiple steps, turning compound **(*S*)-256** into a product which is accessible towards the vitaime E precursor.

Our attempt at this was to hydrogenate the imidazole ring to form diamine **(*S*)-382**, which could be hydrolysed into diamine **(*S*)-257**; we could then carry out the diazotisation to form the benzyne precursor, benzotriazole **(*S*)-161** (Scheme 158).

After considering that a *tert*-alkyl cation intermediate on the imidiazole ring could probably be formed by protonation on nitrogen, subsequent reduction by intermolecular hydride-transfer with triethylsilane (Et_3SiH)[86] could give the saturated ring **(*S*)-382**. We therefore practised this method on the commercially available analogue, 2-methylbenzimidiazole **383** (Scheme 159).



Scheme 158

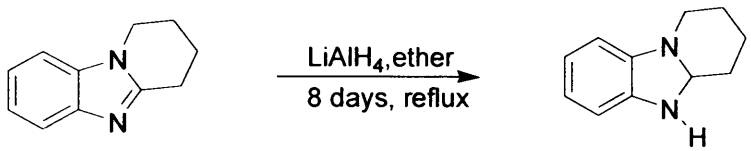


383 384 385

Scheme 159

The reaction was carried out by stirring the methylbenzimidiazole **383** with Et_3SiH (1 eq.), and trifluoroacetic acid (TFA) in dichloromethane overnight at room temperature. No reaction occurred according to the ^1H NMR spectrum; two equivalents of the hydride reagent as well as the strong acid (TFA) were then added, and the same result was obtained.

According to a report by Garner *et.al.*,[87] the imidazole ring in benzimidazole and its alkyl derivatives, shows considerable stability towards reduction, since hydrogenation over platinum catalysts effects only the benzene ring, to produce tetrahydrobenzimidazoles. The difficulty with this transformation resides mainly in the instability of the dihydrobenzimidazole derivatives, which tend to aromatisation and revert to benzimidazoles. Garner[87] had found that the reduction of the imidazole **386** with a large excess of $LiAlH_4$ in boiling ether for 8 days gave the dihydro counterpart **387** in quantitative yield (Scheme 160).



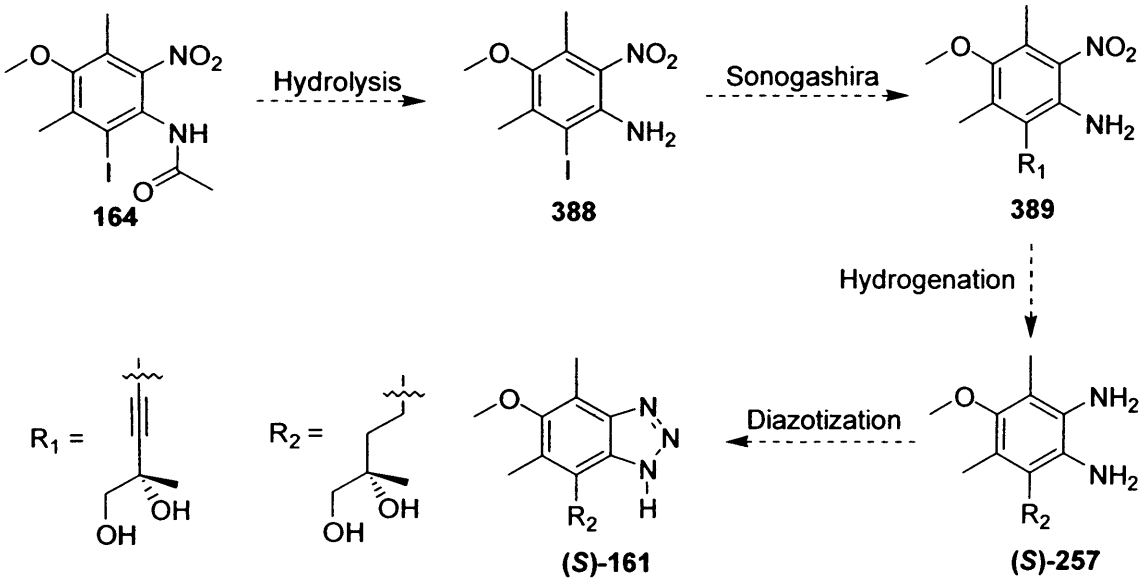
386 387

Scheme 160

We therefore applied these forcing conditions to our model compound, 2-methylbenzimidiazole **383**. After refluxing with $LiAlH_4$ (3 eq.) for 24 hours in THF, we found no clear evidence of the reduced product from ^1H NMR spectra, and the crude material was mainly the unreacted starting material. This suggested that our desired product was less stable than the above derivative **387**; and that the tautomerism of the imidazole ring had also stablised the starting material. This meant reducing our chiral methylbenzimidiazole **(*S*)-256** would need these forcing conditions for an even longer time than 8 days, and we could not take the risk that the other functions would not be affected. Also, this prolonged

reaction time was not practical for our synthetic route. For these reasons, we decided to abandon this attempt and continue our work towards enantiomerically enriched chroman (*S*)-**44** by another route.

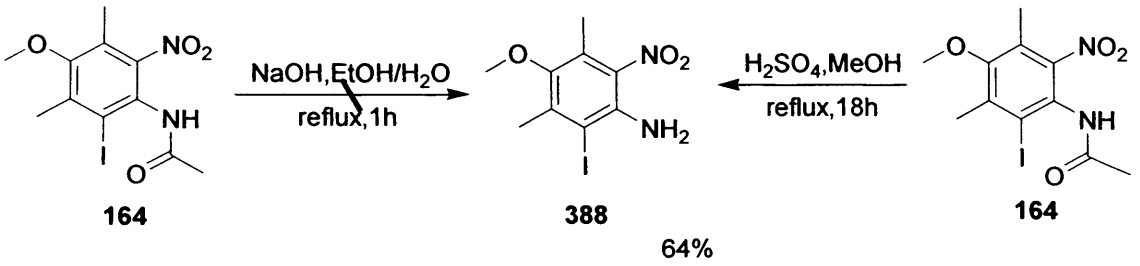
Since it was the amide group which caused the side reaction (it was attacked by the nucleophilic amine), we then planned to hydrolyse the amide before the hydrogenation reaction (Scheme 161).



Scheme 161

Compared to the original scheme, in which the acetyl group was removed after diazotisation, this new plan did not add any extra steps. Further, the amine **388** should be readily prepared from iodide **164**; if the Sonogashira coupling was successful, there would be only two steps (hydrogenation and diazotisation) towards the benzyne precursor.

The hydrolysis reaction was carried out in a hot sodium hydroxide (7 eq.) solution.[88] After a simple aqueous work up, we found that no reaction had occurred and the starting material was recovered (Scheme 162).



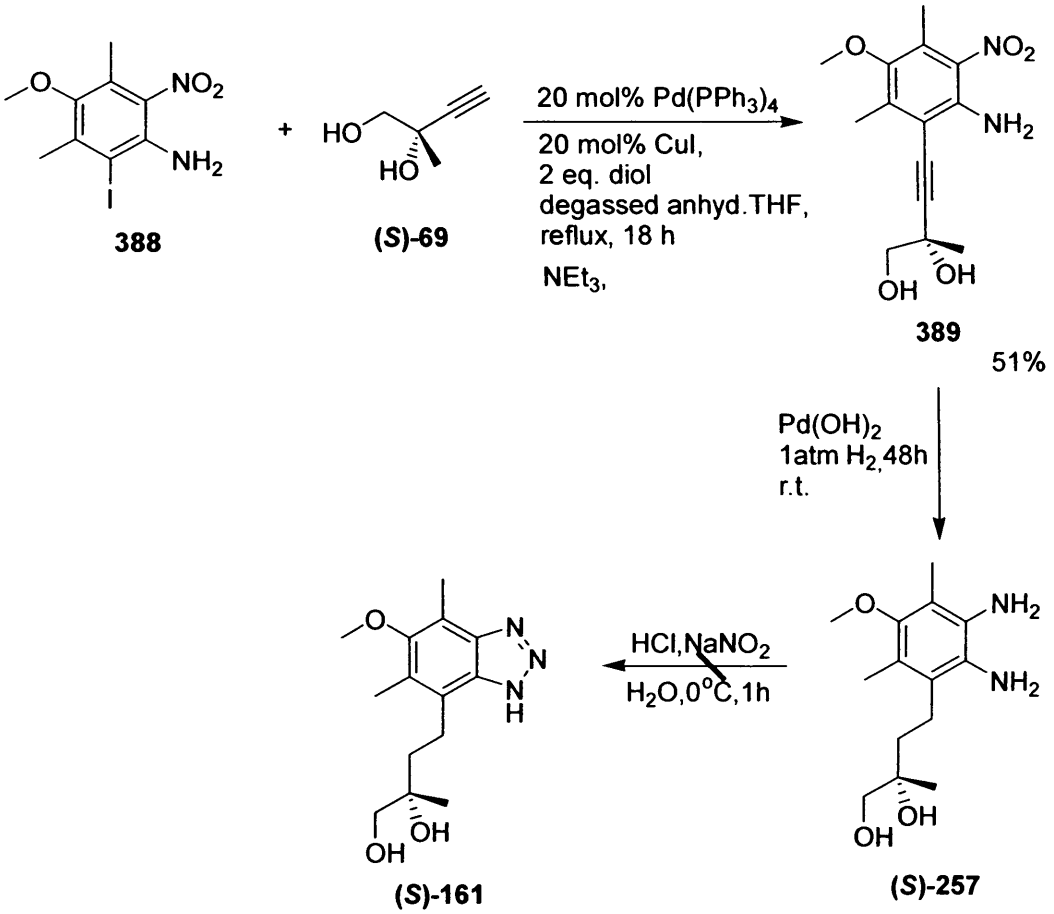
164 **388** 64% **164**

Scheme 162

Since the amide function was resistant to strong base (as above), we tried strong acid conditions. Following Renneberg's report,[89] our amide **164** was treated with concentrated H_2SO_4 in methanol; after 18 hours under reflux, the free amine **388** was obtained as an orange-yellow solid in a moderate yield (64%).

Our attempt at coupling the amine **388** and diol **(*S*)-69** by the general Sonogashira method was successful and gave the desired product **389** in a reasonable yield (51%) as an orange yellow-solid, after column chromatography (Scheme 163).

The subsequent hydrogenation was believed to have delivered the diamine **(*S*)-257** according to ^{1}H NMR analysis, but to our disappointment, the following diazotisation reaction[90] failed to give the benzotriazole **(*S*)-161**, as the ^{1}H NMR spectrum of the product was not identical with its racemic counterpart, which had been proven to be the correct compound and went through to the iodo-chroman **44**. The lack of carbon-hydrogen bonding change from this reaction made it difficult to identify the product by its ^{1}H NMR / ^{13}C NMR spectra.



Scheme 163

The failure of the above route might be because it involves the highly polar diamine **(*S*)-257**.

The above set of experiments could prove that our original route was more accessible towards the vitamin E precursor, as long as the Sonogashira coupling product **(*S*)-163** was purified extremely carefully, to get rid of traces of the impurities. Crystalisation should be an efficient way of purification, although part of the product would be lost.

Until now, extensive efforts on this subject have made and the validity of our methodology towards the vitamin E precursor has been proved by the racemic compounds, except the unoptimized yield of the final methylation step. The enantiomerically enriched side chain diol **(*S*)-69** has finally been synthesised successfully on a preparative scale, by seven linear steps. Therefore the enantioselective synthesis of the vitamin E precursor can possibly be claimed. Due to time constrains, this part of the project was stopped at this point.

Chapter Three

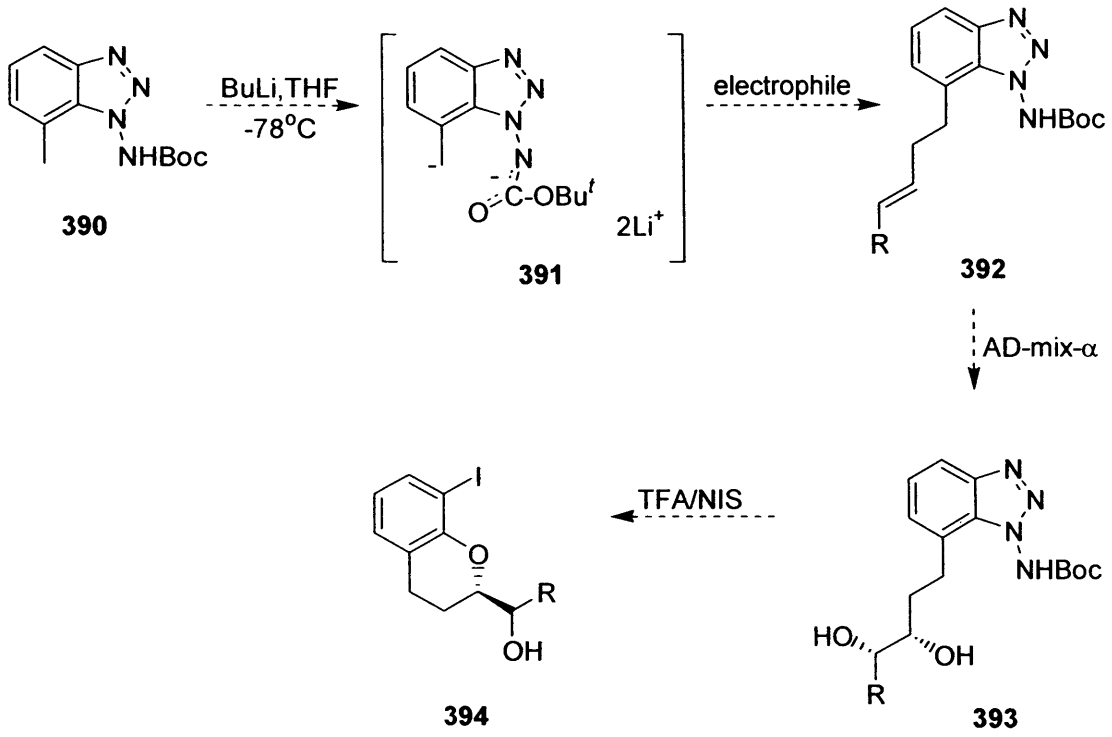
A Preliminary Investigation of a Tandem AD-mix / Benzyne Trapping Sequence

3.1 Introduction

As it was introduced in Chapter 1, Little's project[42] had arisen from the hypothesis that *ortho*-lithiation chemistry could be utilised to generate a new and general route to substituted benzyne precursors (Section 1.1.3) which could subsequently undergo cyclisations involving benzynes. During Little's exploration and investigations, a variety of chromans, chromenes and also iodoxanthenes were synthesised by the intramolecular trappings of benzynes by alcohols and phenols (Section 1.1.5, 1.1.6 and 1.1.7). Introduction of the necessary hydroxide groups was achieved directly by coupling or condensation of the benzotriazole moieties with acetylenic alcohols (racemic) or benzaldehydes (Section 1.1.4, 1.1.7). But this method has a limitation when contributing to natural product synthesis, in which it usually involves stereochemistry. While stereogenic centres could be incorporated into these electrophiles, it proved difficult to create single stereoisomers at the new secondary (or tertiary) alcohol site. Further, in some cases, the very presence of a secondary benzylic alcohol caused problems (*vide supra*). During our work on synthesising a vitamin E precursor, the chiral core was introduced by an AD-mix reaction on the terminal alkene followed by transformation to the required alkyne (Section 2.11). This led to a further idea: would it be possible to homologate the dianions **391** by addition of an unsaturated side chain which could subsequently be *bis*-hydroxylated asymmetrically? Other work by Little and Birkett[1,31,42] has shown that suitable diols tend to cyclise regioselectively with a strong preference for six- rather than five-membered ring formation. It also seems that neither four- or seven- membered rings can be obtained by this method.

An example of the idea is shown in Scheme 164. Starting with the 7-methyl derivative **390**, deprotonation to the dianion **391** followed by regiospecific alkylation using an allylic bromide should give the homologues **392**. Subsequent *bis*-hydroxylation should then provide the diols **393**, hopefully with high levels of enantioenrichment.

Our 'standard' protocol for benzyne generation might then be expected to lead to the iodochromans **394**.



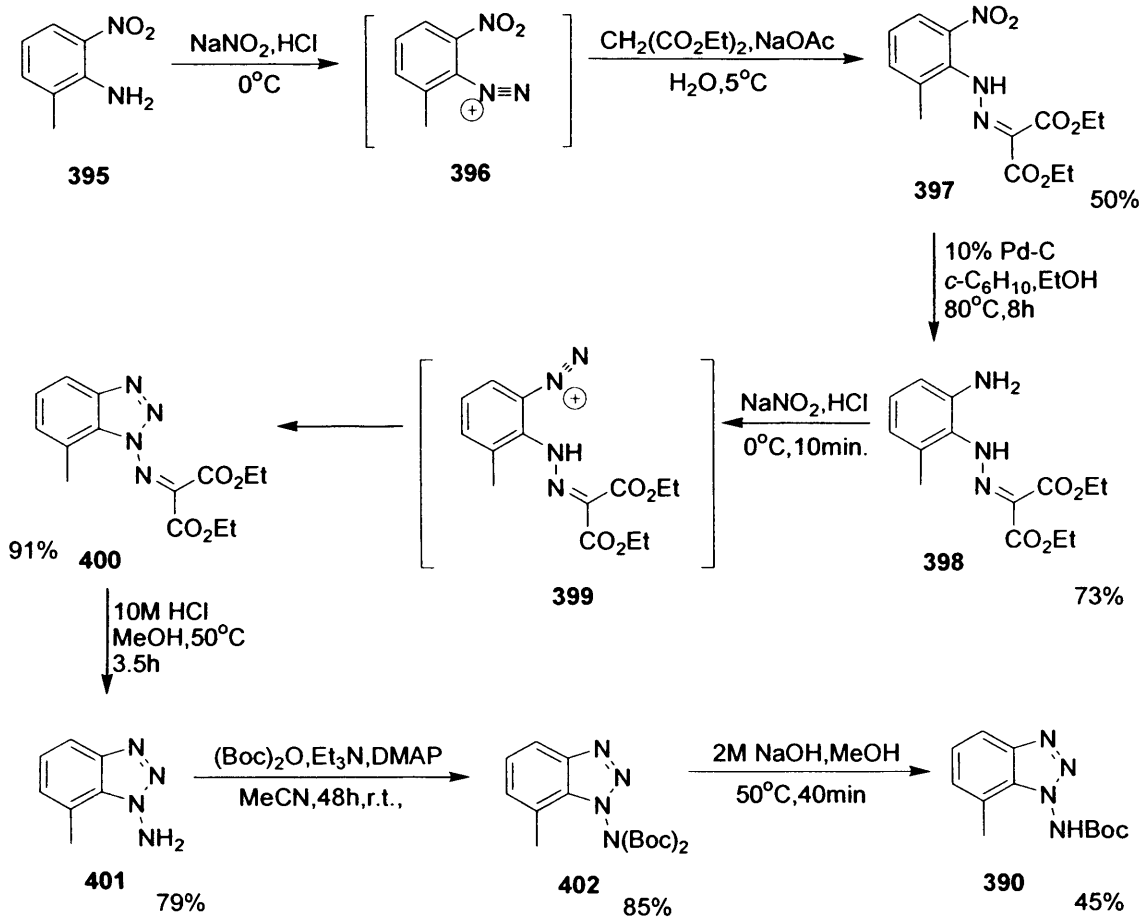
Scheme 164

7-Methyl-benzotriazol-1-amine **390** can be prepared from the corresponding commercially available nitroaniline in six steps, following Campbell and Rees' route,[91] modified by Birkett.[1d]

Clearly, there are many alternatives to this initial idea. The aim during this present project was to attempt to establish the principle expressed in Scheme 164 and to try and extend it, if successful, to *bis*-benzyne generation.

3.2 Synthesis of *N*-Boc-1-Aminobenzotriazole 390

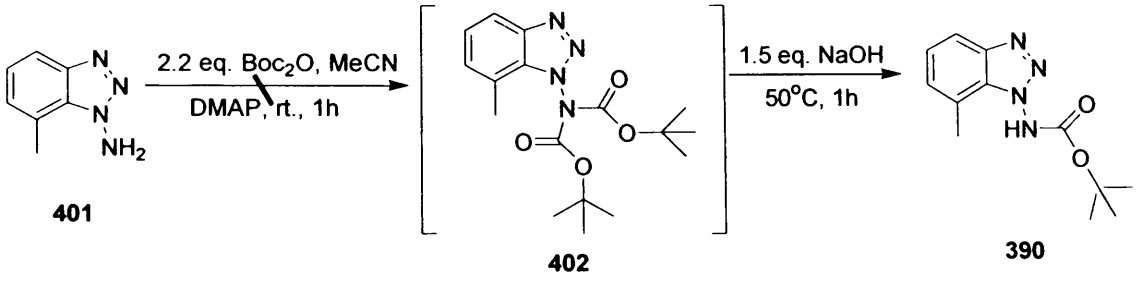
In pursuit of the idea above, the required *N*-Boc-1-aminobenzotriazole **390** was prepared following the route outlined in Scheme 165.



Scheme 165

Diazotisation of nitroaniline **395** and immediate trapping of the resulting diazonium salt **396** in a buffered, aqueous emulsion of diethyl malonate gave the product **397** as a brown solid. Purification by column chromatography and recrystallization led to the pure iminomalonate **397** as yellow crystals in a moderate yield (50%). Subsequent reduction of the nitro group by transfer hydrogenation,[45] using the combination of 10% Pd / C and cyclohexene in boiling ethanol, led to amine **398** after crystallisation (73%). Following our original method in Scheme 76 (section 2.6), this was then diazotised to form the salt **399**, which underwent rapid cyclization to give the protected aminobenzotriazole **400** in excellent yield (91%). Hydrolysis by 10M hydrochloric acid in methanol at 50°C gave the aminobenzotriazole **401** in a reasonable yield (79%).

Attempts to obtain the *mono*-Boc-protected aminobenzotriazole **390** by Little's one-pot, two-step procedure (Scheme 5, section 1.1.2) failed to deliver any product and the starting material was recovered (Scheme 166).



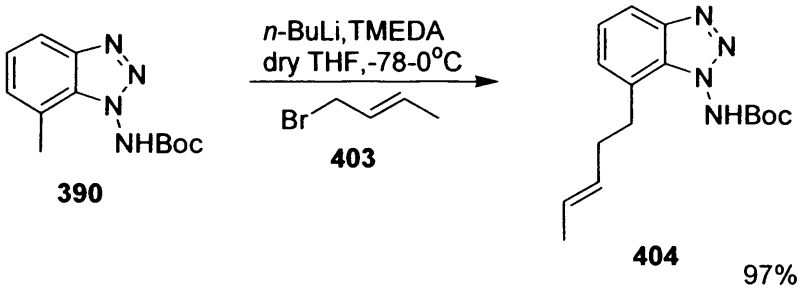
Scheme 166

This was possibly owing to the steric hindrance from the extra methyl group, which had prevented the free amine from attacking the electrophile. Thus, we increased the substitution time with di-*tert*-butyl dicarbonate ($(Boc)_2O$) by 42 hours, however, after hydrolysis with aqueous 2M NaOH, a mixture of the *bis*-Boc adduct **402** (~40%) and the starting amine **401** was formed according to ^1H NMR analysis. We then modified the condensation conditions by adding 2.2 equivalents of triethylamine; after a prolonged 65 hours stirring at room temperature, tlc analysis showed that conversion to the *bis*-Boc adduct **402** was complete. Unfortunately, the subsequent base hydrolysis using Little's conditions failed to remove any of the Boc group and the *bis*-Boc adduct **402** was re-isolated as the sole product (80%). However, treatment of this with 2M NaOH in methanol as the co-solvent successfully furnished the selectively deprotected product after 40 minutes at 50°C (45%). Therefore, Little's one-pot process has failed in our hands with 7-methyl aminobenzotriazole **401** which, after all, needs the original two-step method. It was unexpected that the methyl group would have such a considerable hindrance effect on both the condensation and hydrolysis reactions.

3.3 Towards the synthesis of (1'R,2R)-2-(1-hydroxyethyl)-8-iodochroman 407

3.3.1 Metallation-alkylation

We now had in hand a sufficient quantity of pure 7-methyl aminobenzotriazole **390**. The next step on our route to chroman derivatives with a chiral core, as shown in Scheme 164 (section 3.1, p.127), was lithiation of substrate **390** with subsequent alkylation by allylic halide electrophiles. We chose (*E*)-crotyl bromide for our first investigation of this subject (Scheme 167).



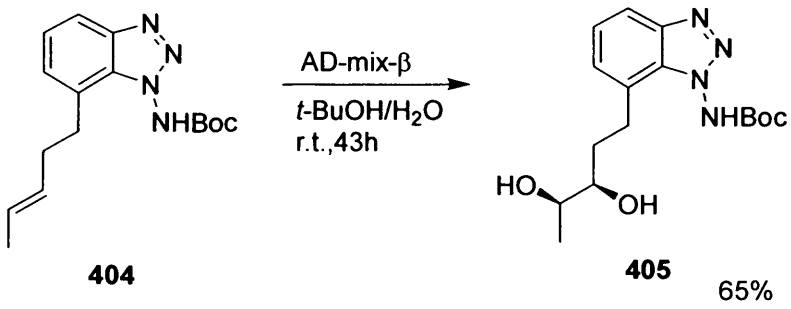
Scheme 167

Following the metallation-substitution procedure developed by Birkett,[1d,2,92] *n*-butyllithium (2.2 eq.) was added to a solution of freshly distilled *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (2.2 eq.) in dry THF at –78°C. After 15 minutes at this temperature, a solution of the aminobenzotriazole **390** in dry THF was added dropwise *via* syringe. This resulted in the formation of a burgundy red solution, which indicated that the metallation was taking place. Stirring this solution for 5 minutes before warming gradually to 0°C for 0.5h was then required for complete formation of the dianion **391**. To ensure regioselective alkylation at the (presumed) more reactive carbanionic centre, the reaction mixture was re-cooled to –78°C prior to addition of the electrophile – a solution of freshly distilled crotyl bromide **403** (1.1 eq.) in THF. After stirring at –78°C for 1h, the reaction was quenched using aqueous ammonium chloride. The resulting suspension was warmed gradually to ambient temperature and subjected to a standard work up. The crude material was separated by column chromatography using hexane/diethyl ether as the mobile phase, and the pure pentenyl aminobenzotriazole **404** was obtained in an excellent yield as a yellow gum.

The use of ethyl acetate as a column eluent was avoided, as the especially nucleophilic amine had been found to acetylate the NHBoc group, according to ^{1}H NMR analysis, and despite the deactivating (protecting) effect of the Boc group.

3.3.2 AD-mix reaction

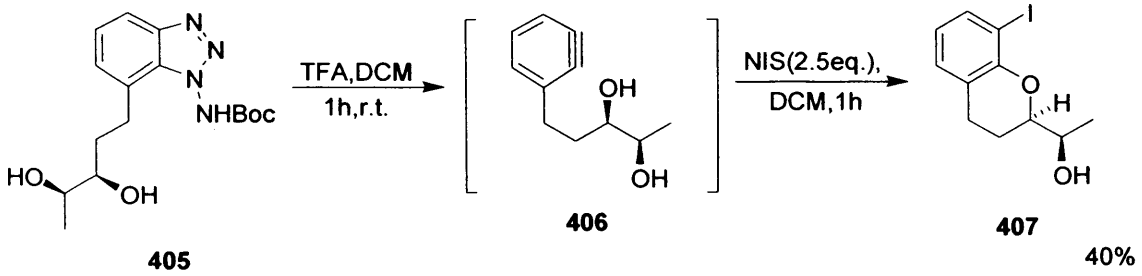
The general method of the AD-mix reaction (see above, pp.99-103) was applied to the pentenyl aminobenzotriazole **404**. The reaction was found to be very sluggish at 0°C; after 36 hours stirring at this temperature, it was found that only ~30% conversion had occurred according to ^{1}H NMR analysis. Presumably, this was due to steric hindrance from the bulky Boc group. The reaction was then repeated at room temperature as has been suggested in the literature[63] for solving this problem. As a result, the reaction was shown to be complete in 43 hours by tlc analysis and afforded the diol **405** in a reasonable yield (65%) after chromatography (Scheme 168).



Scheme 168

3.3.3 Deprotection-benzyne cyclisation

Using our well developed deprotection-cyclisation procedure on the N-Boc benzotriazole **71** we were delighted to find that this successfully delivered a new iodo-chroman **407** in a slightly disappointing yield of 40%.

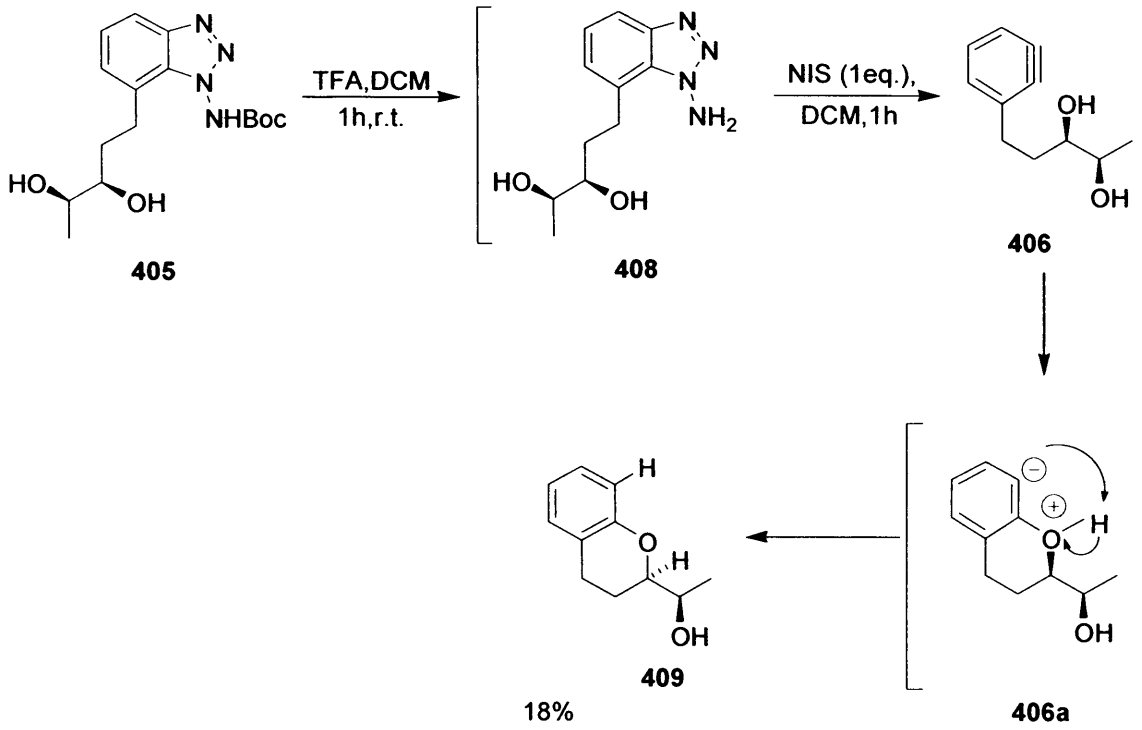


405 **406** **407** 40%

Scheme 169

The crude product, after purification by column chromatography, gave a optical rotation of $[\alpha]_D^{29} = -7.36$. The racemic form of this chroman **407** was also synthesised for the purpose of determining the enantiomeric excess (ee.) using chiral HPLC. The *bis*-hydroxylation on alkene **404** was repeated but with quinuclidine in place of $(DHQD)_2PHAL$ ligand, before another deprotection-cyclisation. Unfortunately, it proved impossible to obtain a clear separation for the (-)-chroman **407** with a small amount of impurity. Therefore, an accurate ee could not be measured. According to ^1H NMR analysis, no evidence was found for seven- membered ring formation.

Also, we investigated the use of one equivalent of NIS in this reaction, instead of the usual 2.5 equivalents. Presumably in this case, the benzyne intermediate formed could attack a hydrogen on the OH group, to form a non-iodinated chroman **409**. Indeed, it was achieved, albeit in a poor yield (18%) (Scheme 170).



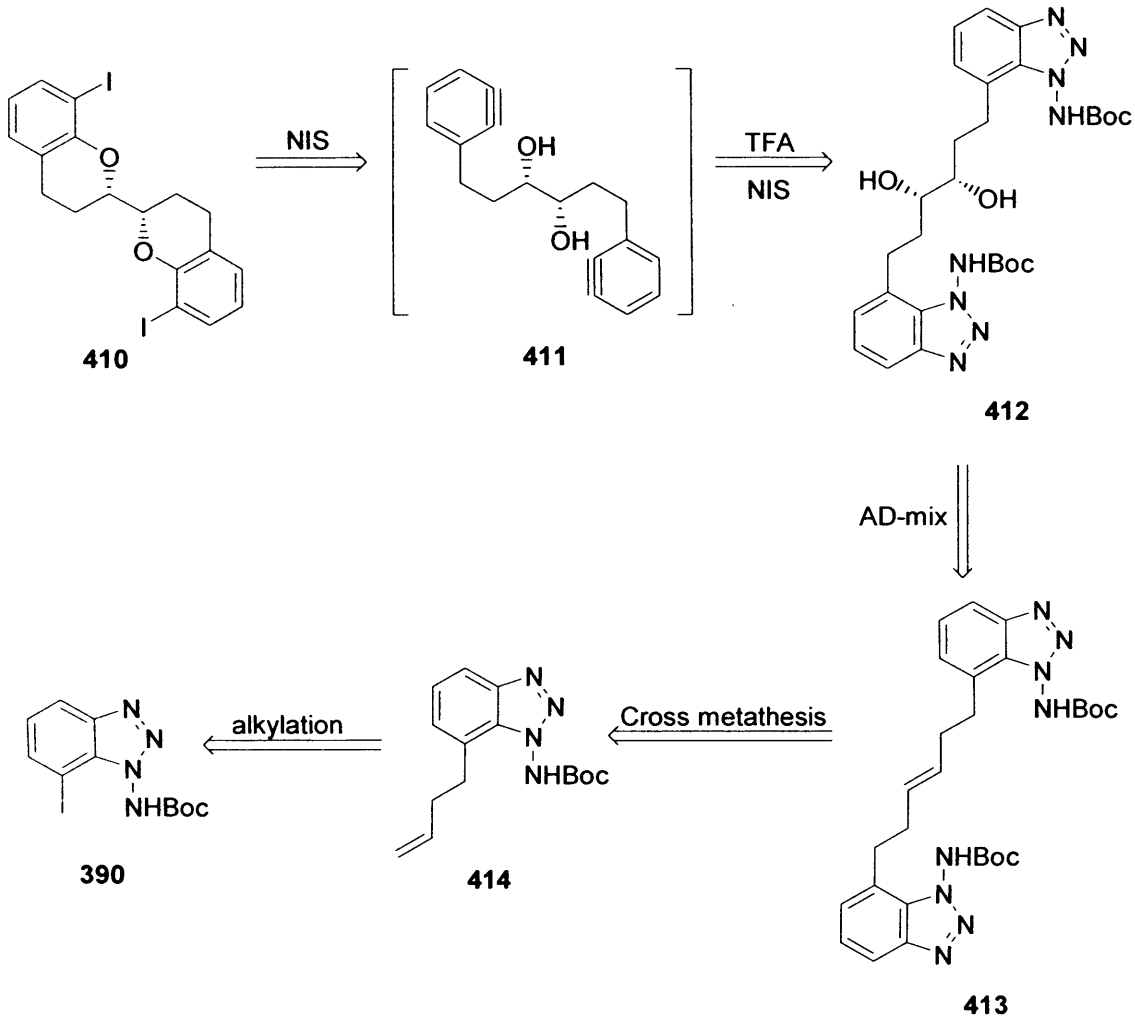
Scheme 170

In this reaction, the NIS added has been consumed by the amino-benzotriazole **408** to form the benzyne **406**, subsequently the intermediate **406a** trapped the hydrogen from the OH cation and gave the chroman **409**. The low yield of this reaction could possibly be improved by adding slightly more (1.3 eq.) of the NIS reagent. But owing to a limit of the synthetic utility of this unsubstituted chroman **409**, any further study on this subject has not been carried on.

3.4 Attempt of *bis*-benzyne cyclisation to form symmetrical dichromans 410

Until now, our benzyne cyclisation with diols had all successfully delivered six-membered rings, in another words, the hydroxide group closer to the benzyne had 'won' and traps the electrophile to form more stable six-membered rings as we had expected; no evidence for seven-membered ring products had been found. Based on this result and the idea that *bis*-benzyne trapping by both OH groups could form dichromans that are useful for natural product synthesis, we began our investigation on this subject. The retrosynthesis from the symmetrical dichroman **410** was thus

planned (Scheme 171). If successful, it will be a considerable enhancement on the scope of our benzyne cyclisation methodology.

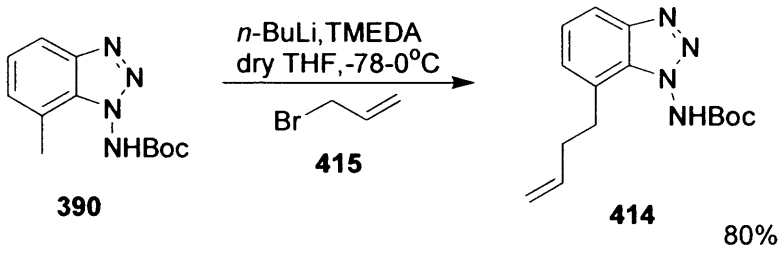


Scheme 171

The dichroman **410**, which is a symmetrical dimeric version of the chroman **407** we had made, was expected to be formed from the dibenzyne intermediate **411**; alternatively, the reaction could give seven-membered rings. Thus, the benzyne precursor, di-benzotriazole **412** was required. Of course, the key cyclisations could and probably do occur in a stepwise manner. An AD-mix reaction should give the diol function from alkene **413**, which could be achieved by cross-metathesis[93] of two molecules of benzotriazole **414** by using Grubb's catalyst. Alternatively, the forgoing Birkett dianion method could be combined with a 1,4-dihalo-2-butene.

3.4.1 Preparation of 7-butene benzotriazole 414

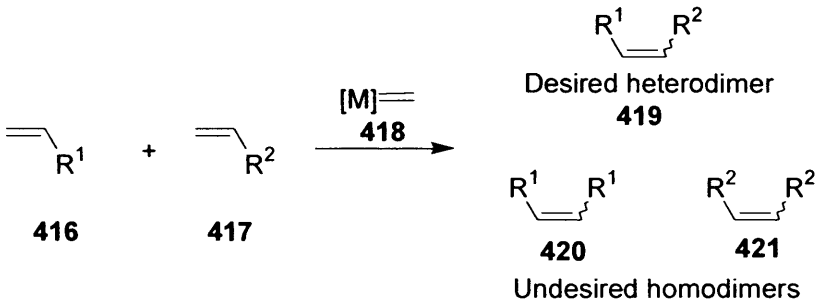
Applying the metallation-alkylation procedure as described above, benzotriazole **390** was reacted with freshly distilled allyl bromide **415** to give the 7-butenyl benzotriazole **414** in a good yield (80%) (Scheme 172).



Scheme 172

3.4.2 Cross-Metathesis

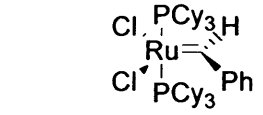
As a unique method for the intermolecular formation of carbon-carbon double bonds, olefin cross-metathesis (CM) has not yet found widespread application in organic synthesis, but is very likely to do so. This is because the general reaction conditions that give high product selectivity have not been developed. The simplified CM reaction between two terminal olefins is depicted in Scheme 173.[93]



Scheme 173

Generally, this reaction proceeds to yield three unique products: the desired heterodimeric product **419** and two undesired homodimeric products **420** and **421**, each as a mixture of olefin isomers. But in the case of self-metathesis ($R^1 = R^2$) that is, the reaction we were carrying out, the unwanted heterodimeric situation would clearly not apply.

The most extensively used catalysts for terminal olefin cross-metathesis is the carbene complex- ruthenium benzylidene **422** (Scheme 174), developed by Grubbs *et al.*[94]

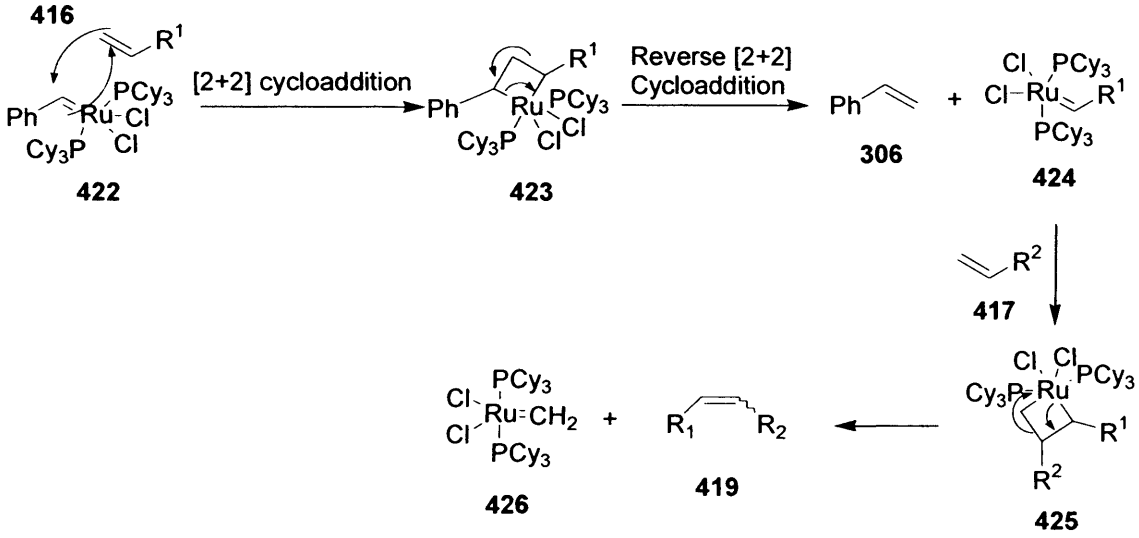


PCy_3 = tricyclohexylphosphine

422

Scheme 174

First, the Grubb's complex **422** adds to one of the alkenes in what can be drawn as a [2+2] cycloaddition to give a four-membered ring as the metalla-cyclobutane **423** (Scheme 175). Reverse of the cycloaddition, but by cleavage of the other two bonds, gives a new carbene complex **424** and styrene **306**.

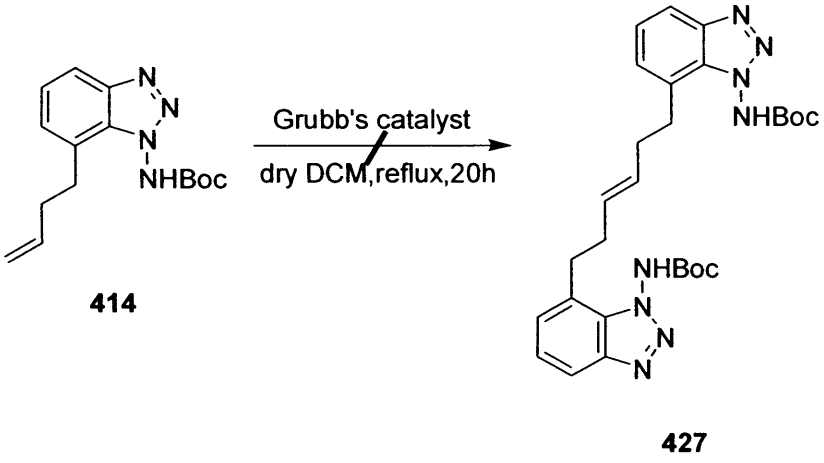


Scheme 175

Next, another [2+2] cycloaddition joins the carbene complex **424** and the other alkene **417** and produces a second metalla-cyclobutene **425**, which can decompose in the same way as the first one to give the desired product **419**, and the third carbene complex **426**. This then attacks another molecule of starting material and the cycle is repeated.

According to a study by Blackwell,[93] all of the olefin CM reactions have favoured the formation of the *trans* isomer. In respect of our aminobenzotriazole **414**, the compatibility of Boc-protected substrates was also probed by Blackwell;[93] it was found that the CM of *N*-Boc derivatives could successfully provide predominantly *trans*-disubstituted amine derivatives (3:1 *E*/*Z*) in good yields.

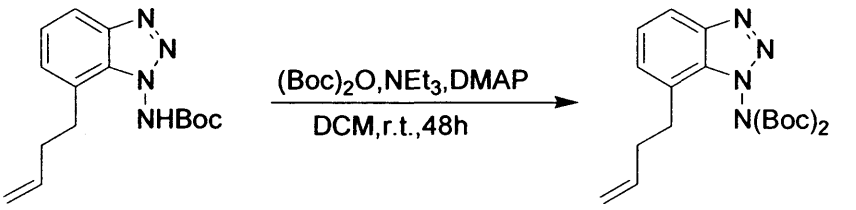
Therefore, we employed the standard CM conditions for homodimerizing our aminobenzotriazole **414** (Scheme 176).



414 **427**

Scheme 176

After refluxing the starting material with Grubb's catalyst **422** (5 mol%) in dry dichloromethane overnight, no reaction had occurred. The procedure was thus repeated but with four times the quantity (20 mol%) of the catalyst; unfortunately, this gave the same result. We suspected that it was the amino group [–NHBoc] which was destroying the Grubb's catalyst, as the 'α-effect' from the nitrogen atom next to the amino function could dramatically enhance its nucleophilicity (see above-this group can react with ethyl acetate during chromatography). To solve this problem, we planned to *bis*-protect the amino group to form the presumably less reactive *bis*-Boc derivative **428** (Scheme 177). This additional group could then be removed by the same method as in the case of the [-NHBoc] derivatives during the deprotection/ benzyne cyclisation process.

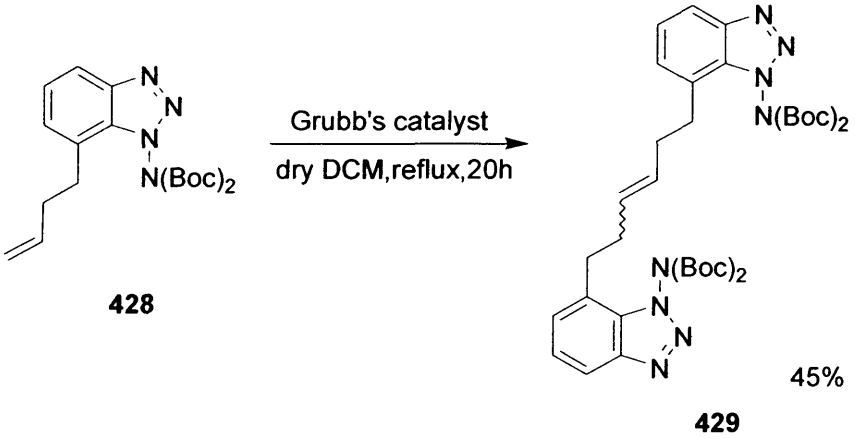


414 428 58%

Scheme 177

Using the same procedure in Scheme 165 (section 3.2) from the free amine **401** to *bis*-Boc **402**, but with 1.1 equivalent of Boc anhydride, the condensation went smoothly and delivered the *bis*-Boc adduct **428** in an acceptable yield (58%).

We were then delighted to find that the subsequent cross metathesis, using the standard conditions, successfully afforded the alkene **429**, despite the presence of the four bulky Boc functions (Scheme 178). After 20 hours under reflux, the reaction was cooled to room temperature. The solvent was removed and the crude material was purified by column chromatography to give alkene **429** in a moderate yield (45%).



428 45%

429

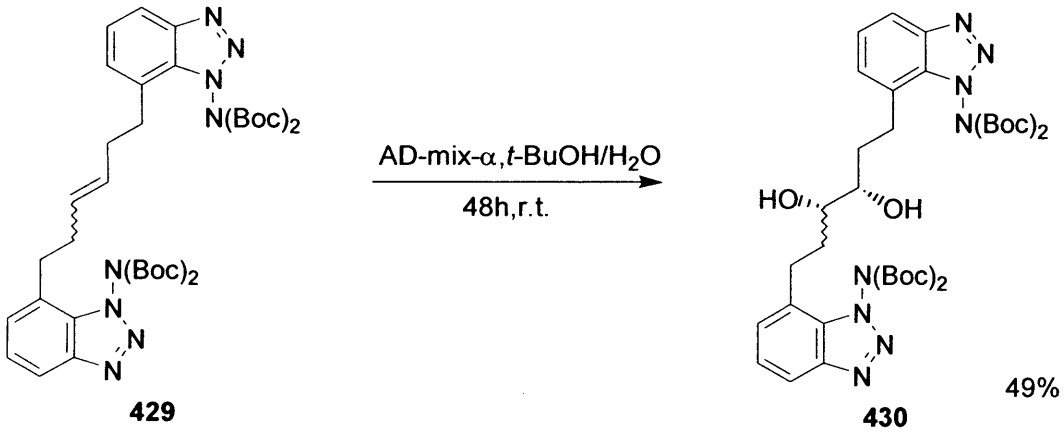
Scheme 178

Integration of ^{1}H NMR spectra showed that the product could be a single isomer, but the possibility of a mixture of two isomers cannot be ruled out. The symmetry of the compound may prevent the determination of a coupling constant, which would confirm the formation of (*E*)-isomer. CHs on the double bond showed a single multiplet. The two CH_2 groups next to the benzene ring show a triplets and a multiplet while the other pair of CH_2s' is a multiplet. These different resonances for the symmetrical CHs and CH_2s could result from multiple conformations of the molecule.

The ^{13}C spectrum shows a doubling of peaks, at δ 85.9 and δ 85.8, of the quaternary carbon of the BOC group, this doubling can either be due to restricted rotation of the BOC group, if only one isomer has formed, or it can be due to the formation of *E* and *Z* isomers. One way of determining which of these possibilities is correct would be the use of variable temperature NMR experiments; the rotamers would coalesce into a single signal, whereas the *E* and *Z* isomers would not.

3.4.3 AD-mix reaction

The AD-mix reaction of the dimer **429** was successful to give the symmetrical diol **430** (Scheme 179), which was ready for the key deprotection / benzyne cyclisation.



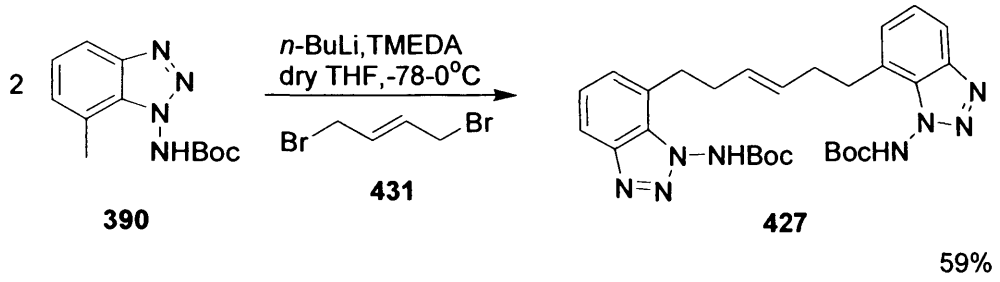
Scheme 179

The reaction was carried out at room temperature for a prolonged 72 hours and delivered the diol **430** in a moderate yield (49%). Again in diol **430** there is a doubling of the Boc quaternary carbon in the ^{13}C spectra, which can be due to the existence of either rotamers or diastereoisomers.

3.4.4 Preparation of *bis*-aminobenzotriazole 427 in a single step and the subsequent AD-mix reaction

Meanwhile, we also applied the original metallation-functionalisation method to aminobenzotriazole **390** with (*E*)-1,4-dibromo-2-butene **431**. If this double lithiation-

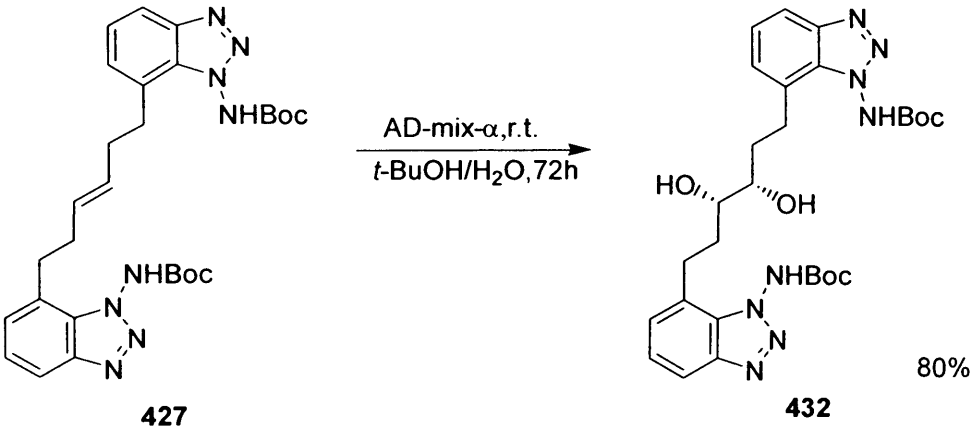
alkylation was successful, the *trans*-diaminobenzotriazole **427** could be obtained in one step (Scheme 180).



Scheme 180

Following the general procedure, 2.4 equivalents of aminobenzotriazole **390** was reacted with 1.5 equivalent of dibromo-butene **431** (98% from Aldrich). As a result, the desired product **427** was obtained as a colourless solid in an improved yield (59%) after column chromatography. ^{1}H NMR spectra showed very similar shifts compared with that obtained from the cross-metathesis-alkene **429**, which is possibly a single (*E*)-isomer. All the four CH_2s appeared as broad peaks and the CHs as a multiplet. Again, these are possibly caused by the free rotation of C-C bonds.

Another advantage of this one-step method is that the *mono*-Boc function provides less steric hindrance for the following AD-mix reaction; thus we favour this route. The subsequent *bis*-hydroxylaion, however, took the same long time at room temperature, but gave an improved yield of the product **432** (Scheme 181).

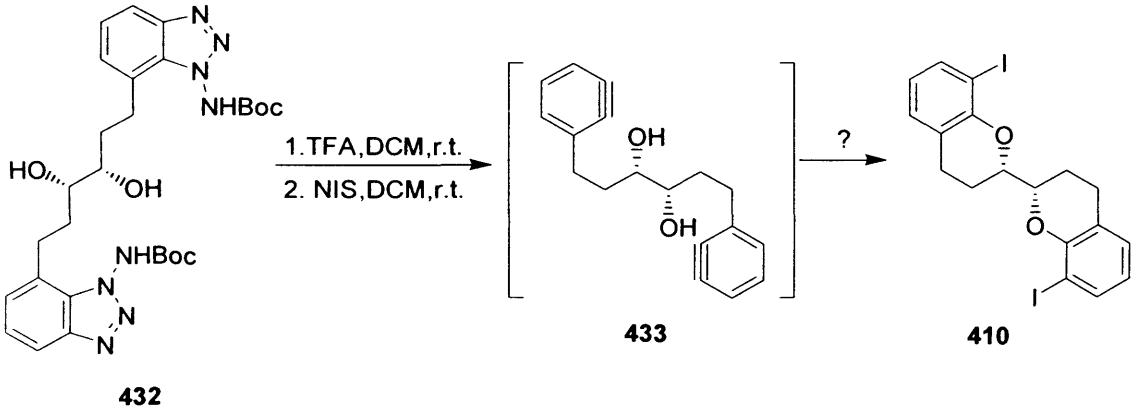


Scheme 181

The reaction was initially carried out at 0°C; after 24 hours' stirring, no reaction had occurred according to tlc. The solution was then gradually warmed to ambient temperature; the reaction was complete after 72 hours at this temperature, to afford the diol **437** as a pale yellow oil in excellent yield. Again, the ^{1}H NMR spectra shows a very similar pattern to diol **430**.

3.4.5 Towards the synthesis of dichromans 410

Finally, we tried our hand at the novel reaction. The normal deprotection / cyclisation process was applied but with twice the amount of the reagents; not surprisingly, the desired product was obtained in a low yield (~20%) after column chromatography.

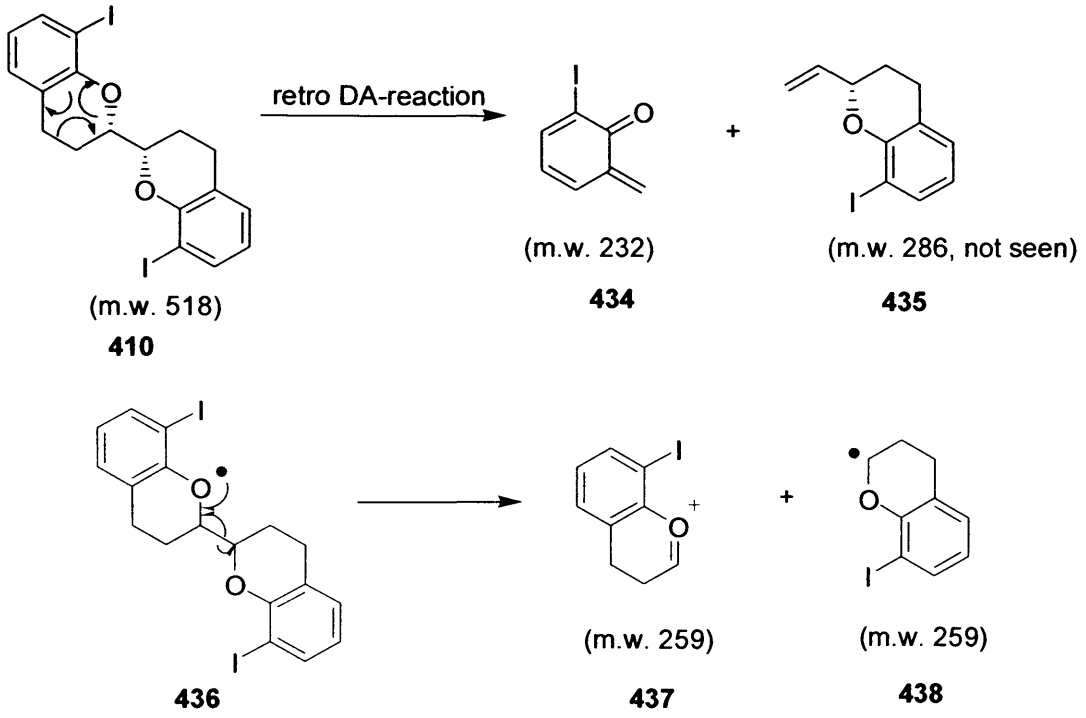


432 **433** **410**

Scheme 182

The ^{1}H NMR spectrum of this compound showed a different pattern compared to the starting material, especially for the methine and methylene resonances. The methylenes next to the benzene ring still showed as multiplets but were positioned from 2.81 to 3.13 ppm (width 0.32 ppm), rather than at 3.12-3.17 ppm in the starting material. Presumably, this could be two double, double doublets overlaping with each other. Although the structure is symmetrical, owing to the possible rotation about the C-C bond at the centre, the methylene protons could be slight different and so they showed as multiplets. The other pair of CH_2s had also changed from a broad singlet at 1.86-2.01 ppm to a multiplet at 1.75-1.98 ppm. The ^{13}C NMR spectrum showed a promising C-I resonance at 80.1 ppm. But mass spectra (EI+) analysis did not support

this conclusion. The calculated mass of the desired compound was 518.132, while ions at 232, 259, 260 (base peak), were found. It might be possible that the chroman decomposed by a retro-Diels-Alder reaction, as showed in Scheme 183. If this did happen, the peak of 232 could be explained. An alternative fragmentation, but involving cleavage of the central carbon bond would account for the ion M/Z 259.



(Likely ionised molecular ion)

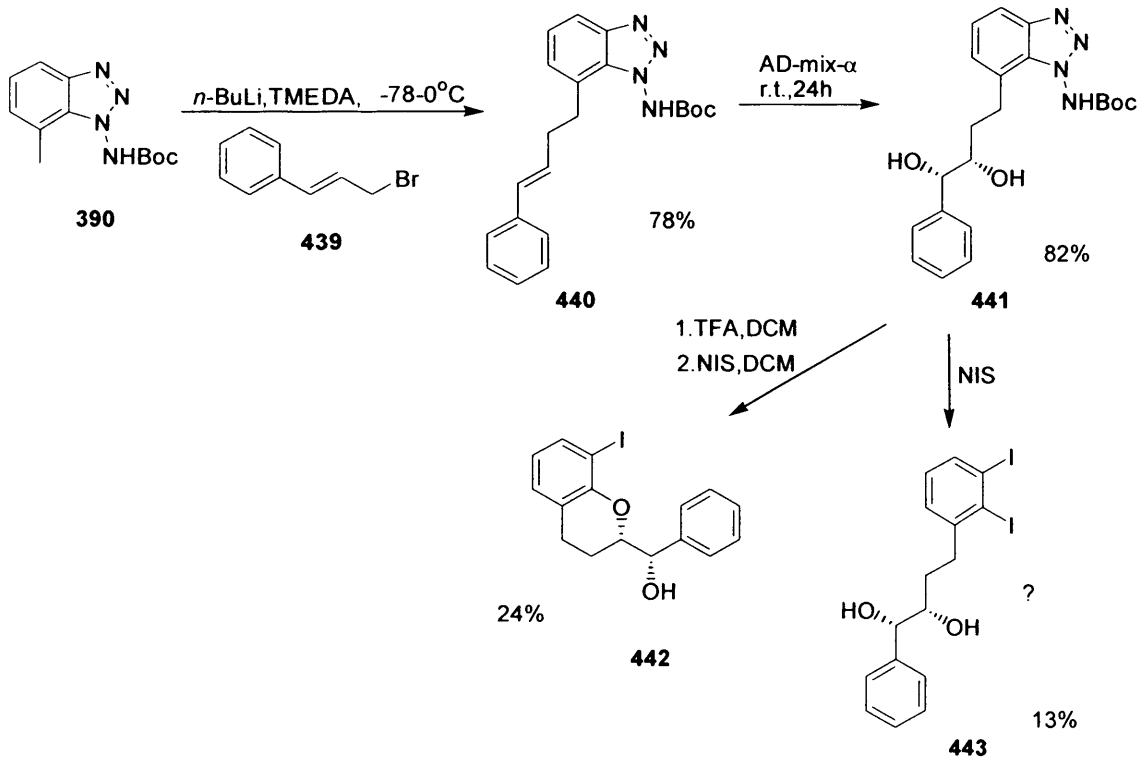
Scheme 183

Further investigation was still needed on this subject. We found that the feasibility of this double benzyne trapping was quite possible. The above work was on rather small scales. Time constrains and diminishing material meant that this could not be repeated; obviously, it needs to be. It should be emphasised again that, during this pilot study, no special efforts were made to measure optical purity as it was far from clear at the outset if any of the chemistry would actually work. The ^{13}C NMR spectra of dimer **429**, diol **430** and **432** show more peaks than expected. Diol **432** is formed from the *trans*-diaminobenzotriazole **427**, so the extra peaks in this case are presumably due to restricted rotation of the Boc groups. The dimer **429** and **430** are produced by cross-

metathesis, so that the extra peaks could conceivably be due to the formation of double-bond isomers. Alternatively they could also be due to restricted rotation. We have no evidence which allows us to distinguish the two possibilities at the present time, and this issue should be addressed as a priority in further work in this area.

3.5 The synthesis of (1'-hydroxy-1'-phenyl)-8-iodochroman 442

As was introduced in sections 1.1.5, 1.1.6 and 1.1.7 (table 3, entry 5; table 4, entry 4, and Scheme 8) in Chapter 1, Little has experienced difficulties deprotecting substrates which contained benzylic hydroxyl functions. Such substrates degraded presumably *via* a benzyl carbocationic intermediate, following proton-assisted loss of the hydroxyl group. Bearing this in mind, we attempted a similar benzyne cyclisation following the sequence outlined in Scheme 184, in which R = Ph. If successful, this would represent significant progress on this subject (Scheme 184).



Scheme 184

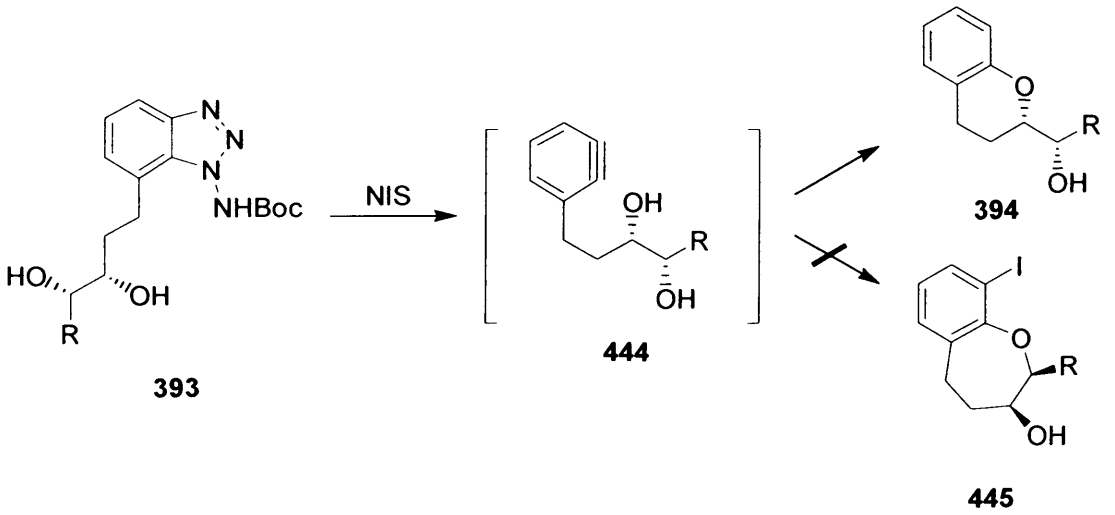
Following the general method of metallation /functionalisation on benzotriazole **390** with cinnamyl bromide **439**, the benzylic alkene **440** was obtained in a good yield.

Subsequent *bis*-hydroxyation gave the diol **441**, which successfully underwent deprotection / benzyne cyclisation and delivered the desired benzylic chroman **442**, albeit in a low yield (24%). Meanwhile, a by-product, which was believed to be diiodobenzene **443** by tlc. analysis (13%) was also found, after the column chromatography. This was believed to be the main reason of the low yield. The degradation that we expected has not been discovered.

In general, a series of non-racemic chromans were achieved by the new route above, through which two stereogenic centers were created using AD-mix reaction. This method could be seen as an extension of Little's benzyne chemistry, which involves single hydroxyl function without chiral centers. The procedure could also increase the feasibility of our benzyne chemistry towards other natural product synthesis.

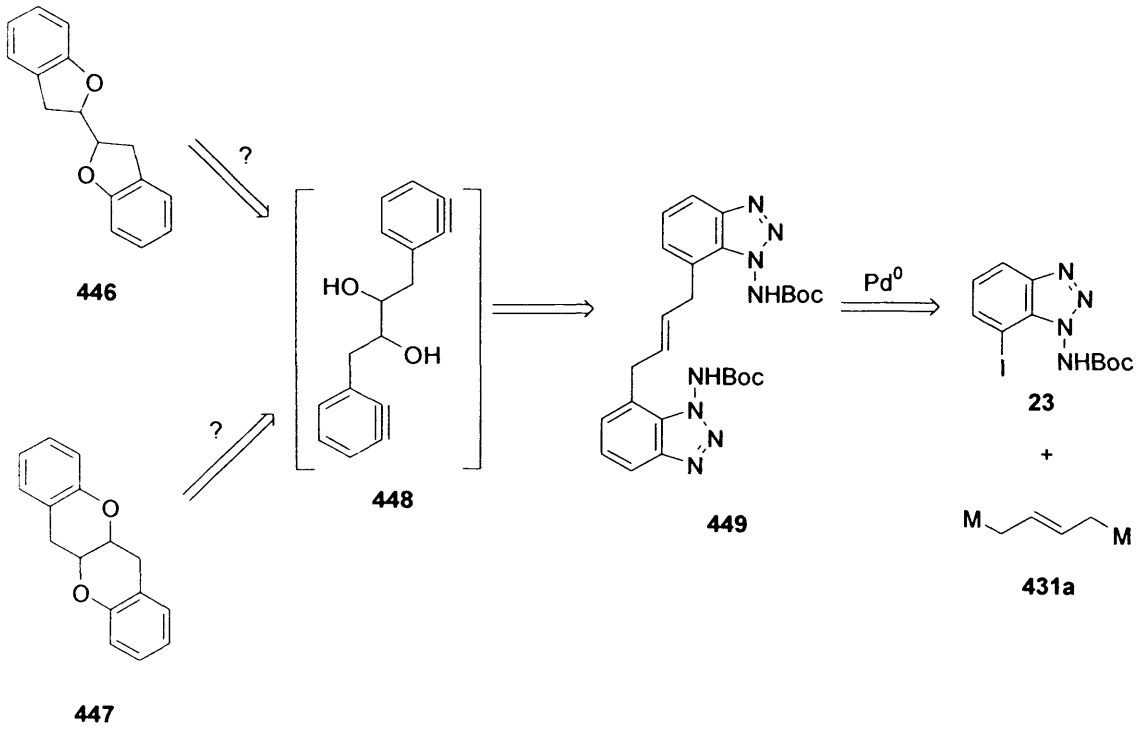
3.6 Further Work

Until now, we had successfully synthesised a series of new chromans from non-racemic diols. During these benzyne cyclisations, there was 'competition' between the two hydroxyls; trapping of the 3'-OH would form a six-membered chroman ring while trapping of the adjacent 4'-OH should furnish the larger seven-membered ring (Scheme 185).



Scheme 185

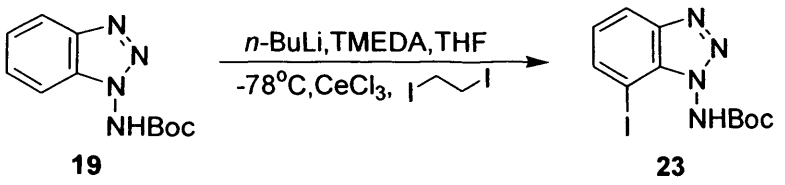
According to our studies, no such seven-membered ring derivatives **445** have been found. Therefore the six-membered ring formation was favoured over its seven-membered counterpart. This could because the 3'-OH was closer towards the benzyne function and the resulting six-membered ring was more stable. This intrigued us and generated another question: when there was a 'competition' between a six-membered ring and a five-membered ring, which one would be more favoured? Thus, we had planned another double benzyne cyclisation, which could possibly give us an answer. The retrosynthetic analysis is showed in Scheme 186. The idea was to synthesise a 2',3'-diol derivative **448**, which could undego benzyne trappings to form two possible products -- the five-membered ring system **446** and a four-fused six-ring-based system **447**; a mixture of the two could also be obtained, of course.



Scheme 186

Regarding the synthesis of the benzyne diol **448**, presumably it could came from the corresponding benzotriazole alkene **449**, which could be made from iodide **23**, presumably by using a palladium catalysed coupling reaction with organometallic reagent **431a** (M=MgX, ZnX, Cu, SnR_3 etc.). The iodide **23** has now been made and was ready for the following study on this subject.

Attempts to prepare the iodide **23** were successful using the cerium exchange chemistry developed by Little (Scheme 187).



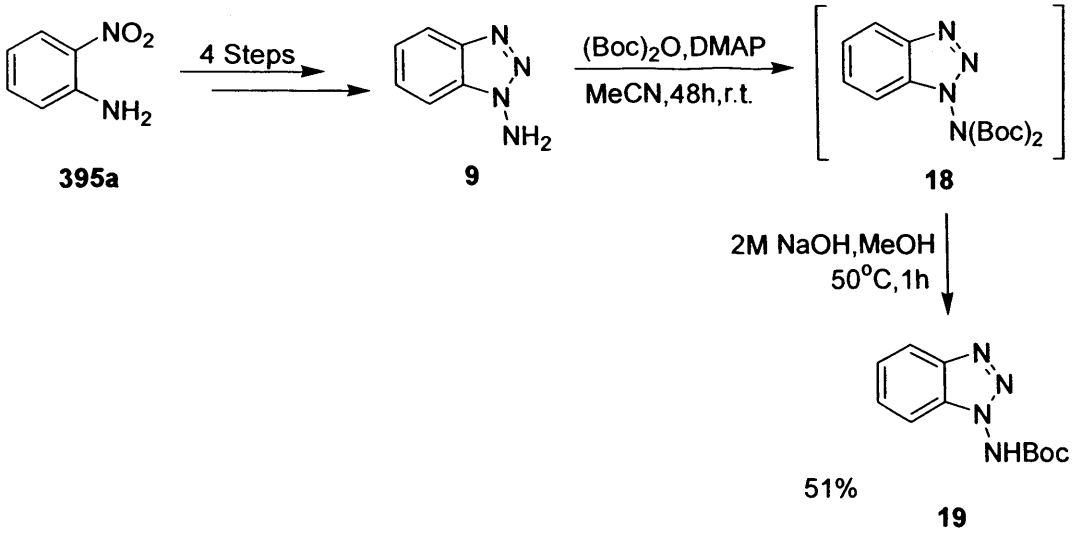
19 **23**

56%

Scheme 187

To a solution of freshly distilled TMEDA in dry THF at -78°C was added butyl lithium. Aminobenzotriazole **19** in dry THF was then added slowly *via* a syringe. The resulting deep purple dianion solution was stirred for 30 minutes at this temperature. Concurrently, a suspension of anhydrous cerium(III) chloride in THF at -78°C was titrated with butyl lithium until the first faint but permanent orange end point. The dianion solution was then rapidly transferred *via* syringe to the anhydrous cerium(III) chloride suspension. The resulting mixture was stirred at -78°C for 3 hours, before the rapid addition of 1,2-diiodoethane in THF. The mixture was gradualy warmed to room temperature and stirring continued overnight, then the reaction was worked up as in the general metallation-functionalisation method. The pure iodination product **23** was obtained as a light brown solid in a moderate yield (56%).

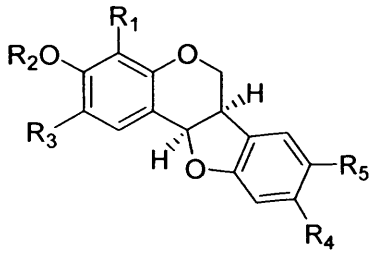
The aminobenzotriazole **19** was prepared in a substantial amount by the same route of its methyl substituted counterpart **390** as showed in Scheme 165, except that the transformation of 1-aminobenzotriazole **9** to *mono*-Boc aminobenzotriazole **19** was accomplished by the one-pot, two step procedure as described in Section 3.2 (Scheme 165). The employment of this route was due to large amount of starting material, nitro aniline **395a**, which was readily available in our laboratory.



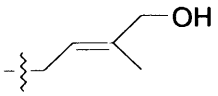
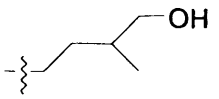
395a 9 18 19

Scheme 188

Hence, at this trial stage of the present project, the necessary precursors are now available to continue. On the other hand, this benzyne cyclisation chemistry could also be applied to the total synthesis of pterocarpans **450** (Scheme 189), which carries a *cis*-fused benzofuranyl-benzopyran skeleton, and which form the second largest group of naturally occurring isoflavonoids. Many of their derivatives exhibit remarkable pharmacological activities such as antifungal, antibacterial and anti-HIV effects.[95]



450

	R_1	R_2	R_3	R_4 R_5
450a		H	H	$-OCH_2O-$
450b	H	H		$-OCH_2O-$

Scheme 189

In 1982, Nakanishi and co-workers[96] also demonstrated that two representatives of these natural products, cabenegrin A-(I) **450a** and cabenegrin A-(II) **450b**, showed activity against snake and spider venom but their mode of action is still to be explored. These orally-active snake venoms antidotes were isolated from the aqueous ethanol extract of a South American plant called locally 'cabeca de negra'. The compounds have also been synthesised.[97]

The retrosynthetic analysis of cabenegrin A-(I) **450a** involving double benzyne cyclisation and is laid out in Scheme 190.

The cabenegrin A-(I) **450a** precursor **451** could be achieved by a Heck-type coupling reaction between pterocarpan **452** and alkene **453** with Pd(0) catalyst. From structure **452** the benzyne precursor **454** can be deduced, which should be ready for benzyne generation/ cyclisation with NIS. Since the benzofuranyl ring could also be formed by a similar manner, *bis*-aminobenzotriazole **455** was thus needed. As there is no iodine on precursor **454**, use of lead *tetra*-acetate[2] $Pb(OAc)_4$ should be necessary for oxidising aminobenzotriazole **455** instead of using NIS. Compound **455** could possibly be prepared by selective reduction of ester **456**.

Chapter Four

Experimental

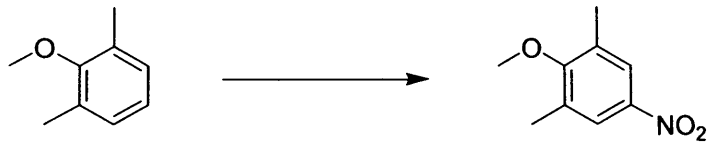
Experimental:

General Details

Infrared spectra were recorded on a Perkin Elmer 1600 series FTIR instrument as thin films. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 400 (400MHz, PFT) instrument, with the ^{13}C being recorded at 100MHz. The following abbreviations were used; s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, br s = broad singlet etc. *J* values are quoted in Hertz. The abbreviations δ_H and δ_C denote ^{1}H and ^{13}C NMR, respectively, taken at 300 K. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) from tetramethylsilane (or chloroform) and are corrected to 0.00 (TMS) and 7.27 ($CHCl_3$) ppm for ^{1}H NMR and 77.30 ($CDCl_3$), centre line, for ^{13}C NMR. Unless otherwise stated, deuteriochloroform was used as solvent for NMR measurements. Molecular weights were determined using a Fisons VG Platform II instrument and CHN microanalytical data were collected on a Perkin Elmer 240C Elemental Analyzer. High resolution mass spectra were obtained courtesy of the EPSRC Mass Spectrometry Service, Swansea University.

All reactions using air / moisture sensitive reagents were performed in oven-dried or flame-dried appraratus, under a nitrogen atmosphere. Solvents and reagents were purified according to procedures set out in 'Purification of Laboratory Chemicals', by D.D. Perrin and W.L.F. Armarego. 'Petrol' refers to light petroleum, b.p. 40-60°C; 'ether' refers to diethyl ether. Unless otherwise stated, butyl lithium refers to n-butyl lithium (various molarities in hexanes). All organic solutions were dried by brief exposure to anhydrous magnesium sulphate. Column chromatography was performed using silica gel (Silica 60A particle size 35-70 micron from Fisher Scientific).

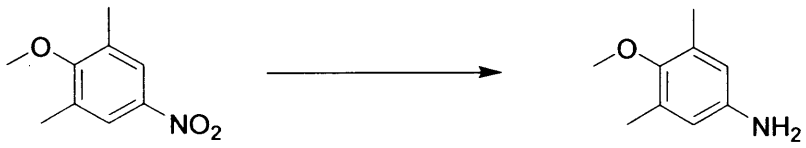
2,6-Dimethyl-4-nitroanisole 51



50 **51**

To an ice-cold solution of 2,6-dimethylanisole **50** (40 g, 294 mmol) in glacial acetic acid (60 ml), nitric acid (70%, 60 ml) was added dropwise. After the addition was complete and the majority of the gas had been evolved, the solution was carefully heated to 65°C to give a pale yellow solution. The solution was then allowed to cool to room temperature before being diluted with water (360 ml). Nitrogen was bubbled through the resulting solution for 0.5h to remove nitrogen dioxide from the now deep brown suspension. The yellow precipitate was collected and washed with copious water. The crude product was recrystallised from ethanol to give the *nitroanisole* **51** as yellow needles (32.6 g, 61%), m.p. 91.5-93.5°C (lit.[44] m.p. 89-91°C), ν_{max}/cm^{-1} 2964, 1590, 1516, 1351, 1006, 898 and 765; δ_H 2.28 (6H, s, 2 × CH_3), 3.71 (3H, s, OCH_3), 7.83 (2H, s, 2 × Ar-H); δ_C 16.8 (2 × CH_3), 60.3 (OCH_3), 124.6 (2 × CH), 132.7 (2 × Ar-C), 143.8 (Ar-C), 162.8 (Ar-C); *m/z* (APcI) 152 (M-29, 100%).

4-Amino-2, 6-dimethylanisole 52

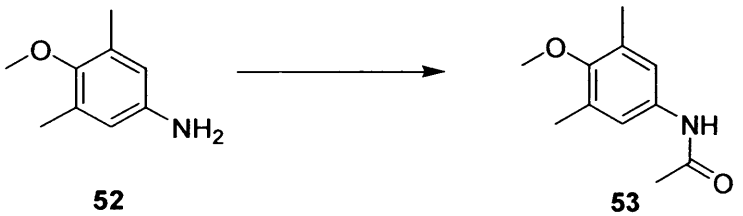


51 **52**

To a suspension of 10% palladium on charcoal (0.65 g) in ethanol (130 ml) at ambient temperature was added portionwise the dimethyl-nitroanisole **51** (10 g, 55 mmol) and cyclohexene (26 g, 32 ml, 330 mmol). The mixture was then refluxed for 14h, then allowed to cool to ambient temperature before being filtered through celite. The filter cake was washed with ethanol and the combined filtrates evaporated to give the *aniline* **52** as a brown

solid (7.562 g, 91%). The crude product was sufficiently pure for further use without further purification and showed m.p. 62-63.4°C, (lit.[98] m.p. 60-61°C), ν_{max}/cm^{-1} 3772, 3612, 3397, 2976, 1605, 1487, 1340, 1219, 1150, 1016, 856; δ_H 2.24 (6H, s, 2 × CH_3), 3.47-3.51 (2H, br s, NH_2), 3.69 (3H, s, OCH_3), 6.39 (2H, s, 2 × Ar-H); δ_C 16.5 (2 × CH_3), 60.4 (OCH_3), 115.7 (2 × Ar-CH), 131.9 (2 × Ar-CH_3), 142.5(Ar-C), 150.0 (Ar-C); *m/z* (APcI) 152 (M^++1, 100%).

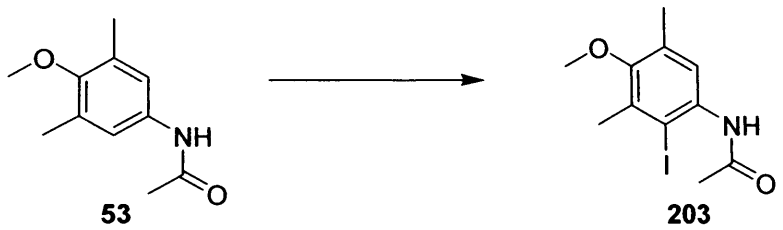
4-Acetamido-2,6-dimethylanisole 53



52 **53**

4-Amino-2,6-dimethylanisole **52** (7.6 g, 50.0 mmol) was stirred in dry tetrahydrofuran (100 ml) with triethylamine (7.4 ml, 53.2 mmol) and the solution cooled in an ice-bath. Acetyl chloride (4.0 ml, 54.1 mmol) was added dropwise before the ice bath was removed and stirring continued overnight. The reaction was quenched with saturated aqueous ammonium chloride (47 ml) and acidified using 2M hydrochloric acid (47 ml). The resulting mixture was extracted with ether (3 × 75 ml) and the combined extracts washed with water (75 ml) and brine (75 ml) then dried and evaporated. The crude product was recrystallised from ethanol to give the *acetamide* **53** as colourless crystals (8.6 g, 89%), m.p. 136-137°C, ν_{max}/cm^{-1} 3315, 2923, 1659, 1612, 1558, 1462, 1221, 1038, 1010, 862; δ_H 2.10 (3H, s, CH_3CO), 2.22 (6H, s, 2 × CH_3), 3.64 (3H, s, OCH_3), 6.94-6.95 (1H, br s, NH), 7.08 (2H, s, 2 × Ar-H); δ_C 16.5 ($\underline{C}H_3CO$), 24.8 (2 × CH_3), 60.2 (OCH_3), 121.1 (3,5-CH), 131.7 (2,6-C), 133.8 (Ar-C), 153.9 (Ar-C), 168.9 (C=O); *m/z* (APcI) 194 (M^+, 100%).

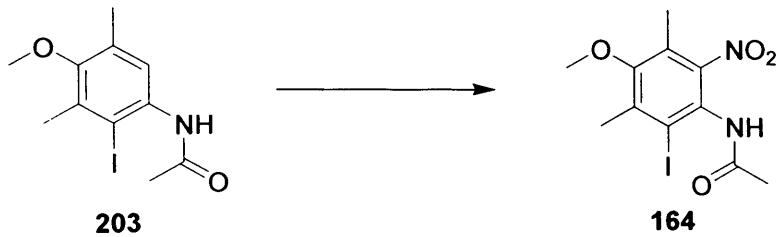
4-Acetamido-2,6-dimethyl-5-iodoanisole 203



53 **203**

A suspension of 4-acetamido-2,6-dimethylanisole **53** (7.4 g, 38.1 mmol) and *N*-iodosuccinimide[99] (12.9 g, 57.2 mmol) in glacial acetic acid (120 ml) was refluxed for 1.5h. The resulting purple solution was cooled to room temperature and neutralised with aqueous 2M sodium hydroxide. The resulting suspension was filtered, the solid washed with water and recrystallized from ethyl acetate to yield the *iodoanisole* **203** (8.5 g, 70%), m.p. 189-191°C, ν_{max}/cm^{-1} 3272, 2924, 1651, 1527, 1461, 1377, 1228, 1160, 1006; δ_H 2.08 (3H, s, CH_3CO), 2.12 (3H, s, CH_3), 2.28 (3H, s, CH_3), 3.52 (3H, s, OCH_3), 7.15-7.25 (1H, br s, NH), 7.61 (1H, s, 3-H); δ_C 16.4 ($\underline{C}H_3CO$), 22.9 (CH_3), 24.8 (CH_3), 60.4 (OCH_3), 96.4 (C-I), 123.0 (3-CH), 131.7 (Ar-C), 134.4 (Ar-C), 135.1 (Ar-C), 153.9 (Ar-C), 168.5(C=O); *m/z* (APcI) 320 (M^++H, 100%) [Found: C, 41.60; H, 4.35; N, 4.36. $C_{11}H_{14}INO_2$ requires C, 41.38; H, 4.42; N, 4.39%].

4-Acetamido-2,6-dimethyl-5-iodo-3-nitroanisole 164

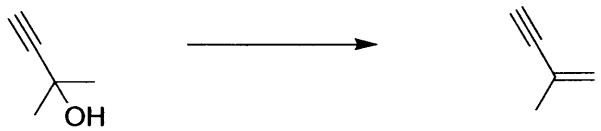


203 **164**

4-Acetamido-2, 6-dimethyl-5-iodoanisole **203** (1.0 g, 3.1 mmol) was stirred in glacial acetic acid (10.0 ml) at ambient temperature. Nitric acid (70%, 2.0 ml) was added dropwise, after which the mixture was stirred at 65°C for 5h. The mixture was allowed to cool to ambient temperature before water (18.0 ml) was added and the solid product collected by filtration, washed with water and recrystallized from aqueous ethanol to give the *nitroiodide* **164** as pale yellow crystals (0.58 g, 52%). m.p. 226-227°C, ν_{max}/cm^{-1} 3617, 3212, 2913, 1667, 1519,

1455, 1376, 1272, 1221, 1039, 989; δ_H 2.17 (3H, s, CH_3CO), 2.22 (3H, s, CH_3), 2.49 (3H, s, CH_3), 3.72 (3H, s, OCH_3), 7.06-7.17 (1H, br s, NH); δ_C 12.2 ($\underline{C}H_3CO$), 23.7 (CH_3), 23.9 (CH_3), 61.0 (OCH_3), 106.3 (C-I), 125.2 (Ar-C), 126.3 (Ar-C), 127.3 (Ar-C), 139.9 (Ar-C), 156.2 (Ar-C), 169.3 (C=O); *m/z* (APcI) 365 (M+H, 100%).

2-Methyl-1-buten-3-yne 205



204 **205**

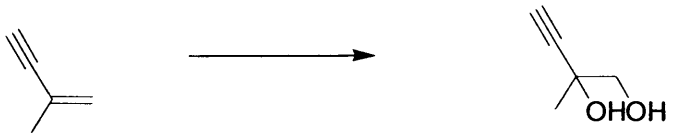
2-Methylbut-3-yn-2-ol **204** (50.0 g, 595.2 mmol) was heated at 90°C (bath) in a distilling flask with an equal weight of *p*-toluene sulphonic acid monohydrate for 3 hours. The butenyne **205** distilled into the receiver as it was formed. Redistillation of the crude product at 50°C (external bath temperature) gave the pure *butenyne* **205** as a highly volatile, colourless liquid (11.4 g, 29%), b.p. 34°C, ν_{max}/cm^{-1} 3300, 3100, 2983, 2926, 1614, 1455, 1374, 1266, 1214, 1171, 1013, 961, 904; δ_H 1.72 (3H, s, CH_3), 2.71 (1H, s, CH), 5.11 (1H, app. s, 1-CH_a), 5.21 (1H, app. s, 1-CH_b). These data are identical to those recorded in the literature.[43,100]

General Procedure of Asymmetric Dihydroxylation Reaction (AD-mix reaction)[63]

A round-bottomed flask, equipped with a magnetic stirrer, is charged with 5 ml of *tert*-butyl alcohol, 5 ml of water, and 1.4 g of AD-mix-α. $MeSO_2NH_2$ (95 mg, 1 equiv.) is added at this point for all 1,2-disubstituted, trisubstituted, and tetrasubstituted olefins. The mixture is stirred at room temperature until both phases are clear. One mmol of olefin is added at once, and the heterogeneous slurry is stirred vigorously at room temperature until tlc indicates the absence of the starting olefin (ca. 24h). The reaction is quenched by the addition of sodium sulfite (1.5 g) and stirring continued for 30-60 min. The reaction mixture is extracted several times with dichloromethane and the combined organic layers washed with 2N KOH to

remove most of the sulphonamide and then dried and concentrated to give a mixture of the crude diol and the ligand. Purification by flash chromatography (silica gel, ether/ hexane) gives the pure diol; the ligand does not elute in these solvent mixtures.

3, 4-Dihydroxy-3-methyl-1-butyne 69



205 **69**

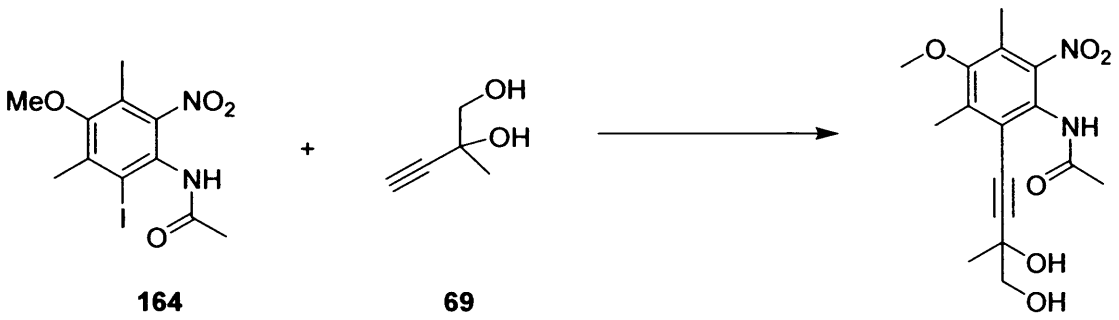
Follwing the general procedure of the AD-mix reaction, treatment of the butyne **205** (3.0 g, 45.5 mmol) with AD-mix-β, containing $(DHQD)_2PHAL$ (0.35 g, 0.45 mmol), potassium ferricyanide (45.0 g, 136.5 mmol), potassium carbonate (18.9 g, 137.0 mmol), potassium osmate dehydrate (33 mg, 0.8 mmol), yielded the *diol* **69** (3.1 g, 67%) as a yellow oil. ν_{max}/cm^{-1} 3430, 2938, 2113, 1622, 1511, 1376, 1244, 1060, 953, 891; δ_H 1.37 (3H, s, CH_3), 2.39 (1H, s, 1-H), 3.44 (H, d *J*~7.6, 4-H_a), 3.60 (1H, d *J*~7.6, 4-H_b); δ_C 25.6 (CH_3), 68.6 (3-C), 70.7 (4-CH_2), 72.6 (1-CH), 86.3 (2-C); *m/z* (APcI) 100 (M^+, 100%). These data are identical to previous data.[42]

General procedure of Sonogashira Coupling

The aryl iodide (3.5 mmol) was stirred in degassed dry tetrahydrofuran (40 ml). Triethylamine (14.0 ml, 95 mmol), *tetrakis*(triphenylphosphine)palladium(0) (0.8 g, 0.7 mmol) was added along with a 1-alkyne (7.0 mmol). The reaction mixture was degassed again, by refluxing under a flow of dry nitrogen for 30 minutes, before copper(I) iodide (133.4 mg, 0.7 mmol) was added. The reaction mixture was then refluxed for ~25h under nitrogen then cooled. Most of the solvent was evaporated and the residue diluted with water (35 ml). The resulting suspension was extracted with dichloromethane (3 × 50 ml) and the

combined extracts dried and concentrated. The crude product was subjected to column chromatography (typically 5% methanol/ chloroform) as stated in the individual experiments.

(±)-4-Acetamido-2,6-dimethyl-5-[3',4'-dihydroxy-3'-methylbut-2'-yn-1-yl]-3-nitroanisole 163

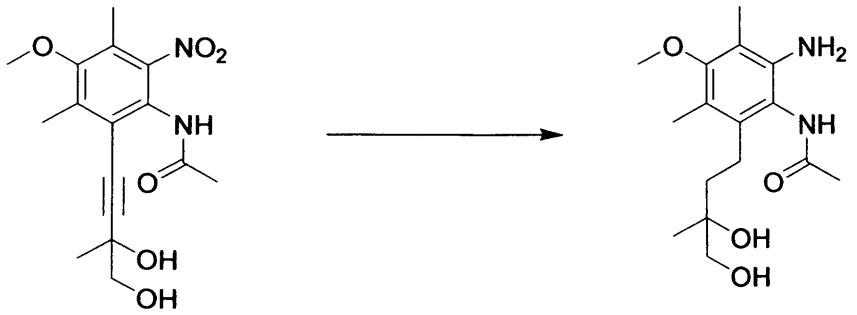


164 **69** **163**

Following the general procedure for Sonogashira coupling, the nitroiodide **164** (1.3 g, 3.5 mmol) was refluxed with triethylamine (14 ml, 95 mmol), *tetrakis*(triphenylphosphine)palladium(0) (0.8 g, 0.7 mmol), copper (I) iodide (113.4 mg, 0.7 mmol) along with diol **69** (0.7 g, 7.0 mmol) in tetrahydrofuran (40 ml) for 25h. The major product crystallized from methanol after chromatography (5% methanol/ chloroform) to give the *diol* **63** as pale yellow, amorphous crystals (500 mg, 1.5 mmol, 43%). m.p. 178-182°C, ν_{max}/cm^{-1} 3822, 3580, 3280, 1667, 1504; δ_H 1.46 (3H, s, 3'-CH_3), 2.13 (3H, s, CH_3CO), 2.23 (3H, s, Ar-CH_3), 2.36 (3H, s, Ar-CH_3), 3.04 (2H, br s, 2×OH), 3.43-3.50 (2H, m, 4'-CH_2), 3.65 (3H, s, OCH_3), 7.54 (1H, br s, NH); δ_C (CD_3OD) 12.1 (CH_3), 15.5 (CH_3), 23.0 (Ar-CH_3), 26.6 (Ar-CH_3), 61.4 (OCH_3), 70.2 (CH_2), 71.4 (3'-C), 78.7 (2'-C), 103.9 (1'-C), 124.3 (Ar-C), 126.2 (Ar-C), 127.7 (Ar-C), 128.3 (Ar-C), 138.6 (Ar-C), 157.8 (Ar-C), 173.4 (C=O); *m/z* (APcI) 319 (M^+ -OH, 100%); HRMS (FAB) calcd. for $C_{16}H_{21}N_2O_6$ $[M+H]^+$ 337.1396; found 337.1400.

(±)-4-Acetamido-2,6-dimethyl-5-[3',4'-dihydroxy-3'-methylbut-1-yl]-3-aminoanisole

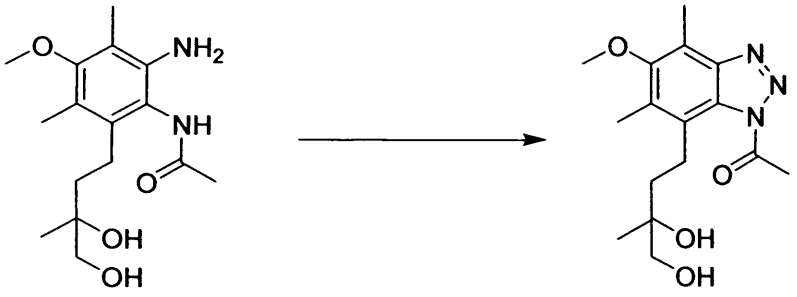
162



163 **162**

To a suspension of 10% palladium hydroxide on carbon (22.2 mg) in methanol (20 ml) at ambient temperature was added the alkyne **163** (111.0 mg, 0.33 mmol). The mixture was stirred under one atmosphere of hydrogen for 48h, then filtered through celite, and the filter cake washed with warm methanol. The combined filtrates were evaporated to yield the *aniline* **162** as a pale yellow gum (101.0 mg, 99%) ν_{max}/cm^{-1} 3418, 1641, 1461, 1121; δ_H 1.09 (3H, s, 3'-CH_3), 1.42 (2H, t, *J*~8.6, 2'-CH_2), 1.71 (2H, d, *J*~6.3 NH_2), 1.95 (3H, s, CH_3CO), 2.04 (3H, s, Ar-CH_3), 2.08 (3H, s, Ar-CH_3), 2.45 (2H, t, *J*~8.6, 1'-CH_2), 2.79 (1H, br s, OH), 2.93 (1H, br s, OH), 3.30-3.36 (2H, m, 4'-CH_2), 3.49 (3H, s, OCH_3), 7.89 (1H, s, NH); δ_C (CD_3OD) 11.0 (CH_3), 12.3 (CH_3), 23.2 (Ar-CH_3), 24.1 (Ar-CH_3), 24.7 (2'-CH_2), 39.5 (1'-CH_2), 60.9 (OCH_3); 70.6 (CH_2OH), 74.1 (3'-C), 115.6 (Ar-C), 119.3 (Ar-C), 119.8 (Ar-C), 139.0 (Ar-C), 142.8 (Ar-C), 158.0 (Ar-C), 174.0 (C=O); *m/z* (APcI) 311 (M^+ +H, 100%), HRMS (FAB) calcd, for $C_{16}H_{27}N_2O_4$ $[M+H]^+$ 311.1965, found 311.1963.

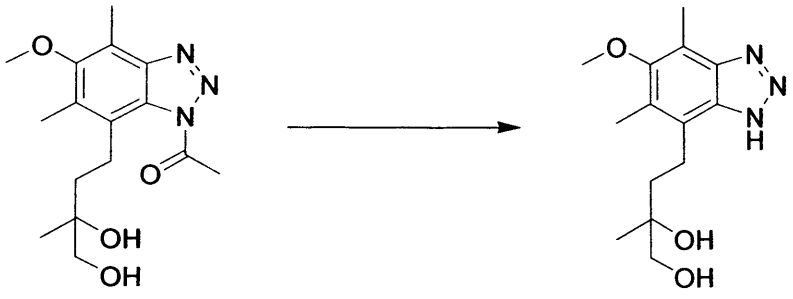
(±)-1-Acetyl-7-(3', 4'-dihydroxy-3'-methylbutan-1-yl)-4,6-dimethyl-5-methoxybenzotriazole 241



162 **241**

To a solution of the aniline **162** (0.17 g, 0.55 mmol) in methanol (1.5 ml) at ambient temperature was added a solution of sodium nitrite (0.11 g, 1.65 mmol) in distilled water (0.3 ml). This solution was then added slowly to a stirred solution of concentrated hydrochloric acid (10 M, 0.5 ml) in distilled water (0.6 ml) maintained at 0°C. Stirring at this temperature was continued for 0.5 h. Water (6 ml) was then added and the aqueous solution was extracted with dichloromethane (3 × 10 ml). The combined organic extracts were dried and evaporated to yield the *benzotriazole* **241** as a colourless solid (0.133 g, 73%). The crude product was sufficiently pure for further use without purification and showed m.p. 99-102°C, ν_{max}/cm^{-1} 3270, 2919, 2862, 2361, 2332, 1745, 1459, 1366, 1309, 1266, 1130, 1094; δ_H 1.24 (3H, s, 3'-CH_3), 1.72 (2H, t, *J*~8.8, 2'-CH_2), 2.38 (3H, s, $COCH_3$), 2.49-2.54 (2H, m, 2 × OH), 2.66 (3H, s, Ar-CH_3), 2.96 (3H, s, Ar-CH_3), 2.99-3.15 (2H, m, 1'-CH_2), 3.41 (1H, dd, *J*~5.9 and 11.3, 4'-H_a), 3.54 (1H, dd, *J*~5.9 and 11.3, 4'-H_b), 3.70 (3H, s, OCH_3); δ_C 9.6 (CH_3), 12.0 (CH_3), 22.1 (Ar-CH_3), 24.3 (Ar-CH_3), 24.9 (2'-CH_2), 37.3 (1'-CH_2), 59.5 (OCH_3), 68.2 (CH_2OH), 71.8 (3'-C), 118.9 (Ar-C), 123.4 (Ar-C), 126.8 (Ar-C), 133.6 (Ar-C), 145.4 (Ar-C), 154.4(Ar-C), 169.6 (C=O); *m/z* (APCI) 322 (M^+ +H, 100%), HRMS (FAB) calcd. for $C_{16}H_{24}N_3O_4$ $[M+H]^+$ 322.1761, found 322.1763.

(±)-7-(3', 4'-dihydroxy-3'-methylbutan-1-yl)-4, 6-dimethyl-5-methoxybenzotriazole 161



241 **161**

The benzotriazole **241** (50.0 mg, 0.16 mmol) was stirred in methanol (1 ml) at ambient temperature. Potassium carbonate (86.0 mg, 0.47 mmol) was added with 2 drops of water. The mixture was stirred at this temperature and the hydrolysis followed by tlc until complete (~4 h). Removal of most of the methanol by evaporation gave a residue which was treated with dichloromethane (10 ml). The resulting mixture was dried and filtered and the solid residue washed with distilled methanol to remove the product attached to the potassium carbonate and magnesium sulphate. Evaporation of the filtrate gave the *NH-benzotriazole* **161** as a colourless solid (44 mg, 99 %), m.p. 250-252°C, ν_{max}/cm^{-1} 3376, 2248, 1621, 1434, 1140, 1071, 998, 880; δ_H (CD_3OD) 1.17 (3H, s, 3'-CH_3), 1.64-1.73 (2H, m, 2'-CH_2), 2.23 (3H, s, Ar-CH_3), 2.45 (3H, s, Ar-CH_3), 2.97-3.03 (2H, m, 1'-CH_2), 3.36 (1H, d, *J*~11.3, 4'-H_a), 3.41 (1H, d, *J*~11.3, 4'-H_b), 3.62 (3H, s, OCH_3); δ_C (CD_3OD) 11.8 (3'-CH_3), 12.6 (Ar-CH_3), 24.4 (Ar-CH_3), 24.6 (2'-CH_2), 39.6 (1'-CH_2), 61.3 (OCH_3), 70.3 (4'-CH_2), 74.4 (3'-C), 115.3 (Ar-C), 124.6 (Ar-C), 127.8 (Ar-C), 142.7 (Ar-C), 145.0 (Ar-C), 153.9 (Ar-C); *m/z* (APcI) 280 (M^+ +H, 100%), HRMS (FAB) calcd. for $C_{14}H_{22}N_3O_3$ $[M+H]^+$ 280.1656, found 280.1652.

***tert*-Butyl 2,2,2-trichloroethylidenecarbamate 288**

287 **288**

To a solution of triphenylphosphine **287** (21.5 g, 58.9 mmol) in dry toluene (47 ml) was added freshly distilled anhydrous chloral (7.9 ml, 81.8 mmol) dropwise. The resulting yellow solution was refluxed for 3 hours under nitrogen before cooling to room temperature. After evaporation of the toluene, triphenylphosphine oxide was precipitated by the addition of dry hexane and filtered off. Evaporation of the filtrate gave the crude *trichloroethylidenecarbamate* **288** (14.44 g, 99 %) as a yellow oil. δ_H 1.51 (9H, s, $C(CH_3)_3$), 8.03 (1H, s, CH); δ_C 27.6 ($C(\underline{C}H_3)_3$), 84.5 ($\underline{C}(CH_3)_3$), 92.7 (CCl_3), 159.0 (CH), 160.8 (C=O). These data are identical to those recorded in the literature.[56]

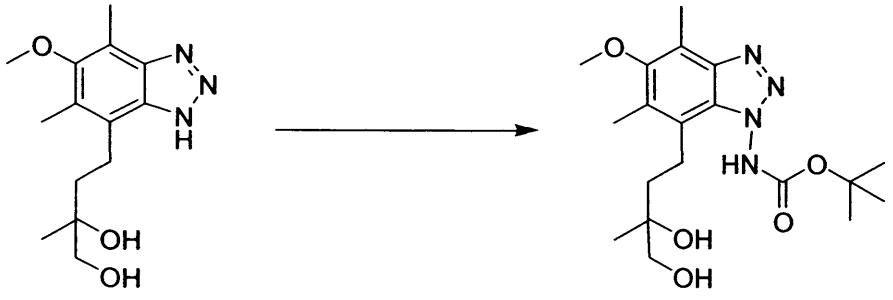
***tert*-Butyl 3-trichloromethyl-2-oxaziridinecarboxylate 280**

288 **280**

A solution of oxone (35.5 g) in chilled water (352 ml) was added at 0 °C to a vigorously stirred mixture of the crude trichloroethylidenecarbamate **288** (14.5 g, 58.9 mmol) in chloroform (180 ml), potassium carbonate (28.0 g, 202.2 mmol) and water (212 ml). After 1 hour stirring, the aqueous phase was discarded and replaced by fresh chilled solutions of potassium carbonate and oxone in water. A total of 8 such cycles was carried out. The organic phase was washed with water (3 × 60 ml), dried and evaporated (bath temperature < 30 °C). The crude product was purified by silica gel column chromatography (dichloromethane) to give the *oxaziridine* **280** (11.0g, 71%) as a foul-smelling colourless oil; ν_{max}/cm^{-1} 2984, 2937, 2359, 1779, 1478, 1396, 1372, 1300, 1248, 1150, 1076, 993, 914, 836,

796, 740; δ_H 0.93 (9H, s, $C(CH_3)_3$), 3.06 (1H, s, CH); δ_C 27.6 ($C(\underline{C}H_3)_3$), 81.1 ($\underline{C}(CH_3)_3$), 87.0 (CH), 93.6 (CCl_3), 158.0 (C=O). These data are identical to those recorded in the literature.[56]

(±)-1-(*tert*-Butoxycarbonylamino)-7-[3', 4'-hydroxy-3'-methylbutan-1'-yl]-4,6-dimethyl-5-methoxy-benzotriazole 71



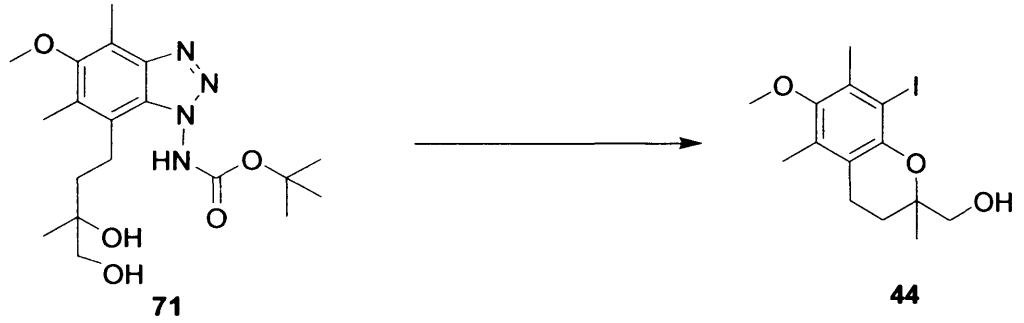
161 **71**

To the *NH*-benzotriazole **161** (30.0 mg, 0.1 mmol) in dry dichloromethane (0.8 ml) at room temperature was added the oxaziridine **280** (52.5 mg, 0.2 mmol) dropwise, and the resulting mixture stirred overnight at this temperature. The solvent was evaporated and the crude product separated by flash column chromatography (silica gel, 5% methanol/chloroform) give the *N-Boc-benzotriazole* **71** (40.0 mg, 94%) as a yellow oil, ν_{max}/cm^{-1} 3274, 2930, 1739, 1452, 1362, 1248, 1158, 1110, 1050, 906, 834, 732; δ_H 1.23 (3H, s, 3'-CH_3), 1.32-1.75 (9H, br s, $C(CH_3)_3$), 1.78 (2H, t, *J*~8.6, 2'-CH_2), 2.30 (3H, s, Ar-CH_3), 2.56 (3H, s, Ar-CH_3), 2.99-3.02 (2H, m, 1'-CH_2), 3.54 (1H, d, *J*~11.3, 4'-H_a), 3.65 (1H, d, *J*~11.3, 4'-H_b), 3.69 (3H, s, OCH_3); δ_C 7.9 (3'-CH_3), 10.9 (Ar-CH_3), 21.9 (Ar-CH_3), 24.9 (2'-CH_2), 27.1 ($C(\underline{C}H_3)_3$), 37.1 (1'-CH_2), 59.5 (CH_2OH), 59.6 (OCH_3), 72.1 (3'-C), 82.4 ($\underline{C}(CH_3)_3$), 109.0 (Ar-C), 124.9 (Ar-C), 126.0 (Ar-C), 129.5 (Ar-C), 139.4 (Ar-C), 152.7 (Ar-C), 156.7 (C=O); *m/z* (APcI) 395 (M^+ +H, 100%), HRMS (FAB) calcd. for $C_{19}H_{31}N_4O_5$ $[M+H]^+$ 395.2289, found 395.2295.

General deprotection/cyclisation procedure:

The *N-tert*-butoxycarbonylamino-benzotriazole (n mmol) was dissolved in dichloromethane (10 ml $mmol^{-1}$) containing trifluoroacetic acid (2 ml $mmol^{-1}$) and the resulting solution stirred at ambient temperature until tlc analysis showed disappearance of the starting material (*ca.* 45 minutes). The volatiles were then evaporated and the residue was put under high vacuum to remove residual trifluoroacetic acid, then dissolved in dichloromethane (10 ml $mmol^{-1}$). Anhydrous potassium carbonate (13 eq.) was then added to basify this solution, after which the solid was filtered off and washed with warm dichloromethane. The filtrate was concentrated to 10 ml $mmol^{-1}$ before solid *N*-iodosuccinimide (2.5 eq.) was added in the dark. The resulting purple solution was stirred for a further 1h then washed with saturated aqueous sodium thiosulfate, dried and evaporated to give the crude product, column chromatography of which in petrol / ethyl acetate (2:1) gave the pure product.

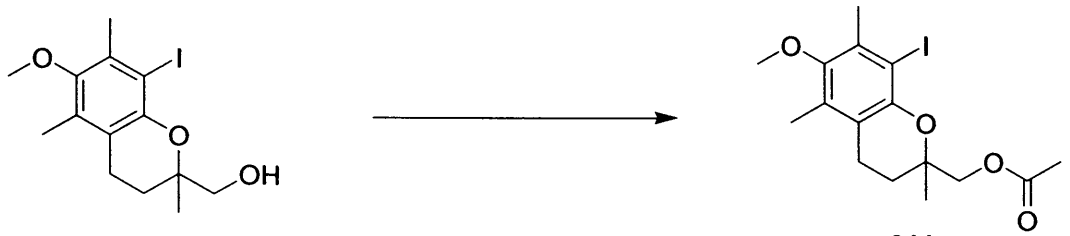
(±)-8-Iodo-6-methoxy-2,5,7-trimethyl chroman-2-methanol 44



Following the general deprotection/ cyclisation procedure, a crude sample of the N-Boc benzotriazole **71** (220.6 mg, 0.56 mmol) was treated with trifluoroacetic acid (1.1 ml) and *N*-iodosuccinimide (378 mg, 1.7 mmol) to give the iodochroman **44** as a yellow gum (43 mg, 21% from NH-benzotriazole **161**). ν_{max}/cm^{-1} 3390, 2936, 1450, 1390, 1219, 1058, 8821; δ_H 1.21 (3H, s, 2-CH_3), 1.67 (1H, ddd, *J*~4.8, 6.0, 13.6, 3-H_a), 1.80-1.90 (1H, m, 3-H_b), 2.08 (3H, s, Ar-CH_3), 2.35 (3H, Ar-CH_3), 2.56-2.60 (2H, m, 4-CH_2), 3.57 (5H, s, CH_2OH and OCH_3); δ_C 11.0 (2-CH_3), 19.2 (Ar-CH_3), 20.9 (Ar-CH_3), 19.4 (3-CH_2), 26.9 (4-CH_2), 59.5

(OCH_3), 68.2 (CH_2OH), 77.5 (2-C), 90.0 (C-I), 117.8 (Ar-C), 128.4 (Ar-C), 132.3 (Ar-C), 146.8 (Ar-C), 149.1 (Ar-C); *m/z* (APcI) 345 (M^+ -OH, 100%), HRMS (FAB) calcd. For $C_{14}H_{23}NO_3$ $[M+NH_4]^+$ 380.0717, found 380.0714.

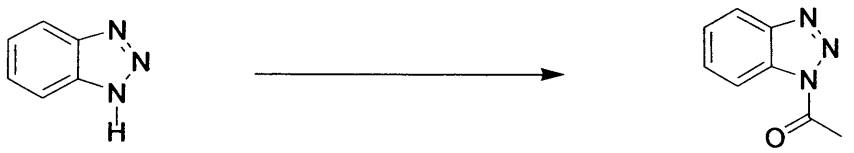
(±)-2-Acetoxymethyl-8-iodo-6-methoxy-2,5,7-trimethylchroman 311



44 **311**

Iodochroman **44** (30.0 mg, 0.08 mmol) was stirred in dry dichloromethane (1.5 ml) with acetyl chloride (0.02 ml, 0.24 mmol) and 4-dimethylaminopyidine (DMAP) (2.0 mg, cat.) was added. The resulting solution was stirred for 18 h before being diluted with dichloromethane (5 ml). The resulting solution was washed with water (2 ml), saturated copper sulphate (2 ml) and saturated potassium carbonate (2 ml) then dried. The crude product was purified by colum chromatography using diethyl ether / hexane (1/ 3) as the eluent to give the pure *acetoxy-chroman* **311** (23.0 mg, 75%) as a yellow gum. ν_{max}/cm^{-1} 2959, 1744, 1450, 1390, 1260, 1057, 800; δ_H 1.28 (3H, s, 2-CH_3), 1.72-1.88 (2H, m, 3-CH_2), 2.05 (3H, s, Ar-CH_3), 2.06 (3H, s, Ar-CH_3), 2.34 (3H, s, $COCH_3$), 2.53 (2H, app. t, *J*~6.9, 4-CH_2), 3.56 (3H, OCH_3), 4.02 (1H, d, *J*~11.3, 1'-H_a), 4.09 (1H, d, *J*~11.3, 1'-H_b); δ_C 11.0 (2-CH_3), 19.4 (Ar-CH_3), 20.0 (Ar-CH_3), 20.9 ($COCH_3$), 20.1 (3-CH_2), 28.7 (4-CH_2), 59.5 (-OCH_2), 67.2 (OCH_3), 74.3 (2-C), 89.1 (C-I), 117.2 (Ar-C), 128.3 (Ar-C), 133.0 (Ar-C), 147.1 (Ar-C), 149.0 (Ar-C), 169.9 (C=O); *m/z* (APcI) 277 (M^+ -I, 100%), HRMS (EI) calcd. For $C_{14}H_{21}IO_4$ $[M]^+$ 404.0479, found 404.0483.

1-Acetyl-benzotriazole 252



2 **252**

To a solution of acetyl chloride (3.6 ml, 50 mmol) and 1-H-benzotriazole **2** (5.95 g, 50 mmol) in dry dichloromethane (300 ml) cooled in an ice bath was added a mixture of triethylamine (5.5 g, 55.0 mmol) and dry dichloromethane (25 ml) dropwise over 30 minutes. The mixture was refluxed for 4 h and then cooled to room temperature. The resulting mixture was washed with water (50 ml), saturated aqueous ammonium chloride (25 ml) and 10% aqueous sodium bicarbonate (25 ml). The organic layer was then dried, evaporated and the residue crystallized from methanol to give the pure *acetyl benzotriazole* **252** (4.78 g, 60%) as colourless crystals showing m.p. 48-50°C, [lit.[50] m.p. 51-52 °C] δ_H 2.95 (3H, s, CH_3), 7.43 (1H, dt, *J*~0.9, 8.3, Ar-CH), 7.58 (1H, dt, *J*~0.9, 8.3, Ar-CH), 8.06 (1H, d, *J*~8.3, Ar-CH), 8.23 (1H, d, *J*~8.3, Ar-CH). These data are identical to those recorded in the literature.[50]

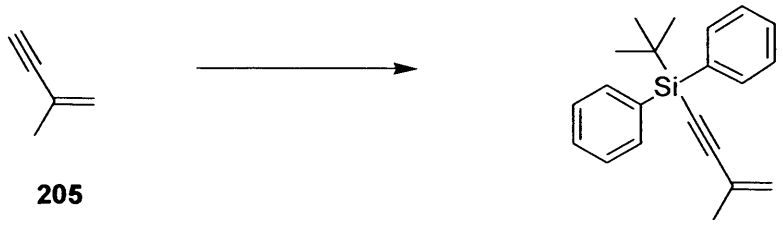
(±)-2-Hydroxy-2-methyl-3- butyn-1-yl benzoate 220

69 **220**

Benzoyl chloride (0.03 ml, 0.22 mmol) was added to a well stirred solution of the diol **69** (20.0 mg, 0.2 mmol) in dry dichloromethane (1.6 ml) containing triethylamine (0.03 ml, 0.22 mmol). The resulting solution was stirred overnight before being diluted with dichloromethane (5 ml) followed by washing with water (3 ml), 1 M hydrochloric acid (2 ml) and brine. The organic solution was then dried and evaporated and the residue purified on a silica column using petrol ether / ethyl acetate (4 / 1) as the eluent to give the pure *benzoate* **220** (29.0 mg, 71%) as a colourless oil, ν_{max}/cm^{-1} 3456, 3284, 2989, 2360, 1722, 1452, 1371,

1274, 1116, 710; δ_H 1.53 (3H, s, CH_3), 2.43 (1H, s, CH), 2.92 (1H, br. s, OH), 4.23 (1H, d, *J*~11.1, 1-H_a), 4.36 (1H, d, *J*~11.1, 1-H_b), 7.36 (2H, t, *J*~7.6, 2 × Ar-CH), 7.49 (1H, t, *J*~7.6, Ar-CH), 8.00 (2H, dd, *J*~1.0, 7.6, 2 × Ar-CH); δ_C 26.4 (CH_3), 67.3 (CH_2), 71.6 (2-C), 73.1 (4-CH), 85.1 (3-C), 128.9 (Ar-CH), 130.0 (Ar-C), 130.2 (Ar-CH), 133.7 (Ar-CH), 166.8 (C=O).

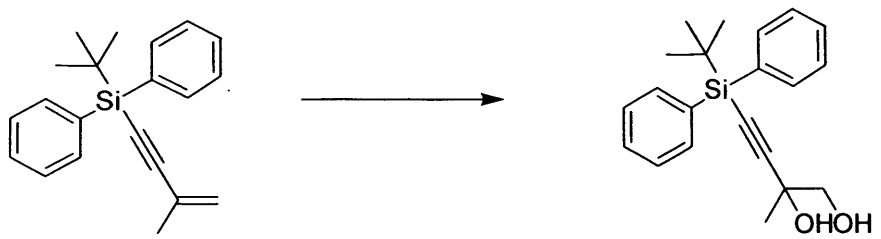
2-Methyl-4-(*tert*-butyldiphenylsillyl)-1-buten-3-yne 315



205 **315**

Butyllithium (2.5M solution in hexane) (24 ml) was added dropwise to a well-stirred solution of the butenyne **205** (4.0 g, 60.0 mmol) in dry tetrahydrofuran (45 ml) cooled in an ice-bath. The solution was stirred for 15 minutes before *tert*-butylchlorodiphenylsilane (16.8 g, 72.0 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 2h. The solvent was then removed after warming to room temperature and the residue was treated with water (10 ml) and ether (10 ml). The separated aqueous layer was extracted with ether (3 × 30 ml) and the combined organic solution were dried and evaporated to give the crude *silane* **315** (17.7 g, 86%) as a light yellow gum, which was suitable for the *bis*-hydroxylation step without further purification, and which showed ν_{max}/cm^{-1} 3428, 3070, 2929, 2856, 2154, 1682, 1589, 1471, 1428, 1390, 1361, 1192, 1110, 1008, 908, 820, 738, 701; δ_H 0.99 (9H, s, $C(CH_3)_3$), 1.92 (3H, s, 2-CH_3), 5.27 (1H, d, *J*~1.7, 1-H_a), 5.41 (1H, d, *J*~1.7, 1-H_b), 7.27-7.33 (6H, m, 6 × Ar-CH), 7.63-7.67 (4H, m, 4 × Ar-CH); δ_C 19.1 ($\underline{C}(CH_3)_3$), 25.4 (2-CH_3), 26.6 ($C(\underline{C}H_3)_3$), 88.5 (4-C), 109.0 (3-C), 123.2 (CH_2), 127.8 (Ar-CH), 129.7 (Ar-CH), 134.8 (Ar-CH), 135.2 (2-C), 135.6 (Ar-C); *m/z* (APcI) 305 (M^++H, 100%).

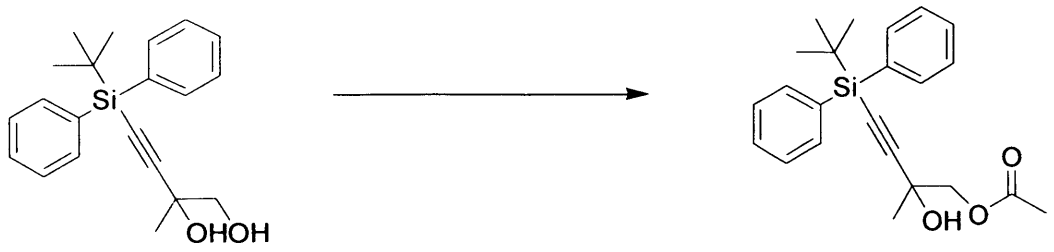
4-(*tert*-Butyldiphenylsilyl)-2-methylbut-3-yne-1,2-diol 316



315 **316**

Following the general procedure of the AD-mix reaction, treatment of the silyl-butenyne **315** (580 mg, 1.7 mmol) with AD-mix-β (2.4 g), yielded the *silyl diol* **316** (440 mg, 70%) as a colourless oil, ν_{max}/cm^{-1} 3426, 2928, 2359, 1635, 1428, 1110, 908, 700; δ_H 1.01 (9H, s, $C(CH_3)_3$), 1.51 (3H, s, 2-CH_3), 3.56 (1H, d, *J*~11.0, 1-H_a), 3.70 (1H, d, *J*~11.0, 1-H_b), 7.29-7.35 (6H, m, 6 × Ar-CH), 7.68 (4H, d, *J*~7.1, 4 × Ar-CH); δ_C 18.5 ($\underline{C}(CH_3)_3$), 24.1 (2-CH_3), 27.0 ($C(\underline{C}H_3)_3$), 58.9 (2-C), 70.7 (CH_2), 84.1 (4-C), 111.6 (3-C), 127.8 (Ar-CH), 129.7 (Ar-CH), 132.9 (Ar-C), 135.5 (Ar-CH).

4-(*tert*-Butyldiphenylsilyl)-2-hydroxy-2-methylbut-3-yn-1-yl acetate 317

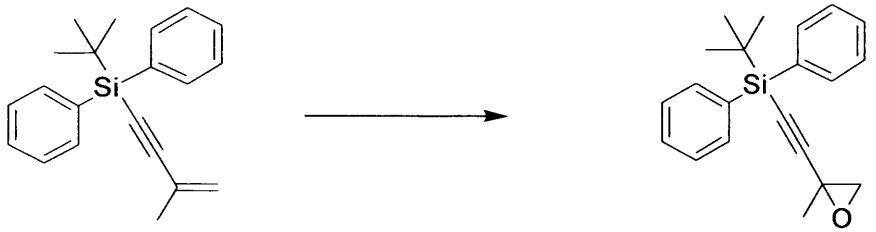


316 **317**

The silyl diol **316** (20.0 mg, 0.05 mmol) was stirred in pyridine (0.5 ml) at room temperature when acetic anhydride (2 drops) was added. The resulting solution was stirred at this temperature for 18 h before being diluted with ether (1 ml). Water (1 ml) was also added and the resulting mixture extracted with ether (3 × 5 ml). The combined extracts were dried and evaporated to afford a crude product which was purified by chromatography using ethyl acetate / petrol ether (20%) as the eluent. The pure *acetate* **317** (19.0 mg, 90%) was obtained as a colourless oil, ee=12.7%, ν_{max}/cm^{-1} 3438, 3070, 2930, 2857, 2173, 1959, 1888, 1745,

1650, 1471, 1428, 1372, 1237, 1110, 1048, 968, 921, 820, 739, 700; δ_H 1.00 (9H, s, 3 × CH_3), 1.55 (3H, s, 2-CH_3), 2.06 (3H, s, $COCH_3$), 2.54 (1H, br s, OH), 4.02 (1H, d, *J*~11.1, 1-H_a), 4.28 (1H, s, *J*~11.1, 1-H_b), 7.29-7.37 (6H, m, 6 × Ar-CH), 7.69 (4H, d, *J*~6.4, 4 × Ar-CH); δ_C 18.5 ($\underline{C}(CH_3)_3$), 25.3 ($C(\underline{C}H_3)_3$), 26.0 (2-CH_3), 27.0 ($CO\underline{C}H_3$), 67.2 (2-C), 71.1 (CH_2), 84.2 (4-C), 110.6 (3-C), 127.8 (Ar-CH), 129.7 (Ar-CH), 132.8 (Ar-C), 135.5 (Ar-CH), 170.9 (C=O).

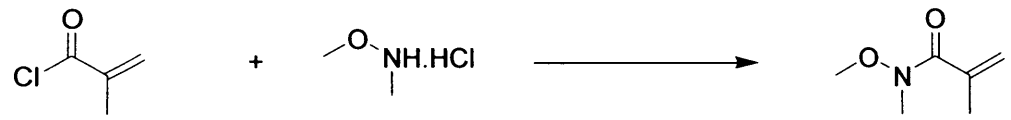
2-(*tert*-Butyldiphenylsilyl)ethynyl-2-methylepoxirane 321



315 **321**

To a well-stirred solution of the silyl butenyne **315** (600 mg, 1.73 mmol) in dichloromethane (9 ml) was added *meta*-chloroperoxybenzoic acid (*m*-CPBA) (600 mg, 3.46 mmol). The resulting suspension was stirred for 2 h at room temperature before saturated aqueous sodium bicarbonate (10 ml) was added. The resulting mixture was extracted with ether (3 × 15 ml) and the combined extracts dried and evaporated to give the crude product which was purified by chromatography using ether /hexane (10%). The pure *oxirane* **321** (590 mg, 95%) was obtained as a yellow oil, ν_{max}/cm^{-1} 3429, 3070, 2958, 2857, 2156, 1958, 1887, 1702, 1589, 1471, 1428, 1362, 1256, 1193, 1111, 1009, 907, 820, 741, 700; δ_H 0.99 (9H, s, $C(CH_3)_3$), 1.57 (3H, s, CH_3), 2.71 (1H, d, *J*~5.6, 3-H_a), 3.03 (1H, d, *J*~5.6, 3-H_b), 7.26-7.35 (6H, m, 6 × Ar-CH), 7.62-7.69 (4H, m, 4 × Ar-CH); δ_C 19.0 ($\underline{C}(CH_3)_3$), 23.3 (C-$\underline{C}H_3$), 27.0 ($C(\underline{C}H_3)_3$), 48.0 (2-C), 56.1 (CH_2), 83.2 (C), 109.2 (C), 128.2 (Ar-CH), 130.5 (Ar-C), 135.2 (Ar-CH), 136.0 (Ar-CH).

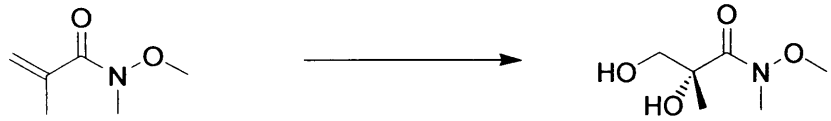
_N_-Methoxy-_N_-methyl methacrylamide 324[70]



327 **328** **324**

Methacryloyl chloride **327** (4.6 ml, 47.8 mmol) and *N,O*-dimethylhydroxylamine hydrochloride **328** (5.1 g, 52.6 mmol) was dissolved in ethanol free chloroform (480 ml) at room temperature. The solution was cooled to 0^0C and pyridine (8.5 ml, 105.2 mmol) was added. The mixture was stirred at ambient temperature for 1 h then the volatiles carefully evaporated. The residue was partitioned between brine and a 1:1 mixture of ether and dichloromethane. The separated organic layer was dried and concentrated to afford the crude amide **324** which was purified by silica gel chromatography using ethyl acetate / petrol ether (50%). The pure *amide* **324** (6.1 g, 47.1 mmol, 99%) was obtained as light yellow oil, ν_{max}/cm^{-1} 3593, 3476, 2934, 1820, 1726, 1656, 1460, 1379, 1177, 1115, 998, 928; δ_H 1.92 (3H, s, $C(CH_3)$), 3.18 (3H, s, $N\text{-}CH_3$), 3.59 (3H, s, OCH_3), 5.18 (1H, app. s, CH_a), 5.24 (1H, app. s, CH_b); δ_C 18.9 ($C(\underline{C}H_3)$), 60.2 ($N\text{-}CH_3$), 116.3 (OCH_3), 139.2 (CH_2), 170.1 ($\underline{C}(CH_3)$), 170.5 (C=O); *m/z* (APcI) 130 (M^++H, 100%).

(+)-(*R*)-2, 3-Dihydroxy-2, *N*-dimethyl-*N*-methoxy propionamide (*R*)-325



324 **(*R*)-325**

Following the general procedure of AD-mix reaction, treatment of methacrylamide **324** (6.1 g, 47.1 mmol) with AD-mix-α yielded the *dihydroxypropionamide* **(*R*)-325** (7.00 g, 91%) as a yellow oil. $[\alpha]_D^{26}$ = +4.3 (*c* 2.0 g/ 100ml, MeOH), (lit[101] $[\alpha]_D^{25}$ = +4.7 (*c* 1.80 g/ 100ml, MeOH)); ν_{max}/cm^{-1} 3440, 3143, 2930, 1636, 1458, 1364, 1181, 1054, 993, 934, 866; δ_H 1.31 (3H, s, $C(CH_3)$), 3.24 (3H, s, $N\text{-}CH_3$), 3.47 (2H, br. s, 2 × OH), 3.54 (1H, d, *J*~11.5, $3\text{-}H_a$),

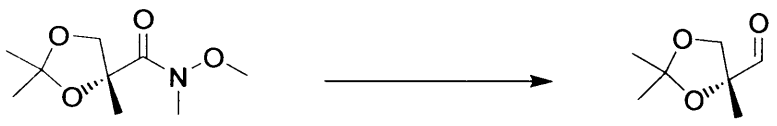
3.70 (3H, s, OCH_3), 3.75 (1H, d, *J*~11.5, 3-H_b); δ_C 21.8 (C($\underline{C}H_3$)), 61.4 (N-CH_3), 68.0 (OCH_3), 76.4 (CH_2), 77.7 ($\underline{C}(CH_3)$, 174.8 (C=O); *m/z* (APcI) 164 (M^++H, 70%).

(*R*)-*N*-Methoxy-*N*-methyl-2,2,5-trimethyl-1,3-dioxolane-5-carboxamide 340

(*R*)-325 **340**

A solution of the dihydroxypropionamide **(*R*)-325** (3.25 g, 19.9 mmol), 2,2-dimethoxypropane (12.3 ml, 99.5 mmol) and *p*-toluenesulphonic acid (76.1 mg, 0.4 mmol) in toluene was heated under reflux (~105 °C) for 2 h. The reaction mixture was cooled to room temperature and the solvent was evaporated to give a yellow oil, which was purified by column chromatography (ethyl acetate / petrol ether, 50%) to give the pure *acetal* **340** (3.60 g, 87%) as a pale yellow oil, ν_{max}/cm^{-1} 3612, 2983, 2936, 1658, 1456, 1372, 1247, 1211, 1118, 1062, 1000, 918, 874, 848; δ_H 1.16 (3H, s, 5-CH_3), 1.25 (3H, s, 2-CH_3), 1.31 (3H, s, 2-CH_3), 3.10 (3H, br res., N-CH_3), 3.53 (3H, s, OCH_3), 3.56 (1H, d, *J*~8.3, 4-H_a), 4.37(1H, d, *J*~8.3, 4-H_b); δ_C 23.4 (5-CH_3), 26.1 (2-CH_3), 27.3 (2-CH_3), 60.7 (N-CH_3), 61.1 (OCH_3), 73.0 (4-CH_2), 77.7 (5-C), 110.7 (2-C), 171.4 (C=O); *m/z* (APcI) 204 (M^++H, 100%).

(*R*)-2,2,5-Trimethyl-1,3-dioxolane-5-carboxaldehyde 341

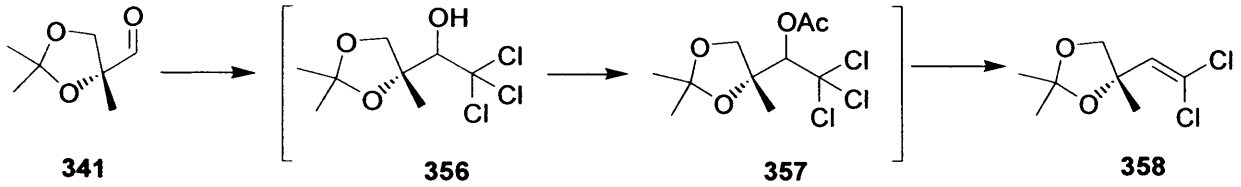


340 **341**

To a solution of the acetal **340** (3.60 g, 17.7 mmol) in dry tetrahydrofuran (180 ml) was added diisobutylaluminium hydride (1 M solution in THF, 53.2 ml, 53.2 mmol) at 0°C. The reaction mixture was stirred at this temperature for 1 h, then poured into 5% hydrochloric acid in ethanol (50 ml) at 0°C and the resulting mixture partitioned between brine (20 ml) and

ether (100 ml). The organic extract was washed with water (15 ml) and then carefully evaporated to give the crude *aldehyde* **341** (2.80 g, 100%) as a yellow oil which was ready for the dichlorination step. ν_{max}/cm^{-1} 3424, 2937, 2358, 1725, 1458, 1373, 1260, 1209, 1104, 1061, 858; δ_H 1.29 (3H, s, CH_3), 1.39 (6H, br res., $C(CH_3)_2$), 3.66 (2H, s, CH_2), 9.59 (1H, s, CH); δ_C 18.2 (CH_3), 25.4 ($C(\underline{C}H_3)_2$), 25.8 ($C(\underline{C}H_3)_2$), 69.8 (CH_2), 76.3 ($\underline{C}(CH_3)$), 83.6 ($\underline{C}(CH_3)_2$), 201.4 (C=O); *m/z* (APcI) 145 (M^++H, 100%).

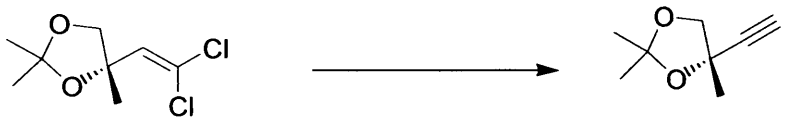
(*S*)-5-(2',2'-Dichloroethen-1'-yl)-2,2,5-trimethyl-1,3-dioxolane 358



To a stirred solution of trichloroacetic acid (4.20 g, 25.4 mmol) and the aldehyde **341** (2.27 g, 15.9 mmol) in *N*,*N*-dimethylformamide (12 ml) at room temperature was added sodium trichloroacetate (4.70 g, 25.4 mmol) in portions. The internal temperature was kept below 35°C by addition control. After the addition was completed, the mixture was stirred at room temperature for 4 h with continuous evolution of CO_2. The solution was then cooled to 5°C and acetic anhydride (3.0 ml, 31.8 mmol) was carefully added. Strong CO_2 evolution was observed. The mixture was allowed to warm to room temperature and stirred for an additional hour, then diluted with acetic acid (15 ml) and cooled to 0°C. To the resulting solution, zinc powder (2.1 g, 31.8 mmol) was added in one portion. The solution was stirred for 1 h at 60°C then cooled to room temperature, diluted with water (10 ml) and extracted with hexanes (3 × 30 ml). The combined organic extracts were washed with water (10 ml) and brine (10 ml) before being dried and carefully concentrated by rotary evaporation. The crude *dichloro alkene* **358** (1.89 g, 57%) was obtained as a pale yellow oil, ν_{max}/cm^{-1} 2988, 2878, 1613, 1451, 1372, 1261, 1210, 1111, 1063, 991, 883, 810; δ_H 1.30 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.42 (3H, s, CH_3), 3.88 (1H, d, *J*~8.6, 4-H_a), 4.09 (1H, d, *J*~8.6, 4-H_b), 6.20

(1H, s, 1'-H); δ_C 24.3 (CH_3), 26.0 (CH_3), 27.2 (CH_3), 73.9 (CH_2), 80.6 (5-C), 109.5 (2-C), 120.2 (CCl_2), 136.0 (1'-CH).

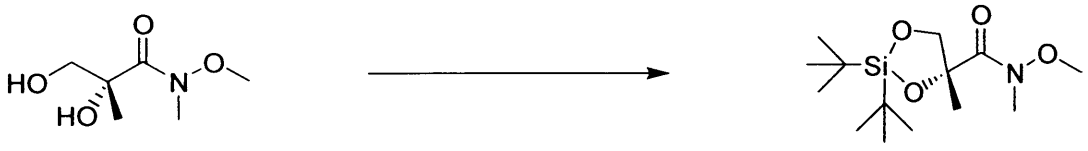
(*S*)-5-Ethynyl-2,2,5-trimethyl-1,3-dioxolane 352



358 **352**

To a stirred solution of dichloro alkene **358** (1.64 g, 7.8 mmol) in dry tetrahydrofuran (10 ml) at -30°C was added butyllithium (9.4 ml of a 2.5 M solution) dropwise *via* a syringe. After the addition was completed, the solution was allowed to slowly warm to 0°C over a one hour period. The reaction was quenched with saturated aqueous ammonium chloride (10 ml) and diluted with ether (30 ml). The aqueous phase was extracted with diethyl ether (3 × 30 ml) and the combined ether solution washed with brine (10 ml) and water (10 ml) to give the crude *acetylene* **352** as a yellow oil (1.1 g, 99%). δ_H 1.28 (3H, s, 5-CH_3), 1.39 (3H, s, 2-CH_3), 1.43 (3H, s, 2-CH_3), 2.35 (1H, s, 2'-H), 3.65 (1H, d, *J*~8.2, 4-H_a), 4.05 (1H, d, *J*~8.2, 4-H_b).

(*R*)-*N*-Methoxyl-*N*-methyl-(2,2-bis(1,1-dimethylethyl)-5-methyl-1,3-dioxa-2-silacyclopent-5-yl)-carboxamide 370

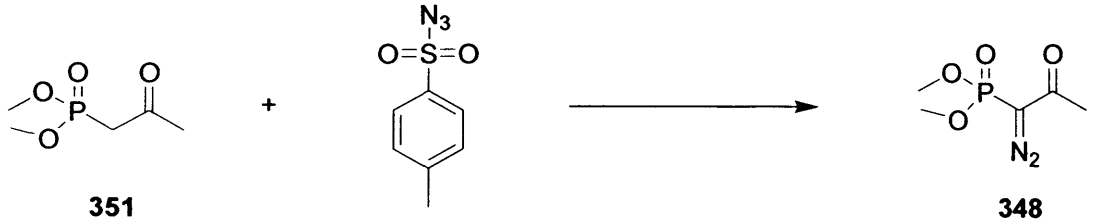


(*R*)-325 **370**

To a stirred solution of the diol **(*R*)-325** (500 mg, 3.0 mmol) and 2,6-lutidine (1.0 ml, 9 mmol) in chloroform (30 ml) at 0°C was added di-*tert* butylsilyl *bis*-(trifluoromethanesulfonate) (1.6 g, 3.6 mmol). The resulting solution was warmed to room temperature and then stirred for another 18 h. Water (5 ml) was added then the solution extracted with dichloromethane (3 × 30 ml). The combined organic extracts were dried and

the crude product was taken to a florisil column using petrol ether as the eluent to give the pure *silyl ether* **370** as a colourless oil (395 mg, 53 %), δ_H 0.97 (18H, s, 2 × $C(CH_3)_3$), 1.48 (3H, s, C-CH_3), 3.62 (1H, d, *J*~6.8, 4-H_a), 3.65 (1H, d, *J*~6.8, 4-H_b), 3.67 (3H, s, OCH_3), 3.73 (3H, s, N-CH_3);

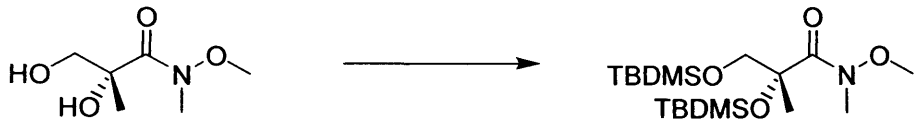
Dimethyl diazoketophosphonate 348[102]



351 **350** **348**

A solution of dimethyl (2-oxopropyl)phosphonate **351** (6.1 g, 36.7 mmol) in dry benzene (38 ml) was added to a stirred suspension of NaH (60%, 15 g, 36.7 mmol) in a mixed solvent of dry benzene (114 ml) and dry tetrahydrofuran (19 ml) at 0-5°C. The reaction mixture was stirred for 1 h at 0°C before tosyl azide **350** (7.20 g, 36.7 mmol) in benzene (20 ml) was added. The reaction mixture was warmed to room temperature and stirred for addition 2 h. The solution was filtered and concentrated before purification by flash column chromatography using ethyl acetate / petrol ether (50%) as eluent to give the pure *diazophosphonate* **348** (4.20 g, 60%) as a pale yellow oil, ν_{max}/cm^{-1} 3516, 2959, 2857, 2401, 2221, 2123, 1658, 1458, 1366, 1276, 1183, 1025, 971, 838, 906, 785; δ_H 2.21 (3H, s, CH_3), 3.77 (3H, s, OCH_3), 3.80 (3H, s, OCH_3); δ_C 27.1 (CH_3), 53.6 (OCH_3), 53.6 (OCH_3), 143.0 ($C=N_2$), 189.8 (C=O); *m/z* (APcI) 193 (M^+ +H, 100%). These data are identical to those previously recorded.[102]

(+)-(*R*)-2,3-Di-(*tert*-Butyldimethylsilyloxy)-2,*N*-dimethyl-*N*-methoxypropionamide 374



(*R*)-325 374

t-Butyldimethylsilyl chloride (23.0g, 152.0 mmol) was added to a stirred solution of dihydroxypropionamide **(*R*)-325** (10.30 g, 63.3 mmol), imidiazole (21.50 g, 316.5 mmol) in *N*, *N*-dimethylformamide (40 ml). The solution was heated to 35°C and stirred overnight under nitrogen. Water (10 ml) was then added and the reaction mixture was cooled to room temperature before extracting with dichloromethane (3 × 50 ml). The combined organic extracts were washed with brine (20 ml) and dried evaporated. The crude product was purified by silica gel chromatography using ethyl acetate/ petrol ether (5%) as eluent. The pure *bis-silylether* **374** (23.2 g, 94%) was obtained as a colourless oil, $[\alpha]_D^{26} = +3.2$ (*c* 2.0 g/ 100ml, chloroform); ν_{max}/cm^{-1} 2934, 2856, 1670, 1472, 1387, 1361, 1251, 1214, 1109, 1033, 837, 778, 723, 682; δ_H 0.00 (3H, s, Si-CH_3), 0.01 (3H, s, Si-CH_3), 0.08 (3H, s, Si-CH_3), 0.11 (3H, s, Si-CH_3), 0.83 (9H, s, C(CH_3)$_3$), 0.84 (9H, s, C(CH_3)$_3$), 1.39 (3H, s, 2-CH_3), 3.25 (3H, s, N-CH_3), 3.65 (3H, s, OCH_3), 3.67 (1H, d, *J*~9.9, 3-CH_a), 3.73 (1H, d, *J*~9.9, 3-CH_b); δ_C -5.9 (Si-CH_3), -5.8 (Si-CH_3), -2.5 (Si-CH_3), -2.3 (Si-CH_3), 18.3 (C(CH$_3$)$_3$), 18.5 (C(CH$_3$)$_3$), 25.8 (C(CH_3)$_3$), 26.1 (C(CH_3)$_3$), 27.7 (2-CH_3), 36.1 (N-CH_3), 60.3 (OCH_3), 69.7 (3-CH_2), 80.2 (2-C), 172.7 (C=O), m/z (APcI) 392 (M^++H, 100%).

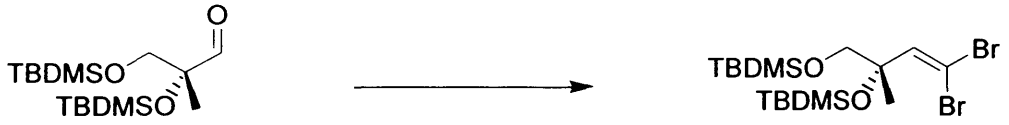
(*R*)-2,3-Di(*tert*-butyldimethylsilyloxy)-2-methylpropanal 375

374 375

A solution of the *bis*-silylether **374** (10.1 g, 25.9 mmol) was stirred in dry ether (260 ml) at -78°C. Lithium aluminium hydride (80 ml of a 1M solution in diethyl ether, 77.7 mmol) was

added dropwise. The reaction mixture was then stirred at this temperature for 40 minutes before being treated with 2M aqueous sodium hydroxide (40 ml). The mixture was then warmed to ambient temperature before being extracted with ether (3 × 100 ml). The combined organic phases were dried and carefully evaporated. The crude *aldehyde* **375** (7.50 g, 88%) was obtained as a pale yellow liquid which was ready for the next step without further purification, ν_{max}/cm^{-1} 2955, 2858, 2359, 1740, 1472, 1388, 1362, 1255, 1156, 1108, 1040, 836, 777, 668; δ_H -0.08 (3H, s, Si- CH_3), -0.06 (3H, s, Si- CH_3), 0.01 (3H, s, Si- CH_3), 0.02 (3H, s, Si- CH_3), 0.80 (9H, s, $C(CH_3)_3$), 0.82 (9H, s, $C(CH_3)_3$), 1.12 (3H, s, 2-CH_3), 3.53 (1H, app. s, 3-H_a), 3.54 (1H, app. s, 3-H_b), 9.51 (1H, s, CHO); δ_C -5.8 (Si- CH_3), -5.7 (Si- CH_3), -3.6 (Si- CH_3), -3.2 (Si- CH_3), 15.2 (2-CH_3), 18.1 ($\underline{C}(CH_3)_3$), 18.2 ($\underline{C}(CH_3)_3$), 25.7 ($C(\underline{C}H_3)_3$), 68.4 (3-CH_2), 80.7 (2-C), 204.6 (C=O); m/z (APcI) 333 (M^++H, 95%).

(+)-(*S*)-1,1-Dibromo-3,4-di-(*tert*-butyldimethylsilyloxy)-3-methyl-but-1-ene 380



375 **380**

Triphenylphosphine (44.0 g, 167.7 mmol) was added to a well stirred solution of carbon tetrabromide (27.8 g, 83.8 mmol) in dry dichloromethane (200 ml).[103] An orange solution was obtained. The aldehyde **375** (13.9 g, 41.9 mmol) was added caused fading of the colour. The solution was stirred at room temperature and followed by tlc (~ 4 h). The reaction mixture was then washed with water (30 ml), the solvent evaporated, and the residue separated by silica gel chromatography using pentane/hexane (50%). The pure *dibromoalkene* **380** (15.2 g, 74%) was obtained as a colourless oil, $[\alpha]_D^{25}$ = +2.7 (*c* 1.90 g/ 100ml, chloroform); ν_{max}/cm^{-1} 2955, 2857, 2361, 1607, 1472, 1388, 1361, 1255, 1108, 1036, 938, 836, 776, 669; δ_H -0.01 (3H, s, Si-CH_3), 0.00 (3H, s, Si-CH_3), 0.04 (3H, s, Si-CH_3), 0.05 (3H, s, Si-CH_3), 0.81 (9H, s, $C(CH_3)_3$), 0.84 (9H, s, $C(CH_3)_3$), 1.38 (3H, s, 3-CH_3), 3.42 (1H, d *J*~9.1, 4-CH_a), 3.52 (1H, d *J*~9.1, 4-CH_b), 6.64 (1H, s, 2-H); δ_C -5.6 (Si-CH_3), -3.0 (Si-

CH_3), -2.3 (Si-CH_3), -2.2 (Si-CH_3), 18.2 (Si-C), 18.3 (Si-C), 22.6 (3-CH_3), 25.8 (C($\underline{C}H_3)_3$), 25.9 (C($\underline{C}H_3)_3$), 69.7 (4-CH_2), 87.3 (3-C), 143.5 (2-CH), 204.5 (1-C); m/z (APcI) 279 (M^+-TBDMS-Br-Me+H, 100%).

1,1-Dibromo-2-phenylethene 379

378 **379**

Follwing the forgoing procedure, benzaldehyde **378** (1.30 g, 12.0 mmol) was stirred with triphenylphosphine (12.6 g, 48.0 mmol) and carbon tetrabromide (8.0 g, 24 mmol) in dry dichloromethane (60 ml) to afford a crude product which was purified by stirring with hexane, filtering and evaporation. The pure dibromo-alkene **379** (1.60 g, 50%) was obtained as a yellow oil, ν_{max}/cm^{-1} 3055, 3023, 1594, 1493, 1444, 1337, 1268, 1198, 1119, 1075, 1030, 920, 863, 778, 745, 721, 692; δ_H 7.24-7.30 (3H, m, 3 × Ar-CH), 7.39 (1H, s, 2-H), 7.43 (2H, dd, J~1.1, 7.3, 2 × Ar-CH); δ_C 54.0 (1-C), 90.1 (2-CH), 128.9 (Ar-CH), 129.1 (Ar-CH), 135.7 (Ar-C), 137.4 (Ar-CH). These data are identical to those previously recorded.[104]

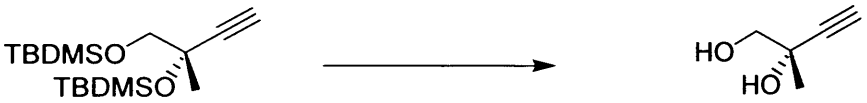
(+)-(*S*)-3,4-Di-(*tert*-butyldimethylsilyloxy)-3-methyl-1-butyne 381

380 **381**

To a stirred solution of the dibromo-alkene **380** (5.25 g, 10.8 mmol) in dry tetrahydrofuran (175 ml) at -30°C was added butyllithium (13 ml of a 2.5 M solution in hexane, 32.5 mmol) dropwise *via* a syringe. After the addition was complete, the solution was allowed to slowly warm to 0°C during one hour. The reaction was quenched with saturated aqueous ammonium chloride (10 ml) and diluted with ether (50 ml). The separated aqueous phase was extracted

with further ether (3 × 50 ml). The combined solutions were washed with brine (20 ml) and water (20 ml) and then dried and evaporated. The crude product was separated using silica gel chromatography using pentane as the eluent. The pure *alkyne* **381** (2.60 g, 59%) was obtained as a colourless oil, $[\alpha]_D^{26} = +3.5$ (*c* 1.0 g/ 100ml, chloroform); ν_{max}/cm^{-1} 3311, 2929, 2857, 1472, 1389, 1361, 1254, 1190, 1119, 1032, 939, 836, 777; δ_H 0.00 (3H, s, Si-CH_3), 0.01 (3H, s, Si-CH_3), 0.10 (3H, s, Si-CH_3), 0.11 (3H, s, Si-CH_3), 0.80 (9H, s, C(CH_3)$_3$), 0.84 (9H, s, C(CH_3)$_3$), 1.36 (3H, s, 3-CH_3), 2.32 (1H, s, 1-H), 3.35 (1H, d, *J*~ 9.5, 4-H_a), 3.47 (1H, d, *J*~ 9.5, 4-H_b); δ_C -5.34 (Si-CH_3), -5.32 (Si-CH_3), -3.0 (Si-CH_3), -2.9 (Si-CH_3), 18.0 (Si-C), 18.3 (Si-C), 25.7 (C($\underline{C}H_3$)$_3$), 25.9 (C($\underline{C}H_3$)$_3$), 27.4 (3-CH_3), 69.9 (2-C), 71.6 (4-CH_2), 72.3 (1-CH), 87.2 (2-C); m/z (APcI) 329 (M^++H, 100%).

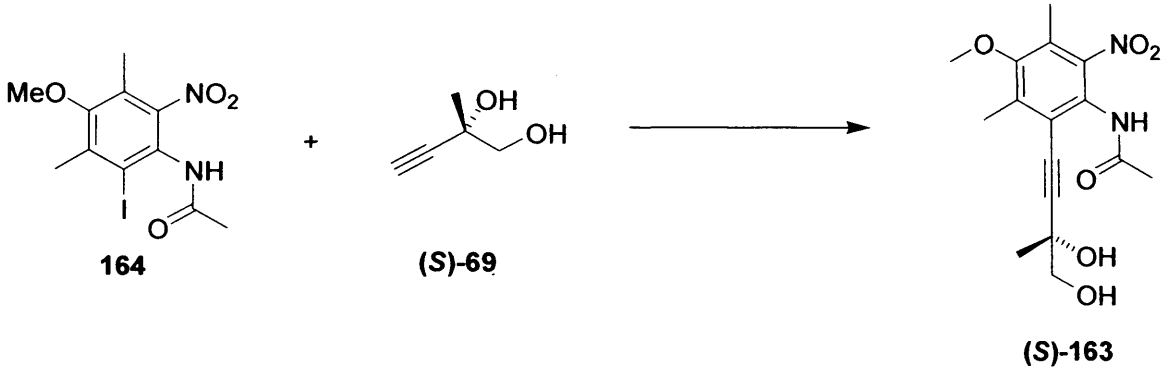
(-)-(*S*)-3, 4-Dihydroxy-3-methyl-1-butyne (*S*)-69[105]



381 **(*S*)-69**

Tetra-n-butylammonium fluoride (7.6 ml of a 1M solution in THF) was added dropwise to a stirred solution of the *bis*-silyl ether **381** (1.00 g, 3.0 mmol) in tetrahydrofuran (30ml) at ambient temperature. The reaction mixture was stirred at this temperature for 2 h. The solvent was then evaporated and the residue was purified by silica gel chromatography with petrol ether / ethyl acetate (5%) as eluent. The purified *diol* **(*S*)-69** (0.25 g, 82%) was then obtained as a yellow oil, $[\alpha]_D^{26} = -0.7$ (*c* 20 g/ 100ml, chloroform); ν_{max}/cm^{-1} 3430, 2938, 2113, 1622, 1511, 1376, 1244, 1060, 953, 891; δ_H 1.40 (3H, s, CH_3), 2.42 (1H, s, CH), 3.42 (1H, d *J*~7.2, 4-H_a), 3.57 (1H, d *J*~7.2, 4-H_b); δ_C 25.6 (CH_3), 68.6 (3-C), 70.7 (2-CH_2), 72.6 (1-CH), 86.3 (2-C); m/z (APcI) 100 (M^+, 100%). These data are identical to those of **69** (racemic) except for optical rotation (p.154).

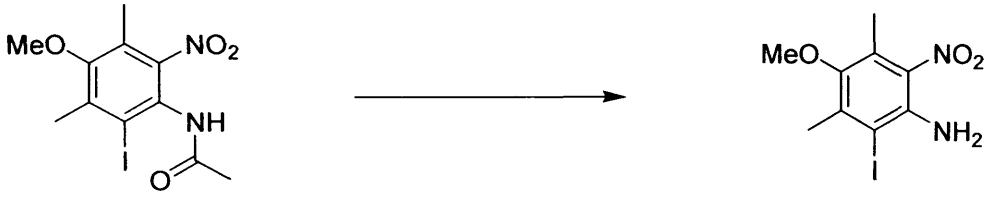
(+)-4-(*S*)-Acetamido-2,6-dimethyl-5-[3',4'-dihydroxy-3'-methylbut-2'-yn-1-yl]-3-nitroanisole (*S*)-163



164 **(*S*)-69** **(*S*)-163**

Following the general procedure of Sonogashira coupling, nitroiodide **164** (364.0 mg, 1.0 mmol) was refluxed with triethylamine (3.6 ml, 26 mmol), *tetrakis*(triphenylphosphine)palladium(0) (578.0 mg, 0.5 mmol), copper (I) iodide (95.0 mg, 0.5 mmol) along with diol **(*S*)-69** (200.0 mg, 2.0 mmol) in dry tetrahydrofuran (10 ml) at 75°C to afford the *diol* **(*S*)-163** (260 mg, 77%) as a colourless solid, $[\alpha]_D^{26}$= +3.5 (*c* 1.9 g / 100ml, methanol) m.p. 173-174.5°C. These data are identical to those of the racemate diol **163** (p.155).

4-Amino-2,6-dimethyl-5-iodo-3-nitroanisole 388

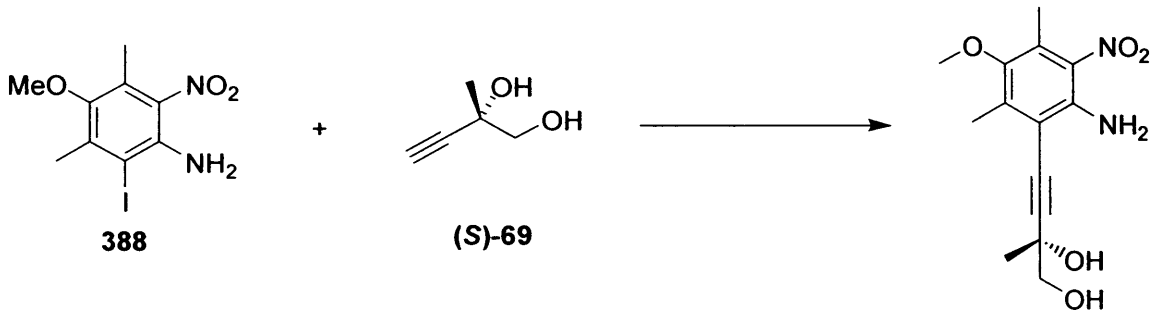


164 **388**

The nitro-iodide **164** (320 mg, 0.88 mmol) was dissolved in methanol before concentrated sulfuric acid (0.18 ml) was added. The resulting yellow solution was heated under reflux for 16 h before being cooled to room temperature. The mixture was poured onto ice (~25 ml) and extracted with dichloromethane (3 × 10 ml) and the combined extracts was dried with $MgSO_4$ and evaporated. Chromatography of the crude product using ethyl acetate / petrol ether (10%) as eluent gave pure *nitroanisole* **388** (180 mg, 64%) as a bright yellow solid, m.p. 214-215°C; ν_{max}/cm^{-1}

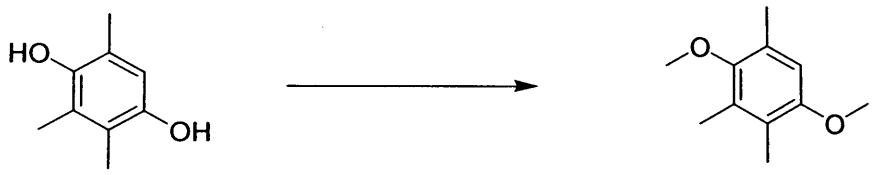
3375, 2925, 2361, 1602, 1455, 1259, 1047, 799, 650; δ_H 2.24 (3H, s, Ar-CH_3), 2.40 (3H, s, Ar-CH_3), 3.58 (3H, s, Ar-OCH_3), 5.25 (2H, br s, NH_2).

(*S*)-4-Amine-2,6-dimethyl-5-[(3'S)-3',4'-dihydroxy-3'-methylbut-2'-yn-1-yl]-3-nitroanisole 389



Follow the general procedure of Sonogashira coupling, nitroanisole **388** (180 mg, 0.55 mmol) was refluxed with triethylamine (2 ml, 14.3 mmol), *tetrakis*(triphenylphosphine)palladium(0) (324.0 mg, 0.28 mmol), copper(I) iodide (53.0 mg, 0.28 mmol) along with diol **(*S*)-69** (110 mg, 1.1 mmol) in dried and degassed tetrahydrofuran (6 ml) to afford *diol* **389** (82 mg, 51%) as a yellow solid, m.p. 173-174.5°C; ν_{max}/cm^{-1} 3377, 2936, 2221, 1603, 1509, 1452, 1376, 1330, 1260, 1198, 1153, 1116, 1054, 998, 912, 873, 767, 733; δ_H 1.50 (3H, s, 3'-CH_3), 2.26 (3H, s, Ar-CH_3), 2.28 (3H, s, Ar-CH_3), 3.05 (2H, br res., 2 × OH), 3.55 (3H, s, OCH_3), 3.56 (1H, d, J~11.0, 4'-H_a), 3.69 (1H, d, J~11.0, 4'-H_b), 5.62 (2H, br res., NH_2); δ_C 13.9 (3'-CH_3), 15.8 (Ar-CH_3), 25.9 (Ar-CH_3), 60.9 (OCH_3), 69.7 (CH_2), 71.2 (3'-C), 78.5 (2'-C), 102.5 (1'-C), 108.8 (Ar-C), 128.9 (Ar-C), 134.8 (Ar-C), 140.2 (Ar-C), 141.0 (C-NH_2), 148.1 (C-NO_2); *m/z* (APcI) 277 (M^+-OH, 100%).

1,4-Dimethoxy-3,5,6-trimethylbenzene 296[58]



295 **296**

Hydroquinone **295** (1.50 g, 10.0 mmol) was stirred in dry acetone (30 ml) containing anhydrous potassium carbonate (3.0 g, 22 mmol). The resulting solution was stirred vigorously and reflux under nitrogen. Dimethyl sulate (2 ml, 21 mmol) in dry acetone (2 ml) was added slowly. The reaction mixture was refluxed overnight before cooling to room temperature. The solution was filtrated and the filtrate evaporated. The residue was treated with water (15 ml) and ether (15 ml) and the water layer separated. The ether solution was washed with 2M aqueous KOH (2 × 3 ml), 2M ammonia (5 ml), water (5 ml) and brine (5 ml) then dried to give the crude *dimethoxy-benzene* **296** (1.70 g, 94%) as a colourless gum which was ready for the iodonation step without further purification, δ_H 1.94 (3H, s, CH_3), 2.02 (3H, s, CH_3), 2.10 (3H, s, CH_3), 3.47 (OCH_3), 3.60 (OCH_3), 6.35 (1H, s, CH). These data are identical to previously recorded.[58b]

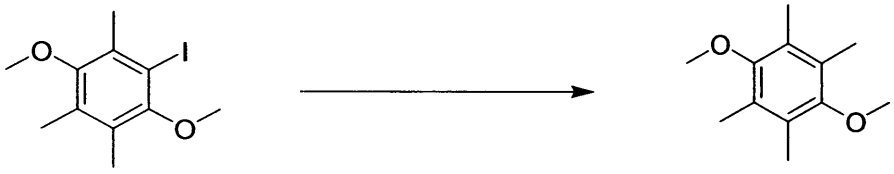
1,4-Dimethoxy-2-iodo-3,5,6-trimethylbenzene 195

296 **195**

N-Iodosuccinimide (2.36 g, 10.5 mmol) was stirred in acetic acid (25 ml) at room temperature. To the solution was added dimethoxy-benzene **296** (1.30 g, 7 mmol) and the resulting mixture refluxed for 1 h then cooled to room temperature. The mixture was basified with aqueous 2M sodium hydroxide until pH >10 was achieved. Solid sodium chloride was added and the solution extracted with dichloromethane (3 × 70 ml). The combined organic phases were washed with aqueous 2 M sodium hydroxide (50 ml), water (50 ml) before being

dried and evaporated. The crude product was recrystallized from ether / hexane to give the pure *iodo-benzene* **195** (1.07 g, 50%) as brown amorphous crystals. m.p. 68-71°C, ν_{max}/cm^{-1} 2933, 1453, 1381, 1311, 1222, 1086, 1038, 1003, 977, 933, 831, 742; δ_H 2.10 (CCH_3), 2.18 (CCH_3), 2.34 (CCH_3), 3.57 (OCH_3), 3.64 (OCH_3); δ_C 13.3 ($C\underline{C}H_3$), 14.3 ($C\underline{C}H_3$), 22.5 ($C\underline{C}H_3$), 60.70 (OCH_3), 60.73 (OCH_3), 96.4 (C-I), 129.1 ($\underline{C}CH_3$), 131.5 ($\underline{C}CH_3$), 132.9 ($\underline{C}CH_3$), 153.3 ($\underline{C}$-OCH_3), 154.4 ($\underline{C}CH_3$).

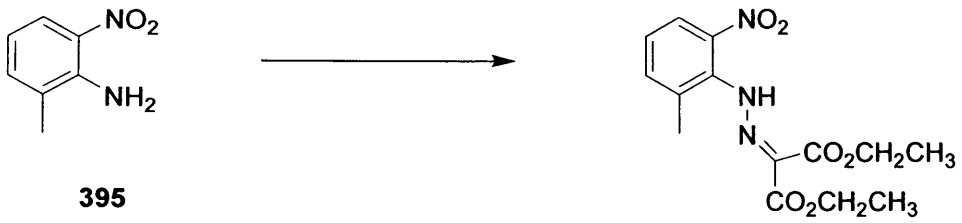
1,4-Dimethoxy-2,3,5,6-tetramethylbenzene 309



195 **309**

To a dry two-necked round bottom flask containing a solution of iodobenzene **195** (155 mg, 0.5 mmol) in 1-methyl-2-pyrrolidinone (NMP) (2.5 ml) at ambient temperature was added triphenylphosphine (13.0 mg, 0.05 mmol), tris-(dibenzylideneacetone)dipalladium(0) chloroform (13.0 mg, 0.0125 mmol) and copper(I) iodide (4.8 mg, 0.025 mmol) under a flow of nitrogen. The mixture was degassed under nitrogen for 20 minutes before the addition of diethylamine (0.16 ml, 1.5 mmol) and tetramethyltin (250 mg, 1.5 mmol) in NMP (1 ml). The solution was heated to 100°C and the stirring continued for 24 hours at this temperature. The resulting suspension was cooled and treated with 10% aqueous sodium sulfite solution (13ml). The mixture was washed with 10% aqueous potassium fluoride (13 ml) and extracted with ether (3 × 25 ml). The combined organic extracts were dried and evaporated to yield a colourless solid. Chromatography of this residue using ethyl acetate / hexane (10%) as the eluent gave the pure tetramethyl-benzene **309** (57mg, 59%) as a colourless solid, m.p. 102-103 °C; ν_{max}/cm^{-1} 801, 1008, 1087, 1453, 2935; δ_H 2.09 (12H, s, 4 × CH_3), 3.55 (6H, s, 2 × OCH_3); δ_C 11.6 (4 × CH_3), 59.2 (2 × OCH_3), 126.6 (Ar-C), 151.7 (Ar-C); *m/z* (APcI) 193 (M^+-H, 100%).

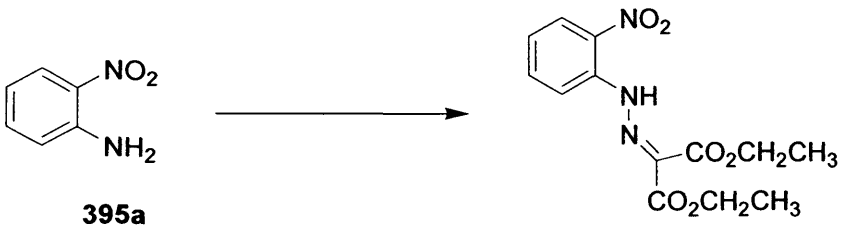
Diethyl 2–((2'-nitro-6'-methylphenyl)hydrazono)propanedioate 397[1d]



395 **397**

To a three-necked round bottom flask containing concentrated hydrochloric acid (10 M, 50 ml) at ambient temperature was added portionwise 2-methyl-6-nitroaniline **395** (26.0 g, 0.17 mol) over a period of 0.5h, with stirring being allowed to continue for a further 0.5h after addition was complete. Deionized water (100 ml) was then added, with the resulting suspension being cooled to 0°C prior to the dropwise addition of a solution of sodium nitrite (13.4 g, 0.19 mol) in deionized water (25 ml) over a period of 1h. The resulting solution was filtered, and the filtrate added dropwise over a period of 1h to a vigourously stirred emulsion of diethyl malonate (26 ml, 0.17 mol) in deionized water (100 ml) at 5°C. Anhydrous sodium acetate (50.0 g) was added portionwise during the addition of the solution, and stirring was allowed to continue for a further period of 1h once addition of the solution was complete. The resulting orange-red suspension was filtered. Flash column chromatography of the solid using ethyl acetate / petrol ether (20%) followed by recrystallization from methanol yielded the *iminomalonate* **397** (27.4 g, 50%) as a yellow crystal, m.p. 68.0-69.3°C (lit.[92] m.p.70-71°C), ν_{max}/cm^{-1} 3188, 2984, 1727, 1687, 1513, 1343, 1293, 1192, 1018, 1091, 802, 739; δ_H 1.28 (3H, t, *J*~7.1, $CH_2C\underline{H}_3$), 1.34 (3H, t, *J*~7.1, $CH_2C\underline{H}_3$), 2.51 (3H, s, Ar-CH_3), 4.20 (2H, q, *J*~7.1, CH_2), 4.33 (2H, q, *J*~7.1, CH_2), 7.04 (1H, t, *J*~8.9, 4'-H), 7.47 (1H, d, *J*~8.9, Ar-H), 7.81 (1H, d, *J*~8.9, Ar-H), 13.45 (1H, br s, NH); δ_C 14.5 (2 × CH_3), 21.5 (Ar-CH_3), 61.7 (CH_2), 62.3 (CH_2), 123.7 (C), 124.0 (Ar-CH), 124.4 (Ar-CH), 132.4 (Ar-C), 135.8 (Ar-C), 138.2 (Ar-CH), 140.7 (C-NO_2), 163.2 (C=O), 163.1 (C=O); *m/z* (APcI) 324 (M^++H, 100%).

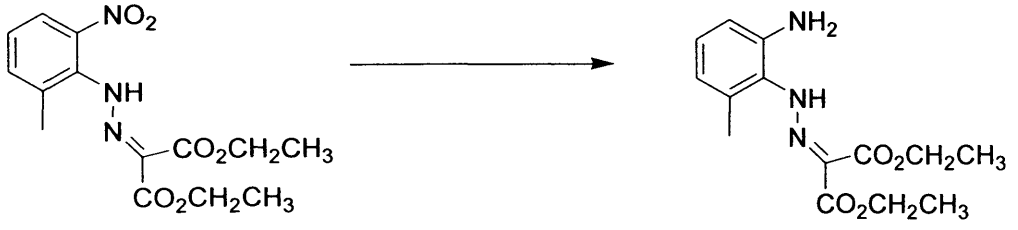
Diethyl 2–((2'-nitrophenyl)hydrazono)propanedioate 397a



395a **397a**

Following the above procedure for making iminomalonate **397**, treatment of nitroaniline **395a** (47.0 g, 0.34 mol) with sodium nitrite (26.9 g, 0.38 mol) and diethyl malonate (55.0 g, 0.34 mol) gave the *iminomalonate* **397a** (74.5 g, 74%) as brown yellow crystals; m.p. 70.1-72.6°C (lit.[2] m.p.72-74°C); ν_{max}/cm^{-1} 3192, 2985, 2360, 1727, 1679, 1611, 1580, 1496, 1370, 1342, 1320, 1278, 1180, 1092, 1016, 859, 810, 783, 743; δ_H 1.32-1.38 (6H, m, 2 × CH_3), 4.29 (2H, q, *J*~7.1, CH_2), 4.36 (2H, q, *J*~7.1, CH_2), 7.06 (1H, dt, *J*~1.0, 7.6, Ar-H), 7.58 (1H, t, *J*~7.6, Ar-H), 8.00 (1H, d, *J*~7.6, Ar-H), 8.15 (1H, dd, *J*~1.0, 7.6, Ar-H), 14.10 (1H, br. s., NH); δ_C 14.5 (CH_3), 14.6 (CH_3), 62.2 (CH_2), 62.6 (CH_2), 117.6 (Ar-CH), 123.1 (Ar-CH), 126.2 (Ar-CH), 126.6 (C), 134.9 (Ar-C), 136.3 (Ar-CH), 139.2 (C-NO_2), 161.6 (C=O), 163.2 (C=O); *m/z* (APcI) 310 (M^++H, 100%).

Diethyl 2–((2'-amino-6'-methylphenyl)hydrazono)propanedioate 398[1d]

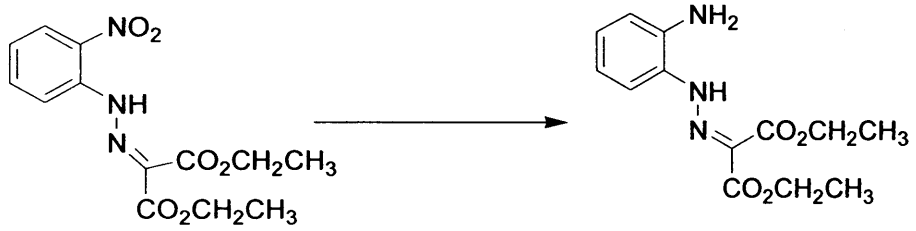


397 **398**

To a suspension of 10% palladium on carbon (1.5 g) in ethanol (77 ml) at ambient temperature was added portionwise the iminomalonate **397** (9.97 g, 31 mmol) and cyclohexene (18.7 ml, 185.4 mmol). The mixture was refluxed for 16h, then allowed to cool to ambient temperature before being filtered through Celite, with the filter cake being washed with further portions of warm ethanol. The combined filtrates were evaporated and the

residue crystallized from ethanol to give the *aniline* **398** (6.62 g, 73%) as orange crystals, m.p. 103-104°C (lit.[1d] m.p. 103-104°C); ν_{max}/cm^{-1} 3370, 2982, 1738, 1488, 1370, 1274, 1096, 1021, 765; δ_H 1.27 (3H, t, *J*~7.1, $CH_2C\underline{H}_3$), 1.34 (3H, t, *J*~7.1, $CH_2C\underline{H}_3$), 2.29 (3H, s, Ar-CH_3), 4.19 (2H, q, *J*~7.1, CH_2), 4.29 (2H, q, *J*~7.1, CH_2), 5.47 (2H, br s, NH_2), 6.48 (1H, d, *J*~7.4, 5'-H), 6.54 (1H, d, *J*~8.0, 3'-H), 6.81 (1H, t, *J*~7.7, 4'-H), 13.42 (1H, br s, NH); δ_C 14.6 ($CH_2\ \underline{C}H_3$), 14.7 ($CH_2\underline{C}H_3$), 18.3 (Ar-CH_3), 61.1 (CH_2), 61.6 (CH_2), 115.6 (1-C), 116.6 (Ar-CH), 120.0 (Ar-CH), 124.7 (6'-C), 126.2 (4'-C), 127.5 (C-N), 138.4 (C-N), 163.3 (C=O), 164.7 (C=O); *m/z* (APcI) 294 (M^++H, 100%).

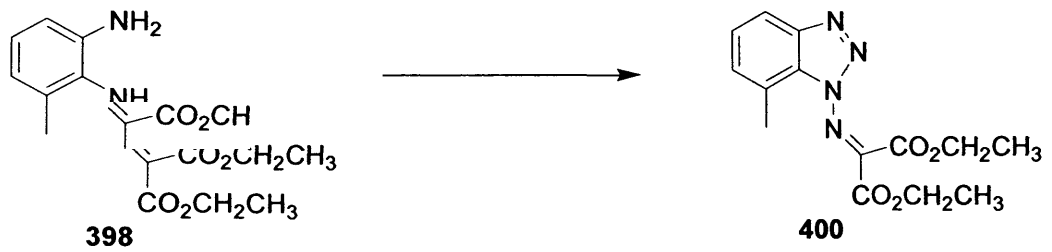
Diethyl 2–((2'-aminophenyl)hydrazono)propanedioate 398a



397a **398a**

Following the above procedure of hydrogenation on iminomalonate **397**, reflux of *iminomalonate* **397a** (5.0 g, 16.8 mmol) with 10% palladium on carbon (200 mg) and cyclohexene (8.0 g, 97.6 mmol) in ethanol (40 ml) gave the *aniline* **398a** (3.9 g, 87%) as orange yellow crystals, m.p. 82°C (lit.[2] m.p. 82°C); δ_H 1.33 (3H, t, *J*~7.1, CH_3), 1.38 (3H, t, *J*~7.1, CH_3), 4.28 (2H, q, *J*~7.1, CH_2), 4.36 (2H, q, *J*~7.1, CH_2), 5.12 (2H, br. s., NH_2), 6.72-6.77 (2H, m, 2× Ar-H), 6.97 (1H, d, *J*~7.1, Ar-H), 7.02 (1H, d, *J*~7.1, Ar-H), 13.15 (1H, br s., NH); *m/z* (APcI) 280 (M^++H, 100%).

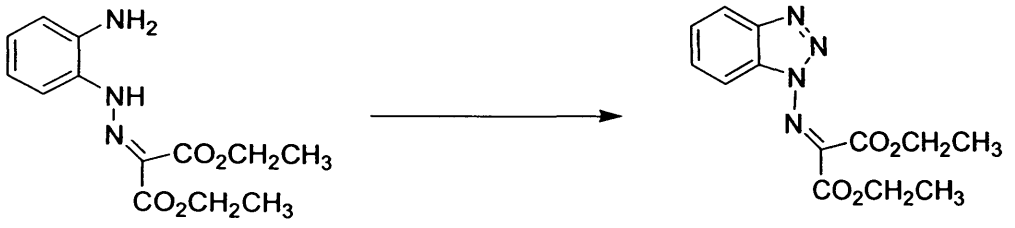
Diethyl 2-(7'-methyl-1H-benzotriazol-1'-iminyl)propanedioate 400



398 **400**

To a suspension of the aniline **398** (6.60 g, 22.6 mmol) in methanol (63 ml) at ambient temperature was added a solution of sodium nitrite (2.0 g, 29.0 mmol) in deionized water (4.5 ml), and the resulting suspension added to a stirred, ice-cold solution of concentrated hydrochloric acid (10 M, 7.4 ml) in water (13.5 ml). The resulting solid was filtered off and recrystallized from aqueous methanol to give the *benzotriazole malonate* **400** (6.20 g, 91%) as light yellow crystals, m.p. 67.0-68.0°C (lit.[1d] m.p. 64-65°C); ν_{max}/cm^{-1} 2984, 1742, 1626, 1445, 1367, 1306, 1240, 1161, 1138, 1080, 1007, 863, 788, 746; δ_H 1.36 (6H, t, *J*~7.2, 2 × CH_3), 2.73 (3H, s, 7'-CH_3), 4.36 (2H, q, *J*~7.2, CH_2), 4.45 (2H, q, *J*~7.2, CH_2), 7.26-7.33(2H, m, 5',6'-CH), 7.80 (1H, d, *J*~7.8, 4'-CH); δ_C 14.2 ($CH_2\underline{C}H_3$), 14.4 ($CH_2\underline{C}H_3$), 17.7 (7'-CH_3), 63.5 ($\underline{C}H_2CH_3$), 63.5 ($\underline{C}H_2CH_3$), 118.4 (Ar-CH), 123.9 (1-C), 126.3 (Ar-CH), 130.8 (7'-C), 131.9 (4'-C), 140.6 (C-N), 145.4 (C-N), 161.0 (C=O), 162.7 (C=O); *m/z* (APcI) 305 (M^++H, 100%). [Found: C, 55.01; H, 5.20; N, 18.27. $C_{14}H_{16}N_4O_4$ requires C, 55.26; H, 5.30; N, 18.41%].

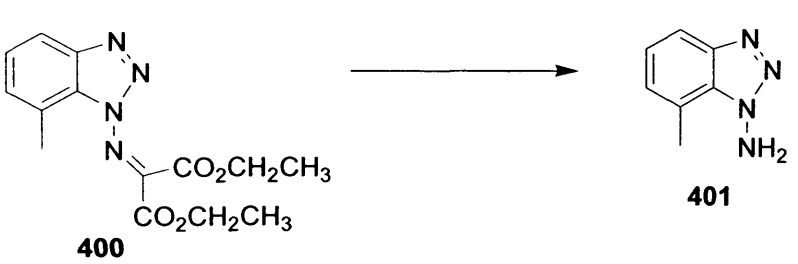
Diethyl 2-(benzotriazol-1'-iminyl)propanedioate 400a



398a **400a**

Following the above procedure of diazotisation, aniline **398a** (17.0 g, 63.8 mmol) was treated with sodium nitrite (4.9 g, 70.6 mmol) and hydrochloric acid (10 M, 20 ml) to give the *benzotriazole malonate* **400a** (16.8 g, 95%) as brown yellow crystals, m.p. 97.0-99.0°C (lit.[2] m.p. 99-100°C); ν_{max}/cm^{-1} 3482, 2983, 2330, 2252, 1748, 1623, 1493, 1448, 1386, 1368, 1234, 1154, 1080, 1212, 919.2, 861, 831, 782, 747, 699; δ_H 1.32-1.36 (6H, m, 2 × CH_3), 4.36 (2H, q, *J*~7.1, CH_2), 4.44 (2H, q, *J*~7.1, CH_2), 7.36 (1H, dt, *J*~0.8, 7.1, Ar-H), 7.52 (1H, t, *J*~7.1, Ar-H), 7.78 (1H, d, *J*~7.1, Ar-H), 7.95 (1H, d, *J*~7.1, Ar-H); δ_C 13.7 (CH_3), 14.0 (CH_3), 63.2 (CH_2), 63.3 (CH_2), 110.8 (Ar-CH), 120.4 (Ar-CH), 125.9 (Ar-CH), 123.0 (Ar-CH), 131.7 (C), 141.2 (Ar-C), 144.8 (Ar-C), 160.4 (C=O), 162.1 (C=O); *m/z* (APcI) 291 (M^++H, 100%).

7-Methyl-benzotriazol-1-amine 401[1d]

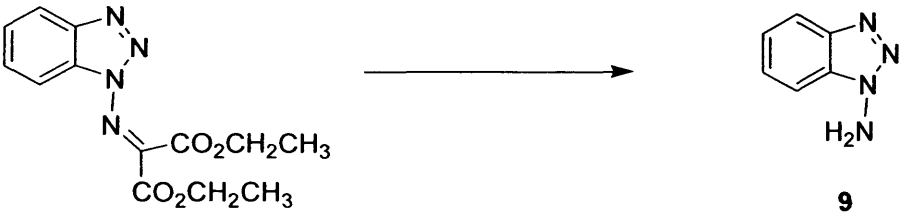


400 **401**

To a stirred solution of the benzotriazole malonate **400** (4.2 g, 14.0 mmol) in methanol (100 ml) maintained at 50°C was added concentrated hydrochloric acid (10 M, 25 ml). After stirring at this temperature for 5h, the solvent was removed under reduced pressure and the residue taken up into 2 M hydrochloric acid (150 ml). The resulting solution was washed with ether (3 × 10 ml), neutralized with solid sodium carbonate and extracted with ether (3 × 25 ml). The combined organic extracts were dried and evaporated to yield a white solid as

the *aminobenzotriazole* **401** (1.6 g, 79%). The crude product was sufficiently pure for further use without purification and showed m.p. 116.0-118.0°C (lit.[1d] m.p. 116-118°C), ν_{max}/cm^{-1} 3308, 3194, 2359, 1655, 1250, 1146, 789, 748; δ_H 2.73 (3H, s, CH_3), 5.66 (2H, br s, NH_2), 7.14-7.19 (2H, m, 5,6-H), 7.74 (1H, dd *J*~1.8, 7.0, 4-H); δ_C 17.3 (CH_3), 117.4 (Ar-CH), 122.1 (7-C), 124.4 (Ar-CH), 128.9 (Ar-CH), 131.1 (C-N); *m/z* (APcI) 149 (M^++H, 100%).

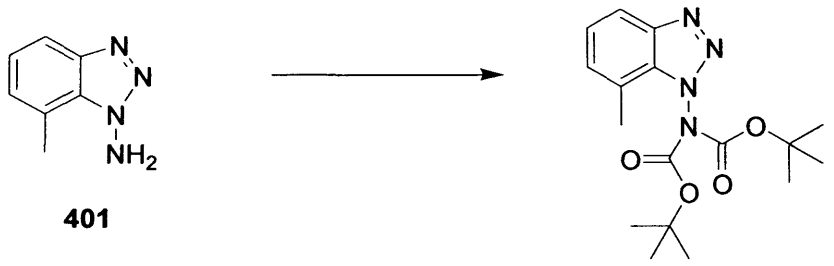
1-Aminobenzotriazole 9



400a **9**

Following the above procedure of deprotection, benzotriazole malonate **400a** (5.00 g, 18.0 mmol) was heated with hydrochloric acid (10M, 25 ml) in methanol (100 ml) at 50 °C to give the *amine* **9** (1.40 g, 57%) as colourless crystals after recrystallization from toluene, m.p. 82-84°C (lit.[2] m.p. 84°C); ν_{max}/cm^{-1} 3316, 1638, 1452, 1241, 1169, 1103, 948, 891, 784, 766, 742; δ_H 5.76 (2H, br s, NH_2), 7.31 (1H, dt, *J*~0.8, 8.4, Ar-CH), 7.46 (1H, dt, *J*~0.8, 8.4, Ar-CH), 7.61 (1H, d, *J*~8.4, Ar-CH), 7.95 (1H, d, *J*~8.4, Ar-CH); δ_C 110.3 (Ar-CH), 120.2 (Ar-CH), 124.6 (Ar-CH), 128.2 (Ar-CH), 132.9 (Ar-C), 144.9 (Ar-C). These data are identical to those previously recorded.[2]

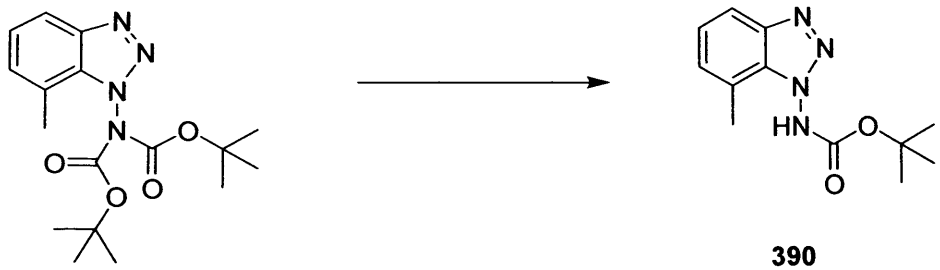
1-[*Bis*(*tert*-butoxycarbonyl)amino]-7-methylbenzotriazole 402[1d]



401 **402**

To a solution of the aminobenzotriazole **401** (1.3 g, 8.8 mmol), triethylamine (1.90 g, 19.3 mmol) and 4-dimethylaminopyidine (65.0 mg, 0.5 mmol) in dry dichloromethane (50 ml) maintained at 0°C, was added dropwise *via* syringe a solution of di-*tert*-butyl dicarbonate (4.20 g, 19.3 mmol) in dry dichloromethane (1.3 ml). Following stirring for 48h at ambient temperature, the mixture was poured into saturated aqueous sodium hydrogencarbonate (10 ml), and the separated organic layer washed with deionized water (10 ml) and brine (10 ml). Evaporation of the dried organic phase afforded a brown gum. Chromatography of this residue using ethyl acetate / petrol (25%) as the eluent gave the *bis-Boc aminobenzotriazole* **402** (2.60 g, 85%) as a pale yellow solid, m.p. 112.0-113.0°C (lit[1d] m.p. 113.0-115.0°C), ν_{max}/cm^{-1} 3431, 2933, 1758, 1613, 1458, 1122, 748.5; δ_H 1.35 (18H, s, 2 × $C(CH_3)_3$), 2.46 (3H, s, 7-CH_3), 7.19-7.25 (2H, m, 5, 6-H), 7.80-7.86 (1H, m, 4-H); δ_C 16.0 (Ar-CH_3), 27.7 ($C(\underline{C}H_3)_3$), 85.9 ($\underline{C}(CH_3)_3$), 118.2 (Ar-CH), 120.0 (7-C), 124.8 (Ar-CH), 129.8 (Ar-CH), 131.0 (C-N), 144.4 (C-N), 148.8 (C=O); *m/z* (APcI) 349 (M^++1, 100%).

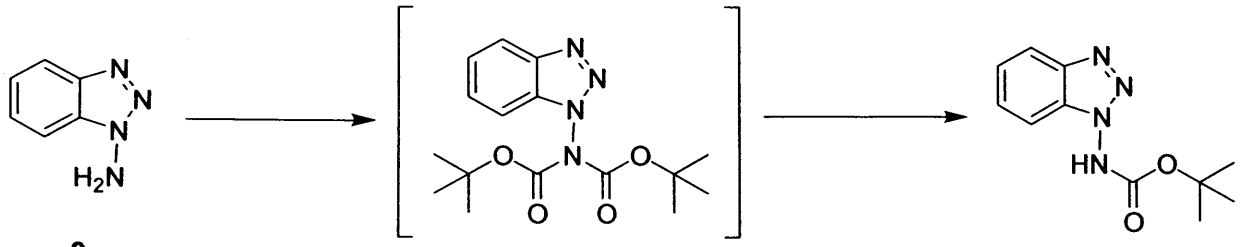
1-(*tert*-Butoxycarbonylamino)-7-methylbenzotriazole 390[1d]



402 **390**

To a stirred solution of the *bis*-Boc aminobenzotriazole **402** (16.20 g, 46.5 mmol) in methanol (290 ml), maintained at 50°C, was added 2M aqueous sodium hydroxide (38 ml). After stirring at this temperature for 40 min, the solvent was removed under reduced pressure to yield a brown residue, which was taken up in dichloromethane (400 ml) and washed with water (30 ml) and brine (30 ml). The the aqueous phase was neutralised with 2M HCl and extracted with dichloromethane (3 × 100 ml). The organic solutions were combined, dried and evaporated to yield a brown oil. Chromatography of this residue using methanol/ chloroform (5%) as the eluent gave an yellow oil which was crystallized from hexane/ ether (50%) to give amorphous, pale yellow crystals of the *N-Boc amine* **390** (5.20 g, 45%), m.p. 105.0-106.0°C (lit.[1d] m.p. 105.0-106.0°C); ν_{max}/cm^{-1} 3171, 2979, 2251, 1749, 1610, 1502, 1457, 1395, 1370, 1253, 1160, 1127, 1065, 912, 870, 819, 791, 733; δ_H 1.53 (9H, br s, $C(CH_3)_3$), 2.63 (3H, s, Ar-CH_3), 7.22-7.30 (2H, m, 5, 6-H), 7.86-7.89 (1H, m, 4-H), 8.41 (1H, br s, NH); δ_C 16.6 (Ar-CH_3), 28.4 ($C(\underline{C}H_3)_3$), 84.1 ($\underline{C}(CH_3)_3$), 118.2 (Ar-CH), 121.3 (7-C), 125.1 (Ar-CH), 130.1 (Ar-CH), 131.8 (C-N), 144.9 (C-N), 154.0 (C=O); *m/z* (APcI) 249 (M^++H, 100%).

Benzotriazol-1-(N-*tert*-butoxycarbonyl) amine 19



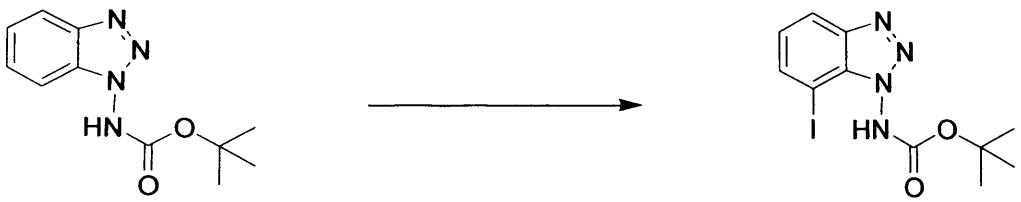
9 **18** **19**

A solution of di-*tert*-butyl dicarbonate (7.20 g, 33.0 mmol) in dry acetonitrile (5 ml) was added during 10 minutes to a stirred solution of 1-aminobenzotriazole **9** (2.00 g, 14.9 mmol) and 4-dimethylaminopyridine (DMAP) (36 mg) in dry acetonitrile (16 ml) maintained at 0 °C. The cooling bath was removed and the solution stirred for 1 h before heating to 50 °C. The solution was then treated with 2M aqueous sodium hydroxide (10.3 ml) and stirred vigorously at this temperature for 1 h. The reaction mixture was allowed to cool to room temperature and the bulk of the volatiles evaporated. The residue was cooled in an ice-bath and carefully neutralised using ice-cold 2M hydrochloric acid. The resulting solution was extracted with ether (5 × 5 ml) and the combined extracts washed with saturated aqueous sodium bicarbonate (3 ml), water (3 ml) and brine (3 ml) then dried and evaporated to give the crude product. Chromatography of this residue using petrol ether / ether (25%) afforded pure *amine* **19** (1.8 g, 51%) as a colourless solid, m.p. 108.0-111.0°C (lit[107] m.p. 102-104°C); ν_{max}/cm^{-1} 3264, 2976, 2387, 2252, 1731, 1619, 1456, 1369, 1254, 1156, 1100, 1020, 999, 912, 820, 738; δ_H 1.43 (9H, br res., $C(CH_3)_3$), 7.32 (1H, dt, *J*~1.2, 8.1, Ar-H), 7.44-7.51 (2H, m, 2 × Ar-H), 7.97 (1H, d, *J*~8.1, Ar-H), 8.16 (1H, br s, NH); δ_C 28.3 ($C(\underline{C}H_3)_3$), 83.9 ($\underline{C}(CH_3)_3$), 109.5 (Ar-CH), 120.3 (Ar-CH), 124.9 (Ar-CH), 129.0 (Ar-CH), 133.0 (Ar-C), 144.3 (Ar-C), 153.9 (C=O); *m/z* (APcI) 235 (M^++H, 100%).

Preparation of anhydrous cerium (III) chloride from cerium (III) chloride heptahydrate ($CeCl_3 \cdot 7H_2O$)

A 250 ml two-necked, round bottomed flask was equipped with a glass stopper and a three-way stopcock, the flask is connected to a trap that is cooled at -78°C in a dry ice-acetone bath and attached to a vacuum pump. The flask is charged with powdered cerium (III) chloride heptahydrate ($CeCl_3 \cdot 7H_2O$) (1.38 g, 3.70 mmol) and evacuated to 0.1-0.2 mm. After gradual warming to 90 °C over 30 min with an oil bath, the flask is heated at 90-100 °C for 2h with intermittent shaking. The system is filled with dry N_2 and cooled to room temperature. The solid is transferred to a mortar and quickly pulverized with a pestle. The resulting white powder and a magnetic stirring bar are placed in the original flask. Gradual warming to 90 °C at 0.1-0.2 mm over 30 minutes, followed by further evacuating at 90-100 °C for 1.5 h with intermittent shaking, gives cerium(III) chloride monohydrate ($CeCl_3 \cdot H_2O$). The cerium(III) chloride monohydrate is gradually warmed to 140 °C over 30 min under reduced pressure (0.1-0.2 mm) without stirring. Heating at 140-150 °C / 0.1-0.2 mm for 2 h with gentle stirring affords a fine, white powder of anhydrous cerium(III) chloride. While the flask was still hot, the area was not immersed in the oil bath was heated by the use of a heat gun in order to remove traces of water. After introduction of nitrogen gas into the flask, the resulting anhydrous cerium(III)chloride was cooled to room temperature. One of the glass stoppers was replaced by a rubber septum under dry nitrogen.

1-(*tert*-Butoxycarbonylamino)-7-iodobenzotriazole 23[107]



19 **23**

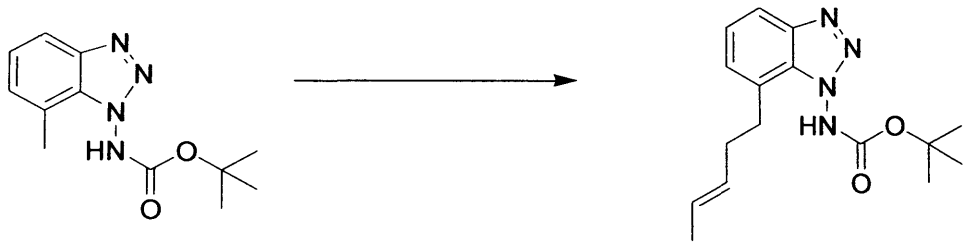
Butyl lithium (4.6 ml of a 2.5 M solution in hexane) was added to a stirred solution of dry *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA) (2.5 ml, 16.8 mmol) in dry tetrahydrofuran (34 ml) maintained at -78°C under dry nitrogen. Stirring was continued for 0.5 h, after which a solution of amine **19** (0.79 g, 3.4 mmol) in dry tetrahydrofuran (30 ml) was added slowly *via* a syringe. The resulting deep purple dianion solution was stirred for 0.5 h at -78°C. Concurrently, a suspension of anhydrous cerium(III) chloride in tetrahydrofuran (100 ml) was cooled to -78°C and titrated with butyl lithium (2.5 M solution in hexane) until the first faint but permanent orange end point (~ 0.34 ml). The dianion solution was then rapidly transferred *via* syringe to the anhydrous cerium(III) chloride suspension. The reaction mixture was stirred at -78°C for 3 h, before the rapid addition of 1,2-diiodoethane (1.0 g, 3.7 mmol) in tetrahydrofuran (4 ml). The reaction mixture was slowly warmed to room temperature and stirred continued for 16 h, then quenched with saturated aqueous ammonium chloride (30 ml) followed by careful acidification with 2M hydrochloric acid, and extracted with ether (3 × 100 ml). The combined extracts were washed with saturated aqueous sodium bicarbonate (30 ml), water (30 ml) and brine (30 ml) then dried and evaporated to give crude material which was subjected to chromatography using diethyl ether / petrol ether (20 %) to give the iodide **23** (0.68 g, 56%) as light brown solid, m.p. 140.0-143.0°C (lit[107] 142-144 °C); ν_{max}/cm^{-1} 3264, 2979, 2251, 1727, 1621, 1576, 1487, 1456, 1394, 1370, 1253, 1157, 1098, 1040, 936, 911, 842, 791, 737; δ_H 1.23 (9H, br res., $C(CH_3)_3$), 7.03 (1H, t, *J*~7.7, Ar-H), 7.85 (1H, d, *J*~7.7, Ar-H), 7.94 (1H, d, *J*~7.7, Ar-H), 8.76 (1H, br. s, NH); δ_C 28.7 ($C(\underline{C}H_3)_3$), 71.0

($\underline{C}(CH_3)_3$), 84.1 (C-I), 121.0 (Ar-CH), 126.6 (Ar-CH), 132.8 (Ar-C), 139.8 (Ar-CH), 144.9 (Ar-C), 153.5 (C=O).

General Procedure for metallation and functionalisation of 7-methyl-1-(*N*-*tert*-butoxycarbonylamino)benzotriazole 390:

Butyllithium (1.6 M solution in hexanes, 2.2 equivalents) was added dropwise to a stirred solution of dry, distilled *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA) (2.2 equivalents) in dry tetrahydrofuran (THF) (10 ml $mmol^{-1}$) maintained at –78°C. Stirring was continued for 0.25 h, after which a solution of the aminobenzotriazole **390** (1 equivalent) in dry THF (1 ml $mmol^{-1}$) was added dropwise *via* syringe. The resulting burgundy red dianion solution was stirred for 5 minutes at –78°C, allowed to warm gradually to 0°C and maintained at this temperature for 0.5h, then recooled to –78°C before the rapid addition of a solution of the electrophile (1.1 equivalents) in dry tetrahydrofuran (1 ml $mmol^{-1}$). The reaction was allowed to stir at –78°C for 1h, upon which saturated aqueous ammonium chloride (10 ml $mmol^{-1}$) was added, the cooling bath removed and the reaction allowed to warm gradually to ambient temperature. The resulting layers were separated and the aqueous layer acidified with 2 M HCl and extracted with ether (3 × 30 ml $mmol^{-1}$). The combined organic extracts were dried and evaporated to give crude material which was subjected to column chromatography using hexane / diethyl ether mixtures to obtain the purified product.

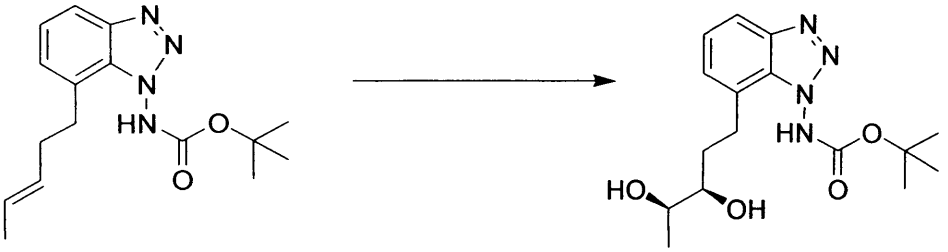
(*E*)-1-(*tert*-Butoxycarbonylamino)-7-(3-pentene-1-yl)-benzotriazole 404



390 **404**

Following the general procedure of metallation and functionalisation, treatment of dianion **391** from the aminobenzotriazole **390** (300 mg, 1.2 mmol) with freshly distilled crotyl bromide **403** (0.13 ml, 1.32 mmol) yielded the *pentene* **404** as a yellow gum (350 mg, 97%), ν_{max}/cm^{-1} 3166, 2932, 1750, 1606, 1455, 1394, 1370, 1252, 1160, 1050, 966, 910, 749; δ_H (rotameric) 1.30-1.53 (9H, br res., $C(CH_3)_3$), 1.54-1.58 (3H, m, 5'-CH_3), 2.24-2.38 (2H, m, 2'-CH_2), 2.94 (2H, t, *J*~8.3, 1'-CH_2), 5.39-5.41 (2H, m, 3', 4'-H), 7.20-7.23 (2H, m, 2 × Ar-H), 7.75-7.79 (1H, m, Ar-H), 8.59 (1H, br s, NH); δ_C 11.9 (5'-CH_3), 27.0 ($C(\underline{C}H_3)_3$), 29.3 (2'-CH_2), 32.7 (1'-CH_2), 82.7 ($\underline{C}(CH_3)_3$), 117.0 (Ar-CH), 123.7 (Ar-CH), 124.3 (=CH), 125.2 (=CH), 127.9 (Ar-CH), 129.8 (7-C), 143.7 (C-N), 152.5 (C-N), 177.2 (C=O); *m/z* (APcI) 302 (M^+, 100%); HRMS (FAB) calcd. for $C_{16}H_{23}N_4O_2$ $[M+H]^+$ 303.1816, found 303.1816.

(3'R, 4'R)-1-(*t*-Butoxycarbonylamino)-7-(3,4-dihydroxypent-1-yl)-benzotriazole 405

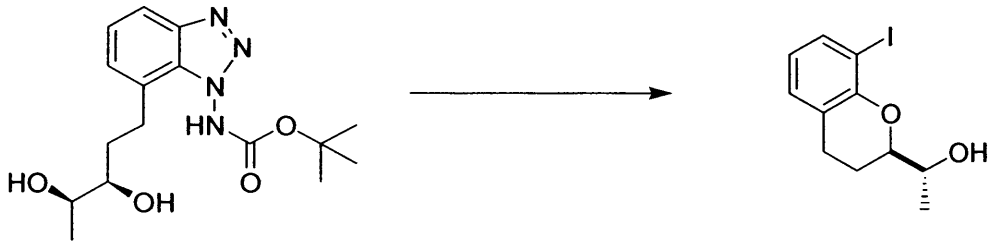


404 **405**

Following the general procedure for an AD-mix reaction, treatment of the pentene **404** (273 mg, 0.9 mmol) with AD-mix-β at room temperature for 42 hours yielded the *diol* **405** (196 mg, 65%) as a yellow gum, ν_{max}/cm^{-1} 3252, 2974, 2361, 1749, 1508, 1456, 1370, 1254, 1159, 912, 733; δ_H (rotameric) 1.08 (3H, d, *J*~6.3, 5'- CH_3), 1.22-1.52 (9H, br s, $C(CH_3)_3$),

1.71-1.80 (2H, m, 2'- CH_2), 2.75 (1H, br s, OH), 3.00-3.13 (2H, br res., 1'-CH_2), 3.13 (1H, br s, OH), 3.35-3.48 (1H, br res, 3'-H), 3.56 (1H, dq, *J*~6.0 and 6.3, 4'-H), 7.22-7.25 (2H, m, 2 × Ar-H), 7.81-7.85 (1H, m, Ar-H), 9.16 (1H, br s, NH); δ_C 18.5 (CH_3), 26.9 ($C(\underline{C}H_3)_3$), 33.8 (2'-CH_2), 52.2 (1'-CH_2), 69.4 (CH), 73.8 (CH), 82.4 ($\underline{C}(CH_3)_3$), 117.0 (Ar-CH), 123.6 (Ar-CH), 124.2 (7-C), 127.8 (Ar-CH), 129.8 (C-N), 143.7 (C-N), 152.9 (C=O); *m/z* (APcI) 336 (M^+, 100%), HRMS (FAB) calcd. for $C_{16}H_{25}N_4O_4$ $[M+H]^+$ 337.1868, found 337.1868.

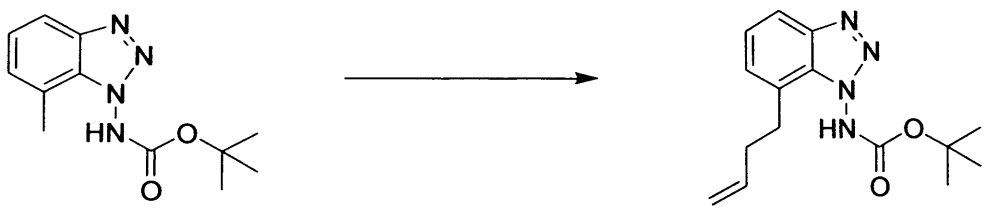
(-)-(1'R,2R)-2-(1-Hydroxyethyl)-8-iodochroman 407



405 **407**

Following the general deprotection/cyclisation procedure, treatment of the diol **405** (74.0 mg, 0.22 mmol) with trifluoroacetic acid (0.44 ml) and *N*-iodosuccinimide (124.0 mg, 0.55 mmol) gave the *chroman* **407** as a yellow gum (20.0 mg, 40%), $[\alpha]_D^{29}$= -7.36, (*c* 6.25 g/ 100ml, chloroform); ν_{max}/cm^{-1} 3367, 2921, 1776, 1454 and 1261; δ_H 1.26 (3H, d, *J*~6.0, CH_3), 1.45-1.61 (1H, br s, OH), 1.67-1.78, (1H, m, 3-H_a), 1.93-1.98 (1H, m, 3-H_b), 2.67 (1H, ddd, *J*~2.7, 5.4, 16.3, 4-H_a), 2.77 (1H, ddd, *J*~5.9, 12.1, 16.3, 4-H_b), 3.78-3.84 (2H, m, 2-H and 1'-H), 6.56 (1H, t, *J*~7.7, 6-H), 7.02 (1H, d, *J*~7.7, 7-H), 7.49 (1H, d, *J* ~7.7, 5-H); δ_C 18.5 (CH_3), 23.9 (CH_2), 24.8 (CH_2), 70.0 (CH), 81.6 (CH), 85.8 (C-I), 122.2 (Ar-CH), 123.1 (4a-C), 130.3 (Ar-CH), 136.9 (Ar-CH) and 142.9 (8a-C); *m/z* (APcI) 286 (M^+-H_2O, 100%), HRMS (NH_4Cl) calcd. for $C_{11}H_{17}INO_2$ $[M+ NH_4]^+$ 322.0298, found 322.0296.

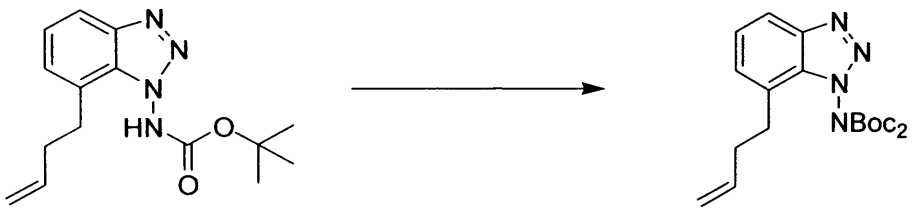
1-(*tert*-Butoxycarbonylamino)-7-(3-butene-1-yl)-benzotriazole 414



390 **414**

Following the general procedure of metallation and functionalisation, treatment of dianion **391** from the aminobenzotriazole **390** (600 mg, 2.4 mmol) with freshly distilled allyl bromide (0.24 ml, 2.7 mmol) yielded the *butene* **414** as a yellow gum (558 mg, 80%), ν_{max}/cm^{-1} 3260, 2928, 1749, 1456, 1370, 1252, 1159, 1022, 913, 749; δ_H 1.34-1.56 (9H, br res., $C(CH_3)_3$), 2.38 (2H, dt, *J*~6.7, 7.3, 2'-CH_2), 3.01 (2H, t, *J*~7.3, 1'-CH_2), 4.95 (1H, dd, *J*~1.5, 10.3, 4'-H_a), 4.99 (1H, dd, *J*~1.5, 17.4, 4'-H_b), 5.75 (1H, tdd, *J*~6.7, 10.3, 17.4, 3'-H), 7.19-7.26 (2H, m, 2 × Ar-H), 7.79-7.85 (1H, m, Ar-H), 8.08 (1H, br s, NH); δ_C 28.1 ($C(\underline{C}H_3)_3$), 29.6 (2'-CH_2), 34.8 (1'-CH_2), 84.0 ($\underline{C}(CH_3)_3$), 115.4 (3'-CH), 115.9 (4'-CH_2), 118.3 (Ar-CH), 124.7 (Ar-CH), 129.1 (Ar-CH), 132.3 (7-C), 144.9 (C-N), 153.3 (C-N), 167.7 (C=O), *m/z* (APcI) 289 (M^+ +H, 100%).

1-(N, N-*bis*-*tert*-Butoxycarbonylamino)-7-(3-butene-1-yl)-benzotriazole 428

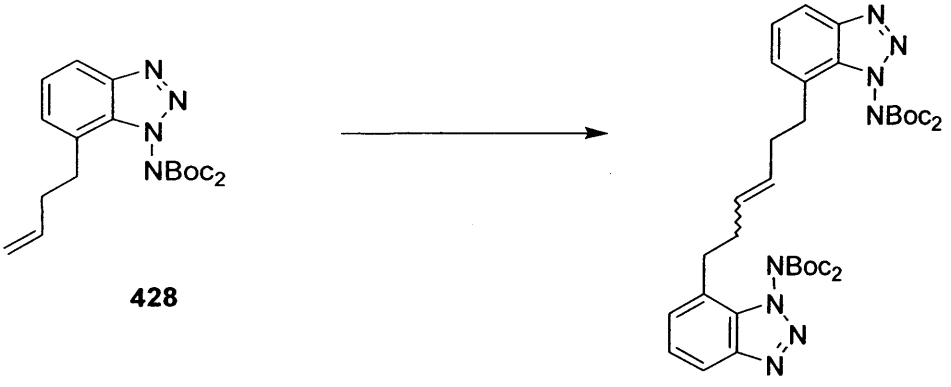


414 **428**

To a solution of the *mono*-Boc benzotriazole **414** (150 mg, 0.52 mmol), triethylamine (0.08 ml, 0.57 mmol) and 4-dimethylaminopyridine (4.0 mg, 0.033 mmol) in dichloromethane (3 ml) maintained at 0°C was added dropwise *via* a syringe a solution of di-*tert*-butyl dicarbonate (124.4 mg, 0.57 mmol) in dichloromethane (0.4 ml). Following stirring for 48h at ambient temperature, the mixture was poured into saturated aqueous sodium hydrogen

carbonate (1 ml), and the separated organic layer washed with water (1 ml) and brine (1 ml). Evaporation of the dried organic phase afforded the crude product which was subjected to chromatography using ethyl acetate/ petrol ether (15%) to give the *bis-Boc derivative* **428** (117 mg, 58%) as a yellow gum, ν_{max}/cm^{-1} 3283, 3166, 2980, 1747, 1641, 1609, 1458, 1371, 1252, 1160, 1124, 913, 863, 801, 750; δ_H 1.36 (18H, s, 2×C$(CH_3)_3$), 2.32 (2H, dt, *J*~6.6, 8.0, 2'-CH_2), 2.84 (2H, t, *J*~8.0, 1'-CH_2), 4.96 (1H, dd, *J*~1.5, 10.3, 4'-H_a), 4.99 (1H, dd, *J*~1.5, 17.1, 4'-H_b), 5.75 (1H, tdd, *J*~6.6, 10.3, 17.1, 3'-H), 7.21-7.28 (2H, m, 2 × Ar-H), 7.82-7.88 (1H, m, Ar-H); δ_C 27.7 (C($\underline{C}H_3)_3$), 29.2 (2'-CH_2), 34.0 (1'-CH_2), 86.0 ($\underline{C}(CH_3)_3$), 115.9 (4'-CH_2), 118.4 (3'-CH), 124.7 (Ar-CH), 128.9 (Ar-CH), 136.9 (Ar-CH), 144.7 (C-N), 148.8 (C-N), 153.5 (C=O); *m/z* (APCI) 389 (M^+ +1, 100%), HRMS (FAB) calcd. for $C_{20}H_{29}N_4O_4$ $[M+H]^+$ 389.2183, found 389.2187.

1,6-Di-[1-*Bis*-(*tert*-butoxycarbonyl)aminobenzotriazole-7-yl]-3-hexene 429

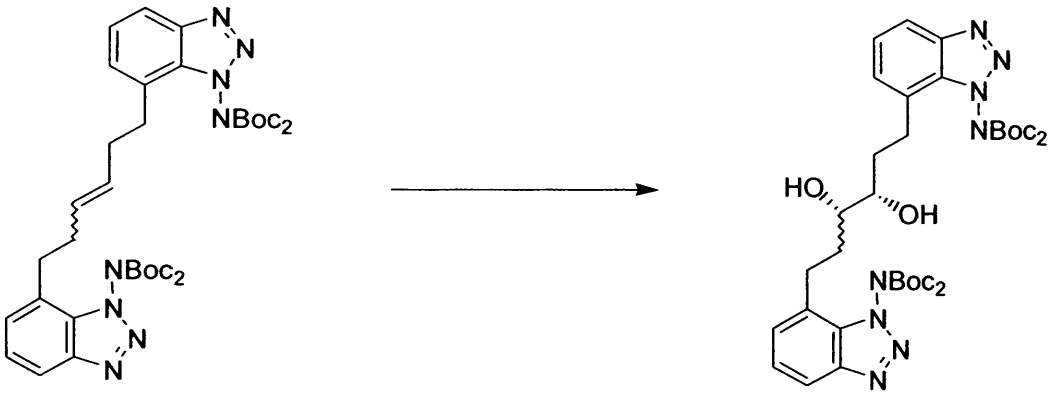


428 **429**

The *bis*-Boc derivative **428** (117.0 mg, 0.30 mmol) was added to a stirred solution of Grubbs' catalyst $(PCy_3)_2RuCl_2$=CHPh (12.4 mg, 0.015 mmol) in dry dichloromethane (1.5 ml). The flask was fitted with a condenser and the red solution was refluxed at 45°C under N_2 for 20 h. The solvent was then evaporated and the product was purified on a silica gel column, eluting with 25%, 30% and 50% ethyl acetate/ petrol ether. The *olefin* **429** was obtained as a colourless oil (50.0 mg, 45%), ν_{max}/cm^{-1} 2925, 2356, 1768, 1457, 1371, 1343, 1243, 1123, 863; δ_H 1.39 (36H, s, 4×C$(CH_3)_3$), 2.27-236 (4H, m, 2, 5-CH_2), 2.75 (2H, t, J~7.4, CH_2), 2.86

(2H, t, *J*~7.2, CH_2), 5.41-5.47 (2H, m, 3, 4-H), 7.17-7.28 (4H, m, Ar-H), 7.89-7.92 (2H, m, Ar-H); δ_C 27.6 (CH_2), 27.7 ($C(\underline{C}H_3)_3$), 29.4 (CH_2), 29.9 (CH_2), 33.0 (CH_2), 85.9 ($\underline{C}(CH_3)_3$), 86.0 ($\underline{C}(CH_3)_3$), 118.5 (=CH), 124.0 (Ar-C), 124.7 (=CH), 129.1 (Ar-CH), 129.4 (Ar-CH), 130.1 (Ar-CH), 144.7 (Ar-C), 144.8 (Ar-C), 148.7 (C=O), 148.8 (C=O), *m/z* (APCI) 705 (M^+-43, 100%), HRMS (FAB) calcd. for $C_{38}H_{53}N_8O_8$ $[M+H]^+$ 749.3981, found 749.3973.

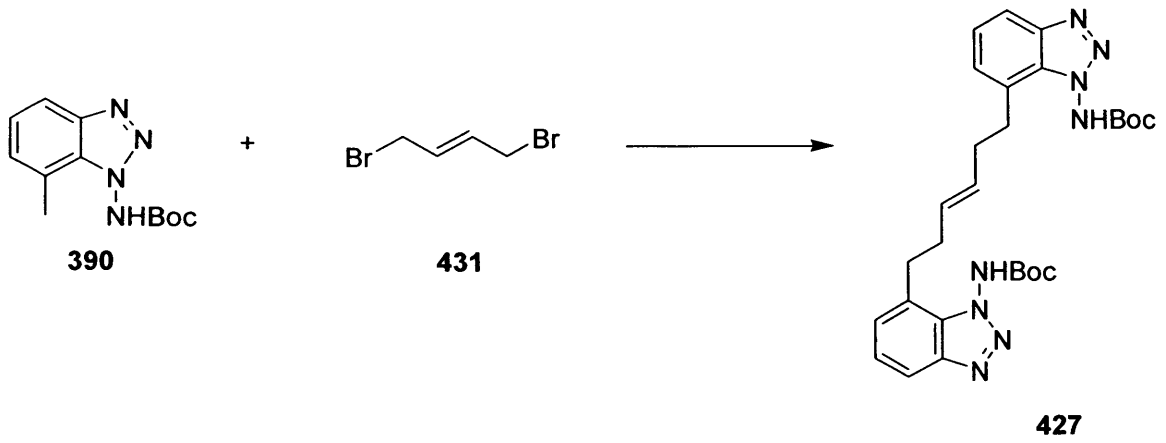
1, 6-Di-[1-Bis-(*tert*-butoxycarbonyl)aminobenzotriazole-7-yl]-3, 4-dihydroxy hexane 430



429 **430**

Following the general procedure of asymmetric dihydroxylation, treatment of the olefin **429** with AD-mix-α yielded the *diol* **430** (40.0 mg, 49%) as a yellow gum. ν_{max}/cm^{-1} 3293, 2924, 1768, 1458, 1371, 1251, 1125, 913, 842, 801, 734; δ_H 1.20 (2H, d, *J*~7.2, 2 × OH), 1.30 (36H, s, 4 × $C(CH_3)_3$), 1.68-1.81 (4H, br res., 2, 5-CH_2), 2.78-2.89 (2H, m, CH_2), 2.96-3.08 (2H, m, CH_2), 3.33-3.38 (1H, m, C<u>H</u>OH), 3.50-3.53 (1H, m, C<u>H</u>OH), 7.23-7.28 (4H, m, 4 × Ar-H), 7.84-7.86 (2H, m, Ar-H); δ_C 25.9 (CH_2), 26.0 (CH_2), 27.7 ($C(\underline{C}H_3)_3$), 32.5 (CH_2), 34.4 (CH_2), 73.1 (CHOH), 73.4 (CHOH), 86.2 ($\underline{C}(CH_3)_3$), 86.3 ($\underline{C}(CH_3)_3$), 118.48 (Ar-CH), 118.54 (Ar-CH), 124.3 (Ar-C), 124.5 (Ar-C), 124.8 (2 × Ar-CH), 129.1 (Ar-CH), 129.2 (Ar-CH), 130.4 (C-N), 130.5 (C-N), 144.7 (C=O), 148.9 (C-N), 149.0 (C-N); *m/z* (APcI) 681 (M^+-101, 100%), HRMS (NH_4Cl) calcd. for $C_{38}H_{58}N_9O_{10}$ $[M+NH_4]^+$ 800.4301, found 800.4305.

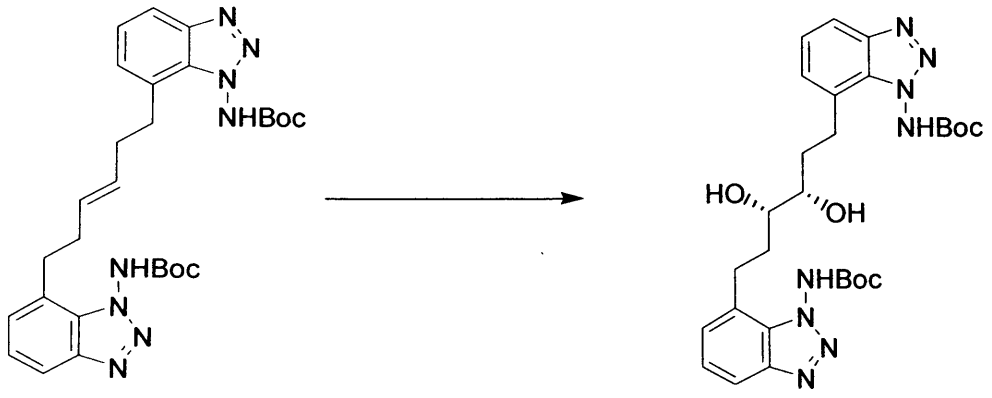
(*E*)-1, 6-Di-(1-N-*tert*-butoxycarbonylaminobenzotriazole-7-yl)-3-hexene 427



390 **431** **427**

Following the general procedure, treatment of the dianion generated from the aminobenzotriazole **390** (600.0 mg, 2.4 mmol) with (*E*)-1,4-dibromo-2-butene (311 mg, 1.5 mmol) yielded crude material which was subjected to chromatography using hexane / diethyl ether (25%) to obtain the *dibenzotriazole* **427** as a colourless solid (390 mg, 59%), m.p. 113.0-114.8^{0}C, ν_{max}/cm^{-1} 2964, 1744, 1454, 1369, 1252,1155, 749; δ_H (CD_3OD) 1.53-1.60 (18H, br res., 2×C(CH_3)$_3$), 2.38-2.44 (4H, br res., 2,5-CH_2), 3.08-3.24 (4H, br res., 1,6-CH_2), 5.59-5.61 (2H, m, 3,4-H), 7.36 (2H, d, *J*~7.0, 2 × Ar-H), 7.40 (2H, t, *J*~7.0, 2 × Ar-H), 7.88 (2H, d, *J*~7.0, 2 × Ar-H); δ_C (CD_3OD) 25.5(C($\underline{C}H_3$)$_3$), 28.4 (2,5-CH_2), 31.9 (1,6-CH_2), 80.9 ($\underline{C}$(CH_3)$_3$), 115.5 (3,4-CH), 123.1 (Ar-CH), 123.9 (Ar-C), 127.5 (Ar-CH), 128.4 (Ar-CH), 142.9 (C=O); *m/z* (APcI) 549 (M^+ +H, 40%); HRMS (FAB) calcd. for $C_{28}H_{37}N_8O_4$ $[M+H]^+$ 549.2932, found 549.2934].

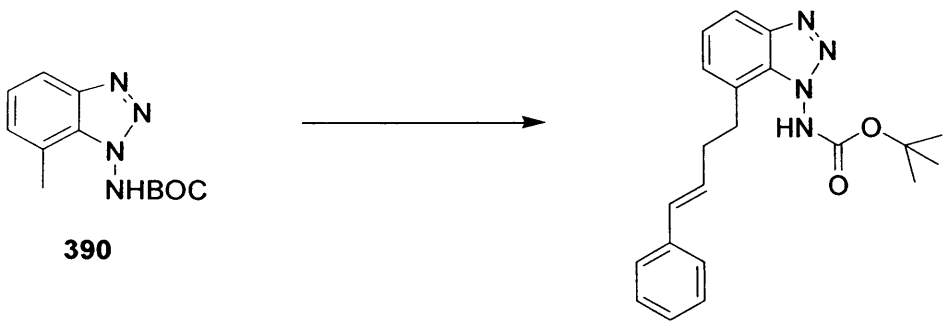
(3S, 4S)-1, 6-Di (1-*tert*-butoxycarbonylaminobenzotriazole-7-yl)-hexane-3, 4-diol 432



427 **432**

Following the general procedure, treatment of the olefin **427** with AD-mix-α reagent yielded the *diol* **432** (386 mg, 80%) as a pale yellow oil. ν_{max}/cm^{-1} 3466, 2982, 2494, 2239, 1726, 1607, 1455, 1250, 1162, 1020, 978, 909, 801, 751; δ_H (CD_3OD) 1.51-1.60 (18H, s, $C(CH_3)_3$), 1.86-2.01 (4H, br s, 2,5-CH_2), 3.12-3.17 (4H, m, 1,6-CH_2), 3.31-3.38 (2H, dt, *J*~7.3, 6.9, 3,4-C<u>H</u>OH), 3.53 (2H, br s, 2×OH), 7.44-7.51 (4H, m, Ar-H), 7.97 (2H, dd, *J*~0.6, 8.0, Ar-H); δ_C (CD_3OD) 27.9 (CH_2), 28.9 ($C(\underline{C}H_3)_3$), 31.6 (CH_2), 35.6 (CH_2), 43.7 (CH_2), 75.0 ($\underline{C}(CH_3)_3$), 84.4 (3,4-CH), 118.8 (Ar-CH), 126.7 (Ar-CH), 127.7 (Ar-C), 130.7 (Ar-CH), 132.6 (C-N), 146.3 (C-N), 156.5 (C=O); *m/z* (APcI) 583 (M^+ +H, 100%), HRMS (FAB) calcd. for $C_{28}H_{39}N_8O_6$ $[M+H]^+$ 583.2987, found 583.2981.

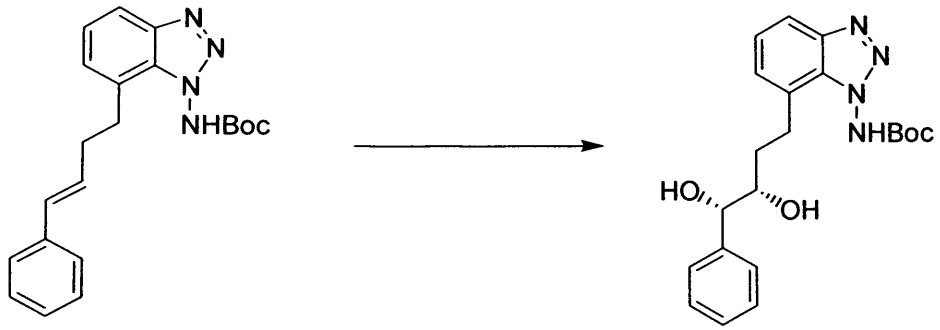
(*E*)-1-(*tert*-Butoxycarbonylamino)-7-(4'-phenyl-3'-butene-1'-yl)-benzotriazole 440



390 **440**

Following the general procedure, treatment of the dianion generated from the aminobenzotriazole **390** (918 mg, 3.7 mmol) with cinnamyl bromide (870 mg, 4.4 mmol) yielded the *title compound* **440** (1.05 g, 78%) as a colourless gum, ν_{max}/cm^{-1} 3458, 2955, 1745, 1494, 1453, 1368, 1253, 1157, 966, 750; δ_H 1.35 (9H, br res., $C(CH_3)_3$), 2.41 (2H, dt, *J*~6.7, 7.1, 2'-CH_2), 3.00 (2H, t, *J*~7.1, 1'-CH_2), 6.10 (1H, dt, *J*~15.9, 6.7, 3'-CH), 6.28 (1H, d, *J*~15.9, 4'-H), 7.03-7.21 (7H, m, Ar-H), 7.66-7.72 (1H, br res., Ar-H), 9.32 (1H, br s, NH); δ_C 28.1 ($C(\underline{C}H_3)_3$), 30.1 (2'-CH_2), 34.0 (1'-CH_2), 83.6 ($\underline{C}(CH_3)_3$), 118.1 (Ar-CH), 124.7 (Ar-C), 125.0 (Ar-CH), 126.0 (Ar-CH), 127.2 (Ar-CH), 128.5 (Ar-CH), 129.0 (Ar-CH), 137.4 (Ar-C), 144.7 (C-N), 153.9 (C-N), 154.1 (C=O); *m/z* (APcI) 365 (M^+ +H, 100%), HRMS (FAB) calcd. for $C_{21}H_{25}N_4O_2$ $[M+H]^+$ 365.1972, found 365.1972.

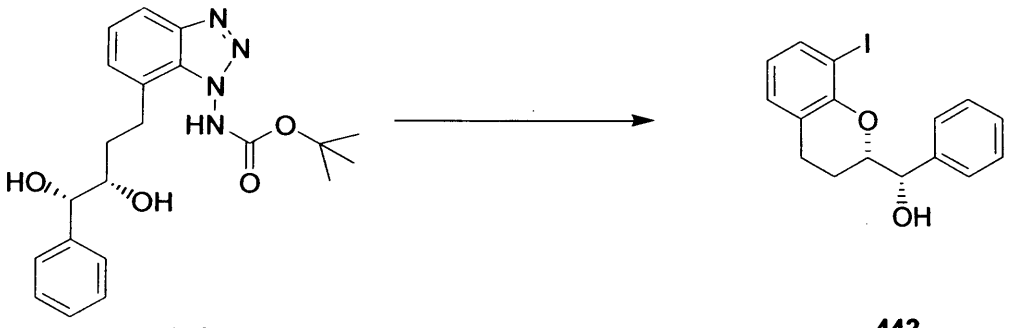
(3S, 4S)-1-(*t*-Butoxycarbonylamino)-7-(3', 4'-dihydroxy-4'-phenyl-butane-1-yl)-benzotriazole 441



440 **441**

Following the general procedure for an AD-mix reaction, treatment of the olefin **440** (737 mg, 2.0 mmol), with AD-mix-α (2.8 g) yielded the *diol* **441** (650 mg, 82%) as a yellow gum, ν_{max}/cm^{-1} 3498, 2915, 1735, 1453, 1368, 1253, 1157; δ_H 1.22-1.35 (9H, br res., $C(CH_3)_3$), 1.46-1.51 (1H, m, OH), 1.54-1.63 (1H, m, OH), 2.83 (1H, app. br s, 2'-H_a), 2.99 (1H, app. br s, 2'-H_b), 3.55 (1H, app. br s, 3'-H), 3.83 (2H, app. br s, 1'-CH_2), 4.30 (1H, d, *J*~6.6, 4'-H), 6.95 (1H, d, *J*~7.0, Ar-H), 7.05-7.19 (6H, m, Ar-H), 7.60 (1H, d, *J*~6.1, Ar-H), 9.70 (1H, br s, NH); δ_C 25.7 (2'-CH_2), 27.1 ($C(\underline{C}H_3)_3$), 33.4 (1'-CH_2), 74.5 (3'-CH), 77.2 (4'-CH), 82.6 ($\underline{C}(CH_3)_3$), 116.9 (Ar-CH), 124.8 (Ar-CH), 126.0 (Ar-C), 126.7 (Ar-CH), 127.2 (Ar-CH), 127.8 (Ar-CH), 128.5 (Ar-CH), 130.8 (Ar-C), 142.0 (C-N), 144.4 (C-N), 154.7 (C=O); *m/z* (APcI) 399 (M^+ +H, 100%), HRMS (FAB) calcd. for $C_{21}H_{27}N_4O_4$ $[M+H]^+$ 399.2027, found 399.2025.

(1'S,2S)-2-[1-Hydroxy-1-phenylmethyl]-8-iodochroman 442



441 **442**

Following the general procedure of benzyne cyclisation, treatment of the diol **441** (628 mg, 1.6 mmol) with TFA (6.3 ml) and NIS (900 mg, 4.0 mmol) generated the chroman **442** (142.0 mg, 24%) as a yellow gum, ν_{max}/cm^{-1} 3564, 2931, 1562, 1494, 1448, 1237, 1194, 1093, 1045, 905, 887, 761, 701; δ_H 1.53-1.70 (2H, m, 3-CH_2), 2.60-2.65 (2H, m, 4-CH_2), 3.12 (1H, br s, OH), 4.01 (1H, ddd, *J*~2.7, 7.8, 10.5, 2-H), 4.65 (1H, d, *J*~7.8, 1'-H), 6.54 (1H, t, *J*~7.6, Ar-CH), 6.91 (1H, d, *J*~7.6, Ar-CH), 7.24-7.39 (5H, m, Ar-CH), 7.49 (1H, d, *J*~7.6, Ar-CH); δ_C 23.5 (3-CH_2), 24.7 (4-CH_2), 77.5 (2-CH), 81.4 (1'-CH), 85.8 (C-I), 122.4 (Ar-CH), 123.2 (Ar-C), 127.4 (Ar-CH), 128.5 (Ar-CH), 128.6 (Ar-CH), 129.7 (Ar-CH), 137.0 (Ar-CH), 139.0 (Ar-C), 152.4 (Ar-C); *m/z* (APcI) 366 (M^+, 100%), HRMS (FAB) calcd. for $C_{16}H_{19}INO_2$ $[M+NH_4]^+$ 384.0455, found 384.0458.

References:

1. a) M.A. Birkett, D.W. Knight and M.B. Mitchell, *Tetrahedron Lett.*, 1993, **34**, 6935; b) M.A. Birkett, D.W. Knight and M.B. Mitchell, *Tetrahedron Lett.*, 1993, **34**, 6939; c) M.A. Birkett, D.W. Knight and M.B. Mitchell, *Synlett.*, 1993, 253; d) M.A. Birkett, D.W. Knight, R.G. Giles and M.B. Mitchell, *J. Chem. Soc., Perkin Trans*, 1, 1998, 2301; e) D.W. Knight and P.B. Little, *J. Chem. Soc., Perkin Trans*, 1, 2001, 1771.
2. C.D. Campbell and C.W.Rees, *J. Chem. Soc.* (C)., 1969, 742.
3. P. Cohen-Fernandes and C.L. Habraken, *J. Org. Chem.*, 1971, **36**, 3084.
4. a) W. Klotzer, H. Baldinger, E.M. Karpitschka and J. Knoflash, *Synthesis*, 1982, 592; b) P. Boak, A. Basha, B. Kokko and D. Loo, *J. Am. Chem. Soc.*, 1986, **108**, 6016; c) C. Greck, L. Bischoff, A. Girard, J. Hajicek and J-P. Genet, *J. Am. Chem. Soc.*, 1994, **131**, 429.
5. S. Schade and G. Boche, *J. Orgmet. Chem.*, 1998, **550**, 381.
6. B.J. Wakefield, ''Organolithium Methods'', Academic Press, London, 1998.
7. a) G. Chaput, G. Jeminet and J. Juillard, *Can. J. Chem.*, 1975, **53**, 2240; b) J-M. Lehn and J.P. Sauvage, *J. Am. Chem. Soc.*, 1975, **97**, 6700.
8. a) S.E. Denmark, J.P.Edwards and O. Nicaise, *J. Org. Chem.*, 1993, **58**, 569; b) D.L. Comins and H. Hong, *J. Org. Chem.* 1996, **61**, 391.
9. J.K. Becconsall, B.E. Job, S. O'Brien and J-P. Genet, *Bull. Chem. Soc. Fr.*, 1994, **131**, 429.
10. a) R.D. Rieke, P.T.-J. Li, T.P. Burns and S.T. Uhm, *J. Org. Chem.*, 1981, **46**, 4323; b) W.-N. Chou, D.L. Clark and J.B. White, *Tetrahedron Lett.*, 1991, **32**, 299.
11. J.M. Buente, L. Castedo, L. Rodriguez de Lera, J.M. Saa, R. Suau and M.C. Vidal, *Tetrahedron Lett.*, 1993, **34**, 2298.
12. a) K.D. James and A.D. Ellington, *Tetrahedron Lett.*, 1998, **39**, 175; b) E.F. Evans, N.J. Lewis, I. Kapfer, G. Macdonald and R.J.K Taylor, *Synth. Commun.*, 1997, **27**, 1819; c) R.S. Lott, V.S. Chauhan and C.H. Stammer, *J. Chem. Soc., Chem. Commun.*,

1979, 495; d) J.R. Hwu, M.L. Jain, S.-C. Tsay and G.H. Hakimelahi, *Tetrahedron Lett.*, 1996, **37**, 2035.

13. S. Brewster, *J. Am. Chem. Soc.*, 1934, **56**, 117.
14. D.L. Boger and J.A. McKie, *J. Org. Chem.*, 1995, **60**, 1271.
15. T. Sugiyama, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 2847.
16. H. Suzuki, *Org. Synth. Coll., Vol* 6, 1998, 700.
17. J.D. Roberts, H.E. Simmons, Jr., L.A. Carlsmith and C.W. Vaughan, *J. Am. Chem. Soc.*, 1953, **75**, 3290.
18. H. Pellissier and M. Santelli, *Tetrahedron*, 2003, **59**, 701.
19. K. Chow and H.W. Moore, *J. Org. Chem.* 1990, **55**, 370.
20. K.C. Caster, C.G. Keck and R.D. Walls, *J. Org. Chem.*, 2001, **66**, 2932.
21. S. Escudero, D. Perez, E. Guitian and L. Castedo, *J. Org. Chem.*, 1997, **62**, 3028.
22. C. Gonzalez, E. Guitian and L. Castedo, *Tetrahedron*, 1999, **55**, 5195.
23. P. Maurin, M. Ibrahim and M. Santelli, *Tetrahedron Lett.*, 2001, **42**, 8147.
24. T. Matsumoto, T. Sohma, S. Hatazaki and K.Suzuki, *Synlett*, 1993, 843.
25. S.P. Khanapure and E.R. Biehl, *Synthesis*, 1991, 33.
26. A.A. Aly, N.K. Mohamed, A.A. Hassan and A.F.E. Mourad, *Tetrahedron*, 1999, **55**, 1111.
27. S. Tripathy, R. LeBlanc and T. Durst, *Org. Lett.*, 1999, **1**, 1973.
28. S. Tripathy, H. Hussain and T. Durst, *Tetrahedron Lett.*, 2000, **41**, 8401.
29. Y. Kita, K. Huiguchi, Y.Yoshida, K. Iio and S. Kitagaki, *J. Am. Chem. Soc.*, 2001, **123**, 3214.
30. E. Yoshikawa, K. V.Radhakrishnan and Y. Yamamoto, *Tetrahedron Lett.*, 2000, **41**, 729.
31. M.A. Birkett, D.W. Knight and P.B. Little, *Tetrahedron*, 2000, **56**, 1013 and references cited therein.
32. R. Chenevert and G. Courchesne, *Tetrahedron Lett.*, 2002, **43**, 7971.

33. L.J. Machlin, 'Vitamin E: a Comprehensive Treatise;' Marcel Decker Inc. New York, 1980.

34. A. Azzi, I. Breyer, M. Feher, *J. Nutrition,* 2000, **130**, 1649.

35. S.K. Niemi and M.J. Salminen, *J. Am. Medical Association*, 2003, **290**, 476.

36. N. Cohen, R.J. Lopresti and G. Saucy, *J. Am. Chem. Soc.*, 1979, **101**, 6710.

37. K. Takabe, K. Okisaka and Y. Uchiyama, *Chem. Lett.*, 1985, 561.

38. E. Mizuguchi and K. Achiwa, *Synlett.*, 1995, 1255.

39. L.F. Tietze and J. Corlitzer, *Synthesis*, 1997, 877.

40. A.O. King and E.I. Negishi, *J. Org. Chem.,* 1978, **43**, 358.

41. R. Barner and M. Schmidt, *Helv. Chim. Acta,* 1979, **62**, 2384.

42. P.B. Little PhD dissertation, Cardiff University, 1999.

43. W.H. Carothers and D.D. Coffman, *J. Am. Chem. Soc.,* 1932, **54**, 4071.

44. T.C. Bruice, N. Kharasch and R.J. Winzler, *J. Org. Chem.*, 1953, **18**, 83.

45. I.D. Entwistle, R.A.W. Johnstone and T.J. Povall, *J. Chem. Soc. Perkin Trans I,* 1975, 1300.

46. K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, 4467.

47. R.D. Stephens and C.E. Castro, *J. Org. Chem.* 1963, **28**, 3313.

48. K. Sonogashira, *J. Orgmet. Chem.,* 2002, **653**, 46.

49. T. Hundettmark, A.F. Littke and S.L. Buchwald, *Org. Lett.,* 2000, **2**, 1729.

50. A.R. Katritzky, N. Shobana and J. Pernak, *Tetrahedron*, 1992, **48**, 7817.

51. R. Garner, G.V. Garner and H. Suschitzky, *J. Chem. Soc., (C),* 1979, 825.

52. R.E. Damschroder and W.D. Peterson, *Org. Synth. Coll. Vol.* 3, 1955, 106.

53. J. Vidal, S. Damestoy, L. Guy and J. Hannachi, *Chem. Eur. J.*, 1997, **3**, 1691.

54. S. Andreae and E. Schmitz, *Synthesis*, 1991, 327, and references cited therein.

55. a) J. Vidal, J. Drouin and A. Collet, *J. Chem. Soc. Chem. Commun.* 1991, 435; b) J. Vidal, L. Guy, S. Sterin and A. Collet, *J. Org. Chem.* 1993, **58**, 4791; c) J. Vidal, S. Pamestoy and A. Collet, *Tetrahedron Lett.*, 1995, **36**, 1439.

56. J. Vidal, J. Hannachi, G. Hourdin and J. Mulatier, *Tetrahedron Lett.*, 1998, **39**, 8845.

57. D.L. Ball and J.O. Edwards, *J. Am. Chem. Soc.* 1956, **78**, 1125.

58. a) M.T. Konieczny, B. Horowska and A. Kunikowski, *J. Org. Chem.* 1999, **64**, 359; b) T.A. Ayers, R.A. Schnettler and G. Marciniak, *Tetrahedron : Asymm.*, 1997, **8**, 45.

59. V. Farina and B. Krishnan, *J. Am. Chem. Soc.,* 1991, **113**, 9585.

60. E. Negishi, T. Takahashi and S. Baba, *J. Am. Chem. Soc.,*1987, **109**, 2393.

61. J.K. Stille, *Angew. Chem., Int. Ed. Engl.,* 1986, **25**, 508.

62. V. Farina, S. Kapadia and B. Krishnan, *J. Org. Chem.*, 1994, **59**, 5905.

63. H.C. Kolb, M.S. VanNieuwenhze and K.B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.

64. M. Tokunaga, L.F. Larrow, F. Kakiuchi and E.N. Jacobsen, *Science*, 1997, **277**, 936.

65. C.Y. Lo, H.Y. Guo and J.J. Lian, *J. Org. Chem.*, 2002, **67**, 3930.

66. C.Y. Jin, R.D. Ramirez and A.S. Gopalan, *Tetrahedron Lett.*, 2001, **42**, 4747.

67. S.E. Schaus, B.D. Brandes and J.F. Larrow, *J. Am. Chem. Soc.*, 2002, **124**, 1307.

68. A. Avenoza, C. Cativiela and J.M. Peregrina, *Tetrahedron : Asymm.*, 2001, **12**, 1383.

69. a) D. G. Brown and E. J. Vethuisen, *J. Org. Chem.*, 1996, **61**, 2540; b) S. Muller, B. Liepold and G. J. Roth, *Synlett*, 1996, 521.

70. S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, 1981, **22**, 3815.

71. K.J. Hale, S. Manaviazar and S.A. Peak, *Tetrahedron Lett.*, 1994, **35**, 425.

72. M. Minato, K. Yamanoto and J. Tsuji, *J. Org. Chem.*, 1990, **55**, 766.

73. S.G. Hentges and K.B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 4263.

74. K.B. Sharpless, W. Amberg and L.Y. Bennani, *J. Org. Chem.*, 1992, **57**, 2768.

75. J.A. Crispino, K.S. Jeong and H.C. Kolb, *J. Org. Chem.*, 1993, **58**, 3785.

76. H.C. Kolb, P.G. Andersson and K.B. Sharpless, *J. Am. Chem. Soc.*, 1994, **116**, 1278.

77. P.O. Norrby, H.C. Kolb and K.B, Sharpless, *J. Am. Chem. Soc.*, 1994, **116**, 8470.

78. J.S. Dung, R.W. Armstrong and O.P. Anderson, *J. Org. Chem.*, 1983, **48**, 3592.

79. Z. Wang, S. Campagna and G. Y. Xu, *Tetrahedron Lett.*, 2000, **41**, 4007.

80. A. Osman and S. Barbara, *J. Org. Chem.*, 2003, **68**, 2398.

81. G. Aranda, M. Cortes, M. Maurs and R. Azerad, *Tetrahedron : Asymm.*, 2001, **12**, 2013.

82. E.J. Corey and P.B. Hopkins, *Tetrahedron Lett.*, 1982, **23**, 4871.

83. T. Lversen and D.R. Bundle, *J. Chem. Soc., Chem. Comm.*, 1981, 1240.

84. a)E.J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, 6190; b) J.E. Baldwin, R.M. Adlington, A.T. Russell and M.L. Smith, *J. Chem. Soc., Chem. Commun*, 1994, 85.

85. N.B. Desai and N. McKelvie, *J. Am. Chem. Soc.*, 1962, **84**, 1745.

86. F.A. Carey and H.S. Tremper, *J. Org. Chem.*, 1971, **36**, 758.

87. R. Garner, G.V. Garner and H. Suschitzky, *J. Chem. Soc.(C)*, 1979, 825.

88. J.E. Baldwin, A.G. Swanson and J.K. Cha, *Tetrahedron*, 1986, 42, 3943.

89. D. Renneberg and P.B. Dervan, *J. Am. Chem. Soc.*, 2003, **125**, 5707.

90. H.B. Gillespie, M. Engelman and F. Spano, *J. Am. Chem. Soc.*,1957, **79**, 2245.

91. C.D. Campbell and C.W. Rees, *J. Chem. Soc. (C)*, 1969, 748 and 752.

92. M.A. Birkett PhD dissertation, Nottingham University, 1994.

93. H.E. Blackwell, D.J. O'Leary and A.K. Chatterjee, *J. Am. Chem. Soc.*, 2000, **122**, 58.

94. P. Schwab, R.H. Grubbs and J.W. Ziller, *J. Am. Chem. Soc.*, 1996, **118**, 100.

95. L. Kiss, T. Kurtan, S. Antus and H. Brunner, *ARKIVOC*, 2003(**v**), 69.

96. M. Nakagava and K. Nakanishi, *Tetrahedron Lett.*, 1982, **23**, 3855.

97. a) M. Ishiguro, T. Tatsuoka and N. Nakatsuka, *Tetrahedron Lett.*, 1982, **23**, 3859; b) A.L. Tokes, G. Litkei and K. Gulacsi, *Tetrahedron*, 1999, **55**, 9283.

98. V. Baliah and V.M. Kanagasabapathy, *Tetrahedron,* 1978, **34**, 3611.

99. K. Tanemura, T. Suzuki and Y. Nishida, *Chem. Lett.*, 2003, **32**, 932.

100. E. Defranq, T. Zesiger and R. Tabacchi, *Helv. Chim. Acta*, 1993, **76**, 425.

101. A. Avenoza, J.H. Busto and F. Corzana, *Tetrahedron : Asymm.*, 2004, **15**, 131.

102. a) P. Callant, L.D. Haenens and M. Vandewalle, *Synth. Commun.*, 1984, **14**, 155; b) W.R.F. Goundry, J.E. Baldwin and V. Lee, *Tetrahedron*, 2003, **59**, 1719.

103. F. Ramirez, N.B. Desai and N. McKelvie, *J. Am. Chem. Soc.*, 1962, **84**, 1745.

104. D.H. Huh, J.S. Jeong and H.B. Lee, *Tetrahedron*, 2002, **58**, 9925.

105. D.W. Knight and P.B. Little, *Tetrahedron Lett.*, 1998, **39**, 5105.

106. F. Kaberia, B. Vickery, G.R. Willey and M.G.B. Drew, *J. Chem. Soc., Perkin Trans* 2, 1980, **11**, 1622.

107. D.W. Knight and P.B. Little, *J. Chem. Soc., Perkin Trans* 1, 2000, 2343.