On the Synthesis of Furan-Containing Fragrance Compounds

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"*...scientific integrity, a principle of scientific thought*
that corresponds to a kind of utter honesty..."
Richard P Feynman

"*You can only get smarter by playing a smarter opponent.*"
Guy Ritchie

"*Try not to become a man of success but rather to become a man of value.*"
Albert Einstein

Abstract

This thesis describes the use of both silver nitrate, and iodine, to promote 5-*endo*-dig cyclisations for the formation of furans. The synthesis of kahweofuran and other furan-containing fragrance compounds is described, along with an investigation into the selectivity of the 5-*endo*-dig cyclisation process.

Chapter **2** describes the synthesis of furan-containing analogues of known fragrance compounds using a silver-catalysed cyclisation methodology. The analysis of some of these compounds by an "expert nose" is discussed.

Chapter **3** describes the synthesis of kahweofuran, a furan-containing compound reported to be one of the major odour constituents of roasted coffee.

Chapter **4** describes an investigation into the cyclisation of triols upon exposure to silver nitrate or iodine when more than one cyclisation pathway is possible.

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Abbreviations and acronyms

Several abbreviations and acronyms have been used throughout this thesis that may not be familiar to the reader. They are listed below:

Ac	acetyl
Å	Angstrom(s)
app.	apparent
APCI	atmospheric pressure chemical ionisation
aq.	aqueous
Ar	aromatic
Bn	benzyl
Boc	*tert*-butoxycarbonyl
b.p.	boiling point
br	broad
Bu	butyl
Bz	benzoyl
cat.	catalytic
cf.	*conferre*
column chromatography	flash column chromatography
COSY	correlation spectroscopy
Cy	cyclohexane
CI	chemical ionisation
d	day(s)
d	doublet
Da	Dalton(s)
DCM	dichloromethane
dd	double doublet
dt	double triplet
DEPT	distortionless Enhancement by Polarization Transfer
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
e.e.	enantiomeric excess
e.g.	*exempli gratia*

EI	electron ionisation
EPSRC	Engineering and Physical Sciences Research Council
eq.	equivalent(s)
ES	electrospray
ether	diethyl ether
Et	ethyl
EWG	electron withdrawing group
g	gram
GC	gas chromatography
Δ	heat
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	hertz
IBX	iodoxybenzoic acid
Inc.	Incorporated
IR	infra-red
J	coupling constant
k	kilo
kg	kilogram
L	ligand
lit.	literature
m	*meta*
m	multiplet
M	molar
MALDI	matrix assisted laser desorption ionisation
mCPBA	3-chloroperoxybenzoic acid
Me	methyl
MHz	megahertz
μmol	micromole(s)
min.	minute(s)
ml	millilitre(s)

mmol	millimole(s)
m.p.	melting point
MS	mass spectrometry
Ms	methane sulfonyl
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOSEY	nuclear Overhauser enhancement spectroscopy
o	*ortho*
p	page
P	product
p	*para*
Ph	phenyl
Pr	propyl
ppb	parts per billion
ppm	parts per million
q	quartet
quin	quintet
r.t.	room temperature
s	singlet
SM	starting material
t	triplet
TBAF	tetra *n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
td	triple doublet
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	toluenesulfonyl
UV	ultra-violet
w/w	weight for weight

Chapter 1: Introduction

1.1 Flavours and Fragrances

The production of flavours and fragrances is a multibillion pound industry.[1] The world's largest flavours and fragrance company is Givaudan, which announced total sales of over £2750 million for 2010.[2] Odourous compounds are used extensively in cosmetic and toiletry products and as additives in many foods and beverages. The structures of these compounds are often either identical to those produced in nature, or analogues of natural products which have been modified to meet a desired criteria.

1.2 Threshold and Character

There are two distinct aspects of an odour: threshold and character. The odour threshold is the concentration at which the presence of the molecule can be detected by smell and is a measure of the potency of the compound. The odour character is a somewhat subjective aspect regarding the smell of the compound.

Due to the complexity of the olfactory system both the perceived odour threshold and character of a compound can vary from person to person. In 1992 Polak carried out a study to determine the odour threshold of two enantiomers of geosmin **1** and **2**, a *potent earthy* smelling material (Scheme **1**).[3] It was reported that the average odour threshold of (–)-geosmin **1** in water was 0.0095 ppb, 11.5 times lower than that of (+)-geosmin **2** in water, which averaged at 0.079 ppb. Examination of the results reveals many points that do not fit the statistical average line. One participant perceived the threshold of (–)-geosmin **1** to be over 30 times lower than that of (+)-geosmin **2**, while two of the fifty participants perceived (+)-geosmin **2** to have a lower threshold than (–)-geosmin.

1 (–)-geosmin 0.0095 ppb

2 (+)-geosmin 0.079 ppb

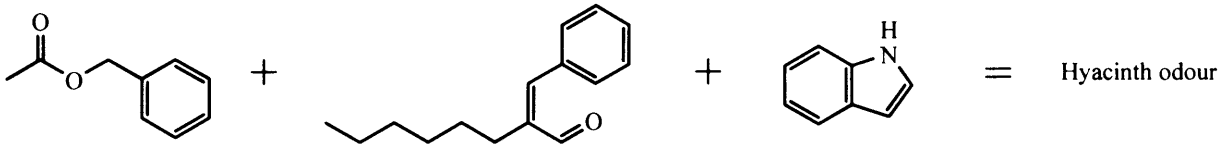
Scheme **1**

The character of an odour can also be perceived differently by different people. An extreme case of this is called a parosmia, an olfactory dysfunction that is characterized by the inability of the

brain to properly identify an odour's "natural" smell. One of the commonest parosmia is the association of sandalwood oil with the smell of urine.[4]

The complexity of the olfactory system means that perceived threshold and character discrepancies are not fully understood.[5] The process of smell begins with interaction of a compound with olfactory receptor neurons which are located on cilia in the inner chamber of the nose. To interact with the olfactory receptors a compound must be volatile enough to reach the inner chamber of the nose and be able to dissolve in nasal mucus. Once dissolved the compound is ferried to receptors on the cilia by odorant binding proteins. Once a cilium is activated, ion channels are opened and the olfactory receptor becomes depolarised. If the threshold limit is reached, the olfactory receptor fires an action potential which travels up an axon to a glomerulus in the olfactory bulb. It is in the olfactory bulb where the structure of the compound is converted into signals that the brain recognises as smell.[6]

There are genes for over 1000 types of olfactory receptor, but each human only has 350–400 of them. These leads to the possibility of over 10^{290} possible combinations of olfactory receptors, a larger number than the total number of people who have ever lived.[7,8] A different combination of olfactory receptors can therefore result in a difference in perceived odour.[9] The situation is further complicated by the combinatorial nature of the sense of smell. Multiple olfactory receptors are triggered by a single odourant.[10,11] This means it is far more likely for two individuals to perceive an odour slightly differently than it is to be perceived by one but not by the other. Compounds which trigger some of the same olfactory receptors can take on a markedly different odour when smelt at the same time. Benzyl acetate **3** is described as *fruity*, hexylcinnamic aldehyde **4** as *fatty* and indole **5** as *faecal*, but when smelt together the mixture is said to be reminiscent of the smell of hyacinth flowers (Scheme **2**).[12]



3
benzyl acetate
fruity

4
hexylcinnamic aldehyde
fatty

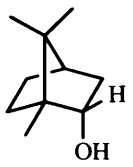
5
indole
faecal

Scheme **2**

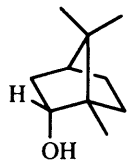
While an odourant's interaction with olfactory receptors can be studied using X-ray crystallography[13] and intracellular ion measurements,[14] the way in which the signals they produce are interpreted in the brain is far harder to determine. It is known that the messages generated in the olfactory bulb are transmitted along the olfactory nerve directly to the brain, where the path of the message divides into two. One route passes into the olfactory cortex at the front of the brain where identification and differentiation between odours occurs. The other passes into the limbic system at the centre of the brain. The limbic system is believed to be the emotional centre of the brain and it is here that many sensory messages are received and interpreted. It is believed that this close link between the olfactory sense and the limbic region is the reason for such a close association between smell and emotion. This emotional response can influence the way in which an individual perceives an odour.[15]

1.3 Stereochemistry

The effect of chirality on odour was once an area of controversy. The difference in the odour of enantiomers was for a long time ignored or claimed to be the result of minute amounts of low-threshold unknown impurities.[16] One of the first indications that enantiomers might have different odours came in 1874 when essential oils containing (1*R*,2*R*,4*S*)-(+)-borneol **6**, or its enantiomer (1*S*,2*S*,4*R*)-(−)-borneol **7**, were found to have different odours (Scheme **3**).[17]



6
(1*R*,2*S*,4*R*)-(+)-borneol

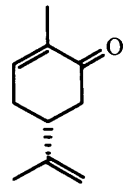


7
(1*S*.2*R*,4*S*)-(−)-borneol

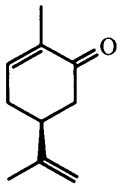
Scheme **3**

Arguably the most famous example of chirality affecting odour is that of the enantiomers (*R*)-(−)-carvone **8** and (*S*)-(+)-carvone **9** which are odourous constituents of spearmint and caraway oil respectively (Scheme **4**).[18] The odour difference between the two compounds is discernible by most people, although 8% of the human population have specific anosmia to (*S*)-(+)-carvone **9**, a condition which means they are unable to perceive its odour.[19] It was not until 1971 that several papers were published regarding the differing odour qualities of the two enantiomers of carvone.[20] The most important of these was by Miller, who unambiguously

showed the odour distinctiveness of the two enantiomers of carvone by chemical interconversion, independent synthesis, and resolution.[21]



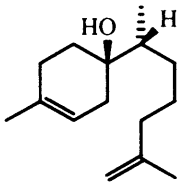
8
(*R*)-(−)-carvone
spearmint



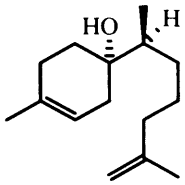
9
(*S*)-(+)-carvone
caraway

Scheme **4**

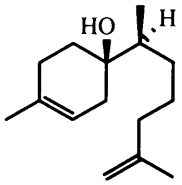
It is also possible for one enantiomer to have an odour, while the other is perceived odourless. Iso-β-bisabolol occurs at a concentration of less than 0.001% in both East Indian and West Australian sandalwood oils and possesses a *strong floral muguet-like* odour. By the synthesis and separation of each stereoisomer of iso-β-bisabolol **10**, **11**, **12**, and **13**, Braun revealed that it was only stereoisomer **10** that possessed the characteristic odour of the oil, with the other stereoisomers being odourless (Scheme **5**).[22]



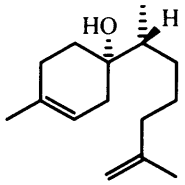
10
muguet odour



11
odourless



12
odourless

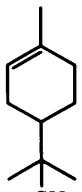


13
odourless

Scheme **5**

1.4 Concentration

The concentration of a compound can have a dramatic effect on its perceived odour. The principal odour and flavour compound in grapefruit is 1-*p*-menthen-8-thiol **14** which has a remarkably low odour threshold of the order of 10^{-5} ppb (Scheme **6**).[23] At concentrations above 10^{4} ppb the molecule imparts a *rubbery*, *sulfurous* odour rather than the more pleasant fresh grapefruit character for which it is known.[24]



14

Scheme **6**

It is a commonly observed phenomenon that the increased concentration of certain compounds can cause desensitisation and result in no odour being perceived. One of the most widely known examples is that of hydrogen sulfide, a highly toxic gas which can be perceived at low concentrations, 0.13–150 ppm, but becomes undetectable at higher concentrations. The chronic toxicity threshold of hydrogen sulfide is 250 ppm, meaning that it is odourless at dangerous concentrations.[25]

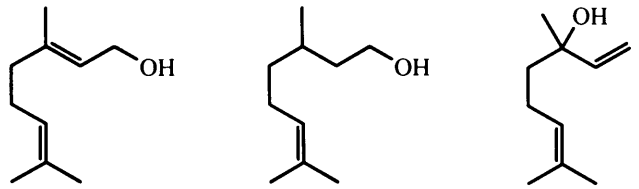
1.5 Rational design of odourants

Odour is defined as "an emanation that is perceived by the sense of smell" and can refer to an emanation composed of more than one compound. An odourant is defined as "any substance capable of stimulating the sense of smell" and refers to a single molecule.[26] For a compound to be an odourant it must be able to reach the nose and thus requires a sufficiently high vapour pressure. Odourants therefore typically have a molecular weight of below 300 Daltons and a low polarity. Despite all the recent research into the mechanism of olfaction, there is little information on the molecular interactions between olfactory receptors and their ligands.[27] It is therefore left to a process known as molecular similarity to guide the design of odourants. Molecular similarity is looked for among compounds of the same odour type. By analogy with the widely used term "pharmacophore", the word "olfactophore" has been coined for a set of structural features responsible for a defined odour-type.[28] The acquisition of reliable structure-odour relationship data is therefore important in the design of odourants. This can be a difficult process due to the previously discussed problems associated with measuring odour quantity and quality. The lack of unity in the language of perfumers and the lack of statistically significant data on the odour of pure compounds, or even on the odour of mixtures of known ratio and configuration, also hinders the rational design of odourants.

1.6 Rose

Geraniol **15** is one of the character impact compounds of rose but it is only present in rose oils at around 30%. Citronellol **16** and linalool **17** are also present in rose oil and compounds of this

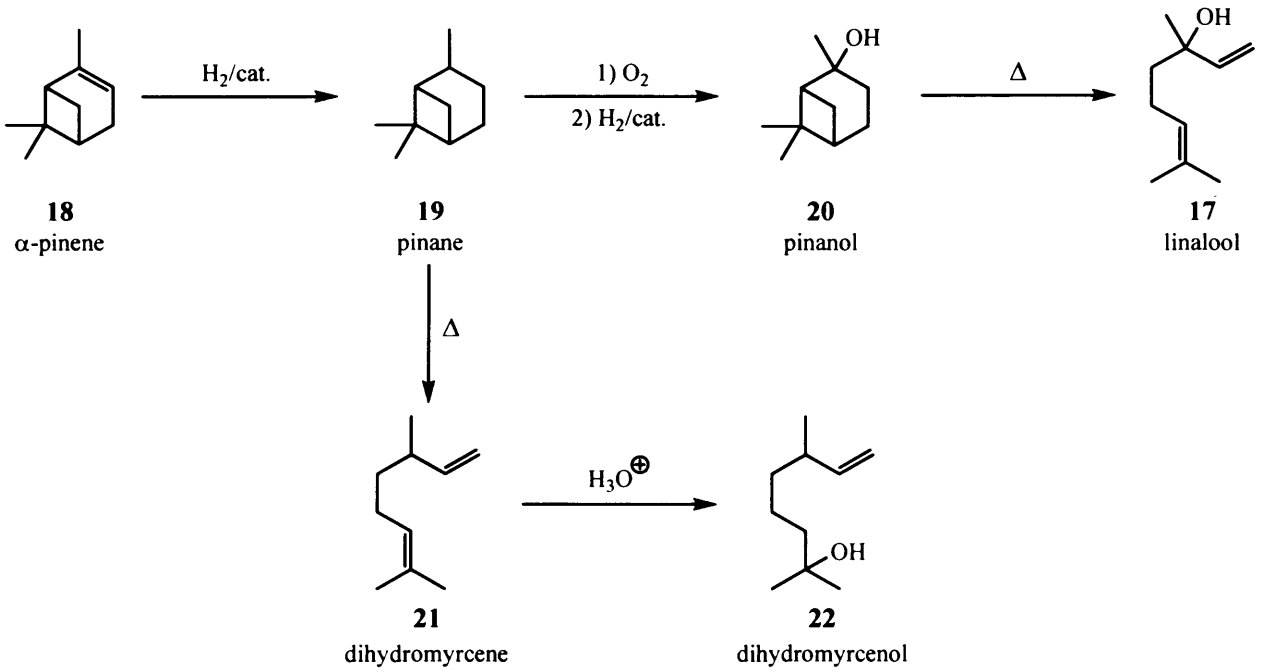
nature are known as rose alcohols (Scheme 7). Natural oils are not suitable commercial sources of rose alcohols due to their high costs.[29]



15 geraniol **16** citronellol **17** linalool

Scheme 7

During the synthesis of natural fragrance compounds, production intermediates and by-products often serve as a source of inspiration for discovery chemists. The synthesis of linalool **17** begins with the hydrogenation of α-pinene **18** to form pinane **19**. Oxidation of pinane **19** forms pinanol **20** which can then undergo pyrolytic ring opening to form linalool **17**, however, incomplete purification of pinanol **20** can lead to the pyrolytic ring opening of remaining pinane **19**, forming dihydromyrcene **21**. Hydration of the trisubstituted double bond gives the synthetic rose alcohol dihydromyrcenol **22** (Scheme 8). High levels of dihydromyrcenol **22** were used in the perfume "Cool Water" by Davidoff in 1988 due the *freshness* of its odour, and began a new fashion in masculine freshness.[29]

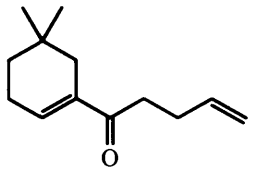


18 α-pinene **19** pinane **20** pinanol **17** linalool

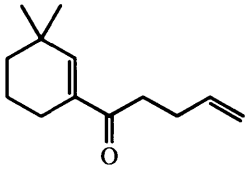
21 dihydromyrcene **22** dihydromyrcenol

Scheme 8

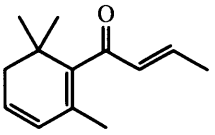
"Cool Water" by Davidoff also contained the *floral, rose-like* ingredient dynascone, which is a mixture of the isomers α-dynascone **23** and β-dynascone **24** (Scheme **9**).[27] These compounds are part of the damascene family which comprises of terpenoid materials derived in nature from the degradation of carotenoids and are another key structural area of floral odourants. The discovery of α- and β-dynascone **23** and **24** is an interesting story which begins with the isolation and structural elucidation of β-damascenone **25** by Kováts in 1967,[30] which despite being considered one of the masterpieces in essential oil analysis was not published until 1987.[31]



23
α-dynascone



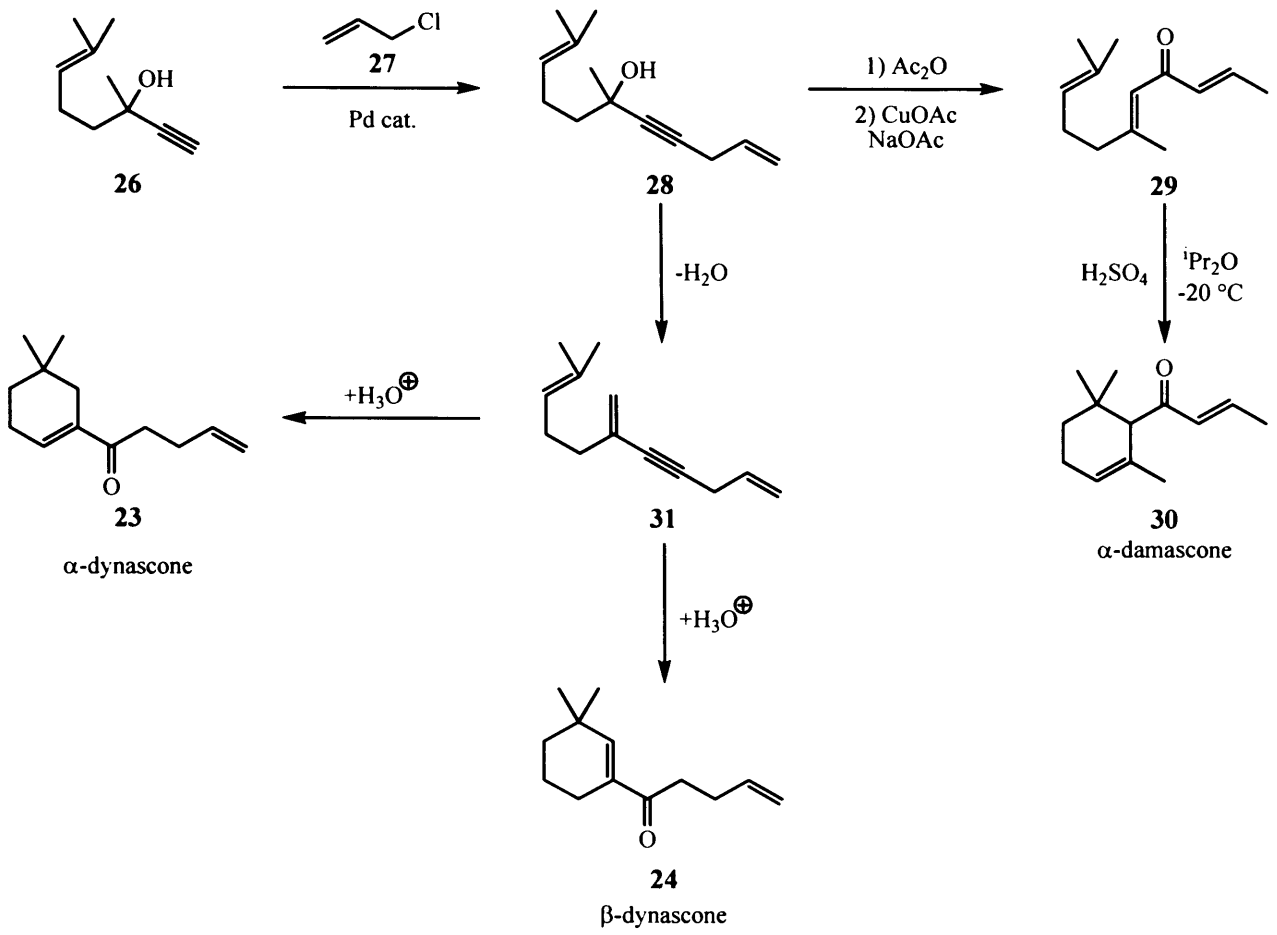
24
β-dynascone



25
β-damascenone

Scheme **9**

Three years after the structural elucidation of damascones, the first synthesis of α-dynascone **23** was reported.[32] The process started with the coupling of allyl chloride **27** and dehydrolinalool **26** to form alcohol **28**. Conversion to the acetate allowed for a copper-catalysed Saucy-Marbet type rearrangement[33] followed by conversion to ketone **29**. An acid-catalysed cyclisation was then successful in producing α-damascone **30**. It was found that the *green aspect* of the odour of the α-damascone **30** produced by this synthesis varied. Analytical investigations showed that this was due to the presence of α-dynascone **23** and β-dynascone **24** which were formed by dehydration of alcohol **28** followed by acid-catalysed cyclisation, hydride-shift and hydrolysis (Scheme **10**).[34]



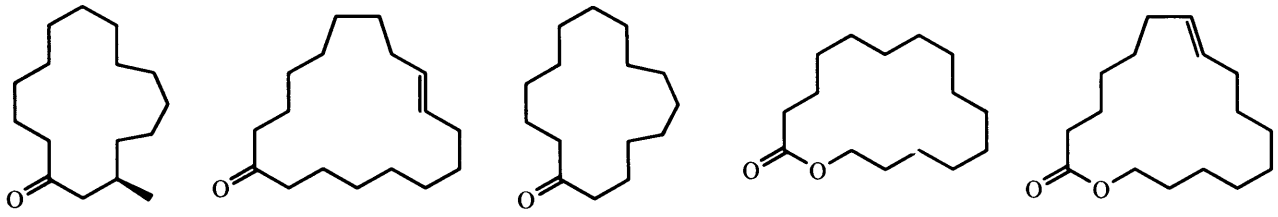
Scheme **10**

1.7 Musks

Along with the nature of the functional groups and the molecular structure of a compound, the molecular mass is also an important factor in determining its volatility. Odourants with molecular masses of around 200 Daltons occur relatively frequently, but masses over 300 Daltons are an exception. Since fragrance compounds differ in volatility, the odour of a perfume composition changes during evaporation. The most volatile compounds are released early on and make up what is known as the *top note* of a perfume. Components of medium volatility make up the *middle note* or *body*. When only the least volatile fragrance ingredients remain, they produce what is known as the *end note* or *dry out*.[35] The musks are of central importance to the fragrance industry and tend to form the *end note* of a perfume composition.[36] The odour of musk is difficult to describe, but is often called *warm*, *sweet*, *powdery* and *animal*, and is usually long-lasting, tenacious and substantive.[27]

Musk is the name originally given to a substance with a penetrating *animalic* odour obtained from the glands of the male musk deer.[37] In 1921 Ružička showed that one of the compounds

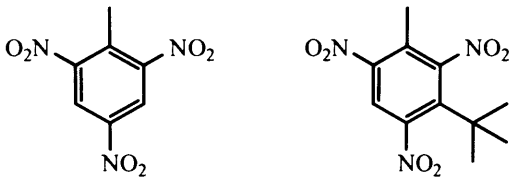
responsible for the characteristic smell of this musk was the macrocycle muscone **32**, which has a *woody-amber* odour.[38] During the first half of the twentieth century macrocyclic ketones and lactones with *musk* odours were isolated from animal sources, *e.g.* civetone **33** and exaltone **34**, and plant sources, *e.g.* exaltolide **35** and (*Z*)-Δ^7-ambrettolide **36** (Scheme **11**).



32 muscone | **33** civetone | **34** exaltone | **35** exaltolide | **36** (*Z*)-Δ^7-ambrettolide

Scheme **11**

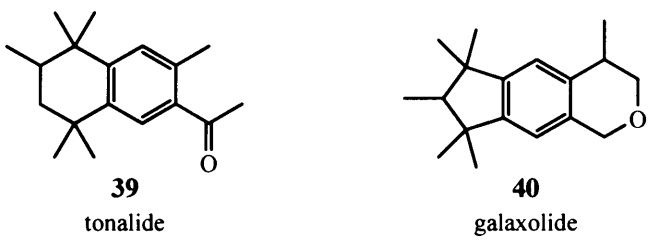
The first synthetic musk was serendipitously discovered by Baur in 1888. While working on improving the explosive trinitrotoluene **37**, he noticed that the product of its *tert*-butylation, musk baur **38**, had a *pleasent, sweet, musky* odour (Scheme **12**).[39] Nitromusks have little use in the modern perfume industry due their phototoxicity and the explosive intermediates often required for their production.[4]



37 trinitrotoluene | **38** musk baur

Scheme **12**

The third class of musks consists of synthetic polycyclic aromatic compounds such as tonalide **39** and galaxolide **40** (Scheme **13**). These types of compounds are now hugely important in the fragrance industry due their *musk* odour and their stability,[40] but their low biodegradability leads to a tendency to bio-accumulate which is a cause of some concern.[41]

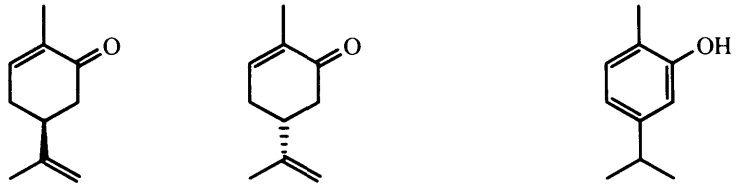


39 tonalide | **40** galaxolide

Scheme **13**

1.8 Mint

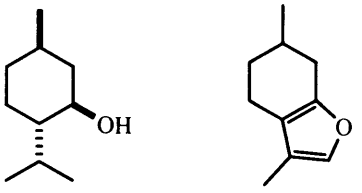
There are many species and sub-species of mint, with each producing a mixture of odourous monocyclic terpenoids. The most important of these are carvone and menthol. Carvone takes its name from caraway (*Carum carvi*), the oil of which contains up to 85% of the (*S*)-enantiomer of carvone **9**. Spearmint oil (*Mentha spicata*) contains up to 75% of the (*R*)-enantiomer of carvone **8**. Carvacrol **41** is a double bond isomer of carvone and can account for up to 85% of the composition of the essential oil obtained from oregano (*Origanum vulgare*) (Scheme **14**).[42] A typical aromatic resonance energy is 113 kJ mol^{-1} and so conversion of carvone to carvacrol **41** by double-bond migration is thermodynamically favourable. This can present problems when handling or distilling carvone and can potentially lead to a lowering of purity, or an uncontrollable exothermic reaction.[29]



9 (*S*)-carvone **8** (*R*)-carvone **41** carvacrol

Scheme **14**

Menthol **42** occurs widely in mint species, particularly cornmint (*Mentha arvensis*) in which it can account for up to 85% of the essential oil. Menthofuran **43**, in which the oxygen atom is bonded to both the 3-carbon of the ring and the 9-carbon is also found in most mint species (Scheme **15**).[29]



42 **43**

Scheme **15**

1.9 Sandalwood

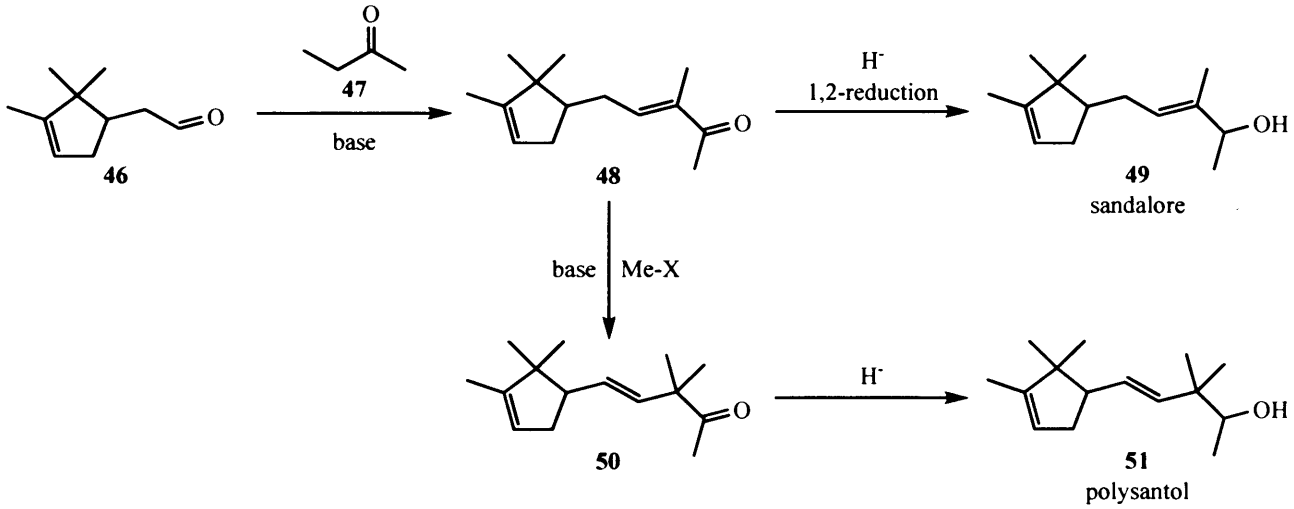
Historical records show that there has been uninterrupted use of sandalwood oil in perfumery for at least 4000 years. The major components of the oil are α-santalol **44**, and β-santalol **45** (Scheme **16**).[29]

44
α-santalol

45
β-santalol

Scheme **16**

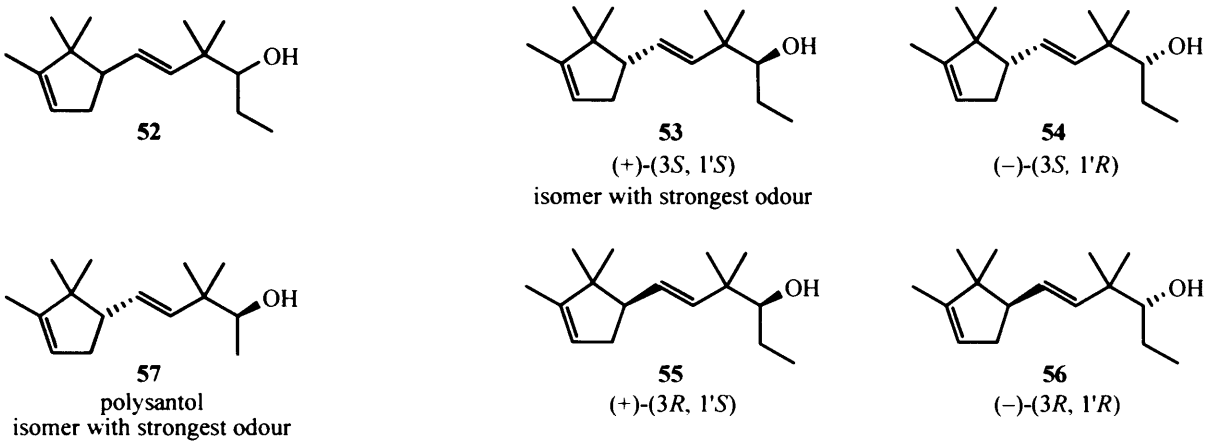
Both isomers contribute to the distinctive *woody* odour of the oil. The β-isomer **45** is more intense and also contributes to the *slightly animalic* and *urinous* character of the oil. Sandalwood oil is obtained by distillation of the wood of the *Santalum album* tree. Cultivation of the tree is difficult due to its parasitic nature and the consequent need for a suitable host. Excessive harvesting has endangered the species and the control of production is now necessary to prevent extinction.[29] Synthetic routes to compounds with *sandalwood-like* odours are therefore of interest to the perfume industry. One class of synthetic sandalwood-substitutes are those derived from campholenic aldehyde **46**.[43] Two typical examples are sandalore **49** and polysantol **51**, which were patented by Givaudan and Firmenich respectively.[29] Sandalore **49** is made by an aldol-type condensations between campholenic aldehyde **46** and butan-2-one **47**, followed by a 1,2-reduction of the resulting unsaturated ketone **48**. The same unsaturated ketone **48** can be alkylated under basic conditions to give ketone **50** which can then be reduced to give polysantol **51** (Scheme **17**).[29]



Scheme **17**

Altarejos recently reported the synthesis of a homologue of polysantol **51**, alcohol **52**.[43] As a mixture of diastereoisomers, the compound was described as *woody*, *leathery*, *spicy* and *sweet*, but devoid of *sandalwood* scent. By a similar synthesis to that shown for polysantol **51**, the

diastereoisomers **53** and **54** were made from (–)-(1*S*)-α-pinene, and the diastereoisomers **55** and **56** were made from (+)-(1*R*)-α-pinene. Each pair of diastereoisomers was separated by column chromatography of their camphanoate derivatives. The odour evaluation of the individual isomers revealed that each had a sandalwood odour, which was surprising when a mixture of them did not. It was perhaps less surprising that the enantiomer with the strongest and most substantive sandalwood odour was that with the same absolute configuration as the most powerful polysantol enantiomer **57** (Scheme **17**).



Scheme **17**

1.10 Sulfur containing odourants

Sulfur containing molecules are widely acknowledged to be potent odourants with many people associating them with unpleasant odours. This is not a modern phenomenon and can be found throughout literary history. The bible associates brimstone (sulfur) and fire as an act of retribution:

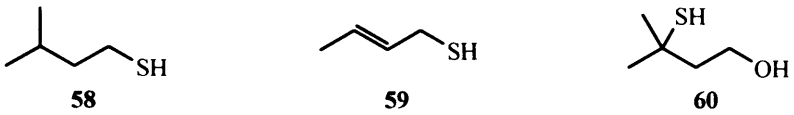
> *The Yahweh rained down on Sodom and Gomorrah*
> *brimstone and fire of his own sending.*
>
> --Genesis 19:24[44]

Shakespeare's Othello, written in 1604, contains a similar association:

> *Blow me about in winds! Roast me in sulphur!*
> *Wash me in steep-down gulfs of liquid fire!*
>
> -- Othello, Act V. Scene II[45]

To the modern day organic chemist, organosulfur compounds bring forth associations with dimethylsulfide or benzenethiol, both of which have potent, disagreeable odours. There is a

wide range of organosulfur compounds formed in nature as secondary metabolites. Many are indeed perceived as foul smelling, such as thiols **58** and **59**, which are two of the principle odour constituents of skunk spray,[46] and tertiary thiol **60** which has been isolated from cat urine (Scheme **18**).[47]



58 **59** **60**

Scheme **18**

While these odours are certainly undesirable, there is an abundance of naturally occurring thiols with pleasant aromas, many of which are crucial to the overall fragrance impact of many food and drink products. Sulfur containing compounds such as **61**, **62**, **63** and **64** are important for the characteristic odour and flavour of many meats (Scheme **19**).[48]

61 raw meat "bloody" **62** lamb **63** pork **64** beef

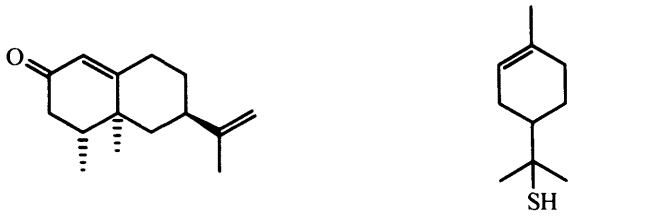
Scheme **19**

Despite being characteristic odour compounds, these molecules normally occur at extremely low concentrations due to their powerful odours.[49]

1.11 Misidentification of odourous compounds

Some sulfur-containing compounds are such powerful odourants that trace amounts of them can dramatically affect the odour of a sample, and can lead to the misidentification of a compound as odourous. The story of the odour of grapefruit provides a fascinating example of this. In 1964 MacLeod reported that the bicyclic conjugated sesquiterpene ketone, nootkatone **65**, was a primary flavour-impact compound in grapefruit.[50] This led MacLeod to suggest that the content of nootkatone **65** should be used as a quality-index standard in grapefruit oil.[51] Stevens reported in 1970 that when nootkatone **65** was crystallised from grapefruit oil, the aroma of the mother liquor was judged to be far more potent and grapefruit-like than nootkatone **65** itself.[52] He did not, however, go on to draw any conclusions as to the importance of nootkatone **65** as a

flavour-impact compound. It was not until 1981 that Shaw suggested that nootkatone **65** might not be the most important flavour component in grapefruit oil after studying the aroma of nootkatone **65** using twelve experienced aroma and taste panel members.[53] Shaw's paper concluded that "*other constituents of (grapefruit) oil modify the flavour of this agent at above-threshold levels*". It was left to Ohloff in 1982 to reveal that 2-(4-methylcyclohex-3-enyl)propane-2-thiol (grapefruit mercaptan) **14** was the potent character-donating constituent of grapefruit, in which it occurs at a below ppb-level (scheme **20**).[23]

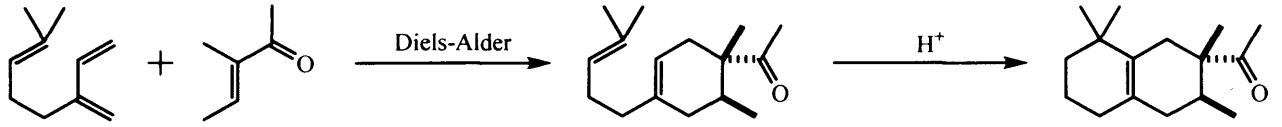


65
nootkatone

14
grapefruit mercaptan
10^{-5} ppb

Scheme **20**

This phenomenon is not restricted to sulfur-containing compounds as is highlighted by the story of Iso E Super **69**.[27] Iso E Super **69** was patented by International Flavors & Fragrances Inc. in 1973 and was believed to possess a *rich, intense woody odour with a shade of amber.*[54] Its industrial synthesis starts with a Diels-Alder reaction[55] between mycene **66** and (*E*)-3-methylpent-3-en-2-one **67**, followed by an acid-catalysed cyclisation (Scheme **21**).

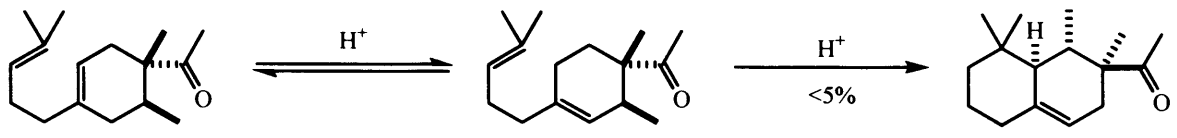


66 **67** **68**

69
Iso E Super
10^{-3} ppb

Scheme **21**

Analysis carried out at Givaudan Roure showed that the compound responsible for the *intense woody* odour of the product of this synthesis was in fact ketone **71**, which has a staggeringly low odour threshold of 10^{-6} ppb.[56] Ketone **71** is a structural isomer of Iso E Super **69** and is produced as a small impurity from intermediate **68** by a protonation-deprotonation equilibrium, followed by an acid-catalysed cyclisation (Scheme **22**).

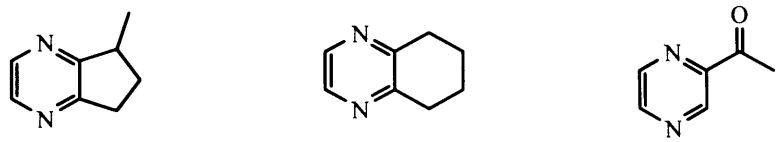


68 **70** **71**
10^{-6} ppb

Scheme **22**

1.12 Furan containing odourants

Heterocycle containing odourants commonly occur in nature. Pyrazines are generally associated with a *nutty* aroma, with methyldihydrocyclopentapyrazine **72** and 5,6,7,8-tetrahydroquinoxaline **73** being typical examples. Another pyrazine, acetylpyrazine **74**, is considered to be reminiscent of popcorn (Scheme **23**).[24]



72 nutty **73** nutty **74** popcorn

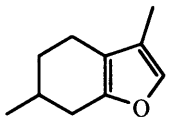
Scheme **23**

Odourants containing the furan moiety can possess a wide range of smells. As previously mentioned, furan **64** is considered to be largely responsible for the smell of roasted beef. The aroma of roasted coffee also comprises of many furan-containing compounds, with furans **75**, **76** and **77** having all been isolated from roasted coffee (Scheme **24**).[57]

64 **75** **76** **77**

Scheme **24**

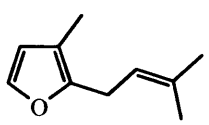
A compound which possesses both a nutty and coffee-like aroma is menthofuran **78**, which is found in most mint species[29] and has odour descriptors of *diffusive, pungent, musty, nutty, pyrazine-like, earthy and coffee* (Scheme **25**).[42]



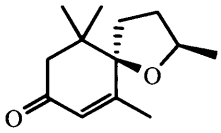
43
menthofuran
nutty, pyrazine-like,
earthy and coffee

Scheme **25**

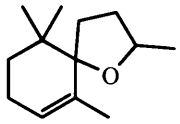
There are many furan containing odourants which have floral odours. Famous examples include rosefuran **78** which is described as *caramel, green* and *minty*,[42] and *cis*-theaspirone **79** which is described as smelling *orris-like, sweet-powdery, floral with tea-like nuances*.[58] The odours of these types of structures can easily move into a fruity area, such as theaspirane **80** which is described as *fruity, especially blackcurrent-like*, and tetrahydrofuran **81**, which possesses a *fruity-citrusy* note (Scheme **26**).



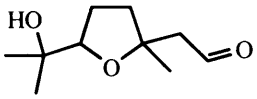
78
rosefuran
caramel, green, minty



79
cis-theaspirone
orris-like, sweet-powdery,
floral with tea-like nuances



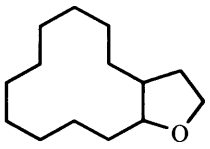
80
theaspirane
fruity, especially
blackcurrent-like



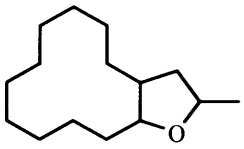
81
fruity-citrusy

Scheme **26**

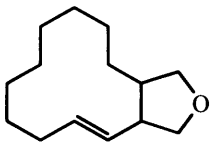
Tetrahydrofuran containing fragrance compounds are also found in the area of amber, such as cyclamber **82** (*woody, dry amber*) and lignoxan **83** (*woody-amber*). Similarly structured compounds can also be found in the area of musk, such as muscogene **84** (*animal, natural musk*) (Scheme **27**).[42]



82
cyclamber
woody, dry amber



83
lignoxan
woody-amber



84
muscogene
animal, natural musk

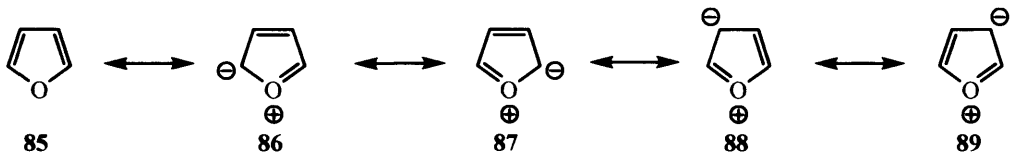
Scheme **27**

1.13 Heterocycles

Heterocycles are inherently important in many modern pharmaceuticals.[59] One of the prevalent features of a heterocycle is the presence of at least one lone pair of electrons on an atom (*e.g.* O, N, S) which provides a basis for electron co-ordination, hydrogen-bonding, reactivity and resonance. Such electronic properties are crucial to a heterocycle's ability to exhibit biological activity. Heterocyclic targets are generally obtained either by late formation of the heteroaromatic ring from a complex acyclic precursor, or by multiple functionalisation of a simple hetereoaromatic predominantly using electrophilic substitution or metallation strategies.[59]

1.14 Structure of furan

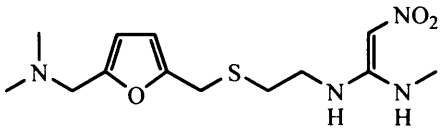
Furan **85** is an oxygen-containing five-membered heteroaromatic ring, the chemistry of which has been an active field of research for a long period of time.[60] Furan **85** derives its aromaticity from the delocalisation of a lone pair of electrons on the oxygen atom. This lone pair is consequently not available for protonation and is not basic. Furan **85** is less aromatic than its nitrogen and sulfur analogues due to the greater electronegativity of oxygen, meaning the mesomeric representations **86**, **87**, **88** and **89** make relatively less of a contribution to its electronic structure (Scheme **28**).



Scheme **28**

1.15 Uses of furan

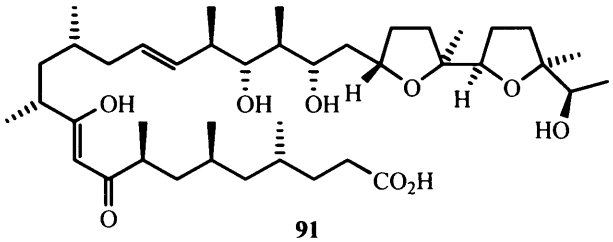
The furan moiety occurs in many plant[61] and marine organisms,[62] the majority of which are terpenoid in character. Compounds containing the aromatic furan ring system can exhibit remarkable biological activity and are therefore employed commercially as pharmaceutical agents, flavours, fragrances, insecticides and anti-leukemic agents.[4] A particularly successful pharmaceutical agent is the drug ranitidine **90**, commonly known as Zantac, which is very effective in the treatment of gastrointestinal disorders (Scheme **29**).[63] It is especially effective for the treatment of stomach ulcers, with the mode of action supposedly relying on its ability to act as a histamine H_2 receptor antagonist, reducing gastric acid secretions and therefore reducing bleeding from the ulcer.



90

Scheme **29**

Furan is also found in its saturated form as a key structural element in many antibiotics. One such example is ionomycin **91**, a member of the polyether family of antibiotics. These antibiotics are of particular interest due to their ability to transport metal ions across lipid bi-layers (Scheme **30**).[64]

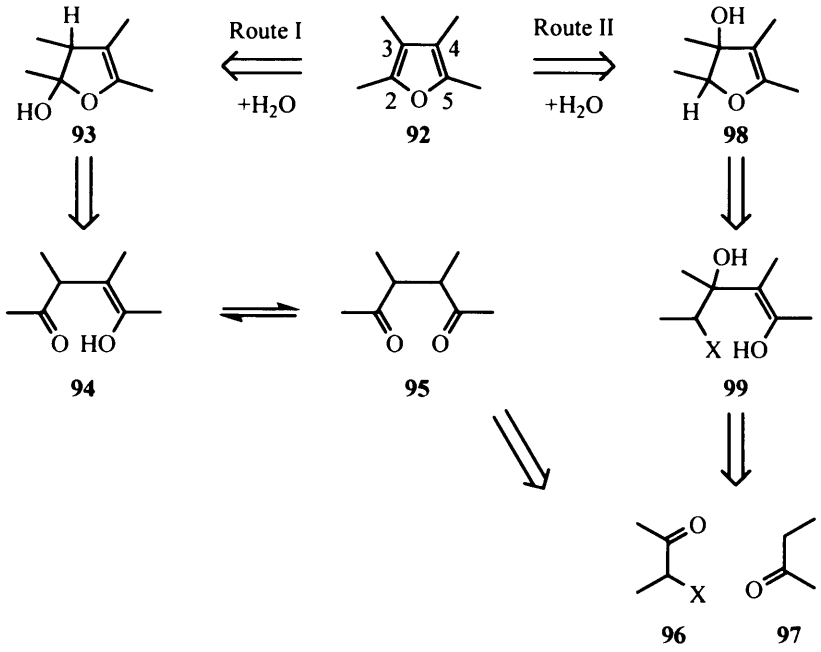


91

Scheme **30**

1.16 Traditional syntheses of furans

Over the years many chemists have investigated the synthesis of polysubstituted furans, leading to many routes being available for their formation. Classic retrosynthetic analysis of furan allows it to be disconnected in two principle ways (Scheme **31**).



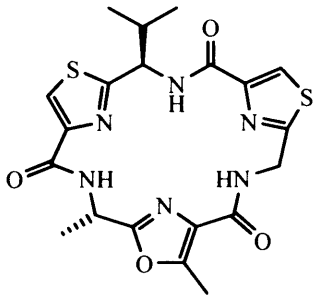
Scheme **31**

Route I shows the addition of water across the furan C-2/C-3 bond with the hydroxyl group adding in the α-position. This is followed by cleavage of the C-2/O-1 bond to give the 1,4-dicarbonyl precursor **95**. The forward process is known as the Paal-Knorr synthesis and involves the treatment of the 1,4-dicarbonyl compound **95** with phosphoric acid, or a similar proton source, resulting in an intramolecular dehydration reaction.[65] The Paal-Knorr synthesis can also be used to prepare thiophenes and pyrroles by treatment of the 1,4-dicarbonyl compound **95** with a source of sulfur or a primary amine.

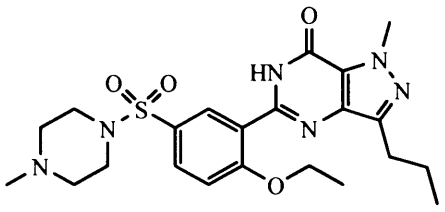
Route II shows the addition of water across the furan C-2/C-3 bond with the hydroxyl group this time adding in the β-position. This is followed by cleavage of the C-2/O-1 bond resulting in the γ-halo-β-hydroxycarbonyl system **99**. Disconnection then delivers the α-halocarbonyl **96**, and carbonyl compound **97**. The forward process is known as the Feist-Benary synthesis and involves an aldol-type reaction between the α-halocarbonyl **96** to the ketone **97** followed by ring-closure and dehydration.[66]

1.17 Rules for ring closure

Ring-forming reactions are common and important processes in organic chemistry due to the large variety of cyclic structures found in nature and also required in synthetic products. An example of this is the natural macrocyclic peptide, nostocyclamide **100**, which contains two thiazoles and one oxazole and is reported to have anti-viral and anti-tumor properties.[67] Viagra **101** is an example of a synthetic pharmaceutical containing multiple cyclic moieties, and is used to treat male erectile dysfunction and pulmonary arterial hypertension (Scheme **32**).[68]



100
Nostocyclamide



101
Viagra

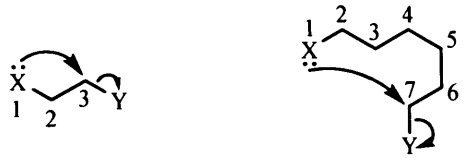
Scheme **32**

The relative ease of ring closing reactions was originally predicted on the basis of thermodynamics and kinetics. In 1976 Baldwin produced a series of papers introducing a set of

rules based on transition-state geometry to explain the relative ease of some ring closing reactions compared to the unfavourable nature of others.[69] These rules can be summarised as follows.

A systematic means for the description of the reaction taking place takes the form "A-B-C":

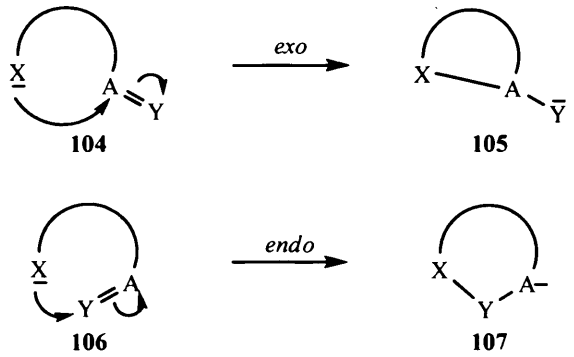
"A" is an integer and refers to the number of atoms contained within the newly formed ring. For the system to be a ring, the number can be no fewer than 3 (*e.g.* **102**), and the rules are shown to be congruous for rings containing up to 7 atoms (*e.g.* **103**) (Scheme **33**).



102 **103**

Scheme **33**

"B" is a term, either *exo* (*e.g.* **104**) or *endo* (*e.g.* **106**), which refers to the position of the bond being broken relative to the one being formed (Scheme **34**).

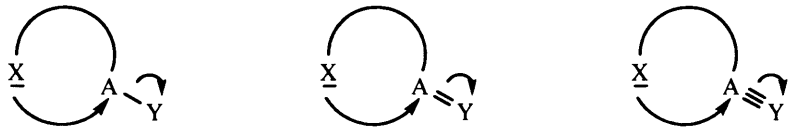


104 **105**

106 **107**

Scheme **34**

"C" describes the level of substitution of the elecrophilic atom at the point of attack. An sp^3 hybridised atom is referred to as being tetrahedral (tet) (*e.g.* **108**), an sp^2 atom as trigonal (trig) (*e.g.* **109**), and an sp atom as digonal (dig) (*e.g.* **110**) (Scheme **35**).



108 tet **109** trig **110** dig

Scheme **35**

The physical basis of the rules lies in the stereochemical requirements of the transition state and therefore describes the kinetic favourability of a reaction. In order to achieve cyclisation, a molecule must adopt a conformation that allows the overlap of appropriate orbitals. This therefore requires the nucleophile to attack the electrophilic centre at a particular angle. The required angle of attack for tetrahedral systems is 180°, for trigonal systems 109°, and for digonal systems 120°. These stereoelectronic requirements can cause some cyclisation reactions to proceed very slowly, and Baldwin's rules summarise these restrictions.

Tetrahedral systems

i.	3 to 7-*exo*-tet	favoured
ii.	5 to 6-*endo*-tet	disfavoured

Trigonal systems

i.	3 to 7-*exo*-trig	favoured
ii.	3 to 5-*endo*-trig	disfavoured
iii.	6 to 7-*endo*-trig	favoured

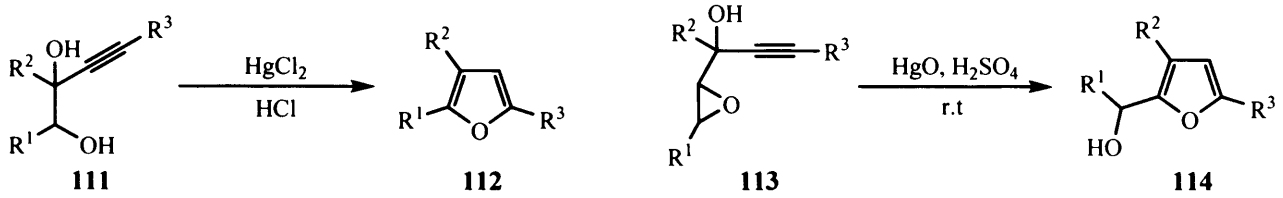
Digonal systems

i.	3 to 4-*exo*-dig	disfavoured
ii.	5 to 7-*exo*-dig	favoured
iii.	3 to 7-*endo*-dig	favoured

Baldwin's rules are only applicable when the internal nucleophile is a first row element. The described geometric constraints can generally be ignored for other elements due to their larger atomic radii and the availability of their *d* orbitals.

1.18 Catalytic synthesis of furans

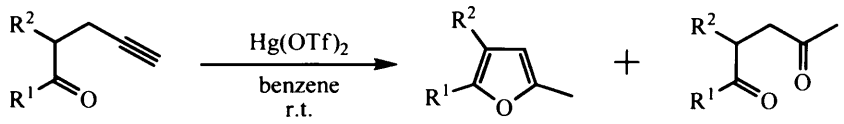
There are many examples in the literature of furan formation using catalytic amounts of transition metal salts. Some of the earliest examples used mercury salts, which allowed furan formation from 3-alkyne-1,2-diols **111**[70] and 1-alkynyl-2,3-epoxyalcohols **113** (Scheme **36**).[71]



111 **112** **113** **114**

Scheme **36**

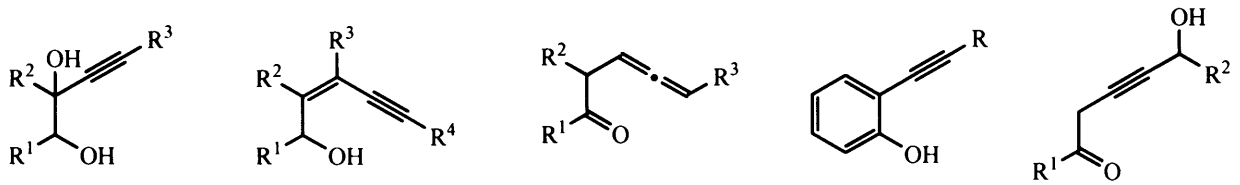
The most successful mercury-catalysed procedure is arguably that of Nishizawa, who showed that furans could be obtained from terminal alkyn-5-ones **115** under mild conditions.[72] The procedure often produces diones **117** as by-products and is not compatible with aldehydes or non-terminal alkynes (Scheme **37**). The reaction also requires the use of benzene as the solvent in order to obtain good yields.



115 **116** 70-100% **117**

Scheme **37**

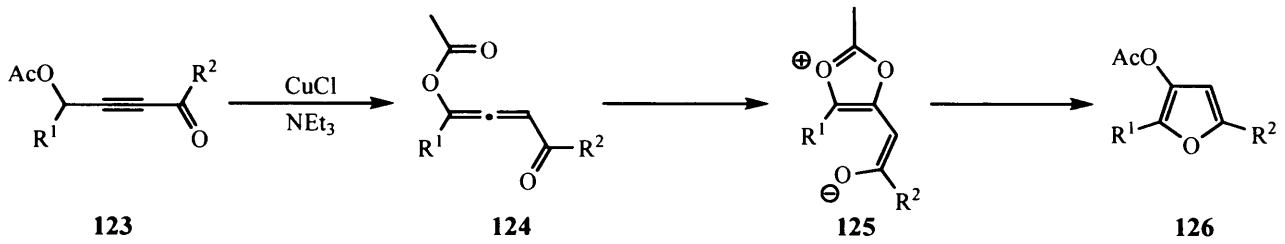
The toxicity of mercury and its salts makes their use undesirable,[73] and so in the mid-1980s palladium became the metal of choice for the catalytic synthesis of furans. It has since been shown that 3-alkyne-1,2-diols **118**,[74] (*Z*)-2-en-4-yn-2-ols **119**,[75] allenyl ketones **120**,[76] *O*-alkynylphenols **121**[77] and alkynones **122**[78] all produce furans upon exposure to palladium catalysts (Scheme **38**). These reactions often give excellent yields, exhibit low toxicity and allow for the use of a broad range of substituents. They do however suffer from extended reaction times, elevated temperatures and variable yields.



118 119 120 121 122

Scheme **38**

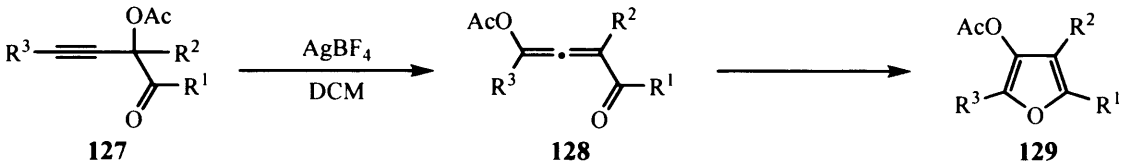
Gevorgyan has shown that tri- and tetrasubstituted furans **126** can be made from α-acyloxyalkynones **123** by exposure to copper(I) chloride.[79] The mechanism proposed by Gevorgyan involves a base-assisted isomeration to allenes **124** followed by an intramolecular nucleophillic attack to form zwitterions **125**, which are converted into furans **126** by an intramolecular Ad_N-E process (Scheme **39**).



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

Scheme **39**

Gevorgyan has also shown that tetrasubstituted furans **129** can be made from α-acyloxy-β-ketoalkynes **127** by exposure to catalytic silver tetrafluoroborate *via* a [3,3]-shift, 1,2-migration and cyclo-isomeration sequence (Scheme **40**).[79]



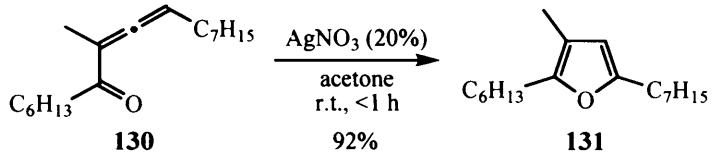
127 **128** **129**

Scheme **40**

1.19 Silver catalysed synthesis of furans

Allenones **130** have been successfully converted into furans by silver-catalysed cyclisations. Much of the work in this area was carried out by Marshall, who in 1990 described the cyclisation of α-allenones **130** to furans **131** with silver nitrate or silver tetrafluoroborate in acetonitrile at 100 °C.[80] It was later shown that the cyclisation could be achieved under less harsh conditions by using a mixture of silver nitrate and calcium carbonate in acetone and water at room

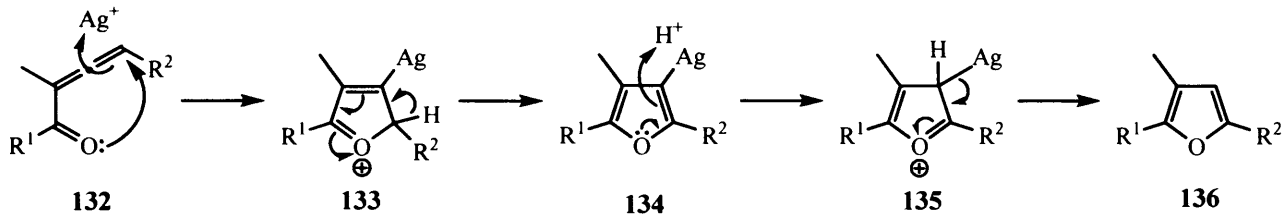
temperature.[81] Marshall went on to optimise the conditions and showed that the transformation of α-allenone **130** to furan **131** can be effected by catalytic silver nitrate in acetone at room temperature with reaction times of under one hour (Scheme **41**).[82]



130 92% **131**

Scheme **41**

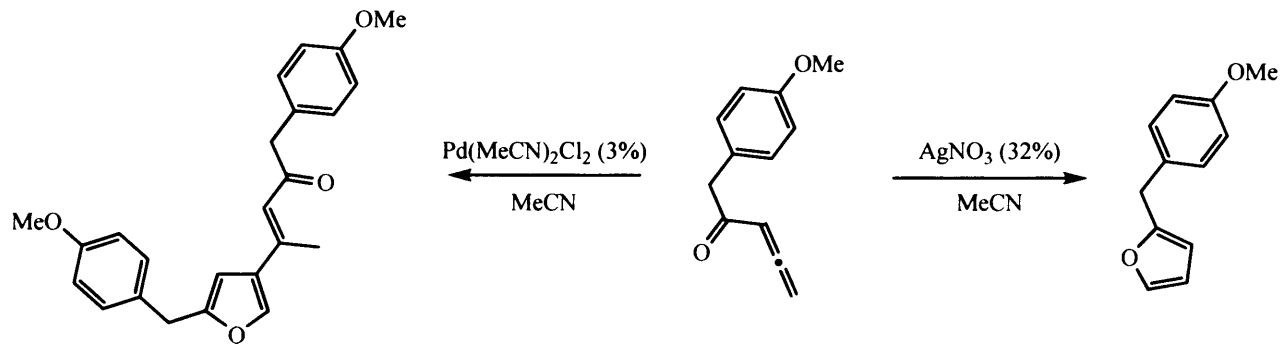
Deuterium labeling experiments carried out on allenone **132** led Marshall to suggest that the mechanism proceeded by Ag^+/H^+ exchange on silver derivative **134** (Scheme **42**).[82]



132 **133** **134** **135** **136**

Scheme **42**

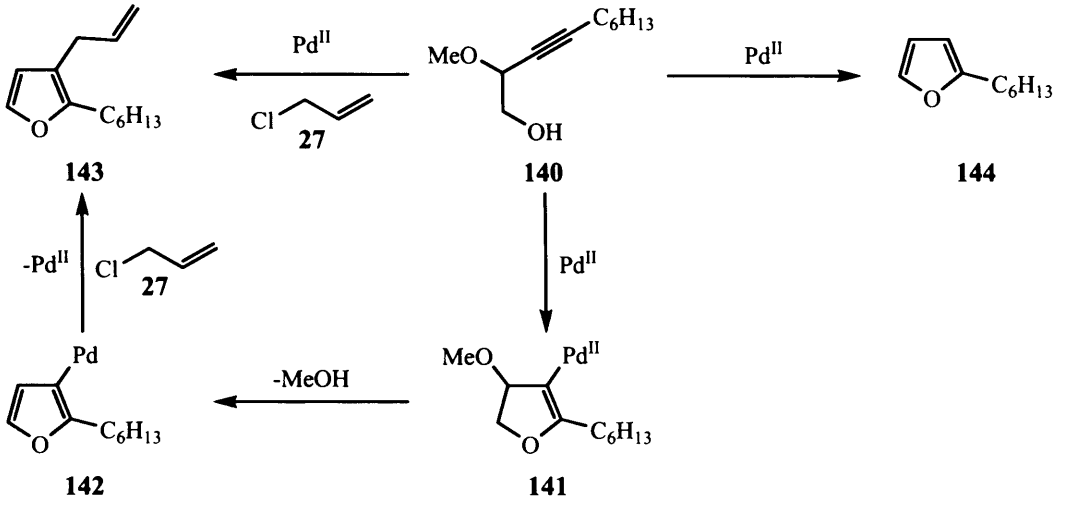
Hashmi compared the silver- and palladium-catalysed cyclisations of α-allenones **137**.[83] Although both reactions were presumed to give the corresponding π-complex intermediates, silver nitrate gave exclusively furans, *e.g.* furan **138**, in good yield whereas palladium(II) mainly afforded dimeric products, *e.g.* furan **139**, resulting from cyclisation and carbometalation (Scheme **43**).



139 72% **137** **138** 89%

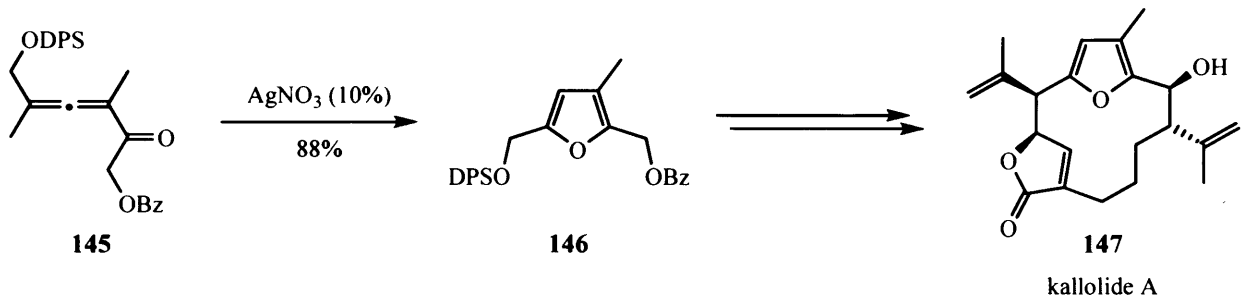
Scheme **43**

Although this carbometallation product is not always desirable, Utimoto has shown that the reaction of the intermediary organopalladium species **142** can be controlled.[74] If 2-methoxy-3-alkyne-1-ol **140** is exposed to palladium(II) in the presence of excess allyl chloride **27**, a one-pot cyclisation and cross-coupling can be carried out to form furan **143** (Scheme **44**).



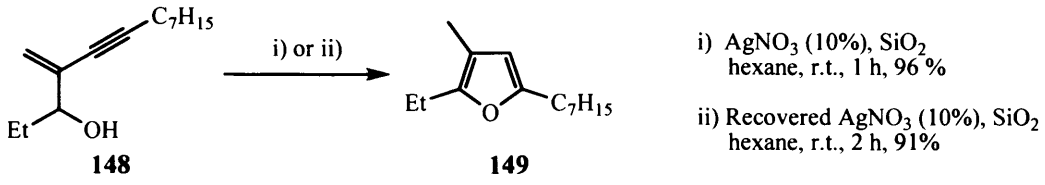
Scheme **44**

The silver-catalysed cyclisation of α-allenones **145** has been successfully applied to the total synthesis of natural products, an example being Marshall's total synthesis of kalloide A **147** (Scheme **45**).[84]



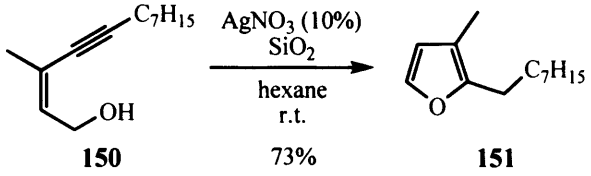
Scheme **45**

By 1995 Marshall had shown that commercially available 10% silver nitrate on silica gel[85] could be used as a heterogeneous catalyst that could be recovered and reused.[86] This was exemplified by the conversion of β-alkynyl allylic alcohol **148** to furan **149** upon exposure to the catalyst in hexane at room temperature with a short reaction time and in excellent yield. A second run on the same scale with the recovered silver nitrate on silica gel required a slightly longer reaction time, but still gave an excellent yield (Scheme **46**).



Scheme **46**

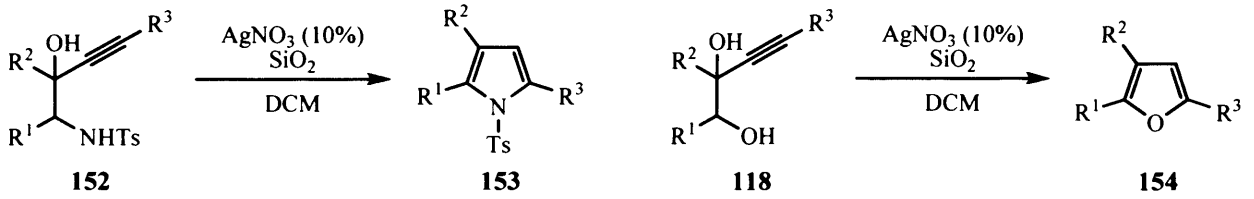
The procedure was also shown to work for γ-alkynyl allylic alcohols **150** (Scheme **47**).[86]



Scheme **47**

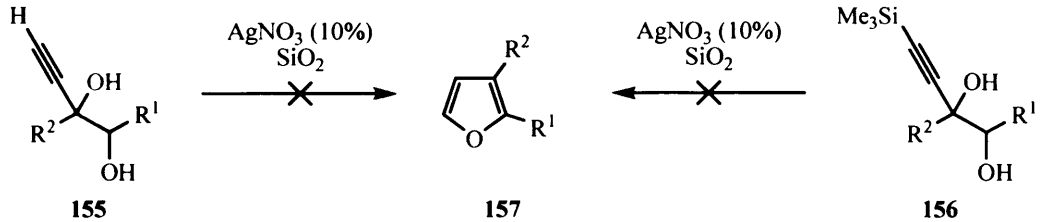
1.20 Silver catalysed cyclisation of 3-alkyne-1,2-diols

Much work has been carried out within the Knight group on silver-catalysed heterocycle formation. Sharland has shown that pyrroles **153** can be formed in excellent yields from 3-alkyne-2-hydroxy-1-sulfonamides **152** by exposure to 10% silver nitrate on silica gel in subdued light.[87] Menzies then went on to show that this methodology was compatible with 3-alkyne-1,2-diols **118** for the synthesis of furans **154** (Scheme **48**).[88,89]



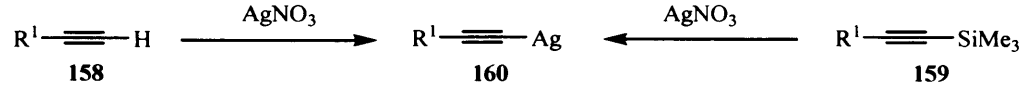
Scheme **48**

There are several limitations to the methodology. The most serious is the complete failure of 1-alkyne-3,4-diols **155**, or the corresponding trimethylsilylated alkynes **156**, to undergo cyclisation (Scheme **49**).



Scheme **49**

This is thought to be due to the ease with which silver acetylides **160** are produced from alkynes[90] **158** and silylated alkynes **159** (Scheme **50**).[91]

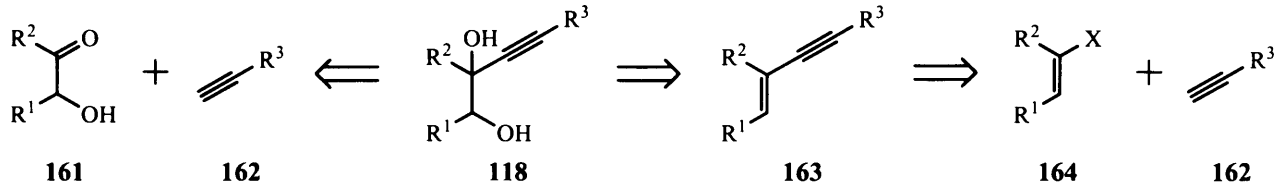


158 **160** **159**

Scheme **50**

The method also appears to be incompatible with the presence of divalent sulfur, resulting in decomposition of the starting material. An extensive search of the literature did not reveal any examples of the silver-catalysed formation of sulfur-containing heterocycles. It is considered that the sulfur-silver interaction is too strong to allow for the interaction of the sulfur atom and the unsaturated C-C bond, meaning that no cyclisation can occur.[92]

The 3-alkyne-1,2-diol precursors **118** are highly accessible and easy to obtain from a number of precursors. Two routes have generally been used for their synthesis:[93] the condensation of acetylenes **162** and α-hydroxy-ketones **161**[94] and the regiospecific dihydroxylation of conjugated enynes **163**,[95] which are themselves available by Sonogashira coupling of alkenyl halides **164** with acetylenes **162** (Scheme **51**).[96] These routes therefore provide ample opportunity for the successful creation of the required 3-alkyne-1,2-diol system **118**.

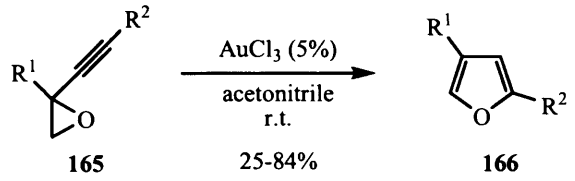


161 **162** **118** **163** **164** **162**

Scheme **51**

1.21 Gold catalysed synthesis of furans

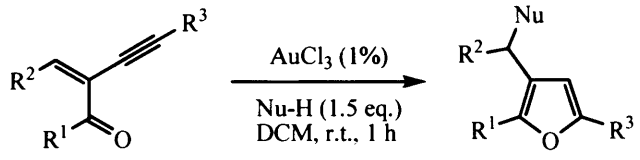
Gold(III) salts and gold(I) complexes have recently been shown to be excellent catalysts for the synthesis of furans. In 2004 Hashmi reported that alkynyl epoxides **165** could be converted into disubstituted furans **166** by exposure to gold(III) chloride in moderate to high yields (Scheme **52**).[97] These reactions highlighted the strength of gold-catalysed cyclisations for the synthesis of furans as they used low catalyst loading, mild conditions and tolerated a range of functional groups.



165 166

Scheme **52**

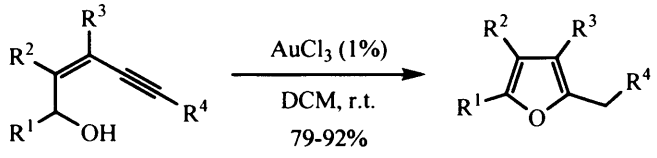
Larock then reported the gold(III) chloride catalysed synthesis of trisubstituted furans **168** from the reaction of 2-(1-alkynyl)-2-alken-1-ones **167** and various nucleophiles under very mild reaction conditions in good to excellent yields (Scheme **53**).[98] Methanol was typically employed as the nucleophile, but primary alcohols and tertiary amines were also shown to be effective.



167 168

Scheme **53**

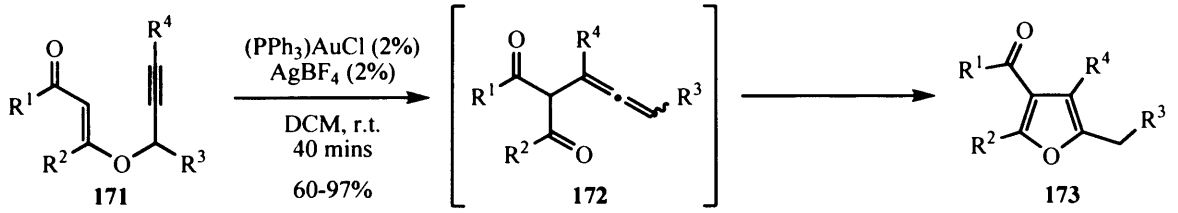
In 2005 Liu showed that tetrasubstituted furans **170** could be formed by the exposure of (*Z*)-enynols **169** to gold(III) chloride under neutral conditions at room temperature (Scheme **54**).[99]



169 170

Scheme **54**

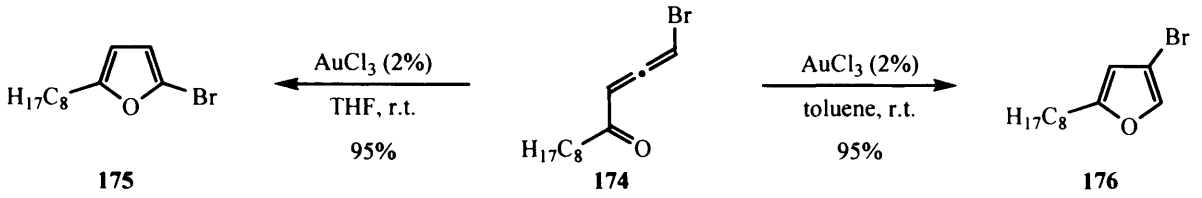
In 2005 Kirsch reported a fascinating set of reactions in which propargyl vinyl ethers **171** underwent Saucy-Marbet type rearrangement[33] and heterocyclisation to form tetrasubstituted furans **173** (Scheme **55**).[100] The reaction did not proceed in the presence of gold(I) chloride or silver tetraborofluorate alone, but when the two catalysts were combined, yields of up to 97% were obtained.



171 172 173

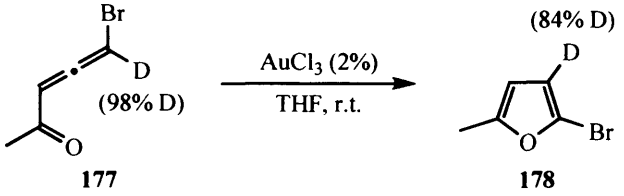
Scheme **55**

The synthetic potential of gold as a catalyst for the synthesis of furans took a major step forward when Gevorgyan reported that it could be used for the synthesis of halofurans.[101] By varying the solvent, Gevorgyan showed that bromoallenyl ketone **174** could be selectively converted into either α-bromofuran **175** or β-bromofuran **176** upon exposure to gold(III) chloride (Scheme **56**).



Scheme **56**

Using deuterium labelling Gevorgyan showed evidence strongly suggesting that the formation of α-bromofuran **178** proceeded *via* a 1,2-hydride shift (Scheme **57**).

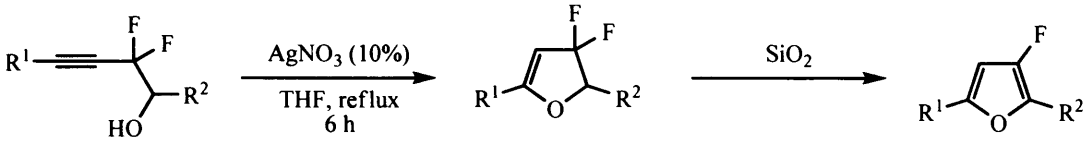


Scheme **57**

The reaction was compatible with both iodine and chlorine as the halo-substituent, and could tolerate a range of functional groups. The reaction was also shown to be able to produce tetrasubstituted β-halofurans.

1.22 Propargylic substituent

While the cyclisation of 3-alkyne-1-ols using gold(I) or gold(III) complexes is well known,[102] these catalysts do not give satisfactory results for the conversion of *gem*-difluorohomopropargyl alcohols **179** to 3,3-difluoro-4,5-dihydrofurans **180**.[103] This was reasoned to be due to the inability of the gold cation to interact sufficiently with the electronically deficient triple bond. After screening a range of transition metals, Hammond found that silver nitrate was the best catalyst for this transformation. Of particular interest was the observation that upon exposure to silica gel, dihydrofurans **180** were converted into fluorofurans **181** (Scheme **58**).

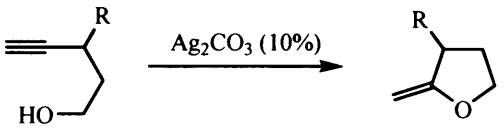


179 **180** **181**

20-79%

Scheme **58**

Further investigation into the effect of the propargylic substituents was carried out by Pale,[104] who showed that an oxygen atom was required in the propargylic position of 4-alkyne-1-ols **182** in order for their cyclisation to be catalysed by silver carbonate (Scheme **59**).



182 **183**

R = H, 6 h, 0%
R = OH, 1 h, 99%
R = OMe, 2.5 h, 99%
R = OTBDPS, 24 h, 99%
R = OAc, 6 h, 0%

Scheme **59**

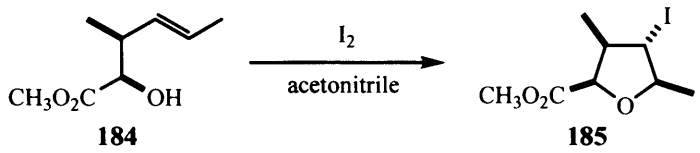
The results showed that the reaction only proceeded when a propargylic oxygen was present. It could also be seen that the reaction took longer to reach completion as the steric bulk of the propargylic alcohol protecting group was increased. The only reported exception to this was the failure of the reaction when the propargylic oxygen was protected by an acetate group. Pale ascribed the failure of this reaction to the electron withdrawing nature of the acetate group, supposing that it impoverished the electron density of the oxygen and precluded its complexation with the silver ion.

1.23 Iodocyclisation

Reactions performed using iodine electrophiles have been known for a long time, with Bougault describing the first iodolactonisation over a century ago.[105] Molecular iodine is an inexpensive, non-toxic and readily available reagent and has been used to affect iodocyclisations for the formation of heterocyclic compounds.[106]

1.24 Iodocyclisation to form tetrahydrofurans

The first reported iodoetherification was an isolated example by Bartlett who showed homoallylic alcohol **184** could be converted into tetrahydrofuran **185** upon exposure to iodine in acetonitrile (Scheme **60**).[107]



184 185

Scheme **60**

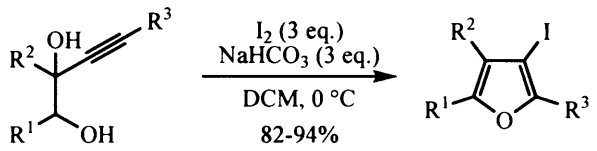
Since this discovery, much work has been carried out within the Knight group on iodine-promoted 5-*endo*-trig cyclisations to form tetrahydrofurans. It has been shown that a crucial feature of these cyclisations is the use of anhydrous acetonitrile as solvent.[108] Furthermore it has been shown that this type of cyclisation can be used to prepare a variety of tetrasubstituted tetrahydrofurans **187** and **189** in a highly stereocontrolled manner from homoallylic alcohols **186** and **188** respectively (Scheme **61**).[109]

186 187 188 189

Scheme **61**

1.25 Iodocyclisation to form furans

A breakthrough moment came when the Knight group reported that 3-alkyne-1,2-diols **118** successfully undergo iodine-promoted 5-*endo*-dig cyclisations followed by dehydration to give β-iodofurans **190** in good to excellent yields.[95] Since then the conditions have been optimised and the formation of highly-substituted β-iodofurans **190** can be effected in dichloromethane using three equivalents of iodine and three equivalents of sodium hydrogen carbonate at 0 °C (Scheme **62**).[94]



118 190

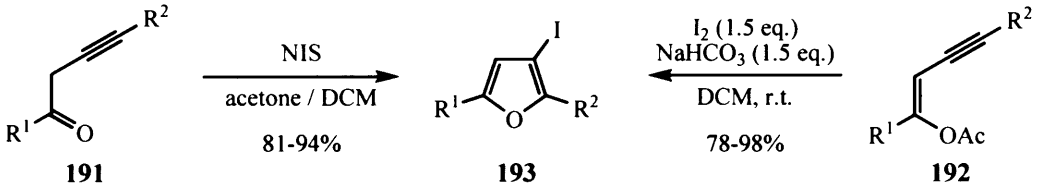
Scheme **62**

Although very successful, the procedure suffers from the requirement of an excess of iodine. This requirement has still not been fully explained, but it has been suggested that it could be due to the involvement of a polyiodine species in the reaction.[110]

The β-iodofuran products are highly amenable to subsequent homologation using a wide range of metallation reactions. Halogen substituents have long occupied a special position in organic chemistry due to their ability to undergo regioselective metallation using halogen-metal exchange.[111] The status of halogen-aryl bonds has more recently been enhanced by the development of a host of predominantly palladium-catalysed coupling methods.[112]

In general the reactivity of furans dictates that α-halo derivatives are usually readily available, while the preparation of β-halo isomers has to rely on suitably powerful directing effects from existing α-substituents.[113] The synthesis of β-iodofurans under mild conditions is therefore a highly valuable transformation.[101]

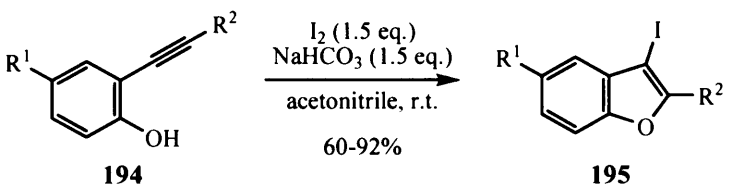
Since the iodocyclisation procedure was disclosed by the Knight group, two other processes have been reported for the synthesis of 2,5-disubstituted 3-iodofurans **193**. The earlier of these was by Dembinski who in 2005 showed that but-3-yn-1-ones **191** could be converted into trisubstituted iodofurans **193** upon exposure to *N*-iodosuccinimide in acetone or dichloromethane.[114] Jiang very recently reported that trisubstituted β-iodofurans **193** can also be made from conjugated enyne acetates **192** by exposure to 1.5 equivalents of iodine and sodium hydrogen carbonate in dichloromethane at room temperature for 8 hours (Scheme **63**).[115]



191 **193** **192**

Scheme **63**

Arcadi has reported an iodocyclisation which yields tetrasubstituted furans, and is an excellent proceedure for the synthesis of 2-substituted-3-iodobenzo[*b*]furans **195** from *o*-alkynylphenols **194** (Scheme **64**).[116]



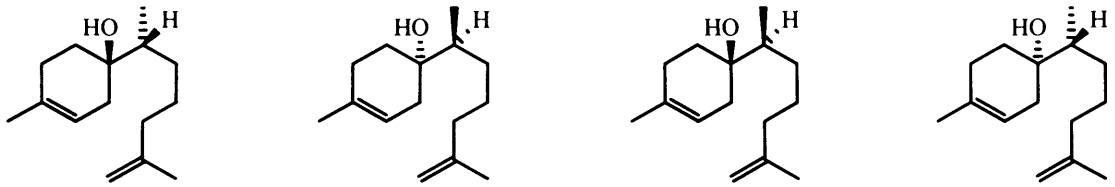
194 **195**

Scheme **64**

Chapter 2: Furan Fragrance Analogues

2.1 Furan fragrance analogues

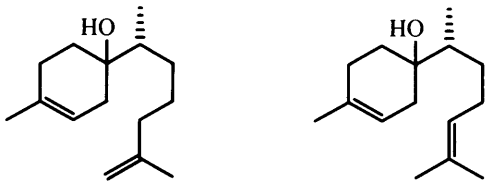
The development of new fragrance ingredients is a difficult challenge due the number and complexity of the receptors in the olfactory system (*cf.* p3). As olfactory receptors are chiral, stereochemistry can affect the odour of a compound, as is demonstrated in the story of iso-β-bisabolol. Iso-β-bisabolol occurs at a concentration of less than 0.001% in both East Indian and West Australian sandalwood oils and possesses a *strong floral muguet-like* odour. As mentioned previously (*cf.* p5), by the synthesis and separation of each enantiomer of iso-β-bisabolol **10**, **11**, **12**, and **13**, Braun revealed that it was only enantiomer **10** that possessed the characteristic odour, with the other stereoisomers being odourless (Scheme **65**).[22]



10 muguet odour | **11** odourless | **12** odourless | **13** odourless

Scheme **65**

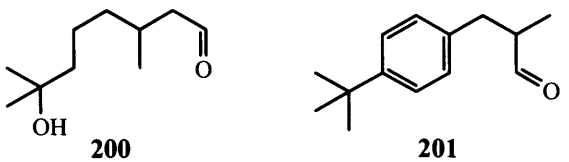
The phenomenon of a slight structural change affecting the odour of a compound is quite common in the field of fragrance. It is interesting to compare the odour properties and structures of iso-β-bisabolol **198** with β-bisabolol **199**, which is also found in sandalwood oil. Changing the position of just one double-bond converts an odorant into an odourless molecule (Scheme **66**).[22]



198 iso-β-bisabolol muguet odour | **199** β-bisabolol odourless

Scheme **66**

There are conversely many examples of very different compounds that have similar odours. Hydroxycitronellal **200** and lilial **201** are examples of compounds that share only a vague similarity in the size and shape of the hydrocarbon region, but both have a similar *white floral* odour (Scheme **67**).[4]

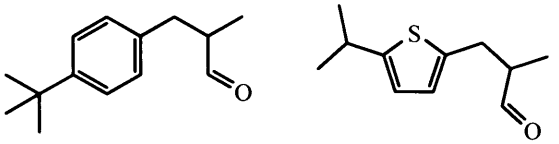


200
hydroxycitronellal
white floral odour

201
lilial
white floral odour

Scheme **67**

The design of new fragrance compounds is therefore made difficult by the unpredictable nature of the relationship between structure and odour. Once a compound with the desired odour properties has been discovered, either by analysis of a natural product or by serendipitous general screening, it is normal practice to prepare a range of analogues. The reasons for this are twofold: first, materials with better odour characteristics than their parent compound can be identified, and second, information about the structural requirements for the desired odour characteristics can be acquired.[4] One particularity interesting and relevant example of a successful fragrance analogue is lioral **202**. Lioral **202**, which contains a thiophene moiety, is a heterocyclic analogue of lilial **201**, but both have a *muguet-like* odour (Scheme **68**).[117]



201
lilial
white floral odour

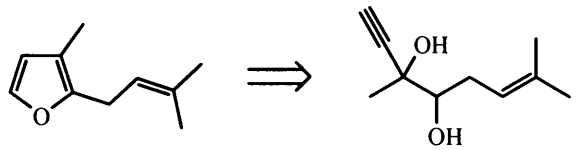
202
lioral
muguet odour

Scheme **68**

These concepts were used to design a range of furan-containing analogues of known fragrance compounds.

2.2 Rosefuran

The present project began with an attempt to synthesise a close homologue of rosefuran **78**. At the current time, the silver cyclisation methodology is not expected to facilitate the synthesis of 3-methyl-2-(3-methylbut-2-enyl)furan (rosefuran) **78** itself, which has the odour descriptors *caramel*, *green* and *minty* (Scheme **69**).[42]

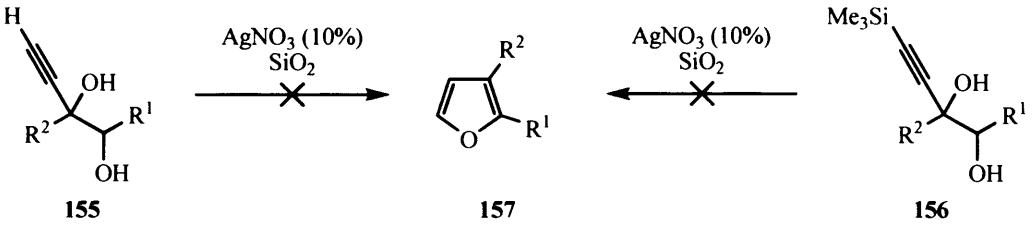


78
rosefuran

203

Scheme **69**

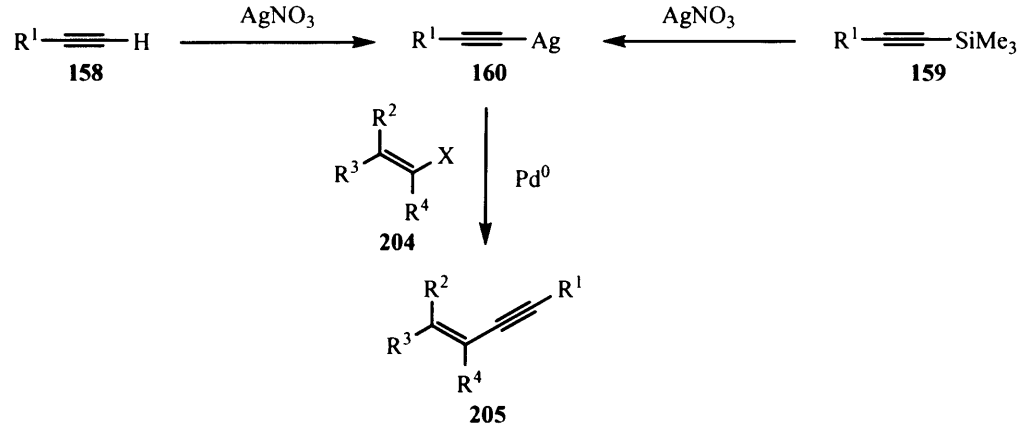
This is due to the failure of the silver cyclisation methodology to produce 2,3-disubstitued furans **157** from either 1-alkyne-2,3-diols **155**, or the corresponding trimethylsilylated alkynes **156** (Scheme **70**) (*cf.* p27).[89]



155 **157** **156**

Scheme **70**

This is thought to be due to the ease in which silver acetylides **160** are produced from alkynes **158**[90] and silylated alkynes **159**.[91] The salts **160** have been shown to undergo palladium-catalysed cross-coupling reactions with vinyl triflates and aryl iodides (Scheme **71**).[118]



158 **160** **159**

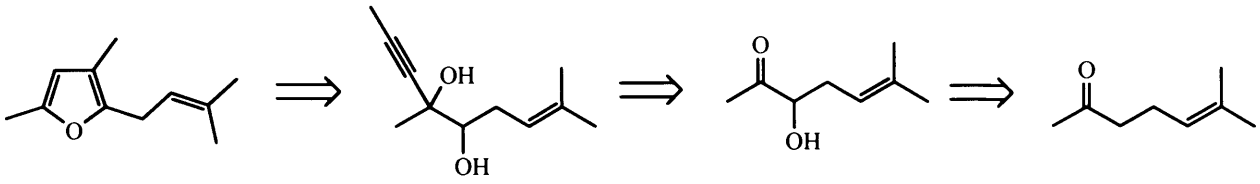
204

205

Scheme **71**

The silver cyclisation methodology should however lend itself to the synthesis of tri-subsituted rosefuran analogue, furan **206** (Scheme **72**). Disconnection of furan **206** therefore leads back to 3-alkyne-1,2-diol **207**, which was hoped to be accessible from ketone **208** by addition of the

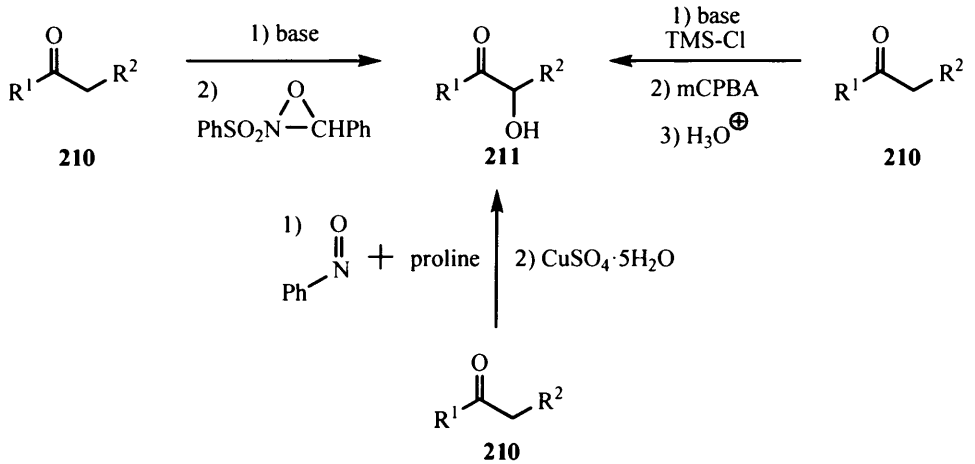
appropriate alkyne. The α-hydroxylation of commercially available 6-methyl-5-hepten-2-one **209** should therefore be a suitable point to start the synthesis.



206 **207** **208** **209**

Scheme **72**

The α-hydroxy carbonyl functionality represents a significant building block in organic synthesis[119] and its importance is reflected in the extensive synthetic research directed towards introducing this group. Noteworthy contributions include the α-oxygenation of enolates with electrophilic oxidising agents[120] and the dihydroxylation or epoxidation of preformed enol ethers.[121,122] More recently there have been major advances in this area which allow the aminooxylation of ketones which can then be exposed to reductive conditions to unmask the hydroxyl functionality (Scheme **73**).[123]

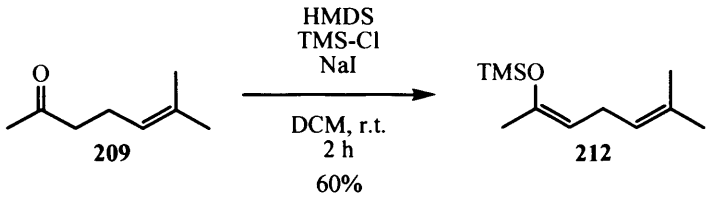


210 **211** **210**

210

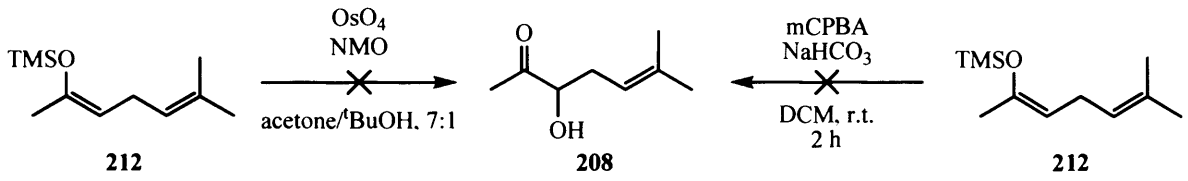
Scheme **73**

A study by Miller has shown that the thermodynamically more stable silyl enol ether can be obtained from ketones when they are exposed to iodotrimethylsilane and hexmethyldisilazane at 25 °C for 2–10 hours.[124] Silyl enol ether **212** was produced from 6-methyl-5-hepten-2-one **209** in moderate yield using this methodology, with iodotrimethylsilane being formed *in situ* by the reaction of chlorotrimethylsilane with catalytic sodium iodide (Scheme **74**).



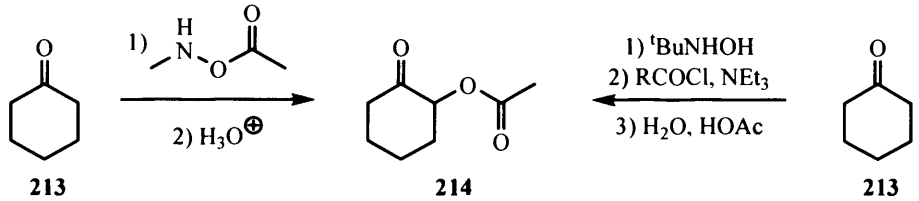
Scheme **74**

Work by McCormick showed a direct literature precedent for the conversion of silyl enol ether **212** into alcohol **208** using 2% osmium tetroxide and one equivalent of 4-methylmorpholine *N*-oxide in a mixture of acetone and *tert*-butanol.[122] During the present project, both this method and an attempted Rubottom oxidation using 3-chloroperoxybenzoic acid[121] failed to produce the desired alcohol **208** (Scheme **75**). It was considered that over-oxidation due to the presence of another double bond may have resulted in these failures. This theory was not supported by McCormick's work which showed that the methodology had been tested for its compatibility with other olefinic functionalities, and no such problems had been reported.



Scheme **75**

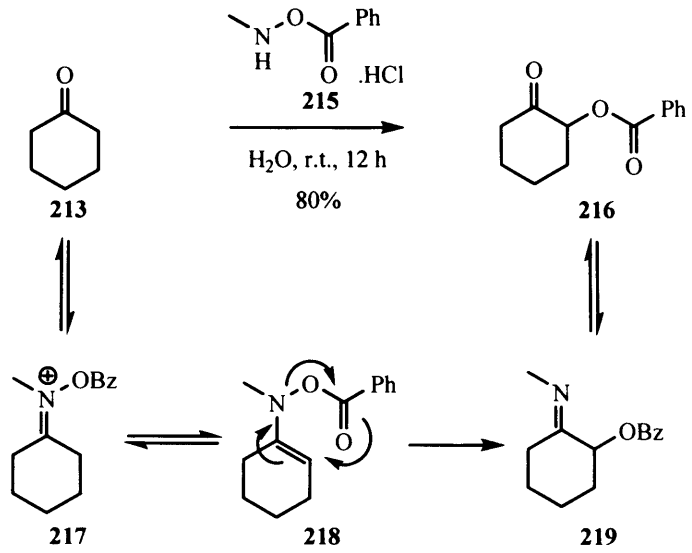
Another review of the literature revealed a recent paper by the Tomkinson group, who were based in Cardiff University, which reported a series of *N*-methyl-*O*-acylhydroxylamines that can be used for the effective α-acyloxylation of both aldehydes and ketones.[125] The groups' work originated from investigations by House[126] and Coates[127] on the conversion of cyclohexanone **213** into 2-acetoxycyclohexanone **214** (Scheme **76**).



Scheme **76**

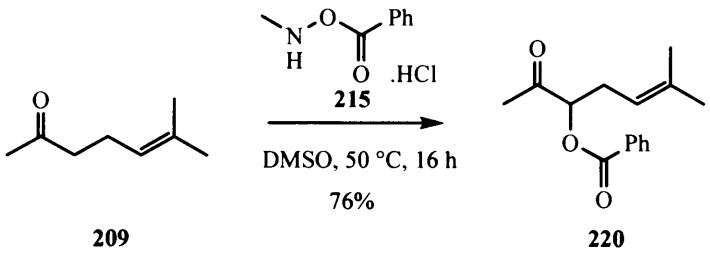
The Tomkinson group had previously described a direct method for the chemospecific α-functionalisation of aldehydes using *N*-*tert*-butyl-*O*-benzoylhydroxylamine hydrochloride.[128]

As the reagent was ineffective for the analogous transformations with ketones, the less stericially hindered *N*-methyl-*O*-benzoylhydroxylamine hydrochloride **215** was developed and shown to be effective for the α-benzoyloxylation of both aldehydes and ketones. Tomkinson supported the proposition of both House and Coates that the reaction occurred by a [3,3]-sigmatropic rearrangement (Scheme **77**).



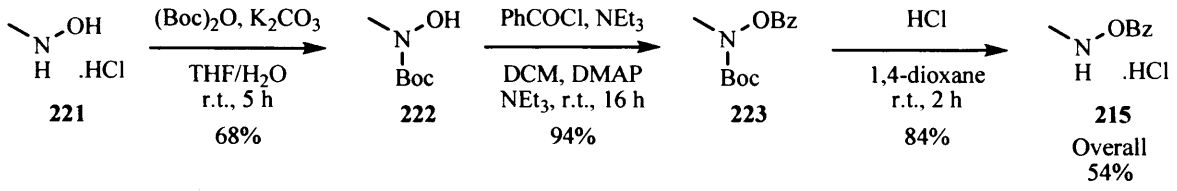
Scheme **77**

A sample of salt **215** was obtained directly from the Tomkinson group. At this point the synthesis of furan **206** was commenced with the reaction of 6-methyl-5-hepten-2-one **209** with salt **215** to yield ester **220** in 76% yield (Scheme **78**).



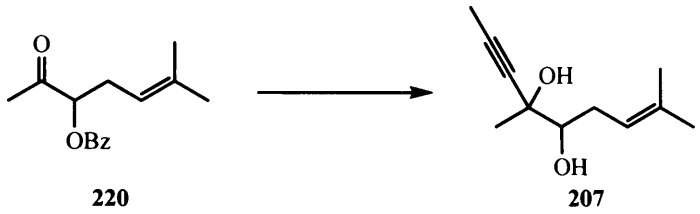
Scheme **78**

Due to the success of the α-benzoyloxylation, salt **215** was made as described in Tomkinson's paper. Protection of commercially available *N*-methylhydroxylamine hydrochloride **221** as the *N*-*tert*-butylcarbamate **222** was followed by acylation using benzoyl chloride to give hydroxylamine **223**. Removal of the protecting group by HCl in dioxane gave the desired salt **215** in 54% overall yield (88% in literature) (Scheme **79**).



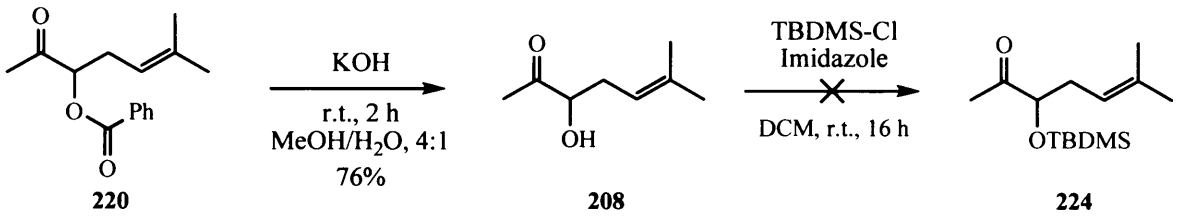
Scheme **79**

The next issue to be addressed was the conversion of benzoyl protected α-hydroxyketone **220** into 3-alkyne-1,2-diol **207** (Scheme **80**).



Scheme **80**

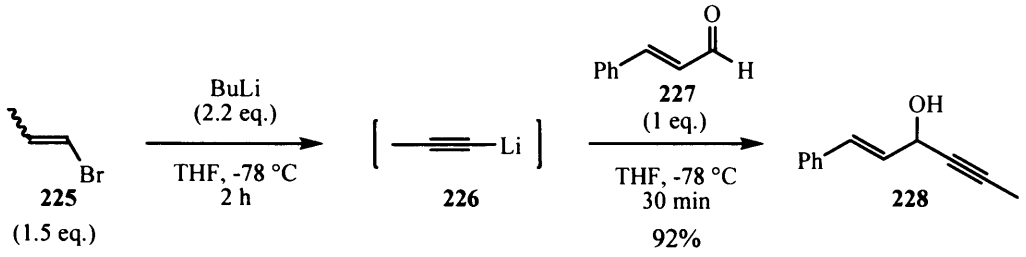
Although the ketone carbonyl of ketone **220** should be more electrophilic than that of the benzoyl ester, concerns over the selectivity of attack by an alkynyl anion lead to the idea of changing the protecting group. Deprotection of ketone **220** using potassium hydroxide in wet methanol successfully gave alcohol **208**. Protection of the secondary alcohol by *tert*-butyldimethylsilyl chloride proved unsuccessful, returning the starting alcohol **208** (Scheme **81**).



Scheme **81**

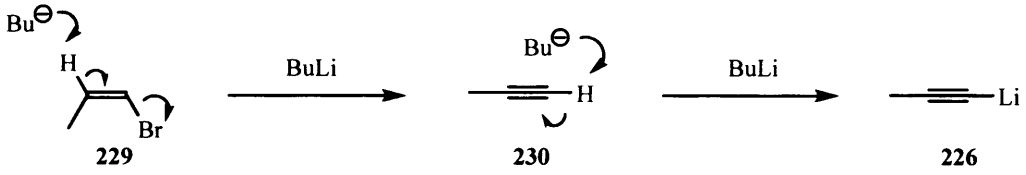
The selective addition of lithiated propyne to the ketone carbonyl of ketone **220** was therefore reconsidered. The use of 1-propynyllithium **226** in the synthesis of organic compounds has been extensive,[129] with one common method of its production being the lithiation of propyne gas with butyllithium.[130] Propyne is relatively expensive and its low boiling point can cause problems with handling.[85] Due to these concerns, Suffert developed a procedure for the generation of 1-propynyllithium **226** from the inexpensive and commercially available starting material (*E/Z*)-1-bromopropene **225** by exposure to butyllithium in anhydrous tetrahydrofuran.[131] Suffert

went on to exemplify the effectiveness of the *in situ* formation of 1-propynyllithium **226** by its reaction with *trans*-cinnamaldehyde **227**, to form alkyne **228** in 92% yield (Scheme **82**).



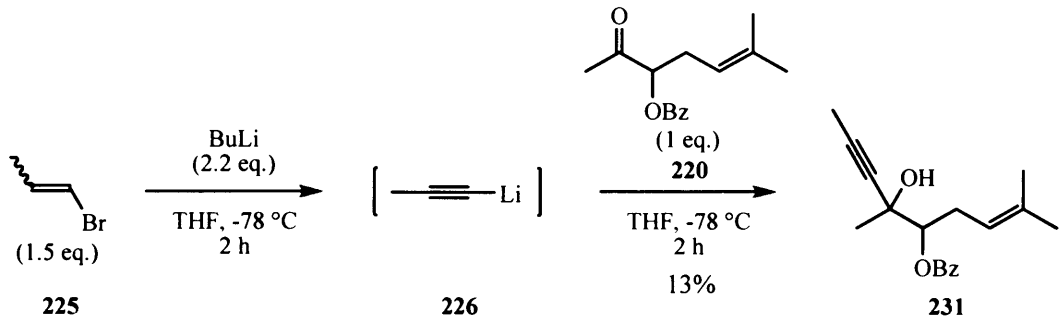
Scheme **82**

It is postulated that the mechanism for the formation of 1-propynyllithium **226** from (*E/Z*)-1-bromopropene **229** is the E_2 elimination of hydrogen bromide, followed by the deprotonation of solvated propyne **230** (Scheme **83**).



Scheme **83**

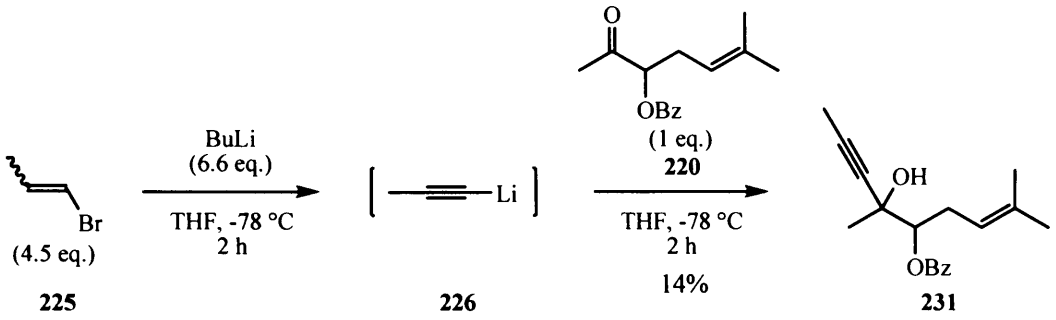
Suffert's success was not matched on ketone **220**, with the methodology giving only a 13% yield of alkyne **231**, returning mostly unreacted starting material (Scheme **84**). It was of interest that no 3-alkyn-1,2-diol **207** was detected by ^{1}H NMR analysis.



Scheme **84**

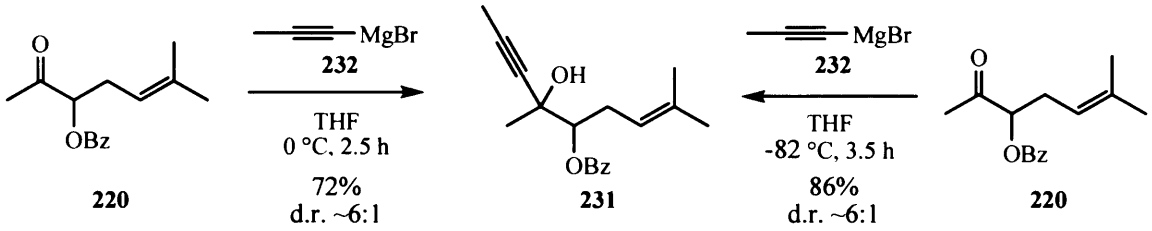
In an attempt to improve the yield, the number of equivalents of (*E/Z*)-1-bromopropene **225** and butyllithium as compared to the number of equivalents of ketone **220** was increased threefold.

This proved equally unsuccessful, giving only a 14% yield of alkyne **231** (Scheme **85**). ^{1}H NMR analysis again revealed that no 3-alkyn-1,2-diol **207** had been formed.



Scheme **85**

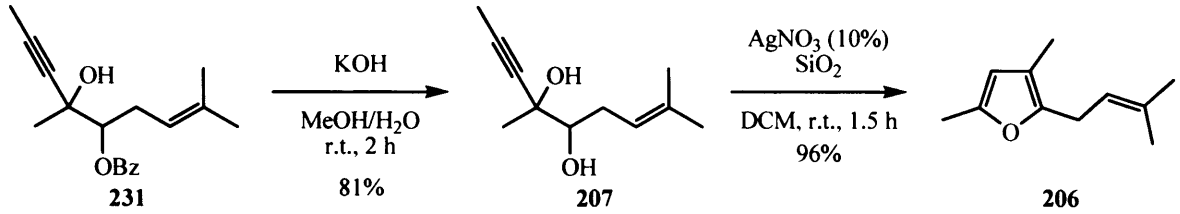
This method of *in situ* 1-propynyllithium **226** formation was abandoned and a bottle of commerical 1-propynylmagnesium bromide **232** in tetrahydrofuran was purchased. Although the formation 3-alkyne-1,2-diol **207** was required for the synthesis, it was considered of interest to see if the ketone carbonyl could be selectively reacted in the presence of the benzoyl protecting group. One equivalent of commerical 1-propynylmagnesium bromide **232** was added to ketone **220** at both 0 °C and –82 °C and left at the stated temperatures until TLC analysis showed no presence of ketone **220**, which took 2.5 hours and 3.5 hours respectively. Yields of 72% and 86% of alkyne **231** were obtained respectively, with both reactions giving an approximately 6:1 diasteromeric ratio (Scheme **86**). The yield cannot be conclusively linked to chemoselectivity of the ketone over the ester as no 3-alkyne-1,2-diol **207** was isolated from either reaction. It is considered that deprotonation to form an enolate should also be faster at higher temperatures and that this may therefore account for the difference in yield. The reactions were not repeated to confirm the accuracy of the yields, leaving the possibility of experimental error open as a cause of the discrepancy.



Scheme **86**

The deprotection of alkyne **231** by treatment with potassium hydroxide in methanol/water gave 3-alkyne-1,2-diol **207** in 81% yield, which went on to cyclise upon exposure to the standard

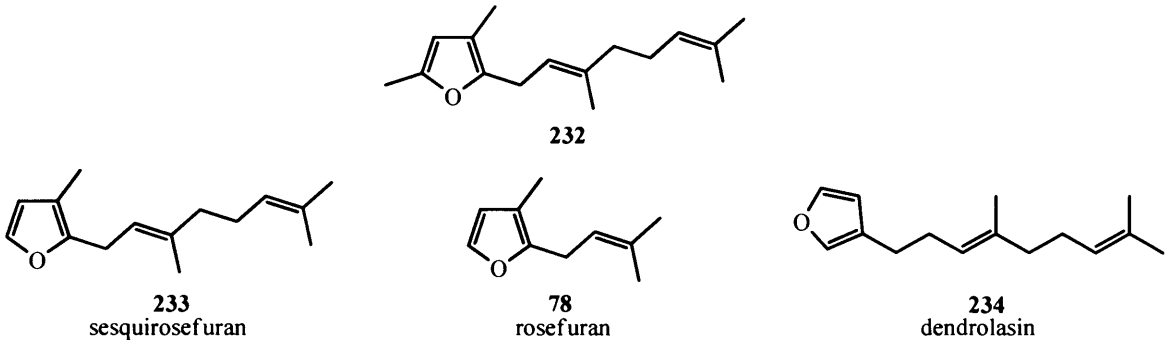
silver cyclisation conditions to give furan **206** in 96% yield (Scheme **87**). The smell of furan **206** was not considered particularly strong by members of the laboratory, but in my opinion it had a sweet and pleasant smell. Furan **206** turned from a colourless liquid to an orange oil after storage at –20 °C under nitrogen atmosphere for one week and so was not accepted for analysis by an "expert nose" when the opportunity arose.



Scheme **87**

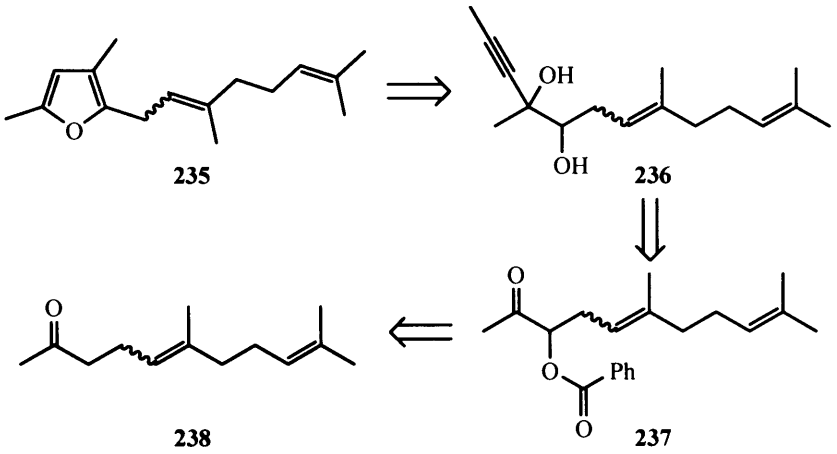
2.3 Sesquirosefuran

The successful synthesis of furan **206** lead to the idea of creating furan **232** (Scheme **88**). Furan **232** is the methyl analogue of sesquirosefuran **233** which is reminiscent in structure to both rosefuran **79** and dendrolasine **234**.[132]



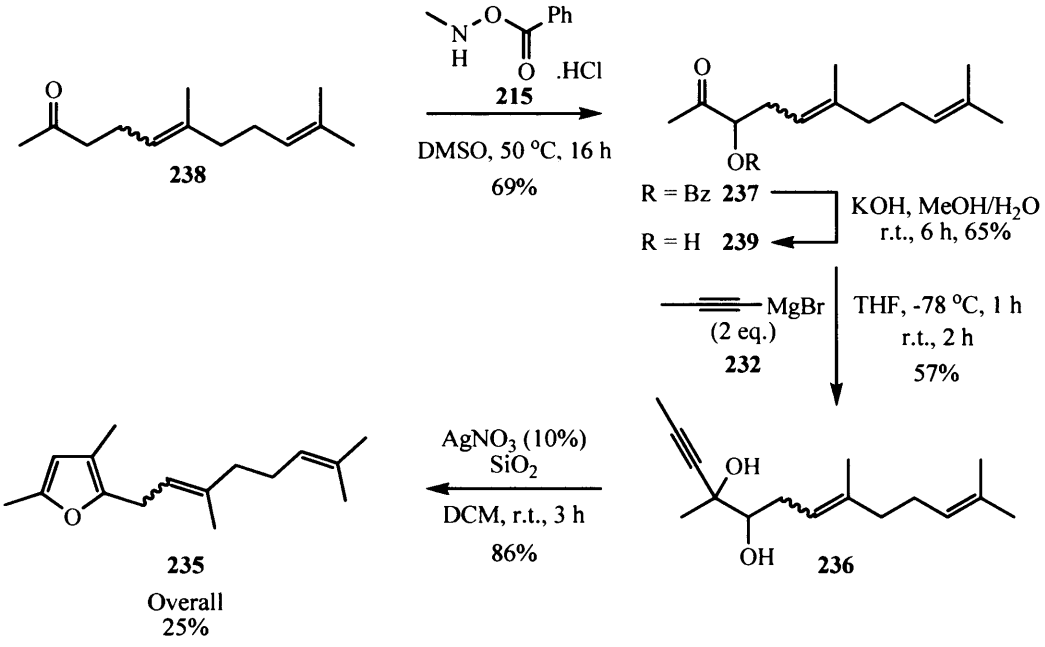
Scheme **88**

Disconnection of furan **235** led back to geranylacetone **238** (Scheme **89**). The commercially sourced sample of geranylacetone **238** contained approximately 35% of the *cis*-isomer, nerylacetone. No attempt to separate the isomers was undertaken at any point in the synthesis. It was considered that if a mixture of the *cis*- and *trans*-isomers of the final furans showed any promise in the area of fragrance, these could be made separately and their fragrances then studied independently.



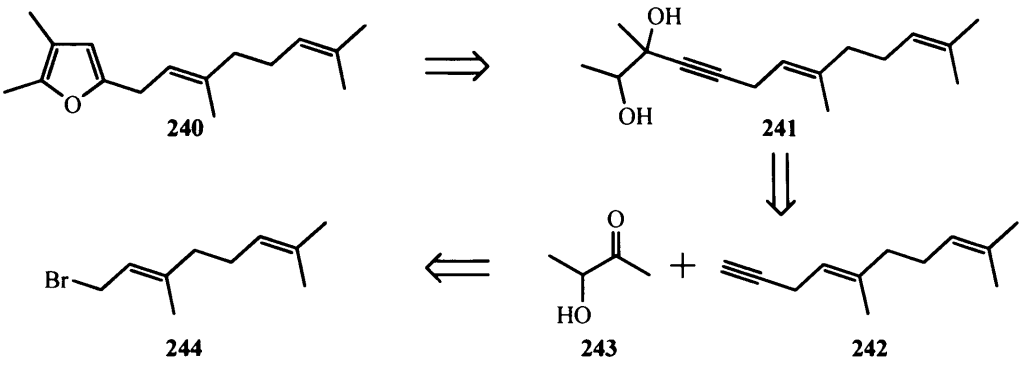
Scheme **89**

α-Benzoyloxylation of (*E/Z*)-geranylacetone **238** using Tomkinson's salt **215** was successful in the formation of ketone **237** in 69% yield. Deprotection of ketone **237** by exposure to potassium hydroxide in methanol/water yielded alcohol **239** in 65% yield, which was treated with two equivalents of commerical 1-propynylmagnesium bromide **232** to allowed Grignard addition to the carbonyl after formation of the alkoxide (*cf.* p44). Cyclisation of the resulting 3-alkyne-1,2-diol **236** under the standard silver cyclisation conditions gave furan **235** as a mixture of its *cis*- and *trans*-isomers (Scheme **90**). The smell of the final products was, in my opinion, weak. Decomposition again prevented the furans **235** from being assessed by an "expert nose".



Scheme **90**

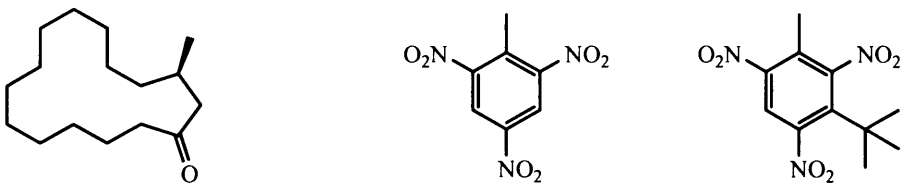
Furan **240**, the 2,4,5-isomer of furan **235**, was also considered for synthesis. Disconnection of furan **240** led back to geranyl bromide **244**, *via* intermediate terminal alkyne **242**. A literature search revealed only one paper containing the structure of terminal alkyne **242**.[133] Previous work within the Knight group has shown that terminal alkyne **242** cannot be made from the reaction of geranyl bromide **244** with lithium acetylide ethylene diamine complex **292**. It was therefore considered that terminal alkyne **242** must suffer from an inherent lack of stability, and so the synthesis of furan **240** was not attempted (Scheme **91**).



Scheme **91**

2.4 Musk

Musk is the name originally given to a substance with a penetrating *animalic* odour obtained from the glands of the male musk deer.[134] In 1921 Ružička showed that one of the compounds responsible for the characteristic smell of the musk was muscone **245**, which has a *woody-amber* odour.[38] The first synthetic musk was serendipitously discovered by Baur in 1888. While working on improving the explosive trinitrotoluene **246**, he noticed that the product of its *tert*-butylation, Musk Baur **247**, had a *pleasant, sweet, musky* odour (Scheme **92**).[39] Nitromusks have little use in the modern perfume industry due to the hazards of explosive intermediates in their production and their phototoxicity.[4] Many synthetic musk-like compounds have since been made and are hugely important in the fragrance industry, but are often relatively expensive to produce (*cf.* p10).[40]



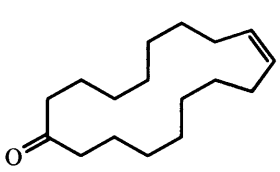
245
muscone
woody-amber

246
trinitrotoluene

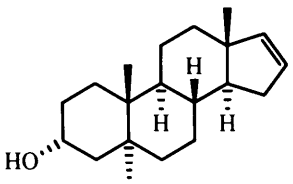
247
Musk Baur

Scheme **92**

In 1944 Ruzicka[135] noted the similarity between civetone **248**, originally extracted from the anal glands of the Civet cat[136] and possessing *clean, musk, dry, animal and sweet* notes,[42] and androstenol **249**, found in boar testes and possessing a *musky* odour (Scheme **93**).[137] The similarities came both in respect to both their musk-like odour, and the number of carbon atoms in their perimeter. Thus the bridging of the cycloheptadecane ring, to give the cyclopentaperhydrophenanthrene skeleton, has little effect on the odour.



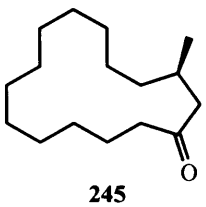
248
civetone
clean, musk, dry, animal and sweet



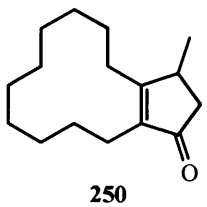
249
androstenol
musky

Scheme **93**

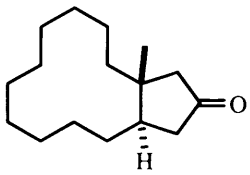
With this concept in mind, McAndrew created a range of bicyclic analogues of muscone **245**. Two of these analogues, enone **250** and ketone **251** he reported to be *distinctly musky, with woody notes* (Scheme **94**).[138]



245
muscone
woody-amber



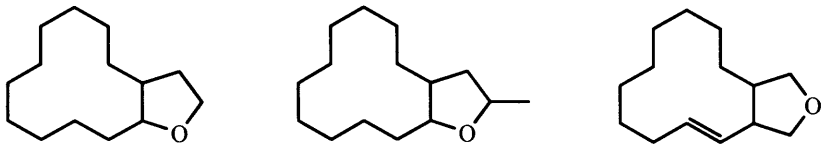
250
distinctly musky, with woody notes



251
distinctly musky, with woody notes

Scheme **94**

On a similar structural line, but bringing the oxygen atom into the ring are the following tetrahydrofuran containing fragrance compounds: cyclamber **252** (*woody, dry amber*), lignoxan **253** (*woody-amber*) and muscogene **254** (*animal, natural musk*) (Scheme **95**).[42]



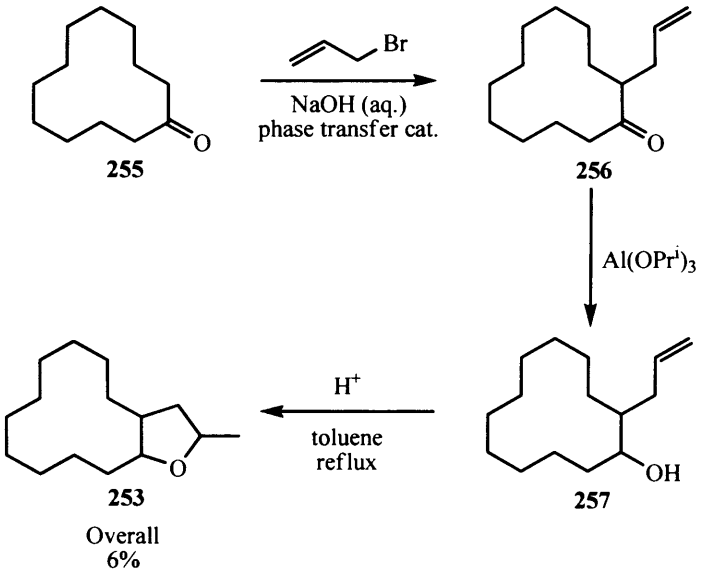
252
cyclamber
woody, dry amber

253
lignoxan
woody-amber

254
muscogene
animal, natural musk

Scheme **95**

Lignoxan **253** was of particular interest as it possessed a trisubstituted tetrahydrofuran, and it was considered that a furan analogue could be made using the silver cyclisation methodology. Gebauer showed in a patent that lignoxan **253** can be made from cyclododecanone **255** in 4 steps in 6% overall yield (Scheme **96**).[139]



255

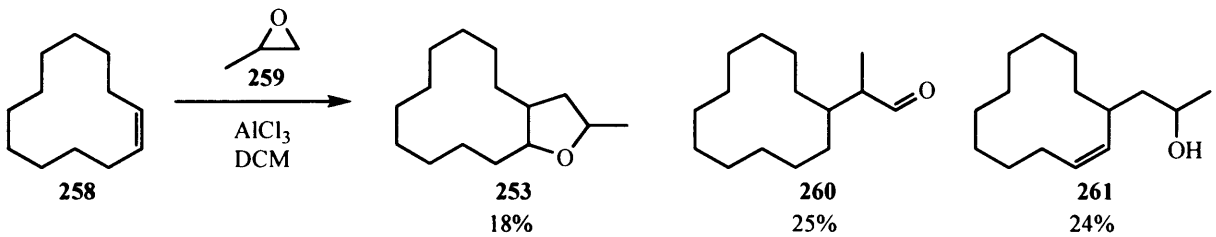
256

253
Overall
6%

257

Scheme **96**

More recently Munro reported a one step synthesis of lignoxan **253**, along with several other products, by the treatment of cyclododecene **258** with propylene oxide **259** in the presence of aluminium trichloride (Scheme **97**).[40]



258

259

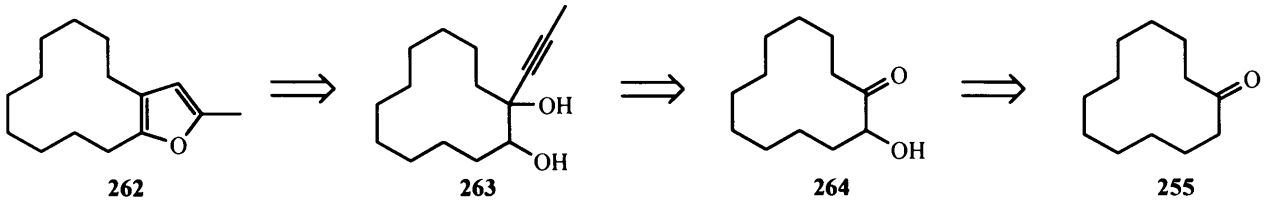
253
18%

260
25%

261
24%

Scheme **97**

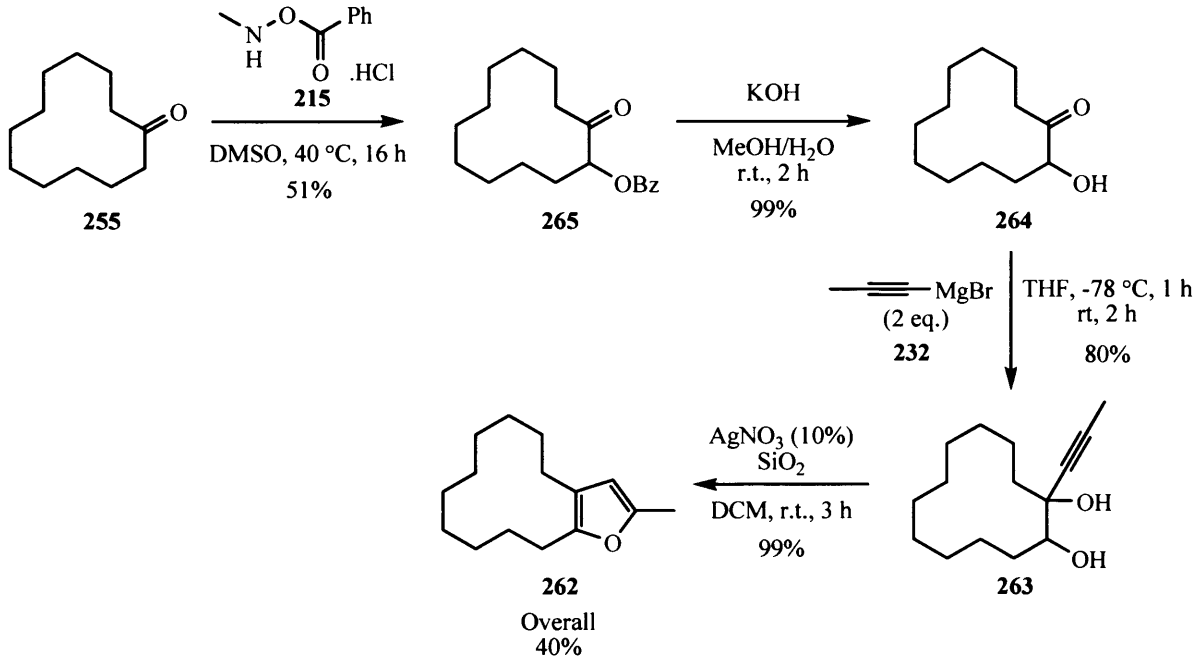
The retrosynthesis of furan **262**, the furan analogue of lignoxan **253**, suggested that it should be accessible from cyclododecanone **255** (Scheme **98**).



262 **263** **264** **255**

Scheme **98**

Cyclododecanone **255** was converted into ketone **265** in 51% yield by exposure to Tomkinson's salt **215** at 40 °C for 16 h. Hydrolysis of the benzoyl group with potassium hydroxide in wet methanol revealed alcohol **264** which was treated with two equivalents of 1-propynylmagnesium bromide **232** to yield 3-alkyne-1,2-diol **263** as an inseparable mixture of diastereoisomers. The silver catalysed cyclisation then proceeded in quantitative yield to give furan **262** (Scheme **99**).



255 **265** **264** **262** **263**

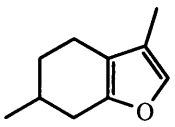
Overall 40%

Scheme **99**

Although the structure of furan **262** initially appeared to pique the interest of the organic chemists at Givaudan, no odour could be detected and so the compound was not accessed by an "expert nose".

2.5 Menthofuran

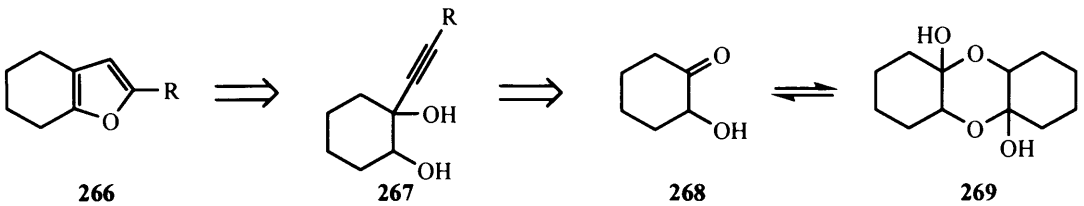
After the successful furan formation on a 12-membered ring, smaller ring sizes were then considered. The synthesis of furan **262** went through the intermediate 3-alkyne-1,2-diol **263** which existed as a pair of inseparable diastereoisomers. It was considered that on a smaller ring, these diastereoisomers might be separable, and more interestingly, might undergo silver catalysed cyclisation at differing rates. A 6-membered ring was initially considered due to its predictable conformational preferences. This brought the structural type into the area of menthofuran **43**, which is found in most mint species[29] and has odour descriptors of *diffusive, pungent, musty, nutty, pyrazine-like, earthy and coffee* (Scheme **100**).[42]



43

Scheme **100**

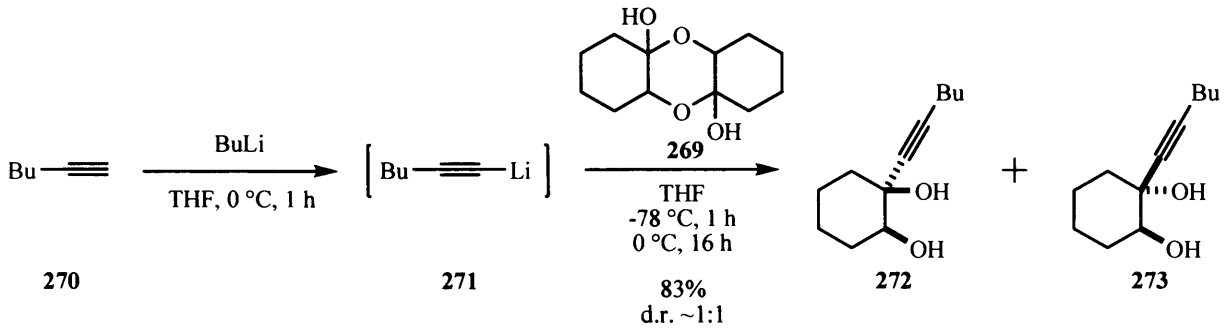
The retrosynthetic analysis of a simple 2-alkyl-4,5,6,7-tetrahydrobenzofuran **266** led back to 2-hydroxycyclohexanone **268** which is commercially available as its dimer **269** (Scheme **101**).



266 **267** **268** **269**
0.5 eq.

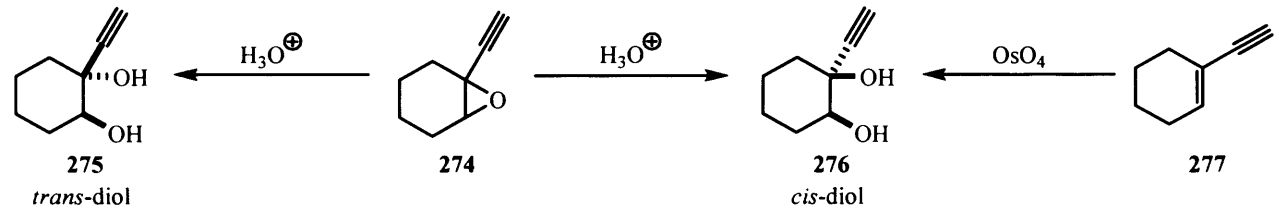
Scheme **101**

2-Hydroxycyclohexanone dimer **269** was treated with lithiated 1-hexyne **271**, which was formed from the reaction of 1-hexyne **270** with butyllithium. The resultant diastereomeric 3-alkyne-1,2-diols, *cis*-diol **272** and *trans*-diol **273**, were separated by repeated column chromatography (Scheme **102**).



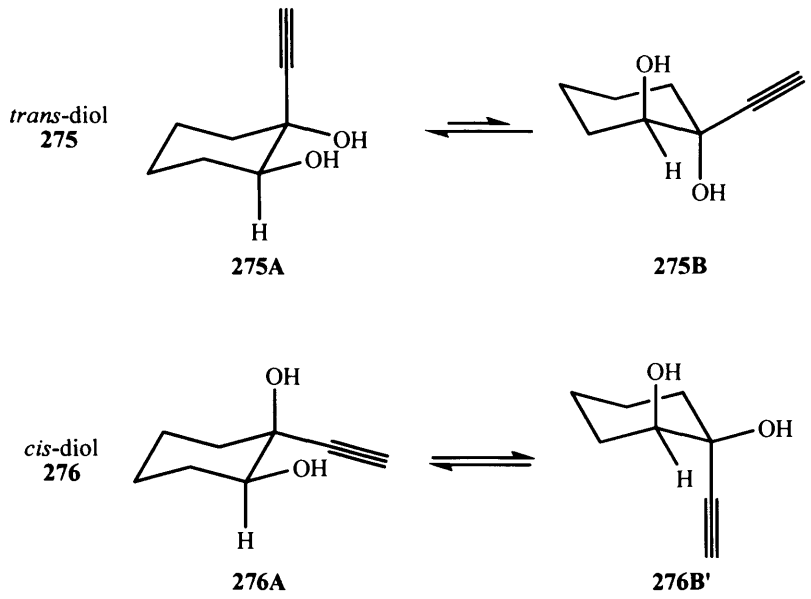
Scheme **102**

^{1}H NMR analysis was initially used in an attempt to confirm the structures of the diasteroisomers **272** and **273**. Despite being known compounds, there was no data in the literature for either of the *n*-butyl-substituted alkynes. Macchia provided spectroscopic data on the terminal alkyne analogues, *trans*-diol **275** and *cis*-diol **276**, which were made from epoxide **274**. He confirmed their diastereochemical relationship by comparison with the authentic *cis*-diol **276** which was made by dihydroxylation of enyne **277** (Scheme **103**). [140]



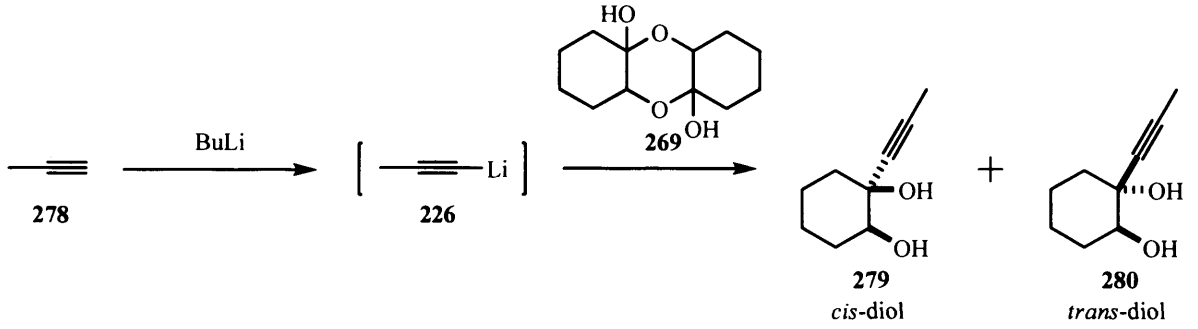
Scheme **103**

Macchia showed that the strength of the O-H absorption in the IR spectrum of *trans*-diol **275** strongly suggested that there was hydrogen bonding between the 1-OH and 2-OH groups and that conformation **275A** was therefore favoured (Scheme **104**). Macchia also noted that in contrast to that of *trans*-diol **275**, the value of the half-bandwidth of the 2-CHOH proton in *cis*-diol **276** was intermediate between those of an axial proton and those of an equatorial proton, and was therefore consistent with an equilibrium between the conformers **276A** and **276B**. Macchia ascribed this result to the very low conformational A-value[141] for the ethynyl group.



Scheme **104**

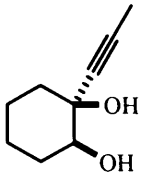
If these conclusions were correct, it would be expected that the distinctive 2-CHOH proton of the *trans*-diol **275** stereoisomers would be axial in the preferred chair conformation, and would exhibit a larger vicinal coupling than that of the *cis*-diol **276** stereoisomers. Macchia unfortunately reported the resonances for both compounds as multiplets. The theory is reassuringly supported by the work of Overman, who synthesised the methyl analogues, *cis*-diol **279** and *trans*-diol **280**, non-stereoselectivly from the reaction of an excess of 1-propynyllithium **226** with 2-hydroxycyclohexanone dimer **269** (Scheme **105**).[142]



Scheme **105**

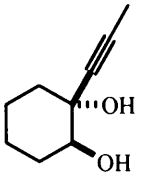
After extensive ^{1}H NMR analysis, Overman reported the *trans*-diol **280** 2-H proton to have a coupling constant of 10.3 Hz and the *cis*-diol **279** 2-H proton to have a coupling constant of 7.9 Hz. With regards to the chemical shift of this distinctive 2-CHOH proton, Overman reported that the *cis*-diol **279** shifted further downfield, to 3.65 ppm, compared to that of the *trans*-diol **280** which came at 3.36 ppm. This is consistent with the findings of Macchia who reported that

the 2-CHOH protons of the *cis*-diol **276** and *trans*-diol **275** resonate at 3.78 ppm and 3.50 ppm respectively (Scheme **106**).



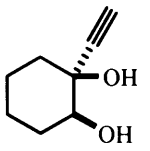
279

cis-diol
3.65 ppm, dd
J = 7.9, 3.9 Hz
$CH_2CH(OH)C$



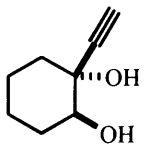
280

trans-diol
3.36 ppm, broad d
J = 10.3 Hz
$CH_2CH(OH)C$



276

cis-diol
3.78 ppm, m
$CH_2CH(OH)C$

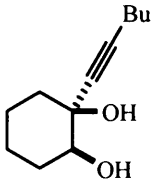


275

trans-diol
3.50 ppm, m
$CH_2CH(OH)C$

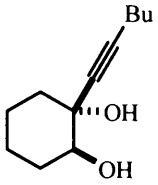
Scheme **106**

It was therefore considered acceptable to assign *cis*-diol **272** as the compound with the higher chemical shift, 3.67 ppm, and smaller and coupling constant, 7.9 Hz. *trans*-Diol **273** was consequently assigned as the compound with the lower chemical shift, 3.37 ppm, and larger coupling constant, 11.2 Hz (Scheme **107**).



272

cis-diol
3.67 ppm, 1H, dd
J = 7.9, 3.7 Hz
$CH_2CH(OH)C$

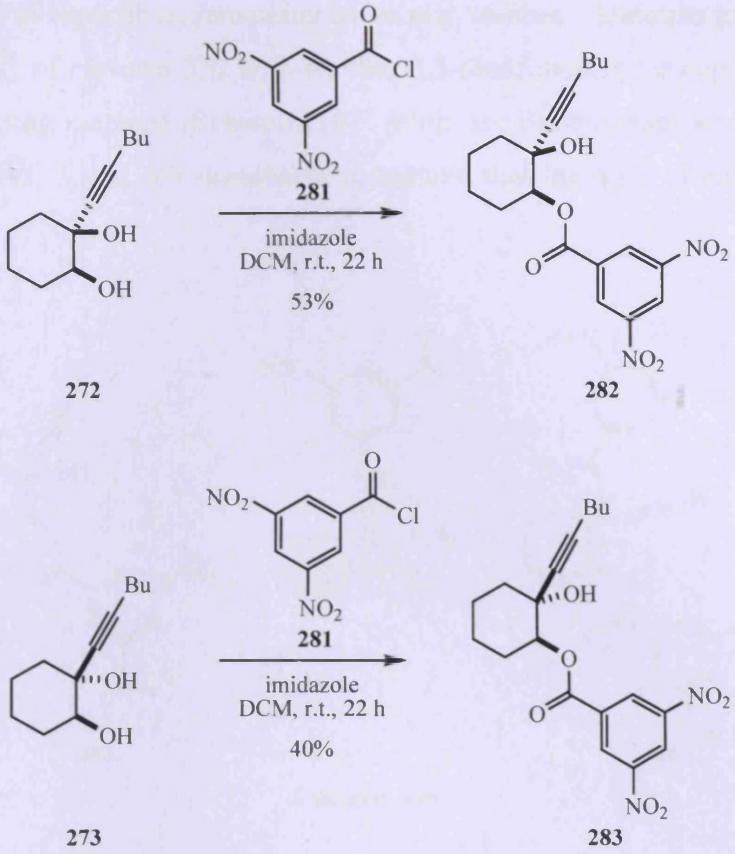


273

trans-diol
3.37 ppm, 1H, dd
J = 11.2, 4.3
$CH_2CH(OH)C$

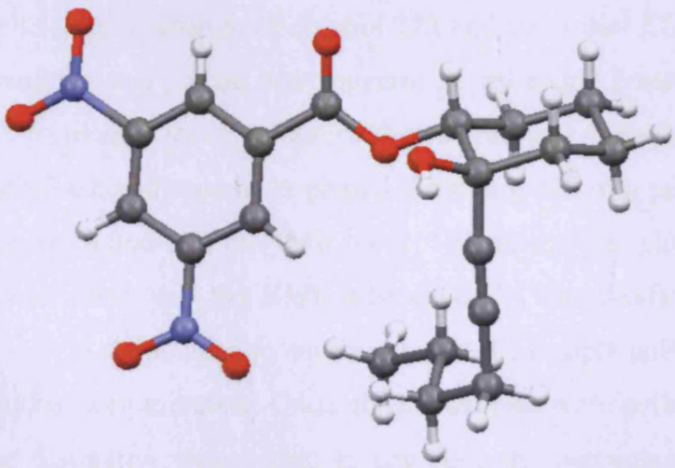
Scheme **107**

To confirm the assignments, crystallisation of the oily residues was attempted, but without success. To encourage the compounds to crystallise, both diastereomers were reacted with 3,5-dinitrobenzoyl chloride **281** to form *cis*-ester **282** and *trans*-ester **283** (Scheme **108**).



Scheme **108**

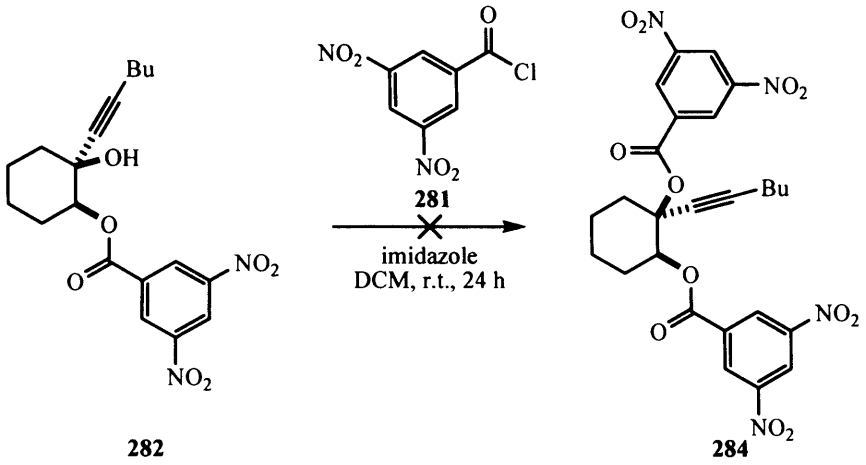
trans-Ester **283** was successfully crystallised from diethyl ether and a crystal structure was obtained by X-ray crystallography confirming the *trans*-nature of the two C-O bonds (Scheme **109**).[143]



X-ray crystal structure of *trans*-ester 283

Scheme **109**

cis-Ester **282** failed to crystallise, remaining as an oily residue. Attempts to further esterify the hydroxyl fuctionality of *cis*-ester **282** with another 3,5-dinitrobenzoyl group failed, returning the majority of the starting material (Scheme **110**). With one diastereoisomer assigned and the ^{1}H NMR data in support, it was felt reasonable to assume that the other compound was the other diastereoismer.

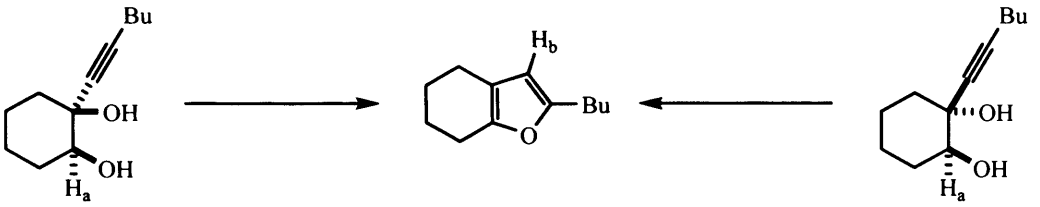


Scheme **110**

During initial investigations, it was shown that when *trans*-diol **273** was exposed to the standard silver cyclisation conditions, TLC revealed it to be fully consumed within 3 h. *cis*-Diol **272** appeared to react more slowly under equivalent conditions with TLC showing unreacted starting material after a period of 12 h.

A kinetic experiment was therefore conducted in an attempt to follow the progress of the reaction. Separate 3.1 mmol samples of *cis*-diol **272** and *trans*-diol **273** were dissolved in 15 ml of deuterated chloroform and placed into separate 50 ml round bottomed flasks. After being allowed to stir for 30 minutes to try to ensure the sample was fully solvated, a 0.10 ml sample was taken from each flask and separately passed through a 270 mm pasture pipette containing a small plug of cotton wool and into an NMR tube. The pipette and plug were washed with 1.00 ml of deuterated chloroform and the NMR tube capped. The catalyst, 0.31 mmol of $AgNO_3$ (10% w/w on silica), was then added to each flask and the sample collection routine repeated at intervals for a period of 240 minutes. Once all the samples were collected, they were analysed by ^{1}H NMR. The distinctive peaks used to calculate the percentage conversion were those representing the 2-C<u>H</u>OH (H_a) proton of the starting materials, and the β-furan-<u>H</u> (H_b) proton of

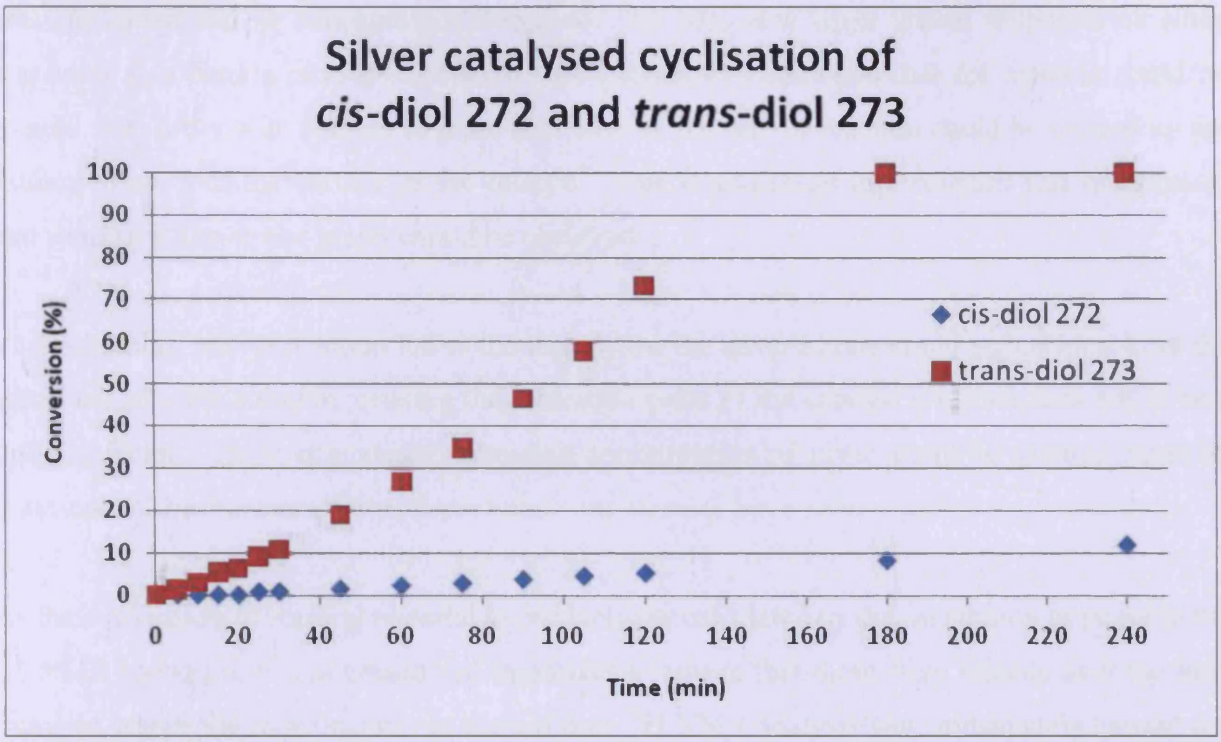
the product. The percentage conversion was calculated by the integration of the H_b peak divided by the sum of the intergrations of the H_a and H_b peaks (Scheme **111**).



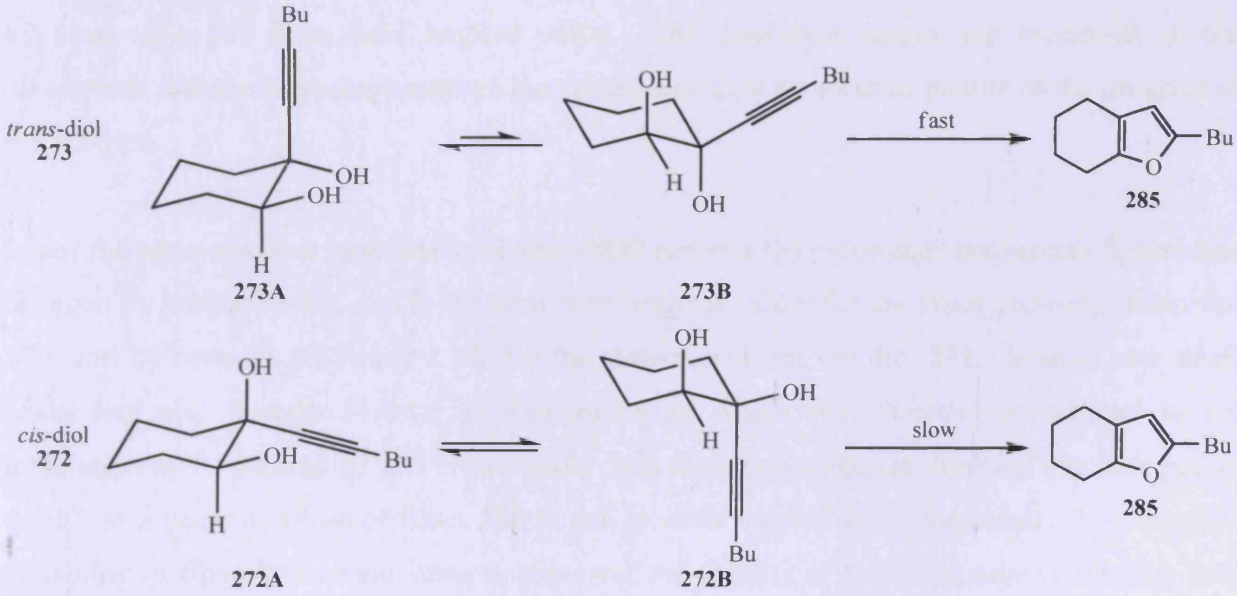
272 **285** **273**

Scheme **111**

The graph shows that *trans*-diol **273** underwent full conversion within 180 minutes. This was faster than *cis*-diol **272** which showed less than 9% conversion after 180 minutes (Scheme **112**). It was originally predicted that *cis*-diol **272** would cyclise faster than *trans*-diol **273**. This was expected due to the ability of the two interacting substituents, the 2-OH and the 1-alkyne, to sit equatorially, as in conformation **272A**. It was believed that their close proximity in this conformation would promote the cyclisation process, but this was not what was experimentally observed. It was also considered that no reaction would take place when *cis*-diol **272** was in conformation **272B** where both the interacting substituents are axial, as their anti-periplanar relationship means there is a considerable distance between them. For a 5-*endo*-dig cyclisation to occur, the nucleophile must be able to reach the π^* anti-bonding orbital on the alkyne. It is therefore considered that *trans*-diol **273**, in which the interacting substituents have a *cis*-configuration, better allows the overlap of the nessesary orbitals, reducing the kinetic barrier for the reaction (Scheme **113**).



Scheme **112**



Scheme **113**

While the experiment confirmed that the pairs of diastereoisomers cyclised at different rates, the shape of the graphs raised questions regarding the mechanism and dynamics of the reaction. The most striking aspect of the *trans*-diol **273** graph was its upward curve, suggesting that the rate of reaction was increasing. It was initially considered that the reaction would be first order with respect to *trans*-diol **273** and that the rate of reaction would therefore decrease as *trans*-diol **273**

was consumed and its concentration deceased. As 10% w/w silver nitrate supported on silica was used as a heterogeneous catalyst, it was alternatively reasoned that the reaction could be pseudo zero order with respect to *trans*-diol **273**, as the rate of reaction could be limited by the saturation point of the surface of the catalyst. This would result in a constant rate of reaction, and a straight line on the graph would be observed.

The increasing rate of reaction led to the theory that the silver nitrate could be leeching from the silica and into the solution, causing the saturation point of the catalyst's surface area not to be a limiting factor. The continuously increasing concentration of silver nitrate in solution could be the cause of the increasing rate of reaction.

As the conversion of starting material to product was calculated by the integration of peaks in the ^{1}H NMR spectrum, it was considered important to ensure that these were reliable over the time frame in which the experiment was carried out. ^{1}H NMR analysis was immediately carried out on the filtered samples taken from both experiments after 30, 75 and 120 minutes. The samples were again analysed by ^{1}H NMR after 375 and 450 minutes and were shown not to have changed by more than 2% from their original value. The consistent values add credibility to the assumption that the percentage conversion values represent an accurate picture of the progress of the reaction.

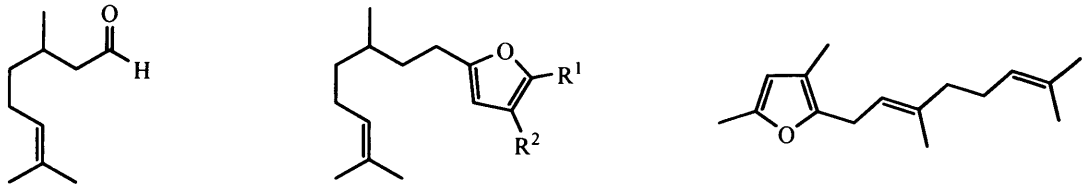
When the same samples were analysed after 4000 minutes the percentage conversion figures had changed by between 6.2% and 9.4% from their original values for the faster cyclising *trans*-diol **273**, and by between 0.3% and 2.2% for the slower cyclising *cis*-diol **272**. Several new small peaks had also become visible, the integration of which was directly proportional to the integration of the β-furan-H (H_b) proton peak. It is therefore suggested that over this time period there was a decomposition of furan **285** to one or more unidentified compounds. The apparent instability of furan **285** raised some doubts over the validity of the percentage conversion data obtained, but it is considered that the decomposition was slow and regular enough to not cause significant errors in the data. These results suggested that leaching of silver nitrate from the silica was not a major factor, and did not explain the upward curve of the graph.

During the reaction, a stoichiometric amount of water is produced, and it was therefore considered that water may be catalysing the reaction. To investigate this it would be nessarsary to carry out the reaction under strictly anhydrous conditions, and also with the addition of

varying quantities of water. The rate and order of the reaction could then be studied to gain information as to the role of water on the reaction.

2.6 Citronellal

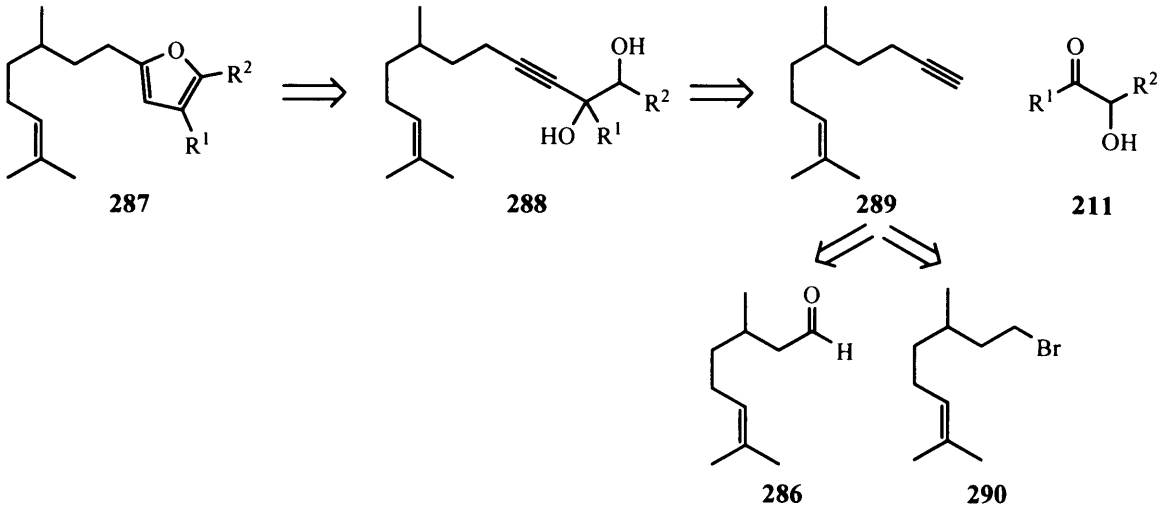
Citronella oil is one of the essential oils obtained from the leaves and stems of different species of *Cymbopogon* and is prized for its lemony scent. Oil from the *Cymbopogon nardus* plant contains about 40% citronellal **286**,[29] which has odour descriptors including *sweet, floral, rosy, waxy and citrus green* (Scheme **114**).[42] Citronellal **286** is used as a fine fragrance ingredient and in 2007 the Ashford site of Quest International (now owned by Givaudan) used 5335 kg of citronellal **286**.[144] It was therefore considered that citronellyl furan analogues **287** would be worthwhile targets. Furans **287** are dihydro analogues of the previously discussed furan **232**, and give the added complication on a stereogenic centre.



286 **287** **232**

Scheme **114**

Disconnection of furan **287** can lead back to two commercially available starting materials, citronellal **286**, or citronellyl bromide **290** (Scheme **115**).

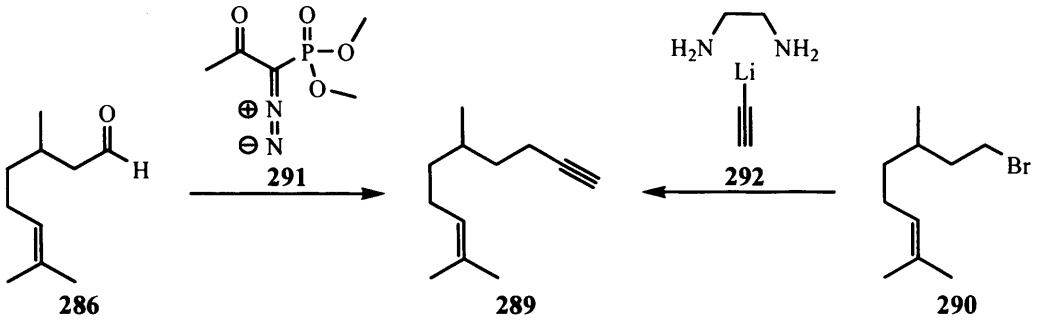


287 **288** **289** **211**

286 **290**

Scheme **115**

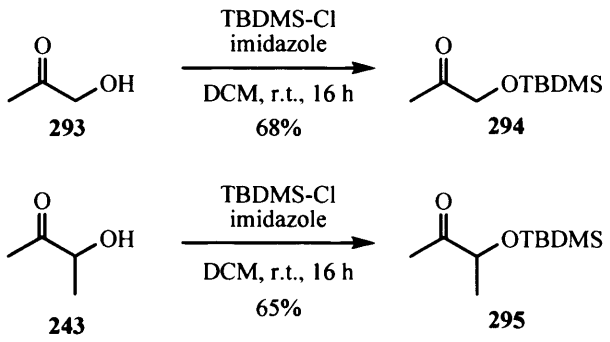
Both can be converted in one step into alkyne **289**, by the Bestmann-Ohira reagent **291**,[145] or lithium acetylide ethylene diamine complex **292**, respectively (Scheme **116**).



Scheme **116**

Citronellyl bromide **290** was chosen despite being more expensive than citronellal **286** as the Bestmann-Ohira reagent **291** is not commercially available, whereas lithium acetylide ethylene diamine complex **292** is commercially available and relatively inexpensive. The stereochemistry of a compound can have a major affect on its fragrance (*cf.* p4).[146] Synthesis of both enantiomers of citronellyl furan **287** was attempted in the hope that a difference in their fragrance would be detected. It was considered that the R-groups should be kept small as the compound was already touching on the upper mass limits of common fragrance compounds.[27] It was therefore decided that the (*R*)- and (*S*)-enantiomer of furan **287** would be made where R^1 = Me, R^2 = H, and where also $R^1 = R^2$ = Me.

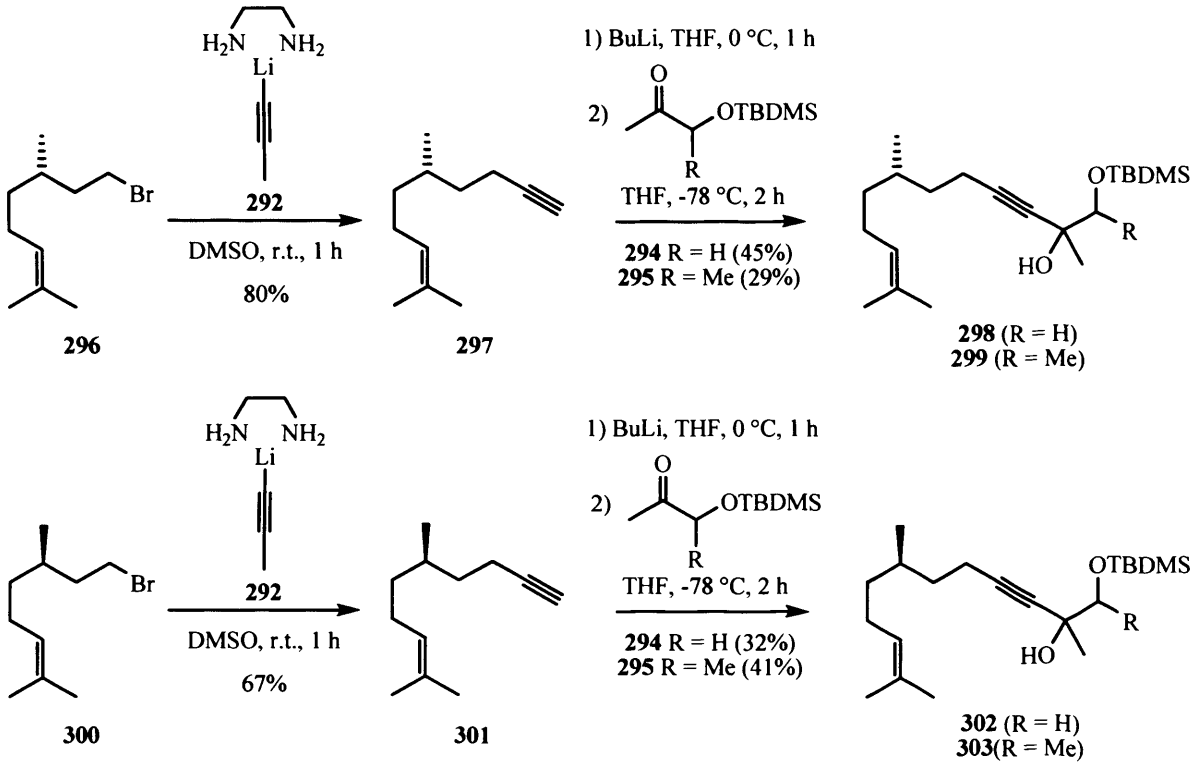
To begin the synthesis, the hydroxyl groups of both acetol **293** and (±)-3-hydroxybutan-2-one **243** were protected using *tert*-butyldimethylsilyl chloride (Scheme **117**).



Scheme **117**

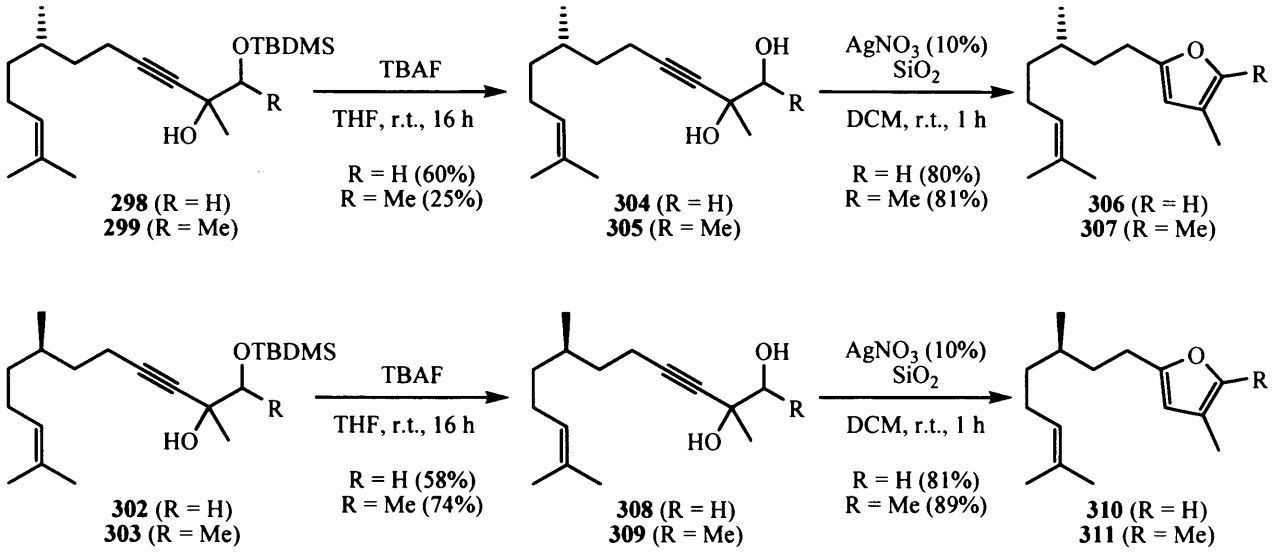
Both (*S*)- and (*R*)-citronellyl bromide, **296** and **300** respectively, were converted into their respective alkynes **297** and **301** by treatment with lithium acetylide ethylene diamine complex

292. Deprotonation of both alkynes **297** and **301** using butyllithium was followed by addition of their corresponding lithium salts to ketones **294** and **295** to give alcohols **298**, **299**, **302**, and **303** as mixtures of diastereoisomers which were not separated (Scheme **118**).



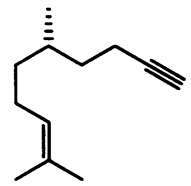
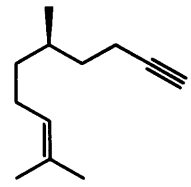
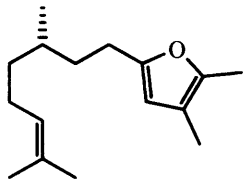
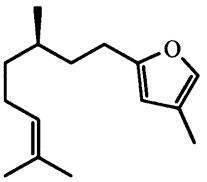
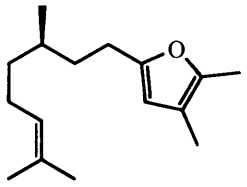
Scheme **118**

The reactions proceeded successfully but with unspectacular yields. Deprotection of alcohols **298**, **299**, **302**, and **303** by tetrabutylammonium fluoride gave 3-alkyne-1,2-diols **304**, **305**, **308**, and **309** which cyclised upon exposure to the standard silver cyclisation conditions to yield furans **306**, **307**, **310**, and **311** (Scheme **119**).



Scheme **119**

Alkynes **297** and **301**, and furans **307**, **310** and **311** gave colourless oils after Kugelrohr distillation and were submitted for level 1 screening to R&T perfumer and "expert nose" Chris Piddock for assessment of their potential as novel fragrance compounds. Furan **306** failed to reach the screening process as it discoloured and formed a viscous gel which failed to produce a colourless oil when distilled. The problem of decomposition and decolouration had affected all the previous furans made during this project and therefore none of them were submitted for screening. The results of the screening are shown in the following table (Scheme **120**).

Compound	Odour descriptors (After given time)			Pass to level 1.1?
	24 hours	4 hours	Fresh	
 **297**	*Odourless*	*Faintly sweet*	*Plastic* *Fatty*	No
 **301**	*Red fruit* *Weak*	*Fatty* *Greasy*	*Plastic* *Fatty* *Slightly fruity*	No
 **307**	*Odourless*	*Red fruit* *Weak*	*Fatty* *Metallic* *Greasy*	No
 **310**	*Weak chemical* *Fatty*	*Chemical* *Metallic* *Sweet*	*Fatty* *Metallic* *Green* *Fruity*	No
 **311**	*Candle Wax*	*Sweet* *Powdery* *Weak*	*Fatty* *Rancid*	No

All samples were prepared as a 10% w/w solution in dipropylene glycol. Smelling of the compounds was performed from a smelling strip, with a solution of the compound having been added to the smelling strip at the time indicated.

Scheme **120**

The results of the level 1 screening session were disappointing, with none of the products reaching level 1.1. It was of interest that different odour descriptors were assigned to enantiomeric alkynes **297** and **301**, and enantiomeric furans **307** and **311**. (*S*)-Alkyne **297** was odourless after 24 hours, while (*R*)-alkyne **301** was said to have hints of *red fruit*. (*S*)-Furan **307** was also odourless after 24 hours, but (*R*)-furan **311** was described as having the faint scent of *candle wax*. A difference between the furans also noted after they had been on the smelling strip for 4 hours with (*S*)-furan **307** having a *red fruit* odour, and (*R*)-furan **311** possessing a *sweet, powdery* fragrance. When smelt fresh all the compounds were described as having a *fatty* note and provoked particularly unkind responses from the perfumer. After the screening furans **307**, **310** and **311** soon discoloured and became viscous oils. It was therefore considered that it was a mixture of decomposition products from the furans, along with the furans themselves may have been assessed for their fragrance and not a clean sample.

2.7 Sandalwood

Historical records show that there has been uninterrupted use of sandalwood oil in perfumery for at least 4000 years. The major components of the oil are α-santalol **44**, and β-santalol **45** (Scheme **121**).[29]

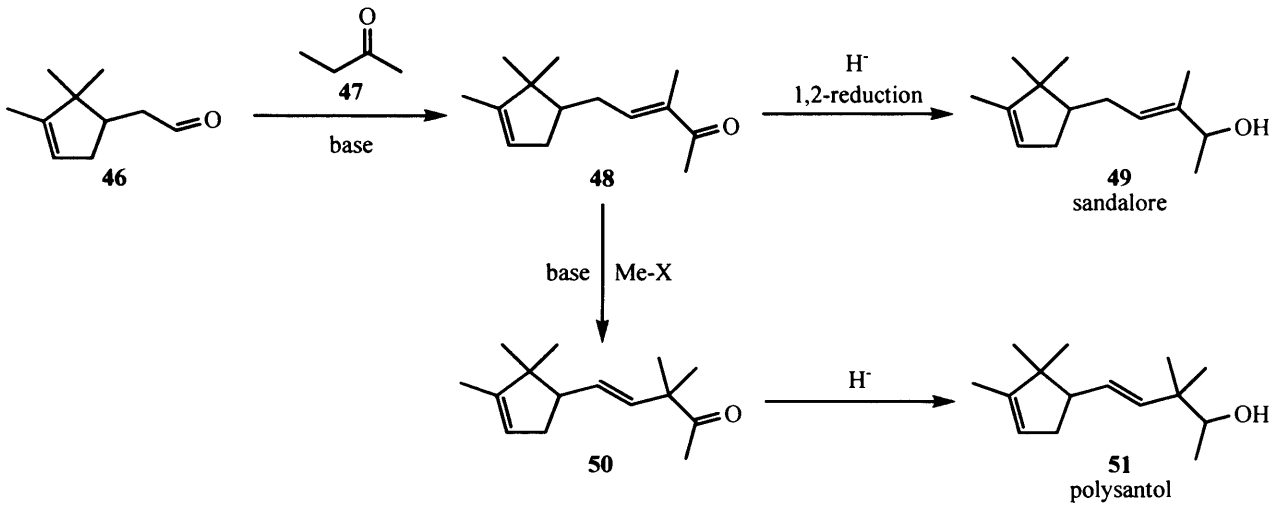
44
α-santalol

45
β-santalol

Scheme **121**

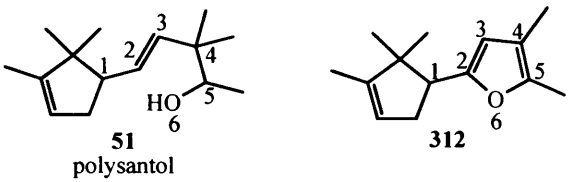
Both isomers contribute to the distinctive *woody* odour of the oil. The β-isomer **45** is more intense and also contributes to the *slightly animalic* and *urinous* character of the oil. Parosmia is an olfactory dysfunction that is characterized by the inability of the brain to properly identify an odor's "natural" smell. One of the commonest parosmias is the association of sandalwood oil with the smell of urine. Sandalwood oil is obtained by distillation of the wood of the *Santalum album* tree. Cultivation of the tree is difficult due to its parasitic nature and consequent need for a suitable host. Excessive harvesting has endangered the species and control of production is now necessary to prevent extinction.[29] Synthetic routes to sandalwood odours are therefore of interest to the perfume industry. One class of sandalwood substitutes are those derived from campholenic aldehyde **46**.[147] Two typical examples are sandalore **49** and polysantol **51**, which

were patented by Givaudan and Firmenich respectively.[29] Sandalore **49** is made by an aldol-type condensation between campholenic aldehyde **46** and butan-2-one **47**, followed by 1,2-reduction of the resulting unsaturated ketone **48**. Unsaturated ketone **48** can alternatively be alkylated under basic conditions to give ketone **50** which can then be reduced to give polysantol **51** (Scheme **122**) (*cf.* p11).



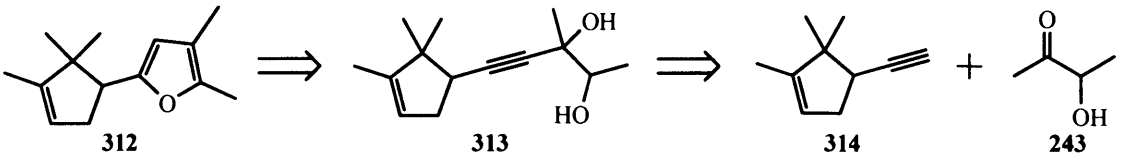
Scheme **122**

Drawing on structural motifs of polysantol **51**, the furan analogue **312** was devised. If numbered counting away from the 5-membered ring as shown, it can be seen that both molecules have π-electron density between the 2- and 3-position, both have methyl substituents at the 4- and 5-position, and both have an oxygen atom in the 6-position (Scheme **123**).



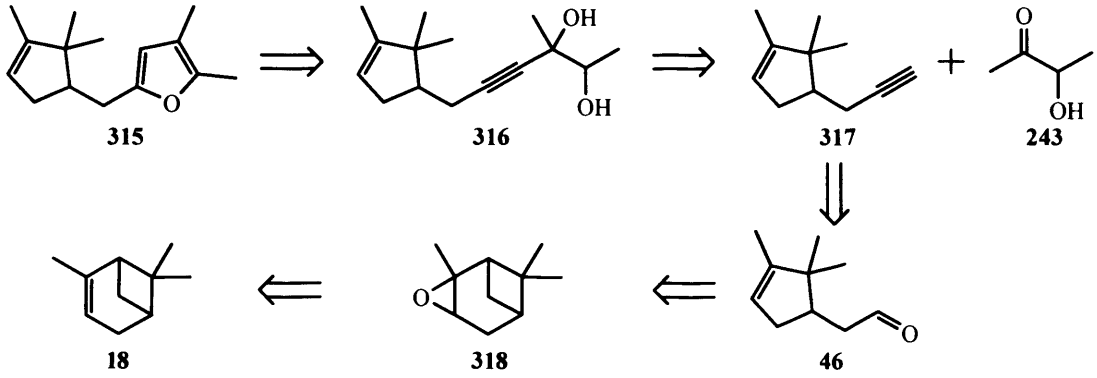
Scheme **123**

Disconnection of furan **312** leads back to 3-alkyne-1,2-diol **313**, which appears to be accessible from alkyne **314** and ketone **243** (Scheme **124**).



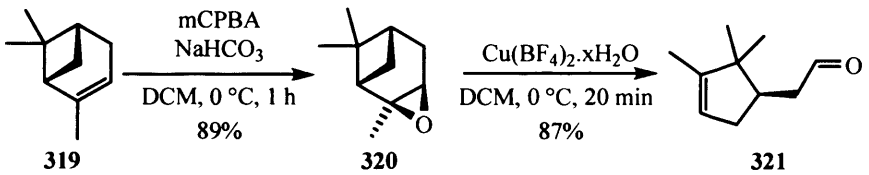
Scheme **124**

A review of the literature revealed that alkyne **314** was not a known compound. When the issue of its synthesis was discussed with chemists at Givaudan, it was revealed that they had access to alkyne **314**. Although the synthetic route could not be disclosed, it was agreed that a sample would be delivered for use in the synthesis. While waiting for the compound to arrive it was found that campholenic aldehyde **46** was readily accessible from α-pinene **18** *via* α-pinene oxide **318**. It was therefore hoped that alkyne **317**, which is the one carbon homologue of alkyne **314**, could be synthesised and furan **315** ultimately made (Scheme **125**).



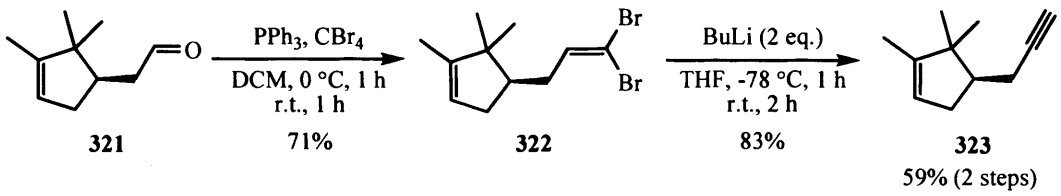
Scheme **125**

Campholenic aldehyde **46** is traditionally prepared by the Lewis acid-promoted Meinwald rearrangement[148] of α-pinene oxide **318**.[43] Graham has recently shown that the use of catalytic copper tetrafluoroborate ($Cu(BF_4).xH_2O$) can convert α-pinene oxide **318** into campholenic aldehyde **46** in 88% yield under mild conditions.[149] (+)-(1*R*)-α-Pinene **319** was epoxidised with 3-chloroperoxybenzoic acid to give (+)-(1S)-α-pinene oxide **320**.[150] This was then subjected to the conditions described by Graham to give campholenic aldehyde **321** in 87% yield (Scheme **126**).



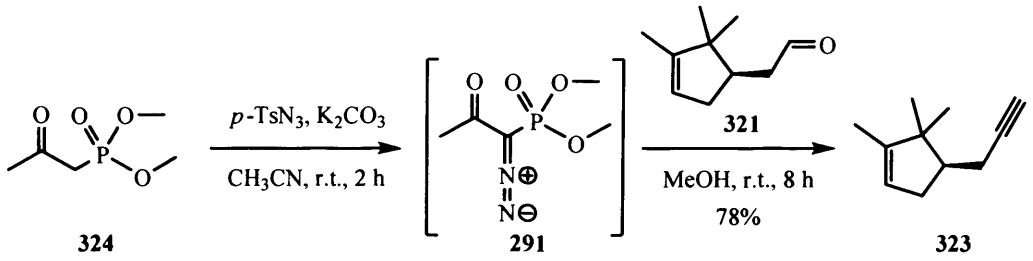
Scheme **126**

Campholenic aldehyde **321** was initially converted into dibromoalkene **322** by treatment with triphenylphosphine and carbon tetrabromide, and then to campholenic alkyne **323** by exposure to butyllithium in 59% overall overall yield using the Corey-Fuchs proceedure (Scheme **127**).[151]



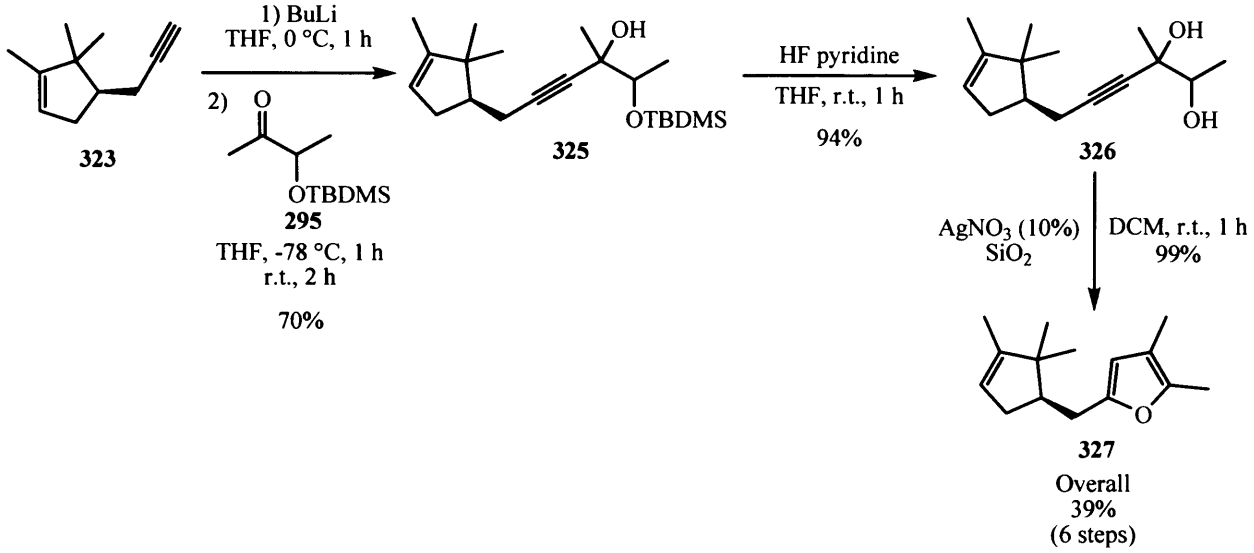
Scheme **127**

It was found that the yield for the overall conversion could be improved if campholenic aldehyde **323** was treated with the Bestmann-Ohira reagent **291**.[145] A drawback to this approach was that Bestmann-Ohira reagent **291** had to be prepared as it is not a commercially available reagent.[85] Much work has been carried out by Bestmann on improving the synthesis and reaction of the Bestmann-Ohira reagent **291**, which it has been shown can now be created *in situ* from dimethyl-2-oxopropylphosphonate **324** and reacted with an aldehyde in a one-pot procedure.[152] Campholenic alkyne **323** was thus prepared using Bestmann's methodology in 78% yield (Scheme **128**).



Scheme **128**

Campholenic alkyne **323** was then deprotonated and added into protected ketone **295** giving alcohol **325** as a 9:1 mixture of diastereoisomers which were not separated. The silicon protecting group was removed using hydrogen fluoride in pyridine solution to reveal 3-alkyne-1,2-diol **326**. Cyclisation occurred smoothly under the standard silver cyclisation conditions to give furan **327** in quantitative yield (Scheme **129**). The smell of furan **327** was consided unremarkable.



Scheme **129**

It was to amused disappointment that when a package arrived from Givaudan which was believed to contain the initially desired alkyne **314**, it was found to contain alkyne **317** which had already been synthesised and used in the synthesis of furan **315** (Scheme **130**). The synthesis of furan **312** was therefore not attempted.

Scheme **130**

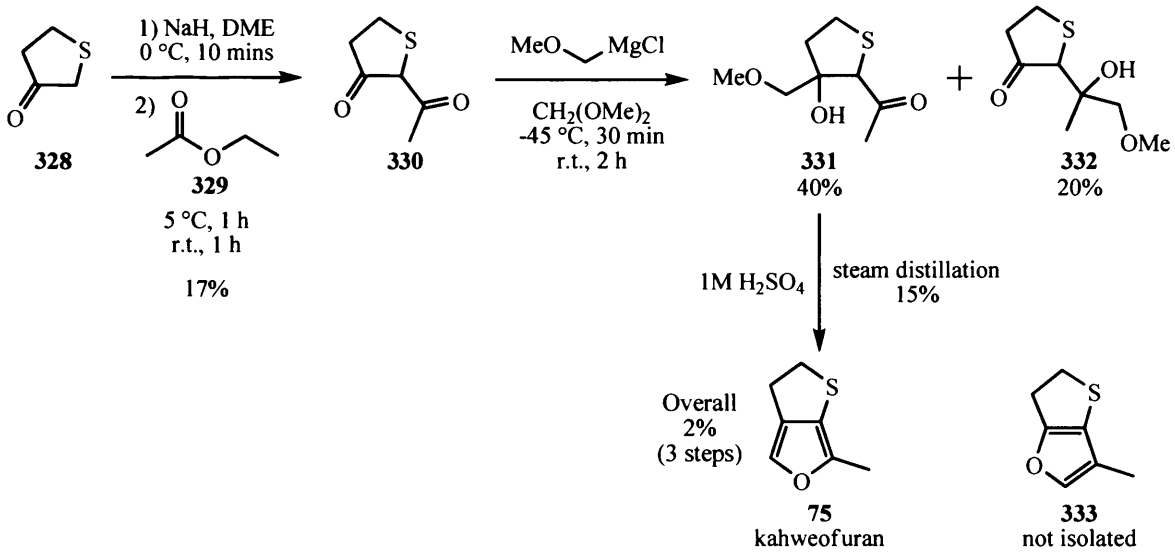
Chapter 3: Kahweofuran

3.1 Kahweofuran

In 1967 detailed analyses of coffee concentrates led to the isolation of a substance with the empirical formula C_7H_8OS but of unknown constitution.[57] In 1971 Büchi reported to have proven the structure though synthesis and comparison of the relevant characterisation data with the natural product.[153] Büchi named the compound "kahweofuran" **75**, from the Arabic word *qahweh*, meaning coffee (Scheme **131**).[154] He went on to describe its smell as follows:

"*Kahweofuran in the pure state has a violent sulfury odor, but in high dilution it develops a pleasant roasted and smoky note*"

Büchi's synthesis began with a Claisen condensation of 3-oxotetrahydrothiophene **328** with ethyl acetate **329** to give diketone **330**, which had to be separated from its regioisomer. This was followed by Grignard addition[155] of methoxymethyl magnesium chloride to give a mixture of products including ketones **331** and **332**. Steam distillation in the presence of dilute sulfuric acid was claimed to give kahweofuran **75** as a single product, which was purified by column chromatography followed by distillation. Furan **333**, an isomer of kahweofuran which could theoretically be made from ketone **332**, was reportedly not isolated (Scheme **131**).

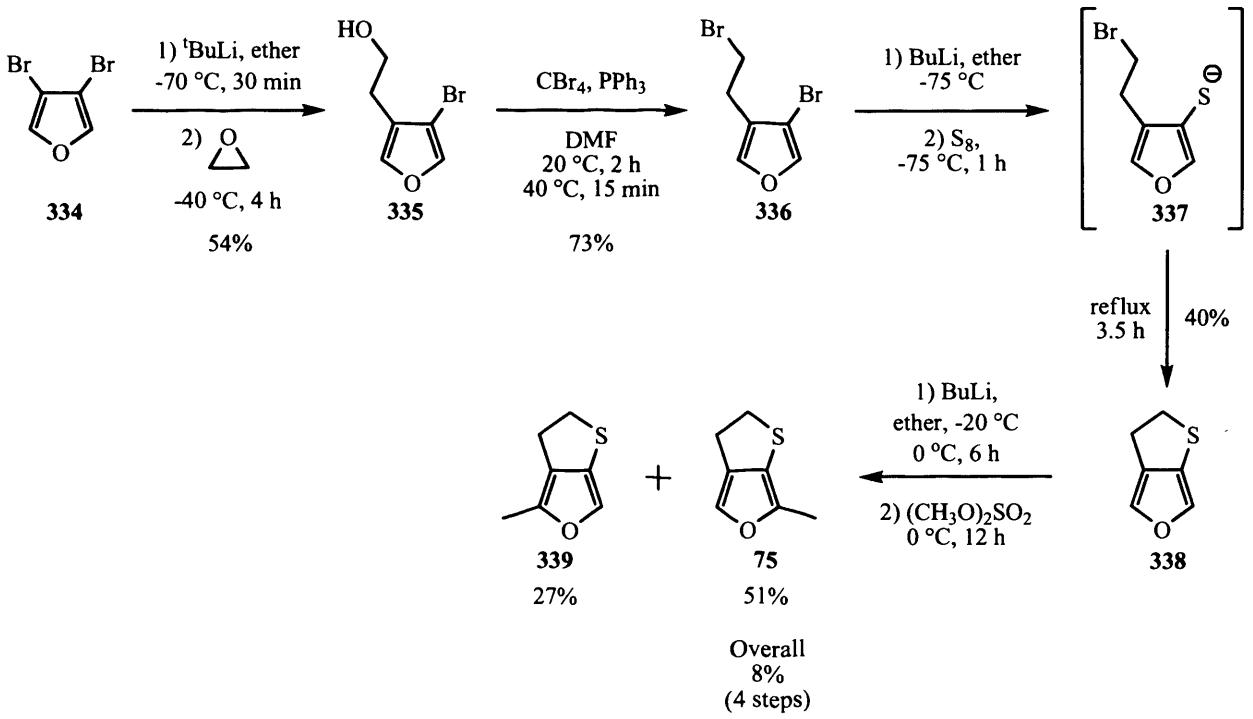


Scheme **131**

Büchi's synthesis suffered from a lack of regioselectivity in the first two steps and thus required difficult isomeric separations. The treatment of ketones **331** and **332** with acid is also not a completely satisfactory proof of structure by synthesis, with a number of alternative reaction

products possible. A question must also be raised as to the stability of kahweofuran **75** under these acidic conditions.

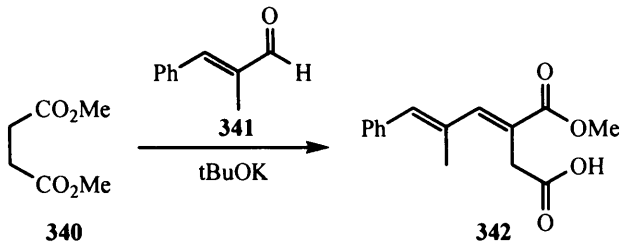
Kahweofuran **75** was not synthesised again until 1986 when Rewicki looked into the synthesis of a range of alkyl substituted 2,3-dihydrothieno[2,3-c]furans which were reported to be aroma compounds of coffee.[156] Rewicki's approach began with the furan moiety already in place, and required the introduction of sulfur, formation of the dihydrothiophene ring, and methylation of the furan ring. Rewicki chose 3,4-dibromofuran **334** as his starting material which he treated with *tert*-butyllithium, followed by ethylene oxide, to give alcohol **335** in 54% yield. Exchange of the alcohol for a bromine atom was performed using methyltriphenoxyphosphonium bromide to give furan **336** in 73% yield. Selective lithium halogen exchange of the aryl bromide followed by reaction with elemental sulfur formed thiolate anion **337** which cyclised to form furan **338**. Treatment of furan **338** with butyllithium followed by exposure to dimethyl sulfate gave kahweofuran **75** in 51% yield, along with furan **339** (Scheme **132**).



Scheme **132**

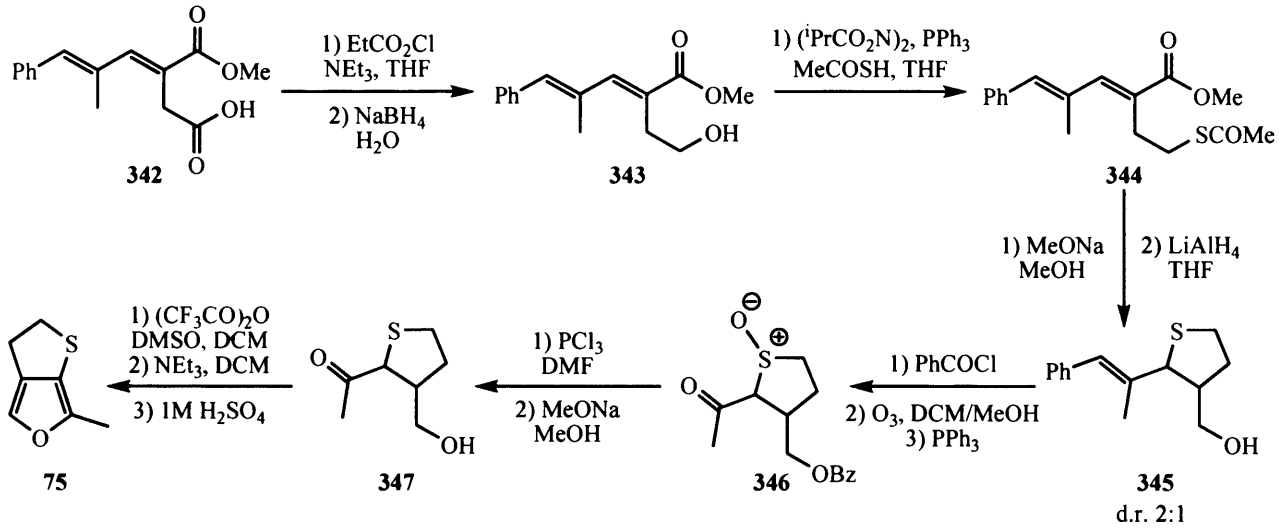
Rewicki's synthesis suffers from low yields and the use of a relatively expensive starting material.[85] The extensive use of organometallic reagents at low temperatures would also be a concern were the reaction to be considered for scale-up.

The next synthesis of kahweofuran **75** came in 1998 when Fuganti published a short paper reporting that it could be made from conjugated ester **342**, which was accessible by Stobbe condensation[157] of α-methylcinnamaldehyde **341** with dimethyl succinate **340** (Scheme **133**).[158]



Scheme **133**

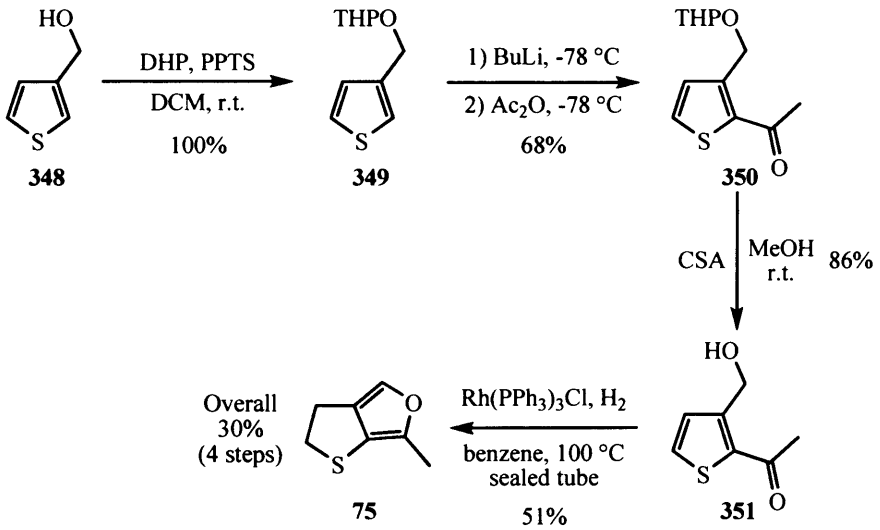
Conjugated ester **342** was reduced *via* its mixed anhydride to give alcohol **343** which was then converted to thioester **344** using Violante's modification[159] of the Mitsunobu reaction.[160] The tetrahydrothiophene ring was then formed by a Baldwin's rules disfavoured 5-*endo*-trig cyclisation under basic conditions. Despite being "disfavoured" this cyclisation is not overly surprising as the larger atomic radii and bond distances of atoms in the second row of the periodic table can allow the usual geometric constraints to be bypassed (*cf.* p20).[69] Reduction of the ester gave alcohol **345** as a 2:1 mixture of diasteroisomers. Alcohol **345** was protected as its benzoate and then subjected to ozonolysis followed by reduction with triphenylphosphine to give sulfoxide **346**. Further reduction of sulfoxide **346** by phosphorus trichloride was followed by basic hydrolysis of the benzoyl ester to give alcohol **347**. A Swern oxidation[161] was then followed by formation of the furan ring by exposure to dilute sulfuric acid to give kahweofuran **75** (Scheme **134**).



Scheme **134**

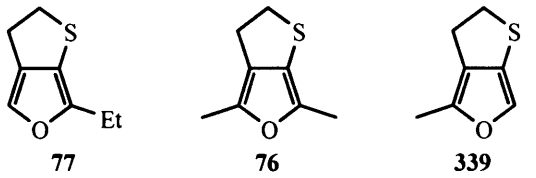
Fuganti's synthesis benefited from containing only regiospecific reactions and from avoiding the use of expensive precursors or organometallic reagents. The synthetic pathway should also allow for the preparation of a variety of 2,3-disubstituted tetrahydrothiophenes. The 13 step synthesis was significantly longer than those which preceded it, and no reaction yields were reported. Although Fuganti does discuss some variations of the route which avoid reactions that are described as "troublesome", the lack of reported yields for any of these routes leaves their advantages somewhat mysterious.

A more efficient synthesis of kahweofuran **75** was recently reported by Katsumura.[162] Thiophene-3-methanol **348** was chosen as the starting material as it contained all the atoms required for the dihydrothiophene ring of kahweofuran **75**, albeit in an over-oxidised form. A tetrahydropyran protecting group was installed to aid regioselective generation of the anion in the 2-position of thiophene **349** by chelation control.[163] The best yield of ketone **350** was reported to be obtained when acetic anhydride was used to quench the anion at –78 °C. The deprotection of ketone **350** by (±)-camphor-10-sulfonic acid gave thiophene **351**. Katsumura failed in his initial attempts to reduce thiophene **351** using dissolving metals. Hydrogenation with palladium on carbon, or platinum dioxide, also failed to reduce thiophene **351**. Kahweofuran **75** was eventually obtained after the treatment of thiophene **351** with Wilkinson's catalyst under an atmosphere of hydrogen in benzene at 100 °C (Scheme **135**). The reaction presumably proceeds *via* a partial reduction of the thiophene to the corresponding dihydrothiophene, which then undergoes an intramolecular condensation and isomerisation to yield kahweofuran **75**.



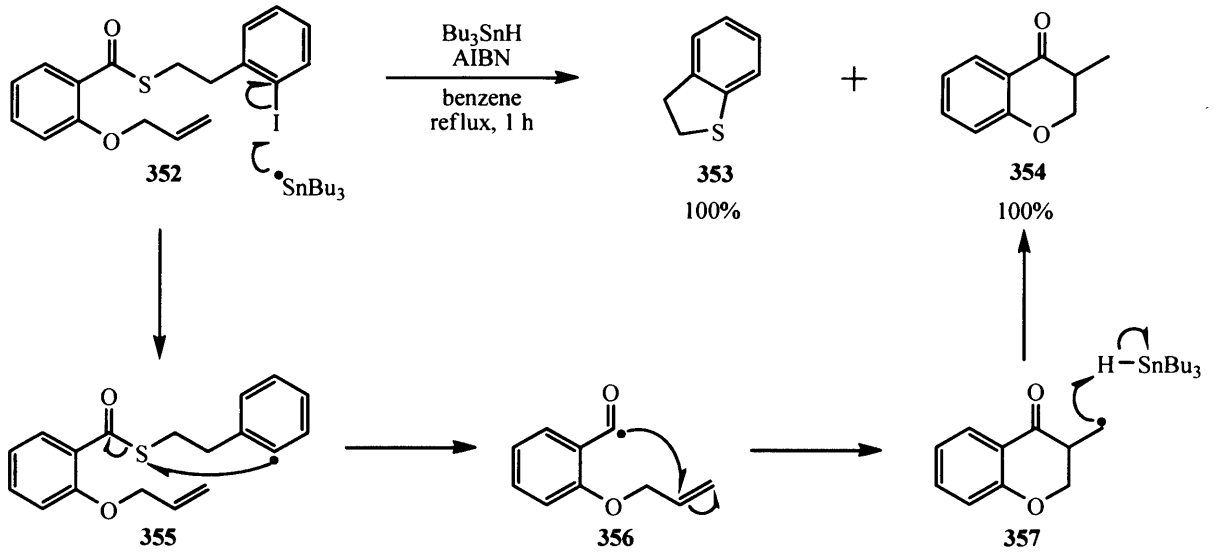
Scheme **135**

Several kahweofuran **75** analogues, furans **77**, **76** and **339** were also made by a similar synthetic pathway, showing the versatility of the synthesis for varying the α-substituents of the furan ring (Scheme **136**).



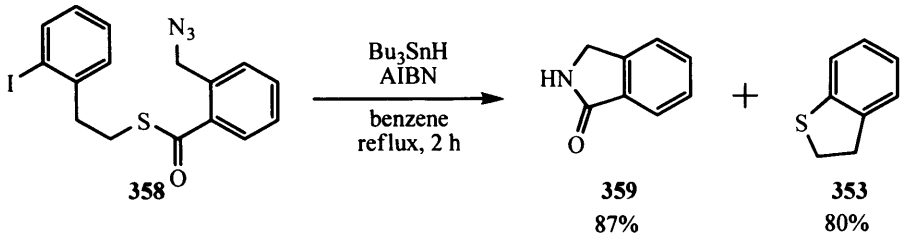
Scheme **136**

During the present project, the idea for a new route to kahweofuran **75** was sparked by a paper published in 1996 by Crich describing the generation of acyl radicals.[164] Crich showed that when aryl iodide **352** was exposed to tributyltin hydride in the presence of the radical initiator azobisisobutyronitrile, aromatic dihydrothiophene **353** and chromanone **354** were formed. Crich suggested that halogen abstraction by a tin radical formed aryl radical **355** which underwent an intramolecular homolytic substitution at the sulfur of the thioester. The resulting acyl radical **356** was then thought to be trapped by the internal double bond before the resulting alkyl radical **357** was quenched (Scheme **137**). In essence the dihydrobenzothiophene **353** is the by-product of Crich's chemistry, which can be considered as an alternative way of generating an acyl radical.



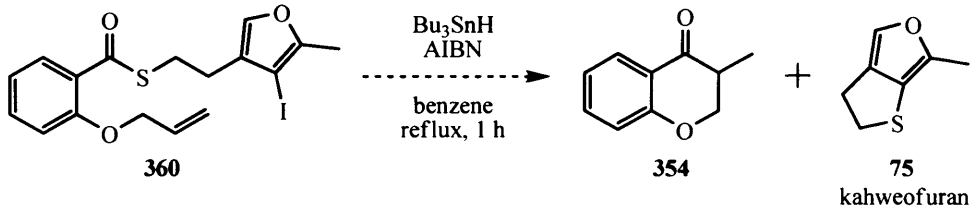
Scheme **137**

In 2002 Spagnolo used Crich's methodology for the formation of acyl radicals to form lactams by using an azide as the radical trap.[165] The resulting intramolecular five-membered cyclisation yielded a cyclised amidyl radical which was further reduced to lactam **359** (scheme **138**).



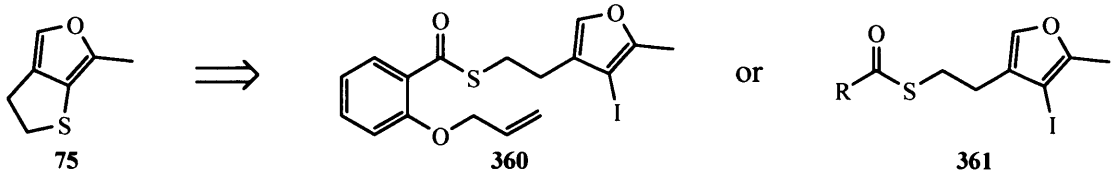
Scheme **138**

Interest regarding kahweofuran **75** was found in the side-product, dihydrothiophene **353**, which was formed in excellent yield during both Crich and Spagnolo's reactions. It was considered that if the methodology could be transferred from a phenyl ring to an appropriate furan, it could be used to close the dihydrothiophene ring of kahweofuran **75** (Scheme **139**). Used to this end, the target of Crich's original work would then become the by-product.



Scheme **139**

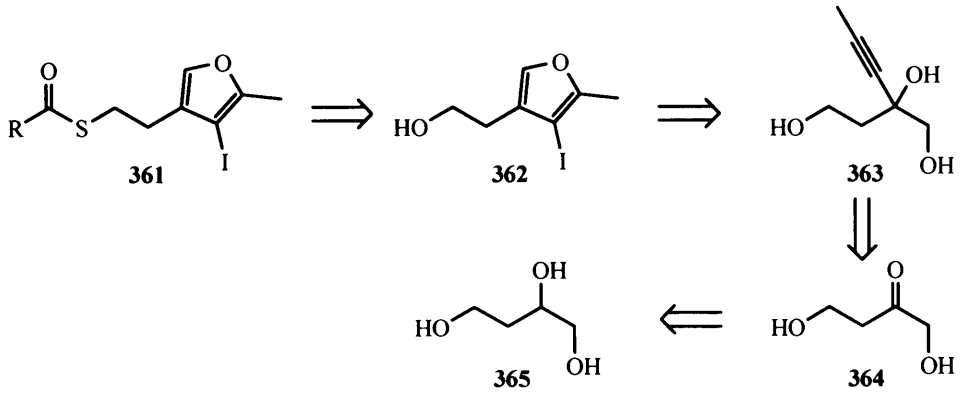
Disconnection of kahweofuran **75** in this manner led to thioester **360** (Scheme **140**). It was considered that an intramolecular radical trap for the acyl radical might not be necessary for the desired reaction to proceed, thus allowing for the use of simpler side chains, *e.g.* thioester **361**.



Scheme **140**

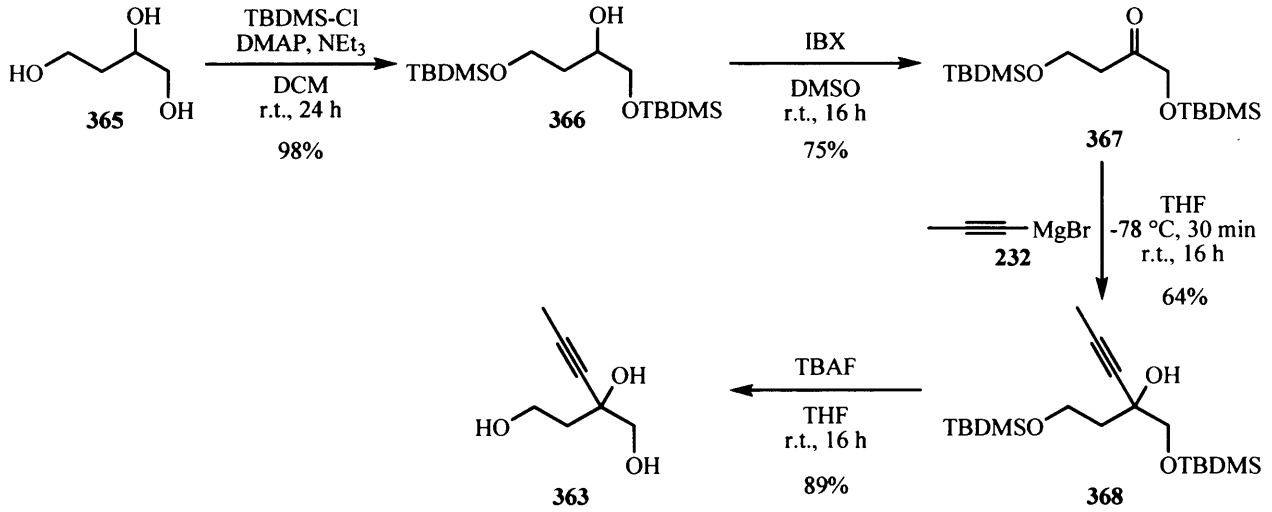
It was considered that thioester **361** should be accessible from iodofuran **362**. The β-iodofuran itself appeared an ideal candidate for synthesis by the iodocyclisation methodology first

developed in the Knight group in 1996,[95] and which has been shown to be particularly versatile (*cf.* p32).[93,94] Disconnection in this manner led back to 3-alkyne-1,2-diol **363** which was thought to be accessible from ketone **364**. The commercially available triol **365** was therefore considered an ideal starting material for the synthesis (Scheme **141**).



Scheme **141**

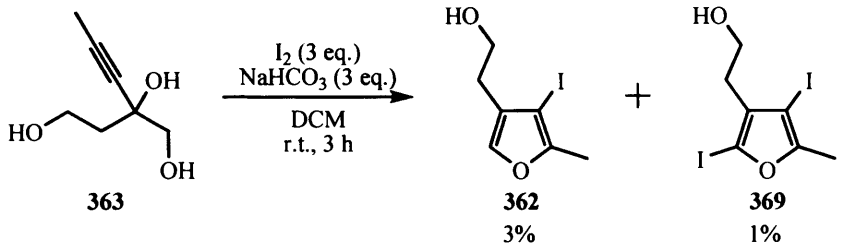
Triol **365** was selectively bis-protected using *tert*-butyldimethylsilyl chloride, and the resulting alcohol **366** oxidised to ketone **367** using 2-iodoxybenzoic acid.[166] The Grignard addition of commercially available 1-propynylmagnesium bromide **232** to the hindered carbonyl of ketone **367** gave alkyne **368** in reasonable yield. This was followed by deprotection using tetrabutylammonium fluoride to yield 3-alkyne-1,2-diol **363** (Scheme **142**).



Scheme **142**

When 3-alkyne-1,2-diol **363** was exposed to the standard iodocyclisation conditions only a small amount of material was recovered following an aqueous work-up. The presence of iodofuran

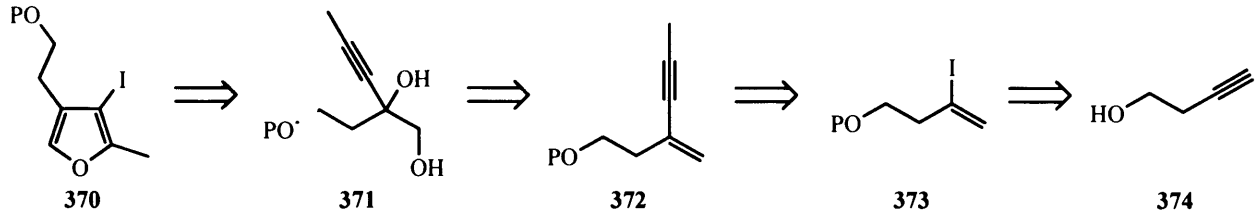
362 was confirmed after column chromatography, albeit in low yield. Based on ^{1}H NMR data it was believed that diiodofuran **369** was also formed during the reaction (Scheme **143**). It is presumed that diiodofuran **369** formed from iodofuran **362** by an electrophilic aromatic substitution reaction with iodine.



Scheme **143**

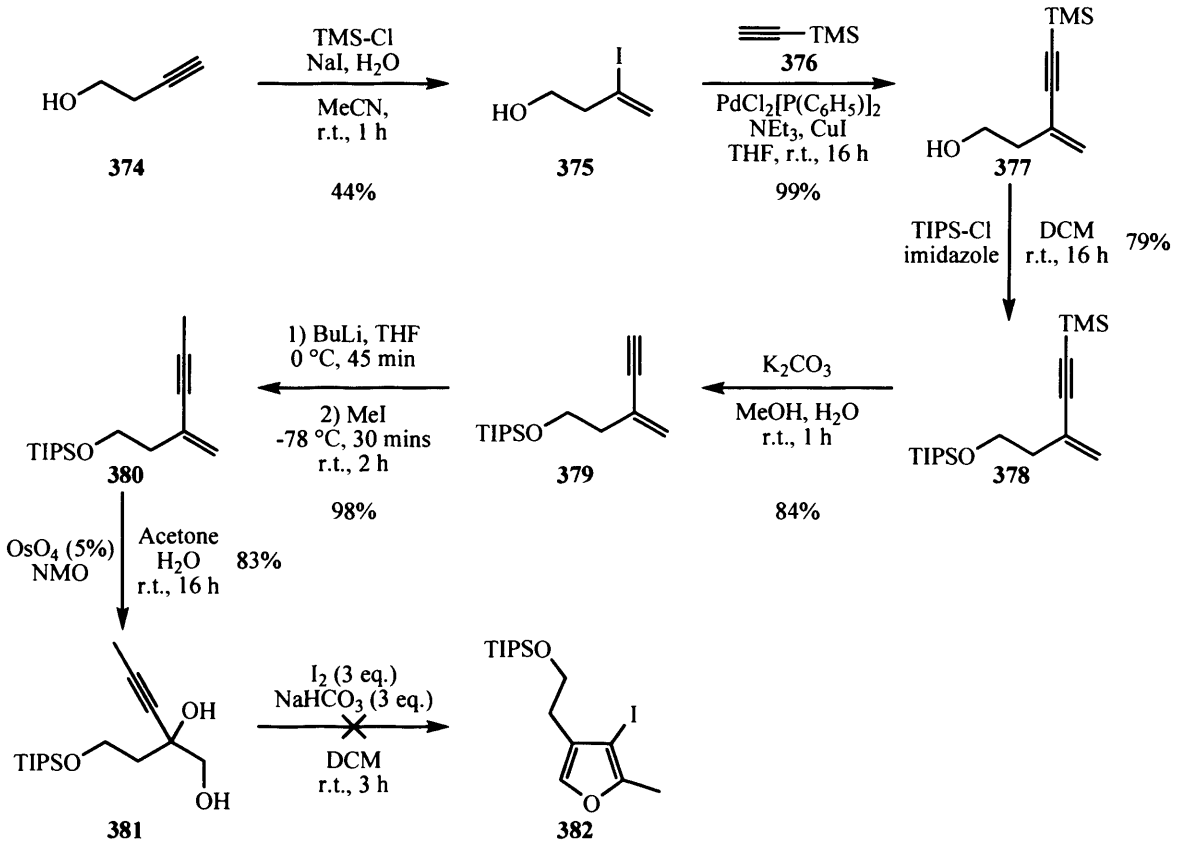
It was therefore assumed that the majority of the highly-polar staring material had remained unreacted and dissolved in the aqueous layer upon work-up. This result led to a body of work being carried out on the cyclisation of triols, which is discussed in Chapter **4** of this thesis (*cf.* p96). A new approach to furan **362** was therefore required. With the iodocyclisation methodology having been shown to work in the presence of a variety of functional groups,[94] it was hoped that protection of the non-participating side-chain alcohol group should allow the reaction to proceed. Selective protection was not deemed possible using the current synthetic route, so a new disconnection was considered.

It was deemed prudent to set up the protected alcohol side-chain before introducing the other alcohol functionalities. It was hoped that this could be achieved by creating the protected enyne **372** which could then be dihydroxylated to give 3-alkyne-1,2-diol **371**. It was considered that enyne **372** could be formed by a transition metal-catalysed coupling reaction on iodoalkene **373** which in turn could be made by Markovnikov hydroiodination of commercially available alkyne **374** (Scheme **144**).[167]



Scheme **144**

3-Butyn-1-ol **374** was exposed to hydrogen iodide which was formed *in situ* from sodium iodide, trimethylsilyl chloride and water in acetonitrile.[168] The reaction produced multiple products, but iodoalkene **375** was isolated in 44% yield after careful column chromatography. The required alkyne functionality was indroduced by a Sonogashira coupling using ethynyltrimethylsilane **376** to give alkyne **377**.[96] A triisopropylsilyl ether was chosen as a suitable protecting group for the alcohol of alkyne **377**. Silyl ether protecting groups find regular use in synthetic organic chemistry due to the ease of their introduction and their susceptibility to nucleophilic attack by fluoride anions.[169] A triisopropylsilyl ether group was chosen due to its greater stability to basic hydrolysis when compared to a *tert*-butyldimethylsilyl or *tert*-butyldiphenylsilyl group.[170] Alkyne **377** was therefore protected using triisopropylsilyl chloride to give alkyne **378**. Basic methanol was used to reveal terminal alkyne **379**, which was subsequently deprotonated using butyllithium and quenched with methyl iodide to yield enyne **380**. The dihydroxylation of enyne **380** proceeded smoothly upon treatment with osmium tetroxide and 4-methylmorpholine *N*-oxide to give 3-alkyne-1,2-diol **381** in 83% yield.[171] The cyclisation of 3-alkyne-1,2-diol **381** under the standard iodocyclisation conditions failed, returning only triisopropylsilyl residues in the organic layer after aqueous work-up (Scheme **145**).



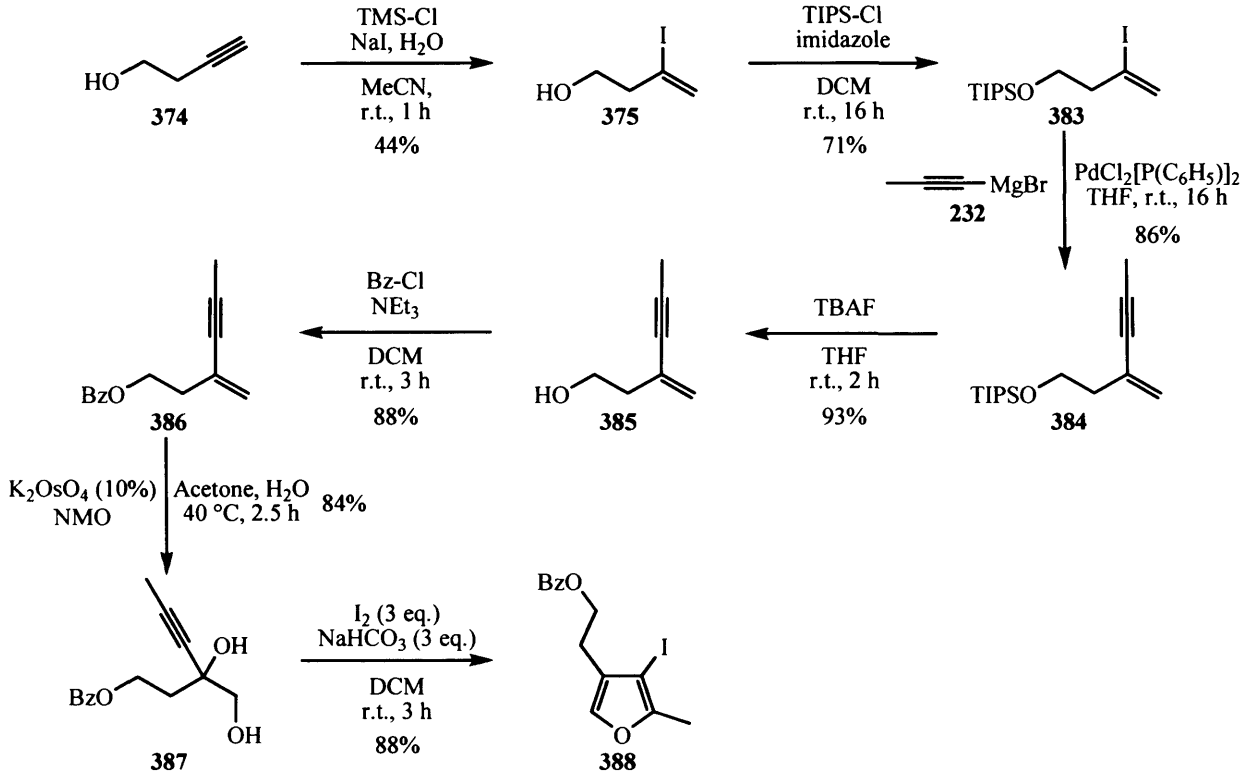
Scheme **145**

This led to the conclusion that the triisopropylsilyl protecting group was not stable to the standard iodocyclisation conditions and was being cleaved faster than furan **382** could be formed. The resulting triol was, once again, failing to cyclise and being lost into the aqueous washings. A protecting group which could survive the iodocyclisation, but which could be removed in the presence of the iodofuran was required. The furan moiety precluded the use of protecting groups which would require oxidative (*para*-methoxybenzyl) or acidic (tetrahydropyran) conditions for removal. The aryl iodide also meant that a protecting group which required removal by reductive hydrogenation (benzyl) would be unsuitable as this functionality would likely be lost. It was considered that a benzoyl ester should survive the iodocyclisation conditions and that the resulting iodofuran should be unaffected by the basic aqueous conditions required for its removal.[169]

A review of the literature suggested that the synthesis may be improved by the use of a Kumada cross-coupling reaction.[172] Although not Nobel Prize winning,[173] Kumada's publication in 1972 on the cross-coupling of organomagnesium compounds with aryl halides using a nickel catalyst marked the beginning of cross-coupling chemistry.[174] The reaction has also been shown to work with palladium as the catalyst. A Kumada cross-coupling reaction has an advantage over many other cross-coupling reactions as it proceeds readily at low temperature. A disadvantage is the limited functional group compatibility of the Grignard reagents which are required for the reaction.[175] Despite suffering from the addition of an extra protection and deprotection step to account for this disadvantage, a new synthesis of kahweofuran **75** was attempted involving a Kumada coupling and employing a benzoyl protecting group.

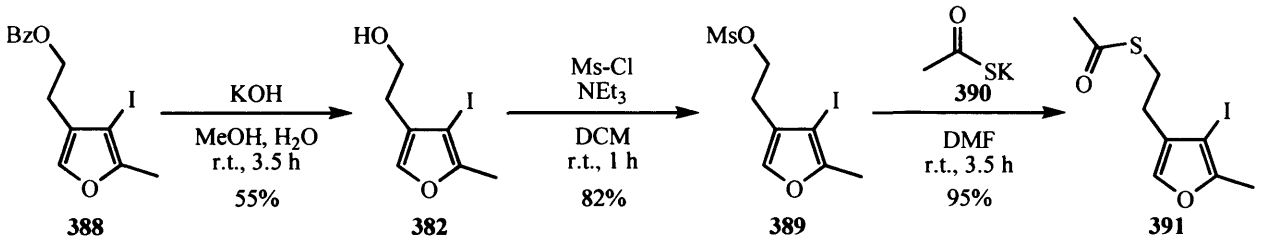
Alcohol **375** was again made from 3-butyn-1-ol **374** before being protected with triisopropylsilyl chloride to give iodoalkene **383**. The Kumada coupling of iodoalkene **383** and 1-propynylmagnesium bromide **232** proceeded smoothly to give alkyne **384** which required no further purification after a simple filtration. Alkyne **384** was deprotected using tetrabutylammonium fluoride to reveal alcohol **385** which was protected as the benzoyl ester to give enyne **386**. The dihydroxylation of enyne **386** with osmium tetroxide and 4-methylmorpholine *N*-oxide was initially problematic, giving a low conversion after 72 hours. A brief investigation showed that the reaction underwent full conversion in much shorter time periods when an "excess" of 4-methylmorpholine *N*-oxide was used. This led to the conclusion that the sample of 4-methylmorpholine *N*-oxide which had been used had decomposed and was therefore not a stoichiometric oxidant. The problem was overcome by the use of a new sample

of 4-methylmorpholine *N*-oxide, which gave satisfactory results when used in stoichiometric quantities. The best yield of 3-alkyne-1,2-diol **387**, 84%, was achieved when the reaction was warmed to 40 °C for 2.5 hours. At room temperature the reaction required 6 hours to undergo full conversion and resulted in a 66% yield. It is postulated that the propargylic tertiary alcohol may be unstable under the aqueous basic conditions of the dihydroxylation and that the longer exposure time at room temperature led to an increased decomposition of 3-alkyne-1,2-diol **387**. Pleasingly the 3-alkyne-1,2-diol **387** successfully underwent cyclisation under the standard iodocyclisation conditions to yield iodofuran **388** (Scheme **146**).



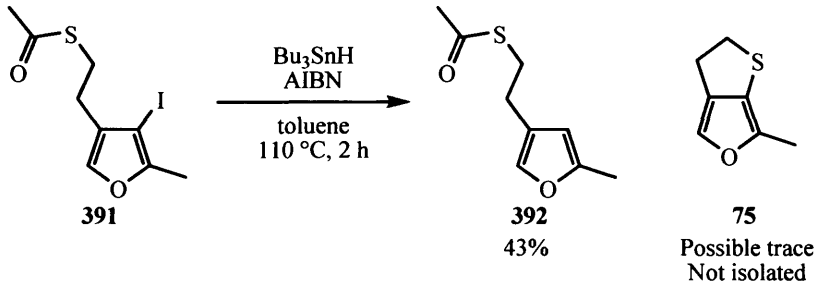
Scheme **146**

With the iodofuran moiety secured, attention turned to the introduction of sulfur and the closing of the dihydrothiophene ring. Hydrolysis of the benzoyl protecting group in basic aqueous methanol revealed alcohol **382** in slightly disappointing yield. Conversion to the mesylate ester **389** allowed thioester **391** to be formed by an S_N2 reaction with potassium thioacetate **390** (Scheme **147**).



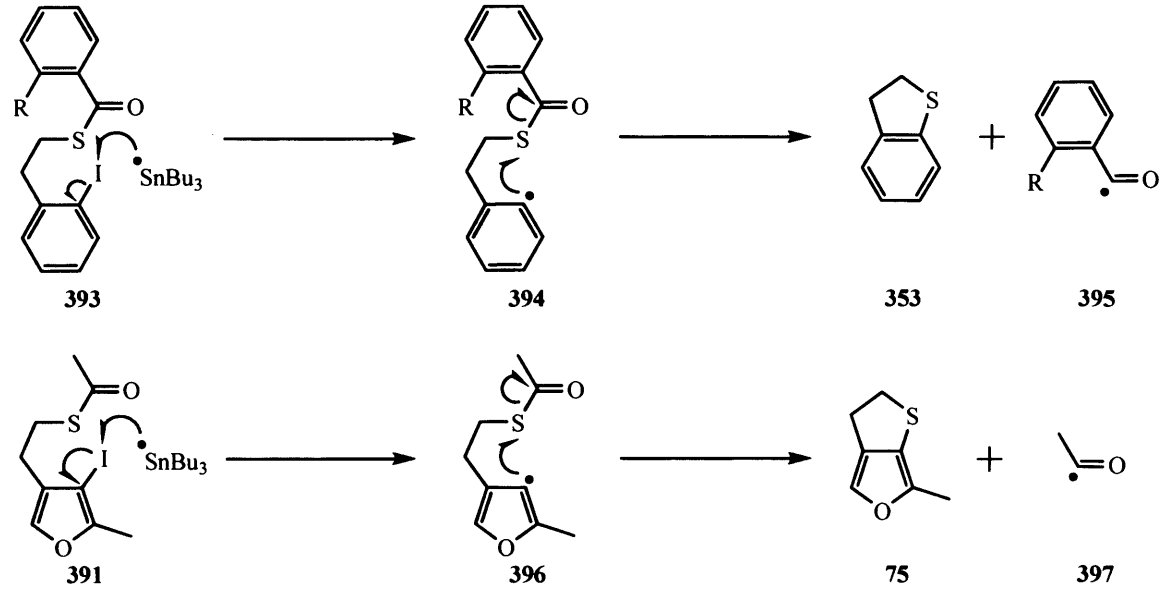
Scheme **147**

Despite not containing the radical trap which Crich had used, it was hoped that thioester **391** would form kahweofuran **75** if the aryl iodide bond could be homolytically cleaved. Crich's method was followed, except that toluene was used in the place of benzene (Scheme **148**).



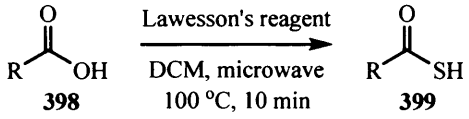
Scheme **148**

^{1}H NMR analysis of the crude reaction mixture suggested that the major product of the reaction was the de-iodinated furan **392**. This was believed due to the appearance of a new singlet at 5.89 ppm which is characteristic of a proton in the β-position of a furan ring. The ^{1}H NMR spectrum of the crude product also revealed a small triplet at 3.63 ppm with a 7.3 Hz coupling which the literature showed to be consistent with the furan-C$\underline{H_2}$CH$_2$ protons of kahweofuran **75**. Kahweofuran **75** was not isolated upon purification of the crude product by column chromatography, but the presence of furan **392** was confirmed, and full characterisation data were obtained. It was therefore supposed that the desired aryl radical was forming, but was being terminated before cyclisation onto the thioester could occur. It was postulated that the failure of the acyl radical to form could be related to its stability. In the work of both Crich and Spagnolo, phenyl substituted acyl radicals of the type **395** were formed, as opposed to the alkyl substituted acyl radical **397** required in the case of thioester **391** (Scheme **149**). It was therefore decided that the reaction should be attempted with the full Crich radical trap present on the thioester to see if this encouraged the formation of kahweofuran **75**.



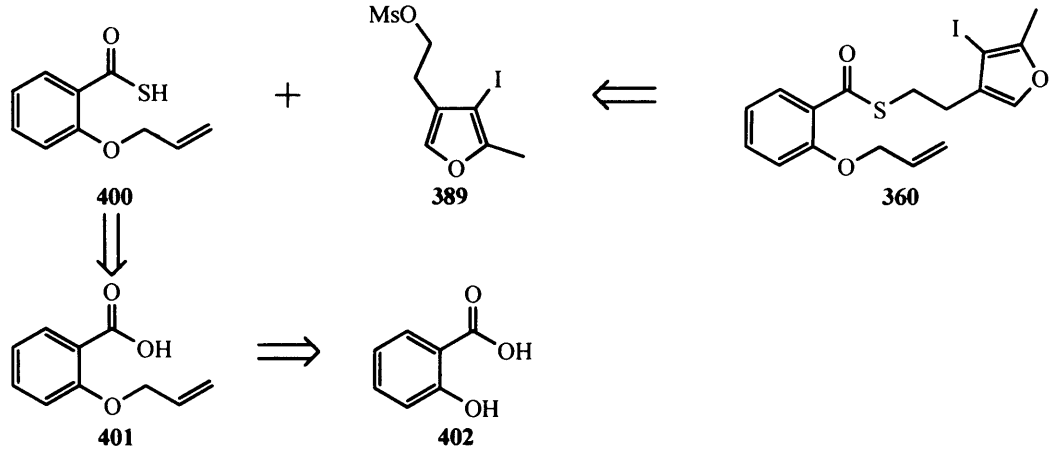
Scheme **149**

While searching the literature for inspiration regarding the formation of thioesters, it was found that Danishefsky had recently published a short paper on the conversion of carboxylic acids **398** into thioacids **399** with Lawesson's reagent (Scheme **150**).[176,177]



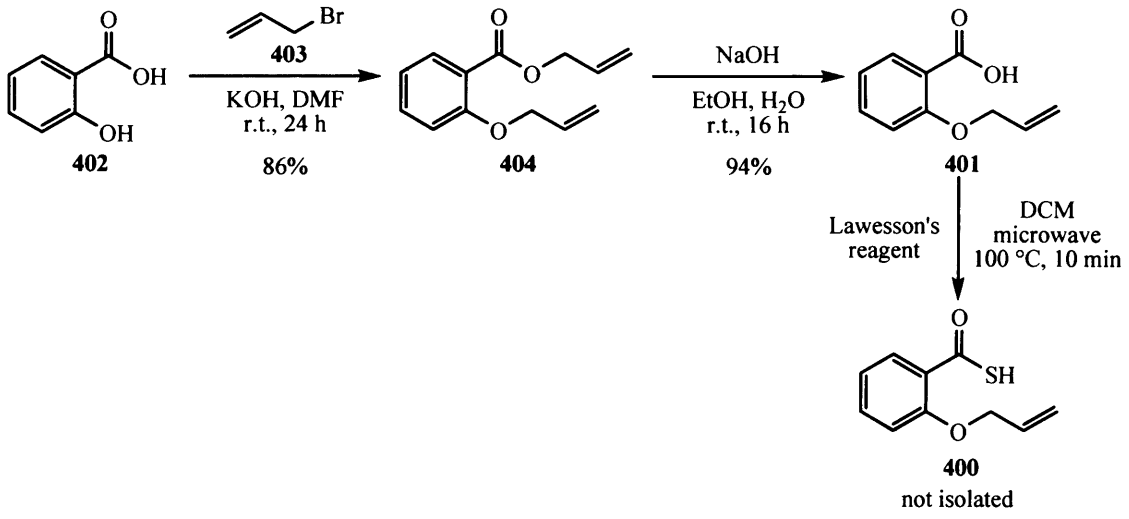
Scheme **150**

The work stood out as being particularly efficient when compared to the methods commonly used for this transformation. Such methods include the pre-forming of an activated carboxylic acid and its reaction with a hydrogen sulfide anion,[178] or coupling of a carboxylic acid with a protected form of hydrogen sulfide before deprotection.[179] It was therefore hoped that thioacid **400** could be prepared from acid **401**, which can be accessed from salicylic acid **402**.[180] The synthesis of thioester **360** was then envisaged by the reaction of thioacid **400** with mesylate **389** (Scheme **151**).



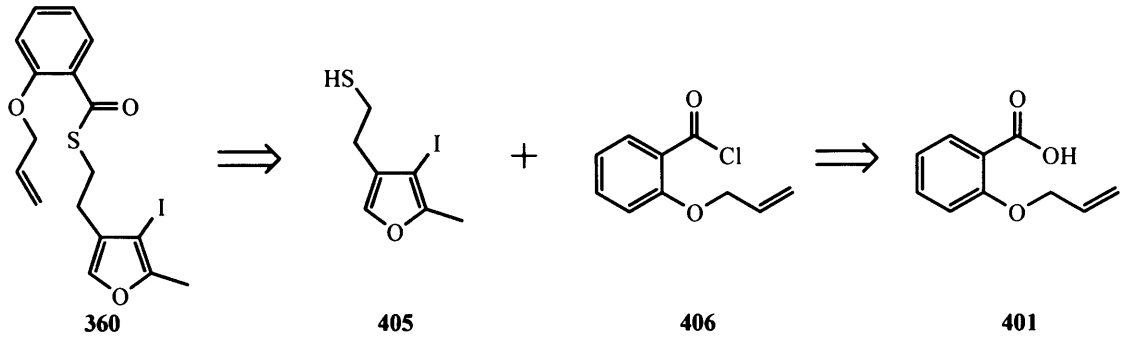
Scheme **151**

Salicylic acid **402** was doubly alkylated using allyl bromide **403** in the presence of potassium hydroxide to give ester **404**. Hydrolysis of the ester functionality was then performed using sodium hydroxide in aqueous ethanol to give the required acid **401** in 94% yield. After acid **401** had been exposed to Danishefsky's conditions the ^{1}H NMR spectrum revealed that the crude reaction mixture contained the starting acid **401** and a new product, possibly thioacid **400**, in an approximately 1:1 ratio (Scheme **152**). The ^{1}H NMR spectrum also showed multiple peaks from unidentified products. Analysis of the ^{13}C NMR data showed a new quaternary peak at 188.5 ppm, a characteristic shift for a thiobenzoic acid.[176] All attempts to isolate thioacid **400** failed, returning only acid **401**. Danishefsky had suggested that the thioacids formed by this method can be purified by filtration followed by flash column chromatography. He also mentioned that some substrates required fast purification due to the instability of the thioacids to column chromatography. It was therefore considered that thioacid **400** may have not been stable on silica gel.



Scheme **152**

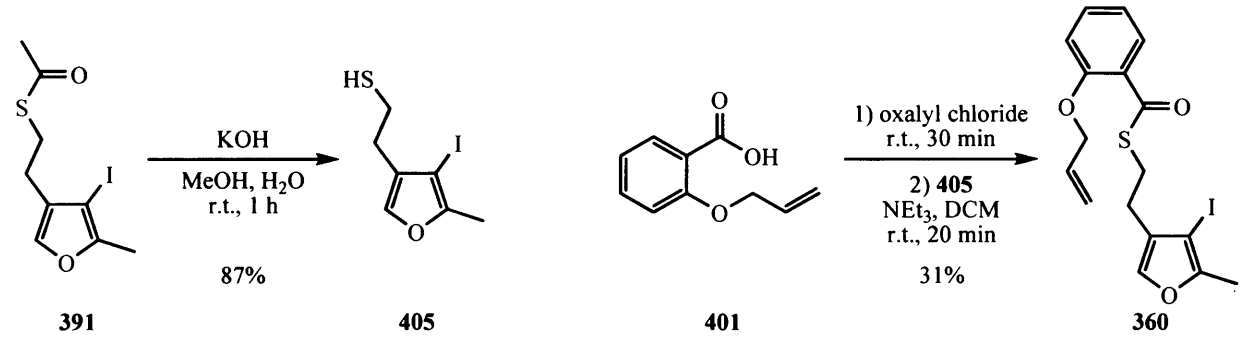
An alternative route for the synthesis of thioester **360** was therefore required. Crich had shown that acid **401** can be converted to an acid chloride **406** using oxalyl chloride.[164] It was therefore envisaged that thioester **360** could be made from acid chloride **406** and thiol **405** (Scheme **152**).



360 **405** **406** **401**

Scheme **153**

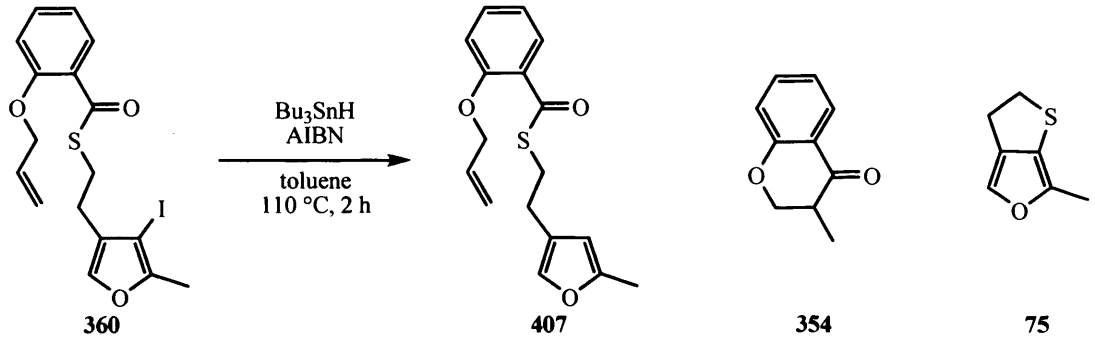
Thiol **405** was made by hydrolysis of the previously discussed thioester **391** and coupled with acid **401** *via* the *in situ* formation of the corresponding acid chloride **406**. Thioester **360** was formed successfully but in disappointing yield (Scheme **154**). The reaction was only attempted once and it was hoped that if the synthesis ultimately proved successful the yield of this step could be significantly improved by optimisation of the conditions.



391 **405** **401** **360**

Scheme **154**

Exposure of thioester **360** to tributyltin hydride and azobisisobutyronitrile in refluxing toluene for 1 hour led to a faint sulfurous smell emanating from the reaction flask. The ^{1}H NMR spectrum of the crude reaction product was difficult to interpret due the large amount of tributyltin residues which were present. The main product of the reaction appeared to be a furan **407**, the de-iodinated form of the starting material. Using the literature data for comparison it was tentatively suggested that the crude reaction mixture also contained traces of ketone **354** and kahweofuran **75** (Scheme **155**).



360 **407** **354** **75**

major product trace trace

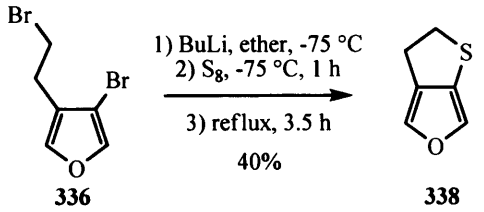
Scheme **155**

The compounds produced from this reaction were not fully separable by column chromatography and so full characterisation data was not obtained. ^{1}H NMR analysis of the fraction possessing a mildly sulfurous smell appeared to reveal a small quantity of kahweofuran **75** along with an overwhelming amount of tributyltin residues. A later fraction, despite containing a mixture of products, went some way to allowing for the identification of furan **407**. ^{1}H NMR analysis of this fraction showed peaks very similar to those of thioester **360**, but with an additional singlet at 5.95 ppm, which was believed to be caused by the proton on the β-position of the furan ring of furan **407**. Further evidence for the presence of furan **407** came from the shift of the peak representing the proton on the α-position of the furan ring, which now came at 7.23 ppm, compared to 7.14 ppm in the starting thioester **360**. This fraction also appeared to contain ketone **354** with the majority of its literature-stated peaks visible.

The failure to form kahweofuran **75** in significant yield from either of the radical cyclisations led to the theory that there was a fundamental difference in the reactivity of the 2,4-substitued furan 3-radical compared to the 1-substituted aryl 2-radical formed in Crich's work. Due to the apparent formation of a small quantity on kahweofuran **75** it was considered that there was a possibility of improving the yield if the reaction conditions were optimised. Despite being considered rather elegant, it was concluded that the radical cyclisation methodology was not atom efficient and that purification could be problematic.[181] Optimisation of the reaction was therefore not attempted and the literature was once again turned to for inspiration as to an alternative synthesis.

During Rewicki's synthesis of kahweofuran **75** it had been shown that if a sulfur anion could be generated while an appropriate leaving group was present on the side-chain, the dihydrothiophene ring could be closed (Scheme **156**) (*cf.* p71).[156] The low yield of this step in

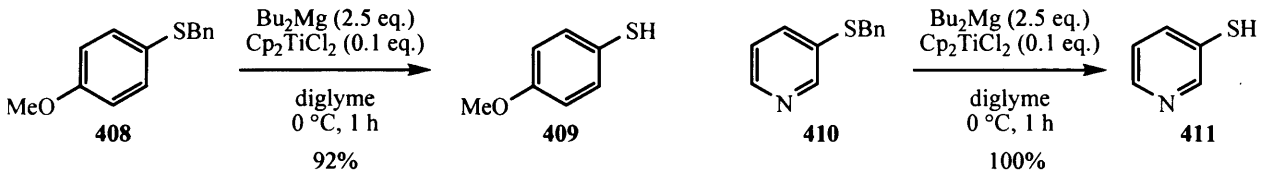
Rewicki's synthesis, and previous experience within the Knight group,[182] suggested that there may be problems with the solubility of elemental sulfur in ether solvents at the low temperatures required for the reaction.



336 **338**

Scheme **156**

An alternative approach towards the creation of a sulfur anion was therefore required. Deprotection of a protected thiol was considered to be a viable method. Benzyl thioethers are commonly used when a thiol is later required to be unmasked. Deprotection of these groups often requires harsh conditions such as the use of strong acids or bases, reduction using alkali metals or stannyl hydrides, or reductive electrolysis.[169] A recent publication by Akao reported a milder method for the deprotection of benzyl protected aryl thiols using dibutylmagnesium in the presence of a catalytic amount of titanocene dichloride.[183] The method was shown to give excellent yields for thiols on both electron-rich aromatics **408** as well as heteroaromatics **410** (Scheme **157**). The basic reaction conditions should ensure the formation of a sulfur anion which would then have the opportunity to perform a nucleophilic attack, were a leaving group suitably positioned.

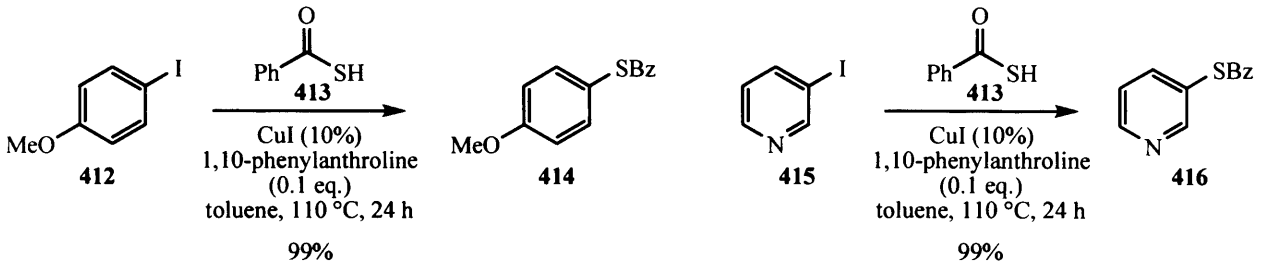


408 **409** **410** **411**

Scheme **157**

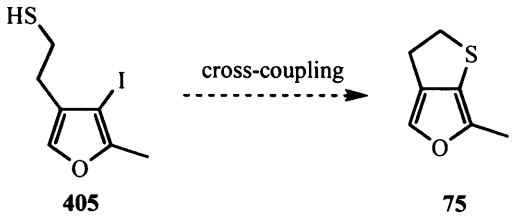
A method was therefore required for the conversion of an aryl iodine into a protected thiol. A recent paper by Sawada described the first transition-metal-catalysed coupling reaction of aryl halides and thiobenzoic acid using 10 mol% copper iodide and 20 mol% 1,10-phenanthroline in toluene (Scheme **158**).[184] The reaction had been shown to be highly effective on both electron rich aromatics **412** as well as heteroaromatics **416**. Although not providing a benzyl thioether, it

was considered that the benzoyl thioester which was installed could be cleaved under aqueous basic, or reductive conditions, to provide the desired sulfur anion.[169]



Scheme **158**

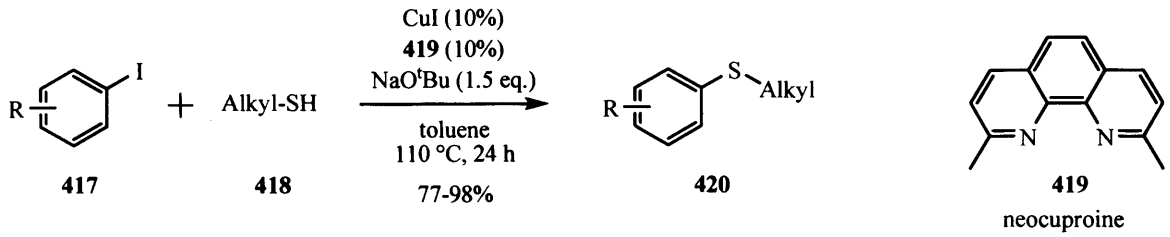
Although a route to kahweofuran **75** which used the cyclisation of a sulfur anion was considered a promising idea, inspiration for a new approach was found in a review by Beletskaya[185] on the development of Ullmann copper-assisted coupling reactions.[186] It was considered that it might be possible to perform an intramolecular C-S bond-forming cross-coupling reaction on thiol **405**, a compound already synthesised during an earlier attempt to synthesis kahweofuran **74** (Scheme **159**).



405 **75**

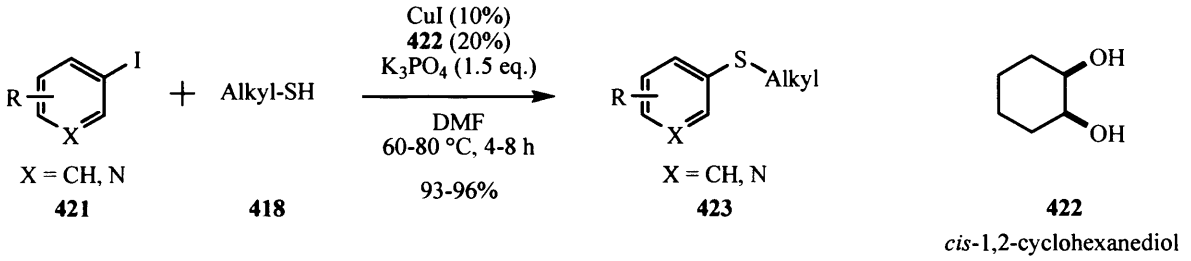
Scheme **159**

The cross-coupling of aryl halides and thiols was first reported by Migita in 1980,[187] and the reaction has since become well known.[188] Although excellent procedures exist for the coupling of aryl triflates with alkyl thiols,[189] and of aryl iodides with aryl thiols,[190] general procedures for the coupling of aryl iodides and alkyl thiols are far rarer.[191,192] The majority of these procedures use catalytic palladium, so it was of interest when Venkataraman reported a general procedure for the formation of aryl-sulfur bonds using catalytic copper iodide and neocuproine **419** along with an excess of sodium *tert*-butoxide (Scheme **160**).[193] Although employing milder conditions than traditional copper-mediated reactions,[194] Venkataraman's method still required the components to survive refluxing toluene for 24 hours. The harshness of the conditions led to concern over their compatibility with small furan-containing compounds such as kahweofuran **75**.



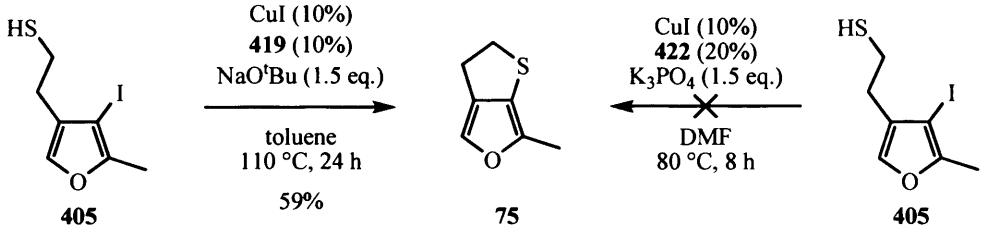
Scheme **160**

Interest in the topic was reignited when a very recent publication by Cook disclosed a new copper-catalysed system for the synthesis of aryl, heteroaryl and vinyl sulfides.[195] Cook's procedure used 10 mol% copper iodide, 20 mol% *cis*-1,2-cyclohexanediol **422** and an excess of potassium phosphate in warm dimethylformamide for up to 8 hours (Scheme **161**).



Scheme **161**

Thiol **405** was exposed to both Venkataraman and Cook's conditions in the hope of forming kahweofuran **75** (Scheme **162**).



Scheme **162**

Although Cook's method failed, Venkataraman's method resulted in a 100% conversion of thiol **405**. ^{1}H NMR analysis of the crude reaction product showed it to contain kahweofuran **75**, with toluene as the only major impurity. Toluene was not fully removed from the crude product due to concerns over the volatility of kahweofuran **75**, which was isolated in 59% yield after column chromatography. The structure was confirmed by NMR (^{1}H, ^{13}C, COSY, HSQC, HMBC) spectroscopy, infra-red spectroscopy, and mass spectrometry analysis. The data obtained were consistent with the published data, as can be seen on the following page (Schemes **163** and **164**).

^{1}H NMR

This thesis ($CDCl_3$)				
ppm	Integration	Splitting	Coupling	
6.99	1 H	app s		
3.63	2 H	t	7.2	
2.88	2 H	td	7.2	1
2.21	3 H	s		

Büchi (CCl_4)				
ppm	Integration	Splitting	Coupling	
6.91	1 H	t	1.5	
3.57	2 H	t	7	
2.81	2 H	t (with fine splitting)	7	1.5
2.17	3 H	s		

Rewicki ($CDCl_3$)				
ppm	Integration	Splitting	Coupling	
6.99	1 H	t	1.5	
3.64	2 H	t	7	
2.90	2 H	"dt"	7	1.5
2.17	3 H	s		

IR

King	Thin film	1633	1577	1103	1070	921
Büchi	$CHCl_3$	1630	1575	1100	1075	920
Rewicki	No data					

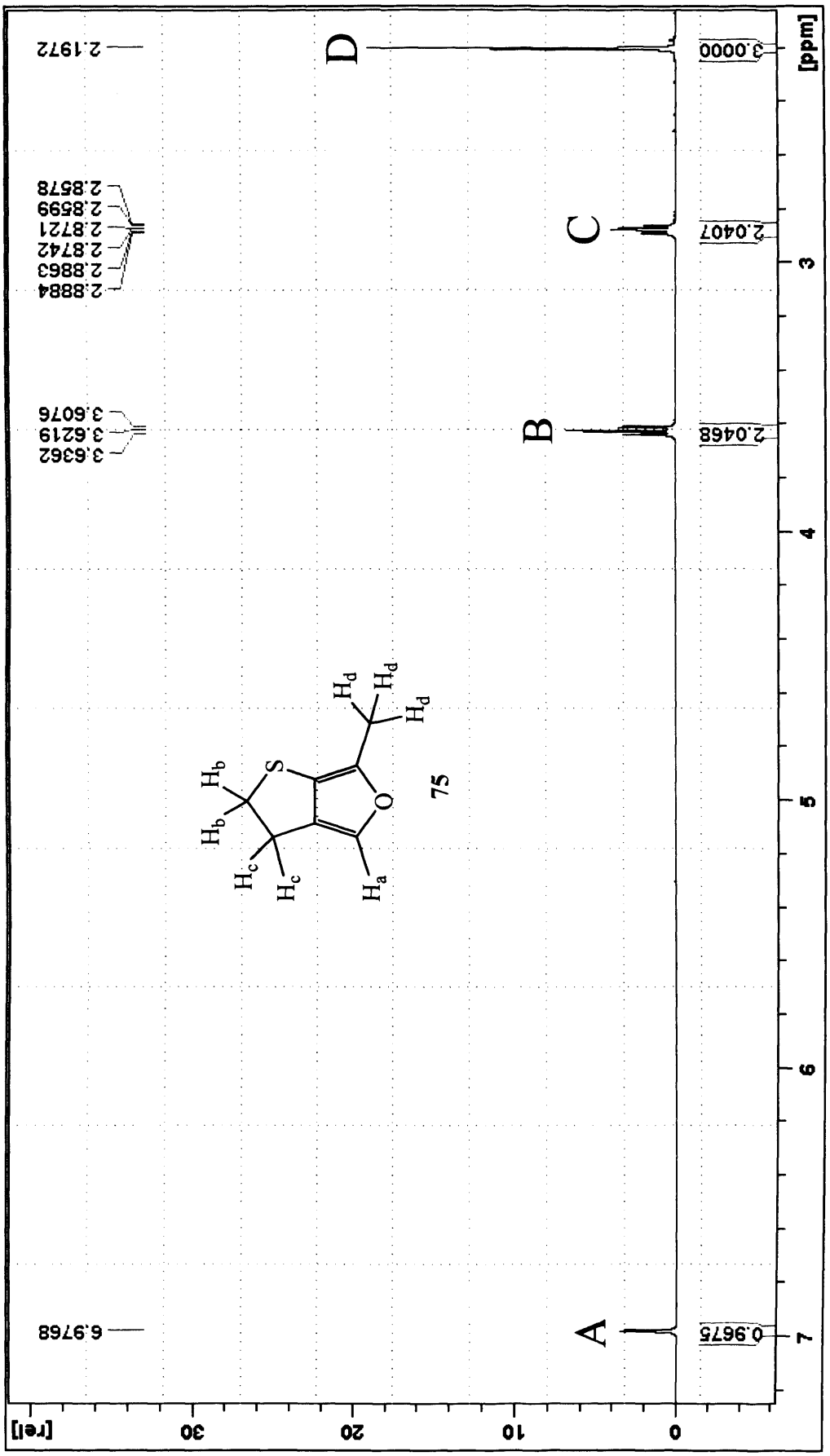
LRMS

King	EI	140.0 (46%)	111.0 (20%)	97.0 (15%)	83.94 (100%)
Büchi	EI	140 (100%)	111 (38%)	97 (29%)	
Rewicki	CI	140 (100%)	111 (52%)	97 (43%)	

HRMS

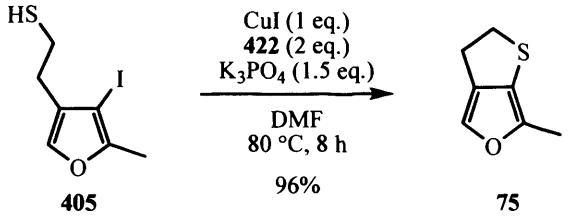
King	*m/z*	140.029
Büchi	No data	
Rewicki	*m/z*	140.03

Scheme **163**


D
C
B
A
2.1972
2.8578
2.8599
2.8721
2.8742
2.8863
2.8884
3.6076
3.6219
3.6362
6.9768
3.0000
2.0407
2.0468
0.9675
[ppm]
[rel]
0
10
20
30
3
4
5
6
7
S
O
H_a
H_b
H_c
H_d
75

Scheme **164**

To give Cook's procedure a greater chance of success, the molar equivalents of the catalyst, copper iodide, and the ligand, neocuproine **422**, were increased tenfold and the reaction repeated. This resulted in a 96% yield of kahweofuran **75** (Scheme **165**). Cook's procedure appeared advantageous over Venkataraman's method due to ease of work-up, which was suspected to have played a major role in the improved isolated yield of kahweofuran **75**. Venkataraman's method did not seem ideal for the isolation of low-boiling, low-polarity products as it required the removal of toluene, a high-boiling, low-polarity solvent. The use of dimethylformamide in Cook's procedure allowed the product to be extracted into a low-boiling, non-polar solvent from which it could be more easily isolated.

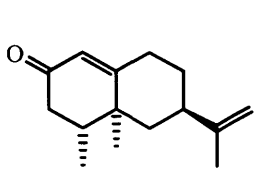


Scheme **165**

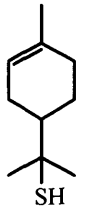
Büchi statement that "*kahweofuran in the pure state has a violent sulfury odor, but in high dilution it develops a pleasant roasted and smoky note*" meant that it was surprising when the sample of kahweofuran **75** isolated possessed only a weak odour.[153] After a sample had been left open to the air for 1 h in a small room, a smell could only be detected when the compound was placed directly under the nose, and then only gave off a faint burnt and sulfury odour. Of the four previous synthesise of kahweofuran **75**, it is only Büchi's original paper that describes the smell of the final compound. Although Rewicki, Fuganti and Katsumura all recognise that kahweofuran **75** has previously been described as a flavour or aroma component of roasted coffee, their papers do not comment on any smell noted during the synthesis. It is therefore tentatively suggested that kahweofuran **75** may not be a major constituent of coffee aroma. It is considered possible that kahweofuran **75** has never previously been made in such purity and that the pleasant odour it had been associated with was due to a minor, highly-fragrant impurity. It may alternatively be that Rewicki, Fuganti and Katsumura did produced clean kahweofuran **75**, but failed to comment on its lack of smell due to the indoctrination of a connection between kahweofuran **75** and a strong odour.

Although this hypothesis has not been proven, stories of this type are not unknown. As mentioned previously, in 1964 MacLeod reported that the bicyclic conjugated sesquiterpene

ketone, nootkatone **65**, was a primary flavour-impact compound in grapefruit.[50] This led MacLeod to suggest that the content of nootkatone **65** should be used as a quality-index standard in grapefruit oil.[51] Stevens reported in 1970 that when nootkatone **65** was crystallised from grapefruit oil, the aroma of the mother liquor was judged to be far more potent and grapefruit-like than nootkatone **65** itself.[52] He did not, however, go on to draw any conclusions as to the importance of nootkatone **65** as a flavour-impact compound. It was not until 1981 that Shaw suggested that nootkatone **65** might not be the most important flavour component in grapefruit oil after studying the aroma of nootkatone **65** using 12 experienced aroma and taste panel members.[53] Shaw's paper concluded that "*other constituents of (grapefruit) oil modify the flavour of this agent at above-threshold levels*". It was left to Ohloff in 1982 to reveal that 2-(4-methylcyclohex-3-enyl)propane-2-thiol (grapefruit mercaptan) **14** was the potent character-donating constituent of grapefruit juice, in which it occurs at a below ppb-level (Scheme **166**) (*cf.* p14).[23]



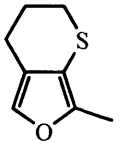
65



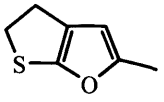
14

Scheme **166**

Although kahweofuran **75** lacked a strong fragrance character, analogues were still considered for synthesis. Dihydrothiopyran **425** was considered as its synthesis would show versatility in the methodology. The structural isomer of kahweofuran, furan **426**, was considered particularly interesting due to its rare heterocyclic system (Scheme **426**).[196] Time restrictions prevented the completion of either analogue, but some progress towards each of them was achieved.



425

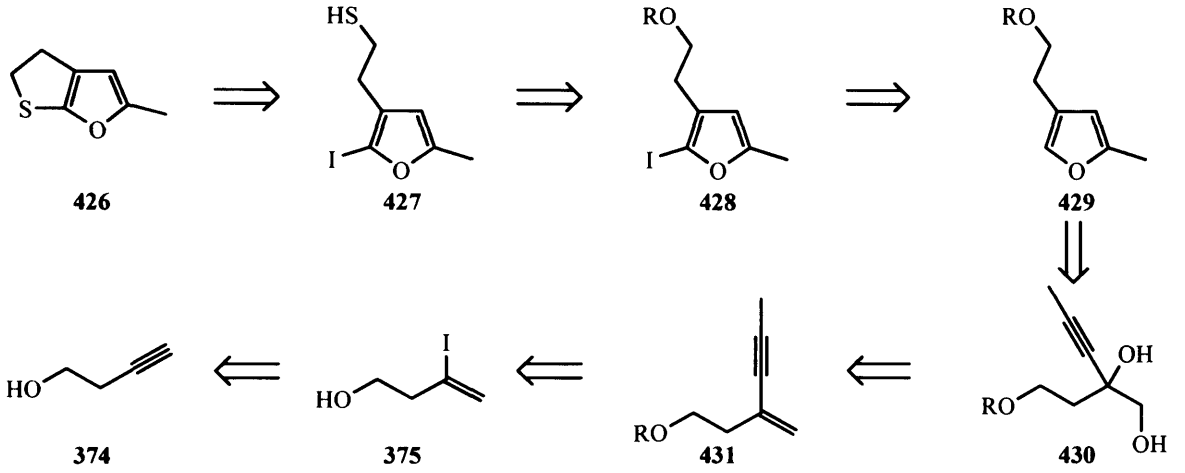


426

Scheme **167**

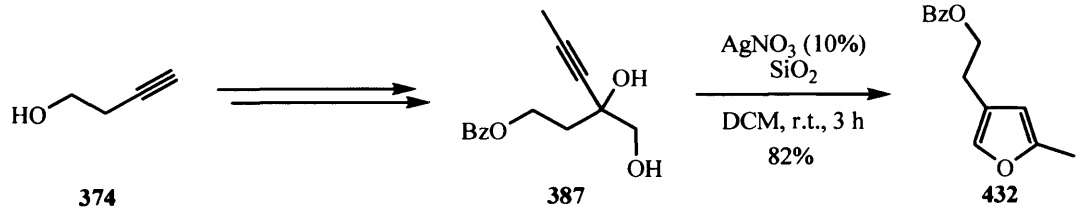
The disconnection of furan **426** suggests that it might be accessible from 3-alkyne-1,2-diol **430**, the same compound as was used in the synthesis of kahweofuran **75**. Silver catalysed cyclisation

of 3-alkyne-1,2-diol **430** should produce furan **429**, which could then be selectively iodinated in the α-position of the furan ring to produce iodofuran **428**.[197] Conversion of the protected alcohol to a thiol should again be possible by mesylation and displacement by potassium thioacetate followed by hydrolysis. The final step was hoped to be achieved by an intramolecular copper iodide catalysed coupling using the conditions employed during the synthesis of kahweofuran **75** (Scheme **168**) (*cf.* p88).



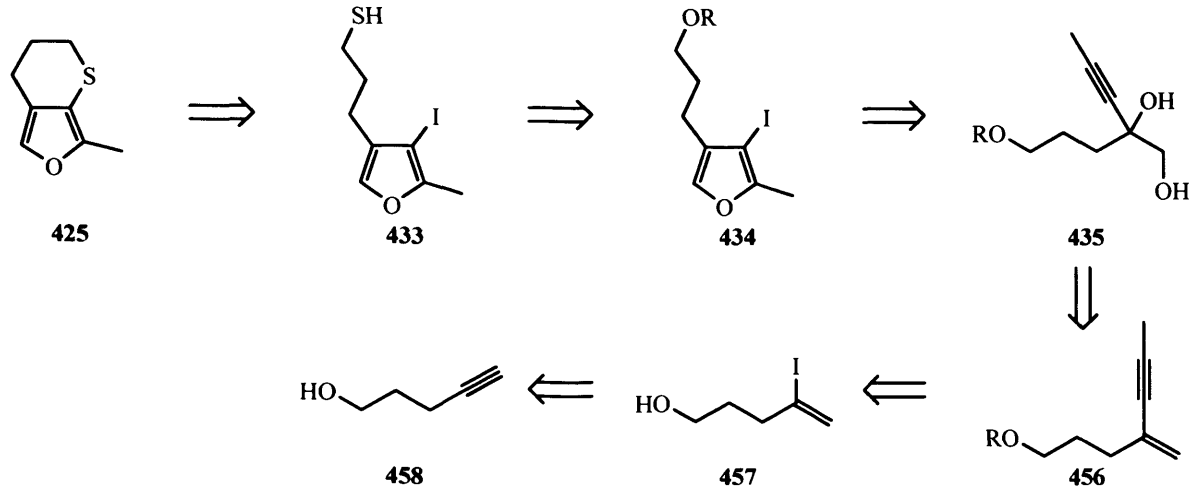
Scheme **168**

Exposure of 3-alkyne-1,2-diol **387** to the standard silver cyclisation conditions produced furan **432** in 82% yield (Scheme **169**). The formation of furan **432** gave great hope for the synthetic route, but no further progress has yet been made in the synthesis due to restrictions of time.



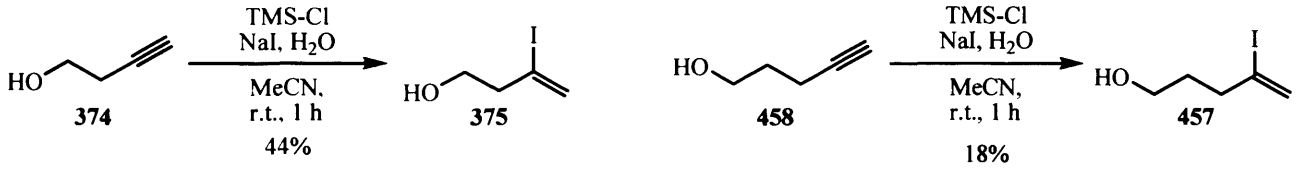
Scheme **169**

The disconnection of dihydrothiopyran **425** suggested that it could be made by a very similar forward synthesis to that of kahweofuran **75**, with the exception of having an extra carbon unit in the side chain (Scheme **170**).



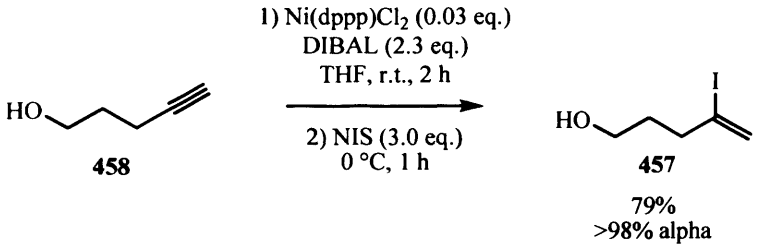
Scheme **170**

The first step in the synthesis of kahweofuran **75** was the hydroiodination of alkyne **374** by exposure to hydrogen iodide which was formed *in situ* (*cf.* p78). This reaction had proved somewhat troublesome, giving a 44% yield after careful column chromatography. When the formation of alcohol **457** was attempted from alkyne **458** by the same method, careful column chromatography was again required and resulted in a disappointing 18% yield (Scheme **171**).



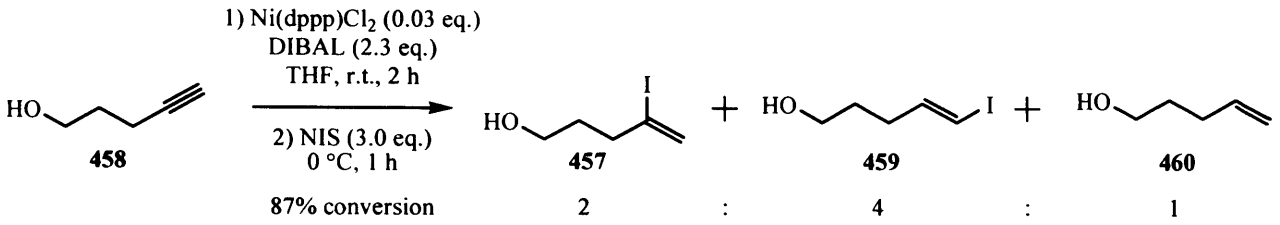
Scheme **171**

It was therefore timely that Hoveyda published an α-selective nickel-catalysed hydroalumination methodology for terminal alkynes which allowed for their conversion to vinyl halides.[198] Before this paper, all existing terminal alkyne hydroaluminations favoured the β-substituted isomer. Hoveyda showed his procedure to work on alkyne **458**, the compound required for the synthesis of dihydrothiopyran **425** (Scheme **172**).



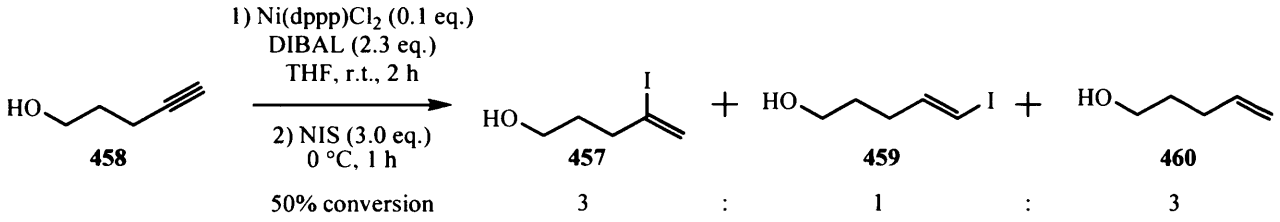
Scheme **172**

These results could not be repeated, with the reaction giving a mixture of the desired alcohol **457**, along with *trans*-iodoalkene **459** and alkene **460** in a roughly 2:4:1 ratio (Scheme **173**). The products could not be fully separated by column chromatography despite multiple attempts.



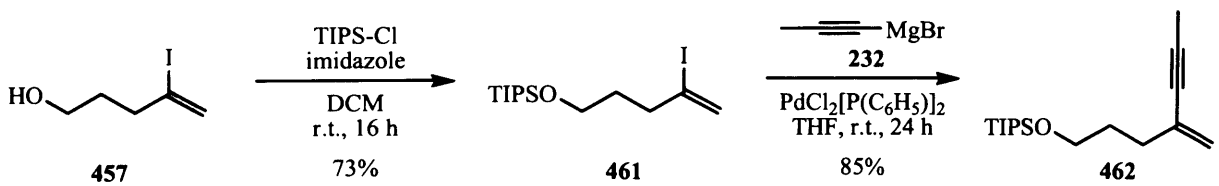
Scheme **173**

To try and improve the yield of alcohol **457**, the catalyst loading was increased to 10% and the reaction repeated. The increased catalyst loading led to the desired alcohol **457** being formed preferentially compared to *trans*-iodoalkene **459**. The reaction resulted in a large amount of the alkene **460**, suggesting that there was a problem with the iodination of the hydroalumination intermediate (Scheme **174**).



Scheme **174**

It was considered that optimisation of the conditions could result in yields comparable to those of Hoveyda. Although the products were not fully separable, the main impurity was alkene **460** which it was considered should not prevent the subsequent reactions of alcohol **457** from succeeding. The crude alcohol **457** was silyl protected to give iodoalkene **461** which was successfully coupled using Kumada-type conditions to give pure enyne **462** (Scheme **175**).



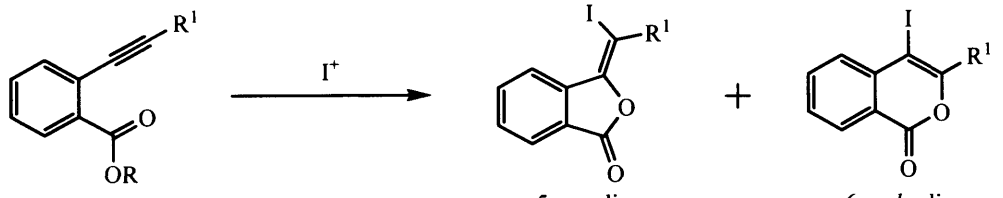
Scheme **175**

Limitations of time meant that the synthesis of dihydrothiopyran **425** could not be completed.

Chapter 4: Competing Cyclisations

4.1 Competing cyclisations

As discussed in the introduction, Baldwin produced a series of papers in 1976 which introduced a set of rules based on transition-state geometry to explain the relative ease of some ring closing reactions compared to the unfavourable nature of others (*cf.* p20).[69] Baldwin's rules have since provided sound guidance in the design and rationalisation of cyclisation processes. While there are arguably very few exceptions to these principles, there are occasional ambiguities amongst some pairs of "favoured" cyclisation pathways. An example of this is the cyclisation of 2-(alkynyl)benzoic acids **463**[199] and esters **464**[200] which can lead to either the ylidenephthalides **465** by 5-*exo*-dig cyclisation, or to isocoumarins **466** by 6-*endo*-dig cyclisation. When the electrophile-driven iodocylisations were carried out using iodine, a mixture of the two products was generally obtained. When the reaction was carried out using iodine monochloride as the iodonium source, the 6-*endo* product was greatly favoured (Scheme **176**).

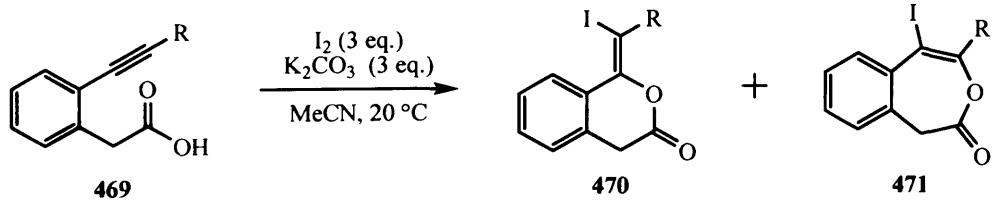


463 R = H
464 R = alkyl

465 **466**

Scheme **176**

Within the Knight group the iodolactonisation of 2-(alkynyl)phenylacetic acids **469** has been studied.[201] It was found that when the alkyne substituent was alkyl, the 6-*exo*-dig pathway was favoured, leading to isochromanones **470**. When the alkyne substituent was an aryl group, particularly an electron-donating aryl group, the 7-*endo*-dig pathway was favoured and benzo[d]oxepinones **471** were formed (Scheme **177**).



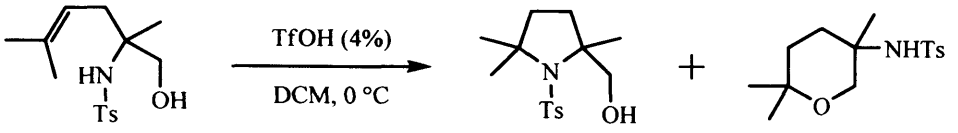
469

470
6-*exo*-dig

471
7-*endo*-dig

Scheme **177**

Very recently the Knight group disclosed that when sulfonamide **472** was exposed to toluenesulfonic acid in dichloromethane at 0 °C, an approximately 1:1 mixture of pyrrolidine **473** and tetrahydropyran **474** was formed (Scheme **178**).[202]



472 **473** **474**

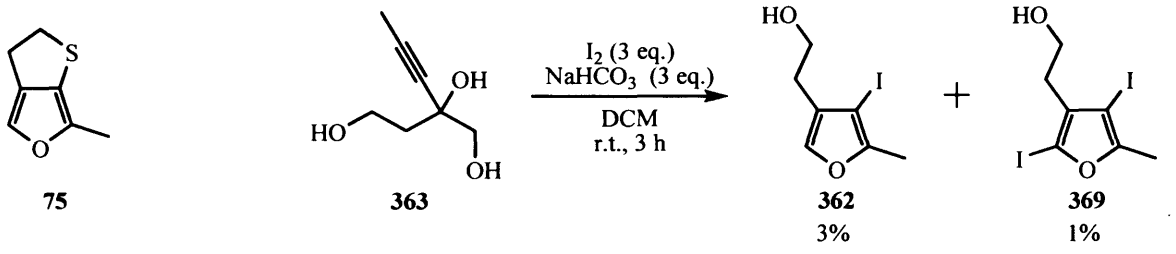
45% 45%

Scheme **178**

This reaction shows the competition of a 5-*endo*-trig cyclisation through the nitrogen of a sulfonamide, against the 6-*endo*-dig cyclisation through the primary alcohol. Although 5-*endo*-trig cyclisations are considered "disfavoured" by Baldwin's rules,[69] the cationic nature of this reaction means that it cannot be considered a true exception.

4.2 5-*Endo*-dig vs 5-*exo*-dig vs 6-*endo*-dig

During earlier discussed attempts towards the synthesis of kahweofuran **75**, it was found that triol **363** cyclised to iodofurans **362** and **369** in very poor yield (*cf.* P78) (Scheme **179**).

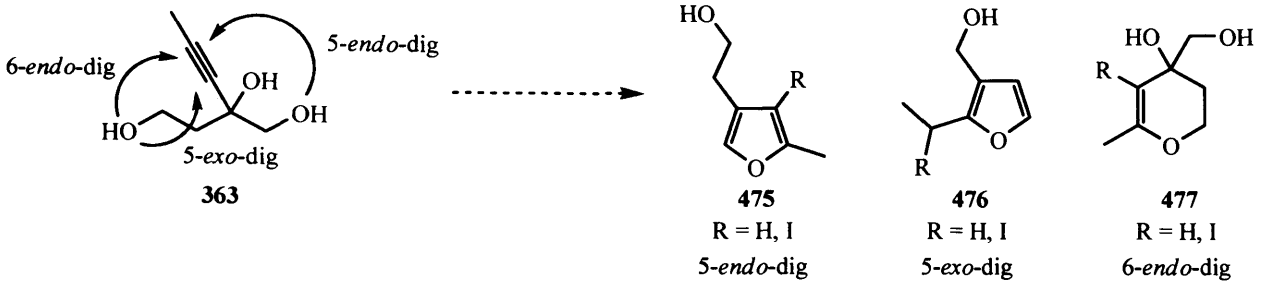


75 **363** **362** **369**

3% 1%

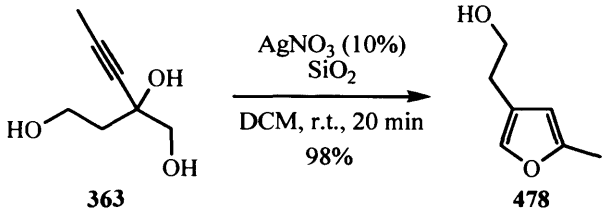
Scheme **179**

No starting material was recovered from the reaction after aqueous work-up, suggesting that the triol was not reacting and instead being lost into the aqueous washings. This assumption was supported by monitoring of the reaction by TLC, which showed the presence of starting material throughout the reaction. The desired reaction requires an iodine-promoted, Baldwin's rules "favoured", 5-*endo*-dig cyclisation.[69] This reaction is in competition with the alternative, and also "favoured", 6-*endo*-dig and 5-*exo*-dig cyclisations (Scheme **180**).



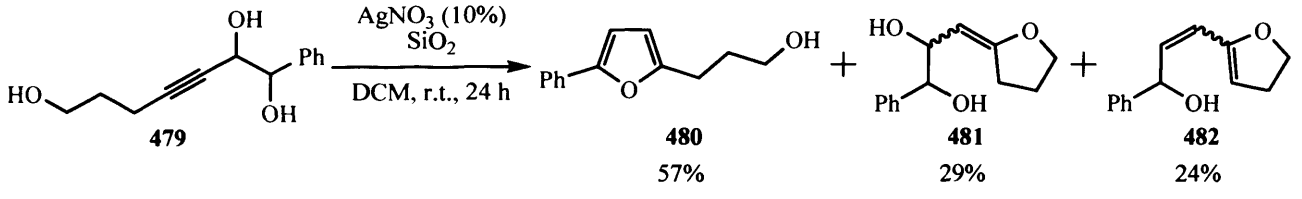
Scheme **180**

When triol **363** was exposed to the standard silver cyclisation conditions, there was 100% conversion of the starting material, and the 5-*endo*-dig product, furan **478**, was isolated in 98% yield (Scheme **181**). No other products were visible in the ^{1}H NMR spectrum of the crude reaction mixture.



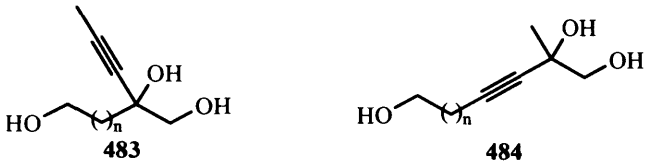
Scheme **181**

The selectivity of the 5-*endo*-dig cyclisation was interesting when considered alongside a reaction carried out by Hayes in which triol **479** was exposed to the same conditions for a 24 hour period. Hayes reported the formation of a 4:2:1 mixture of the 5-*endo*-dig product, furan **480**, together with the alternative 5-*exo*-dig products, tetrahydrofuran-2-ylidene **481** and dihydrofuran **482** (Scheme **182**).[203]



Scheme **182**

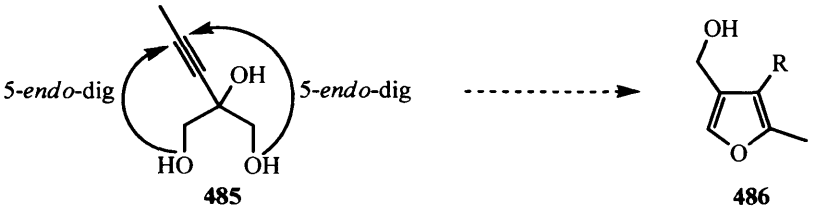
It was therefore envisaged that a range of triols with competing cyclisation possibilities, such as triols **483** and **484**, could be synthesised and their reactions upon exposure to the standard iodocyclisation and silver cyclisation conditions studied (Scheme **183**).



Scheme **183**

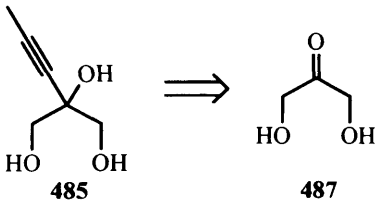
4.3 5-*endo*-dig vs 5-*endo*-dig

Triol **485** was first investigated, in which a pair of competing 5-*endo*-dig cyclisation possibilities were available (Scheme **184**). It was of interest to see if the silver cyclisation would work on such a small, highly-polar molecule.



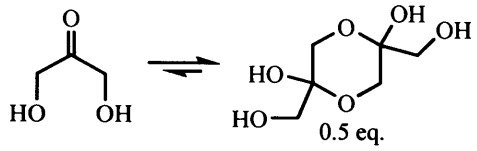
Scheme **184**

Disconnection of triol **485** suggested that it should be accessible from 1,3-dihydroxyacetone **487** (Scheme **185**).



Scheme **185**

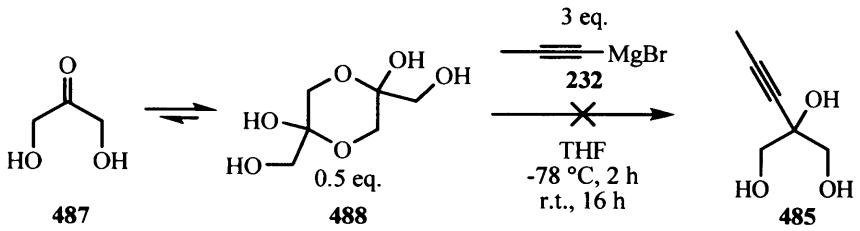
1,3-Dihydroxyacetone **487** is commercially available as its dimer **488** (Scheme **186**) and is the active ingredient in most sunless tanning products due to the brown colour that is produced when a Maillard reaction occurs between it and the free guanido group of arginine in the dead layer on the skin surface.[204]



487 **488**

Scheme **186**

It was initially hoped that triol **485** could be formed from the reaction of 1,3-dihydroxyacetone **487** with three equivalents of commercially available 1-propynylmagnesium bromide **232**. The reaction failed to produce the desired triol **485** and returned only a low yield of the starting material (Scheme **187**).

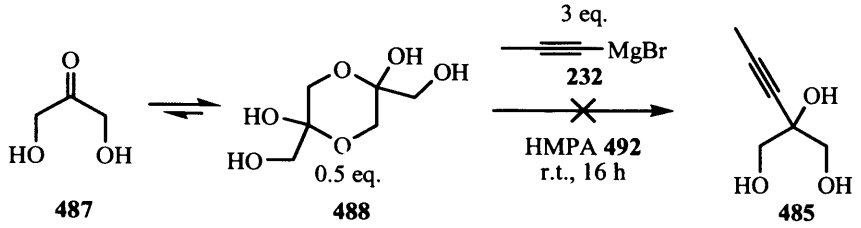


487 **488** **485**

Scheme **187**

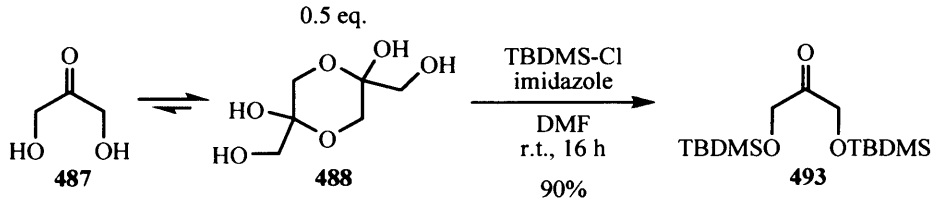
Upon investigation it was discovered that 1,3-dihydroxyacetone dimer **488** was poorly soluble in tetrahydrofuran, leading to the conclusion that the majority of the starting material had been lost into the aqueous washings. 1,3-Dihydroxyacetone dimer **488** also had poor solubility in diethyl ether, *tert*-butyl methyl ether and butyl diglyme. The use of a higher polarity solvent was therefore considered, but the options were limited by their compatibility with Grignard reagents. Grignard reagents have been shown to add to the carbonyl group of dimethylformamide, reduce dimethyl sulfoxide, and abstract an α-hydrogen from sulfolane.[205] It has however been shown that at low temperatures the phosphoramide, hexamethylphosphoramide , suffers much less from these problems.[206]

Grignard addition to 1,3-dihydroxyacetone dimer **488** was attempted using desiccant-dried hexamethylphosphoramide as the solvent (Scheme **188**). The 1,3-dihydroxyacetone dimer **488** visibly appeared to dissolve, but no product formation was detected by TLC analysis, and only a low yield of starting material was recovered from the reaction. It was considered that even if any of triol **485** was formed, it would likely be lost into the aqueous washings upon work-up. An alternative approach was therefore required.



Scheme **188**

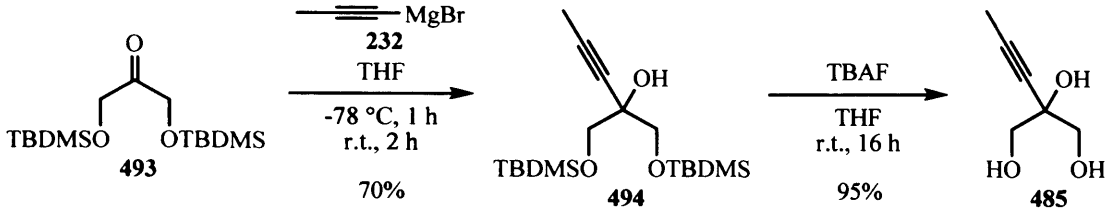
It was considered that protection of the alcohol functionalities of 1,3-dihydroxyacetone **487** should allow the Grignard addition to proceed, and would facilitate the isolation of the product. Bulky silyl groups were chosen due to their low polarity and the instant availability of *tert*-butyldimethylsilyl chloride in the laboratory. Literature precedent for the formation of ketone **493** was found, although two of the papers examined contained somewhat surprising statements. Jeong's paper quoted a 90% yield of ketone **493**, but upon closer inspection it appears Jeong had been confused by using 1,3-dihydroxyacetone **487** in its dimeric form **488**, and had actually achieved only a 45% yield.[207] An impressive 100% yield of ketone **493** was quoted in a paper by Tamm who followed a procedure in which the only purification was a filtration through silica gel with dichloromethane. This raised questions as to the fate of the excess *tert*-butyldimethylsilyl chloride which was used.[208] Despite these reservations, the *tert*-butyldimethylsilyl *bis*-protection of 1,3-dihydroxyacetone **487** proceeded smoothly in dimethylformamide in the presence of imidazole, giving a 90% yield of ketone **493** after column chromatography (Scheme **189**).



Scheme **189**

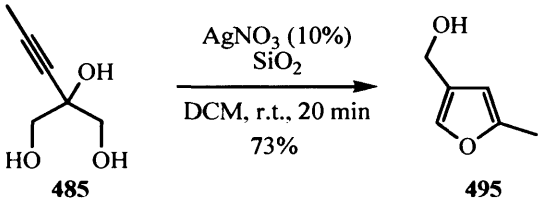
Treatment of ketone **493** with commercial 1-propynylmagnesium bromide **232** in tetrahydrofuran yielded alcohol **494** in reasonable yield. Alcohol **494** was exposed to tetrabutylammonium fluoride in tetrahydrofuran at room temperature for 16 hours before the volatiles were removed on a rotary evaporator to give the crude product as a dark sludge. Concerns over the isolation of triol **485** due to its high-polarity and high water-solubility were proven to be unfounded. Purification of the crude material by column chromatography using a graduated solvent system of ethyl acetate and methanol (99:1 → 9:1), followed by evaporation of

any volatiles using a rotary evaporator allowed triol **485** to be isolated in 95% yield (Scheme **190**).



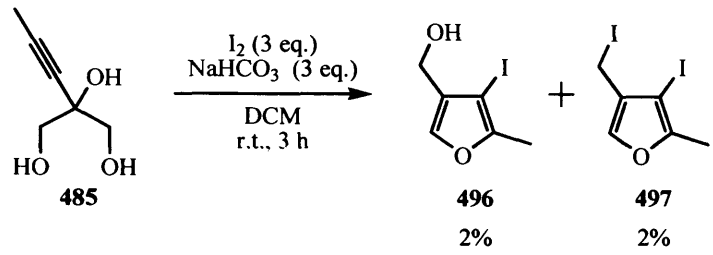
Scheme **190**

Triol **485** underwent full conversion upon exposure to the standard silver cyclisation conditions for 20 minutes. ^{1}H NMR and TLC analysis of the crude reaction mixture showed furan **495** to be the only observed product. Furan **495** was isolated in 73% yield, with losses being attributed to the volatility of the product (Scheme **191**).



Scheme **191**

After triol **485** was exposed to the standard iodocyclisation conditions, only a small amount of material was recovered following aqueous work-up. A ^{1}H NMR spectrum of the expected product, furan **496**, would be predicted to contain peaks in the regions of 7, 4, and 2 ppm. ^{1}H NMR analysis of the crude reaction product showed two sets of peaks in each of these three regions. This led to the unlikely idea that the compound existed as a pair of rotamers due to the bulky nature of the iodine. This theory was dismissed after ^{1}H NMR analysis was carried out at the raised temperature of 50 °C and the ratio of the integration of the peaks remained constant. Further investigation showed that two spots could be seen by TLC analysis, suggesting that two compounds were present in the crude reaction mixture. Furan **496**, and what was believed to be diiodofuran **497**, was isolated after column chromatography (Scheme **192**). Although not fully characterised, the identity of diiodofuran **497** was consistent with all the ^{1}H and ^{13}C NMR data obtained. The alkyl iodide moiety was strongly suggested by the presence of a resonance in the ^{13}C NMR spectrum at –4.5 ppm, characteristic of an alkyl iodide, and shown to be a CH_2 by the DEPT 135 NMR spectrum.

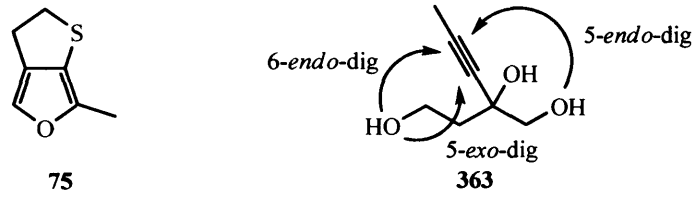


Scheme **192**

Although not proven, and it is believed that diiodofuran **497** was formed from furan **496** by displacement of the alcohol by an iodide anion.

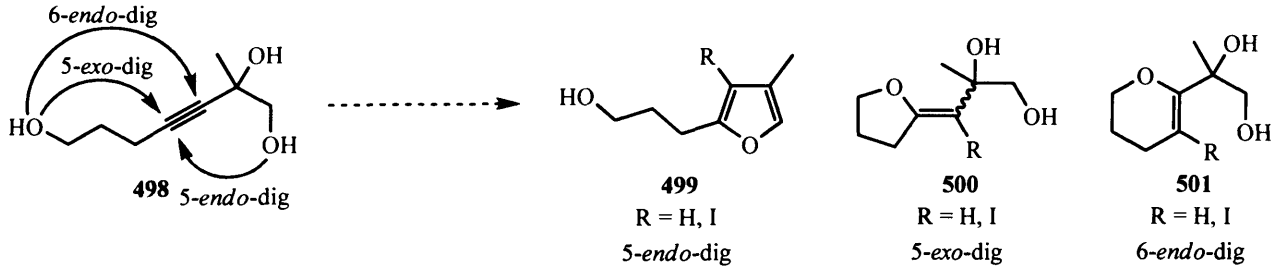
4.4 "Alternative" 5-*endo*-dig vs 5-*exo*-dig vs 6-*endo*-dig

During the earlier discussed failed attempt towards kahweofuran **75**, triol **363** was synthesised and exposed to the standard silver cyclisation and iodocyclisation conditions (*cf.* p99). Triol **363** had the possibility of undergoing a 5-*endo*-dig, 5-*exo*-dig or 6-*endo*-dig cyclisation (Scheme **193**). The silver cyclisation showed selectivily for the 5-*endo*-dig furan product, and the iodocyclisation showed no reaction, returning the majority of the starting material.



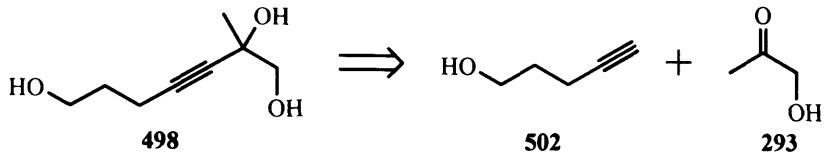
Scheme **193**

It is also possible to set up this same set of cyclisation possibilities in an alternative arrangement, such as in triol **498** (Scheme **194**).



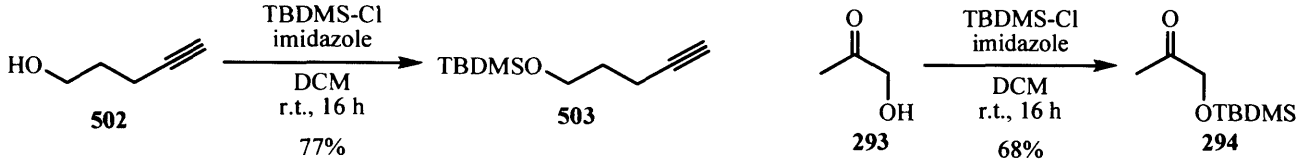
Scheme **194**

Disconnection of triol **498** showed that it should be accessible from commercially available 4-pentyn-1-ol **502** and hydroxyacetone **293** (Scheme **195**).



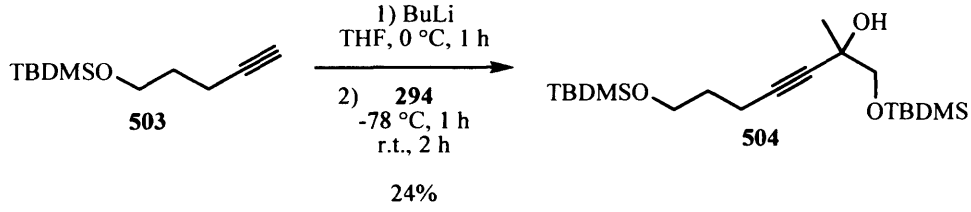
Scheme **195**

Both 4-pentyn-1-ol **502** and hydroxyacetone **293** were protected with *tert*-butyldimethylsilyl chloride to give alkyne **503** and ketone **294** respectively (Scheme **196**).



Scheme **196**

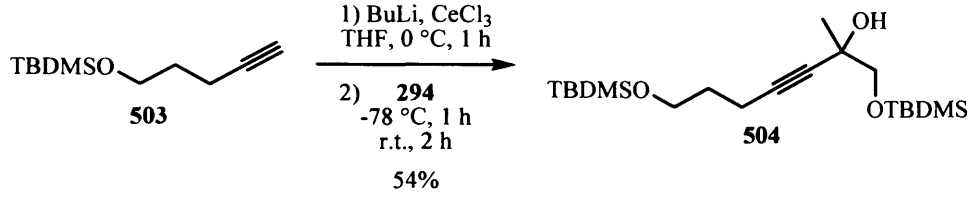
After alkyne **503** was treated with butyllithium and exposed to ketone **294**, ^{1}H NMR analysis of the crude reaction mixture showed a 32% conversion of the starting alkyne **503**. Alcohol **504** was isolated in 24% yield, along with a large proportion of the starting materials (Scheme **197**). It was therefore considered that the lithiated alkyne may be deprotonating alpha to the carbonyl of ketone **294**, in preference to undergoing nucleophilic attack at the carbonyl.



Scheme **197**

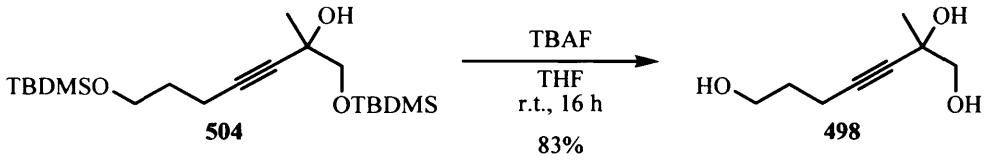
Imamoto has shown that cerium(III) chloride can be employed to improve the yield of nucleophilic addition products from the reaction of organolithium reagents with easily enolizable ketones.[209] He reported that organocerium reagents are significantly less basic than the corresponding organolithiums and exhibit a pronounced affinity for a carbonyl group. This characteristic reactivity is ascribed to the strong oxophilicity of trivalent cerium.

When the addition of alkyne **503** to ketone **294** was carried out in the presence of dried cerium chloride, ^{1}H NMR analysis showed an 80% conversion of alkyne **503**, and alcohol **504** was isolated in the improved yield of 54% (Scheme **198**).



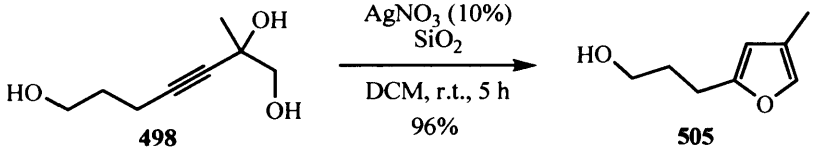
Scheme **198**

The deprotection of alcohol **504** was carried out by exposure to tetrabutylammonium fluoride in tetrahydrofuran. Triol **498** was isolated using the previously discussed method which involved evaporation of the volatiles followed by column chromatography of the crude reaction products (Scheme **199**) (*cf.* p102).



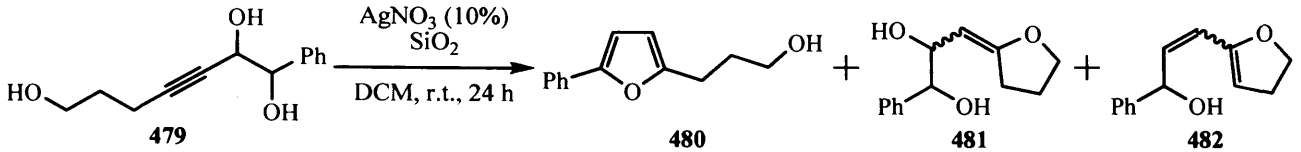
Scheme **199**

Triol **498** underwent full conversion when exposed to the standard silver cyclisation conditions for 5 hours. The reaction was selective for the 5-*endo*-dig product, furan **505**, which was isolated in 96% yield (Scheme **200**).



Scheme **200**

The selectivity of the 5-*endo*-dig cyclisation product from 1-methyl triol **498** is in contrast to the mixture of products obtained by Hayes from the 2-phenyl triol **479** (Scheme **201**) (*cf.* p99). It is tentatively suggested that the electron withdrawing nature of the phenyl group in the 1-position may reduce the rate at which the alcohol group in the 1-position can cyclise, allowing the competing alcohol group in the 7-position the opportunity to react with the activated alkyne.

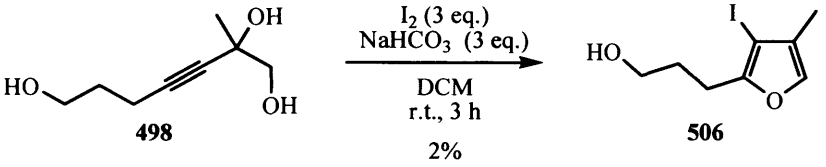


479 **480** **481** **482**

57% 29% 24%

Scheme **201**

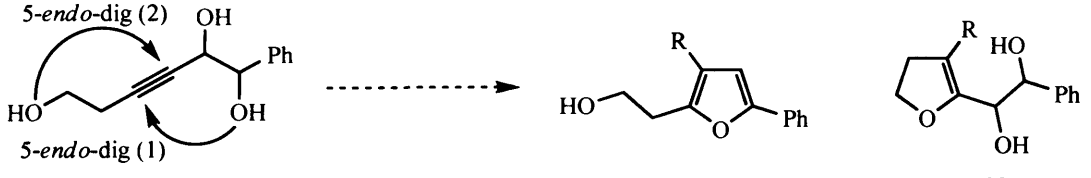
After triol **498** had been exposed to the standard iodocyclisation conditions only a small amount was recovered after aqueous work-up. ^{1}H NMR analysis of the crude reaction product revealed multiple unidentified compounds along with what appeared to be iodofuran **506**. Column chromatography allowed the purification of iodofuran **506** to the extent that it could be characterised (Scheme **202**).



498 **506**

Scheme **202**

In order to investigate the role which a phenyl group plays in the cyclisation of triols under the standard silver cyclisation conditions, triol **507** was considered for investigation. Triol **507** is similar to the triol used by Hayes, triol **479**, with the exception of having a one carbon shorter side-chain. Triol **507** would have the opportunity to undergo two different 5-*endo*-dig cyclisations (Scheme **203**).



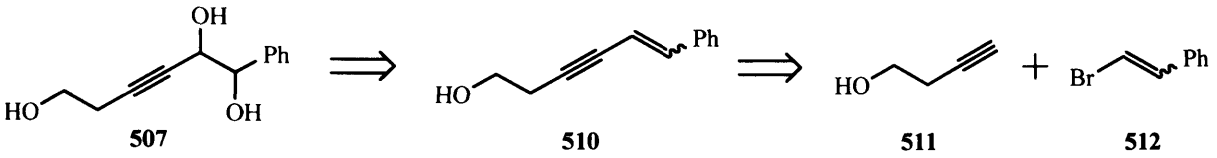
507 **508** **509**

R = H, I R = H, I

5-*endo*-dig (1) 5-*endo*-dig (2)

Scheme **203**

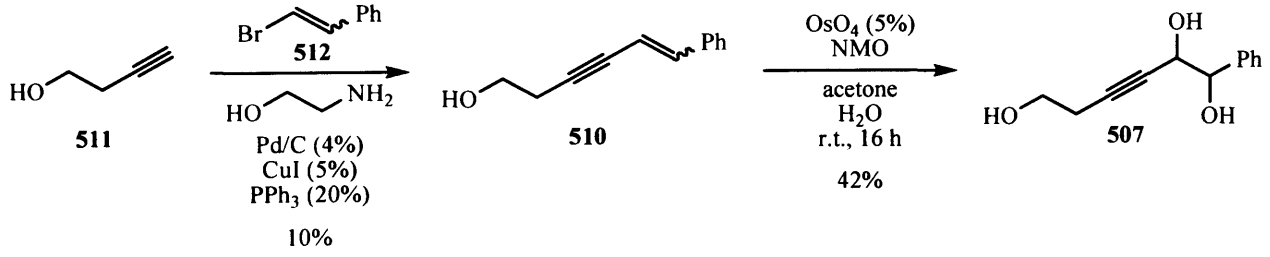
The disconnection of triol **507** suggests that it could be made by dihydroxylation of enyne **510**. It was hoped that enyne **510** could be made by a Sonogashira-type coupling of 3-butyn-1-ol **511** and β-bromostyrene **512** (Scheme **204**).



Scheme **204**

Transition metal catalysed cross-coupling reactions are important processes for constructing new carbon-carbon bonds.[210] The palladium-catalysed coupling of terminal alkynes with aryl halides was first reported by Sonogashira in 1975,[96] and has become the most attractive and powerful tool for $C(sp^2)$-C(sp) bond formation.[210] In 1990 Casalnuovo reported the first palladium-catalysed alkylation in aqueous media, reporting the use of water to be advantageous in terms of catalyst-product separation and for reasons of economy and safety.[211] Gazmán then showed that the economy of the reaction could be improved further by the use palladium on carbon as the catalyst in the place of more common and expensive catalysts such as tetrakis(triphenylphosphine)palladium(0) and *bis*(triphenylphosphine)palladium(II) dichloride.[212] In 2005 Pal reported an excellent general procedure for the synthesis of arylalkynes in water using 2-aminoethanol and catalytic amounts of palladium on carbon, copper iodide and triphenylphosphine.[213]

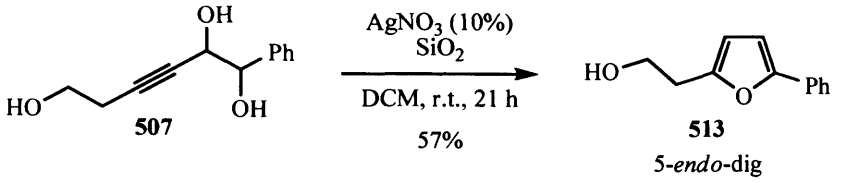
In the present project Pal's methodology was used to couple 3-butyn-1-ol **511** with (*E*/*Z*)-β-bromostyrene **512** to form enyne **510** as a mixture of stereoisomers. Dihydroxylation of enyne **510** proceeded in the presence of osmium tetroxide and 4-methylmorpholine *N*-oxide to yield triol **507** (Scheme **205**).



Scheme **205**

When triol **507** was exposed to the standard cyclisation conditions, furan **513** was the only identifiable product. Analysis by TLC revealed that triol **507** had not undergone complete conversion after 6 hours, which is a longer time period than had been experience with any of the

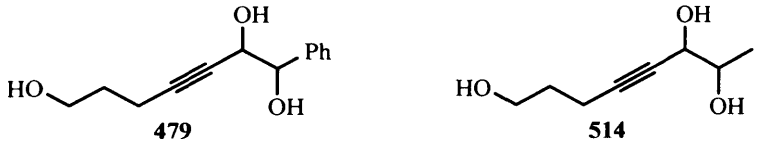
previously tested triols which took between 0.3 and 5 hours. Triol **507** underwent full conversion within 21 hours and was isolated in 57% yield (Scheme **206**).



Scheme **206**

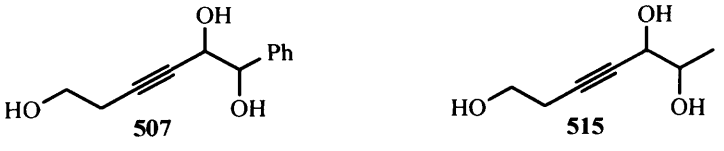
The longer exposure time to silver nitrate on silica is considered to be the cause of the relatively low yield. Silver carbonate on celite, known as Fétizon's reagent,[214] is a mild oxidant possessing very diverse oxidation capabilities.[215] It is therefore considered that silver nitrate on silica may be an oxidant capable of oxidising furan **513** and thus resulting in its decomposition.

From the long reaction time of Hayes' triol **479** (24 hours) and triol **507** (21 hours), it appeared that the presence of a phenyl group in the 1-position reduced the rate at which the alcohol in the 1-positions could cyclise. It would therefore be of interest to expose triol **514**, which has a methyl group in the 1-position, to the standard silver cyclisation conditions and compare the products and reaction time to that of the reaction of Hayes' triol **479**. (Scheme **207**)



Scheme **207**

Further information on the role of the phenyl group in the 1-position could be gained from running a kinetic experiment to compare the rate of reaction of the 1-phenyl substituted triol **507** with the 1-methyl substituted triol **515** (Scheme **208**).

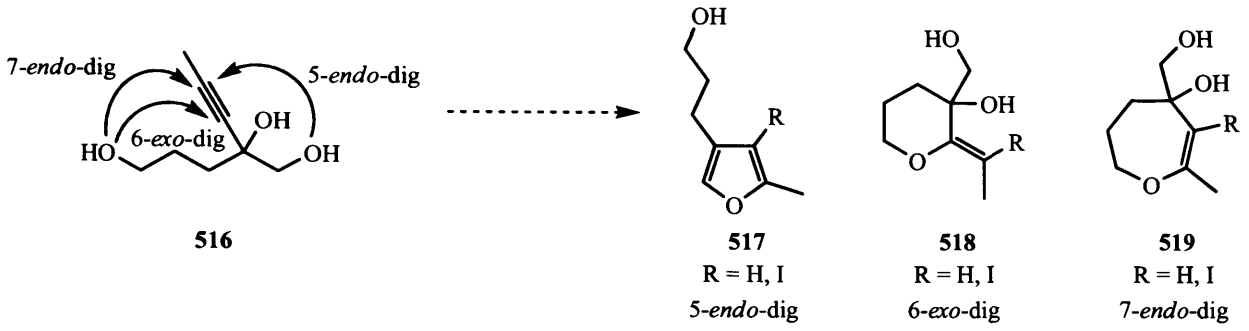


Scheme **208**

At the present time neither of these experiments has been attempted.

4.5 5-*endo*-dig vs 6-*exo*-dig vs 7-*endo*-dig

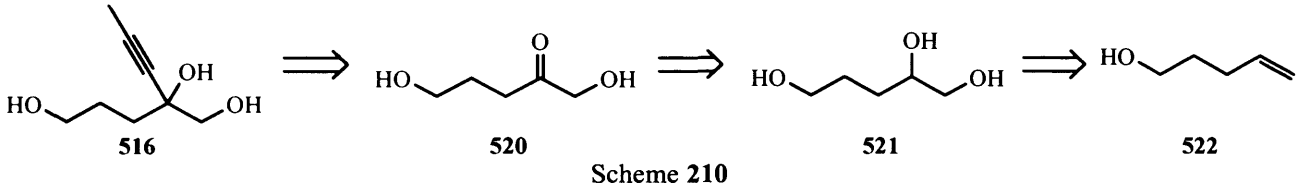
The next system to be tested was triol **516**, which gave 5-*endo*-dig, 6-*exo*-dig and 7-*endo*-dig cyclisation possibilities (Scheme **209**).



516 **517** R = H, I 5-*endo*-dig **518** R = H, I 6-*exo*-dig **519** R = H, I 7-*endo*-dig

Scheme **209**

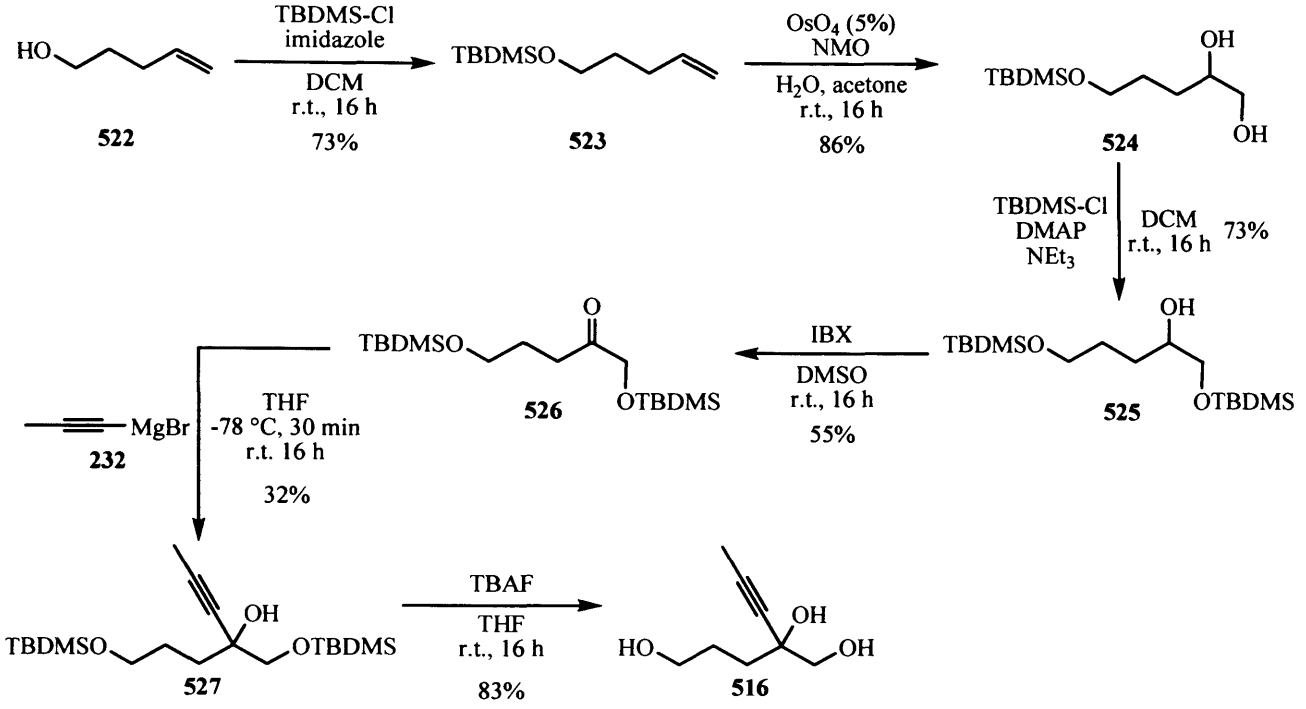
The disconnection of triol **516** led back to ketone **520** which itself was envisaged as being accessible from triol **521**. Triol **521** was hoped to be made from commercially available 4-penten-1-ol **522** (Scheme **210**).



516 **520** **521** **522**

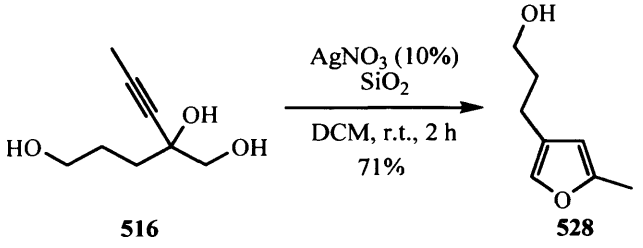
Scheme **210**

4-Penten-1-ol **522** was protected using *tert*-butyldimethylsilyl chloride to give alkene **523**, which was dihydroxylated using osmium tetroxide and 4-methylmorpholine *N*-oxide to give diol **524** in 86% yield. The selective protection of diol **524** by *tert*-butyldimethylsilyl chloride led to alcohol **525**, which was oxidised to ketone **526** by exposure to iodoxybenzoic acid. The addition of commercially available 1-propynylmagnesium bromide **232** to ketone **526** yielded alkyne **527** in disappointing yield. It was considered that the presence of dried cerium chloride may improve the yield of this reaction, but this has not yet been attempted. The deprotection of alkyne **527** by tetrabutylammonium fluoride resulted in triol **516** (Scheme **211**).



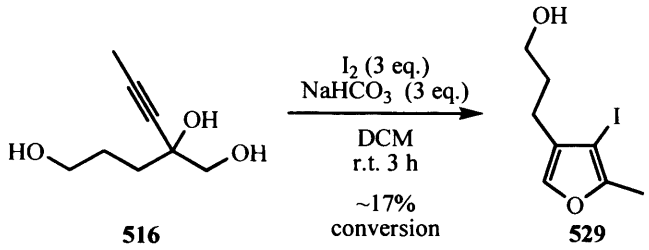
Scheme **211**

Exposure of triol **516** to the standard silver cyclisation conditions for two hours resulted in a 100% conversion of the starting material and the formation of the 5-*endo*-dig product, furan **528**, as the sole product in 71% yield (Scheme **212**).



Scheme **212**

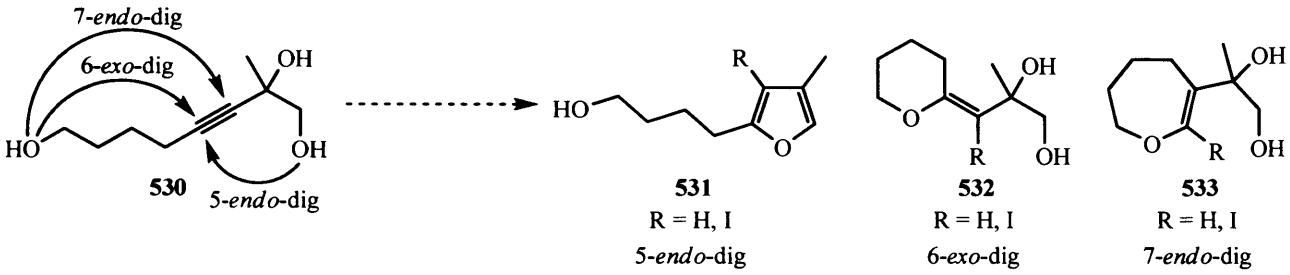
After triol **516** was exposed to the standard iodocyclisation conditions, but before any aqueous washing, a sample was removed from the reaction mixture. The solvent was removed, and NMR analysis of the crude product was performed. ^{13}C NMR analysis strongly suggested the presence of starting triol **516** and iodofuran **529**, with ^{1}H NMR analysis supporting this and showing an approximate 17% conversion of triol **516** to iodofuran **529** (Scheme **213**). No other compounds could be identified.



Scheme **213**

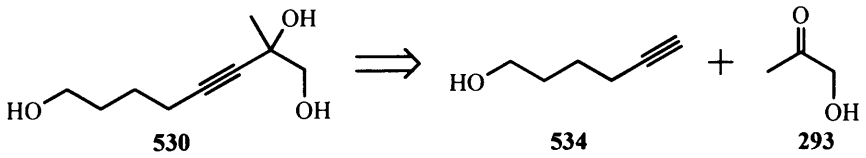
4.6 "Alternative" 5-*endo*-dig vs 6-*exo*-dig vs 7-*endo*-dig

Triol **530** gives an alternative way of setting up competing 5-*endo*-dig, 6-*exo*-dig and 7-*endo*-dig cyclisations (Scheme **214**).



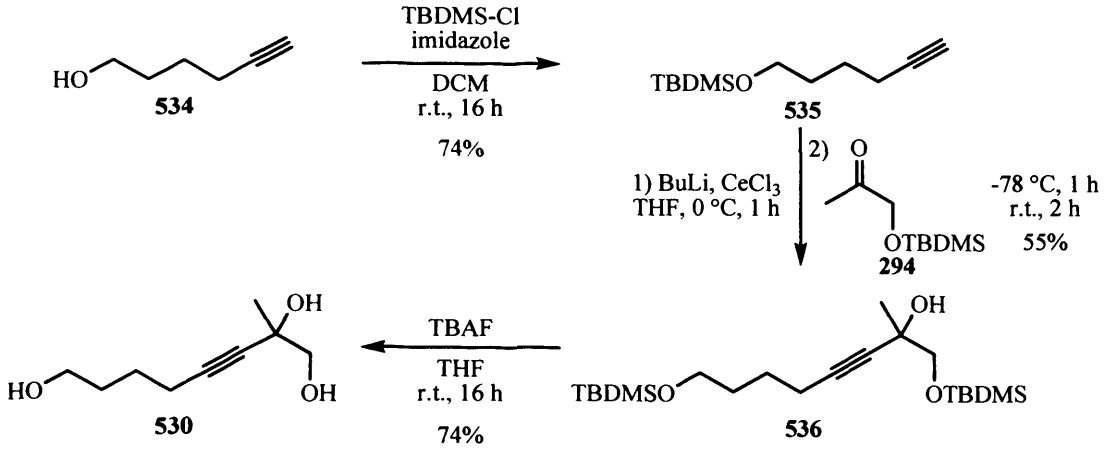
Scheme **214**

The disconnection of triol **530** suggests that it should be accessible from 5-hexyn-1-ol **534** and hydroxyacetone **293** (Scheme **215**).



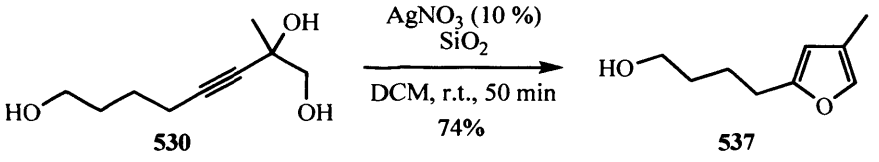
Scheme **215**

The silyl protection of 5-hexyn-1-ol **534** by *tert*-butyldimethylsilyl chloride gave alkyne **535**. Alkyne **535** was deprotonated with butyllithium in the presence of cerium(III) chloride and added into ketone **294** to give alcohol **536** in 55% yield. The deprotection of alcohol **536** with tetrabutylammonium fluoride led to the desired triol **530** (Scheme **216**).



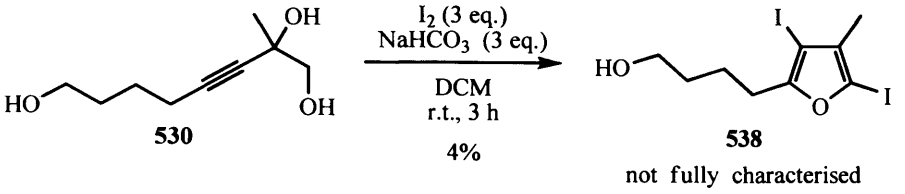
Scheme **216**

Triol **530** continued the trend of the previous triols and selectively underwent a 5-*endo*-dig cyclisation when exposed the standard silver cyclisation conditions. ^{1}H NMR analysis of the crude product showed 100% conversion of triol **530**, and furan **537** as the only product (Scheme **217**).



Scheme **217**

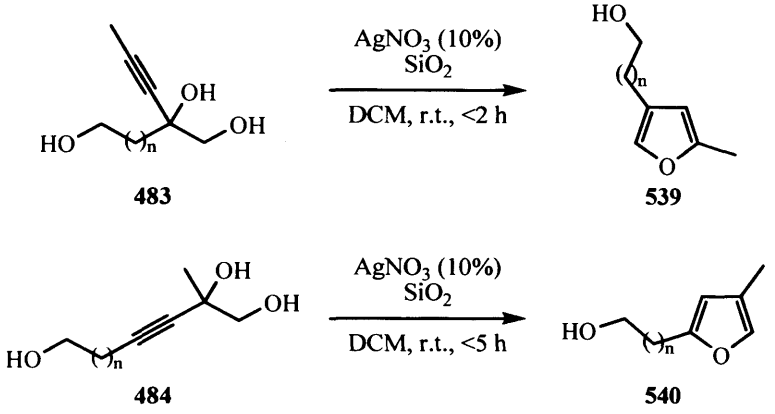
After triol **530** had been exposed to the standard iodocylisation conditions and the standard work-up of washing with saturated aqueous sodium sulfite, the ^{1}H NMR specturm of the crude product proved difficult to interpret. Triplets at 3.66 ppm (CH_2 next to OH) and 2.74 ppm (CH_2 next to a furan) along with a singlet 2.08 ppm (CH_3 in the β-position of the furan) suggested the presence of a 5-*endo*-dig cyclisation product. The lack of a signal in the aromatic region which would correspond to a proton in the α-position of the furan led to the tentative suggestion that diiodofuran **538** may have formed (Scheme **218**). No further evidence either supporting or against this suggestion was obtained due to the low purity, and small quantity of material available (~4 mg).



Scheme **218**

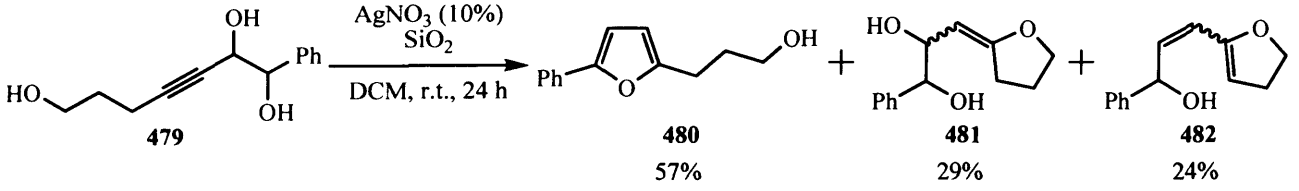
4.7 Conclusion

Although not comprehensive, the study has shown that when triols of the type **483** and **484** are exposed to 10% silver nitrate (at 10% w/w loading on silica gel) in dichloromethane at room temperature they form the 5-*endo*-dig cyclisation products, furans **539** and **540** respectively, in under 5 hours (Scheme **219**).



Scheme **219**

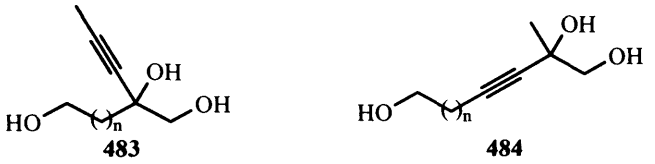
These results are particularly interesting when compared alongside the cyclisation of triol **479**, which had previously been carried out in the Knight group (*cf.* p107).[203] When a phenyl substituent was present in the 1-position, a mixture of products was obtained (Scheme **220**).



Scheme **220**

It would therefore seem prudent to carry out a series of experiments in which the position and type of substituents were varied.

The study has also shown that triols of the type **483** and **484** are not suitable precursors for iodocyclisations in the presence of three equivalents of iodine and sodium hydrogen carbonate in dichloromethane at room temperature (Scheme **221**).



483 **484**

Scheme **221**

Recent work within the Knight group as suggested that these iodocyclisations can be dramatically affected by the choice of solvent.[216] It is therefore considered that a solvent screening may reveal conditions under which the iodocyclisation of triols can occur in reasonable yield.

Chapter 5: Experimental

5.1 General experimental details

Reagents were obtained from Aldrich, Alfa Aesar, Lancaster, Fluka and Strem chemical suppliers and used as received unless otherwise specified. Solvents and reagents were purified according to the procedures of Perrin, Armarego and Perrin.[217] Dichloromethane and toluene were dried by refluxing over, and distilling from, calcium hydride. Ethanol was dried by refluxing over magnesium, followed by distillation. Anhydrous diethyl ether and anhydrous tetrahydrofuran were obtained by refluxing over sodium with sodium benzophenone ketyl as indicator, followed by distillation. "Petrol" refers to petroleum ether b.p. 40-60 °C, "ether" refers to diethyl ether. All aqueous solutions were saturated unless otherwise stated. "Dried" refers to the addition of dried magnesium sulfate ($MgSO_4$) to remove trace amounts of water. "Filtered" refers to the removal of solid residues by gravity filtration of organic solutions through filter paper. "Evaporated" refers to the distillation of volatiles using a Büchi rotary evaporator attached to a 20 L Charles Austen pump at approx. 8 mbar, heated with a water bath typically between 20 and 40 °C. "Degassed" refers to bubbling N_2 through the solvent for 30 minutes.

All reactions using air/moisture sensitive reagents were performed in oven-dried or flame-dried apparatus, under a nitrogen atmosphere. Solid carbon dioxide and an acetone bath (-78 °C) or an ice-water bath (0 - 5 °C) were used to obtain low temperatures. "r.t." stands for room temperature. "b.p." stands for boiling point. "m.p." stands for melting point. Heated reactions were conducted in a stirred oil bath heated on a magnetically stirred hotplate. All reactions were followed and monitored by TLC, ^1H NMR, ^{13}C NMR and mass spectrometry as appropriate.

TLC analysis refers to analytical thin layer chromatography, using aluminium-backed plates coated with Merck Kieselgel 60 GF254. Product spots were viewed either by the quenching of UV fluorescence, or by staining with a solution of 2% aqueous potassium permanganate. Column chromatography refers to flash column chromatography using head pressure by means of compressed air according to the procedure of Still,[218] and using Merck Kieselgel 60 H silica or Matrix silica 60. Ozone was produced by a Ozone Solutions OZV-8 8 gm/hr Ozone Generator with air as the inlet gas.

Melting points were recorded using a Kofler Heated Stage Micro Melting Point Apparatus and are uncorrected.

Infra-red spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 1600 series FTIR instrument as a thin film between sodium chloride plates unless otherwise stated, in which case samples were run in a nujol mull (Nujol) or dissolved in dichloromethane (DCM) between sodium chloride plates. All absorptions are quoted in wave numbers (cm^{-1}).

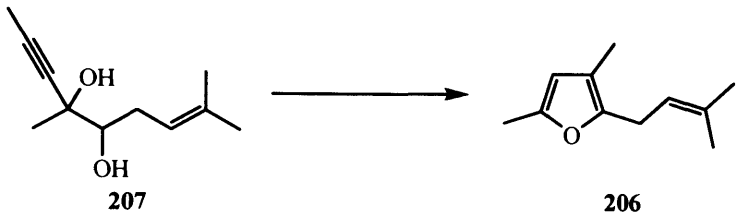
^{1}H NMR spectra (δ_H) were recorded using an Avance Bruker DPX 500 (500 MHz), with ^{13}C NMR spectra (δ_C) recorded at 125MHz unless otherwise stated. In which case ^{1}H NMR spectra (δ_H) were recorded using an Avance Bruker DPX 400 instrument (400 MHz) or an Avance Bruker DPX 250 instrument (250 MHz). Spectra were obtained as dilute solutions in deuterated chloroform, unless otherwise stated, in which case spectra were obtained in dilute solutions of fully deuterated acetone (acetone-d^6) or fully deuterated dimethyl sulfoxide (DMSO-d^6). The chemical shifts were recorded relative to residual chloroform (7.26 or 77.0 ppm) as an internal standard unless otherwise stated, in which case chemical shifts were recorded relative to partially deuterated acetone (2.05 or 29.84 ppm), or partially deuterated dimethyl sulfoxide (2.50 or 39.52).[219] Abbreviations used for the multiplicities are s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet), dd (doublet of doublets), dt (doublet of triplets), td (triplet of doublets), m (unresolved multiplet), *app.* (apparent) or as a combination of these multiplicities. All coupling constants (*J*) are recorded in Hertz (Hz). Assignments were made on the basis of chemical shift and coupling constant data using DEPT-90, DEPT-135, COSY, NOESY, HSQC and HMBC experiments where required.

Mass spectrometric data was determined using a Waters GCT Premier instrument using electron ionisation (EI) unless otherwise stated. In which case mass spectrometric data was determined by a Waters LCT Premier XE instrument (LRMS) or Agilent 5975C Series GC/MSD (GC-MS) using pressure chemical ionisation (APCI) or electrospray ionisation (ES). High resolution mass spectrometric data were determined with the molecular formula corresponding to the observed signal using the most abundant isotopes of each element.

A literature reference associated with title of compound means it is not a novel compound and any data recorded in this thesis matches well with those reported in the associated references, unless otherwise stated.

Compounds in the experimental are in numerical order, except for kahweofuran **75** (p161). Due to reterosynthetic analysis in the text, intermediates may appear after the final product.

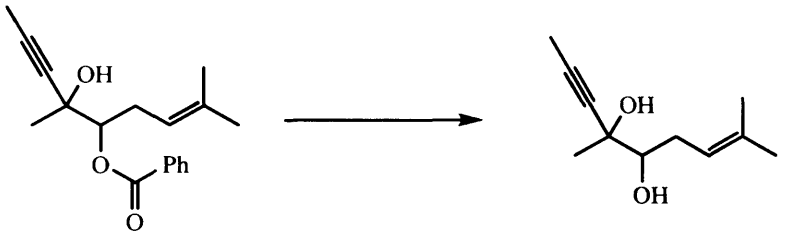
3,5-Dimethyl-2-(3-methylbut-2-enyl)furan 206



207 **206**

Silver nitrate on silica gel (0.03 g, ~10 wt. %, 0.02 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **207** (0.03 g, 0.16 mmol) in dichloromethane (2 ml) at r.t. under subdued light and left to stir for 1.5 h. The mixture was filtered through a pad of silica gel with dichloromethane (30 ml) and the filtrate dried, filtered and evaporated to yield *furan* **206** (0.03 g, 96%) as a colourless liquid; δ_H 5.74 (1H, s, α-furan-H), 5.25 (1H, t, *J* 7.0, CH_2CH=C), 3.23 (2H, d, *J* 7.0, furan-CH_2CH), 2.21 (3H, s, α-furan-CH_3), 1.91 (3H, s, β-furan-CH_3), 1.72 (3H, s, CH=C(CH_3)$_2$), 1.71 (3H, s, CH=C(CH_3)$_2$); δ_C 149.1 (C), 148.2 (C), 132.5 (C), 120.6 (CH), 114.0 (C), 108.8 (CH), 25.6 (CH_3), 25.2 (CH_2), 17.7 (CH_3), 13.4 (CH_3), 9.8 (CH_3).

(2*RS*,3*RS*)-4,8-Dimethylnon-7-en-2-yne-4,5-diol 207



231 **207**

Potassium hydroxide (0.04 g, 2.0 mmol) was added to a solution of alcohol **231** (0.29 g, 1.0 mmol) in methanol/water (10 ml, 4:1) and allowed to stir at r.t. for 2 h. The mixture was diluted with ether (50 ml) and washed with aqueous sodium hydrogen carbonate (3 x 10 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 6:4) to yield *alcohol* **207** (0.15 g, 81%) as a colourless oil, as an inseparable 3:1 mixture of diastereoisomers; *major diastereoisomer* δ_H 5.23 (1H, *app.* t, *J* 7.0, CH_2CH=C), 3.38 (1H, dd, *J* 9.2, 2.5, CCH(OH)CH_2), 3.06 (1H, bs, OH), 2.34 (1H, bs, OH), 2.28–2.21 (2H, m, CH(OH)CH_2CH), 1.83 (3H, s, C≡CCH_3), 1.71 (3H, s, CH=C(CH_3)$_2$), 1.62 (3H, s, CH=C(CH_3)$_2$), 1.40 (3H, s, CH_3C(OH)); δ_C 134.8 (C), 120.2 (CH), 81.3 (C), 80.3 (C),

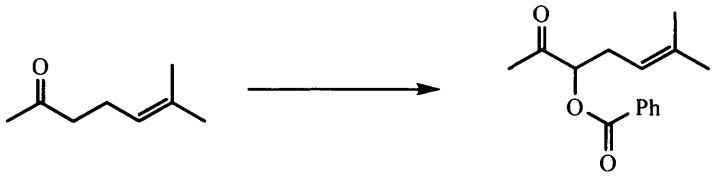
78.0 (CH), 71.2 (C), 31.3 (CH_2), 26.0 (CH_3), 25.8 (CH_3), 17.9 (CH_3), 3.5 (CH_3); LRMS m/z 164.12 ($[M–H_2O]^+$, 29%), 149.10 ($[M–H_2O–CH_3]^+$, 64%), 96.05 (100%).

_N_-Methyl-_O_-benzoyl hydroxylamine hydrochloride 215[125]

223 215

Gaseous hydrogen chloride, generated from the slow addition of concentrated sulfuric acid (ca. 50 ml) to ammonium chloride (ca. 50 g) was bubbled through a solution of hydroxylamine **223** (30.6 g, 0.12 mol) in 1,4-dioxane for 2 h. The resulting white precipitate was filtered and washed with cold ether and dried under high vacuum to give the *hydrochloride salt* **215** (16.1 g, 84%) as a colourless solid; m.p. 127–129 °C (lit. m.p. 129–129.5 °C); δ_H (DMSO-d^6) 10.83 (1H, bs, NH), 7.96–7.94 (2H, m, Ar-H), 7.75–7.72 (1H, m, Ar-H), 7.59–7.56 (2H, m, Ar-H), 2.99 (3H, s, CH_3); δ_C (DMSO-d^6) 163.5 (C), 134.8 (CH), 129.5 (CH), 129.3 (CH), 126.2 (C) 36.6 (CH_3).

(3*RS*)-6-Methyl-2-oxohept-5-en-3-yl benzoate 220



209 220

6-Methyl-5-hepten-2-one **209** (1.0 g, 7.9 mmol) was added to a stirred solution of hydrochloride salt **215** (1.9 g, 10.3 mmol) in dimethyl sulfoxide (15 ml) at r.t., before being warmed to 50 °C and left to stir for 16 h. The solution was allowed to cool to r.t. before being diluted with ether (150 ml) and washed with aqueous brine (5 x 50 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 4:1) to yield *ketone* **220** (1.48 g, 76%) as a colourless liquid; δ_H 8.08–8.06 (2H, m, Ar-H), 7.59–7.56 (1H, m, Ar-H), 7.47–7.44 (2H, m, Ar-H), 5.22 (1H, dd, *J* 6.7, 5.7, C(O)CH(OBz)CH_2), 5.20–5.17 (1H, m, CH_2CH=C), 2.63–2.60 (2H, m, CHCH_2CH), 2.21 (3H, s, CH_3C(O)), 1.70 (3H, s, CH=C(CH_3)$_2$), 1.65 (3H, s, CH=C(CH_3)$_2$); δ_C 205.4 (C), 166.0 (C), 135.8 (C), 133.3 (CH), 129.7

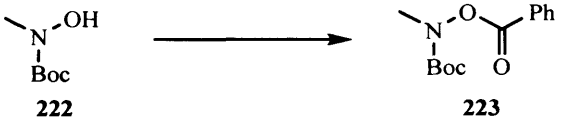
(CH), 129.4 (C), 128.4 (CH), 117.4 (CH), 78.9 (CH), 29.4 (CH_2), 26.6 (CH_3), 25.7 (CH_3), 17.8 (CH_3).

_N_-Methyl-_N_-Boc hydroxylamine 222[125]

221 **222**

Potassium carbonate (12.4 g, 0.09 mol) was added to a stirred solution of *N*-methyl hydroxylamine hydrochloride **221** (15 g, 0.18 mol) in tetrahydrofuran/water (80 ml, 1:1) at 0 °C, followed by dropwise addition of di-*tert*-butyl dicarbonate (43.2 g, 0.20 mol) in tetrahydrofuran (60 ml). The mixture was left to stir for 2 h before being allowed to warm to r.t. and left to stir for a further 3 h. The mixture was concentrated *in vacuo* and the residue dissolved in dichloromethane (100 ml), washed with water (3 x 40 ml) and brine (50 ml) and the organic fraction dried, filtered and evaporated. The product was purified by distillation to yield *hydroxylamine* **222** (17.9 g, 68%) as a colourless liquid; b.p. 0.8 mbar, 56–62 °C (lit. b.p. 1 mbar, 84–87 °C); ν_{max} 3268, 1697, 1043, 1025; δ_H 8.00 (1H, bs, O<u>H</u>), 3.14 (3H, s, NC<u>H</u>$_3$), 1.46 (9H, s, C(C<u>H</u>$_3$)$_3$); δ_C 157.7 (C), 81.6 (C), 37.9 (CH_3), 28.2 (CH_3).

_N_-Methyl-_N_-Boc-_O_-benzoyl hydroxylamine 223[125]

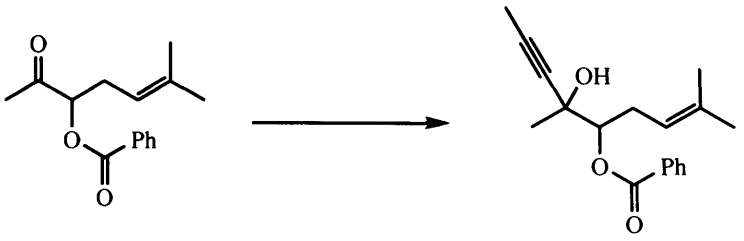


222 **223**

Benzoyl chloride (19.3 g, 0.14 mol) was added dropwise to a stirred solution of hydroxylamine **222** (17.9 g, 0.12 mol), 4-(dimethylamino)pyridine (0.3 g, 2.5 mmol) and triethylamine (12.3 g, 0.12 mol) in dichloromethane (300 ml) at 0 °C before being allowed to warm to r.t. and left to stir for 16 h. The mixture was concentrated *in vacuo* and the residue triturated with light petroleum, filtered, diluted with dichloromethane (200 ml), washed with saturated sodium hydrogen carbonate solution (2 x 60 ml), water (60 ml) and brine (60 ml). The organic fraction was dried, filtered and evaporated to give the *hydroxylamine* **223** (30.6 g, 94%) as a colourless liquid; ν_{max} 2981, 2936, 1774, 1727, 1334, 1244, 1205, 1152, 872, 775; δ_H 8.03–8.01 (2H, m, Ar-<u>H</u>), 7.61–

7.58 (1H, m, Ar-H), 7.44–7.41 (2H, m, Ar-H), 3.19 (3H, s, NCH_3), 1.42 (9H, s, $C(CH_3)_3$); δ_C 168.3 (C), 156.4 (C), 135.3 (CH), 133.2 (C), 131.4 (CH), 129.0 (CH), 83.5 (C), 39.6 (CH_3), 28.0 (CH_3).

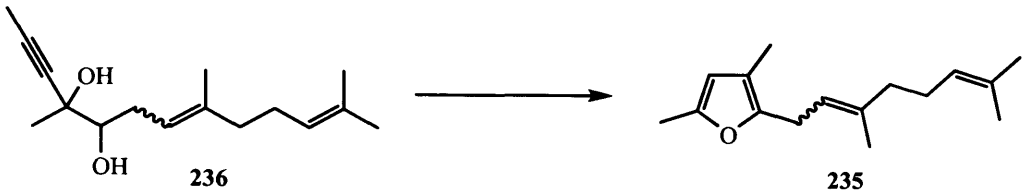
(2*RS*,3*RS*)-2,6-Dimethyl-6-hydroxy-non-2-en-7-yn-5-yl benzoate 231



220 **231**

A solution of commercial 1-propynylmagnesium bromide in tetrahydrofuran (2.8 ml, 0.5 M, 1.4 mmol) was added dropwise to a stirred solution of ketone **220** (0.35 g, 1.4 mmol) in tetrahydrofuran (20 ml) under nitrogen at –82 °C and left to stir for 2 h. The reaction was quenched with aqueous ammonium chloride before being allowed to warm to r.t., concentrated *in vacuo*, and the residue dissolved in ethyl acetate (50 ml) and washed with water (3 x 20 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 4:1) to yield *alcohol* **231** (0.35 g, 85%) as a colourless liquid, as an inseparable 6:1 mixture of diastereoisomers; *major diastereoisomer* δ_H 8.07–8.05 (2H, m, Ar-H), 7.58–7.54 (1H, m, Ar-H), 7.46–7.43 (2H, m, Ar-H), 5.20–5.16 (1H, m, CH_2CH=C), 5.16–5.14 (1H, dd, *J* 8.9, 3.9, $CCH(OBz)CH_2$), 2.67–2.57 (2H, m, $CHCH_2CH$), 2.43 (1H, bs, OH), 1.86 (3H, s, $C{\equiv}CCH_3$), 1.61 (6H, s, $CH{=}C(CH_3)_2$), 1.49 (3H, s, $CH_3C(OH)$); δ_C 166.1 (C), 134.6 (C), 132.9 (CH), 130.1 (C), 129.7 (CH), 128.3 (CH), 119.5 (CH), 81.3 (C), 80.3 (C), 79.3 (CH), 70.2 (C), 29.2 (CH_2), 26.8 (CH_3), 25.7 (CH_3), 17.8 (CH_3), 3.5 (CH_3); LRMS m/z 268.15 ($[M–H_2O]^+$, 7%), 253.12 ($[M–H_2O–CH_3]^+$, 8%), 105.03 (100%); HRMS calculated for $C_{18}H_{20}O_2$ $[M–H_2O]^+$ 268.1463, found 268.1469.

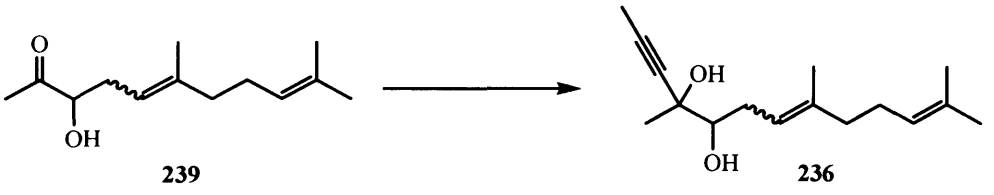
(*E/Z*)-2-(3,7-Dimethylocta-2,6-dienyl)-3,5-dimethylfuran 235



236 235

Silver nitrate on silica gel (0.46 g, ~10 wt. %, 0.3 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **236** (0.35 g, 1.5 mmol) in dichloromethane (10 ml) at r.t. under subdued light and left to stir for 3 h. The mixture was filtered through a pad of silica gel with dichloromethane (30 ml) and the filtrate dried, filtered and evaporated to yield *furan* **239** (0.32 g, 99%) as a colourless liquid, as an inseparable 1.5:1 mixture of *E/Z* isomers; *E-isomer* δ_H 5.73 (1H, s, furan-H), 5.28–5.24 (1H, m, $CH_2CH{=}C(CH_3)_2$), 5.11–5.07 (1H, m, $CH_2CH{=}C(CH_3)CH_2$), 3.23 (2H, d, *J* 6.9, furan-CH_2CH), 2.21 (3H, s, α-furan-CH_3), 2.13–1.99 (4H, m, CCH_2CH_2CH), 1.90 (3H, s, β-furan-CH_3), 1.69 (3H, s, CH_3), 1.67 (3H, d, *J* 1.0, CH_3), 1.59 (3H, s, CH_3); δ_C 149.1, 148.2, 136.1, 131.4, 124.2, 120.5, 114.0, 108.8, 36.6, 26.6, 25.7, 25.2, 17.7, 16.1, 13.5, 9.8. *Z-isomer* δ_H 5.17–5.13 (1H, m, $CH_2CH{=}C(CH_3)CH_2$), 1.71 (3H, d, *J* 1.3, CH_3), 1.63 (3H, s, CH_3) only 3 distinct peaks; δ_C 148.1, 136.3, 131.7, 121.2, 26.5, 24.9 only 6 distinct peaks.

(*E/Z*)-4,8,12-Trimethyltrideca-7,11-dien-2-yne-4,5-diol 236

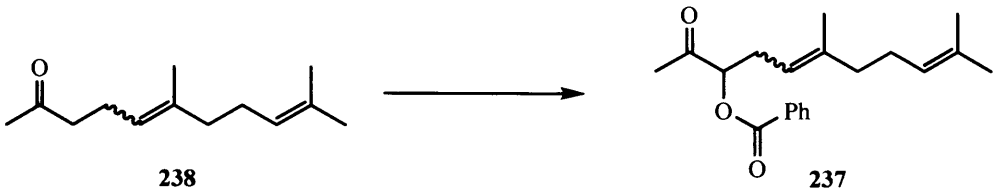


239 236

A solution of commercial 1-propynylmagnesium bromide in tetrahydrofuran (9.6 ml, 0.5 M, 4.8 mmol) was added dropwise to a stirred solution of alcohol **236** (0.46 g, 2.2 mmol) in tetrahydrofuran (20 ml) under nitrogen at –78 °C. The mixture left to stir for 1 hour before being allowed to warm to r.t. and left to stir for a further 2 h. The reaction mixture was quenched by dropwise addition of aqueous ammonium chloride (10 ml), concentrated *in vacuo*, and the residue dissolved in ethyl acetate (40 ml) and washed with water (3 x 30 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 7:3) to yield *3-alkyne-1,2-diol* **236** (0.31 g, 57%) as a colourless solid, as an inseparable 1.5:1 mixture of *E/Z* isomers; *E-isomer* δ_H 5.30–5.24 (1H, m, $CH_2CH{=}C(CH_3)_2$), 5.11–5.05 (1H, m, $CH_2CH{=}C(CH_3)CH_2$), 3.57–3.54 (1H, m, $C(O)CH(OH)CH_2$), 2.45–2.37 (2H,

m, CHC$\underline{H}_2$CH), 2.23–2.02 (4H, m, CC$\underline{H}_2$C$\underline{H}_2$CH), 1.87 (3H, s, C$\underline{H}_3$), 1.85 (3H, s, C$\underline{H}_3$), 1.69 (3H, s, C$\underline{H}_3$), 1.65 (3H, s, C$\underline{H}_3$), 1.60 (3H, s, C$\underline{H}_3$); *Z-isomer* δ_H 5.14–5.10 (1H, m, $CH_2C\underline{H}$=C(CH_3)CH_2), 3.55–3.53 (1H, m, C(O)C$\underline{H}$(OH)CH_2), 2.39–2.31 (2H, m, CHC$\underline{H}_2$CH), 1.86 (3H, s, C$\underline{H}_3$), 1.85 (3H, s, C$\underline{H}_3$), 1.75 (3H, d, *J* 1.1, C$\underline{H}_3$), 1.65 (3H, s, C$\underline{H}_3$), 1.62 (3H, s, C$\underline{H}_3$) only 8 distinct peaks.

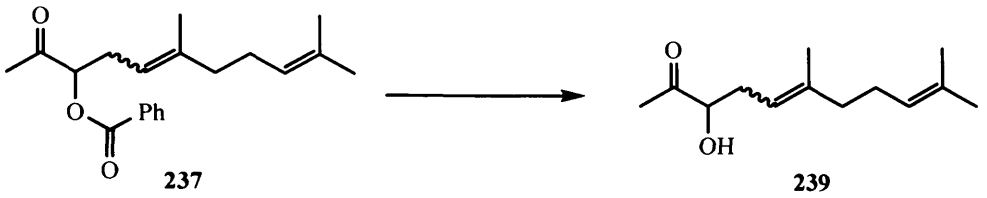
(*E/Z*)-6,10-Dimethyl-2-oxoundeca-5,9-dien-3-yl benzoate 237



238 **237**

(*E/Z*)-6,10-dimethylundeca-5,9-dien-2-one **237** (1.0 g, 5.2 mmol) was added to hydrochloride salt **215** (1.1 g, 5.7 mmol) in dimethyl sulfoxide (15 ml) at r.t. before being warmed to 50 °C and left to stir for 16 h. The solution was allowed to cool to r.t., diluted with ethyl acetate (150 ml) and washed with aqueous brine (5 x 50 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 9:1) to yield *ketone* **237** (1.1 g, 69%) as a colourless liquid, as an inseparable 1.5:1 mixture of *E/Z* isomers; *E-isomer* δ_H 8.08–8.07 (2H, m, Ar-$\underline{H}$), 7.61–7.58 (1H, m, Ar-$\underline{H}$), 7.48–7.45 (2H, m, Ar-$\underline{H}$), 5.25 (1H, dd, *J* 6.8, 5.7, C(O)C$\underline{H}$(OBz)CH_2), 5.23–5.19 (1H, m, $CH_2C\underline{H}$=C(CH_3)$_2$), 5.05–5.03 (1H, m, $CH_2C\underline{H}$=C(CH_3)CH_2), 2.65–2.61 (2H, m, CHC$\underline{H}_2$CH), 2.22 (3H, s, C$\underline{H}_3$C(O)), 2.07–2.01 (4H, m, CC$\underline{H}_2$C$\underline{H}_2$CH), 1.68 (3H, s, C$\underline{H}_3$), 1.65 (3H, s, C$\underline{H}_3$), 1.58 (3H, s, C$\underline{H}_3$); δ_C 205.6 (C), 166.0 (C), 139.6 (C), 133.4 (CH), 131.6 (C), 129.8 (CH), 129.5 (C), 128.5 (CH), 123.9 (CH), 117.4 (CH), 78.9 (CH), 39.7 (CH_2), 32.0 (CH_2), 29.5 (CH_2), 26.7 (CH_3), 25.6 (CH_3), 17.6 (CH_3), 16.2 (CH_3); *Z-isomer* δ_H 5.22-5.19 (1H, m, C(O)C$\underline{H}$(OBz)CH_2), 5.22–5.19 (1H, m, $CH_2C\underline{H}$=C(CH_3)$_2$), 5.12–5.08 (1H, m, $CH_2C\underline{H}$=C(CH_3)CH_2), 1.72 (3H, d, *J* 1.0, C$\underline{H}_3$), 1.63 (3H, s, C$\underline{H}_3$), 1.56 (3H, s, C$\underline{H}_3$) only 6 distinct peaks; δ_C 205.4 (C), 166.1 (C), 139.5 (C), 132.0 (C), 123.8 (CH), 118.1 (CH), 79.1 (CH), 29.2 (CH_2), 26.6 (CH_3), 25.7 (CH_3) only 10 distinct peaks.

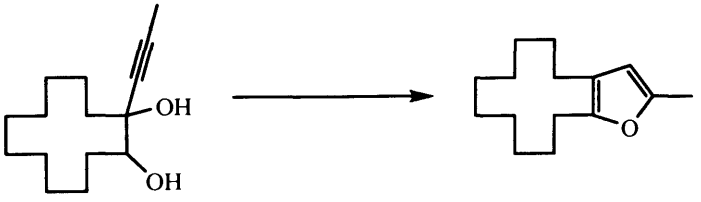
(*E/Z*)-3-Hydroxy-6,10-dimethylundeca-5,9-dien-2-one 239



237 239

Potassium hydroxide (0.04 g, 7.6 mmol) was added to a stirred solution of ketone **237** (0.12 g, 0.4 mmol) in methanol/water (5 ml, 4:1) at r.t. and left to stir for 6 h. The mixture was diluted with dichloromethane (50 ml) and washed with aqueous sodium hydrogen carbonate (3 x 10 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 4:1) to yield *alcohol* **239** (0.49 g, 65%) as a colourless liquid, as an inseparable 1.5:1 mixture of isomers; *E-isomer* δ_H 5.13–5.08 (1H, m, $CH_2C\underline{H}=C(CH_3)_2$), 5.07–5.03 (1H, m, $CH_2C\underline{H}=C(CH_3)CH_2$), 4.26–4.20 (1H, m, $C(O)C\underline{H}(OH)CH_2$), 3.41 (1H, bs, $O\underline{H}$), 2.55–2.53 (1H, m, $CHC\underline{H}_2CH$), 2.45–2.41 (1H, m, $CHC\underline{H}_2CH$), 2.19 (3H, s, $C\underline{H}_3C(O)$), 2.09–2.00 (4H, m, $CC\underline{H}_2C\underline{H}_2CH$), 1.68 (3H, s, $C\underline{H}_3$), 1.64 (3H, s, $C\underline{H}_3$), 1.59 (3H, s, $C\underline{H}_3$); δ_C 209.6 (C), 139.3 (C), 131.7 (C), 124.0 (CH), 117.6 (CH), 76.6 (CH), 39.7 (CH_2), 32.3 (CH_2), 26.4 (CH_2), 25.7 (CH_3), 23.5 (CH_3), 17.7 (CH_3), 16.3 (CH_3); *Z-isomer* δ_H 2.58–2.56 (1H, m, $CHC\underline{H}_2CH$), 2.39–2.35 (1H, m, $CHC\underline{H}_2CH$), 1.72 (3H, d, *J* 1.3, $C\underline{H}_3$), 1.68 (3H, s, $C\underline{H}_3$), 1.61 (3H, s, $C\underline{H}_3$) only 5 distinct peaks; δ_C 139.4 (C), 131.9 (C), 123.9 (CH), 118.4 (CH), 32.1 (CH_2) only 5 distinct peaks.

2-Methyl-4,5,6,7,8,9,10,11,12,13-decahydrocyclododeca[b]furan 262[138]

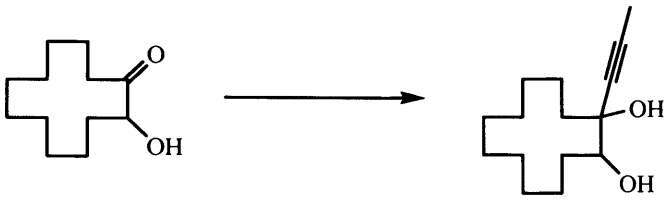


263 262

Silver nitrate on silica gel (0.46 g, ~10 wt. %, 0.3 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **263** (0.35 g, 1.5 mmol) in dichloromethane (10 ml) at r.t. under subdued light and left to stir for 1.5 h. The mixture was filtered through a pad of silica gel with dichloromethane (30 ml) and the filtrate dried, filtered and evaporated to yield *furan* **262** (0.32 g,

99%) as a colourless solid; δ_H 5.75 (1H, *app.* s, furan-H), 2.56 (2H, t, *J* 6.6, furan-CH_2CH_2), 2.31 (2H, t, *J* 6.7, furan-CH_2CH_2), 2.23 (3H, d, *J* 0.6, CH_3), 1.73–1.67 (2H, m, CH_2), 1.61-1.56 (2H, m, CH_2), 1.38–1.30 (8H, m, CH_2), 1.26–1.17 (4H, m, s, CH_2).

(1*RS*,2*RS*)-1-(Prop-1-ynyl)cyclododecane-1,2-diol 263



264 **263**

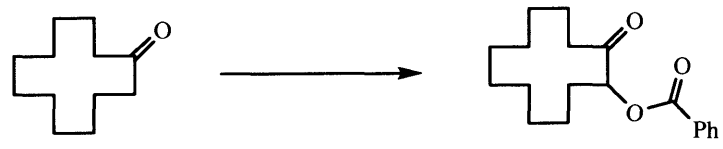
A solution of commercial 1-propynylmagnesium bromide in tetrahydrofuran (8.2 ml, 0.5 M, 4.1 mmol), was added dropwise to a solution of alcohol **264** (0.37 g, 1.9 mmol) in tetrahydrofuran (20 ml) under nitrogen at –78 °C. The mixture left to stir for 1 hour before being allowed to warm to r.t. and left to stir for a further 2 h. The reaction mixture was quenched by dropwise addition of aqueous ammonium chloride (5 ml), concentrated *in vacuo*, and the residue dissolved in ethyl acetate (20 ml) and washed with water (3 x 5 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 6:4) to yield *3-alkyne-1,2-diol* **263** (0.35 g, 80%) as a colourless solid, as a 7:1 mixture of diastereoisomers; *major diastereoisomer* δ_H 3.75 (1H, *app.* d, *J* 9.1, CCH(OH)CH_2), 2.66 (1H, bs, OH), 2.17 (1H, bs, OH), 1.93–1.52 (4H, m, CH_2), 1.87 (3H, s, CH_3), 1.41–1.24 (16H, m, CH_2); δ_C 82.0 (C), 81.0 (C), 74.8 (C), 73.5 (CH), 34.9 (CH_2), 29.9 (CH_2), 25.8 (CH_2), 25.3 (CH_2), 23.7 (CH_2), 22.8 (CH_2), 22.4 (CH_2), 22.3 (CH_2), 22.0 (CH_2), 20.5 (CH_2), 18.3 (CH_3); *minor diastereoisomer* δ_H 3.71 (1H, *app.* d, *J* 8.4, CCH(OH)CH_2), 3.03 (1H, bs, OH) only 2 distinct peaks; δ_C 80.7 (C), 80.6 (C), 74.2 (C), 72.8 (CH), 35.6 (CH_2), 29.7 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 23.3 (CH_2), 22.6 (CH_2), 22.4 (CH_2), 22.2 (CH_2), 21.9 (CH_2) only 13 distinct peaks.

(2*RS*)-2-Hydroxycyclododecanone 264[220]

265 **264**

Potassium hydroxide (0.07 g, 1.3 mmol) was added to a solution of ketone **265** (0.2 g, 0.7 mmol) in methanol/water (10 ml, 4:1) at r.t. and left to stir for 2 h. The mixture was diluted with ether (50 ml) and washed with aqueous sodium hydrogen carbonate (3 x 10 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 6:4) to yield *alcohol* **264** (0.13 g, 99%) as a colourless solid; m.p. 77–79 °C (lit. m.p. 75–76 °C); δ_H 4.32 (1H, *app.* td 5.2, 2.3, CC<u>H</u>(OH)CH_2), 3.57 (1H, d, *J* 5.2, O<u>H</u>), 2.99–2.92 (1H, m, $CH_2C\underline{H_2}C(O)$), 2.17–2.05 (2H, m, $C\underline{H_2}$), 1.92–1.79 (2H, m, $C\underline{H_2}$), 1.51–1.43 (1H, m, $C\underline{H_2}$), 1.35–1.14 (12H, m, $C\underline{H_2}$), 1.13–1.04 (1H, m, CH_2), 0.81–0.72 (1H, m, CH_2); δ_C 212.7 (C), 76.4 (CH), 34.1 (CH_2), 30.6 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 23.8 (CH_2), 22.5 (CH_2), 22.3 (CH_2), 21.9 (CH_2), 21.2 (CH_2), 18.6 (CH_2).

(1*RS*)-2-Oxocyclododecyl benzoate 265[221]



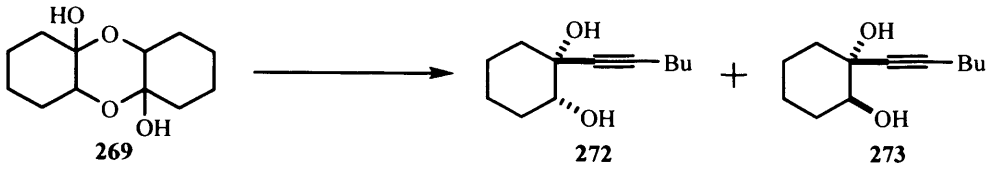
255 **265**

Cyclododecanone **255** (1.0 g, 6.2 mmol) was added to a stirred solution of hydrochloride salt **215** (1.3 g, 6.8 mmol) in dimethyl sulfoxide (15 ml) at r.t., before being warmed to 40 °C and left to stir for 16 h. The solution was allowed to cool to r.t., diluted with ethyl acetate (250 ml) and washed with aqueous brine (5 x 100 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 9:1) to yield *ketone* **265** (0.94 g, 51%) as a colourless solid; m.p. 95–97 °C (lit. m.p. 96–97 °C); δ_H 8.09–8.07 (2H, m, Ar-<u>H</u>), 7.59–7.56 (1H, m, Ar-<u>H</u>), 7.47–7.44 (2H, m, Ar-<u>H</u>), 5.35 (1H, dd, *J* 7.0, 3.1, CC<u>H</u>(OBz)CH_2), 2.77 (1H, ddd, *J* 18.1, 10.4, 3.4, $CH_2C\underline{H_a}H_bC(O)$), 2.52 (1H, ddd, *J* 18.1, 6.8, 3.6, $CH_2CH_a\underline{H_b}C(O)$), 2.16–2.09 (1H, m, $CH_2C\underline{H_2}CH$), 2.03–1.95 (2H, m, $CH_2C\underline{H_2}CH$, $C\underline{H_2}$), 1.66–1.55 (2H, m, $C\underline{H_2}C\underline{H_2}$), 1.42–1.24 (12H, m, $C\underline{H_2}$); δ_C 206.3 (C), 165.9 (C), 133.2 (CH),

129.7 (CH), 129.6 (C), 128.4 (CH), 79.0 (CH), 34.7 (CH_2), 27.8 (CH_2), 26.3 (CH_2), 26.0 (CH_2), 23.7 (CH_2), 22.7 (CH_2), 22.2 (CH_2), 22.2 (CH_2), 21.1 (CH_2), 19.5 (CH_2).

(1*R*,2*R* and 1*S*,2*S*)-1-(Hex-1-ynyl)cyclohexane-1,2-diol 272[89]

(1*R*,2*S* and 1*S*,2*R*)-1-(Hex-1-ynyl)cyclohexane-1,2-diol 273



269 272 273

A solution of butyllithium in hexanes (38.5 ml, 2.5 M, 96.4 mmol), was added dropwise to a stirred solution of 1-hexyne **270** (7.2 g, 87.6 mmol) in tetrahydrofuran (100 ml) at 0 °C and left to stir for 1 hour. The mixture was cooled to –78 °C before a solution of 2-hydroxycyclohexanone **269** (5 g, 21.9 mmol) in tetrahydrofuran (50 ml) was added dropwise and left to stir for 1 h. The mixture was allowed to warm to r.t. and left to stir for 16 h. The reaction mixture was quenched by dropwise addition of aqueous ammonium chloride (20 ml), concentrated *in vacuo*, and the residue dissolved in diethyl ether (100 ml) and washed with water (3 x 20 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 6:4) to yield *cis-diol* **272** (3.3 g, 41%) as a colourless oil and *trans-diol* **273** (3.4 g, 42%) as a colourless oil;

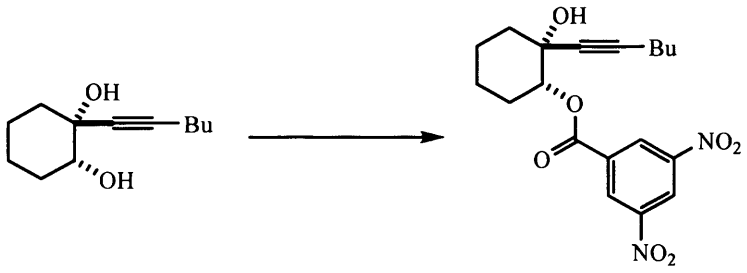
cis-diol **272**:

ν_{max} 3400, 2937, 2861, 2237, 1460, 1446, 1249, 1173, 1065, 1000, 954, 701; δ_H 3.67 (1H, dd, *J* 7.9, 3.7, $CH_2C\underline{H}(OH)C$), 2.38 (1H, bs, O<u>H</u>), 2.33 (1H, bs, O<u>H</u>), 2.21 (2H, t, *J* 7.1, $C{\equiv}CC\underline{H_2}CH_2$), 2.00–1.96 (1H, m, $CH_2C\underline{H_2}C(OH)(C{\equiv}CBu)CH$), 1.79–1.73 (1H, m, $CH_2C\underline{H_2}CH(OH)C$), 1.69–1.53 (4H, m, $C\underline{H_2}C\underline{H_2}C\underline{H_2}C\underline{H_2}$), 1.51–1.44 (2H, m, $CH_2C\underline{H_2}CH_2CH_3$), 1.46–1.40 (1H, m, $CH_2CH_2C\underline{H_2}CH_2$), 1.43–1.37 (2H, m, $CH_2C\underline{H_2}CH_3$), 1.35–1.28 (1H, m, $CH_2C\underline{H_2}CH_2CH_2$), 0.91 (3H, t, *J* 7.3, $C\underline{H_3}$); δ_C 85.5 (C), 82.5 (C), 74.4 (CH), 70.3 (C), 35.7 (CH_2), 30.7 (CH_2), 28.4 (CH_2), 21.9 (CH_2), 21.8 (CH_2), 21.4 (CH_2), 18.3 (CH_2), 13.6 (CH_3); LRMS m/z 178.14 ([M–H_2O]$^+$, 9%), 91.05 (100%); HRMS calculated for $C_{12}H_{18}O$ [M–H_2O]$^+$ 178.1358, found 178.1352.

trans-diol **273**:

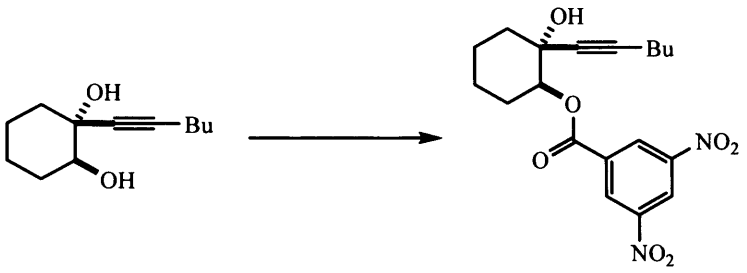
ν_{max} 2406, 2937, 2861, 2240, 1742, 1449, 1378, 1251, 1036, 866; δ_H 3.37 (1H, dd, *J* 11.2, 4.3, $CH_2C\underline{H}(OH)C$), 2.79 (1H, bs, O<u>H</u>), 2.26 (2H, t, *J* 7.1, $C{\equiv}CC\underline{H_2}CH_2$), 2.04–2.01 (1H, m, $CH_2C\underline{H_2}C(OH)(C{\equiv}CBu)CH$), 1.94–1.89 (1H, m, $CH_2C\underline{H_2}CH(OH)C$), 1.80 (1H, bs, O<u>H</u>), 1.72–1.67 (1H, m, $CH_2C\underline{H_2}CH_2CH_2$), 1.65–1.62 (1H, m, $CH_2CH_2C\underline{H_2}CH_2$), 1.56–1.58 (7H, m, $C\underline{H_2}CH_2C\underline{H_2}C\underline{H_2}$, $CH_2C\underline{H_2}C\underline{H_2}CH_3$), 1.32–1.23 (1H, m, $CH_2C\underline{H_2}CH_2CH_2$), 0.92 (3H, t, *J* 7.3, $C\underline{H_3}$); δ_C 88.3 (C), 79.5 (C), 77.2 (CH), 74.1 (C), 37.8 (CH_2), 32.2 (CH_2), 30.9 (CH_2), 24.2 (CH_2), 23.3 (CH_2), 22.0 (CH_2), 18.4 (CH_2), 13.6 (CH_3); LRMS m/z 178.14 ($[M–H_2O]^+$, 11%), 91.05 (100%); HRMS calculated for $C_{12}H_{18}O$ $[M–H_2O]^+$ 178.1358, found 178.1354.

(1*R*,2*R* and 1*S*,2*S*)-1-(Hex-1-ynyl)-2-(3,5-dinitrobenzoate)cyclohexane-1-ol 282



3,5-Dinitrobenzoyl chloride **281** (0.24 g, 1.0 mmol), was added to a stirred solution of *cis*-diol **272** (0.20 g, 1.0 mmol) and imidazole (0.08 g, 1.2 mmol) in dichloromethane (10 ml) at r.t. and left to stir for 16 h. The mixture was diluted with dichloromethane (10 ml) and washed with aqueous ammonium chloride (3 x 10 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 4:1) to yield *alcohol* **282** (0.16 g, 40%) as a colourless oil; δ_H 9.21–9.20 (1H, m, Ar-<u>H</u>), 9.15–9.14 (2H, m, Ar-<u>H</u>), 5.28 (1H, dd, *J* 7.2, 3.7, $CH_2C\underline{H}(CO_2Ar)C$), 2.43 (1H, bs, O<u>H</u>), 2.15 (2H, t, *J* 7.0, $C{\equiv}CC\underline{H_2}CH_2$), 2.02–1.90 (3H, m, $C\underline{H_2}CH_2CH_2C\underline{H_2}CH$), 1.82–1.76 (1H, m, $CH_2C\underline{H_2}C(OH)(C{\equiv}CBu)CH$), 1.75–1.65 (2H, m, $CH_2C\underline{H_2}C\underline{H_2}CH_2$), 1.62–1.56 (1H, m, $CH_2C\underline{H_2}CH_2CH_2$), 1.54–1.49 (1H, m, $CH_2CH_2C\underline{H_2}CH_2$), 1.42–1.37 (2H, m, $CH_2C\underline{H_2}CH_2CH_3$), 1.34–1.27 (2H, m, $CH_2C\underline{H_2}CH_3$), 0.80 (3H, t, *J* 7.3, $C\underline{H_3}$); δ_C 162.1,(C), 148.6 (C), 134.2 (C), 129.4 (CH), 122.3 (CH), 86.6 (C), 81.1 (CH), 78.7 (C), 69.0 (C), 36.4 (CH_2), 30.5 (CH_2), 27.2 (CH_2), 21.8 (CH_2), 21.7 (CH_2), 21.4 (CH_2), 18.2 (CH_2),13.4 (CH_3).

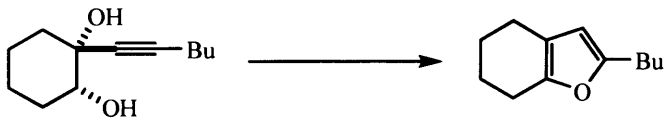
(1*R*,2*S* and 1*S*,2*R*)-1-(Hex-1-ynyl)-2-(3,5-dinitrobenzoate)cyclohexane-1-ol 283



273 283

3,5-Dinitrobenzoyl chloride **281** (0.14 g, 0.6 mmol), was added to a stirred solution of *trans*-diol **273** (0.12 g, 0.6 mmol) and imidazole (0.05 g, 0.7 mmol) in dichloromethane (10 ml) at r.t. and left to stir for 16 h. The mixture was diluted with dichloromethane (10 ml) and washed with aqueous ammonium chloride (3 x 10 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 4:1) and recrystallised from deuteriochloroform to yield *alcohol* **283** (0.13 g, 53%) as a colourless solid; m.p. 96–99 °C; ν_{max} (nujol) 3486, 2233, 1716, 1549, 1343, 1294, 864; δ_H 9.19–9.18 (1H, m, Ar-H), 9.16–9.15 (2H, m, Ar-H), 4.95 (1H, dd, *J* 10.7, 4.2, $CH_2CH(CO_2Ar)C$), 2.63 (1H, bs, OH), 2.32 (2H, t, *J* 7.0, $C{\equiv}CCH_2CH_2$), 2.08–2.02 (2H, m, $CH_2CH_2CH_2CH_2$), 1.79-1.69 (3H, m), 1.65–1.54 (4H, m), 1.47–1.37 (3H, m), 0.89 (3H, t, *J* 7.3, CH_3); δ_C 162.0,(C), 148.5 (C), 134.2 (C), 129.5 (CH), 122.3 (CH), 88.0 (C), 80.8 (CH), 79.0 (C), 71.5 (C), 39.1 (CH_2), 30.7 (CH_2), 29.0 (CH_2), 23.5 (CH_2), 22.8 (CH_2), 21.9 (CH_2), 18.2 (CH_2),13.4 (CH_3); LRMS m/z 390.14 ($[M]^+$, 2%), 372.13 ($[M–H_2O]^+$, 4%), 79.05 (100%); HRMS calculated for $C_{19}H_{22}N_2O_7$ $[M]^+$ 390.1427, found 390.1432.

2-Butyl-4,5,6,7-tetrahydrobenzofuran 285[222]

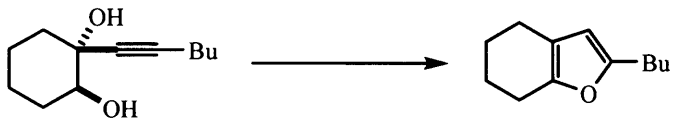


272 285

Silver nitrate on silica gel (0.087 g, ~10 wt. %, 0.05 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **272** (0.10 g, 0.5 mmol) in dichloromethane (5 ml) at r.t. under subdued light and left to stir for 9 h. The mixture was filtered through a pad of silica gel with dichloromethane (30 ml) and the filtrate dried, filtered and evaporated and the product purified by column

chromatography (petrol/ethyl acetate, 49:1) to yield *furan* **285** (0.07 g, 72%) as a colourless liquid; δ_H 5.79 (1H, s, furan-H), 2.58 (2H, t, *J* 7.9, furan-$CH_2CH_2CH_2CH_3$), 2.58–2.58 (2H, m, $CH_2CH_2CH_2CH_2$), 2.40-2.37 (2H, m, $CH_2CH_2CH_2CH_2$), 1.85–1.80 (2H, m, $CH_2CH_2CH_2CH_2$), 1.75–1.69 (2H, m, $CH_2CH_2CH_2CH_2$), 1.64–1.48 (2H, m, $CH_2CH_2CH_2CH_3$), 1.43–1.36 (2H, m, $CH_2CH_2CH_3$), 0.95 (3H, t, *J* 7.4, CH_3); δ_C 154.2 (C), 148.6 (C), 117.1 (C), 105.4 (CH), 30.4 (CH_2), 27.9 (CH_2), 23.3 (CH_2), 23.2 (CH_2), 23.1 (CH_2), 22.3 (CH_2), 22.1 (CH_2), 13.8 (CH_3); LRMS m/z 178.14 ($[M]^+$, 13%), 135.08 ($[M-C_3H_7]^+$, 100%); HRMS calculated for $C_{12}H_{18}O$ $[M]^+$ 178.1358, found 178.1360.

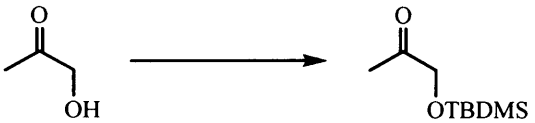
2-Butyl-4,5,6,7-tetrahydrobenzofuran 285[222]



273 **285**

Silver nitrate on silica gel (0.087 g, ~10 wt. %, 0.05 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **273** (0.10 g, 0.5 mmol) in dichloromethane (5 ml) at r.t. under subdued light and left to stir for 2 h. The mixture was filtered through a pad of silica gel with dichloromethane (30 ml) and the filtrate dried, filtered and evaporated to yield *furan* **285** (0.08 g, 95%) as a colourless liquid; data same as previous in all respects.

1-(*tert*-Butyldimethylsilyloxy)propan-2-one 294[223]

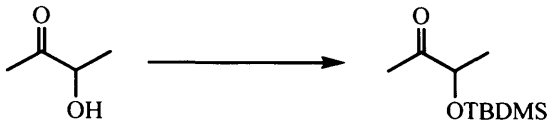


293 **294**

tert-Butyldimethylsilyl chloride (10.17 g, 67.5 mmol) was added to a stirred solution of alcohol **293** (5.00 g, 67.5 mmol) and imidazole (5.51 g, 81.0 mmol) in dichloromethane (400 ml) at r.t. and left to stir for 16 h. The mixture was diluted with dichloromethane (200 ml) and washed with aqueous ammonium chloride (3 x 300 ml). The organic fraction was dried, filtered and evaporated and the product purified by distillation to yield *ketone* **294** (8.70 g, 68%) as a colourless liquid; b.p. 4 mbar, 51–53 °C (lit. b.p. 27 mbar, 100 °C); ν_{max} 2955, 2888, 2858, 1720,

1472, 1355, 1255, 1119, 839, 779; δ_H 4.15 (2H, s, C(O)C<u>H</u>$_2$O), 2.17 (3H, s, C<u>H</u>$_3$C(O)), 0.92 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.09 (6H, s, Si(C<u>H</u>$_3$)$_2$); δ_C 209.3 (C), 69.5 (CH_2), 25.9 (CH_3), 25.7 (CH_3), 18.3 (C), –5.4 (CH_3); GC-MS m/z 174 ($[M–CH_3]^+$, 3%), 131 $[M–C_4H_9]^+$, 100%).

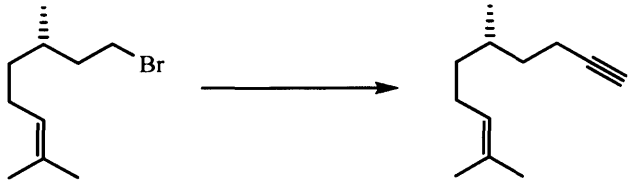
(3*RS*)-3-(*tert*-Butyldimethylsilyloxy)butan-2-one 295[224]



243 **295**

tert-Butyldimethylsilyl chloride (8.55 g, 56.8 mmol) was added to a stirred solution of alcohol **243** (5.00 g, 56.8 mmol) and imidazole (4.64 g, 68.1 mmol) in dichloromethane (400 ml) at r.t. and left to stir for 16 h. The mixture was diluted with dichloromethane (200 ml) and washed with aqueous ammonium chloride (3 x 300 ml). The organic fraction was dried, filtered and evaporated and the product purified by distillation to yield *ketone* **295** (7.46 g, 65%) as a colourless liquid; b.p. 4 mbar, 55–57 °C; δ_H 4.08 (1H, q, *J* 6.2, CC<u>H</u>(OTBDMS)CH$_3$), 2.13 (3H, s, C<u>H</u>$_3$C(O)), 1.21 (3H, d, *J* 6.2, CHC<u>H</u>$_3$), 0.88 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.03 (6H, s, Si(C<u>H</u>$_3$)$_2$); δ_C 212.6 (C), 74.9 (CH), 25.6 (CH_3), 24.7 (CH_3), 20.6 (CH_3), 18.0 (C), –5.4 (CH_3), –5.4 (CH_3).

(*S*)-5,9-Dimethyldec-8-en-1-yne 297[225]

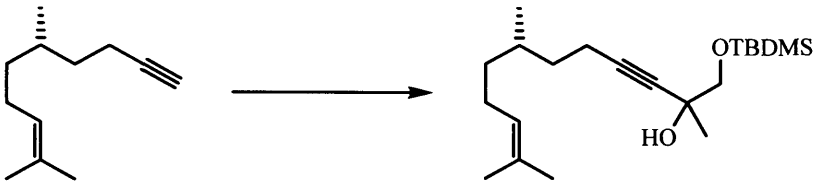


296 **297**

Lithium acetylide ethylenediamine complex **292** (0.58 g, 90%, 5.7 mmol) was added to a stirred solution of (*S*)-citronellyl bromide **296** (0.50 g, 2.3 mmol) in dimethyl sulfoxide (5 ml) under nitrogen at r.t. and left to stir for 1 hour. The mixture was quenched with ice (5 g) and neutralised to pH 7 with dropwise addition of 0.3 M H_2SO_4 (~10 ml). The mixture was washed with *tert*-butyl methyl ether (5 x 20 ml) and the organic fraction washed with brine (3 x 5 ml) before being dried, filtered and evaporated. The product was purified by distillation to yield *alkyne* **297** (0.30 g, 80%) as a colourless liquid; b.p. 4 mbar, 59–61 °C (51 mbar, 110–120 °C);

δ_H (400 MHz) 5.12–5.08 (1H, m, C=C<u>H</u>CH_2), 2.27–2.10 (2H, m, C=CHC<u>H</u>$_2$$CH_2$), 2.06–1.94 (2H, m, CH_2C<u>H</u>$_2$C≡CH), 1.93–1.91 (1H, m, C≡C<u>H</u>), 1.68 (3H, s, (C<u>H</u>$_3$)$_2$C=CH), 1.62–1.58 (2H, m, CH_2CH_2C<u>H</u>$_2$C<u>H</u>$(CH_3)CH_2$C), 1.61 (3H, s, (C<u>H</u>$_3$)$_2$C=CH), 1.39–1.30 (2H, m, CH_2C<u>H</u>$_2$CH(CH_3)C<u>H</u>$_2CH_2$), 1.20–1.10 (1H, m, CHC<u>H</u>$_2CH_2$C), 0.82 (3H, d, *J* 6.6, C<u>H</u>$_3$CH); δ_C (100 MHz) 131.1 (C), 124.6 (CH), 84.7 (C), 67.9 (CH), 36.6 (CH_2), 35.5, (CH_2), 31.6 (CH), 25.6 (CH_3), 25.4 (CH_2), 19.0 (CH_3), 17.6 (CH_3), 16.1 (CH_2); GC-MS m/z 164 ($[M]^+$, 3%), 149 ($[M-CH_3]^+$, 21%), 69 (100%).

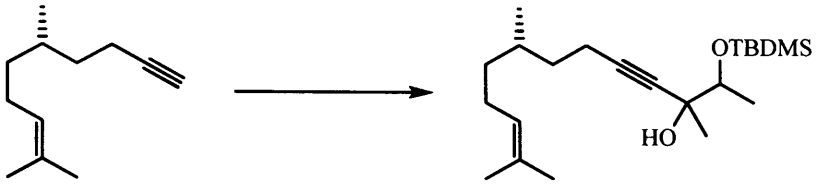
(2*RS*,7*S*)-1-(*tert*-Butyldimethylsilyloxy)-2,7,11-trimethyldodec-10-en-3-yn-2-ol 298



297 298

A solution of butyllithium in hexanes (2.9 ml, 2.5 M, 7.3 mmol) was added dropwise to a solution of alkyne **297** (1.0 g, 6.1 mmol) in tetrahydrofuran (20 ml) under nitrogen at 0 °C and left to stir for 1 hour before being cooled to –78 °C. A solution of ketone **294** (1.2 g, 6.1 mmol) in tetrahydrofuran (10 ml) was added dropwise and the mixture left to stir for 30 min. before being allowed to warm to r.t. and stirred for 2 h. The mixture was quenched with aqueous ammonium chloride (10 ml), concentrated *in vacuo*, and the residue dissolved in *tert*-butyl methyl ether (30 ml) and washed with water (3 x 10 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 19:1) to yield *alcohol* **298** (1.0 g, 48%) as a colourless liquid; δ_H (400 MHz) 5.11–5.05 (1H, m, CC<u>H</u>CH_2), 3.62 (1H, d, *J* 9.5, CC<u>H</u>$_2$O), 3.47 (1H, d, *J* 9.5, CC<u>H</u>$_2$O), 2.81 (1H, s, O<u>H</u>), 2.25–2.10 (2H, m, C=CHC<u>H</u>$_2$$CH_2$), 2.05–1.85 (2H, m, CH_2C<u>H</u>$_2$C≡CH), 1.68–1.67 (3H, m, (C<u>H</u>$_3$)$_2$C=CH), 1.60–1.59 (3H, m, (C<u>H</u>$_3$)$_2$C=CH), 1.58–1.53 (2H, m, CH_2CH_2C<u>H</u>$_2$C<u>H</u>$(CH_3)CH_2$C), 1.38 (3H, s, C<u>H</u>$_3$C(OH)), 1.36–1.25 (2H, m, CH_2C<u>H</u>$_2$CH(CH_3)C<u>H</u>$_2CH_2$), 1.18–1.07 (1H, m, CHC<u>H</u>$_2CH_2$C), 0.91 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.86 (3H, d, *J* 6.5, C<u>H</u>$_3$CH), 0.09 (6H, s, Si(C<u>H</u>$_3$)$_2$); δ_C (100 MHz) 131.1 (C), 124.7 (CH), 83.9 (C), 82.1 (C), 71.1 (CH_2), 67.9 (C), 36.6 (CH_2), 35.7 (CH_2), 31.6 (CH), 25.8 (CH_3), 25.7 (CH_3), 25.7 (CH_3), 25.4 (CH_2), 19.0 (CH_3), 18.4 (C), 17.6 (CH_3), 16.3 (CH_2), –5.3 (CH_3); GC-MS m/z 334 ($[M-H_2O]^+$, 1%), 319 ($[M-CH_3-H_2O]^+$, 1%), 277 ($[M-C_3H_9-H_2O]^+$, 9%), 131 (100%).

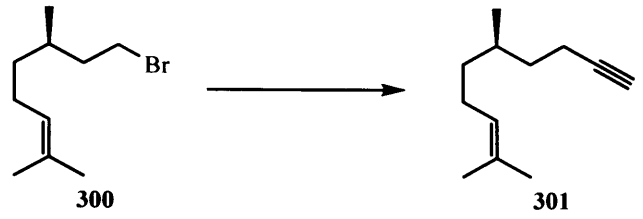
(1*RS*,2*RS*,7*S*)-2-(tert-Butyldimethylsilyloxy)-3,8,12-trimethyltridec-11-en-4-yn-3-ol 299



297 299

A solution of butyllithium in hexanes (2.9 ml, 2.5 M, 7.3 mmol) was added dropwise to a solution of alkyne **297** (1.0 g, 6.1 mmol) in tetrahydrofuran (20 ml) under nitrogen at 0 °C and left to stir for 1 hour before being cooled to –78 °C. A solution of ketone **295** (1.2 g, 6.1 mmol) in tetrahydrofuran (10 ml) was added dropwise and the mixture left to stir for 30 min. before being allowed to warm to r.t. and stirred for 2 h. The mixture was quenched with aqueous ammonium chloride (10 ml), concentrated *in vacuo*, and the residue dissolved in *tert*-butyl methyl ether (30 ml) and washed with water (3 x 10 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 19:1) to yield *alcohol* **299** (0.75 g, 34%) as a colourless liquid, as a 4:1 mixture of diastereoisomers; *major diastereoisomer* δ_H (400 MHz) 5.08 (1H, t, *J* 6.8, CC$\underline{H}$CH$_2$), 3.65 (1H, q, *J* 6.1, CC$\underline{H}$(CH$_3$)O), 2.71 (1H, s, O$\underline{H}$), 2.25–2.12 (2H, m, C=CHC$\underline{H}_2$CH$_2$), 2.01–1.90 (2H, m, CH$_2$C$\underline{H}_2$C≡CH), 1.66 (3H, s, (C$\underline{H}_3$)$_2$C=CH), 1.59 (3H, m, (C$\underline{H}_3$)$_2$C=CH), 1.62–1.48 (2H, m, CH$_2$CH$_2$C$\underline{H}_2$C$\underline{H}$(CH$_3$)CH$_2$C), 1.36 (3H, s, CC(C$\underline{H}_3$)(OH)CH), 1.34–1.21 (2H, m, CH$_2$C$\underline{H}_2$CH(CH$_3$)C$\underline{H}_2$CH$_2$), 1.24 (3H, d, *J* 6.3, CCH(C$\underline{H}_3$)O), 1.18–1.07 (1H, m, CHC$\underline{H}_2$CH$_2$C), 0.90 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.86 (3H, d, *J* 6.3, CH2CH(C$\underline{H}_3$)CH$_2$), 0.08 (6H, s, Si(C$\underline{H}_3$)$_2$); δ_C (100 MHz) 131.1 (C), 124.7 (CH), 84.9 (C), 81.5 (C), 75.2 (CH), 71.3 (C), 36.8 (CH$_2$), 35.8 (CH$_2$), 31.5 (CH), 26.6 (CH$_3$), 25.9 (CH$_3$), 25.8 (CH$_3$), 25.5 (CH$_2$), 19.1 (CH$_3$), 19.0 (CH$_3$), 18.1 (C), 17.7 (CH$_3$), 16.5 (CH$_2$), –5.3 (CH$_3$); GC-MS m/z 348 ([M–H$_2$O]$^+$, 1%), 333 ([M–CH$_3$–H$_2$O]$^+$, 1%), 291 ([M–C$_3$H$_9$–H$_2$O]$^+$, 3%), 75 (100%); *minor diastereoisomer* δ_H (400 MHz) 3.80 (1H, q, *J* 6.0, CC$\underline{H}$(CH$_3$)O), 2.61 (1H, s, O$\underline{H}$) only 2 distinct peaks.

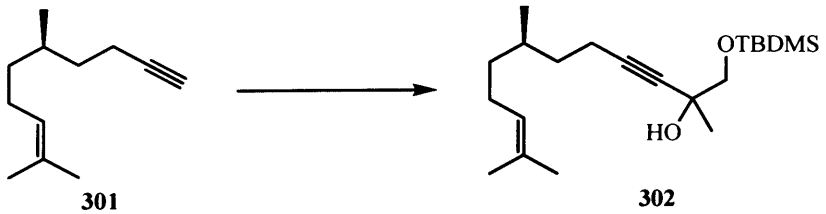
(*R*)-5,9-Dimethyldec-8-en-1-yne 301[225]



300 301

Lithium acetylide ethylenediamine complex **292** (5.6 g, 90%, 54.7 mmol) was added to a stirred solution of (*R*)-Citronellyl bromide **300** (4.0 g, 18.3 mmol) in dimethyl sulfoxide (15 ml) under nitrogen at r.t. and left to stir for 1 hour. The mixture was quenched with ice (15 g) and neutralised to pH 7 by dropwise addition of 2 M H_2SO_4 (~15 ml). The mixture was washed with *tert*-butyl methyl ether (5 x 30 ml), and the organic washings washed with brine (3 x 30 ml), before being dried, filtered and evaporated. The product was purified by distillation to yield *alkyne* **301** (2.2 g, 67%) as a colourless liquid; b.p. 4 mbar, 59–61 °C (51 mbar, 110–120 °C); δ_H (400 MHz) 5.12–5.08 (1H, m, CC<u>H</u>CH_2), 2.27–2.10 (2H, m, C=CHC<u>H</u>$_2CH_2$), 2.06–1.94 (2H, m, $CH_2C\underline{H}_2C{\equiv}CH$), 1.93–1.91 (1H, m, C≡C<u>H</u>), 1.68 (3H, s, $(C\underline{H}_3)_2C{=}CH$), 1.62–1.58 (2H, m, $CH_2CH_2C\underline{H}_2C\underline{H}(CH_3)CH_2C$), 1.61 (3H, s, $(C\underline{H}_3)_2C{=}CH$), 1.39–1.30 (2H, m, $CH_2C\underline{H}_2CH(CH_3)C\underline{H}_2CH_2$), 1.20–1.10 (1H, m, $CHC\underline{H}_2CH_2C$), 0.82 (3H, d, *J* 6.6, $C\underline{H}_3CH$); δ_C (100 MHz) 131.1 (C), 124.7 (CH), 84.7 (C), 67.9 (CH), 36.6 (CH_2), 35.5, (CH_2), 31.6 (CH), 25.6 (CH_3), 25.4 (CH_2), 19.0 (CH_3), 17.6 (CH_3), 16.1 (CH_2); GC-MS m/z 164 ($[M]^+$, 4%), 149 ($[M-CH_3]^+$, 17%), 69 (100%).

(2*RS*,7*R*)-1-(tert-Butyldimethylsilyloxy)-2,7,11-trimethyldodec-10-en-3-yn-2-ol 302

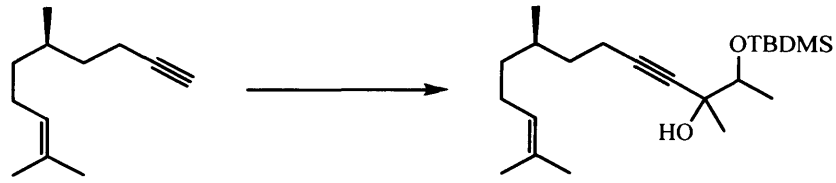


301 302

A solution of butyllithium in hexanes (1.8 ml, 2.5 M, 4.4 mmol) was added dropwise to a stirred solution of alkyne **301** (0.6 g, 3.7 mmol) in tetrahydrofuran (20 ml) under nitrogen at 0 °C and left to stir for 1 hour before being cooled to –78 °C. A solution of ketone **294** (0.7 g, 3.7 mmol) in tetrahydrofuran (10 ml) was added dropwise and the mixture left to stir for 30 min. before

being allowed to warm to r.t. and stirred for 2 h. The mixture was quenched with aqueous ammonium chloride (10 ml), concentrated *in vacuo*, and the residue dissolved in *tert*-butyl methyl ether (30 ml) and washed with water (3 x 10 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 19:1) to yield *alcohol* **302** (0.4 g, 32%) as a colourless liquid; δ_H (400 MHz) 5.12–5.03 (1H, m, CC$\underline{H}$CH$_2$), 3.62 (1H, d, *J* 9.5, CC$\underline{H}_2$O), 3.48 (1H, d, *J* 9.5, CC$\underline{H}_2$O), 2.81 (1H, s, O$\underline{H}$), 2.26–2.11 (2H, m, C=CHC$\underline{H}_2$CH$_2$), 2.06–1.86 (2H, m, CH$_2$C$\underline{H}_2$C≡CH), 1.69–1.68 (3H, m, (C$\underline{H}_3$)$_2$C=CH), 1.61–1.60 (3H, m, (C$\underline{H}_3$)$_2$C=CH), 1.59–1.53 (2H, m, CH$_2$CH$_2$C$\underline{H}_2$C$\underline{H}$(CH$_3$)CH$_2$C), 1.39 (3H, s, C$\underline{H}_3$C(OH)), 1.37–1.26 (2H, m, CH$_2$C$\underline{H}_2$CH(CH$_3$)C$\underline{H}_2$CH$_2$), 1.19–1.08 (1H, m, CHC$\underline{H}_2$CH$_2$C), 0.92 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.87 (3H, d, *J* 6.5, C$\underline{H}_3$CH), 0.10 (6H, s, Si(C$\underline{H}_3$)$_2$); δ_C (100 MHz) 131.1 (C), 124.7 (CH), 83.9 (C), 82.1 (C), 71.1 (CH$_2$), 67.9 (C), 36.6 (CH$_2$), 35.7 (CH$_2$), 31.6 (CH), 25.8 (CH$_3$), 25.7 (CH$_3$), 25.7 (CH$_3$), 25.4 (CH$_2$), 19.1 (CH$_3$), 18.5 (C), 17.7 (CH$_3$), 16.4 (CH$_2$), –5.3 (CH$_3$); GC-MS m/z 334 ([M–H$_2$O]$^+$, 1%), 319 ([M–CH$_3$–H$_2$O]$^+$, 1%), 277 ([M–C$_3$H$_9$–H$_2$O]$^+$, 5%), 131 (100%).

(1*RS*,2*RS*,7*R*)-2-(tert-Butyldimethylsilyloxy)-3,8,12-trimethyltridec-11-en-4-yn-3-ol 303

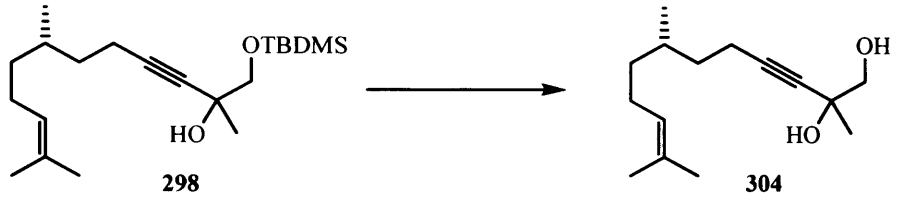


301 **303**

A solution of butyllithium in hexanes (1.8 ml, 2.5 M, 4.4 mmol) was added dropwise to a stirred solution of alkyne **301** (0.6 g, 3.7 mmol) in tetrahydrofuran (20 ml) under nitrogen at 0 °C and left to stir for 1 hour before being cooled to –78 °C. A solution of ketone **295** (0.7 g, 3.7 mmol) in tetrahydrofuran (10 ml) was added dropwise and the mixture allowed to warm to r.t. and left to stir for 2 h. The mixture was quenched with aqueous ammonium chloride (10 ml), concentrated *in vacuo*, and the residue dissolved in *tert*-butyl methyl ether (30 ml) and washed with water (3 x 10 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 19:1) to yield *alcohol* **303** (0.55 g, 41%) as a colourless liquid, as a 9:1 mixture of diastereoisomers; *major diastereoisomer* δ_H (400 MHz) 5.08 (1H, t, *J* 6.8, CC$\underline{H}$CH$_2$), 3.65 (1H, q, *J* 6.1, CC$\underline{H}$(CH$_3$)O), 2.69 (1H, s, O$\underline{H}$), 2.25–2.12 (2H, m, C=CHC$\underline{H}_2$CH$_2$), 2.01–1.90 (2H, m, CH$_2$C$\underline{H}_2$C≡CH), 1.66 (3H, s, (C$\underline{H}_3$)$_2$C=CH), 1.59 (3H, m, (C$\underline{H}_3$)$_2$C=CH), 1.62–1.48 (2H, m, CH$_2$CH$_2$C$\underline{H}_2$C$\underline{H}$(CH$_3$)CH$_2$C), 1.36 (3H, s,

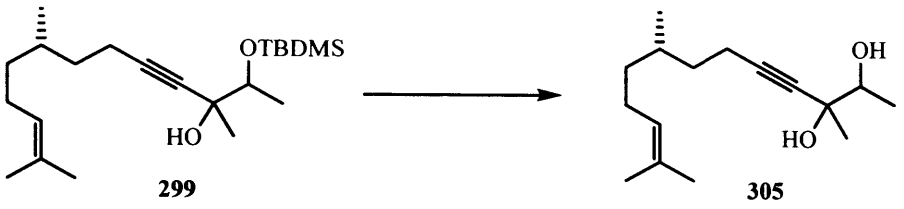
CC(C$\underline{H}_3$)(OH)CH), 1.34–1.21 (2H, m, $CH_2C\underline{H}_2CH(CH_3)C\underline{H}_2CH_2$), 1.24 (3H, d, *J* 6.3, CCH(C$\underline{H}_3$)O), 1.18–1.07 (1H, m, $CHC\underline{H}_2CH_2C$), 0.90 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.86 (3H, d, *J* 6.3, CH2CH(C$\underline{H}_3$)CH_2), 0.08 (6H, s, Si(C$\underline{H}_3$)$_2$); δ_C (100 MHz) 131.2 (C), 124.9 (CH), 84.9 (C), 81.5 (C), 75.2 (CH), 71.4 (C), 36.8 (CH_2), 35.8 (CH_2), 31.6 (CH), 26.6 (CH_3), 25.9 (CH_3), 25.8 (CH_3), 25.5 (CH_2), 19.1 (CH_3), 19.0 (CH_3), 18.1 (C), 17.7 (CH_3), 16.5 (CH_2), –5.3 (CH_3); GC-MS m/z 333 ($[M–CH_3–H_2O]^+$, 1%), 309 ($[M–C_3H_9]^+$, 2%), 291 ($[M–C_3H_9–H_2O]^+$, 3%), 75 (100%); *major diastereoisomer* δ_H (400 MHz) 3.80 (1H, q, *J* 6.0, CC$\underline{H}$(CH$_3$)O), 2.60 (1H, s, O$\underline{H}$) only 2 distinct peaks.

(2*RS*,7*S*)-2,7,11-Trimethyldodec-10-en-3-yne-1,2-diol 304[89]



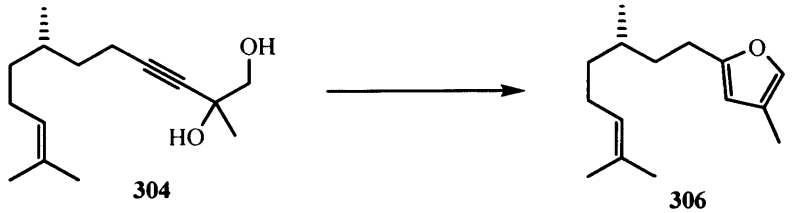
A solution of tetrabutylammonium fluoride in tetrahydrofuran (3.5 ml, 1 M, 3.5 mmol) was added dropwise to a stirred solution of alcohol **298** (1.0 g, 2.9 mmol) in tetrahydrofuran (10 ml) at r.t. and left to stir for 16 h. The mixture was concentrated *in vacuo* the product purified by column chromatography (petrol/ethyl acetate, 1:1) to yield *3-alkyne-1,2-diol* **304** (0.42 g, 60%) as a colourless oil; δ_H (400 MHz) 5.09–5.05 (1H, m, CC$\underline{H}CH_2$), 3.59 (1H, dd, *J* 10.8, 2.6, CC$\underline{H}_2$O), 3.45 (1H, dd, *J* 10.8, 7.7, CC$\underline{H}_2$O), 2.98 (1H, *app.* s, O$\underline{H}$), 2.61 (1H, bs, O$\underline{H}$), 2.26–2.11 (2H, m, C=CHC$\underline{H}_2CH_2$), 2.02–1.88 (2H, m, $CH_2C\underline{H}_2C{\equiv}CH$), 1.67 (3H, d, *J* 1.0, (C$\underline{H}_3$)$_2$C=CH), 1.59 (3H, s, (C$\underline{H}_3$)$_2$C=CH), 1.55–1.45 (2H, m, $CH_2CH_2C\underline{H}_2C\underline{H}(CH_3)CH_2C$), 1.41 (3H, s, C$\underline{H}_3$C(OH)), 1.36–1.26 (2H, m, $CH_2C\underline{H}_2CH(CH_3)C\underline{H}_2CH_2$), 1.17–1.08 (1H, m, $CHC\underline{H}_2CH_2C$), 0.86 (3H, d, *J* 6.6, C$\underline{H}_3$CH); δ_C (100 MHz) 131.3 (C), 124.7 (CH), 85.4 (C), 81.7 (C), 70.9 (CH_2), 68.7 (C), 36.7 (CH_2), 35.8 (CH_2), 31.8 (CH), 25.8 (CH_3), 25.7 (CH_3), 25.5 (CH_2), 19.1 (CH_3), 17.7 (CH_3), 16.4 (CH_2); GC-MS m/z 238 ($[M]^+$, 1%), 220 ($[M–H_2O]^+$, 18%), 205 ($[M–CH_3–H_2O]^+$, 11%), 69 (100%).

(1*RS*,2*RS*,7*S*)-3,8,12-Trimethyltridec-11-en-4-yne-2,3-diol 305



A solution of tetrabutylammonium fluoride in tetrahydrofuran (2.5 ml, 1 M, 2.5 mmol) was added dropwise to a stirred solution of alcohol **299** (0.75 g, 2.1 mmol) in tetrahydrofuran (10 ml) at r.t. and left to stir for 16 h. The mixture was concentrated *in vacuo* and the product purified by column chromatography (petrol/ethyl acetate, 1:1) to yield *3-alkyne-1,2-diol* **305** (0.13 g, 25%) as a colourless oil, as a 5:1 mixture of diastereoisomers; *major diastereoisomer* δ_H (400 MHz) 5.10–5.04 (1H, m, CC<u>H</u>CH_2), 3.62–3.55 (1H, m, CC<u>H</u>$(CH_3)O$), 3.23 (1H, bs, O<u>H</u>), 2.55 (1H, bs, O<u>H</u>), 2.25–2.10 (2H, m, C=CHC<u>H</u>$_2CH_2$), 1.97–1.85 (2H, m, $CH_2C\underline{H}_2C{\equiv}CH$), 1.63 (3H, d, *J* 1.0, $(C\underline{H}_3)_2C{=}CH$), 1.56 (3H, s, $(C\underline{H}_3)_2C{=}CH$), 1.52–1.44 (2H, m, $CH_2CH_2C\underline{H}_2C\underline{H}(CH_3)CH_2C$), 1.35 (3H, s, CC$(C\underline{H}_3)$(OH)CH), 1.31–1.26 (2H, m, $CH_2C\underline{H}_2CH(CH_3)C\underline{H}_2CH_2$), 1.22 (3H, d, *J* 6.3, CCH$(C\underline{H}_3)$O), 1.17–1.08 (1H, m, CHC<u>H</u>$_2CH_2C$), 0.83 (3H, d, *J* 6.7, CH2CH$(C\underline{H}_3)CH_2$); δ_C (100 MHz) 131.3 (C), 124.7 (CH), 86.0 (C), 80.7 (C), 74.4 (CH), 71.9 (C), 36.7 (CH_2), 35.8 (CH_2), 31.7 (CH), 26.1 (CH_3), 25.7 (CH_3), 25.4 (CH_2), 19.1 (CH_3), 18.4 (CH_3), 17.7 (CH_3), 16.4 (CH_2); GC-MS m/z 234 ($[M–H_2O]^+$, 27%), 219 ($[M–CH_3–H_2O]^+$, 6%), 109 (100%); *minor diastereoisomer* δ_H (400 MHz) 3.73–3.67 (1H, m, CC<u>H</u>(CH_3)O), 2.93 (1H, bs, O<u>H</u>), 2.72 (1H, bs, O<u>H</u>) only 3 distinct peaks.

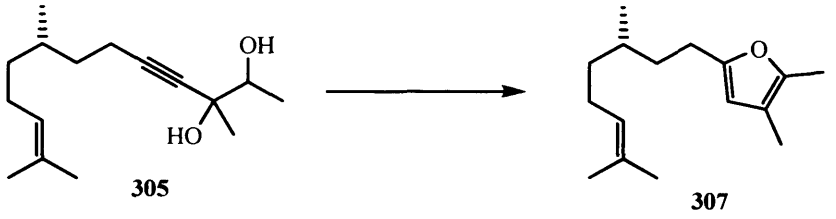
(*S*)-2-(3,7-Dimethyloct-6-enyl)-4-methylfuran 306[89]



Silver nitrate on silica gel (0.60 g, ~10 wt. %, 0.4 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **304** (0.42 g, 1.8 mmol) in dichloromethane (10 ml) at r.t. under subdued light and left to stir for 1 hour. The mixture was filtered through a pad of silica gel with

dichloromethane (30 ml) and the filtrate dried, filtered and evaporated to yield *furan* **306** (0.32 g, 80%) as a colourless liquid; b.p 2 mbar, oven temp. 210 °C; δ_H (400 MHz) 7.10–7.07 (1H, m, α-furan-H), 5.89–5.78 (1H, m, β-furan-H), 5.18–5.11 (1H, m, $CCHCH_2$), 2.71–2.51 (2H, m, furan-CH_2CH_2), 2.15–2.10 (2H, m, $C{=}CHCH_2CH_2$), 2.04–2.01 (3H, m, furan-CH_3), 1.75–1.72 (3H, m, $(CH_3)_2C{=}CH$), 1.73–1.65 (1H, m, $CH_2CH(CH_3)CH_2$), 1.65 (3H, s, $(CH_3)_2C{=}CH$), 1.55–1.46 (2H, m, $CH(CH_3)CH_2CH_2$), 1.45–1.35 (1H, m, $C{=}CCH_2CH_2CH(CH_3)$), 1.28–1.18 (1H, m, $C{=}CCH_2CH_2CH(CH_3)$), 0.96 (3H, d, *J* 6.4, $CH_2CH(CH_3)CH_2$); δ_C (100 MHz) 156.7 (C), 137.2 (CH), 131.1 (C), 124.9 (CH), 120.3 (C), 107.3 (CH), 36.9 (CH_2), 35.0 (CH_2), 32.0 (CH), 25.7 (CH_2), 25.7 (CH_3), 25.5 (CH_2), 19.3 (CH_3), 17.6 (CH_3), 9.8 (CH_3); GC-MS m/z 220 ($[M]^+$, 43%), 205 ($[M–CH_3]^+$, 4%), 109 (100%). $[\alpha]_D^{291} = +6.3°$.

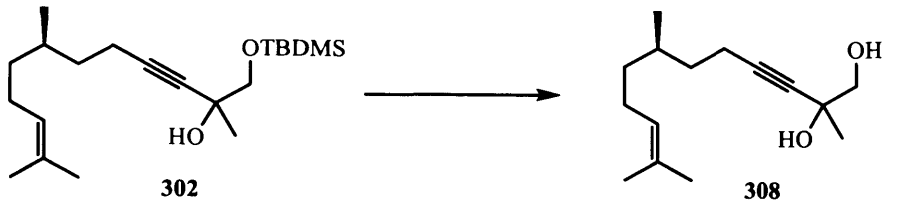
(*S*)-5-(3,7-Dimethyloct-6-enyl)-2,3-dimethylfuran 307



305 **307**

Silver nitrate on silica gel (0.18 g, ~10 wt. %, 0.1 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **305** (0.13 g, 0.5 mmol) in dichloromethane (5 ml) at r.t. under subdued light and left to stir for 1 hour. The mixture was filtered through a pad of silica gel with dichloromethane (30 ml) and the filtrate dried, filtered and evaporated to yield *furan* **307** (0.10 g, 81%) as a colourless liquid; b.p. 2 mbar, oven temp. 219–221 °C; δ_H (400 MHz) 5.78 (1H, s, furan-H), 5.17–5.10 (1H, m, $CCHCH_2$), 2.65–2.47 (2H, m, furan-CH_2CH_2), 2.20 (3H, s, α-furan-CH_3), 2.10–1.96 (2H, m, $C{=}CHCH_2CH_2$), 1.93 (3H, s, β-furan-CH_3), 1.73 (3H, s, $(CH_3)_2C{=}CH$), 1.70–1.68 (1H, m, $CH_2CH(CH_3)CH_2$), 1.65 (3H, s, $(CH_3)_2C{=}CH$), 1.57–1.44 (2H, m, $CH(CH_3)CH_2CH_2$), 1.45–1.35 (1H, m, $C{=}CCH_2CH_2CH(CH_3)$), 1.26–1.15 (1H, m, $C{=}CCH_2CH_2CH(CH_3)$), 0.95 (3H, d, *J* 6.2, $CH_2CH(CH_3)CH_2$); δ_C (100 MHz) 153.6 (C), 145.0 (C), 131.0 (C), 124.9 (CH), 114.1 (C), 107.6 (CH), 36.9 (CH_2), 35.2 (CH_2), 32.0 (CH), 25.7 (CH_3), 25.6 (CH_2), 25.5 (CH_2), 19.4 (CH_3), 17.6 (CH_3), 11.2 (CH_3), 9.9 (CH_3); GC-MS m/z 234 ($[M]^+$, 34%), 219 ($[M–CH_3]^+$, 2%), 109 (100%). $[\alpha]_D^{291} = +11.4°$.

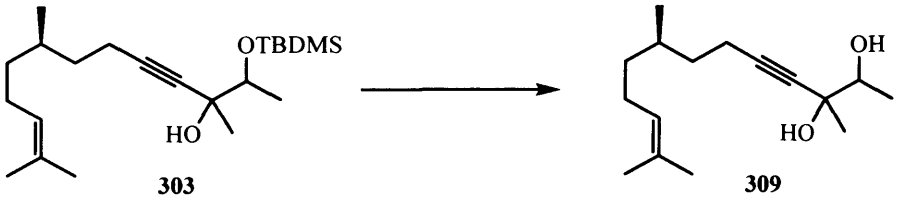
(2*RS*,7*R*)-2,7,11-Trimethyldodec-10-en-3-yne-1,2-diol 308



302 **308**

A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.3 ml, 1 M, 1.3 mmol) was added dropwise to a stirred solution of alcohol **302** (0.40 g, 1.1 mmol) in tetrahydrofuran (10 ml) at r.t. and left to stir for 16 h. The mixture was concentrated *in vacuo* the product purified by column chromatography (petrol/ethyl acetate, 1:1) to yield *diol* **308** (0.16 g, 58%) as a colourless oil; δ_H (400 MHz) 5.09–5.05 (1H, m, CC$\underline{H}$CH$_2$), 3.59 (1H, dd, *J* 10.9, 2.6, CC$\underline{H}_2$O), 3.45 (1H, dd, *J* 10.7, 7.7, CC$\underline{H}_2$O), 2.98 (1H, *app.* s, O$\underline{H}$), 2.61 (1H, bs, O$\underline{H}$), 2.26–2.11 (2H, m, C=CHC$\underline{H}_2$CH$_2$), 2.02–1.88 (2H, m, CH$_2$C$\underline{H}_2$C≡CH), 1.67 (3H, d, *J* 1.0, (C$\underline{H}_3$)$_2$C=CH), 1.59 (3H, s, (C$\underline{H}_3$)$_2$C=CH), 1.55–1.45 (2H, m, CH$_2$CH$_2$C$\underline{H}_2$C$\underline{H}$(CH$_3$)CH$_2$C), 1.41 (3H, s, C$\underline{H}_3$C(OH)), 1.36–1.26 (2H, m, CH$_2$C$\underline{H}_2$CH(CH$_3$)C$\underline{H}_2$CH$_2$), 1.17–1.08 (1H, m, CHC$\underline{H}_2$CH$_2$C), 0.86 (3H, d, *J* 6.6, C$\underline{H}_3$CH); δ_C (100 MHz) 131.2 (C), 124.6 (CH), 85.2 (C), 81.5 (C), 70.5 (CH$_2$), 68.5 (C), 36.6 (CH$_2$), 35.6 (CH$_2$), 31.6 (CH), 25.6 (CH$_3$), 25.5 (CH$_3$), 25.3 (CH$_2$), 19.0 (CH$_3$), 17.3 (CH$_3$), 16.3 (CH$_2$); GC-MS m/z 220 ([M–H$_2$O]$^+$, 11%), 205 ([M–CH$_3$–H$_2$O]$^+$, 9%), 69 (100%).

(1*RS*,2*RS*,7*R*)-3,8,12-Trimethyltridec-11-en-4-yne-2,3-diol 309

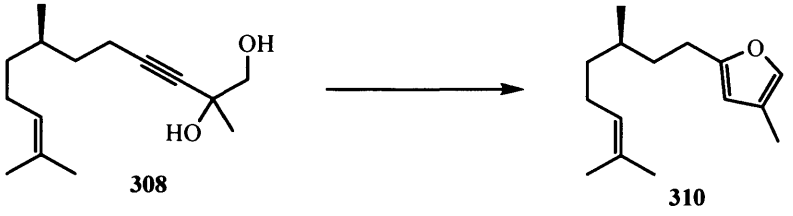


303 **309**

A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.9 ml, 1 M, 1.9 mmol) was added dropwise to a stirred solution of alcohol **303** (0.55 g, 1.6 mmol) in tetrahydrofuran (10 ml) at r.t. and left to stir for 16 h. The mixture was concentrated *in vacuo* the product purified by column chromatography (petrol/ethyl acetate, 1:1) to yield *diol* **209** (0.28 g, 74%) as a colourless oil, as a 9:1 mixture of diastereoisomers; *major diastereoisomer* δ_H (400 MHz) 5.08–5.04 (1H, m, CC$\underline{H}$CH$_2$), 3.56 (1H, qd, *J* 6.5, 6.5, CC$\underline{H}$(CH$_3$)O), 3.00 (1H, s, O$\underline{H}$), 2.21–2.15 (2H, m, C=CHC$\underline{H}_2$CH$_2$), 1.99–1.87 (2H, m, CH$_2$C$\underline{H}_2$C≡CH), 1.86 (1H, d, *J* 6.5, O$\underline{H}$), 1.65 (3H, d, *J* 1.0,

($C\underline{H}_3)_2C$=CH), 1.58 (3H, s, ($C\underline{H}_3)_2C$=CH), 1.55–1.47 (2H, m, $CH_2CH_2C\underline{H}_2C\underline{H}(CH_3)CH_2C$), 1.37 (3H, s, $CC(C\underline{H}_3)(OH)CH$), 1.34–1.26 (2H, m, $CH_2C\underline{H}_2CH(CH_3)C\underline{H}_2CH_2$), 1.24 (3H, d, *J* 6.3, $CCH(C\underline{H}_3)O$), 1.17–1.08 (1H, m, $CHC\underline{H}_2CH_2C$), 0.83 (3H, d, *J* 6.6, $CH2CH(C\underline{H}_3)CH_2$); δ_C (100 MHz) 131.2 (C), 124.6 (CH), 86.0 (C), 80.5 (C), 74.3 (CH), 71.9 (C), 36.6 (CH_2), 35.7 (CH_2), 31.6 (CH), 25.9 (CH_3), 25.6 (CH_3), 25.3 (CH_2), 19.0 (CH_3), 18.3 (CH_3), 17.6 (CH_3), 16.3 (CH_2); GC-MS m/z 234 ($[M–H_2O]^+$, 25%), 219 ($[M–CH_3–H_2O]^+$ 6%), 109 (100%); *minor diastereoisomer* 3.73–3.71 (1H, m, $CC\underline{H}(CH_3)O$) only 1 distinct peak.

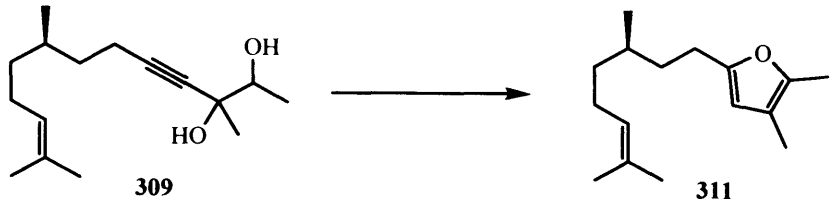
(*R*)-2-(3,7-Dimethyloct-6-enyl)-4-methylfuran 310



308 **310**

Silver nitrate on silica gel (0.11 g, ~10 wt. %, 0.07 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **308** (0.16 g, 0.67 mmol) in dichloromethane (5 ml) at r.t. under subdued light and left to stir for 1 hour. The mixture was filtered through a pad of silica gel with dichloromethane (30 ml) and the filtrate dried, filtered and evaporated to yield *furan* **310** (0.12 g, 81%) as a colourless liquid; δ_H (400 MHz) 7.09–7.06 (1H, m, α-furan-H), 5.88–5.76 (1H, m, β-furan-H), 5.15–5.10 (1H, m, $CC\underline{H}CH_2$), 2.67–2.52 (2H, m, furan-$C\underline{H}_2CH_2$), 2.09–1.93 (2H, m, C=$CHC\underline{H}_2CH_2$), 2.02–2.00 (3H, m, furan-$C\underline{H}_3$), 1.72 (3H, d, *J* 1.2, ($C\underline{H}_3)_2C$=CH), 1.70–1.65 (1H, m, $CH_2C\underline{H}(CH_3)CH_2$), 1.63 (3H, s, ($C\underline{H}_3)_2C$=CH), 1.52–1.45 (2H, m, $CH(CH_3)C\underline{H}_2CH_2$), 1.44–1.35 (1H, m, C=$CCH_2C\underline{H}_2CH(CH_3)$), 1.25–1.16 (1H, m, C=$CCH_2C\underline{H}_2CH(CH_3)$), 0.94 (3H, d, *J* 6.2, $CH_2CH(C\underline{H}_3)CH_2$); δ_C (100 MHz) 156.8 (C), 137.2 (CH), 131.1 (C), 124.9 (CH), 120.4 (C), 107.3 (CH), 36.9 (CH_2), 35.0 (CH_2), 32.0 (CH), 25.7 (CH_2), 25.7 (CH_3), 25.5 (CH_2), 19.3 (CH_3), 17.6 (CH_3), 9.8 (CH_3); GC-MS m/z 220 ($[M]^+$, 26%), 205 ($[M–CH_3]^+$, 1%), 109 (100%). $[\alpha]_D^{291} = -7.8°$.

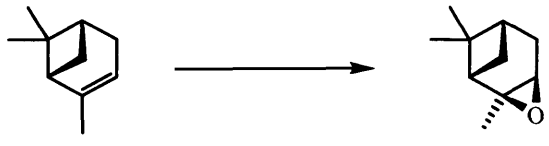
(*R*)-5-(3,7-Dimethyloct-6-enyl)-2,3-dimethylfuran 311



309 311

Silver nitrate on silica gel (0.12 g, ~10 wt. %, 0.07 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **309** (0.18 g, 0.71 mmol) in dichloromethane (5 ml) at r.t. under subdued light and left to stir for 1 hour. The mixture was filtered through a pad of silica gel with dichloromethane (30 ml) and the filtrate dried, filtered and evaporated to yield *furan* **311** (0.16 g, 96%) as a colourless liquid; δ_H (400 MHz) 5.78 (1H, s, furan-H), 5.17–5.13 (1H, m, $CCHCH_2$), 2.65–2.50 (2H, m, furan-CH_2CH_2), 2.20 (3H, s, α-furan-CH_3), 2.11–1.95 (2H, m, $C=CHCH_2CH_2$), 1.94 (3H, s, β-furan-CH_3), 1.73 (3H, d, *J* 1.0, $(CH_3)_2C=CH$), 1.70–1.67 (1H, m, $CH_2CH(CH_3)CH_2$), 1.65 (3H, s, $(CH_3)_2C=CH$), 1.59–1.48 (2H, m, $CH(CH_3)CH_2CH_2$), 1.48–1.37 (1H, m, $C=CCH_2CH_2CH(CH_3)$), 1.27–1.18 (1H, m, $C=CCH_2CH_2CH(CH_3)$), 0.96 (3H, d, *J* 6.2, $CH_2CH(CH_3)CH_2$); δ_C (100 MHz) 153.7 (C), 145.2 (C), 131.2 (C), 125.0 (CH), 114.2 (C), 107.7 (CH), 37.0 (CH_2), 35.3 (CH_2), 32.1 (CH), 25.8 (CH_3), 25.7 (CH_2), 25.6 (CH_2), 19.5 (CH_3), 17.7 (CH_3), 11.3 (CH_3), 10.0 (CH_3); GC-MS m/z 234 ($[M]^+$, 20%), 219 ($[M-CH_3]^+$, 1%), 109 (100%). $[\alpha]_D^{291} = -8.9°$.

(1*R*)-(+)-2,7,7-Trimethyl-3-oxatricyclo[4.1.1.02,4]octane 320[226]

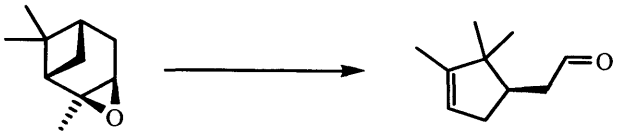


319 320

(1*R*)-(+)-α-Pinene **319** (2.0 g, 14.7 mmol) was added dropwise to a stirred solution of mCPBA (3.3 g, 18.9 mmol), and $NaHCO_3$ (1.6 g, 19.0 mmol) in dichloromethane (100 ml) at r.t. and left to stir for 1 hour. Aqueous sodium sulfite (20 ml) was then added and the reaction left to stir for 30 min. The mixture was washed with water (2 x 25 ml) and the organic fraction dried, filtered and evaporated yield *epoxide* **320** (2.0 g, 92%) as a colourless liquid; δ_H 3.07 (1H, dd, *J* 4.2, 1.1,

CC<u>H</u>CH$_2$), 2.03–1.87 (4H, m), 1.74–1.70 (2H, m), 1.34 (3H, s, C<u>H</u>$_3$), 1.29 (3H, s, C<u>H</u>$_3$), 0.93 (3H, s, C<u>H</u>$_3$).

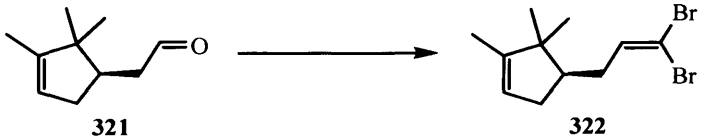
(*R*)-2-(2,2,3-Trimethylcyclopent-3-enyl)acetaldehyde 321[227]



320 321

$Cu(BF_4)_2.xH_2O$ (0.20 g, ~0.9 mmol), was added to a stirred solution of epoxide **320** (0.50 g, 3.3 mmol) in dichloromethane (20 ml) at r.t. and left to stir for 20 min. The mixture was diluted with dichloromethane (20 ml) and washed with water (3 x 10 ml). The organic fraction was dried, filtered and evaporated yield *aldehyde* **321** (0.44 g, 87%) as a colourless liquid; δ_H (400 MHz) 9.80 (1H, t, *J* 2.3, $CH_2C\underline{H}(O)$), 2.25–2.22 (1H, m, $CH_2C\underline{H}$=C), 2.53 (1H, ddd, *J* 15.6, 4.3, 2.1, $CHC\underline{H}_2CH(O)$), 2.44–2.35 (2H, m, $CHC\underline{H}_2CH$, $CHC\underline{H}_2CH(O)$), 2.32–2.24 (1H, m, $CHC\underline{H}_2CH$), 1.94–1.85 (1H, m, $C\underline{H}CH_2CH(O)$), 1.63–1.61 (3H, m, CH=C(C<u>H</u>$_3$)C), 1.00 (3H, s, C(C<u>H</u>$_3$)$_2$), 0.79 (3H, s, C(C<u>H</u>$_3$)$_2$).

(*R*)-4-(3,3-Dibromoallyl)-1,5,5-trimethylcyclopent-1-ene 322

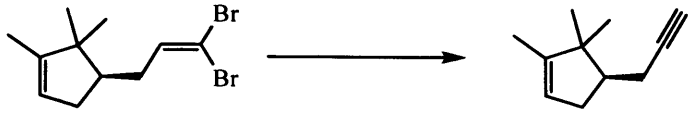


321 322

Triphenylphosphene (11.2 g, 42.8 mmol) in dichloromethane (50 ml) was added dropwise to a stirred solution of CBr_4 (7.1 g, 21.4 mmol) in dichloromethane (25 ml) under nitrogen at 0 °C and allowed to stir for 20 min. Aldehyde **321** (3.3 g, 10.7 mmol) in dichloromethane (15 ml) was added dropwise before the mixture was allowed to warm to room temperature and left to stir for 30 min. The mixture was concentrated *in vacuo*, and the residue triturated with vigorously stirred pentane (100 ml), and filtered through a sinter. The filtrate was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 9:1) to yield *alkene* **322** (4.7 g, 71%) as a colourless liquid; δ_H (400 MHz) 6.42 (1H, t, *J* 7.2, $CH_2C\underline{H}$=CBr_2), 5.24–5.21 (1H, m, C=C<u>H</u>CH_2), 2.32–2.19 (2H, m, $CHC\underline{H}_2CH$,

$CHC\underline{H}_2CH=CBr_2$), 2.11–2.03 (1H, m, $CHC\underline{H}_2CH$), 1.94–1.84 (2H, m, $C\underline{H}C\underline{H}_2CH=CBr_2$), 1.61–1.60 (3H, m, $CH=C(C\underline{H}_3)C$), 1.00 (3H, s, $C(C\underline{H}_3)_2$), 0.81 (3H, s, $C(C\underline{H}_3)_2$).

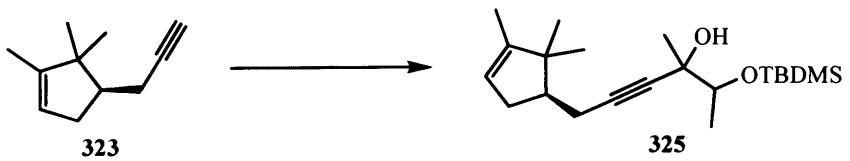
(*R*)-1,5,5-Trimethyl-4-(prop-2-ynyl)cyclopent-1-ene 323



322 323

A solution of butyllithium in hexanes (14.9 ml, 2.5 M, 37.3 mmol) was added dropwise to a stirred solution alkene **322** (5 g, 16.2 mmol) in tetrahydrofuran (100 ml) under nitrogen at –78 °C and left to stir for 1 hour. The mixture was allowed to warm to r.t. and left to stir for 30 min. The mixture was quenched by dropwise addition of aqueous ammonium chloride (20 ml), concentrated *in vacuo*, and the residue dissolved in ether (200 ml) and washed with water (3 x 50 ml). The organic fraction was dried, filtered and evaporated and the product purified by distillation to yield *alkyne* **323** (2.0 g, 83%) as a colourless liquid; b.p. 0.5 mbar, 39–41 °C; ν_{max} 3312, 2957, 2929, 2360, 2118, 1715, 1463, 1361, 1014, 799; δ_H (400 MHz) 5.23–5.22 (1H, m, $C=C\underline{H}CH_2$), 2.46–2.39 (1H, m, $CHC\underline{H}_2CH$), 2.30 (1H, ddd, *J* 16.5, 5.8, 2.7, $CHC\underline{H}_2C$), 2.17 (1H, ddd, *J* 16.4, 9.1, 2.7, $CHC\underline{H}_2C$), 2.08–2.01 (1H, m, $CHC\underline{H}_2CH$), 1.99–1.91 (1H, m, $C\underline{H}CH_2C\equiv CH$), 1.94 (1H, t, *J* 2.7, $C\equiv C\underline{H}$), 1.60–1.59 (3H, m, $CH=C(C\underline{H}_3)C$), 1.04 (3H, s, $C(C\underline{H}_3)_2$), 0.81 (3H, s, $C(C\underline{H}_3)_2$); δ_C 148.1 (C), 121.4 (CH), 84.4 (C), 68.3 (CH), 48.8 (CH), 46.7 (C), 35.7 (CH_2), 26.0 (CH_3), 22.6 (CH_3), 19.5 (CH_3), 19.3 (CH_2).

(1*RS*,2*RS*,6*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-methyl-6-(2,2,3-trimethylcyclopent-3-enyl)hex-4-yn-3-ol 325



323 325

A solution of butyllithium in hexanes (0.33 ml, 2.5 M, 0.82 mmol) was added dropwise to a stirred solution of alkyne **323** (0.10 g, 0.68 mmol) in tetrahydrofuran (10 ml) under nitrogen at 0 °C and left to stir for 1 hour before being cooled to –78 °C. Ketone **295** (0.13 g, 0.68 mmol) was added dropwise and the mixture left to stir for 1 hour before being allowed to warm to r.t. and

left to stir for 2 h. The mixture was quenched by dropwise addition of aqueous ammonium chloride (5 ml), concentrated *in vacuo*, and the residue dissolved in ethyl acetate (30 ml) and washed with water (3 x 10 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 9:1) to yield *alcohol* **325** (0.17 g, 72%) as a colourless liquid, as a 9:1 mixture of diastereoisomers; *major diastereoisomer* δ_H (400 MHz) 5.12 (1H, *app.* s, C=C<u>H</u>CH$_2$), 3.65 (1H, q, *J* 6.2, CC<u>H</u>(OTBDMS)CH$_3$), 2.74 (1H, bs, O<u>H</u>), 2.40 (1H, dd, *J* 15.2, 7.2, CHC<u>H$_2$</u>CH), 2.31 (1H, dd, *J* 16.5, 5.9, CHC<u>H$_2$</u>C≡C), 2.22–2.14 (1H, m, CHC<u>H$_2$</u>C≡C), 2.06–2.01 (1H, m, CHC<u>H$_2$</u>CH), 1.99–1.92 (1H, m, C<u>H</u>CH$_2$C≡C), 1.60–1.59 (3H, m, CH=C(C<u>H$_3$</u>)C), 1.38 (3H, s, CC(OH)(C<u>H$_3$</u>)CH), 1.26 (3H, d, *J* 6.1, CH(OTBDMS)C<u>H$_3$</u>), 1.04 (3H, s, CC(C<u>H$_3$</u>)$_2$CH), 0.91 (9H, s, SiC(C<u>H$_3$</u>)$_3$), 0.80 (3H, s, CC(C<u>H$_3$</u>)$_2$CH), 0.10 (3H, s, Si(C<u>H$_3$</u>)$_2$), 0.08 (3H, s, Si(C<u>H$_3$</u>)$_2$); δ_C 148.2 (C), 121.4 (CH), 96.2 (C), 81.6 (C), 75.3 (CH), 71.4 (C), 49.0 (CH), 46.7 (C), 35.8 (CH_2), 26.5 (CH_3), 26.1 (CH_3), 25.8 (CH_3), 25.7 (CH_3), 19.5 (CH_3), 19.0 (CH_2), 18.0 (C), 12.5 (CH_3), –4.1 (CH_3), –4.9 (CH_3); *minor diastereoisomer* δ_H (400 MHz) 3.81 (1H, q, *J* 6.3, CC<u>H</u>(OTBDMS)CH$_3$), 1.18 (3H, d, *J* 6.2, CH(OTBDMS)C<u>H$_3$</u>) only 2 distinct peaks.

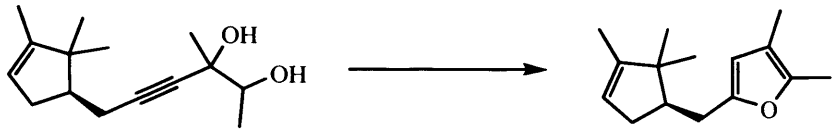
(1*RS*,2*RS*,6*R*)-3-Methyl-6-(2,2,3-trimethylcyclopent-3-enyl)hex-4-yne-2,3-diol 326

325 **326**

A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.4 ml, 1 M, 1.4 mmol) was added dropwise to a stirred solution of alcohol **325** (0.3 g, 1.2 mmol) in tetrahydrofuran (10 ml) at r.t. and left to stir for 16 h. The mixture was concentrated *in vacuo*, and the product purified by column chromatography (petrol/ethyl acetate, 3:2) to yield *3-alkyne-1,2-diol* **326** (0.09 g, 44%) as a colourless oil, as a 9:1 mixture of diastereoisomers; *major diastereoisomer* δ_H (400 MHz) 5.17 (1H, *app.* s, C=C<u>H</u>CH$_2$), 3.55 (1H, q, *J* 6.1, CC<u>H</u>(OH)CH$_3$), 3.19 (1H, bs, O<u>H</u>), 2.47 (1H, bs, O<u>H</u>), 2.36 (1H, *app.* dd, 14.9, 7.2, CHC<u>H$_2$</u>CH), 2.28 (1H, dd, *J* 16.5, 5.9, CHC<u>H$_2$</u>C≡C), 2.16 (1H, dd, *J* 16.4, 8.4, CHC<u>H$_2$</u>C≡C), 2.01–1.95 (1H, m, CHC<u>H$_2$</u>CH), 1.95–1.89 (1H, m, C<u>H</u>CH$_2$C≡C), 1.55 (3H, d, *J* 1.6, CH=C(C<u>H$_3$</u>)C), 1.36 (3H, s, CC(OH)(C<u>H$_3$</u>)CH), 1.23 (3H, d, *J* 6.3, CH(OH)C<u>H$_3$</u>), 0.99 (3H, s, CC(C<u>H$_3$</u>)$_2$CH), 0.77 (3H, s, CC(C<u>H$_3$</u>)$_2$CH); δ_C 148.0 (C), 121.3 (CH), 85.6 (C), 80.8 (C), 74.3 (CH), 71.9 (C), 48.8 (CH), 46.6 (C), 35.7 (CH_2), 26.0 (CH_3), 25.9

(CH_3), 19.5 (CH_3), 19.4 (CH_2), 18.3 (CH_3), 12.4 (CH_3); LRMS m/z 218.17 ($[M-H_2O]^+$, 42%), 203.14 ($[M-H_2O-CH_3]^+$, 95%), 91.05 (100%); HRMS calculated for $C_{15}H_{22}O$ $[M+H_2O]^+$ 218.1671, found 218.1669; *minor diastereoisomer* δ_H (400 MHz) 3.74 (1H, q, *J* 6.3, CC<u>H</u>(OH)CH_3), 2.87 (1H, bs, O<u>H</u>), 2.69 (1H, bs, O<u>H</u>), 1.34 (3H, s, CC(OH)(C<u>H</u>$_3$)CH) only 4 distinct peaks.

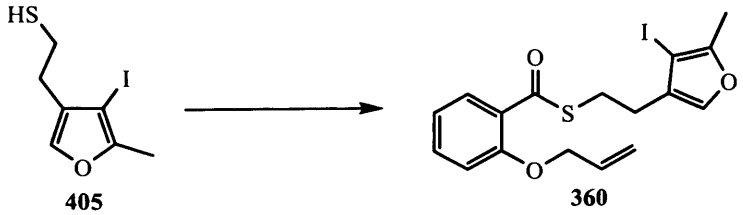
(*R*)-2,3-Dimethyl-5-((2,2,3-trimethylcyclopent-3-enyl)methyl)furan 327



326 **327**

Silver nitrate on silica gel (0.06 g, ~10 wt. %, 0.04 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **326** (0.09 g, 0.38 mmol) in dichloromethane (5 ml) at r.t. under subdued light and left to stir for 3 h. The mixture was filtered through a pad of silica gel with dichloromethane (30 ml) and the filtrate dried, filtered and evaporated to yield *furan* **327** (0.08 g, 96%) as a colourless liquid; δ_H 5.77 (1H, s, furan-<u>H</u>), 5.25–5.23 (1H, m, C=C<u>H</u>CH_2), 2.68 (1H, dd, *J* 14.9, 4.5, $CHC\underline{H}_2$-furan), 2.47 (1H, dd, *J* 14.9, 10.8, $CHC\underline{H}_2$-furan), 2.31–2.35 (1H, m, $CHC\underline{H}_2CH$), 2.17 (3H, s, α-furan-C<u>H</u>$_3$), 2.17–2.10 (1H, m, C<u>H</u>CH_2-furan), 1.95–1.89 (1H, m, $CHC\underline{H}_2CH$), 1.90 (3H, s, β-furan-C<u>H</u>$_3$), 1.63–1.61 (3H, m, CH=C(C<u>H</u>$_3$)C), 0.98 (3H, s, CC(C<u>H</u>$_3$)$_2$CH), 0.84 (3H, s, CC(C<u>H</u>$_3$)$_2$CH); δ_C 152.9 (C), 148.3 (C), 145.1 (C), 121.7 (CH), 114.1 (C), 108.3 (CH), 48.8 (CH), 46.7 (C), 35.8 (CH_2), 28.6 (CH_2), 25.7 (CH_3), 19.6 (CH_3), 12.6 (CH_3), 11.2 (CH_3), 9.9 (CH_3).

S-2-(4-Iodo-5-methylfuran-3-yl)ethyl 2-(allyloxy)benzothioate 360



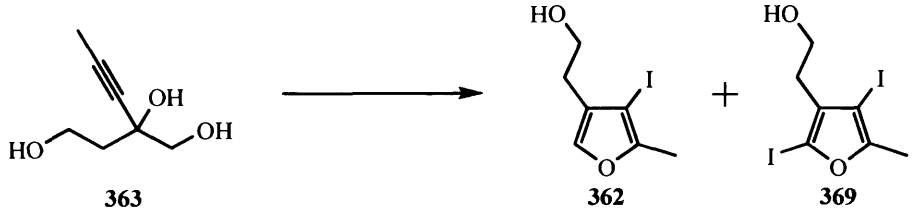
405 **360**

Oxalyl chloride (0.02 g, 0.57 mmol) was added dropwise to acid **401** (0.04 g, 0.14 mmol) under nitrogen at r.t. and left with stirring for 1 hour. The mixture was concentrated under a flow of

nitrogen followed by concentration *in vacuo*. The residue was dissolved in dichloromethane (2 ml) followed by addition of triethylamine (0.04 g, 0.38 mmol) and thiol **405** (0.04 g, 0.14 mmol) and left to stir for 20 min. The mixture was diluted with dichloromethane (10 ml) and washed with 0.5 M aqueous NaOH (2 x 5 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ether, 49:1 → 9:1) to yield *thioester* **360** (0.018 g, 31%) as a colourless liquid; ν_{max} 3062, 2956, 1719, 1451, 1273, 1112, 710; δ_H 7.82–7.80 (1H, m, Ar-H), 7.50–7.44 (1H, m, Ar-H), 7.29 (1H, s, furan-H), 7.04–6.01 (1H, m, Ar-H), 7.00–6.98 (1H, m, Ar-H), 6.16–6.08 (1H, m, $CH_2CH{=}CH_2$), 5.51 (1H, dd, *J* 17.2, 1.5, $CH_2CH{=}CH_2$), 5.34 (1H, dd, *J* 10.6, 1.3, $CH_2CH{=}CH_2$), 4.69 (2H, d, *J* 5.1, $ArOCH_2CH$), 3.24 (2H, t, *J* 7.5, SCH_2CH_2), 3.24 (2H, t, *J* 7.4, furan-CH_2CH_2), 2.35 (3H, s, CH_3); δ_C 190.8 (C), 156.9 (C), 153.2 (C), 138.1 (CH), 133.4 (CH), 132.7 (CH), 129.7 (CH), 127.4 (C), 126.1 (C), 120.6 (CH), 118.0 (CH_2), 113.5 (CH), 69.8 (CH_2), 68.4 (C), 28.9 (CH_2), 26.3 (CH_2), 13.5 (CH_3); LRMS m/z 427.99 ($[M]^+$, 26%), 387.96 ($[M–I]^+$, 10%), 161.03 (100%); HRMS calculated for $C_{17}H_{17}IO_3S$ $[M]^+$ 427.9943, found 427.9948.

4-Iodo-5-methylfuran-3-ethan-1-ol 362

2-(2,4-Diiodo-5-methylfuran-3-yl)ethanol 369



363 **362** **369**

Iodine (0.26 g, 1.0 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **363** (0.05 g, 0.3 mmol) and K_2CO_3 (0.14 g, 1.0 mmol) in dichloromethane (10 ml) at r.t. and left to stir for 3 h. The mixture was washed with aqueous sodium sulfite (3 x 5 ml) and the organic fraction dried, filtered and evaporated to yield *iodofuran* **362** (0.003 g, 3%) and *diiodofuran* **369** (0.001 g, 1%) as a brown liquid;

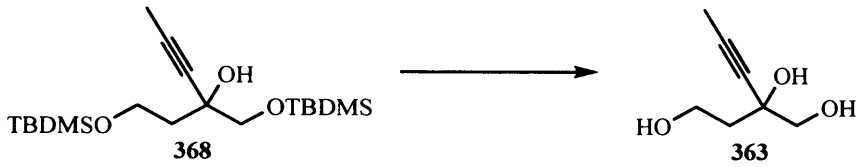
furan **362**:

δ_H 7.24 (1H, *app.* s, α-furan-H), 3.77 (2H, t, *J* 6.4, $HOCH_2CH_2$), 2.59 (2H, td, *J* 6.4 0.8, CH_2CH_2-furan), 2.33 (3H, s, CH_3); δ_C 153.5 (C), 138.4 (CH), 124.0 (C), 69.5 (C), 61.4 (CH_2), 29.5 (CH_2), 13.6 (CH_3); LRMS m/z 251.96 ($[M]^+$, 100%), 220.95 ($[M–CH_2OH]^+$, 74%); HRMS calculated for $C_7H_9IO_2$ $[M]^+$ 251.9647, found 251.9646.

diiodofuran **369**:

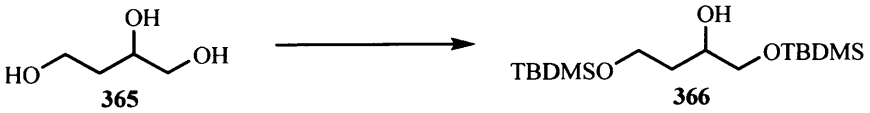
δ_H 4.72 (1H, dd, *J* 10.0, 1.4, HOC$\underline{H}_2$CH$_2$), 4.54 (1H, d, *J* 10.0, HOC$\underline{H}_2$CH$_2$), 3.32 (1H, dd, *J* 7.2, 1.4, CH$_2$C$\underline{H}_2$-furan), 3.25 (1H, d, *J* 7.2, CH$_2$C$\underline{H}_2$-furan).

2-(Prop-1-ynyl)butane-1,2,4-triol 363



A solution of tetrabutylammonium fluoride in tetrahydrofuran (3.1 ml, 1 M, 3.1 mmol) was added dropwise to a stirred solution of alcohol **368** (0.52 g, 1.4 mmol) in tetrahydrofuran (20 ml) at r.t. and left to stir for 16 h. The mixture was concentrated *in vacuo*, and the product purified by column chromatography (ethyl acetate/methanol, 19:1) to yield *3-alkyne-1,2-diol* **363** (0.19 g, 89%) as a colourless oil; ν_{max} 3389, 2923, 2247, 1649, 1434, 1055, 887; δ_H (400 MHz) 4.19–4.13 (1H, m, CC$\underline{H}_2$OH), 3.94–3.91 (1H, m, CC$\underline{H}_2$OH), 3.66–3.56 (2H, m, HOC$\underline{H}_2$CH$_2$), 3.54 (1H, bs, O$\underline{H}$), 2.37 (1H, bs, O$\underline{H}$), 2.32 (1H, bs, O$\underline{H}$), 2.08–2.01 (1H, m, CH$_2$C$\underline{H}_2$C), 1.84 (3H, s, C$\underline{H}_3$), 1.78 (1H, ddd, *J* 15.5, 5.1, 3.0, CH$_2$C$\underline{H}_2$C); δ_C 82.5 (C), 79.4 (C), 72.2 (C), 70.1 (CH$_2$), 60.1 (CH$_2$), 39.2 (CH$_2$), 3.6 (CH$_3$); LRMS (APCI) m/z 130.09 ([M–CH$_2$]$^+$, 100%).

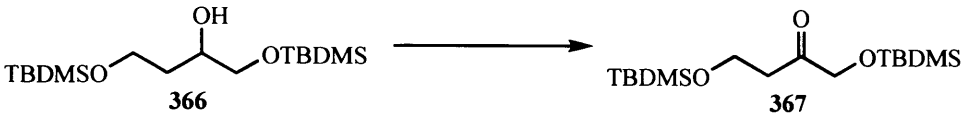
(2*RS*)-1,4-Bis-(*tert*-butyldimethylsilyloxy)butan-2-ol 366



TDBMS-Cl (6.44 g, 42.7 mmol) was added to a stirred solution of 1,2,4-butanetriol **365** (2.0 g, 19.4 mmol), NEt$_3$ (4.51 g, 44.6 mmol) and 4-(dimethylamino)pyridine (0.24 g, 1.9 mmol) in dichloromethane (100 ml) at r.t. and left to stir for 24 h. The mixture was diluted with dichloromethane (100 ml) and washed with aqueous ammonium chloride (3 x 50 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 19:1) to yield *alcohol* **366** (6.32 g, 98%) as a colourless liquid; ν_{max} 3475, 2956, 2858, 1744, 1472, 1257, 1095, 836, 777; δ_H 3.87–3.77 (3H, m, OC$\underline{H}_2$CH$_2$C$\underline{H}$(OH)CH$_2$), 3.59 (1H, dd, *J* 9.9, 4.9, CH(OH)C$\underline{H}_2$O), 3.51 (1H, dd, *J* 9.9, 6.5,

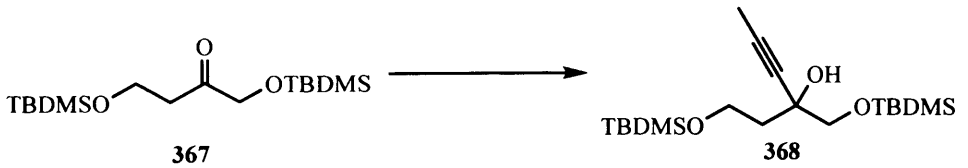
CH(OH)C$\underline{H}_2$O), 3.04 (1H, bs, O$\underline{H}$), 1.73–1.60 (2H, m, $CH_2C\underline{H}_2CH(OH)$), 0.90 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.89 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.05 (12H, s, Si(C$\underline{H}_3$)$_2$); δ_C 70.8 (CH), 67.1 (CH_2), 61.1 (CH_2), 35.4 (CH_2), 25.9 (CH_3), 18.3 (C), 18.2 (C), –5.4 (CH_3), –5.5 (CH_3) (only 9 peaks visible); LRMS (APCI) m/z 335.24 ($[M+H]^+$, 100%); HRMS (APCI) calculated for C_4H_7IO $[M+H]^+$ 335.2438, found 335.2442.

(2*RS*)-1,4-Bis-(*tert*-butyldimethylsilyloxy)butan-2-one 367



Alcohol **366** (2.0 g, 6.0 mmol) was added dropwise to a stirred solution of 2-iodoxybenzoic acid (3.4 g, 12.0 mmol) in dimethyl sulfoxide (20 ml) under nitrogen at r.t. and left to stir for 16 h. The mixture was diluted with water (300 ml) and washed with ether (5 x 100 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 19:1) to yield *ketone* **367** (1.49 g, 75%) as a colourless liquid; ν_{max} 2929, 2858, 1723, 1472, 1256, 1167, 1106, 840, 778; δ_H 4.22 (2H, s, C(O)C$\underline{H}_2$O), 3.90 (2H, t, *J* 6.3, OC$\underline{H}_2CH_2$), 2.65 (2H, t, *J* 6.3, $CH_2C\underline{H}_2$(O)C), 0.92 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.87 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.09 (6H, s, Si(C$\underline{H}_3$)$_2$), 0.05 (6H, s, Si(C$\underline{H}_3$)$_2$); δ_C 209.1 (C), 70.0 (CH_2), 58.5 (CH_2), 41.6 (CH_2), 25.9 (CH_3), 25.8 (CH_3), 18.3 (C), 18.2 (C), –5.5 (CH_3), –5.5 (CH_3); LRMS (APCI) m/z 333.23 ($[M+H]^+$, 21%), 100.08 (100%); HRMS (APCI) calculated for $C_{16}H_{37}O_3Si_2$ $[M+H]^+$ 333.2281, found 333.2283.

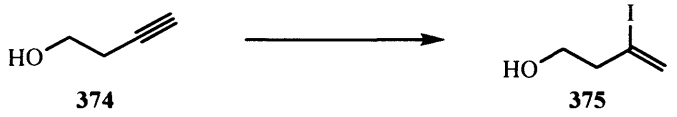
(2*RS*)-1,4-Bis-(*tert*-butyldimethylsilyloxy)-2-(Prop-1-ynyl)butan-2-ol 368



A solution of commercial 1-propynylmagnesium bromide **232** in tetrahydrofuran (5.9 ml, 0.5 M, 3.0 mmol) was added dropwise to a stirred solution of ketone **367** (0.82 g, 2.5 mmol) in tetrahydrofuran (20 ml) under nitrogen at –78 °C and left to stir for 30 min. The mixture was allowed to warm to r.t. and left to stir for 16 h. The reaction was quenched with aqueous

ammonium chloride, concentrated *in vacuo*, and the residue dissolved in ethyl acetate (50 ml) and washed with water (3 x 10 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 9:1) to yield *alcohol* **368** (0.92 g, 64%) as a colourless liquid; ν_{max} 3491, 2929, 2253, 1471, 1255, 1090, 837, 778; δ_H 4.17 (1H, s, O<u>H</u>), 4.12–4.07 (1H, m, OC<u>H</u>$_2$CH$_2$), 3.94–3.89 (1H, m, OC<u>H</u>$_2$CH$_2$), 3.61 (1H, d, *J* 9.7, CC<u>H</u>$_2$O), 3.59 (1H, d, *J* 9.7, CC<u>H</u>$_2$O), 1.98–1.93 (1H, m, CH$_2$C<u>H</u>$_2$C), 1.83 (3H, s, C<u>H</u>$_3$), 1.82–1.77 (1H, m, CH$_2$C<u>H</u>$_2$C), 0.90 (18H, s, SiC(C<u>H</u>$_3$)$_3$), 0.10 (3H, s, Si(C<u>H</u>$_3$)$_2$), 0.08 (3H, s, Si(C<u>H</u>$_3$)$_2$), 0.08 (6H, s, Si(C<u>H</u>$_3$)$_2$); δ_C 80.6 (C), 80.5 (C), 71.7 (C), 70.3 (CH_2), 61.1 (CH_2), 39.3 (CH_2), 25.9 (CH_3), 18.4 (C), 18.2 (C), 3.6 (CH_3), –5.3 (CH_3), –5.3 (CH_3), –5.5 (CH_3), –5.6 (CH_3) (only 14 peaks visible); LRMS (APCI) m/z 373.26 ([M+H]$^+$, 34%), 355.25 ([M–OH]$^+$, 100%); HRMS (APCI) calculated for $C_{19}H_{41}O_3Si_2$ [M+H]$^+$ 373.2594, found 373.2576.

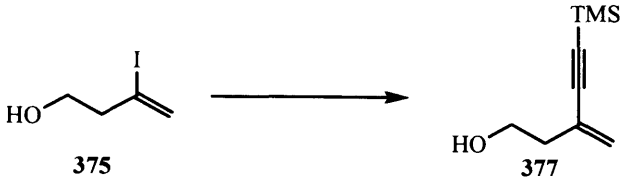
3-Iodobut-3-en-1-ol 375[228]



374 **375**

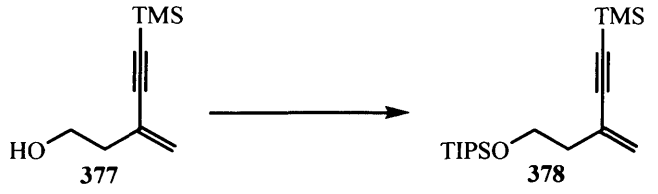
Trimethylsilyl chloride (11.46 g. 0.11 mol) was added dropwise to a stirred solution of NaI (15.80 g, 0.11 mol) in acetonitrile (70 ml). Water (0.96 g, 0.05 mmol) was then added dropwise and the mixture left to stir for 10 min. The mixture was cooled to 0 °C and 3-butyn-1-ol **374** (3.69 g, 0.05 mmol) was added dropwise. The mixture was allowed to warm to r.t. and left to stir for 1 hour. The mixture was diluted by dropwise addition of water (20 ml), concentrated *in vacuo*, and the residue dissolved in ether (200 ml) and washed with brine (3 x 50 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 3:2) to yield *alcohol* **375** (4.57 g, 44%) as a colourless liquid that turned light brown upon exposure to air and light; ν_{max} 3839, 2939, 2881, 1617, 1195, 1126, 1047, 898; δ_H 6.18 (1H, dt, *J* 1.3, 1.2, C=C<u>H</u>$_2$), 5.72 (1H, d, *J* 0.9, C=C<u>H</u>$_2$), 5.86 (1H, d, *J* 1.3, C=C<u>H</u>$_2$), 3.76 (2H, t, *J* 5.5, OC<u>H</u>$_2$CH$_2$), 2.63 (2H, td, *J* 5.8, 1.0, CH$_2$C<u>H</u>$_2$CI), 1.49 (1H, bs, O<u>H</u>); δ_C 128.4 (CH_2), 107.4 (C), 60.9 (CH_2), 48.1 (CH_2); LRMS m/z 197.95 ([M]$^+$, 60%), 83.95 (100%); HRMS calculated for C_4H_7OI [M]$^+$ 197.9545, found 197.9542.

3-Methylene-5-(trimethylsilyl)pent-4-yn-1-ol 377



NEt_3 (3.02 g, 29.9 mmol), bis(triphenylphosphine)palladium(II) dichloride (0.16 g, 0.2 mmol), CuI (0.02 g, 0.1 mmol) and ethynyltrimethylsilane **376** (2.95 g, 30.0 mmol) were added to a stirred solution of iodoalkene **375** (4.57 g, 23.1 mmol) in tetrahydrofuran (200 ml) under nitrogen at r.t. and left to stir for 16 hours. The mixture was filtered through silica before being concentrated *in vacuo*, and the residue dissolved in ethyl acetate (200 ml) and washed with aqueous ammonium chloride (3 x 100 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ether, 4:1) to yield *alkyne* **377** (3.88 g, 100%) as a colourless liquid; δ_H 5.49 (1H, d, *J* 1.6, C=C$\underline{H}_2$), 5.36 (1H, d, *J* 1.8, C=C$\underline{H}_2$), 3.81 (2H, t, *J* 6.0, HOC$\underline{H}_2$CH$_2$), 2.42 (2H, t, *J* 6.0, CH$_2$C$\underline{H}_2$C), 0.19 (9H, s, CSi(C$\underline{H}_3$)$_3$); δ_C 128.1 (C), 124.5 (CH_2), 104.7 (C), 95.0 (C), 60.9 (CH_2), 40.3 (CH_2), –0.1 (CH_3).

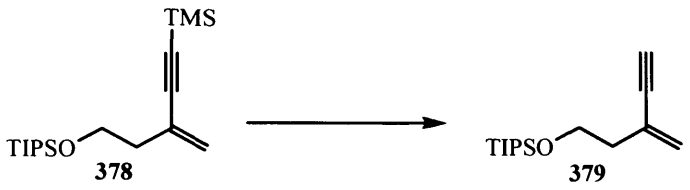
Triisopropyl(3-methylene-5-(trimethylsilyl)pent-4-yn-1-yloxy)silane 378



Triisopropylsilyl chloride (0.79 g, 4.1 mmol) was added dropwise to a stirred solution of alcohol **377** (0.66 g, 3.9 mmol) and imidazole (0.32 g, 4.7 mmol) in dichloromethane (30 ml) at r.t. and left to stir for 16 hours. The mixture was diluted with dichloromethane (20 ml) and washed with aqueous ammonium chloride (3 x 25 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 49:1) to yield *alkyne* **378** (1.00 g, 79%) as a colourless liquid; δ_H 5.41 (1H, d, *J* 1.9, C=C$\underline{H}_2$), 5.30 (1H, d, *J* 1.8, C=C$\underline{H}_2$), 3.85 (2H, t, *J* 7.0, OC$\underline{H}_2$CH$_2$), 2.39 (2H, t, *J* 6.9, CH$_2$C$\underline{H}_2$C), 1.13–1.01 (3H, m, (CH$_3$)$_2$C$\underline{H}$Si), 1.06 (18H, d, *J* 7.3, (C$\underline{H}_3$)$_2$CHSi), 0.17 (9H, s, CSi(C$\underline{H}_3$)$_3$); δ_C 128.4 (C), 123.7 (CH_2), 105.3 (C), 94.0 (C), 61.9 (CH_2), 40.8 (CH_2), 18.0 (CH_3), 12.0 (CH), –0.1 (CH_3); LRMS

(APCI) m/z 325.24 ([M+H]$^+$, 56%), 279.09 (100%); HRMS (APCI) calculated for $C_{18}H_{37}OSi_2$ [M+H]$^+$ 325.2383, found 325.2369.

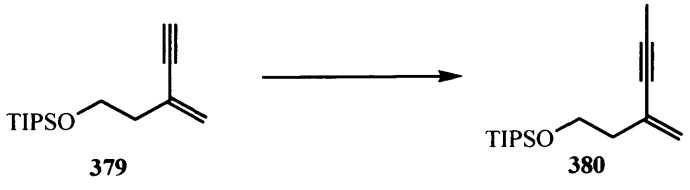
Triisopropyl(3-methylenepent-4-yn-1-yloxy)silane 379



378 **379**

Potassium carbonate (2.07 g, 15.0 mmol) was added to a stirred solution of alkene **378** (4.86 g, 15.0 mmol) in methanol/water (30 ml, 1:1) at r.t. and left to stir for 1 hour. The mixture was diluted with water (200 ml) and washed with ethyl acetate (5 x 200). The organic fraction was washed with brine (3 x 100 ml) before being dried, filtered and evaporated and the product purified by column chromatography (petrol/ether, 49:1) to yield *alkene* **379** (3.18 g, 84%) as a colourless liquid; ν_{max} 3314, 3099, 2944, 2867, 2143, 1613, 1464, 1250, 1109, 1071, 883; δ_H 5.48 (1H, s, C=C$\underline{H}_2$), 5.37 (1H, s, C=C$\underline{H}_2$), 3.85 (2H, t, *J* 6.9, OC$\underline{H}_2$CH$_2$), 2.87 (1H, s, C≡C$\underline{H}$), 2.40 (2H, t, *J* 6.8, CH$_2$C$\underline{H}_2$C), 1.15–1.05 (3H, m, (CH$_3$)$_2$C$\underline{H}$Si), 1.06 (18H, d, *J* 5.5, (C$\underline{H}_3$)$_2$CHSi); δ_C 127.5 (C), 124.6 (CH$_2$), 84.0 (C), 76.9 (CH), 61.7 (CH$_2$), 40.6 (CH$_2$), 18.0 (CH$_3$), 12.0 (CH); LRMS m/z 209.13 ([M–C$_3$H$_7$]$^+$, 38%), 83.95 (100%).

Triisopropyl(3-methylenehex-4-yn-1-yloxy)silane 380

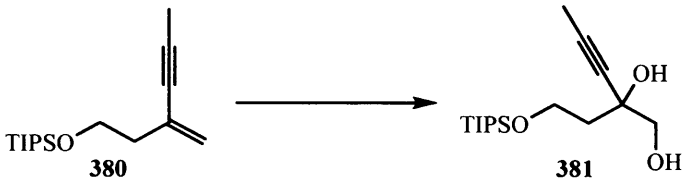


379 **380**

A solution of butyllithium in hexanes (2.6 ml, 2.5 M, 6.5 mmol) was added dropwise to a stirred solution of alkyne **379** (1.47 g, 5.9 mmol) in tetrahydrofuran (100 ml) at 0 °C and left to stir for 45 min. The mixture was cooled to –78 °C before MeI (0.91 g, 6.4 mmol) was added dropwise and left to stir for 30 min. before being allowed to warm to r.t. and left to stir for a 2 hours. The mixture was quenched with aqueous ammonium chloride (20 ml), concentrated *in vacuo*, and the residue dissolved in ether (200 ml) and washed with water (3 x 50 ml). The organic fraction was

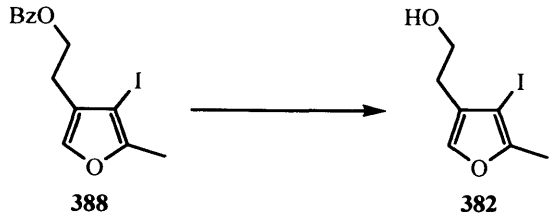
dried, filtered and evaporated and the product purified by column chromatography (petrol/ether, 49:1) to yield *alkene* **380** (1.53 g, 98%) as a colourless liquid; ν_{max} 3095, 2943, 2866, 2228, 1615, 1463, 1257, 1108, 1069, 882; δ_H 5.27 (1H, s, C=C$\underline{H}_2$), 5.19 (1H, s, C=C$\underline{H}_2$), 3.83 (2H, t, *J* 7.0, OC$\underline{H}_2$CH$_2$), 2.37 (2H, t, *J* 6.9, CH$_2$C$\underline{H}_2$C), 1.93 (3H, s, C≡CC$\underline{H}_3$), 1.13–1.05 (3H, m, (CH$_3$)$_2$C$\underline{H}$Si), 1.06 (18H, d, *J* 5.0, (C$\underline{H}_3$)$_2$CHSi); δ_C 128.8 (C), 121.4 (CH$_2$), 85.6 (C), 80.0 (C), 62.1 (CH$_2$), 41.2 (CH$_2$), 18.0 (CH$_3$), 12.0 (CH), 4.1 (CH$_3$); LRMS (APCI) m/z 267.21 ([M+H]$^+$, 9%), 117.09 (100%); HRMS (APCI) calculated for $C_{16}H_{31}OSi$ [M+H]$^+$ 267.2144, found 267.2136.

(2*RS*)-2-(2-(Triisopropylsilyloxy)ethyl)pent-3-yne-1,2-diol 381



Potassium osmate dihydrate (0.03 g, 0.08 mmol) was added to a solution of alkyne **380** (0.20, 0.79 mmol) and NMO (0.44 g, 3.76 mmol) in acetone/water (10 ml, 1:1) at r.t. and left to stir for 5.5 hours. Aqueous sodium sulfite (10 ml) was added and the mixture left to stir for 30 min. The mixture was concentrated *in vacuo*, and the residue dissolved in ether (300 ml) and washed with aqueous ammonium chloride (3 x 100 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 3:2) to yield *3-alkyne-1,2-diol* **381** (0.20 g, 83%) as a colourless oil; ν_{max} 3419, 2943, 2867, 2248, 1713, 1464, 1256, 1096, 883, 735, 682; δ_H 4.79 (1H, bs, O$\underline{H}$), 4.31–4.26 (1H, m, OC$\underline{H}_2$CH$_2$), 4.31–4.26 (1H, m, OC$\underline{H}_2$CH$_2$), 3.60 (1H, d, *J* 11.1, CC$\underline{H}_2$OH), 3.51 (1H, d, *J* 11.1, CC$\underline{H}_2$OH), 2.48 (1H, bs, O$\underline{H}$), 2.13–2.07 (1H, m, CH$_2$C$\underline{H}_2$C), 1.84 (3H, s, C$\underline{H}_3$), 1.70–1.65 (1H, m, CH$_2$C$\underline{H}_2$C), 1.16–1.05 (3H, m, (CH$_3$)$_2$C$\underline{H}$Si), 1.07 (18H, d, *J* 3.1, (C$\underline{H}_3$)$_2$CHSi); δ_C 81.9 (C), 79.7 (C), 72.2 (C), 61.6 (CH$_2$), 69.9 (CH$_2$), 38.7 (CH$_2$), 17.8 (CH$_3$), 11.7 (CH), 3.5 (CH$_3$); LRMS (APCI) m/z 301.22 ([M]$^+$, 63%), 283.21 ([M–H$_2$O]$^+$, 100%); HRMS (APCI) calculated for $C_{16}H_{33}O_3Si$ [M+H]$^+$ 301.2199, found 301.2195.

2-(4-Iodo-5-methylfuran-3-yl)ethanol 382



388 382

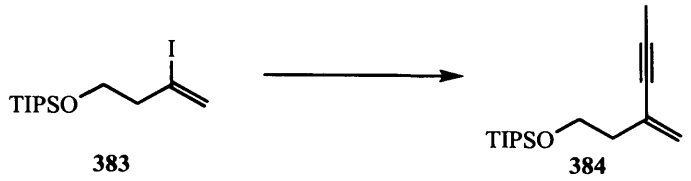
Potassium hydroxide (0.79 g, 14.0 mmol) was added to a stirred solution of furan **388** (1.67 g, 4.7 mmol) in methanol/water (30 ml, 2:1) and left to stir for 2 hours. The mixture was diluted with dichloromethane (300 ml) and washed with water (3 x 50 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (dichloromethane) to yield *alcohol* **382** (0.65 g, 55%) as a colourless liquid; ν_{max} 3360, 2918, 1600, 1560, 1122, 1050, 922, 857; δ_H (400 MHz) 7.23 (1H, *app.* s, furan-H), 3.77 (2H, t, *J* 6.4, $HOC\underline{H}_2CH_2$), 2.59 (2H, td, *J* 6.4, 0.9, $CH_2C\underline{H}_2$-furan), 2.32 (3H, s, $C\underline{H}_3$); δ_C (62.5 MHz) 153.3, 138.4, 124.0, 68.5, 61.3, 29.5, 13.6; LRMS m/z 251.96 ($[M]^+$, 20%), 220.95 ($[M-CH_2OH]^+$, 16%), 83.94 (100%); HRMS calculated for $C_7H_9IO_2$ $[M]^+$ 251.9647, found 251.9647.

(3-Iodobut-3-enyloxy)triisopropylsilane 383[229]

375 383

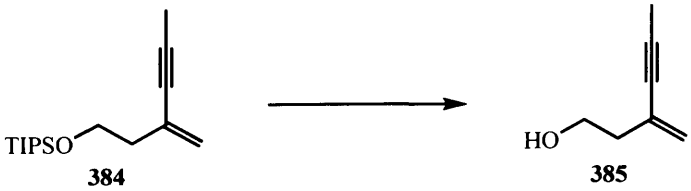
Triisopropylsilyl chloride (3.6 g, 18.6 mmol) was added to a stirred solution of alcohol **375** (3.5 g, 17.7 mmol) and imidazole (1.4 g, 21.2 mmol) in dichloromethane (100 ml) at r.t. and left to stir for 16 hours. The mixture was diluted with dichloromethane (100 ml) and washed with aqueous ammonium chloride (3 x 50 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 49:1) to yield *iodoalkene* **383** (4.5 g, 71%) as a colourless liquid; ν_{max} 2942, 2866, 1617, 1463,1256, 1111, 1070, 883, 682; δ_H 6.10 (1H, dt, *J* 1.3, 1.3, C=C$\underline{H}_2$), 5.76 (1H, d, *J* 1.4, C=C$\underline{H}_2$), 3.81 (2H, t, *J* 6.4, HOC$\underline{H}_2$), 2.62 (2H, td, *J* 6.4, 1.0, $HOCH_2C\underline{H}_2$), 1.14–1.04 (3H, m, $(CH_3)_2C\underline{H}Si$), 1.06 (18H, d, *J* 5.0, $(C\underline{H}_3)_2CHSi$); δ_C 127.3 (CH_2), 107.6 (C), 62.1 (CH_2), 48.6 (CH_2), 18.0 (CH_3), 12.0 (CH); LRMS m/z 311.03 ($[M-C_3H_7]^+$, 84%), 228.95 (100%).

Triisopropyl(3-methylenehex-4-yn-1-yloxy)silane 384



A solution of commercial 1-propynylmagnesium bromide **232** in tetrahydrofuran (23.4 ml, 0.5 M, 11.7 mmol) was added dropwise to a solution of iodoalkene **383** (2.86 g, 8.0 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.28 g, 0.4 mmol) in tetrahydrofuran (100 ml) at r.t. and left to stir for 16 hours. The mixture was quenched by dropwise addition of aqueous ammonium chloride (20 ml) concentrated *in vacuo*, and the residue dissolved in ether (200 ml) and washed with water (3 x 100 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ether, 49:1) to yield *alkene* **384** (1.83 g, 86%) as a colourless liquid; ν_{max} 3095, 2943, 2866, 2228, 1615, 1463, 1257, 1108, 1069, 882; δ_H 5.27 (1H, s, C=C$\underline{H}_2$), 5.19 (1H, s, C=C$\underline{H}_2$), 3.83 (2H, t, *J* 7.0, OC$\underline{H}_2$CH$_2$), 2.37 (2H, t, *J* 6.9, CH$_2$C$\underline{H}_2$C), 1.93 (3H, s, C≡CC$\underline{H}_3$), 1.13–1.05 (3H, m, (CH$_3$)$_2$C$\underline{H}$Si), 1.06 (18H, d, *J* 5.0, (C$\underline{H}_3$)$_2$CHSi); δ_C 128.8 (C), 121.4 (CH$_2$), 85.6 (C), 80.0 (C), 62.1 (CH$_2$), 41.2 (CH$_2$), 18.0 (CH$_3$), 12.0 (CH), 4.1 (CH$_3$); LRMS (APCI) m/z 267.21 $[M+H]^+$ 9%, 117.09 (100%); HRMS (APCI) calculated for $C_{16}H_{31}OSi$ $[M+H]^+$ 267.2144, found 267.2136.

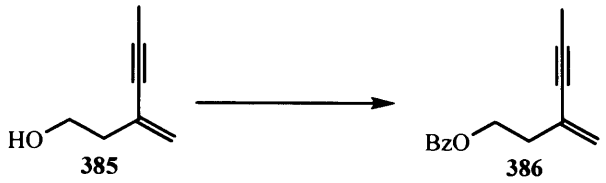
3-Methylenehex-4-yn-1-ol 385



A solution of tetrabutylammonium fluoride in tetrahydrofuran (16.7 ml, 1 M, 16.7 mmol) was added dropwise to a stirred solution of alcohol **384** (4.4 g, 16.7 mmol) in tetrahydrofuran (40 ml) at r.t. and left to stir for 2 hours. The mixture was concentrated *in vacuo*, and the product purified by column chromatography (petrol/ether, 7:3) to yield *alcohol* **385** (1.7 g, 93%) as a colourless liquid; ν_{max} 3350, 2918, 2226, 1671, 1438, 1049, 900; δ_H 5.33 (1H, s, C=C$\underline{H}_2$), 5.23 (1H, s, C=C$\underline{H}_2$), 3.78 (2H, t, *J* 6.1, HOC$\underline{H}_2$), 2.37 (2H, t, *J* 6.1, HOCH$_2$C$\underline{H}_2$), 1.93 (3H, s,

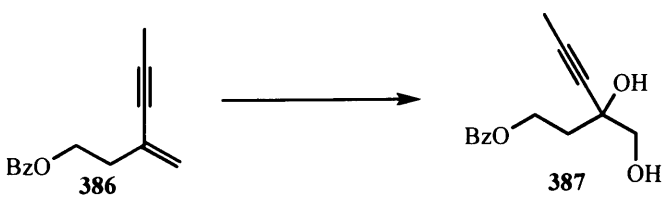
C≡CC<u>H</u>$_3$); δ_C 128.4 (C), 122.2 (CH_2), 86.4 (C), 79.4 (C), 60.8 (CH_2), 40.7 (CH_2), 4.1 (CH_3); LRMS m/z 110.07 ($[M]^+$, 10%), 95.05 ($[M-CH_3]^+$, 13%), 83.92 (100%); HRMS calculated for $C_7H_{10}O$ $[M]^+$ 110.0732, found 110.0831.

3-Methylenehex-4-ynyl benzoate 386



Benzoyl chloride (2.75 g, 19.5 mmol) was added to a stirred solution of alkyne **385** (1.95 g, 17.8 mmol) and NEt_3 (4.94 g, 35.5 mmol) in dichloromethane (100 ml) at 0 °C before being allowed to warm to r.t. and left to stir for 3 hours. The mixture was diluted with dichloromethane (100 ml) and washed with aqueous ammonium chloride (3 x 50 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 19:1) to yield *alkene* **386** (3.35 g, 88%) as a colourless liquid; ν_{max} 3093, 3063, 2960, 2918, 2228, 1721, 1603, 1452, 1272, 1116, 906, 734, 711; δ_H 8.05–8.03 (2H, m, Ar-<u>H</u>), 7.56–7.53 (1H, m, Ar-<u>H</u>), 7.44–7.41 (2H, m, Ar-<u>H</u>), 5.35 (1H, *app.* s, C=C<u>H</u>$_2$), 5.28 (1H, d, *J* 1.1, C=C<u>H</u>$_2$), 4.48 (2H, t, *J* 6.6, OC<u>H</u>$_2$CH$_2$), 2.58 (2H, t, *J* 6.6, OCH$_2$C<u>H</u>$_2$C), 1.92 (3H, s, C≡CC<u>H</u>$_3$); δ_C 166.5 (C), 132.8 (CH), 130.3 (C), 129.5 (CH), 128.3 (CH), 128.0 (C), 122.0 (CH_2), 86.5 (C), 79.2 (C), 63.1 (CH_2), 36.7 (CH_2), 4.14 (CH_3); LRMS (APCI) m/z 215.11 ($[M+H]^+$, 100%); HRMS (APCI) calculated for $C_{14}H_{15}O_2$ $[M+H]^+$ 215.1072, found 215.1076.

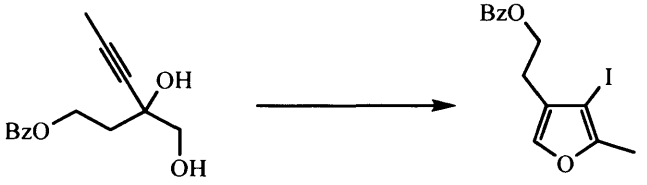
(3*RS*)-3-Hydroxy-3-(hydroxymethyl)hex-4-ynyl benzoate 387



Potassium osmate dihydrate (0.01 g, 0.05 mmol) was added to a solution of alkyne **386** (0.10, 0.47 mmol) and NMO (0.28 g, 2.35 mmol) in acetone/water (4 ml, 1:1) at r.t. and left to stir for 2.5 hours. Aqueous sodium sulfite (4 ml) was added and the mixture left to stir for 30 min. The

mixture was concentrated *in vacuo*, and the residue dissolved in ether (100 ml) and washed with aqueous ammonium chloride (3 x 20 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 2:3) to yield *3-alkyne-1,2-diol* **387** (0.09 g, 84%) as a colourless oil; ν_{max} 3418, 2921, 2250, 1717, 1602, 1584, 1277, 1110, 710; δ_H 8.05–8.04 (2H, m, Ar-H), 7.58–7.55 (1H, m, Ar-H), 7.46–7.43 (2H, m, Ar-H), 4.72–4.67 (1H, m, OCH_2CH_2), 4.60–4.55 (1H, m, OCH_2CH_2), 3.69 (1H, d, *J* 11.1, CCH_2OH), 3.57 (1H, d, *J* 11.1, CCH_2OH), 3.00 (1H, bs, OH), 2.20–2.10 (2H, m, OCH_2CH_2C), 2.16 (1H, bs, OH), 1.73 (3H, s, CH_3); δ_C 166.8 (C), 133.0 (CH), 130.1 (C), 129.6 (CH), 128.4 (CH), 82.7 (C), 78.9 (C), 70.2 (C), 70.1 (CH_2), 61.5 (CH_2), 36.7 (CH_2), 3.5 (CH_3); LRMS (ES) m/z 271.09 ($[M+Na]^+$, 100%); HRMS (ES) calculated for $C_{14}H_{16}NaO_4$ $[M+Na]^+$ 271.0946, found 271.0940.

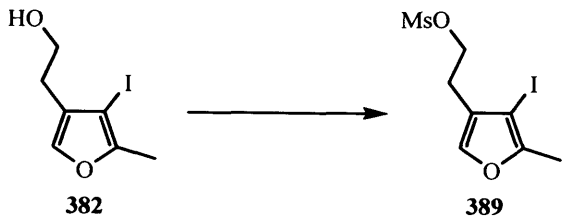
2-(4-Iodo-5-methylfuran-3-yl)ethyl benzoate 388



387 **388**

Iodine (1.40 g, 5.5 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **387** (0.45 g, 1.8 mmol) and $NaHCO_3$ (0.46 g, 5.5 mmol) in dichloromethane (100 ml) at r.t. and left to stir for 1.5 hours. The mixture was washed with aqueous sodium sulfite (3 x 50 ml) and the organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ether, 9:1) to yield *furan* **388** (0.57 g, 88%) as a colourless liquid; ν_{max} 3422, 2919, 2854, 1716, 1602, 1558, 1451, 1274, 1111, 710; δ_H ($(CD_3)_2CO$) 8.05–8.03 (2H, m, Ar-H), 7.58–7.55 (1H, m, Ar-H), 7.46–7.43 (2H, m, Ar-H), 7.26 (1H, m, furan-H), 4.47 (2H, t, *J* 6.8, OCH_2CH_2), 2.80 (2H, m, CH_2CH_2-furan), 2.33 (3H, s, CH_3); δ_C 166.4 (C), 153.3 (C), 138.3 (CH), 132.9 (CH), 130.2 (C), 129.6 (CH), 128.3 (CH), 123.9 (C), 68.5 (C), 63.5 (CH_2), 26.0 (CH_2), 13.5 (CH_3); LRMS (APCI) m/z 357.00 ($[M+H]^+$, 100%), 231.10 ($[M-I+H]^+$, 46%); HRMS (APCI) calculated for $C_{14}H_{14}IO_3$ $[M+H]^+$ 356.9988, found 356.9977.

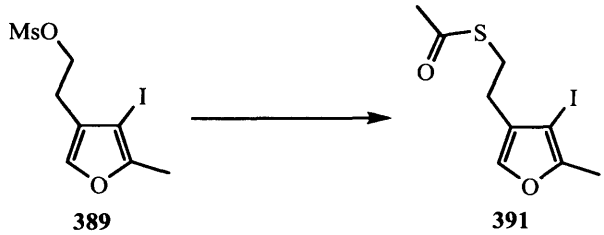
2-(4-Iodo-5-methylfuran-3-yl)ethyl methanesulfonate 389



382 389

Ms-Cl (0.13 g, 1.2 mmol) was added dropwise to a stirred solution of alcohol **382** (0.24 g, 1.0 mmol) and NEt_3 (0.15 g, 1.4 mmol) in dichloromethane (10 ml) at r.t. and left to stir for 5 min. The mixture was diluted with dichloromethane (5 ml) and washed with aqueous ammonium chloride (3 x 5 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ether, 7:3) to yield *mesylate* **389** (0.26 g, 82%) as a colourless solid; m.p. 48–50 °C; ν_{max} (nujol) 1601, 1558, 1343, 1163, 966, 799, 763, 730; δ_H (400 MHz, $(CD_3)_2CO$) 7.49 (1H, s, furan-H), 4.38 (2H, t, *J* 6.8, $OC\underline{H}_2CH_2$), 3.09 (3H, s, $C\underline{H}_3SO_3CH_2$), 2.78 (2H, td, *J* 6.8, 0.8, $CH_2C\underline{H}_2$-furan), 2.31 (3H, s, furan-$C\underline{H}_3$); δ_C (62.5 MHz) 153.6, 138.8, 122.4, 68.0, 67.9, 37.5, 26.4, 13.5; LRMS m/z 330.95 ($[M+H]^+$, 100%); HRMS (APCI) calculated for $C_8H_{12}IO_4S$ $[M+H]^+$ 330.9501, found 330.9494.

S-2-(4-Iodo-5-methylfuran-3-yl)ethyl ethanethioate 391

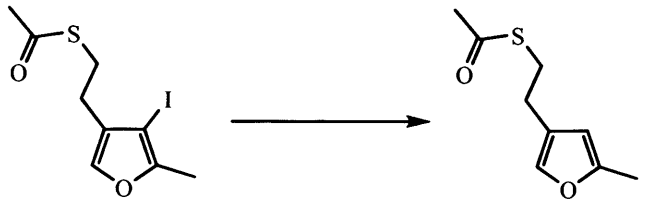


389 391

Potassium thioacetate **390** (0.04 g, 0.32 mmol) was added to a stirred solution of mesylate **389** (0.05 g, 0.16 mmol) in tetrahydrofuran (2 ml) at r.t. and left to stir for 3.5 hours. The mixture was diluted with aqueous ammonium chloride (5 ml), concentrated *in vacuo*, and the residue dissolved in ether (20 ml) and washed with aqueous ammonium chloride (3 x 5 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 9:1) to yield *thioester* **391** (0.05 g, 95%) as a colourless liquid; ν_{max} 3362, 2918, 2852, 1695, 1558, 1436, 1353, 1134, 1051, 924; δ_H (400 MHz) 7.18 (1H, s, furan-H), 3.06 (2H, t, *J* 7.4, $SC\underline{H}_2CH_2$), 2.58 (2H, t, *J* 7.4, $CH_2C\underline{H}_2$-furan), 2.34 (3H, s, $C\underline{H}_3C(O)SCH_2$), 2.32

(3H, s, furan-C$\underline{H}_3$); δ_C 195.3 (C), 153.1 (C), 137.9 (CH), 125.7 (C), 68.2 (C), 30.5 (CH_3), 28.4 (CH_2), 26.3 (CH_2), 13.5 (CH_3); LRMS m/z 309.95 ($[M]^+$, 2%), 83.95 (100%); HRMS calculated for $C_9H_{11}IO_2S$ $[M]^+$ 309.9525, found 309.9528.

S-2-(5-Methylfuran-3-yl)ethyl ethanethioate 392



391 **392**

A mixture of thioester **391** (0.05 g, 0.17 mmol), Bu_3SnH (0.07 g, 0.25 mmol) and AIBN (0.01 g, 0.09 mmol) in degassed toluene (5 ml) under nitrogen was heated to reflux and left to stir for 1 hour. The mixture was allowed to cool to r.t., concentrated *in vacuo* and the product purified by column chromatography (petrol/ether, 9:1) to yield *furan* **392** (0.01 g, 43%) as a colourless liquid; ν_{max} 3366, 2924, 2855, 1771, 1695, 1436, 1354, 1133, 953, 920; δ_H 7.10 (1H, s, α-furan-$\underline{H}$), 5.89 (1H, s, β-furan-$\underline{H}$), 3.04 (2H, t, *J* 7.4, SC$\underline{H}_2$$CH_2$), 2.63 (2H, t, *J* 7.4, CH_2C$\underline{H}_2$-furan), 2.33 (3H, s, C$\underline{H}_3$C(O)SCH_2), 2.25 (3H, s, furan-C$\underline{H}_3$); δ_C 195.7 (C), 152.5 (C), 137.4 (CH), 123.9 (C), 106.8 (CH), 30.7 (CH_3), 29.5 (CH_2), 25.3 (CH_2), 13.6 (CH_3); LRMS m/z 184.06 ($[M]^+$, 28%), 141.04 ($[M–C_2H_3O]^+$, 19%), 108.04 (100%); HRMS calculated for $C_9H_{12}O_2S$ $[M]^+$ 184.0558, found 184.0558.

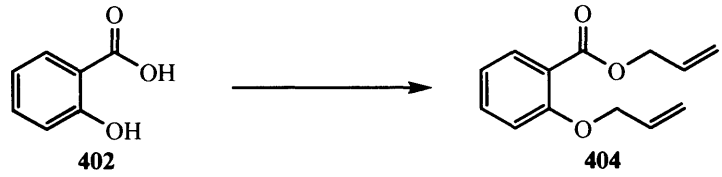
2-(Allyloxy)benzoic acid 401[230]

404 **401**

Ester **404** (2.7 g, 12.5 mmol) was added to a stirred solution of sodium hydroxide (1.0 g, 25.0 mmol) in a mixture of water (30 ml) and ethanol (20 ml) at r.t. and left to stir for 16 hours. The mixture was washed ether (20 ml) before the aqueous fraction was acidified to pH 3 with aqueous hydrochloric acid (36%) and washed with ether (3 x 20 ml). The organic fraction was

dried, filtered and evaporated to yield *acid* **401** (2.1 g, 94%) as a colourless liquid; ν_{max} 2923, 2853, 2360, 2342, 1771, 1674, 1635, 1595, 1483, 1447, 1285, 1195, 916, 758; δ_H 10.75 (1H, bs, OH), 8.13–8.11 (1H, m, Ar-H), 7.53–7.50 (1H, m, Ar-H), 7.10–7.07 (1H, m, Ar-H), 7.04–7.02 (1H, m, Ar-H), 6.10–6.02 (1H, m, $CH_2CH=CH_2$), 5.49–5.45 (1H, m, $CH_2CH=CH_2$), 5.40–5.38 (1H, m, $CH_2CH=CH_2$), 4.77–4.76 (2H, m, OCH_2CH); δ_C 165.8 (C), 157.2 (C), 134.9 (CH), 133.5 (CH), 130.9 (CH), 122.1 (CH), 120.2 (CH_2), 117.8 (C), 113.0 (CH), 70.5 (CH_2); LRMS m/z 178.06 $[M]^+$ 47%, 121.02 (100%); HRMS calculated for $C_{10}H_{10}O_3$ $[M]^+$ 178.0630, found 178.0624.

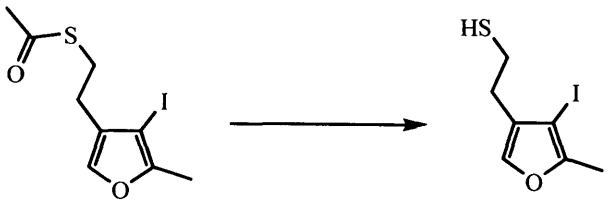
Allyl 2-(allyloxy)benzoate 404[230]



402 **404**

Allyl bromide **403** (3.9 g, 31.9 mmol) was added dropwise to a stirred solution of 2-hydroxybenzoic acid **402** (2.0 g, 14.5 mmol) and potassium hydroxide (1.8 g, 31.9 mmol) in dimethylformamide (25 ml) at r.t. and left to stir for 24 hours. The mixture was diluted with water (250 ml) and washed with ether (3 x 200 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 9:1) to yield *ester* **404** (2.7 g, 86%) as a colourless liquid; ν_{max} 3081, 2934, 1728, 1601, 1490, 1450, 1302, 1247, 1074, 755; δ_H 7.85–7.82 (1H, m, Ar-H), 7.47–7.42 (1H, m, Ar-H), 7.01–6.97 (1H, m, Ar-H), 6.97–6.95 (1H, m, Ar-H), 6.11–6.02 (1H, m, $CH_2CH=CH_2$), 6.09–5.99 (1H, m, $CH_2CH=CH_2$), 5.51 (1H, dtd, *J* 17.2, 1.7, 1.6, $CH_2CH=CH_2$), 5.42 (1H, dtd, *J* 17.2, 1.5, 1.5, $CH_2CH=CH_2$), 5.31–5.28 (1H, m, $CH_2CH=CH_2$), 5.29–5.25 (1H, m, $CH_2CH=CH_2$), 4.81 (2H, ddd, *J* 5.6, 1.4, 1.4, C(O)OCH_2CH), 4.63 (2H, ddd, *J* 4.8, 1.6, 1.6, ArOCH_2CH); δ_C 165.9, 158.1, 133.4, 132.7, 132.3, 131.8, 120.4, 120.4, 118.1, 117.5, 113.5, 69.4, 65.5; LRMS m/z 218.09 ($[M]^+$, 2%), 83.94 (100%); HRMS calculated for $C_{13}H_{14}O_3$ $[M]^+$ 218.0943, found 218.0944.

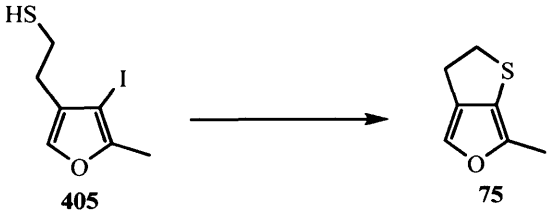
2-(4-Iodo-5-methylfuran-3-yl)ethanethiol 405



391 405

Potassium hydroxide (0.13 g, 2.3 mmol) was added to a stirred solution of thioester **391** (0.23 g, 0.8 mmol) in a mixture of methanol/water (6 ml, 2:1) at r.t. and left to stir for 5 min. The mixture was diluted with ether (50 ml) and washed with aqueous ammonium chloride (3 x 20 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ether, 19:1) to yield *thiol* **405** (0.18 g, 87%) as a colourless liquid; ν_{max} 3411, 2920, 2851, 2362, 2343, 1771, 1558, 1440, 1123, 1050, 923; δ_H 7.20 (1H, s, furan-H), 2.87 (2H, t, *J* 7.5, $HSC\underline{H}_2CH_2$), 2.72 (2H, t, *J* 7.5, $CH_2C\underline{H}_2$-furan), 2.31 (3H, s, $C\underline{H}_3$); δ_C 153.3 (C), 138.0 (CH), 125.7 (C), 68.3 (C), 37.7 (CH_2), 26.2 (CH_2), 13.6 (CH_3); LRMS m/z 267.94 ($[M]^+$, 42%), 141.04 ($[M-I]^+$, 100%); HRMS calculated for C_7H_9IOS $[M]^+$ 267.9419, found 267.9411.

6-Methyl-2,3-dihydrothieno[3,2-c]furan (Kahweofuran) 75[156]

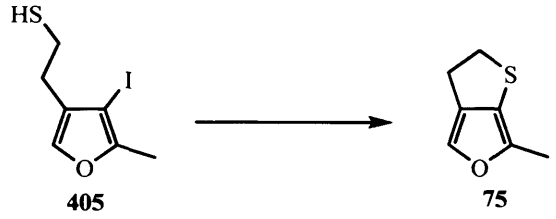


405 75

Potassium phosphate (24 mg, 113 μmol), CuI (14 mg, 75 μmol) and *cis*-1,2-cyclohexanediol **422** (17 mg, 149 μmol) were added to a stirred solution of thiol **405** (20 mg, 75 μmol) in dimethylformamide (3 ml) under nitrogen at r.t. before being warmed to 80 °C for 8 h. The mixture was allowed to cool to r.t., diluted with water (6 ml) and washed with dichloromethane (3 x 10 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol) to yield *kahweofuran* **75** (10 mg, 71 μmol, 96%) as a colourless liquid; ν_{max} 2917, 2848, 2360, 2342, 1633, 1577, 1431, 1265, 1103, 921; δ_H 6.99 (1H, *app.* s, furan-H), 3.63 (2H, t, *J* 7.2, $SC\underline{H}_2CH_2$), 2.88 (2H, td, *J* 7.2, 1.0, $SCH_2C\underline{H}_2$), 2.21 (3H, s, $C\underline{H}_3$); δ_C 140.5 (C), 132.0 (C), 131.8 (CH), 122.2 (C), 42.2 (CH_2), 25.9 (CH_2), 12.8 (CH_3); LRMS m/z

140.03 ([M]$^+$, 46%) 83.94 (100%); HRMS calculated for C_7H_8OS [M]$^+$ 140.0296, found 140.0294.

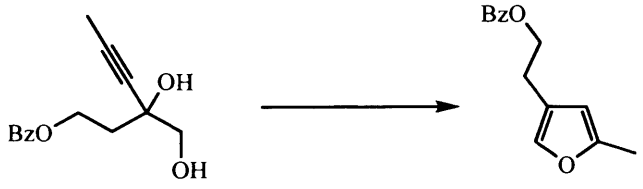
6-Methyl-2,3-dihydrothieno[3,2-c]furan (Kahweofuran) 75[156]



405 **75**

Sodium *tert*-butoxide (35 mg, 365 μmol), CuI (5 mg, 24 μmol) and neocuproine **419** (5 mg, 24 μmol) were added to a stirred solution of thiol **405** (65 mg, 243 μmol) in degassed toluene (10 ml) under nitrogen at r.t. before being warmed to reflux for 24 h. The mixture was allowed to cool to r.t, filtered, and the filtrate evaporated and the crude product purified by column chromatography (petrol) to yield *kahweofuran* **75** (20 mg, 142 μmol, 59%) as a colourless liquid; data same as previous in all respects

5-Methylfuran-4-ethyl benzoate 432

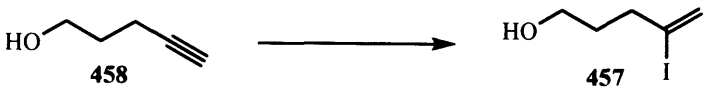


387 **432**

Silver nitrate on silica gel (0.16 g, ~10 wt. %, 0.09 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **387** (0.23 g, 0.92 mmol) in dichloromethane (10 ml) at r.t. under subdued light and left to stir for 50 min. The mixture was filtered through a pad of silica gel with dichloromethane and the filtrate dried, filtered and evaporated to yield *furan* **432** (0.19 g, 89%) as a colourless liquid; ν_{max} 3422, 3063, 2956, 2921, 1719, 1276, 1115, 711; δ_H 8.05–8.03 (2H, m, Ar-H), 7.58–7.54 (1H, m, Ar-H), 7.46–7.43 (2H, m, Ar-H), 7.18 (1H, s, α-furan-H), 5.95 (1H, *app.* s, β-furan-H), 4.45 (2H, t, *J* 6.9, OCH_2CH_2), 2.84 (2H, t, *J* 6.8, OCH_2CH_2), 2.26 (3H, d, *J* 0.7, furan-CH_3); δ_C (62.5 MHz) 166.5 (C), 152.5 (C), 137.8 (CH), 132.9 (CH), 130.3 (C), 129.6 (CH), 128.4 (CH), 121.7 (C), 107.1 (CH), 64.7 (CH_2), 24.8 (CH_2), 13.5 (CH_3); LRMS m/z

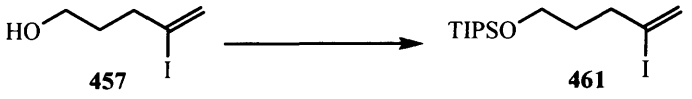
230.09 ([M]$^+$, 6%), 108.72 (100%); HRMS calculated for $C_{14}H_{14}O_3$ [M]$^+$ 230.0943, found 230.0939.

4-Iodopent-4-en-1-ol 457[198]



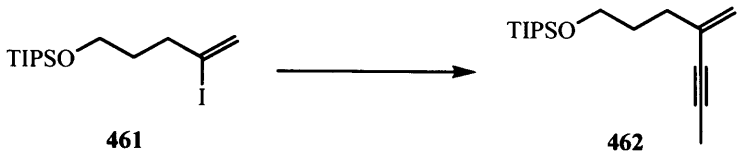
Trimethylsilane chloride (13.3 g. 0.12 mol) was added dropwise to a stirred solution of NaI (15.7 g, 0.12 mol) in acetonitrile (70 ml). Water (1.11 g, 0.06 mmol) was then added dropwise and the mixture left to stir for 10 min. The mixture was cooled to 0 °C and 4-pentyn-1-ol **458** (4.0 g, 0.05 mmol) was added dropwise. The mixture was allowed to warm to r.t. and left to stir for 1 hour. The mixture was diluted by dropwise addition of water (20 ml), concentrated *in vacuo*, and the residue dissolved in ether (200 ml) and washed with brine (3 x 50 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 7:3) to yield *alcohol* **457** (1.8 g, 18%) as a colourless liquid that turned light brown upon exposure to air and light; δ_H 6.07 (1H, d, *J* 1.2, C=C$\underline{H}_2$), 5.72 (1H, d, *J* 0.9, C=C$\underline{H}_2$), 3.67 (2H, t, *J* 6.3, OC$\underline{H}_2$CH$_2$), 2.51 (2H, t, *J* 7.2, CH$_2$C$\underline{H}_2$Cl), 1.82-1.75 (2H, tt, *J* 7.4, 6.4, CH$_2$C$\underline{H}_2$CH$_2$).

(4-Iodopent-4-enyloxy)triisopropylsilane 461



Triisopropylsilyl chloride (1.75 g, 9.1 mmol) was added to a stirred solution of alcohol **457** (1.84 g, 8.7 mmol) and imidazole (0.71 g, 10.4 mmol) in dichloromethane (50 ml) at r.t. and left to stir for 16 h. The mixture was diluted with dichloromethane (100 ml) and washed with aqueous ammonium chloride (3 x 25 ml). The organic fraction was dried, filtered and evaporated to yield *iodoalkene* **461** (2.34 g, 73%) as a colourless liquid; ν_{max} 2942, 2866, 1617, 1463, 1247, 1200, 1105, 1069; δ_H 6.04–6.03 (1H, d, *J* 1.4, C=C$\underline{H}_2$), 5.69 (1H, *app.* s, C=C$\underline{H}_2$), 3.69 (2H, t, *J* 6.1, OC$\underline{H}_2$CH$_2$), 2.52–2.49 (2H, m, OCH$_2$CH$_2$C$\underline{H}_2$), 1.76-1.71 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$), 1.12–1.02 (3H, m, (CH$_3$)$_2$C$\underline{H}$Si), 1.06 (18H, d, *J* 6.7, (C$\underline{H}_3$)$_2$CHSi); δ_C 125.5 (CH$_2$), 112.1 (C), 61.4 (CH$_2$), 41.8 (CH$_2$), 32.3 (CH$_2$), 18.0 (CH$_3$); 11.9 (CH); LRMS m/z 325.06 ([M–C$_3$H$_7$]$^+$, 32%), 83.94 (100%).

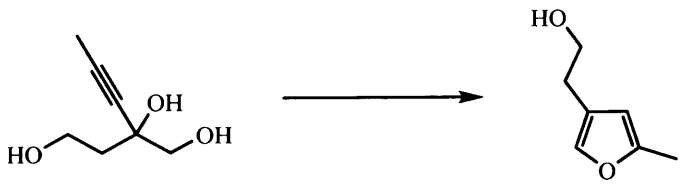
Triisopropyl(4-methylenehept-5-ynyloxy)silane 462



461 462

A solution of commercial 1-propynylmagnesium bromide **232** in tetrahydrofuran (19.0 ml, 0.5 M, 9.5 mmol) was added dropwise to a solution of iodoalkene **461** (2.34 g, 6.3 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.22 g, 0.3 mmol) in tetrahydrofuran (50 ml) at r.t. and left to stir for 24 h. The mixture was quenched by dropwise addition of aqueous ammonium chloride (20 ml), concentrated *in vacuo*, and the residue dissolved in ether (100 ml) and washed with water (3 x 50 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ether, 49:1) to yield *alkene* **462** (0.88 g, 85%) as a colourless liquid; δ_H 5.21 (1H, d, *J* 1.5, C=C$\underline{H}_2$), 5.15 (1H, d, *J* 1.6, C=C$\underline{H}_2$), 3.69 (2H, t, *J* 6.4, OC$\underline{H}_2$CH$_2$), 2.21 (2H, t, *J* 7.5, OCH$_2$CH$_2$C$\underline{H}_2$), 1.93 (3H, s, C≡CC$\underline{H}_3$), 1.78-1.73 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$) 1.11–1.04 (3H, m, (CH$_3$)$_2$C$\underline{H}$Si), 1.06 (18H, d, *J* 4.6, (C$\underline{H}_3$)$_2$CHSi); δ_C 131.9 (C), 119.7 (CH$_2$), 85.4 (C), 80.1 (C), 62.5 (CH$_2$), 33.9 (CH$_2$), 31.4 (CH$_2$), 18.0 (CH$_3$); 12.0 (CH), 4.1 (CH$_3$).

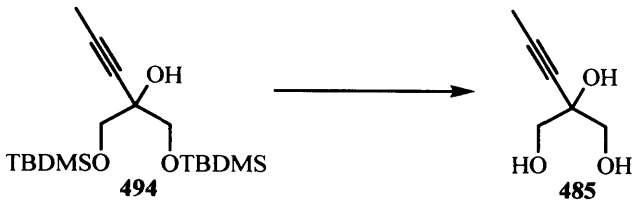
5-Methylfuran-3-ethanol 478[231]



363 478

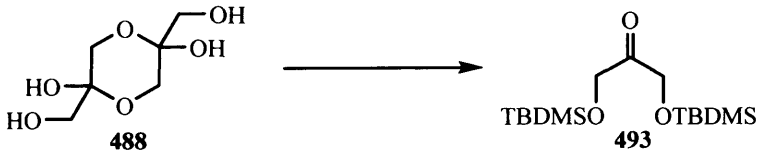
Silver nitrate on silica gel (0.09 g, ~10 wt. %, 0.06 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **363** (0.08 g, 0.55 mmol) in dichloromethane (2 ml) at r.t. under subdued light and left to stir for 20 min. The mixture was filtered through a pad of silica gel with dichloromethane and the filtrate dried, filtered and evaporated to yield *furan* **478** (0.07 g, 98%) as a colourless liquid; δ_H 7.15 (1H, s, α-furan-$\underline{H}$), 5.90 (1H, *app.* s, β-furan-$\underline{H}$), 3.75 (2H, t, *J* 6.4, HOC$\underline{H}_2$CH$_2$), 2.62 (2H, t, *J* 6.4, CH$_2$C$\underline{H}_2$-furan), 2.26 (3H, d, *J* 0.7, C$\underline{H}_3$); δ_C 152.8 (C), 138.0 (CH), 122.0 (C), 107.0 (CH), 63.5 (CH$_2$), 28.5 (CH$_2$), 13.5 (CH$_3$).

(2*RS*)-2-(Prop-1-ynyl)propane-1,2,3-triol 485



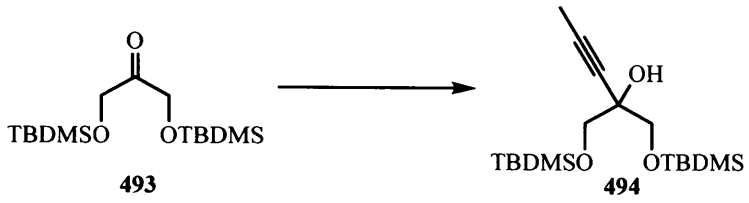
A solution of tetrabutylammonium fluoride in tetrahydrofuran (4.0 ml, 1 M, 4.0 mmol) was added dropwise to a stirred solution of alcohol **494** (0.65 g, 1.8 mmol) in tetrahydrofuran (20 ml) at r.t. and left to stir for 16 h. The mixture was concentrated *in vacuo*, and the product purified by column chromatography (ethyl acetate/methanol, 19:1) to yield *3-alkyne-1,2-diol* **485** (0.22 g, 95%) as a colourless oil; ν_{max} 3418, 2925, 2248, 1434, 1105, 922, 881; δ_H 3.74–3.68 (4H, m, 2 x C$\underline{H}_2$), 3.00 (1H, s, C≡CC(CH$_2$)$_2$O$\underline{H}$), 2.23 (2H, t, *J* 6.6, 2 x CH$_2$O$\underline{H}$), 1.87 (3H, s, C$\underline{H}_3$); 83.29 (C), 77.70 (C), 71.57 (C), 67.38 (CH$_2$), 3.61 (CH$_3$); LRMS m/z 112.05 ([M–H$_2$O]$^+$, 5%) 99.02 (100%); HRMS calculated for $C_6H_8O_2$ [M]$^+$ 112.0524, found 112.0526.

1,3-Bis-(*tert*-butyldimethylsilyloxy)propan-2one 493[232]



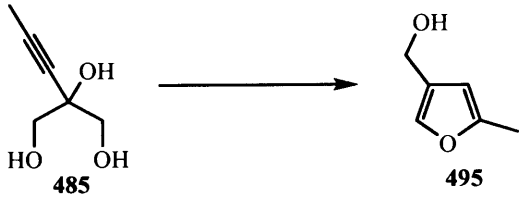
tert-Butyldimethylsilyl chloride (2.5 g, 16.7 mmol) was added to a stirred solution of 1,3-dihydroxyacetone dimer **488** (2.0 g, 11.1 mmol) and imidazole (1.1 g, 16.7 mmol) in dichloromethane (200 ml) at r.t. and left to stir for 16 h. The mixture was diluted with dichloromethane (100 ml) and washed with aqueous ammonium chloride (3 x 100 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 19:1) to yield *ketone* **493** (6.4 g, 90%) as a colourless liquid; ν_{max} 2930, 2858, 1743, 1254, 1139, 1101, 838, 779; δ_H 4.41 (4H, s, 2 x C$\underline{H}_2$), 0.91 (18H, s, 2 x SiC(C$\underline{H}_3$)$_3$), 0.08 (12H, s, 2 x Si(C$\underline{H}_3$)$_2$); δ_C 208.6 (C), 67.9 (CH$_2$), 25.8 (CH$_3$), 18.3 (C), –5.5 (CH$_3$); LRMS (APCI) m/z 319.21 ([M+H]$^+$, 23%), 312.13 (100%); HRMS (APCI) calculated for $C_{15}H_{35}O_3Si_2$ [M+H]$^+$ 319.2125, found 319.2133.

(2*RS*)-1,3-Bis-(*tert*-butyldimethylsilyloxy)-2-(prop-1-ynyl)propan-2-ol 494



A solution of commercial 1-propynylmagnesium bromide in tetrahydrofuran (7.5 ml, 0.5 M, 3.8 mmol) was added dropwise to a solution of ketone **493** (1.0 g, 3.1 mmol) in tetrahydrofuran (50 ml) under nitrogen at –78 °C. The mixture left to stir for 1 hour before being allowed to warm to r.t. and left to stir for a further 2 h. The reaction mixture was quenched by dropwise addition of aqueous ammonium chloride (10 ml), concentrated *in vacuo*, and the residue dissolved in ethyl acetate (100 ml) and washed with water (3 x 50 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 19:1) to yield *alcohol* **494** (0.8 g, 70%) as a colourless liquid; ν_{max} 3550, 2929, 2858, 2254, 1472, 1255, 1132, 1101; δ_H 3.69 (2H, d, *J* 9.5, 2 x C<u>H</u>$_2$), 3.59 (2H, d, *J* 9.5, 2 x C<u>H</u>$_2$), 2.89 (1H, s, O<u>H</u>), 1.82 (3H, s, C≡CC<u>H</u>$_3$), 0.90 (18H, s, 2 x SiC(C<u>H</u>$_3$)$_3$), 0.08 (6H, s, Si(C<u>H</u>$_3$)$_2$), 0.08 (6H, s, Si(C<u>H</u>$_3$)$_2$); δ_C 81.2 (C), 79.2 (C), 71.1 (C), 65.8 (CH_2), 25.8 (CH_3), 18.3 (C), 3.6 (CH_3), –5.4 (CH_3), –5.4 (CH_3); LRMS m/z 341.23 ($[M–H_2O]^+$, 100%); HRMS calculated for $C_{18}H_{37}O_2Si_2$ $[M]^+$ 341.2327, found 341.2332.

5-Methylfuran-3-methanol 495[233]

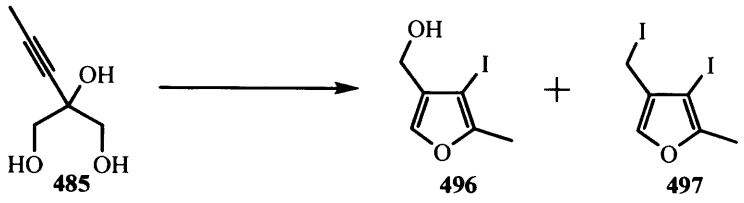


Silver nitrate on silica gel (0.29 g, ~10 wt. %, 0.17 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **485** (0.22 g, 1.69 mmol) in dichloromethane (10 ml) at r.t. under subdued light and left to stir for 45 min. The mixture was filtered through a pad of silica gel with dichloromethane and the filtrate dried, filtered and evaporated to yield *furan* **495** (0.14 g, 73%) as a colourless liquid; δ_H (400 MHz) 7.26 (1H, *app.* s, α-furan-<u>H</u>), 6.03 (1H, *app.* s, β-furan-<u>H</u>),

4.49 (2H, d, *J* 3.7 C<u>H</u>$_2$), 2.27 (3H, d, *J* 0.7, C<u>H</u>$_3$); δ_C 153.1 (C), 138.4 (CH), 121.1 (C), 106.9 (CH), 56.5 (CH_2), 13.4 (CH_3).

(4-Iodo-5-methylfuran-3-yl)methanol 496

3-Iodo-4-(iodomethyl)-2-methylfuran 497



Iodine (0.322 g, 1.27 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **485** (0.055 g, 0.42 mmol) and $NaHCO_3$ (0.107 g, 1.27 mmol) in dichloromethane (5 ml) at r.t. and left to stir for 3 h. The mixture was washed with aqueous sodium sulfite (3 x 5 ml) and the organic fraction dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 3:2) to yield *iodofuran* **496** (0.002 g, 2%) and *diiodofuran* **497** (0.003 g, 2%) as a colourless liquids;

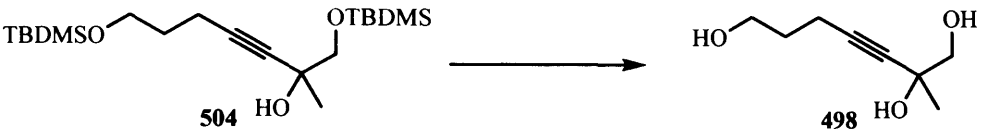
iodofuran **496**

δ_H 7.35 (1H, *app.* s, furan-<u>H</u>), 4.44 (2H, d, *J* 0.5, C<u>H</u>$_2$), 2.33 (3H, s, C<u>H</u>$_3$); δ_C 154.0 (C), 139.2 (CH), 127.6 (C), 65.7 (C), 57.5 (CH_2), 13.4 (CH_3); LRMS m/z 237.95 ($[M]^+$, 100%); HRMS calculated for $C_6H_7O_2I$ $[M]^+$ 237.9491, found 237.9490.

diiodofuran **497**

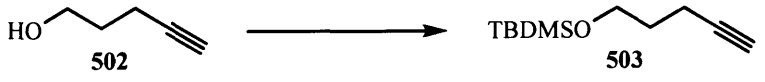
δ_H 7.46 (1H, *app.* s, furan-<u>H</u>), 4.14 (2H, d, *J* 0.5, C<u>H</u>$_2$), 2.32 (3H, s, C<u>H</u>$_3$); δ_C 154.5 (C), 139.0 (CH), 125.6 (C), 67.6 (C), 13.6 (CH_3), –4.5 (CH_2).

(2*RS*)-2-Methylhept-3-yne-1,2,7-triol 498



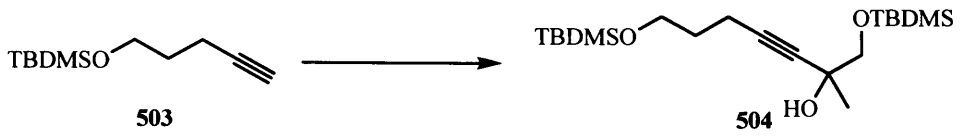
A solution of tetrabutylammonium fluoride in tetrahydrofuran (3.0 ml, 1 M, 3.0 mmol) was added dropwise to a stirred solution of alcohol **504** (0.53 g, 1.4 mmol) in tetrahydrofuran (30 ml) at r.t. and left to stir for 16 h. The mixture was concentrated *in vacuo*, and the product purified by column chromatography (ethyl acetate/methanol, 49:1) to yield *3-alkyne-1,2-diol* **498** (0.18 g, 83%) as a colourless oil; ν_{max} 3357, 2935, 2243, 1703, 1433, 1052; δ_H 4.35 (1H, bs, O<u>H</u>), 4.11 (1H, bs, O<u>H</u>), 3.94 (1H, bs, O<u>H</u>), 3.06 (2H, t, *J* 6.2, HOC<u>H</u>$_2$CH$_2$), 3.47 (1H, d, *J* 10.8, OC<u>H</u>$_2$C(CH3)(OH)C≡C), 3.40 (1H, d, *J* 10.8, OC<u>H</u>$_2$C(CH3)(OH)C≡C), 2.24 (2H, t, *J* 7.1, C<u>H</u>$_2$C≡C), 1.62–1.67 (2H, m, C<u>H</u>$_2$CH$_2$C≡C), 1.34 (3H, s, C<u>H</u>$_3$); δ_C 84.1 (C), 83.5 (C), 71.2 (CH_2), 68.5 (C), 61.0 (CH_2), 32.4 (CH_2), 26.4 (CH_3), 15.5 (CH_2); LRMS 140.08 ($[M–H_2O]^+$, 100%); HRMS calculated for $C_8H_{12}O_2$ $[M–H_2O]^+$ 140.0837, found 140.0837.

1-(*tert*-**Butyldimethylsilyloxy)pent-1-yne 503**[234]



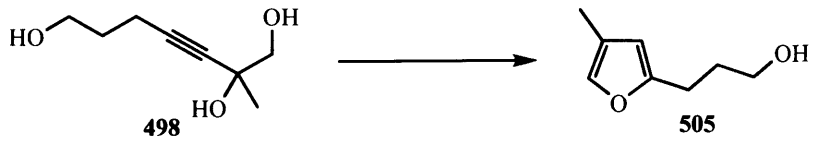
tert-Butyldimethylsilyl chloride (0.98 g, 6.5 mmol) was added to a stirred solution of alcohol **502** (0.50 g, 5.9 mmol) and imidazole (0.49 g, 7.1 mmol) in dichloromethane (30 ml) at r.t. and left to stir for 16 h. The mixture was diluted with dichloromethane (20 ml) and washed with aqueous ammonium chloride (3 x 25 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 49:1) to yield *alkyne* **503** (0.91 g, 77%) as a colourless liquid; ν_{max} 3313, 2954, 2858, 2120, 1256, 1107, 1072, 836, 776; δ_H 3.70 (2H, t, *J* 6.0, OC<u>H</u>$_2$CH$_2$), 2.27 (2H, td, *J* 7.1, 2.7, CH$_2$C<u>H</u>$_2$C≡C), 1.93 (1H, t, *J* 2.7, C≡C<u>H</u>), 1.75–1.70 (2H, tt, *J* 7.0, 6.1, CH$_2$C<u>H</u>$_2$CH$_2$), 0.89 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.06 (6H, s, Si(C<u>H</u>$_3$)$_2$); δ_C 84.3 (C), 68.2 (CH), 61.4 (CH_2), 31.5 (CH_2), 25.9 (CH_3), 18.3 (C), 14.8 (CH_2), –5.4 (CH_3); LRMS m/z 183.12 ($[M-CH_3]^+$, 2%), 141.07 ($[M–C_4H_9]^+$, 100%); HRMS calculated for $C_{10}H_{19}OSi$ $[M]^+$ 183.1205, found 183.1201.

(2*RS*)-1,7-Bis-(*tert*-butyldimethylsilyloxy)-2-methylhept-3-yn-2-ol 504



A solution of butyllithium in hexanes (1.1 ml, 2.5 M, 2.8 mmol) was added dropwise to a stirred solution of alkyne **503** (0.50 g, 2.5 mmol) and $CeCl_3$ (0.62 g, 2.5 mmol) in tetrahydrofuran (20 ml) under nitrogen at 0 °C and left to stir for 1 hour before being cooled to –78 °C. Aldehyde **294** (0.53 g, 1.1 mmol) was added dropwise and the mixture left to stir for 1 hour before being allowed to warm to r.t. and left to stir for 2 h. The mixture was quenched by dropwise addition of aqueous ammonium chloride (5 ml), concentrated *in vacuo*, and the residue dissolved in ethyl acetate (30 ml) and washed with water (3 x 10 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 9:1) to yield *alkyne* **504** (0.53 g, 54%) as a colourless liquid; δ_H 3.67 (2H, t, *J* 6.1, $OC\underline{H}_2CH_2$), 3.63 (1H, d, *J* 9.5, $OC\underline{H}_2C(CH_3)(OH)C{\equiv}C$), 3.48 (1H, d, *J* 9.5, $OC\underline{H}_2C(CH_3)(OH)C{\equiv}C$), 2.81 (1H, s, O<u>H</u>), 2.27 (2H, t, *J* 7.1, $C\underline{H}_2C{\equiv}C$), 1.72–1.66 (2H, m, $CH_2C\underline{H}_2CH_2$), 1.39 (3H, s, $CC\underline{H}_3$), 0.92 (9H, s, $SiC(C\underline{H}_3)_3$), 0.89 (9H, s, $SiC(C\underline{H}_3)_3$), 0.09 (3H, s, $Si(C\underline{H}_3)_2$), 0.09 (3H, s, $Si(C\underline{H}_3)_2$), 0.05 (6H, s, $Si(C\underline{H}_3)_2$); δ_C 83.4 (C), 82.4 (C), 71.1 (CH_2), 68.0 (C), 61.6 (CH_2), 31.7 (CH_2), 25.9 (CH_3), 25.8 (CH_3), 25.8 (CH_3), 18.4 (C), 18.3 (C), 15.1 (CH_2), –5.3 (CH_3), –5.4 (CH_3); LRMS m/z 75.02 (100%).

4-Methylfuran-2-propan-1-ol 505[235]



Silver nitrate on silica gel (0.02 g, ~10 wt. %, 0.01 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **498** (0.02 g, 0.06 mmol) in dichloromethane (5 ml) at r.t. under subdued light and left to stir for 5 h. The mixture was filtered through a pad of silica gel with dichloromethane and the filtrate dried, filtered and evaporated to yield *furan* **505** (0.02 g, 96%) as a colourless liquid; ν_{max} 3382, 3155, 2253, 1793, 1469, 1383, 1096, 906, 733; δ_H 7.06 (1H, *app.* s, α-furan-<u>H</u>), 5.88 (1H, s, β-furan-<u>H</u>), 3.69 (2H, t, *J* 6.3, $C\underline{H}_2OH$), 2.68 (2H, t, *J* 7.4,

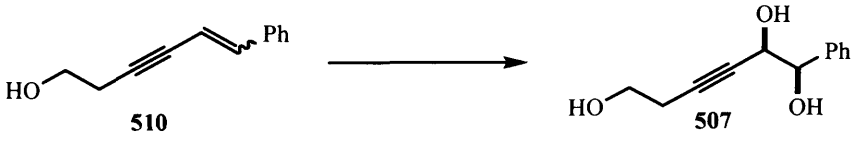
furan-C$\underline{H}_2$CH$_2$), 1.98 (3H, d, *J* 1.1, C$\underline{H}_3$), 1.88 (2H, tt, *J* 7.3, 6.4, CH$_2$C$\underline{H}_2$CH$_2$); δ_C 155.5 (C), 137.5 (CH), 120.5 (C), 107.9 (CH), 62.2 (CH_2), 31.0 (CH_2), 24.4 (CH_2), 9.8 (CH_3); LRMS m/z 140.08 ($[M]^+$, 2%), 122.10 ($[M-H_2O]^+$, 21%), 85.93 (100%); HRMS calculated for $C_8H_{12}O_2$ $[M]^+$ 140.0837, found 140.0839.

3-Iodo-4-methylfuran-2-propan-1-ol 506

498 **506**

Iodine (0.17 g, 0.65 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **498** (0.03 g, 0.21 mmol) and $NaHCO_3$ (0.05 g, 0.64 mmol) in dichloromethane (5 ml) at r.t. and left to stir for 1.5 h. The mixture diluted with dichloromethane (5 ml) was washed with aqueous sodium sulfite (3 x 5 ml) and the organic fraction dried, filtered and evaporated to yield *iodofuran* **506** (0.002 g, 2%) as a red liquid; ν_{max} 3373, 2926, 2253, 1463, 1384, 1096, 1049, 907, 733; δ_H 7.26 (1H, s, α-furan-$\underline{H}$), 3.68 (2H, t, *J* 6.3, CH$_2$C$\underline{H}_2$OH), 2.82 (2H, t, *J* 7.3, furan-C$\underline{H}_2$CH$_2$), 2.08 (3H, s, C$\underline{H}_3$), 1.93–1.90 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$); δ_C 154.6 (C), 140.5 (CH), 120.8 (C), 72.3 (C), 61.8 (CH_2), 30.7 (CH_2), 24.3 (CH_2), 12.5 (CH_3).

(1R,2R and 1S,2S)-1-Phenylhex-3-yne-1,2,6-triol 507[89]



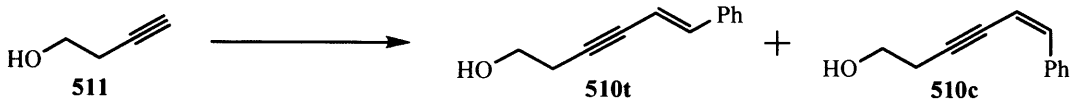
510 **507**

OsO_4 (0.01 g, 0.1 mmol) was added to a stirred solution of alkene **510** (0.18 g, 1.1 mmol) and NMO (0.14 g, 1.2 mmol) in acetone/water (10 ml, 1:1) at r.t. and left to stir for 16 h. Aqueous sodium sulfite (5 ml) was added and the mixture left to stir for 30 min. The mixture was concentrated *in vacuo*, and the residue dissolved in ethyl aceate (150 ml) and washed with brine (3 x 50 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (ethyl acetate) to yield *diol* **507** (0.09 g, 42%) as a colourless oil; ν_{max} 3359, 2916, 2224, 1454, 1331, 1261, 1197, 1040, 763, 701; δ_H 7.44–7.42 (2H, m, Ar-$\underline{H}$), 7.39–7.31 (3H, m, Ar-$\underline{H}$), 4.70 (1H, d, *J* 6.9, CH(OH)C$\underline{H}$(OH)Ar), 4.41 (1H, dt, *J* 6.9, 2.1,

CCH(OH)CH(OH)), 3.63 (2H, t, *J* 6.0, HOCH$_2$CH$_2$), 2.41 (2H, td, *J* 6.0, 2.1, CH$_2$CH$_2$C); δ_C 139.3 (C), 128.4 (CH), 128.3 (CH), 127.0 (CH), 84.7 (C), 79.9 (C), 77.6 (CH), 67.6 (CH), 60.8 (CH_2), 23.1 (CH_2).

(*E*)-6-Phenylhex-5-en-3-yn-1-ol 510t[236]

(*Z*)-6-Phenylhex-5-en-3-yn-1-ol 510c



A mixture of (*E*/*Z*)-β-bromostyrene **512** (2.00 g, 10.9 mmol, *E*/*Z* 9:1), triphenylphosphine (0.57 g, 2.2 mmol), copper iodide (0.10 g, 0.6 mmol) and 2-aminoethanol (2.00 g, 32.8 mmol) were added to a stirred suspension of palladium on carbon (0.47 g, 10 %, 0.4 mmol) in degassed water (100 ml) under nitrogen at r.t. and the mixture left to stir for 30 min. 3-Butyn-1-ol **511** (1.15 g, 16.4 mmol) was added dropwise and the mixture warmed to 80 °C and left to stir for 10 h, then allowed to cool to r.t. and filtered through celite. The filtrate was washed with ethyl acetate (3 x 100 ml) and the organic fraction dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 1:1) to yield *(E)-alkene* **510t** and *(Z)-alkene* **510c** (0.19 g, 10%) as a colourless liquid, as a 9:1 ratio of *E*/*Z* isomers;

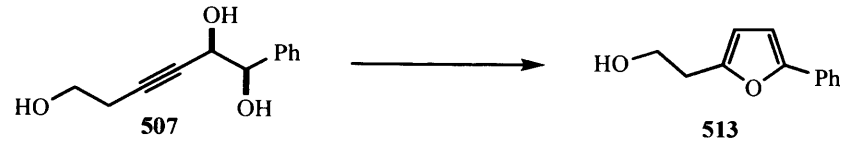
(E)-alkene **510t**

ν_{max} 3308, 3026, 2951, 2889, 2212, 1596, 1491, 1448, 1041, 955, 748, 692; δ_H 7.27–7.26 (2H, m, Ar-H), 7.23–7.20 (2H, m, Ar-H), 7.18–7.16 (1H, m, Ar-H), 6.82 (1H, d, *J* 16.2, ArCH=CH), 6.06 (1H, dt, 16.3, 2.2, CH=CHC), 3.68 (2H, t, *J* 6.4, CH$_2$CH$_2$OH), 2.55 (2H, td, *J* 6.3, 2.1, CCH$_2$CH$_2$); δ_C 140.8 (CH), 136.2 (C), 128.6 (CH), 128.3 (CH), 126.0 (CH), 108.1 (CH), 88.8 (C), 81.4 (C), 61.0 (CH_2), 23.9 (CH_2); LRMS m/z 172.09 ([M]$^+$, 53%), 141.07 ([M–CH$_2$OH]$^+$, 100%); HRMS calculated for $C_{12}H_{12}O$ [M]$^+$ 172.0888, found 172.0893.

(Z)-alkene **510c**

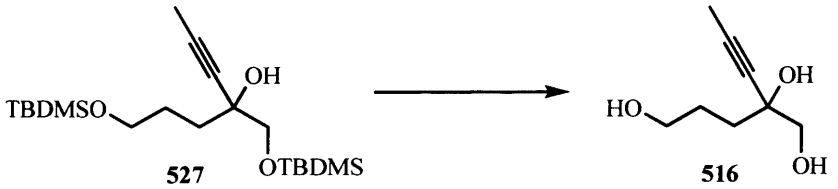
6.51 (1H, d, *J* 11.9, ArCH=CH), 3.72 (2H, t, *J* 6.3, CH$_2$CH$_2$OH) only 2 distinct peaks; δ_C 138.1 (CH), 136.4 (C), 128.3 (CH), 128.1 (CH), 107.6 (CH), 93.5 (C), 80.7 (C), 60.9 (CH_2), 24.1 (CH_2) only 9 distinct peaks.

5-Phenylfuran-2-ethanol 513[89]



Silver nitrate on silica gel (0.07 g, ~10 wt. %, 0.04 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **507** (0.09 g, 0.43 mmol) in dichloromethane (5 ml) at r.t. under subdued light and left to stir for 21 h. The mixture was filtered through a pad of silica gel with dichloromethane and the filtrate dried, filtered and evaporated to yield *furan* **513** (0.5 g, 57%) as a colourless liquid; δ_H 7.55–7.53 (2H, m, Ar-H), 7.29–7.25 (2H, m, Ar-H), 7.16–7.12 (1H, m, Ar-H), 6.48 (1H, d, *J* 3.2, 3-furan-H), 6.09 (1H, d, *J* 3.2, 4-furan-H), 3.82 (2H, t, *J* 6.4, $HOCH_2CH_2$), 2.85 (2H, t, *J* 6.4, CH_2CH_2-furan); δ_C 152.9 (C), 152.5 (C), 130.9 (C), 128.6 (CH), 127.0 (CH), 123.4 (CH), 108.7 (CH), 105.7 (CH), 61.0 (CH_2), 31.7 (CH_2); LRMS m/z 188.08 ($[M]^+$, 25%), 157.06 ($[M–CH_2OH]^+$, 100%); HRMS calculated for $C_{12}H_{12}O_2$ $[M]^+$ 188.0837, found 188.0835.

(2*RS*)-2-(Prop-1-ynyl)pentane-1,2,5-triol 516



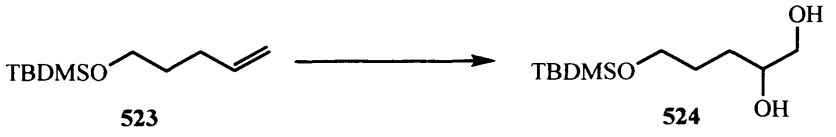
A solution of tetrabutylammonium fluoride in tetrahydrofuran (2.2 ml, 1 M, 2.2 mmol) was added dropwise to a stirred solution of alkyne **527** (0.38 g, 1.0 mmol) in tetrahydrofuran (20 ml) at r.t. and left to stir for 16 h. The mixture was concentrated *in vacuo*, and the product purified by column chromatography (ethyl acetate/methanol, 19:1) to yield *3-alkyne-1,2-diol* **516** (0.15 g, 94%) as a colourless oil; ν_{max} 3401, 2923, 2362, 2247, 1647, 1443, 1060, 922; δ_H 4.49 (1H, bs, OH), 3.34 (2H, bs, OH), 3.72–3.69 (1H, m, $HOCH_2CH_2$), 3.64–3.60 (1H, m, $HOCH_2CH_2$), 3.60 (1H, d, *J* 11.3, CCH_2OH), 3.51 (1H, d, *J* 11.2, CCH_2OH), 1.88–1.70 (4H, m, $CH_2CH_2CH_2C$), 1.83 (3H, s, CH_3); δ_C 81.7 (C), 79.7 (C), 71.4 (CH_2), 69.5 (C), 62.5 (CH_2), 34.8 (CH_2), 27.3 (CH_2), 3.5 (CH_3); LRMS m/z 140.02 ($[M–H_2O]^+$, 4%), 109.05 (100%); HRMS calculated for $C_8H_{12}O_2$ $[M–H_2O]^+$ 140.0837, found 140.0837.

tert-Butyldimethyl(pent-4-enyloxy)silane 523[237]

522 523

tert-Butyldimethylsilyl chloride (3.84 g, 25.5 mmol) was added to a stirred solution of 4-penten-1-ol **522** (2.0 g, 23.2 mmol) and imidazole (1.9 g, 68.1 mmol) in dichloromethane (100 ml) at r.t. and left to stir for 16 h. The mixture was diluted with dichloromethane (100 ml) and washed with aqueous ammonium chloride (3 x 50 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 19:1) to yield *iodoalkene* **523** (3.38 g, 73%) as a colourless liquid; ν_{max} 3079, 2930, 2858, 1642, 1472, 1255, 1102, 836, 775; δ_H 5.86–5.78 (1H, m, $CH_2C\underline{H}=CH_2$), 5.04–4.99 (1H, m, $CH_2CH=C\underline{H_2}$), 4.96–4.94 (1H, m, $CH_2CH=C\underline{H_2}$), 3.62 (2H, t, *J* 6.48, $OC\underline{H_2}CH_2$), 2.13–2.08 (2H, m, $CH_2C\underline{H_2}CH$), 1.64–1.58 (2H, m, $CH_2C\underline{H_2}CH_2$), 0.89 (9H, s, $SiC(C\underline{H_3})_3$), 0.05 (6H, s, $Si(C\underline{H_3})_2$); δ_C 138.6 (CH), 114.5 (CH_2), 62.5 (CH_2), 32.0 (CH_2), 30.0 (CH_2), 26.0 (CH_3), 18.3 (C), –5.3 (CH_3); LRMS (APCI) m/z 201.17 ($[M+H]^+$, 100%); HRMS (APCI) calculated for $C_{11}H_{25}OSi$ $[M+H]^+$ 201.1675, found 201.1670.

(2*RS*)-5-(*tert*-Butyldimethylsilyloxy)pentane-1,2-diol 524[238]

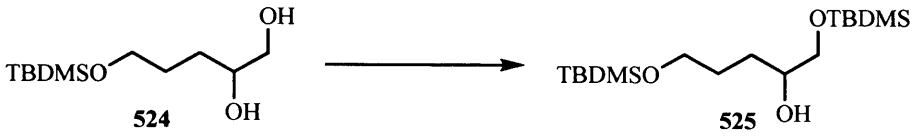


523 524

OsO_4 (0.14 g, 0.6 mmol) was added to a solution of alkene **523** (2.40 g, 12.0 mmol) and NMO (1.39 g, 12.0 mmol) in acetone/water (30 ml, 1:1) at r.t. and left to stir for 16 h. Aqueous sodium sulfite (20 ml) was added and the mixture left to stir for 30 min. The mixture was concentrated *in vacuo*, and the residue dissolved in ether (300 ml) and washed with aqueous ammonium chloride (3 x 100 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 3:7) to yield *diol* **524** (2.81 g, 86%) as a colourless oil; ν_{max} 3375, 2929, 2858, 1743, 1472, 1255, 1098, 938, 836, 776; δ_H 3.73–3.69 (2H, m, $OC\underline{H_2}CH_2$), 3.68–3.61 (2H, m, $CC\underline{H_2}OH$), 3.48 (1H, bs, O<u>H</u>), 3.48–3.44 (1H, m, $CH_2C\underline{H}(OH)CH_2$), 2.08 (1H, bs, O<u>H</u>), 1.75–1.59 (3H, m, $CH_2C\underline{H_2}C\underline{H_2}CH$), 1.53–1.46 (1H, m, $CH_2C\underline{H_2}CH(OH)$), 0.90 (9H, s, $SiC(C\underline{H_3})_3$), 0.08 (6H, s, $Si(C\underline{H_3})_2$); δ_C 71.9 (CH), 66.9 (CH_2),

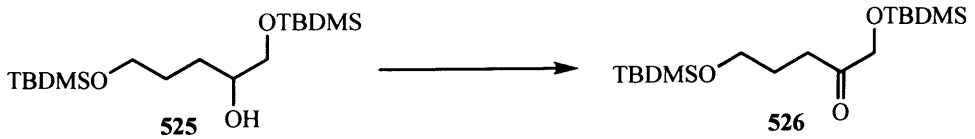
63.6 (CH_2), 31.0 (CH_2), 29.1 (CH_2), 25.9 (CH_3), 18.3 (C), –5.4 (CH_3), –5.4(CH_3); LRMS (APCI) m/z 235.17 ($[M+H]^+$, 66%), 117.09 (100%); HRMS (APCI) calculated for $C_{11}H_{27}O_3Si$ $[M+H]^+$ 235.1729, found 235.1732.

(2*RS*)-1,5-Bis-(*tert*-butyldimethylsilyloxy)pentan-2-ol 525[239]



tert-Butyldimethylsilyl chloride (0.52 g, 3.4 mmol) was added to a stirred solution of diol **524** (0.80 g, 3.4 mmol), NEt_3 (0.35 g, 3.5 mmol) and 4-(dimethylamino)pyridine (0.04 g, 0.3 mmol) in dichloromethane (20 ml) at r.t. and left to stir for 16 h. The mixture was diluted with dichloromethane (20 ml) and washed with aqueous ammonium chloride (3 x 20 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 9:1) to yield *alcohol* **525** (0.81 g, 68%) as a colourless liquid; ν_{max} 3434, 2929, 2858, 1472, 1255, 1097, 836, 776; δ_H 3.66–3.61 (2H, m $OC\underline{H}_2CH_2$), 3.66–3.61 (1H, m $CH_2C\underline{H}(OH)CH_2$), 3.60 (1H, dd, *J* 9.8, 4.0, $CH(OH)C\underline{H}_2O$), 3.44 (1H, dd, *J* 9.6, 7.0, $CH(OH)C\underline{H}_2O$), 2.75 (1H, d, *J* 3.4, O<u>H</u>), 1.72–1.59 (2H, m, $CH_2C\underline{H}_2CH_2$), 1.59–1.52 (1H, m, $CH_2C\underline{H}_2CH$), 1.47–1.40 (1H, m, $CH_2C\underline{H}_2CH$), 0.90 (9H, s, $SiC(C\underline{H}_3)_3$), 0.89 (9H, s, $SiC(C\underline{H}_3)_3$), 0.07 (6H, s, $Si(C\underline{H}_3)_2$), 0.05 (6H, s, $Si(C\underline{H}_3)_2$); δ_C 71.7 (CH), 67.3 (CH_2), 63.3 (CH_2), 29.7 (CH_2), 29.0 (CH_2), 26.0 (CH_3), 25.9 (CH_3), 18.4 (C), 18.3 (C), –5.1 (CH_3), –5.4 (CH_3); LRMS (APCI) m/z 349.26 ($[M+H]^+$, 100%), 331.25 ($[M–OH]^+$, 10%); HRMS (APCI) calculated for $C_{17}H_{41}O_3Si_2$ $[M+H]^+$ 349.2594, found 349.2608.

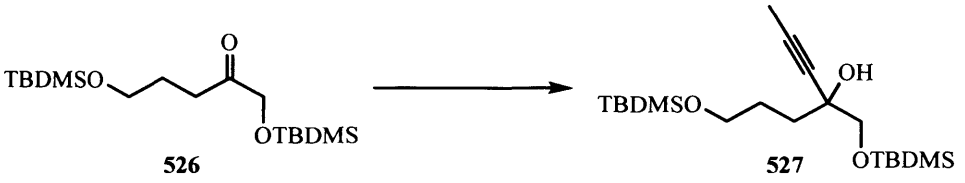
1,5-Bis-(*tert*-butyldimethylsilyloxy)pentan-2-one 526[240]



Alcohol **525** (2.12 g, 6.1 mmol) was added dropwise to a stirred solution of 2-iodoxybenzoic acid (3.4 g, 12.2 mmol) in dimethyl sulfoxide (20 ml) under nitrogen at r.t. and left to stir for 16 h. The mixture was diluted with water (300 ml) and washed with ether (5 x 100 ml). The

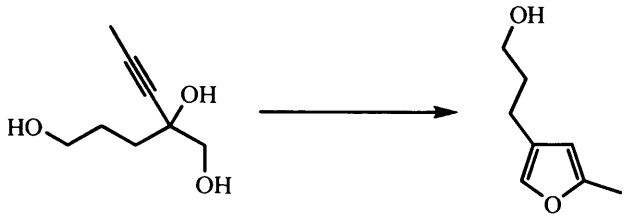
organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 9:1) to yield *ketone* **526** (1.16 g, 55%) as a colourless liquid; ν_{max} 2955, 2930, 2858, 1720, 1472, 1255, 1107, 838, 777; δ_H 4.17 (2H, s, C(O)C$\underline{H}_2$O), 3.62 (2H, t, *J* 6.1, OC$\underline{H}_2$CH$_2$), 2.59 (2H, t, *J* 7.3, CH$_2$C$\underline{H}_2$C(O)), 1.82–1.76 (2H, m, CH$_2$C$\underline{H}_2$CH$_2$), 0.92 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.88 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.08 (6H, s, Si(C$\underline{H}_3$)$_2$), 0.03 (6H, s, Si(C$\underline{H}_3$)$_2$); δ_C 211.1 (C), 69.3 (CH$_2$), 62.1 (CH$_2$), 34.8 (CH$_2$), 26.2 (CH$_2$), 25.9 (CH$_3$), 25.8 (CH$_3$), 18.3 (C), –5.4 (CH$_3$), –5.5 (CH$_3$) (only 10 peaks visible); LRMS (APCI) m/z 347.24 ([M+H]$^+$, 86%), 100.08 (100%); HRMS (APCI) calculated for $C_{17}H_{39}O_3Si_2$ [M+H]$^+$ 347.2438, found 347.2436.

(2*RS*)-1,5-Bis-(*tert*-butyldimethylsilyloxy)-2-(prop-1-ynyl)pentan-2-ol 527



A solution of commercial 1-propynylmagnesium bromide **232** in tetrahydrofuran (6.0 ml, 0.5 M, 3.0 mmol) was added dropwise to a stirred solution of ketone **526** (0.69 g, 2.0 mmol) and $CeCl_3$ (0.5 g, 2.0 mmol) in tetrahydrofuran (20 ml) under nitrogen at –78 °C and left to stir for 30 min. The mixture was allowed to warm to r.t. and left to stir for 16 h. The reaction was quenched with aqueous ammonium chloride (10 ml), concentrated *in vacuo*, and the residue dissolved in ethyl acetate (50 ml) and washed with water (3 x 10 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 9:1) to yield *alkyne* **527** (0.24 g, 32%) as a colourless liquid; ν_{max} 3416, 2955, 2929, 2858, 2251, 1472, 1255, 1100, 837, 777; δ_H 3.68–3.65 (2H, m, OC$\underline{H}_2$CH$_2$), 3.63 (1H, d, *J* 9.5, CC$\underline{H}_2$O), 3.54 (1H, d, *J* 9.5, CC$\underline{H}_2$O), 3.19 (1H, s, O$\underline{H}$), 1.84–1.65 (4H, m, OCH$_2$C$\underline{H}_2$C$\underline{H}_2$C), 1.82 (3H, s, C≡CC$\underline{H}_3$), 0.91 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.90 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.09 (3H, s, Si(C$\underline{H}_3$)$_2$), 0.08 (3H, s, Si(C$\underline{H}_3$)$_2$), 0.06 (3H, s, Si(C$\underline{H}_3$)$_2$), 0.06 (3H, s, Si(C$\underline{H}_3$)$_2$); δ_C 80.5 (C), 80.5 (C), 71.1 (C), 70.1 (CH$_2$), 63.5 (CH$_2$), 35.1 (CH$_2$), 27.8 (CH$_2$), 26.0 (CH$_3$), 25.9 (CH$_3$), 18.4 (C), 3.5 (CH$_3$), –5.3 (CH$_3$), –5.4 (CH$_3$) (only 13 peaks visible); LRMS (APCI) m/z 387.27 ([M+H]$^+$, 17%), 369.26 ([M–OH]$^+$, 100%); HRMS (APCI) calculated for $C_{20}H_{43}O_3Si_2$ [M+H]$^+$ 387.2751, found 387.2736.

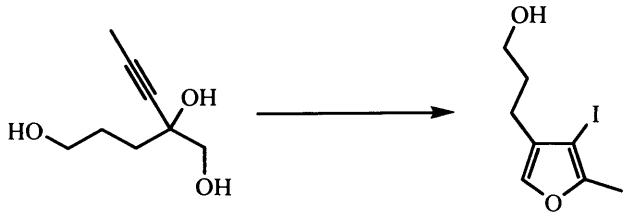
5-Methylfuran-3-propan-1-ol 528



516 **528**

Silver nitrate on silica gel (0.02 g, ~10 wt. %, 0.01 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **516** (0.02 g, 0.12 mmol) in dichloromethane (2 ml) at r.t. under subdued light and left to stir for 2 h. The mixture was filtered through a pad of silica gel with dichloromethane and the filtrate dried, filtered and evaporated to yield *furan* **518** (0.01 g, 71%) as a colourless liquid; δ_H 7.07 (1H, s, α-furan-H), 5.87 (1H, s, β-furan-H), 3.67 (2H, t, *J* 6.4, CH_2CH_2OH), 2.45 (2H, t, *J* 7.5, furan-CH_2CH_2), 2.25 (3H, s, CH_3), 1.82–1.77 (2H, m, $CH_2CH_2CH_2$); δ_C 152.4 (C), 136.9 (CH), 125.3 (C), 107.0 (CH), 62.4 (CH_2), 32.7 (CH_2), 21.2 (CH_2), 13.5 (CH_3); LRMS m/z 140.08 ($[M]^+$, 6%), 85.94 (100%); HRMS calculated for $C_8H_{12}O_2$ $[M]^+$ 140.0837, found 140.0838.

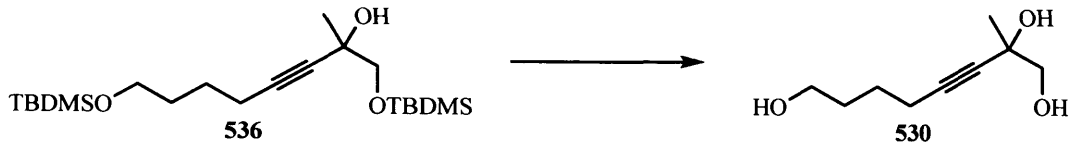
4-Iodo-5-methylfuran-3-propan-1-ol 529



516 **529**

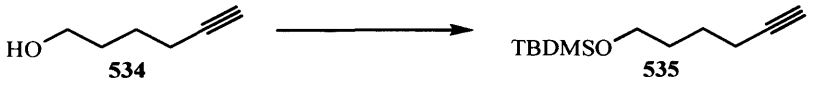
Iodine (0.38 g, 1.5 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **516** (0.08 g, 0.5 mmol) and $NaHCO_3$ (0.12 g, 1.5 mmol) in dichloromethane (10 ml) at r.t. and left to stir for 3 h. The mixture was washed with aqueous sodium sulfite (3 x 5 ml) and the organic fraction was dried, filtered and evaporated to yield *furan* **529** (0.004 g, 4%) as a brown liquid; δ_H 7.12 (1H, s, furan-H), 3.65 (2H, t, *J* 6.4, CH_2CH_2OH), 2.36 (2H, t, *J* 8.6, furanCH_2CH_2), 2.15 (3H, s, CH_3), 1.92–1.88 (2H, m, $CH_2CH_2CH_2$); δ_C 153.0 (C), 137.3 (CH), 127.2 (C), 68.7 (C), 53.4 (CH_2), 31.7 (CH_2), 22.4 (CH_2), 13.5 (CH_3).

(2*RS*)-2-Methyloct-3-yne-1,2,8-triol 530



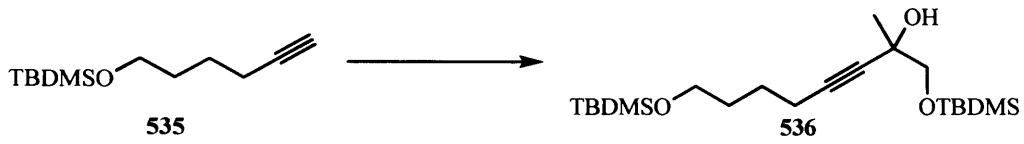
A solution of tetrabutylammonium fluoride in tetrahydrofuran (2.5 ml, 1 M, 2.5 mmol) was added dropwise to a stirred solution of alcohol **536** (0.46 g, 1.2 mmol) in tetrahydrofuran (30 ml) at r.t. and allowed to stir for 16 h. The mixture was concentrated *in vacuo* and the product purified by column chromatography (ethyl acetate/methanol, 9:1) to yield *3-alkyne-1,2-diol* **530** (0.15 g, 74%) as a colourless oil; ν_{max} 3375, 2938, 2870, 2244, 1726, 1375, 1254, 1053, 735; δ_H 3.70 (1H, bs, O<u>H</u>), 3.66 (2H, t, *J* 6.3, HOC<u>H</u>$_2$CH$_2$), 3.59 (1H, d, *J* 10.9, CC<u>H</u>$_2$OH), 3.45 (1H, d, *J* 11.0, CC<u>H</u>$_2$OH), 3.35 (1H, bs, O<u>H</u>), 2.83 (1H, bs, O<u>H</u>), 2.24 (2H, t, *J* 6.7, CH$_2$C<u>H</u>$_2$C), 1.69–1.62 (2H, m, HOCH$_2$CH$_2$C<u>H</u>$_2$), 1.62–1.55 (2H, m, CH$_2$C<u>H</u>$_2$CH$_2$C), 1.40 (3H, s, C<u>H</u>$_3$); δ_C 84.6 (C), 82.4 (C), 70.8 (CH$_2$), 68.5 (C), 62.0 (CH$_2$), 31.5 (CH$_2$), 25.6 (CH$_3$), 24.7 (CH$_2$), 18.4 (CH$_2$); LRMS m/z 154.10 ([M]$^+$, 27%), 79.05 (100%); HRMS calculated for $C_9H_{14}O_2$ [M–H$_2$O]$^+$ 154.0994, found 154.0989.

1-(*tert*-Butyldimethylsilyloxy)hex-5-yne 535[241]



tert-Butyldimethylsilyl chloride (0.84 g, 5.6 mmol) was added to a stirred solution of 5-hexyn-1-ol **534** (0.5 g, 5.1 mmol) and imidazole (0.42 g, 6.1 mmol) in dichloromethane (20 ml) at r.t. and left to stir for 16 h. The mixture was diluted with dichloromethane (20 ml) and washed with aqueous ammonium chloride (3 x 20 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 49:1) to yield *alkyne* **535** (0.80 g, 74%) as a colourless liquid; ν_{max} 3314, 2930, 2858, 2119, 1255, 1108 836; δ_H 3.63 (2H, t, *J* 6.0, OC<u>H</u>$_2$CH$_2$), 2.21 (2H, td, *J* 6.9, 2.6, CH$_2$C<u>H</u>$_2$C), 1.94 (1H, t, *J* 2.6, C≡C<u>H</u>), 1.66–1.55 (4H, m, CH$_2$C<u>H</u>$_2$C<u>H</u>$_2$CH$_2$), 0.89 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.05 (6H, s, Si(C<u>H</u>$_3$)$_2$); δ_C 84.5 (C), 68.2 (CH), 62.6 (CH$_2$), 31.8 (CH$_2$), 26.0 (CH$_3$), 25.0 (CH$_2$), 18.3 (C), 18.2 (CH$_2$), –5.3 (CH$_3$).

(2*RS*)-1,8-Bis-(*tert*-butyldimethylsilyloxy)-2-methyloct-3-yn-2-ol 536



A solution of butyllithium in hexanes (1.0 ml, 2.5 M, 2.4 mmol) was added dropwise to a solution of alkyne **535** (0.46 g, 2.2 mmol) and $CeCl_3$ (0.88 g, 2.4 mmol) in tetrahydrofuran (10 ml) under nitrogen at 0 °C and stirred for 1 hour before being cooled to –78 °C. A solution of ketone **294** (0.45 g, 2.4 mmol) in tetrahydrofuran (10 ml) was added and the mixture stirred for 30 min. before being allowed to warm to r.t. and left to stir for a further 2 h. The mixture was quenched with aqueous ammonium chloride (10 ml), concentrated *in vacuo*, and the residue dissolved in ethyl acetate (50 ml) and washed with water (3 x 10 ml). The organic fraction was dried, filtered and evaporated and the product purified by column chromatography (petrol/ethyl acetate, 9:1) to yield *alcohol* **536** (0.48 g, 55%) as a colourless liquid; ν_{max} 3452, 2929, 2858, 2243, 1719, 1472, 1255, 1106, 838, 776; δ_H 3.62 (1H, d, *J* 9.5, $OC\underline{H}_2CH_2$), 3.61 (2H, t, *J* 6.1, $CC\underline{H}_2O$), 3.48 (1H, d, *J* 9.5, $OC\underline{H}_2CH_2$), 2.80 (1H, s, O<u>H</u>), 2.21 (2H, t, *J* 6.9, $CH_2C\underline{H}_2C$), 1.63–1.51 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 1.39 (3H, s, $CC\underline{H}_3$), 0.92 (9H, s, $SiC(C\underline{H}_3)_3$), 0.89 (9H, s, $SiC(C\underline{H}_3)_3$), 0.09 (3H, s, $Si(C\underline{H}_3)_2$), 0.09 (3H, s, $Si(C\underline{H}_3)_2$) 0.04 (6H, s, $Si(C\underline{H}_3)_2$); δ_C 83.6 (C), 82.5 (C), 71.2 (CH_2), 68.0 (C), 62.7 (CH_2), 32.0 (CH_2), 26.0 (CH_3), 25.8 (CH_3), 25.8 (CH_3), 25.1 (CH_2), 18.5 (CH_2), 18.4 (C), 18.3 (C), –5.3 (CH_3), –5.3 (CH_3), –5.4 (CH_3); LRMS 383.28 $[M+H]^+$ 100%; HRMS (APCI) calculated for $C_{21}H_{43}O_2Si_2$ $[M+H]^+$ 383.2802, found 383.2784.

4-Methylfuran-2-butan-1-ol 537[97]

Silver nitrate on silica gel (0.03 g, ~10 wt. %, 0.02 mmol) was added to a stirred solution of 3-alkyne-1,2-diol **530** (0.03 g, 0.17 mmol) in dichloromethane (5 ml) at r.t. under subdued light and left to stir for 50 min. The mixture was filtered through a pad of silica gel with ethyl acetate and the filtrate dried, filtered and evaporated to yield *furan* **537** (0.02 g, 74%) as a colourless liquid; ν_{max} 3366, 2939, 1743, 1618, 1551, 1456, 1341, 1117, 1067; δ_H 7.05 (1H, s, α-furan-<u>H</u>),

5.86 (1H, s, β-furan-H), 3.66 (2H, t, *J* 6.3, CH_2CH_2OH), 2.60 (2H, t, *J* 7.3, furan-CH_2CH_2), 1.98 (3H, s, furan-CH_3), 1.73–1.67 (2H, m, $CH_2CH_2CH_2OH$), 1.64–1.59 (2H, m, furan-$CH_2CH_2CH_2$); δ_C 156.0 (C), 137.3 (CH), 120.4 (C), 107.7 (CH), 62.7 (CH_2), 32.2 (CH_2), 27.7 (CH_2), 24.2 (CH_2), 9.8 (CH_3); LRMS m/z 154.10 ($[M]^+$, 27%), 95.05 (100%); HRMS calculated for $C_9H_{14}O_2$ $[M]^+$ 154.0994, found 154.0989.

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