Studies Towards the Total Synthesis of Colchicine

A Thesis Presented by

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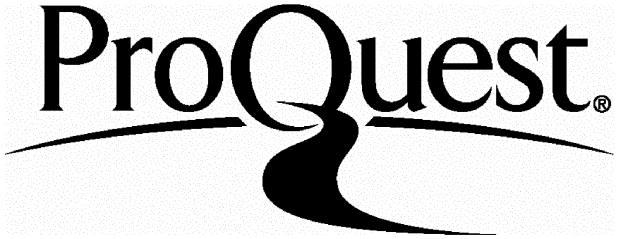

This thesis is

dedicated to my wife, Grace

and

written in memory of my father-in-law, Mr. P. Au,
who passed away during the preparation of this work.

Abstract

This thesis is divided into three chapters.

In the first chapter, brief accounts of the occurrence, isolation and structural determination, biological properties and biogenesis of colchicine are presented. Moreover, since one of the key structural features of colchicine is the tropolonyl ring C, significant preparative methods for tropones and tropolones are briefly reviewed. The general drawbacks of the previous syntheses of colchicine itself due to the tautomeric nature of the tropolonyl ring C are discussed and the key steps of each of the previous syntheses are also highlighted.

In the second chapter, the general strategies of the total synthesis of (-)-colchicine employed in this project are discussed and two synthetic approaches are then described. The first approach, to which most of the work was directed, involves the cycloaromatisation of a 12-membered macrocycle containing an enediyne moiety *via* a Bergman cyclisation. The efforts made towards the synthesis of this macrocycle are divided into two areas, namely the investigations into the generation of the stereocentre and the construction of the macrocyclic framework. Although an advanced acyclic precursor for ring closure containing all of the requisite functionality was prepared, initial cyclisation studies were unsuccessful. The second approach involves a transition metal-mediated [2+2+2] cycloaddition of a tethered diyne and an appropriate cyclopropenone derivative. The synthesis of the diyne precursor and model studies of the [2+2+2] cycloaddition protocol are described.

The third chapter provides a formal description of experimental results and procedures.

Contents

Acknowledgements

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Above all, I must thank affectionately Mum and Lil, who have shaped my life with great care and love, and Grace, with whom I delightfully share it.

Abbreviations and Denotations

Δ	Heat
hν	Irradiation
Ac	Acetyl
Ar	Aryl
Aq	Aqueous
Bn	Benzyl
Bu	Butyl
Bz	Benzoyl
c	concentration
CI	Chemical ionisation
^{13}C NMR	Carbon-13 Nuclear Magnetic Resonance
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisobutylaluminium Hydride
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
Et	Ethyl
EI	Electron ionisation
Eq	Equivalent
FAB	Fast Atom Bombardment
HMDS	1,1,1,3,3,3-Hexamethyldisilazane
^{1}H NMR	Proton Nuclear Magnetic Resonance
HPLC	High Performance Liquid Chromatography
i	iso
KHMDS	Potassium Bis(trimethylsilyl)amide
L	Ligand
LDA	Lithium Diisopropylamide
LG	Leaving Group
LiHMDS	Lithium Bis(trimethylsilyl)amide
m	multiplet
m	meta
Me	Methyl

Ms, Mesyl	Methanesulfonyl
n	normal
NaHMDS	Sodium Bis(trimethylsilyl)amide
P	Protecting group
p	para
Pr	Propyl
Ph	Phenyl
Pyr	Pyridine
q	quartet
r.t.	room temperature
s	singlet
s, sec	secondary
t	triplet
t, tert	tertiary
TBDMS	*t*-Butyldimethylsilyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
T.L.C.	Thin Layer Chromatography
TMS	Trimethylsilyl
Tf	2,2,2-Trifluoromethansulfonyl
Ts, Tosyl	*p*-Toluenesulfonyl

This arrow indicates an occurred reaction

This arrow indicates a failed or envisaged reaction


This arrow indicates a retrosynthetic operation


These two bonds indicate the relative stereochemistry of atoms


Theses two bonds indicate the absolute stereochemistry of atoms

CHAPTER ONE : INTRODUCTION

1.1. Occurrence, Isolation and Structural Determination

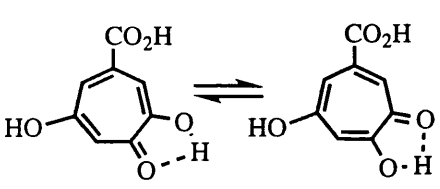
Judging from the number of relevant publications, colchicine can be described, without doubt, as one of the most interesting alkaloids existing in nature. Since its isolation by Pelletier and Caventou in 1820[1], a constant stream of research related to colchicine has been reported in hundreds of publications, which have been duly reviewed[2] on several occasions. This alkaloid is the toxic principle of *Colchicum autumnale* while it and its analogues also exist in a number of other *Colchicum* plants. The colchicinic alkaloids usually give a positive ferric chloride test after acid hydrolysis, indicating the presence of phenolic or tropolonic moieties. Moreover, colchicine was found in some other genera belonging to the liliaceae family, namely *Merendera, Androcymbium, Gloriosa* and *Littoria*.[2(c),(d)]

Colchicum autumnale is a perennial meadow saffron which can be found over an extensive geographical area encompassing England, southern Europe and northern Africa. Colchicine can be extracted from all parts of the plant, with the highest concentration being in the flowers. However, due to the greater gross weight, the greatest amount of colchicine is found in the corms[2(a),(b)]. The content of colchicine is season-dependent and the highest percentage with respect to dry weight of the plant occurs when fruiting begins in Spring.

After Pelletier and Caventou[1] had isolated an amorphous toxic principle from the alcoholic extracts of *C. autumnale,* Geiger[2(a)] named a crystalline solid he obtained from a similar extraction 'colchicine'. However, in 1857 Oberlin[2(a)] found that the crystalline solid Geiger obtained was actually the hydrolysed product of the amorphous toxic principle. Therefore, he renamed the crystalline substance colchiceine and the initial amorphous material colchicine. More than 60 years later, in 1915, Clewer, Green and Tutin managed to acquire solvent-free, crystalline colchicine as pale yellow

needles.

Elemental analysis indicated a formula of $C_{22}H_{24}O_6N$ for colchicine. After a series of investigations, the alkaloid was found to be a tricyclic compound containing a trimethoxybenzenoid ring A and a seven-membered ring B. Furthermore, although the aromatic nature of tropones was unknown at the time, Dewar correctly suggested a tautomeric structure for stipitatic acid (**1**)[3] possessing an aromatic tropolonic ring and thus opened the investigations into a new class of aromatic compounds. He then



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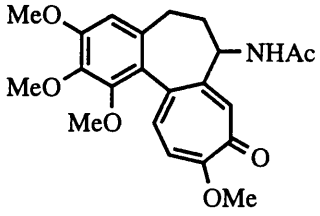
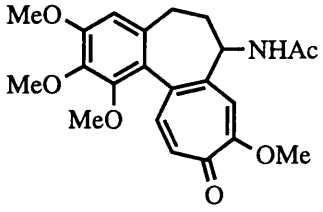
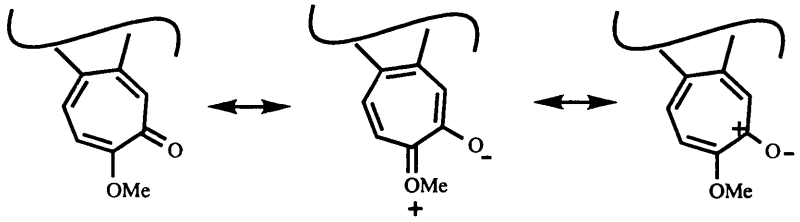


2a

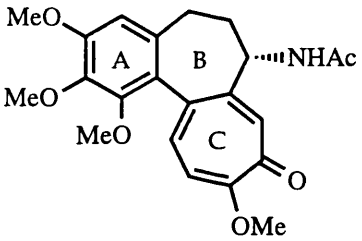


2b

proposed two isomeric structures, (**2a**) and (**2b**), containing tropolonic rings C for colchicine [4]. He also suggested that the high solubility of colchicine was due to an ionic resonance of the tropolonic ring, as shown in Scheme 1.



Scheme 1



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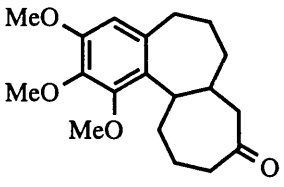

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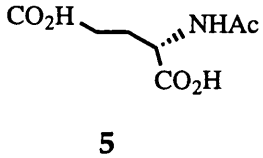

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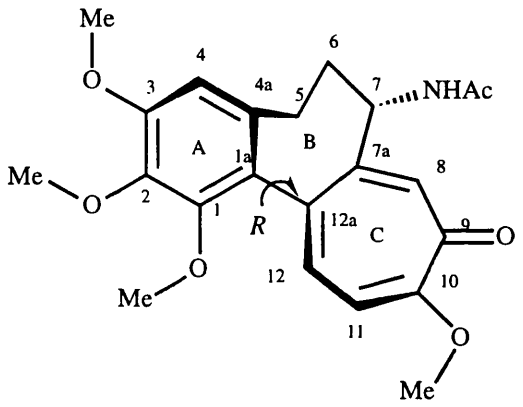
It was later proven by both chemical deduction and by X-ray diffraction that natural colchicine (**3**) is indeed the α–isomer of (**2a**). The relative positions of the carbonyl and methoxy groups of ring C were confirmed by Loewenthal[5] by an unambiguous synthesis of (**4**), a reductive degradation product of colchicine[6].

Moreover, the configuration of the chiral centre was identified by Corrodi and Hardegger[7] when they obtained *N*-acetyl-L-glutamic acid (**5**) by drastic oxidation of colchicine. The first X-ray crystallography of colchicine was reported by King *et al*[8] in 1952. A more detailed study of a crystalline dihydrate was undertaken by Margulis and Lessinger[9] in 1978, and revealed that colchicine exists as two similar conformers in this hydrated form. The carbon-carbon bonds of the tropolonyl ring C were found to be localised in alternate short and long lengths and the ring itself is not planar, indicating a limited degree of aromatisation. While ring B is boat-shaped, ring C has a dihedral angle of 51° (or 53° in the other conformer) with the planar benzenoid ring A. This leads to a skewed structure (Scheme 2) of the biaryl unit with *R* chirality.



Scheme 2

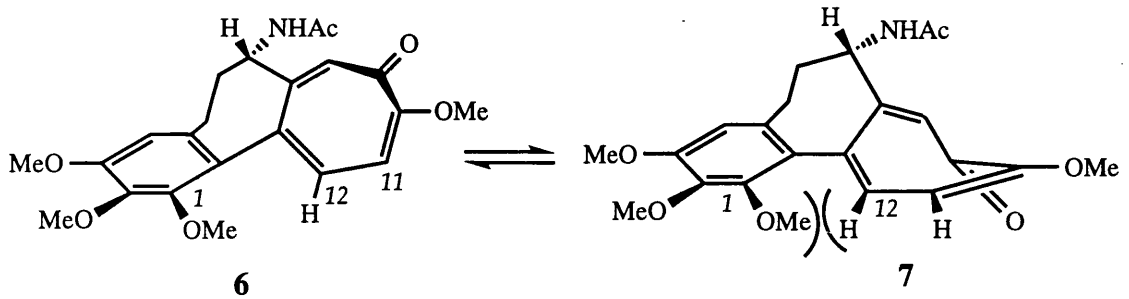
1.2. Biological Properties

Seeds of *Colchicum* plants are believed to have been used medicinally by ancient Egyptians due to the abundance of the plants in northern Africa and the ancient Egyptians' vast knowledge of herbal medicine[2(b)]. In the first century, the botanist-physician Dioscorides made careful observations on *Colchicon* (*Colchicum autumnale*) and recorded it in his classical work *De Materia Medica* as a dangerous poison. As time went by, various sources mentioned a herb called *hermodactyl* to relieve the pain caused by gout. In 1788, after a long period of confusion and investigation, *hermodactyl* was eventually identified as the plant studied by Dioscorides, that is, *C. autumnale*. Its use in treating gout had since then been advocated by many physicians and pharmacists.

Despite its medicinal capacity, colchicine is extremely poisonous. It is so potent that, according to one report[2(a)], the lethal dosage to a human adult is only 3 milligrams. It attacks the central nervous systems of mammals and causes death in 3 to 6 hours by vasomotor paralysis. The relatively slow action of the drug is probably due to its slow absorption into the target organs.

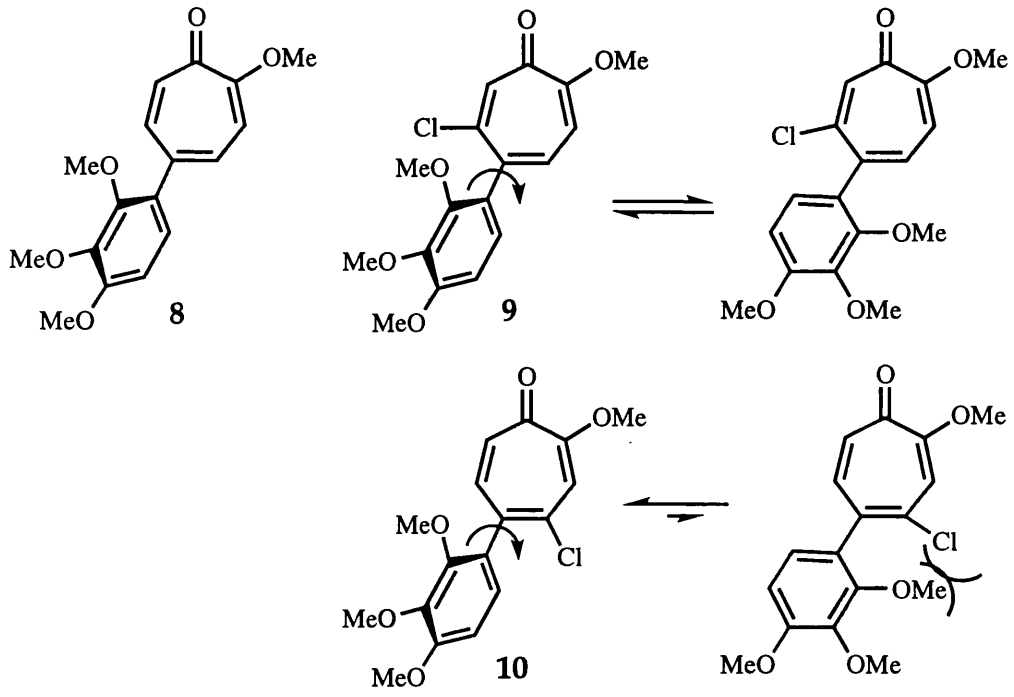
In 1930's, Dustin[2(a),(b)] discovered that an amazingly high proportion of cells was arrested at the metaphase of mitosis when tissues were treated with colchicine and thus this alkaloid was found to be a 'mitotic poison' which brings mitosis to a sudden halt at the metaphase. Further investigations[10] showed that colchicine depolymerises microtubules[10a] by binding stoichiometrically to tubulin, the dimeric subunit of microtubules, in a non-covalent manner. Because of the effect of colchicine on microtubules, the alkaloid also affects other cellular functions that are related to microtubules, such as intracellular transport of vesicles or ameboid movements. Polymorphonuclear leukocytes ('white blood cells') have been observed to be 'demobilised' by a colchicine-induced dissolution of microtubules. As these leukocytes are involved in the inflammatory process, this action may be related to the antigout effect of colchicine.

Interestingly, an increase in π-conjugation was observed in colchicine by ultraviolet spectroscopy when it binds to tubulin[11]. It is postulated that the binding provides the energy for the change from the skewed structure (**6**) in the isolated ground state to a 'flatter' conformation (**7**) of higher energy (Scheme 3). The conformer (**7**) has enhanced conjugation compared with (**6**) because the dihedral angle between the



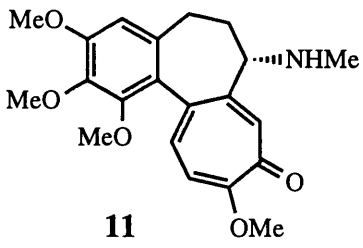
Scheme 3

benzenoid ring A and the tropolonyl ring C has decreased from 51° to around 19°. However, a penalty is paid in energy terms since ring C of (**7**) becomes boat-shaped and steric repulsion between the C-1 methoxy group and the C-12 proton becomes stronger. Banwell *et al*[13] have reported that the 6-chloro-5-aryltroponoid (**9**) showed comparable biological activities to the interesting 5-aryltroponoid (**8**)[13], while the 4-chloro-isomer (**10**) was much less active. A possible reason may lie in the fact that the 4-chloro-isomer (**10**) was unable to twist in the indicated sense (Scheme 4) and thus flatten due to the increased steric hindrance between the chlorine atom and one of the benzenoid methoxyl groups. There is of course no such problem in the case of (**9**). Thus the conformational change and the atropisomerism around the benzene-tropolone axis of colchicine may play an important role in the binding to tubulin.



Scheme 4

The interesting biological properties of colchicine have led to an investigation of its use as an antitumor agent. The primary trial results revealed that colchicine did show antitumor properties on animals when used in concentrations close to the toxic dosage. Nevertheless, its high general toxicity has precluded it and its close analogues from clinical use[2(f),(g),(h)]. However, further studies have been made on less toxic analogues such as *N*-deacetyl-*N*-methylcolchicine (**11**).



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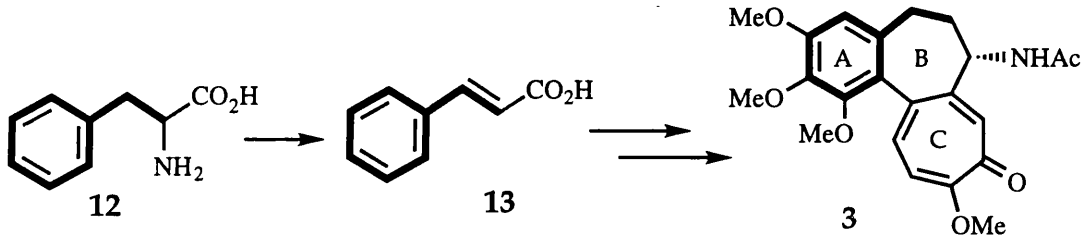
Moreover, colchicine has also been used extensively in agriculture[2(b),14] for inducing polyploidy in crops like oat, barley and wheat, as well as other functions.

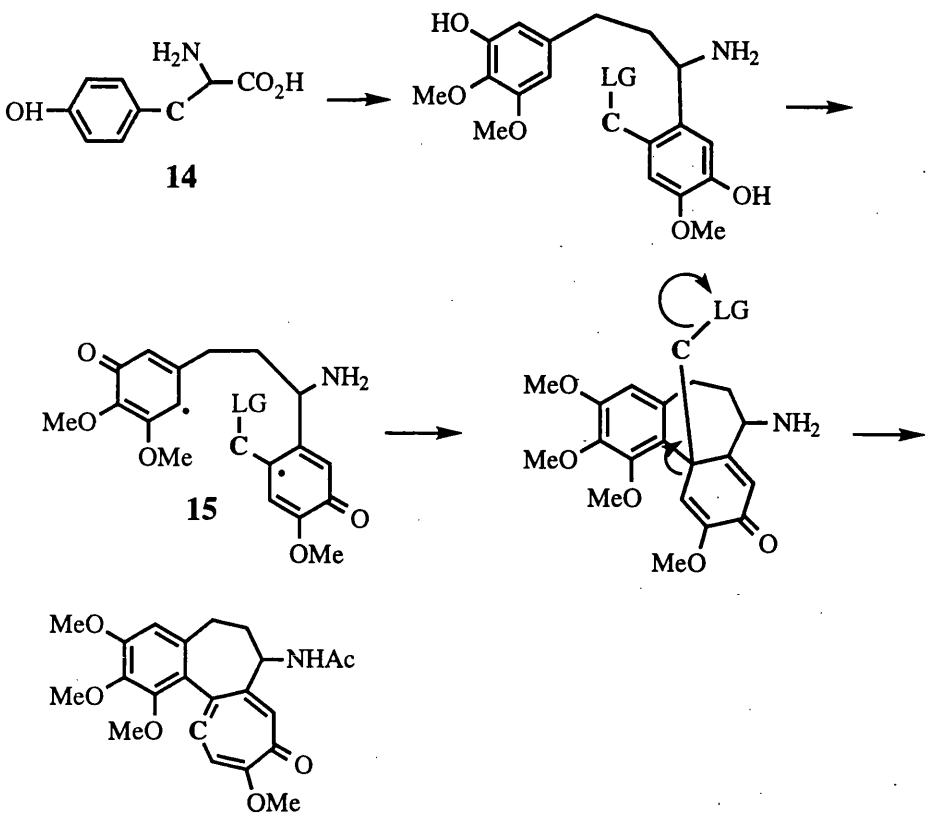
1.3. Biogenesis

The biosynthesis[15] of colchicine in nature has been studied in detail by the groups of Battersby[16] and Leete[17] respectively. The benzenoid ring A was shown by a series of feeding and degradation experiments to be derived from cinnamic acid (**13**) and hence from phenylalanine (**12**) (Scheme 5). Following a suggestion by Robinson

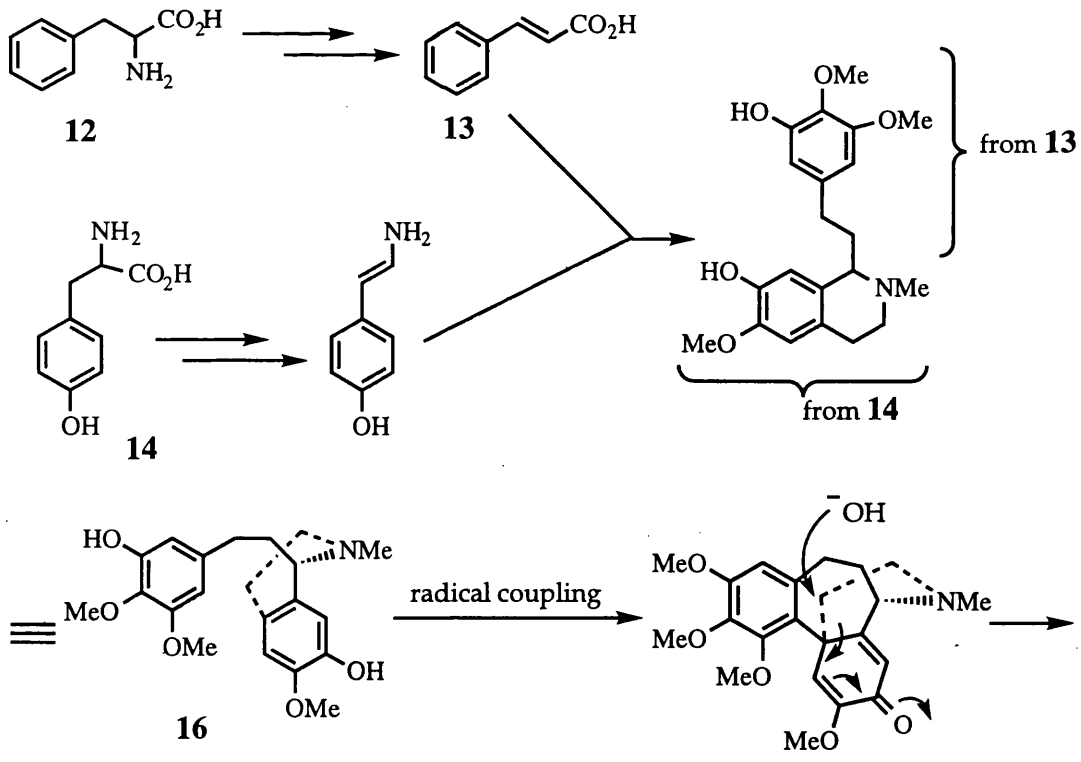


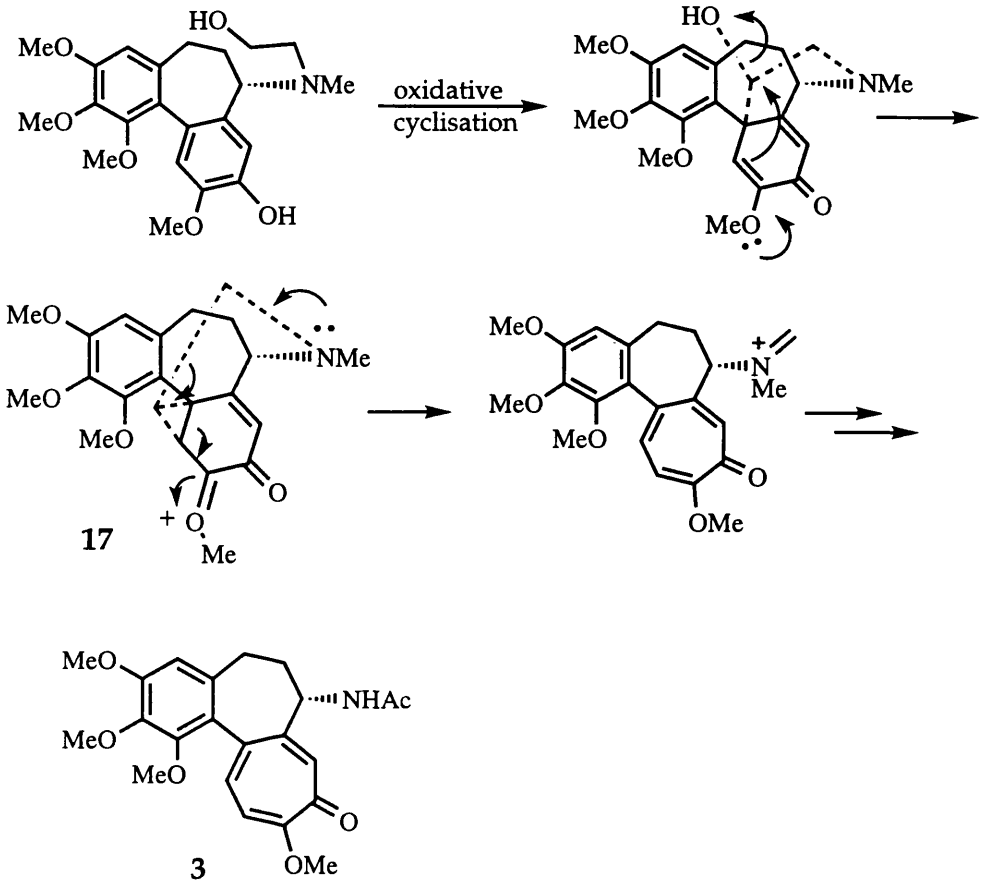
Scheme 5

and Anet[18] that the synthesis of tropones in nature might be related to those required in phenols and flavones, both groups fed labelled tyrosine (**14**) to *Colchicum* plants (Scheme 5a) and found that radioactivity was exclusively confined at the C-12 position of colchicine, thereby indicating that the tropolonyl ring C originated from phenolic tyrosine. Hence intramolecular coupling of a diradical such as (**15**) followed by a ring expansion as indicated in Scheme 5a was proposed as a mechanism for formation of the tricyclic framework. Battersby further elegantly demonstrated that autumnaline (**16**), another natural product, is an intermediate in the biogenesis of colchicine (Scheme 6). It was then proposed that ring C might be formed *via* ring expansion of an intermediate cyclopropane derivative (**17**).



Scheme 5a




HO
MeO
MeO
MeO
MeO
OH
NMe
oxidative
cyclisation
HO
MeO
MeO
MeO
MeO
NMe
O
MeO
MeO
MeO
NMe
O
+ O
Me
17
MeO
MeO
MeO
+
N
Me
O
OMe

MeO
MeO
MeO
NHAc
O
OMe
3

Scheme 6

1.4. Preparation of Tropones and Tropolones

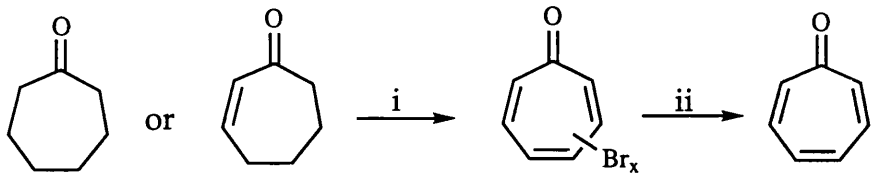
In addition to its interesting biological properties, colchicine has also proven to be a jewel in the crown of synthetic organic chemistry. This is appropriately reflected by the number of total or formal total syntheses[19] and related approaches to colchicine which have been reported over the last three decades. Although the structure of colchicine, containing only a single stereocentre, is relatively simple by the standards of modern synthetic organic chemistry, it remains as an ongoing challenge to the organic chemist. A major reason is the paucity of general, easily accessible methodologies for construction of the tropolonyl ring C in a regiocontrolled manner. As the chemistry of tropones and tropolones has been reviewed[20], only a brief account of the more significant methods to prepare tropones and tropolones are included in this introduction.

1.4.1. Preparation of Simple Tropone Derivatives

Available synthetic routes of tropones can in essence be divided into three district categories of reactions, namely (A) oxidation of preformed seven-membered ring systems, (B) [4+3] cycloaddition or annulation reactions of the [4+3] type, and (C) ring expansion reactions of suitably constituted six-membered ring precursors.

(A). Oxidation of Preformed Seven-membered Ring Systems

(i) One of the earliest preparative methods of tropones, which is still widely used, involves the bromination of cycloheptanone or cycloheptenone derivatives to yield a mixture of bromotropones[21] (Scheme 7). The bromine atoms can then be removed by hydrogenolysis using poisoned palladium catalyst.

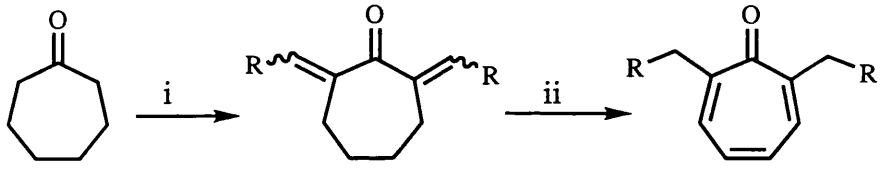


x=1-3

i. Br_2, AcOH, ii. H_2, Pd-C, $CaSO_4$ etc.

Scheme 7

(ii) Cycloheptanone derivatives undergo aldol condensation[22] or Mannich reaction to form the symmetrical ketone (**18**), which can then be rearranged and dehydrogenated using palladium on carbon to afford 2,7-disubstituted tropones (**19**) (Scheme 8).

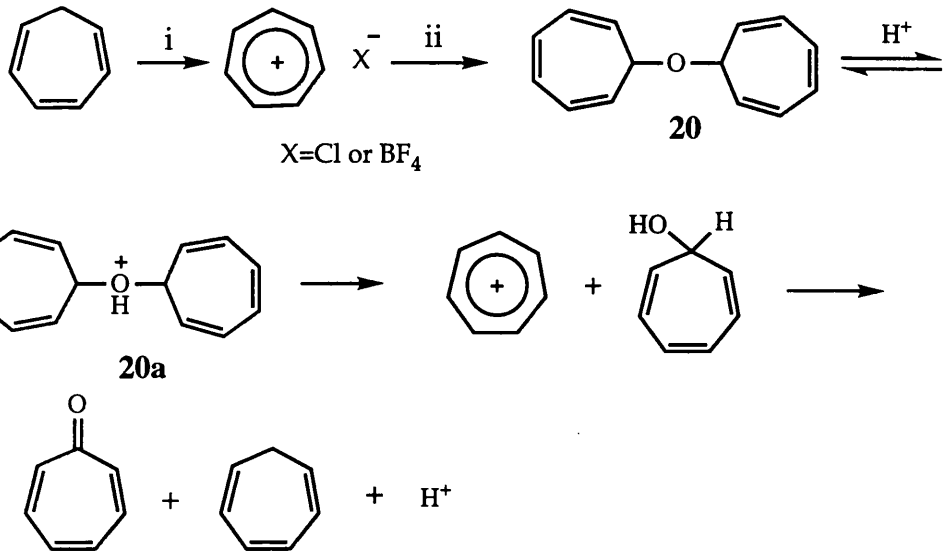


18 **19**

i. RCHO, H^+ or R'_2NH, ii. Pd-C

Scheme 8

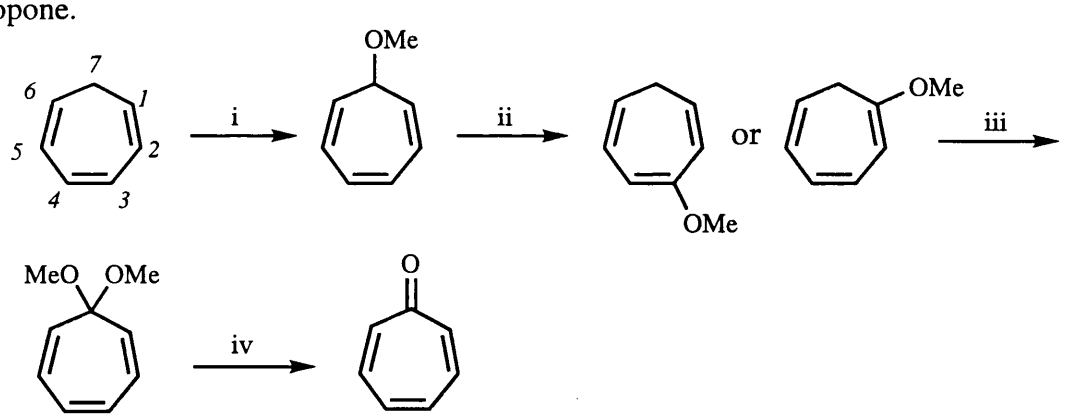
(iii) While cycloheptatriene can be oxidised directly to tropone with either selenium dioxide[23] or chromium trioxide[24], it is converted to aromatic tropylium ion upon treatment with phosphorus pentachloride or triphenylcarbenium tetrafluoroborate. Tropylium ion reacts with alkali[25] to form ditropyl ether (**20**), which can provide tropone and cycloheptatriene *via* the disproportionation of the oxonium ion (**20a**) (Scheme 9). The same products were also obtained when tropylium ion was treated with dimethylsulfoxide or sodium carbonate[26], although the mechanism is not clear.



i. PCl_5 or Ph_3CBF_4, ii. NaOH

Scheme 9

(iv) Shono *et al*[27] found that cycloheptatriene was converted to 7-methoxycyclo-heptatriene by anodic oxidation in methanol with suitable supporting electrolytes (Scheme 10). Thermal isomerisation of this product *via* a series of sigmatropic rearrangements to 3- or 1-methoxycycloheptatriene followed by further anodic oxidation gave 7,7-dimethoxycycloheptatriene, which could then be hydrolysed to tropone.



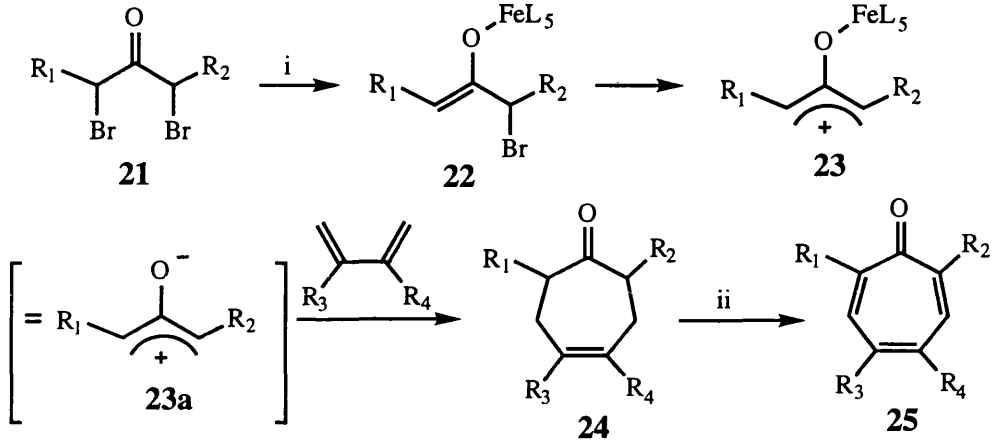
i. -e⁻, Et_4NOTs/NaOMe, MeOH, ii. heat, iii. -e⁻, iv. H^+

Scheme 10

(B). [4+3] Cycloaddition and Related Annulation Reactions

(i) As a result of an elegant investigation undertaken by Noyori *et al*[28], α,α'-dibromoketones (**21**) were found to be converted to the iron enolate (**22**) upon treatment

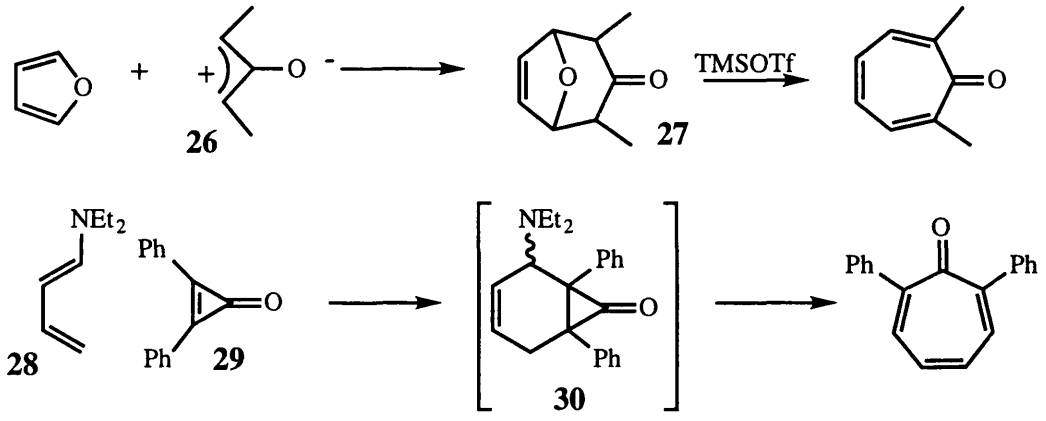
of diiron nonacarbonyl (Scheme 11). This enolate transforms to the cationic species (**23**), which is formally equivalent to the dipole (**23a**), and then undergoes a formal π4s + π2s cycloaddition with 1,3-dienes leading to the observed [4+3] cycloadduct (**24**). The cycloadduct was then converted to tropone (**25**) in good yields by a bromination-dehydrobromination sequence using lithium chloride in DMF as a dehydrohalogenating agent.



i. $Fe_2(CO)_9$, ii. NBS etc.; LiCl/DMF

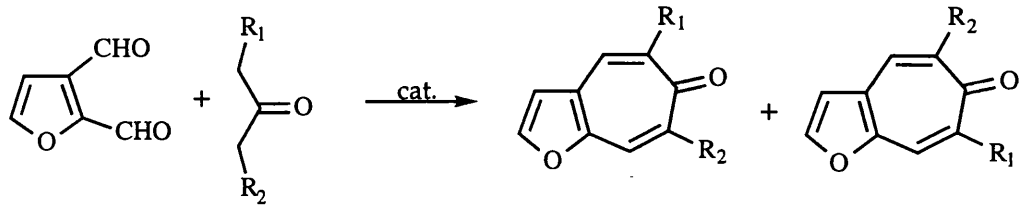
Scheme 11

A variant[29] of this method provided the bicyclic ketone (**27**) from the reaction between the dipole (**26**) and pyrrole (Scheme 12). Treatment of the ketone (**27**) with Lewis acid formed 2,7-dimethyltropone. It was also found that diphenylcyclopropenone (**29**) underwent [4+2] cycloaddition with diene (**28**) to form 2,7-diphenyltropone *via* a bicyclic intermediate (**30**), which lost diethylamine to afford the tropone[30].

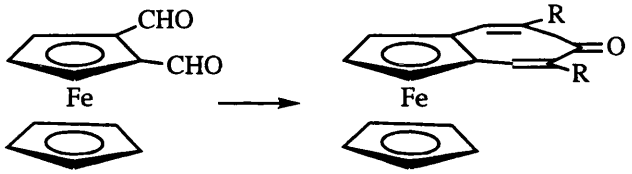


Scheme 12

(ii) Aldol-type cyclisation[20(b)] between appropriate dialdehyde and ketone would give isomeric tropones (Scheme 13) and this method has been extended to ferrocene derivatives[31] (Scheme 14). However, due to the lack of regiocontrol in the formation of the products, this method is limited to the use of symmetrical ketones.



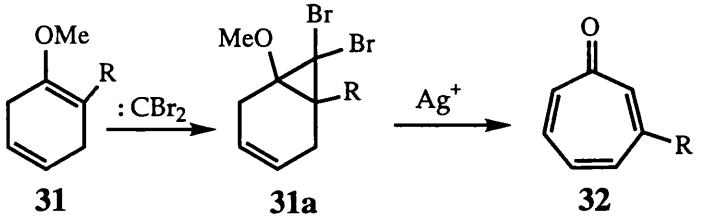
Scheme 13

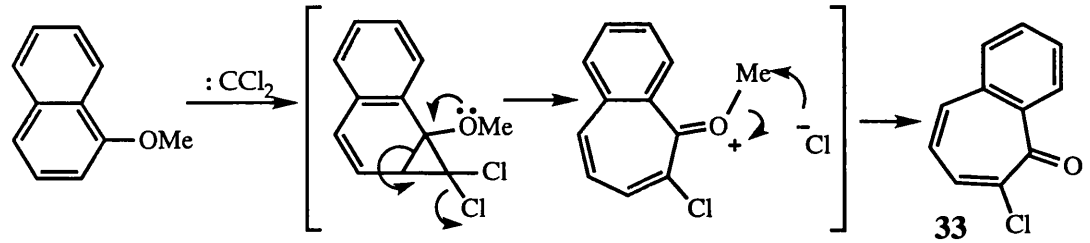


Scheme 14

(C). Ring Expansion *via* Cyclopropane Derivatives

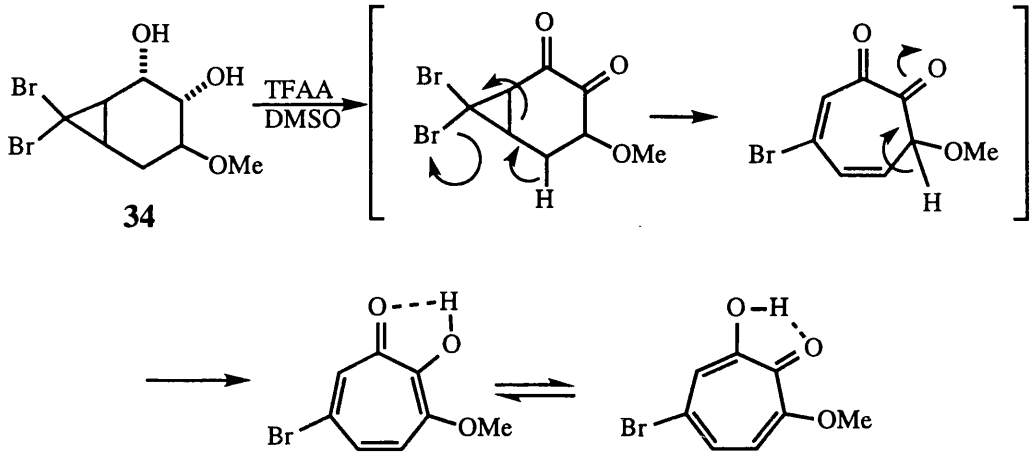
(i) Ring opening of the *gem* dihalocyclopropane (**31a**) obtained from a carbene addition to the Birch reduction product (**31**) can be induced by silver(I) to afford tropone[32] (**32**) (Scheme 15). If the double bond of a benzenoid compound such as 1-methoxynaphthalene is sufficiently nucleophilic, carbene addition can occur to generate the 2-chlorotropone (**33**) directly *via* the *in situ* formation of a cyclopropyl intermediate[33].





Scheme 15

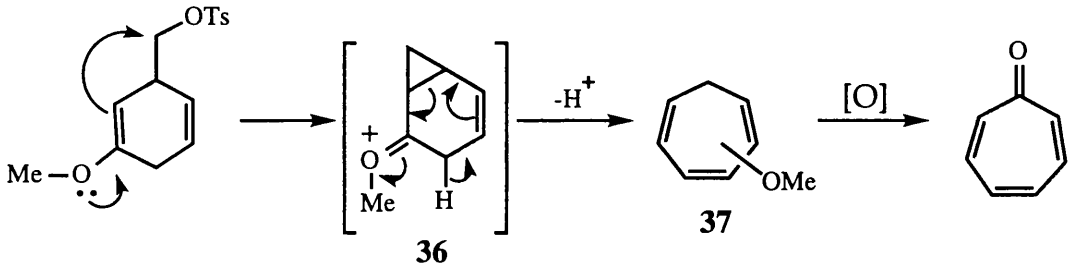
Moreover, oxidation of the diol (**34**) with trifluoroacetic anhydride (TFAA)-'activated' DMSO also provided the tropolone (**35**) *via* the *in situ* ring expansion of the initially produced bicyclic diketone as shown in Scheme 16[34].



34 **35**

Scheme 16

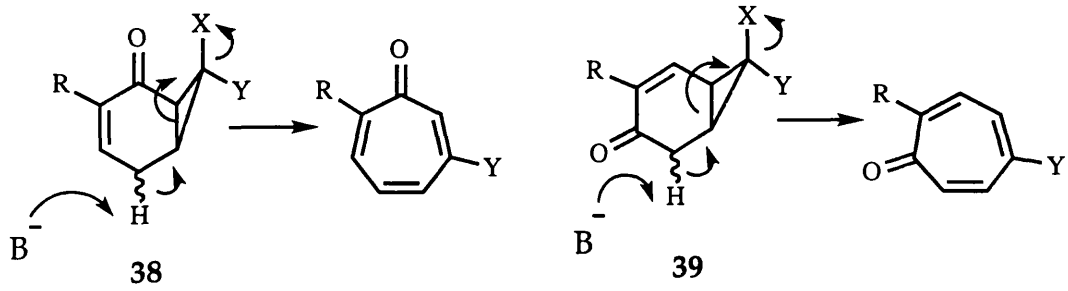
(ii) Cyclopropyl compound (**36**) have also been formed as an intermediate in the intramolecular displacement[35] reaction of cyclohexenone derivatives. Oxidation of the resulting cycloheptatriene (**37**) can then afford tropone (Scheme 17).



36 **37**

Scheme 17

(iii) Banwell *et al*[36] reported that tropones and tropolones could be formed by regioselective ring-opening of the cyclohexenone derivatives (**38**) and (**39**) (Scheme 18). The authors achieved the syntheses of a number of troponyl and tropolonyl compounds employing this method including the first regioselective syntheses of both desacetamidoisocolchicine (**52**) and colchicine (**2a**) (*vide infra*).

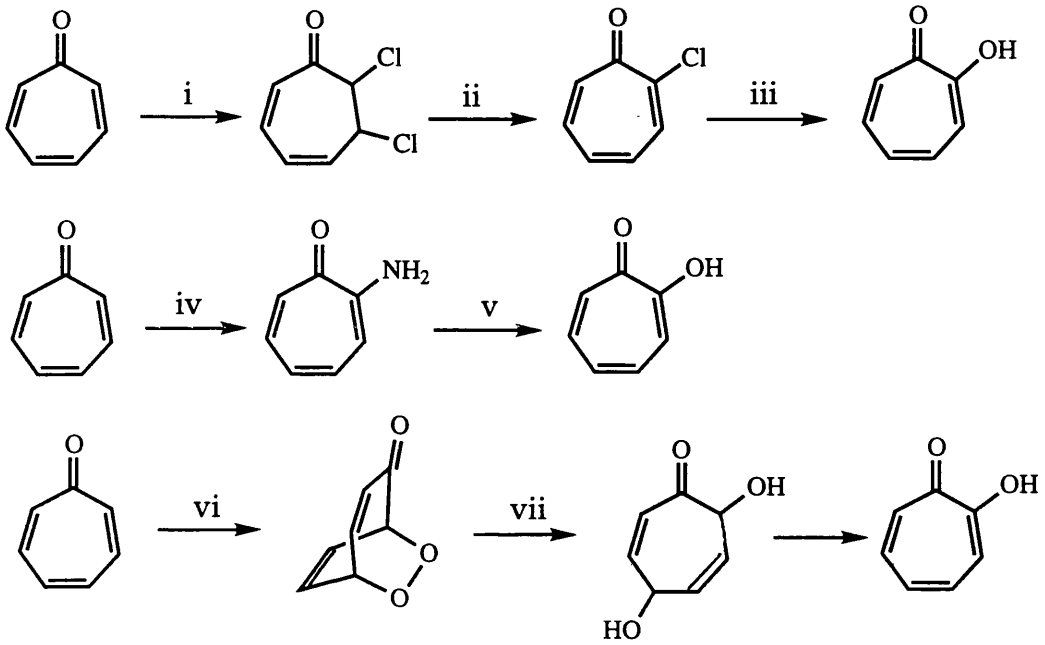


X=Hal, Y=Hal, H or alkyl
R=H, alkyl or alkoxyl

Scheme 18

1.4.2. Preparation of Simple Tropolone Derivatives

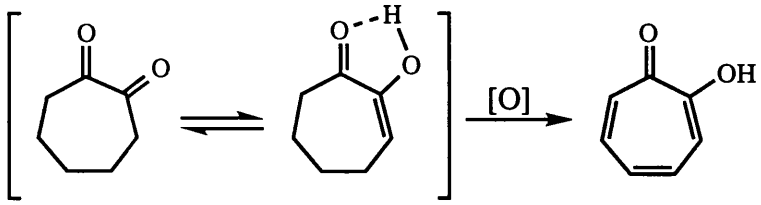
Tropolones can be formed from tropones according to the reaction sequences shown in Scheme 19[20(c)] and many of the preparative methods for tropone construction listed above can also be modified to give tropolones as products using appropriate



i. Cl_2, CCl_4, ii. $NaHCO_3$, iii. HCOOH, iv. NH_2NH_2 or NH_2OH, v. ^-OH, vi. O_2, $h\nu$, vii. $CS(NH_2)_2$

Scheme 19

reactants. For instance, cyclohepta-1,2-dione can be converted to tropolone by the bromination-dehydrobromination sequence[37] in a similar manner to that used for preparing tropones from cycloheptanones, or simply by treatment with *N*-bromosuccinimide[38] (Scheme 20). However, the following methods are still of

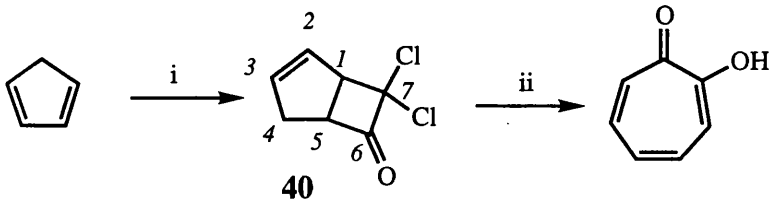


Scheme 20

sufficient importance and also provide insight into the 'aromatic' character of this ring system.

(A) Stevens' Method of Transannular Ring Fission

In 1965 Stevens *et al*[39] reported that cyclopentadiene reacted with dichloroketene generated *in situ* to give the cyclobutenone (**40**), which was then hydrolysed to tropolone with potassium acetate in acetic acid (Scheme 21). The

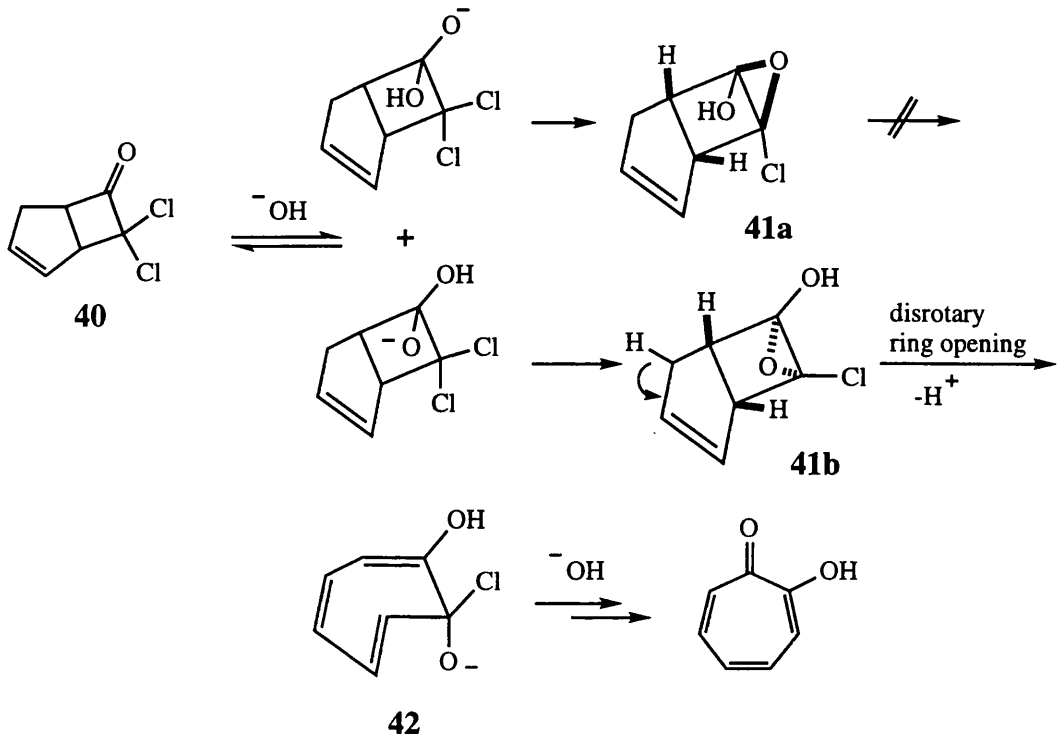


40

i. $Cl_2CHCOCl$, Et_3N, ii. KOH, AcOH

Scheme 21

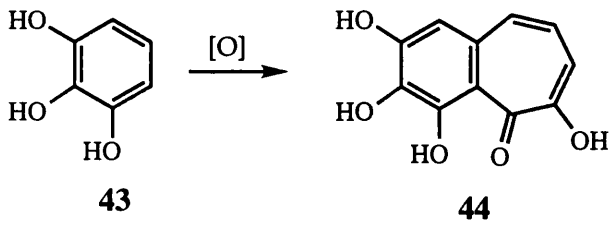
mechanism of the hydrolysis has been studied on a number of occasions. Bartlett and co-workers[40] found that the reaction does not proceed *via* the obvious pathway of 4,7-elimination of hydrogen chloride. Brady and Hieble[41] further demonstrated that the adduct (**40**) reacts with base to form a pair of oxyanions leading to the epoxides (**41a**) and (**41b**) (Scheme 21a). The *endo* epoxide (**41b**) then undergoes disrotary ring opening *via* a desired *trans* displacement to form the anion (**42**), which is converted to tropolone by base. However, the *exo* epoxide (**41a**) is unable to undergo such ring opening due to steric reasons.



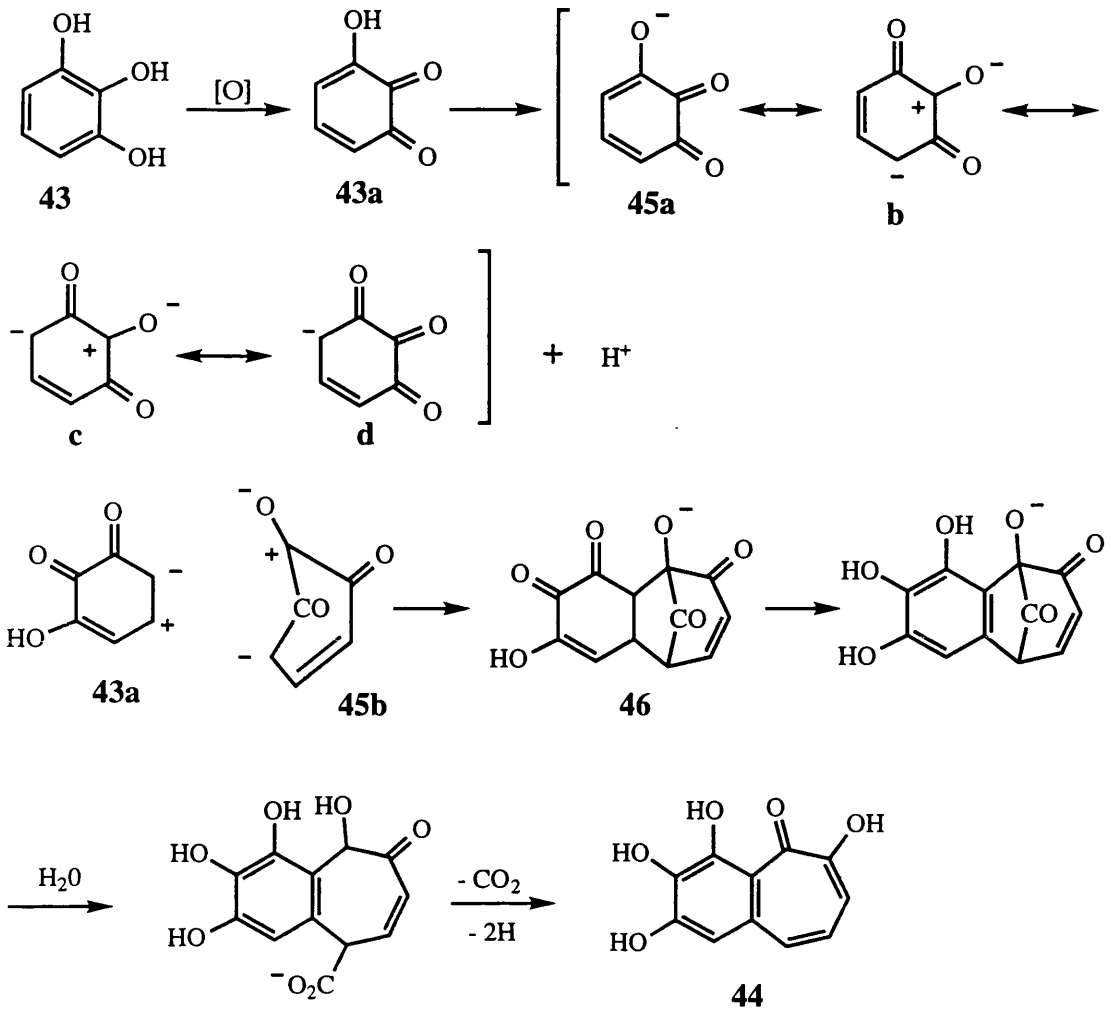
Scheme 21a

(B) Pyrogallol Condensation

Oxidation of pyrogallol[42] (**43**) either by electrolysis or chemical reagents such as sodium iodate or potassium permanganate (Scheme 22) gives the well-known purpurogallol (**44**), which contains a tropolonyl ring and has been used as the starting material in several total syntheses of colchicine[19(a-c)]. The mechanism of this condensation is not well clear but Horner *et al*[43] proposed that pyrogallol (**43**) is oxidised to the diketone (**43a**), which forms the resonant anionic structures (**45a-d**) upon proton dissociation (Scheme 22a). The zwitterionic form of (**43a**) then couples with (**45b**) to form the bicyclic intermediate (**46**), which undergoes subsequent aromatisation, decarboxylation and further oxidation to provide purpurogallol (**44**).

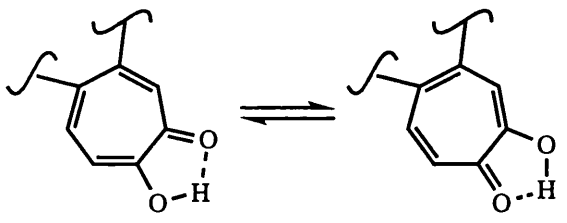


Scheme 22



Scheme 22a

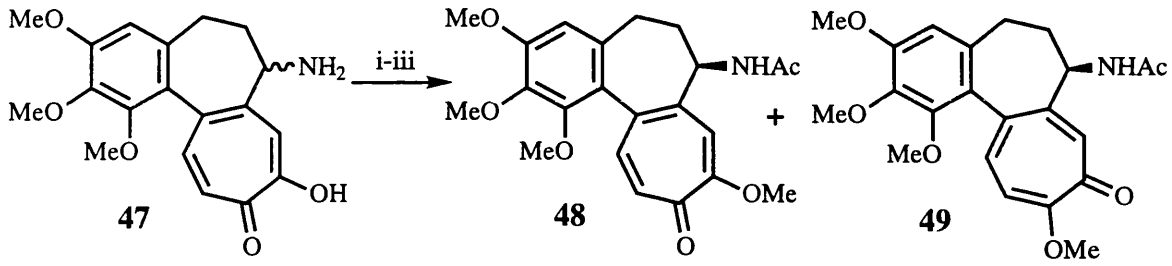
Apart from a few notable exceptions such as those shown in Schemes 16 and 18, it should be noted that the methods attained above are not applicable to the preparation of an α–tropolonyl ether in a regioselective manner. As we shall see in the following section, this diosphenol problem (as summarised in Scheme 23) was a considerable stumbling block in all but one of the total syntheses of colchicine.



Scheme 23

1.5. Previous Syntheses

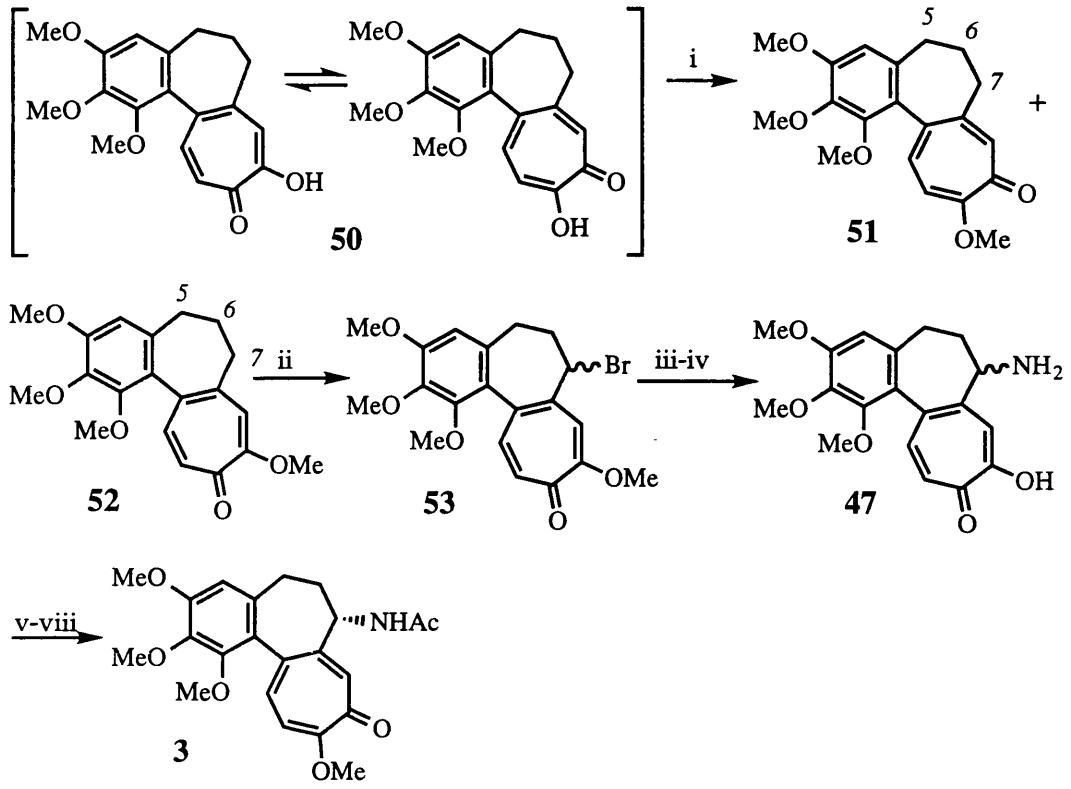
The first total syntheses of colchicine were conducted independently and published in the early sixties by Eschenmoser *et al*[19(a)] and Tamelen *et al*[19(b)]. Prior to these two reports, in 1957, Corridi and Hardegger[44] resolved racemic desacetylcolchiceine (**47**) using *d*-camphor-10-sulfonic acid and converted the (+)-desacetylcolchiceine thus obtained to the unnatural (+)-isocolchicine (**48**) and (+)-



i. resolution with *d*-camphor-10-sulfonic acid, ii. Ac_2O, iii CH_2N_2

Scheme 24

colchicine (**49**) by a sequence involving *N*-acetylation and *O*-methylation (Scheme 24). Recognising the significance of this work, both Eschenmoser and Tamelen planned desacetamidocolchiceine (**50**) to be the key intermediate of the their syntheses (Scheme 25). Thus, at a late stage of the syntheses, desacetamidocolchiceine (**50**), existing as a pair of tautomers, was methylated with diazomethane to a regioisomeric mixture of desacetamidocolchicine (**51**) and desacetamidoisocolchicine (**52**). As the C-7 position of desacetamidocolchicine (**51**) was electronically unfavourable for allylic bromination by NBS, only desacetamidoisocolchicine (**52**) was converted to the bromide (**53**), which was then transformed to desacetylcolchiceine (**47**) through amination and hydrolysis. Then the sequence developed by Corridi and Hardegger was applied to convert desacetylcolchiceine (**47**) to colchicine (**3**).



i. CH_2N_2, ii. NBS, iii. NH_3, or NaN_3 and then H_2, Pd, iv. NaOH, v. resolution, vi. CH_2N_2, vii. separation, viii. Ac_2O, Pyr

Scheme 25

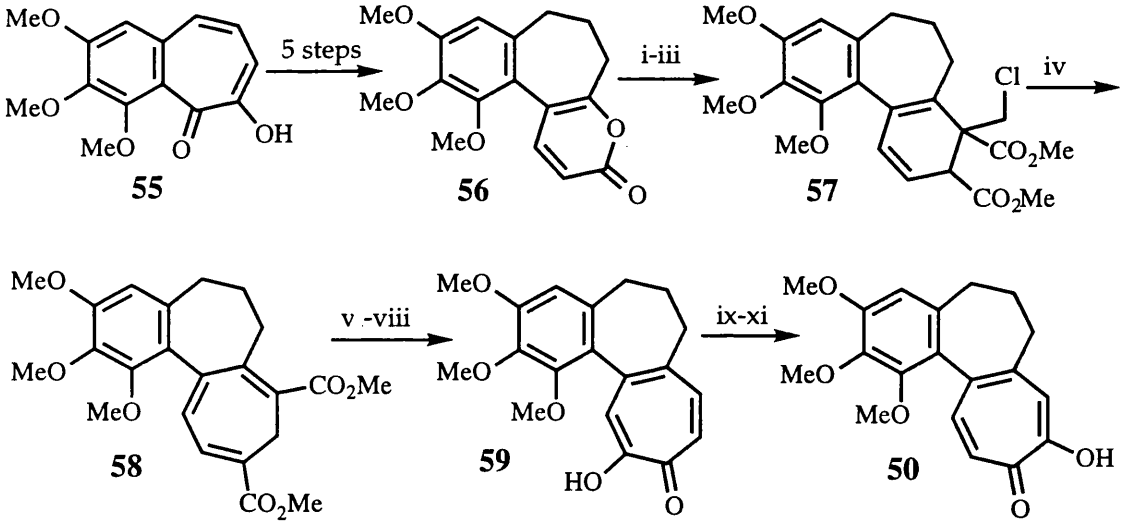
Obviously, the main drawback of this approach was that after each methylation on the tropolonyl ring C, half of the resulting material was not suitable for further elaboration. This tautomeric diosphenol problem was a considerable disadvantage and certainly destroyed the overall yields. Nevertheless, these studies established desacetamidocolchiceine (**50**) and desacetamidoisocolchicine (**52**) to be the key intermediates or target molecules for a number of later total or formal total syntheses of colchicine.

Detailed discussion of every reported synthesis of colchicine is clearly beyond the scope of this report and hence only the key steps will be described in this section. The syntheses will be divided into two categories according to whether desacetamido-precursors (**50**) or (**52**) were or were not involved. Although both Evans *et al* and Banwell *et al* undertook the synthesis of desacetamidoisocolchicine (**52**), they have also used the same methodologies to achieve the syntheses of colchicine without involving desacetamidoisocolchicine (**52**) and hence their work will be described in the second category.

1.5.1. Category I : Syntheses involving desacetamido-precursors

A) Eschenmoser *et al* (1961)[19(a)]

Trimethyl purpurogallin (**55**) was converted in five steps to the α-pyrone (**56**), which gave the diester (**57**) *via* a Diels-Alder reaction with chloromethylmaleic anhydride (Scheme 26). This diester was ready for a ring expansion to form the diester (**58**) containing the skeleton of colchicine. From the diester (**58**), the tropolone (**59**) was formed through oxidation and decarboxylation. It was then isomerised to desacetamidocolchiceine (**50**) by treatment with *p*-toluenesulfonyl chloride, followed by ammonia and then potassium hydroxide.



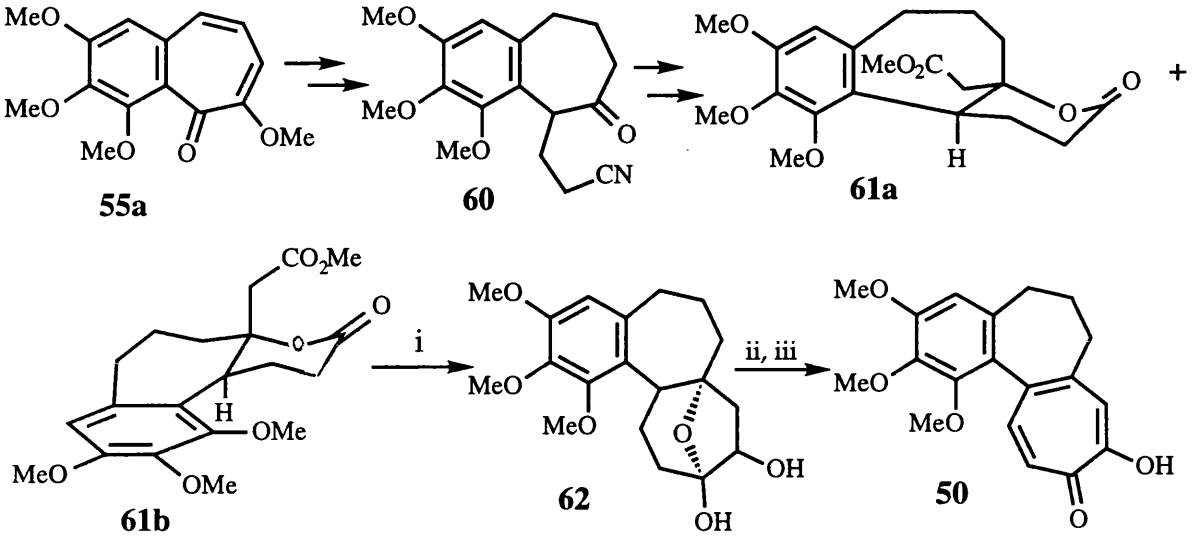
i. chloromethylmaleic anhydride, ii. H^+, iii. CH_2N_2, iv. *t*-BuOK, v. NaOH, MeOH, vi. OsO_4, $NaHCO_3$, $KClO_3$, vii. NaOH, viii. SiO_2, ix. TsCl, x. NH_3, xi, KOH

Scheme 26

B) Tamelen *et al* (1961)[19(b)]

Tetramethyl purpurogallin (**55a**) (Scheme 27) was converted to the nitrile (**60**), and hence to a pair of diastereomeric lactones (**61a**) and (**61b**) *via* a sequence involving Reformatsky reaction. While the major *cis*-isomer (**61a**) did not provide any desired product, the minor *trans*-isomer (**61b**) was capable of undergoing an acyloin-type

cyclisation to form the diol (**62**) containing the seven-membered ring C. This difference is due to the fact that the carbonyl groups of only the *trans*-isomer (**61b**) are sufficiently proximate for the reaction to proceed. The diol (**62**) was then hydrolysed and oxidised to desacetamidocolchiceine (**50**).

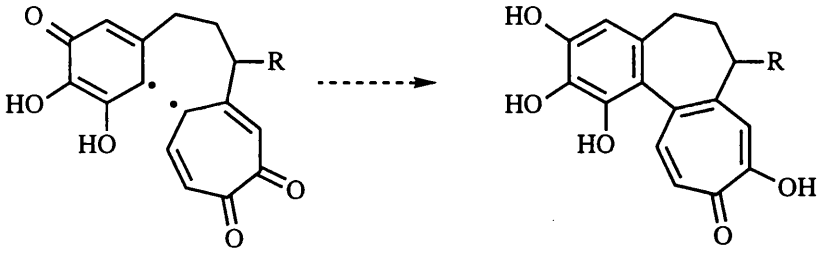


i. Na, NH_3, ii. TsOH, iii. NBS

Scheme 27

C) Scott *et al* (1965)[19(c)]

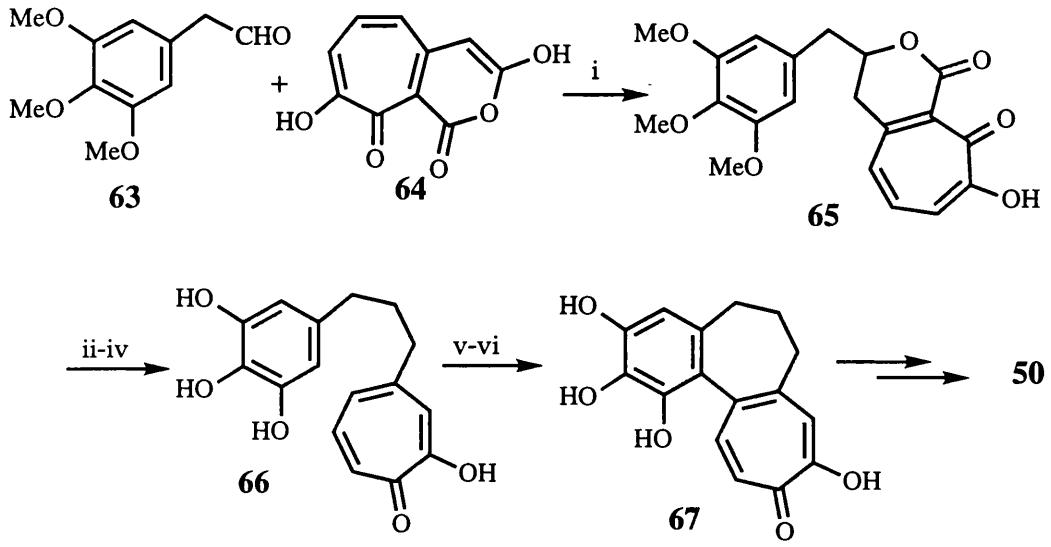
This work could be described as the first biomimetically inspired synthesis of colchicine although the route followed is not exactly that of the biogenesis (see section 1.3). The synthetic plan was invoked by the hypothesis[18] that in nature ring B might be formed by a phenolic coupling between rings A and C (Scheme 28). Thus, in this



Scheme 28

synthesis, rings A and C were tethered by heating the aldehyde (**63**) and the anhydride (**64**) at 100°C (Scheme 29). The resulting lactone (**65**) was further pyrolysed and transformed to the required precursor (**66**) ready for the oxidative coupling. However,

as the product (**67**) from the coupling would be even more prone to oxidation than the starting precursor (**66**), it was very difficult to isolate product (**67**). After much experimentation, the oxidation was finally achieved using ferric chloride in an acidic, biphasic medium and the product (**67**) was obtained by paper chromatography in an inert atmosphere, albeit in low yield.

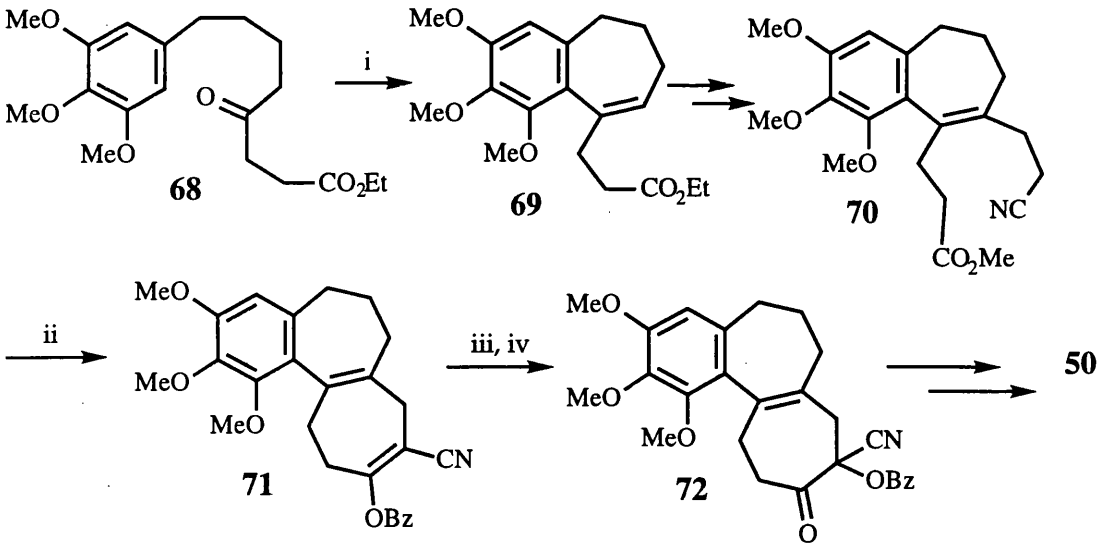


i. 100°C, ii. 190-200°C, iii. H_2, Pd, iv. HBr, v. $FeCl_3$, H_2SO_4, $CHCl_3$, EtOH, H_2O, vi. separation

Scheme 29

D) Martel *et al* (1965)[19(f)]

In this work, the authors planned to form ring C of colchicine by an intramolecular Dieckmann condensation of the cyanoester (**70**). Therefore, the ketoester (**68**) was treated with anhydrous *p*-toluenesulfonic acid to form the bicyclic ester (**69**) possessing rings A and B (Scheme 30). The ester (**69**) was then converted *via* a multi-step sequence to the cyanoester (**70**), which underwent regioselectively Dieckmann condensation with potassium metal in refluxing toluene to provide the enolate (**71**). Upon saponification and treatment of benzoyl peroxide, the enolate was converted to the ketocyanohydrin (**72**), which was subsequently transformed to desacetamidocolchiceine (**50**).

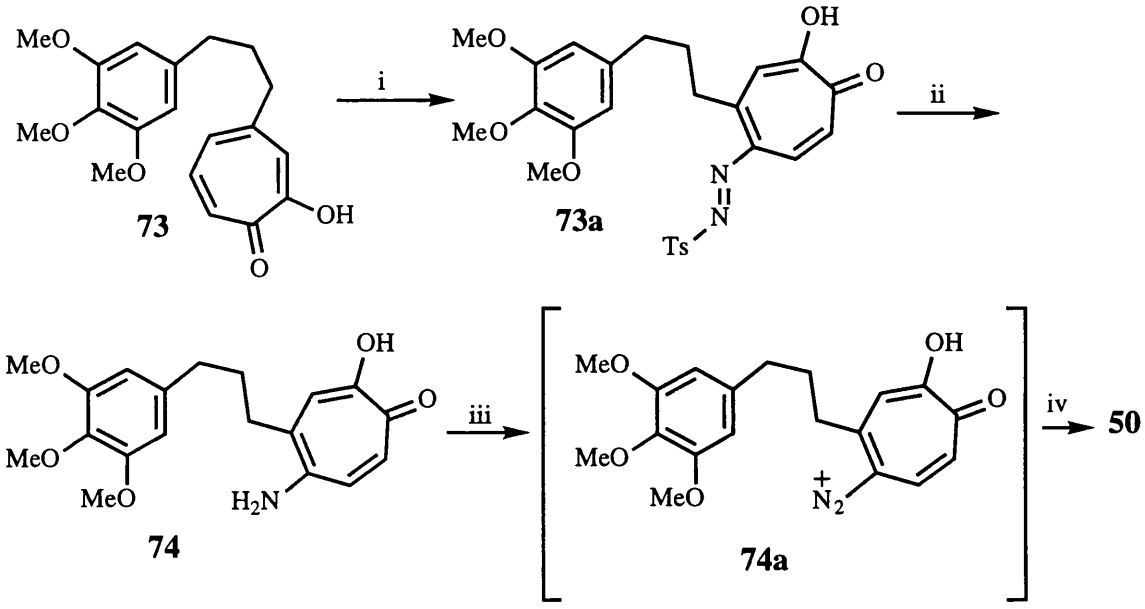


i. dry TsOH, ii. K; BzCl, iii. NaOH, iv. benzoyl peroxide

Scheme 30

E) Kaneko and Matsui (1968) and Kato *et al* (1974)[19] (g) and (h)

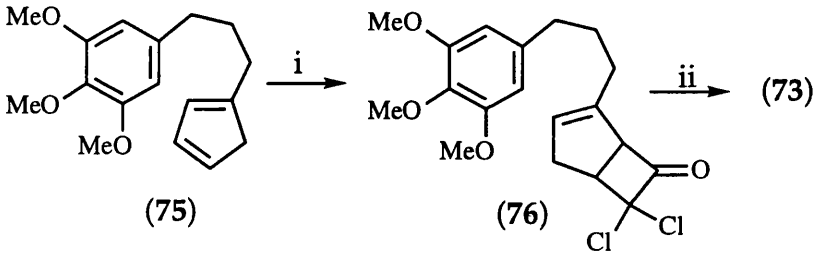
In an attempt to improve the cyclisation undertaken by Scott *et al*, Kaneko and Matsui constructed the aminotropolone (**74**) from Scott's intermediate (**73**) *via* the azo compound (**73a**) (Scheme 31). The aminotropolone (**74**) was then converted to the diazonium cation (**74a**) *in situ* and desacetamidocolchiceine was then obtained in 5% yield from the subsequent copper-mediated cyclisation.



i. TsN_2Cl, ii. H_2, Pd, iii. isoamyl nitrite, cat. H_2SO_4, iv. Cu

Scheme 31

Kato *et al* also achieved a formal synthesis of colchicine by carrying out a ketene cycloaddition to the cyclopentadiene (**75**) (Scheme 32) to form the Stevens-type adduct (**76**), which was then converted to the tropolone (**73**) by using literature procedure.



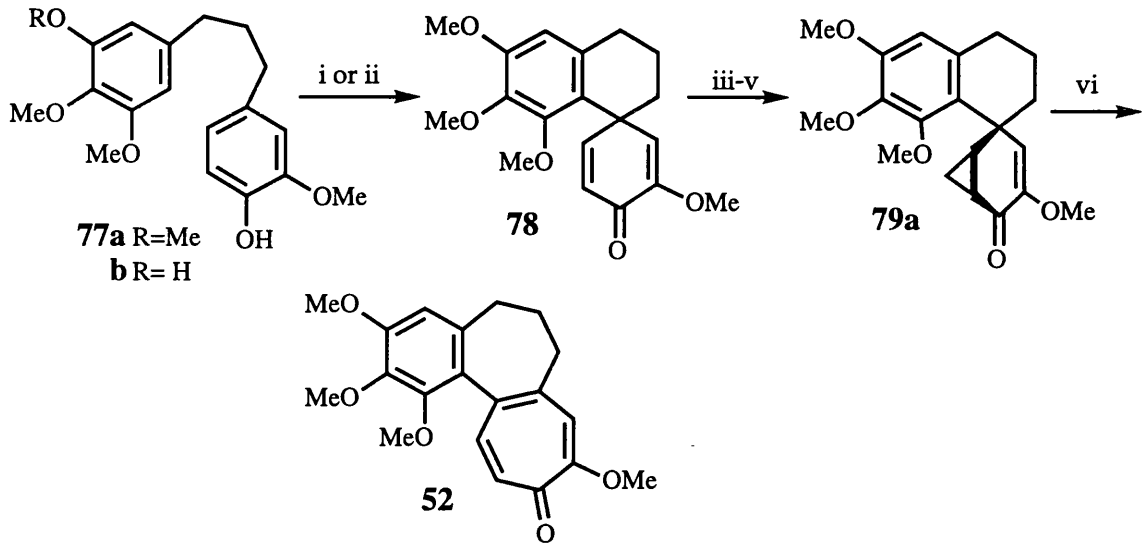
(75) (76)

i. $Cl_2C{=}C{=}O$, ii. AcOH, KOAc, H_2O

Scheme 32

F) Tobinaga *et al* (1974)[19(i)]

In this case, the authors based their synthetic plan (Scheme 33) on the hypothetical biosynthesis by Anet and Robinson[18] that tropolones were generated in nature *via* phenols. Thus the spirodienone (**78**) was formed from the 1,3-diarylpropanes (**77a**) by anodic oxidation or from the phenol (**77b**) by intramolecular oxidative phenol coupling with an iron(III)-DMF complex followed by methylation, respectively. The cyclopropane (**79a**), formed in a subsequent highly regioselective Simmons-Smith reaction, was then treated with a mixture of acetic anhydride and sulfuric acid to give desacetamidoisocolchicine (**52**) *via* the opening of the cyclopropyl ring in 90% yield. Presumably, the high regioselectivity of the Simmons-Smith reaction was mainly due to steric reasons. The stereochemistry of the cyclopropane (**79a**) was identified when Evans *et al* unexpectedly found that it was the key intermediate of their own synthesis (See 1.5.2(C)).

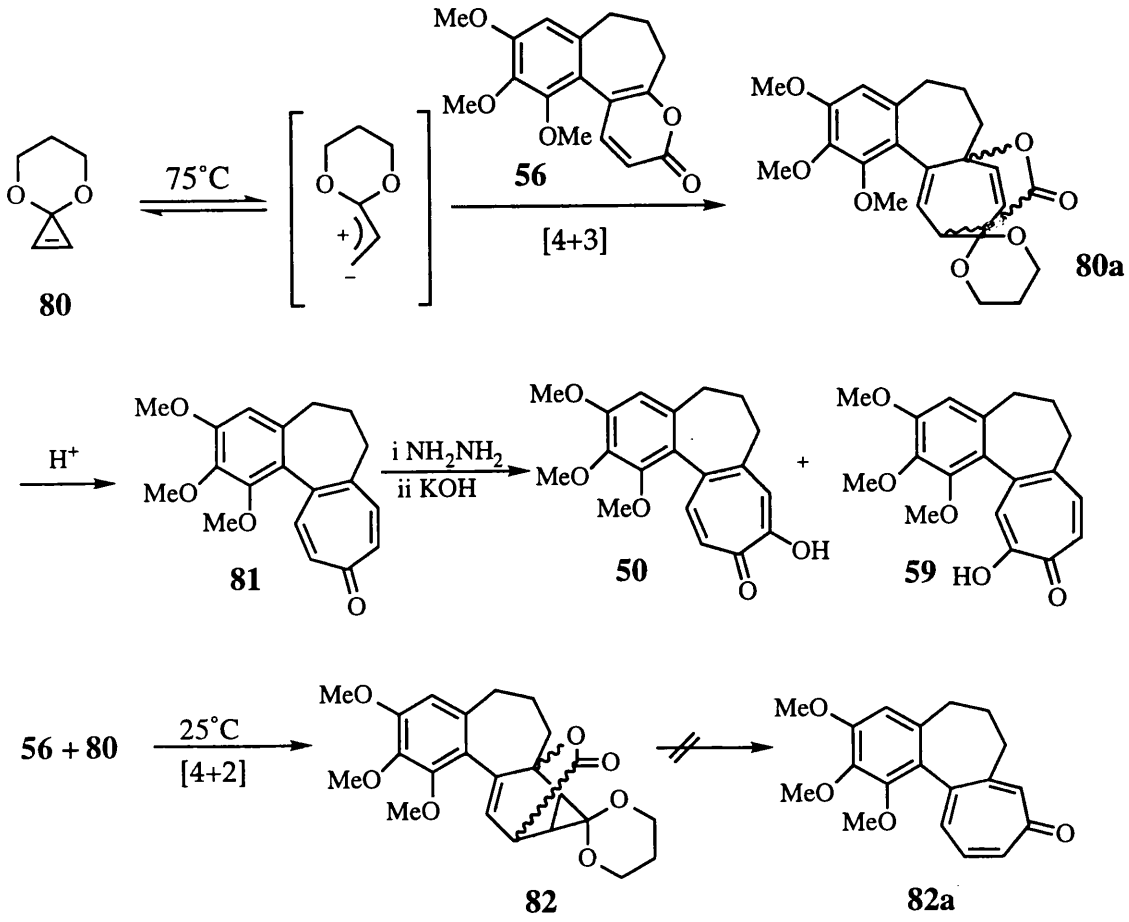


i. for (**77a**), anodic oxidation, ii. for (**77b**), Fe(III), then CH_2N_2, iii. $NaBH_4$, iv, Zn-Cu, CH_2I_2, v. CrO_3, vi. Ac_2O-H_2SO_4 (2:1)

Scheme 33

G) Boger *et al* (1986)[19(k)]

Boger's synthesis relied on reaction of the Eschenmoser's pyrone (**56**) with the cyclopropenone ketal (**80**) *via* a [4+3] cycloaddition giving the adduct (**80a**), which on extrusion of carbon dioxide and subsequent hydrolysis afforded the tropone (**81**) (Scheme 34). A hydroxyl group was then introduced with hydrazine followed by potassium hydroxide to obtain the target molecule (**50**) and its regioisomer (**59**), which can be tautomerised to the desired product (**50**) *via* literature procedure. The authors also conducted the initial cycloaddition in a Diels-Alder mode by operating at a lower temperature and under a higher pressure to give the cyclopropane (**82**). Surprisingly, however, their efforts to achieve the subsequent retro Diels-Alder reaction were unsuccessful and hence their attempt to synthesise the tropone (**82a**) were thwarted.

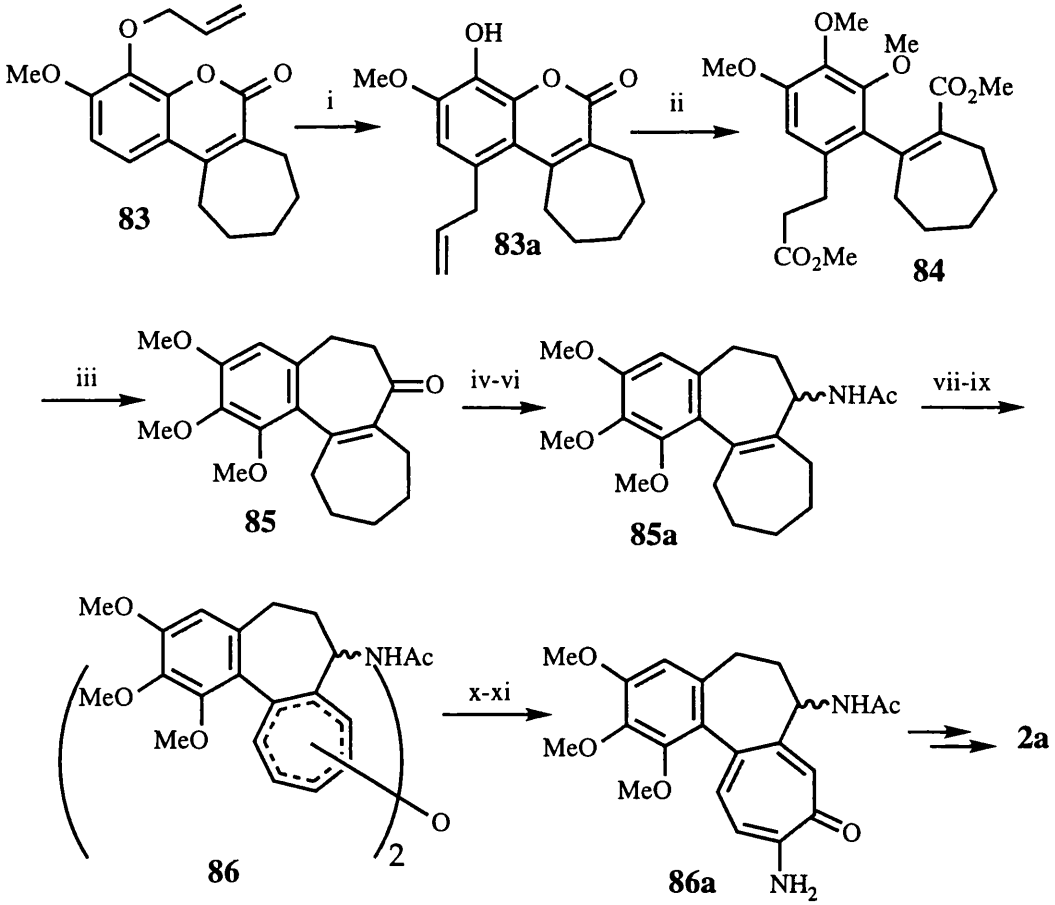

MeO
MeO
OMe
56
75°C
[4+3]
80
80a
H+
i NH2NH2
ii KOH
81
50
59
HO
OH
56 + 80
25°C
[4+2]
82
82a

Scheme 34

1.5.2. Category II : Syntheses not involving desacetamido-precursors

A) Nakamura *et al* (1962) and Wenkert *et al* (1989)[19(c) and 19(l)]

Clasien-type rearrangement was utilised in Nakamura's synthesis (Scheme 35) to form the phenol (**83a**) from the lactone (**83**). After a 5-step operation, the phenol (**83a**) was converted to the diester (**84**), which cyclised upon treatment with acetic anhydride to the tricyclic ketone (**85**). Conversion of the ring B keto group to amide functionality led to (**85a**), which was then transformed *via* the ditropyl ether (**86**) and aminotropone (**86a**) to racemic colchicine (**2a**).

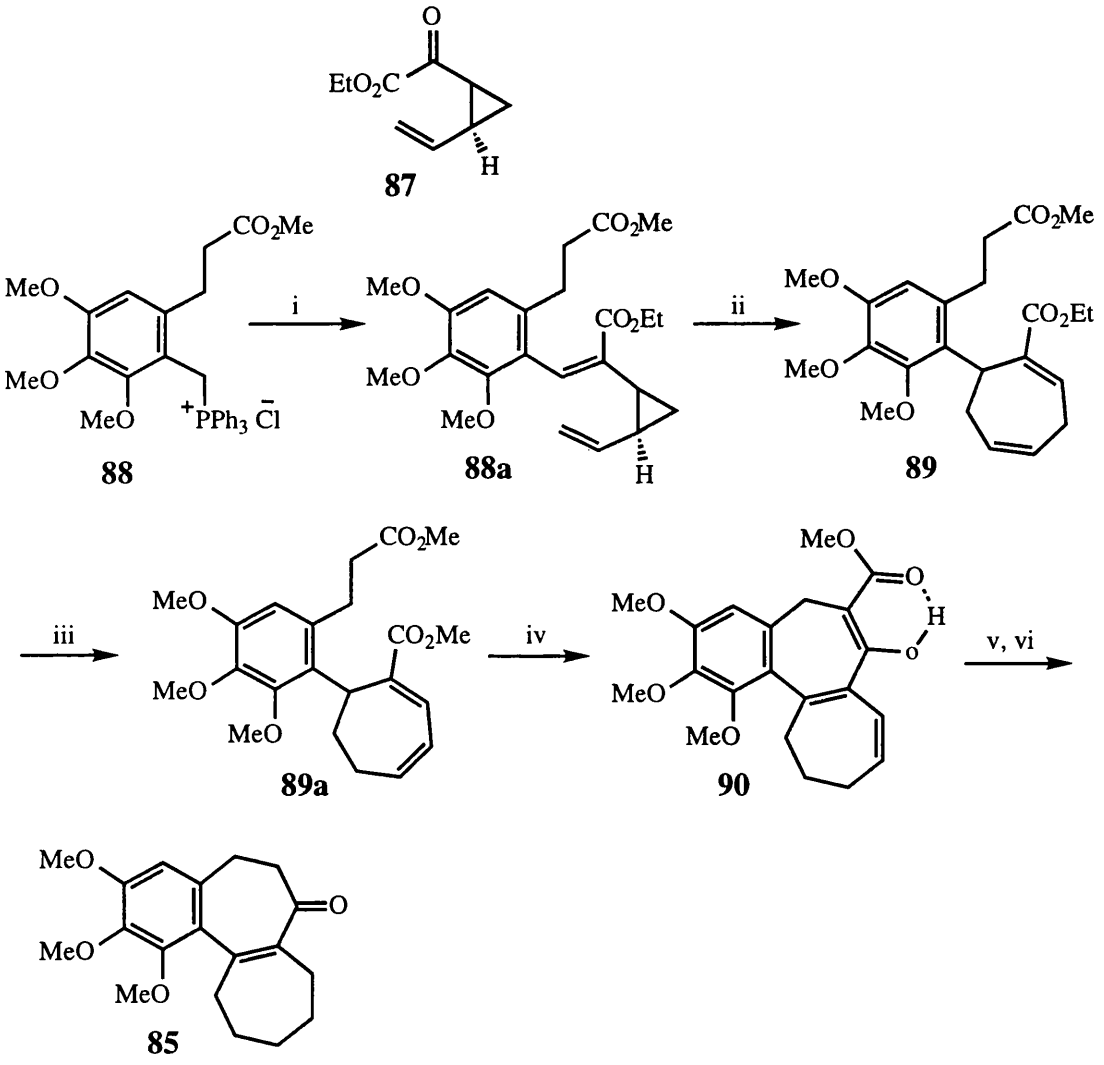


i. $PhNH_2$, 200°C, ii. 5 steps, iii. Ac_2O, H_2SO4, iv. NH_2OH, v. $LiAlH_4$, vi. Ac_2O, Pyr, vii. NBS, collidine, viii, PCl_5, ix, NaOH, x, HCl, xi. NH_2NH_2

Scheme 35

Almost thirty years later, Wenkert and Kim achieved a formal total synthesis of colchicine by employing the versatile ketoester[45] (**87**) in the construction of the ketone

(**85**) (Scheme 35a). To this end, coupling of the ketoester (**87**) with the phosphonium salt (**88**) in the presence of base formed the divinylcyclopropane derivative (**88a**), which cyclised to the cycloheptadiene (**89**) by heating in refluxing xylene for 24 hours. Upon transesterification and isomerisation with sodium methoxide, the compound (**89**) was converted to (**89a**), which underwent Dieckmann cyclisation under forceful conditions to form the enol ester (**90**). Subsequent acid-catalysed hydrolysis followed by hydrogenation then provided Nakamura's ketone (**85**) and hence accomplished the formal total synthesis.

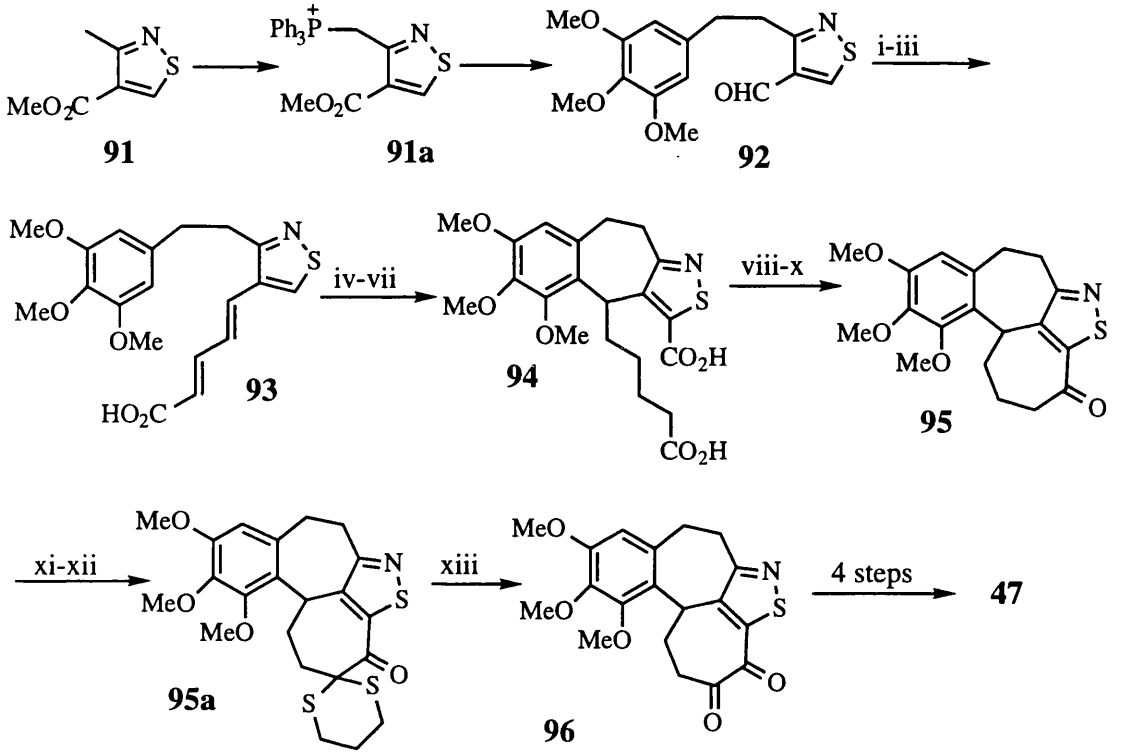


i. LDA, **87**; ii. xylene, reflux; iii. NaOMe; iv. Na, cat. NaOMe, xylene, reflux; v. H^+; vi. H_2, Pd/C

Scheme 35a

B) Woodward *et al* (1963)[19(d)]

The brilliant conception of R.B. Woodward was to introduce the nitrogen atom by using the isothiazole (**91**) both as a masked nitrogen moiety and as a directing platform for the construction of rings B and C (Scheme 36). The phosphonium salt



i. $Ph_3PCHCHCHCO_2Me$, ii. NaOH, iii. I_2, iv. $HClO_4$(aq), v. N_2H_4, H_2O_2, Cu(II), vi. lithium *o*-biphenyl, vii. CO_2, viii. CH_2N_2, ix. NaH, x. H^+, xi. NaH/EtO_2CH, xii. $(TsOSCH_2)_2CH_2$, xiii, $Hg(OAc)_2$, H^+

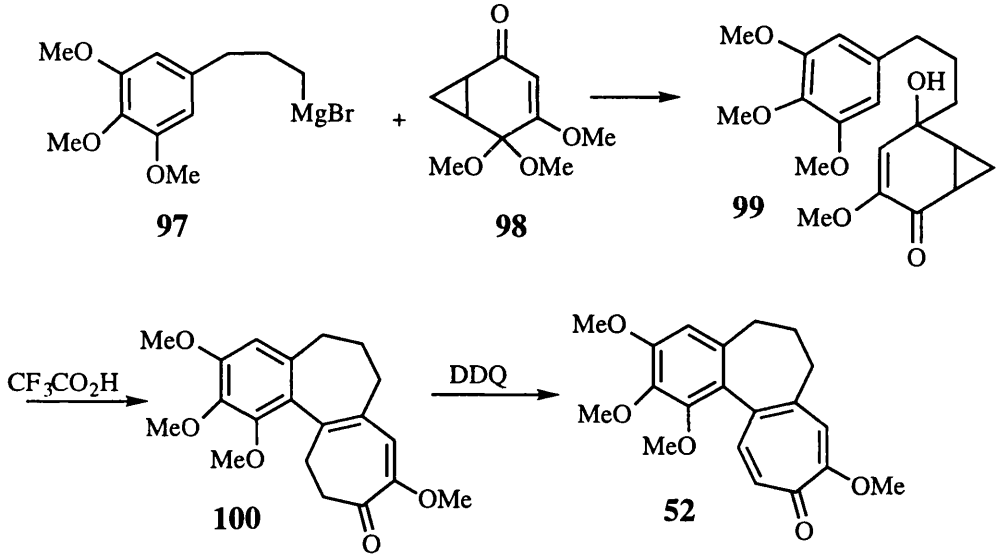
Scheme 36

(**91a**) of the isothiazole was coupled with 3,4,5-trimethoxybenzaldehyde and transformed in 4 steps to the aldehyde (**92**), which was then converted to the conjugated acid (**93**). Cyclisation to generate ring B was then achieved by the action of perchloric acid. A second carboxyl group was introduced on the isothiazole ring by using *O*-biphenyl lithium as a base and carbon dioxide giving the diacid (**94**), which, after esterification with diazomethane, underwent Dieckmann cyclisation with sodium hydride to provide the ketone (**95**) possessing the tricyclic skeleton of colchicine. The ketone (**95**) was then converted to the thioketal (**95a**) and the removal of the dithiane moiety using mercury diacetate formed the diketone (**96**). The subsequent 4-step

operation converted the diketone (**96**) to desacetylcolchiceine (**47**), which can be transformed to racemic colchicine using literature procedure (see Schemes 24 and 25).

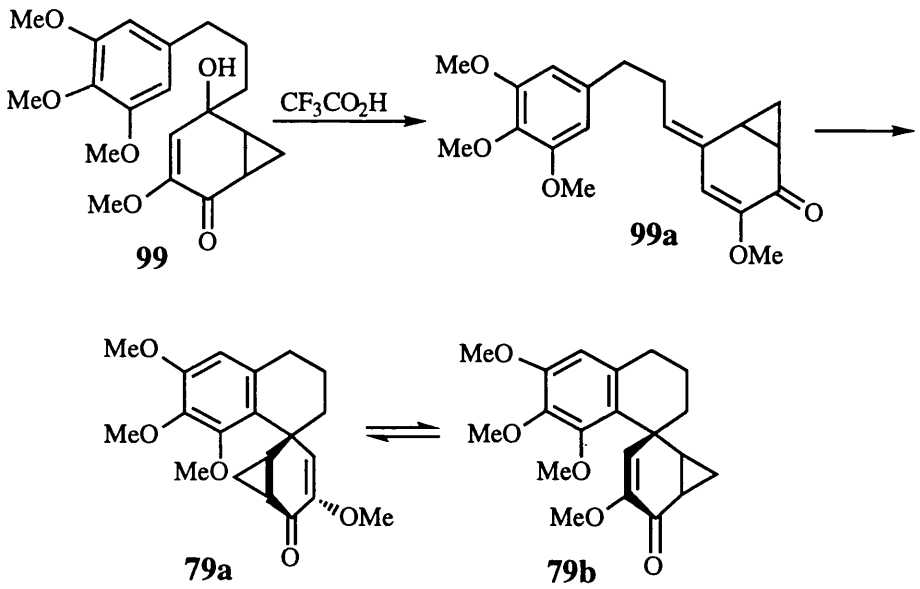
C) Evans *et al* (1981)[19(j)]

A synthesis of desacetamidoisocolchicine (**52**) and a total synthesis of (±)-colchicine were reported by the authors in the same article using the same methodology. The cyclopropyl ketone (**98**) was used as the key intermediate in constructing rings B and C. Thus, in the synthesis of desacetamidoisocolchicine (**52**)



Scheme 37

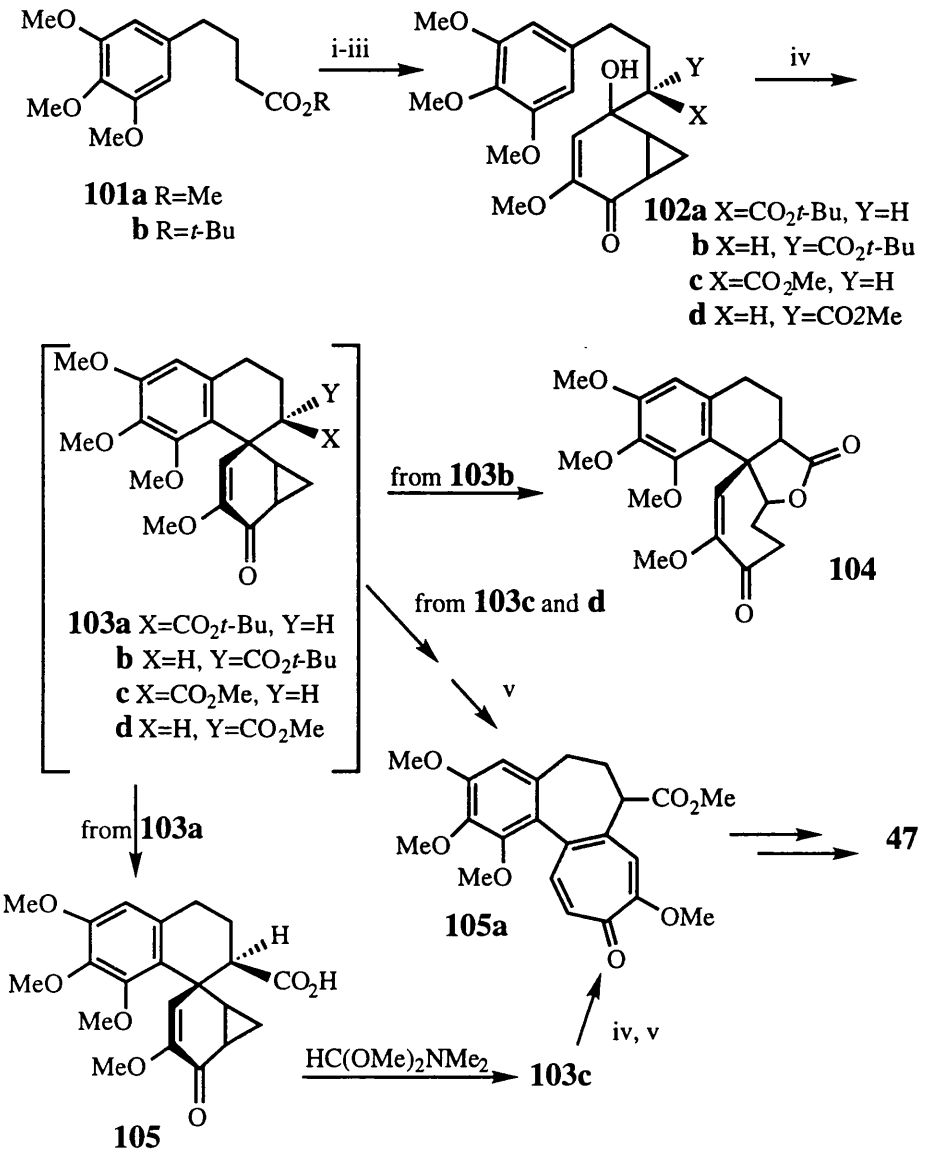
(Scheme 37), the Grignard reagent (**97**) and the ketone (**98**) were coupled to form the allyl alcohol (**99**). Treatment of the alcohol (**99**) with trifluoroacetic acid led to the dihydrotropolone (**100**), which was then dehydrogenated to the target compound (**52**) with DDQ. Quenching the reaction mixture shortly after treatment of the alcohol (**99**) with trifluoroacetic acid revealed the formation of the unstable intermediate (**99a**) (Scheme 37a), which cyclised to a pair of interconverting diastereoisomeric spirans (**79a**) and (**79b**). Only one of the spirans, (**79a**), which was found to be identical to the intermediate obtained by Tobinaga's group, would undergo subsequent cyclopropy ring opening to form the dihydrotropolone (**100**).



Scheme 37a

In the synthesis of colchicine (Scheme 38), the acetamido group was initially introduced as an ester group. Therefore, the esters (**101a**) and (**101b**) were coupled with the ketone (**98**) and the allyl alcohols (**102a-d**) were obtained upon hydrolysis of the resultant unstable ketals. Treatment of a mixture of the alcohols (**102a**) and (**102b**) with boron trifluoride provided the acid (**105**) and the lactone (**104**) presumably *via* the spirans (**103a**) and (**103b**). The *t*-butylcarboxyl group of (**103b**) was found to be situated ideally for participating in the acid-catalysed opening of the cyclopropyl ketone moiety with loss of the *t*-butyl group and hence the formation of the lactone (**104**). However, the diastereoisomeric spiran (**103a**) was not sterically suitable to undergo such operations and therefore was hydrolysed to the acid (**105**), which was converted to the methyl ester (**103c**) for the ease of handling. In the cases of the methyl esters (**102c**) and (**102d**), treatment with boron trifluoride formed the spirans (**103c**) and (**103d**) without any contamination by the lactone (**104**). This result indicated that, in contrast to (**103b**), the ester group of (**103d**) did not participate the opening of the cyclopropyl ring. As a result, the compound (**105a**) could be formed by heating the alcohols (**102c**) and (**102d**) with excess boron trifluoride at 90°C followed by DDQ oxidation. Compound (**105a**) was then transformed to desacetylcolchiceine (**47**) *via* a sequence of reactions involving Curtius rearrangement. As previously described,

desacetylcolchiceine (**47**) can be converted to colchicine by known procedure.

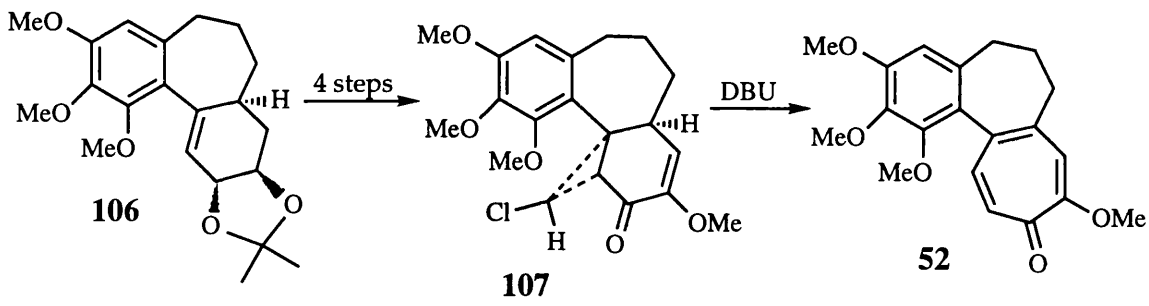


i. LDA; ii. **98**; iii. $(CO_2H)_2$; iv $BF_3{\cdot}Et_2O$; v. DDQ

Scheme 38

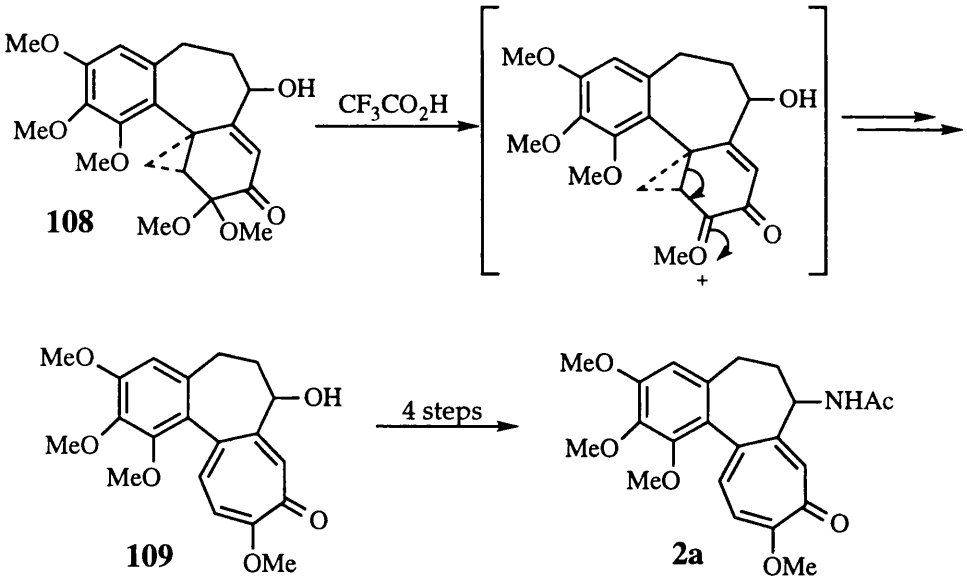
D) Banwell *et al* (1992)[19(m-o)]

Syntheses of both desacetamidoisocolchicine (**52**) and (±)-colchicine (**2a**) were achieved by the authors employing a biomimetic strategy inspired by Battersby's elegant demonstration that the biogenesis of ring C of colchicine involves a ring expansion of an appropriate cyclopropyl derivative (Scheme 6). Thus, in the former synthesis (Scheme 39), the enone-cyclopropane (**107**) was constructed from the



Scheme 39

acetonide (**106**) *via* cyclopropanation with chlorocarbene. This was then exposed to base leading to the target molecule (**52**). This strategy was further improved in the synthesis of colchicine (Scheme 40) by constructing the ketal (**108**), which on the treatment of acid formed the alcohol (**109**). Remarkably, the tropolonyl ring C was formed regioslectively. After converting the hydroxyl group to an acetamido group, the synthesis of (±)-colchicine (**2a**) was achieved without encountering the problem arising from methylating colchiceine derivatives.



Scheme 40

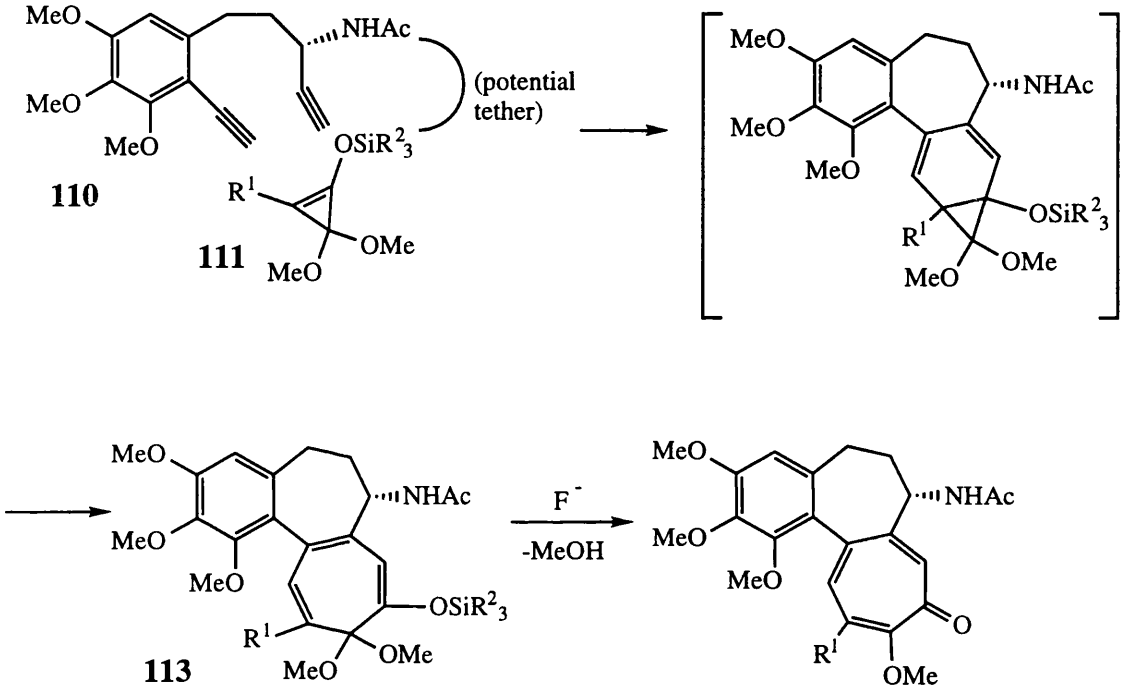
CHAPTER TWO : RESULTS and DISCUSSION

As we have hopefully seen from the foregoing introduction, an enormous body of elegant work on the total synthesis of colchicine has already been undertaken. Nevertheless, apart from the racemic synthesis by Banwell *et al* reported during the course of this project in 1992-3, all syntheses have suffered from a dramatic lack of regioselectivity in generating the ring C tropolone. A significant loss in overall yield is experienced when ring C was formed by methylation of free tropolones. Moreover, further losses of yield are also incurred if desacetamidocolchiceine (**50**) is used as a key intermediate. Thus, in the first instance, half of the material is not of further use (Scheme 26) after the methylation step to give desacetamidocolchicine (**51**) and desacetamidoisocolchicine (**52**) since only the latter compound can react with NBS to introduce the necessary bromine atom at C-7 position. Secondly, in the syntheses of (-)-colchicine (**3**), once again half of the material must be discarded when the racemic desacetylcolchiceine (**47**) is resolved.

Therefore, we can conclude that, both in terms of an asymmetric synthesis and in terms of solving the 'diosphenol problem', regio- and stereoselective total synthesis of (-)-colchicine (**3**) is still a highly attractive goal. Moreover, none of the routes developed this far is sufficiently flexible to provide access to a range of unnatural analogues which could provide valuable insight into the mode of action of this intriguing compound. Our intention was therefore to incorporate novel methodology for the formation of a variety of substituted tropolone rings at a late stage in the synthesis.

Three preliminary aims and objectives were set when we devised the general strategies of the synthesis. Firstly, no methylation of free tropolone should be involved. Secondly, the C-7 stereocentre should be introduced in asymmetric fashion. Thirdly, in stark contrast to the stepwise approaches of the previous syntheses, we sought to form both rings B and C in a single reaction step.

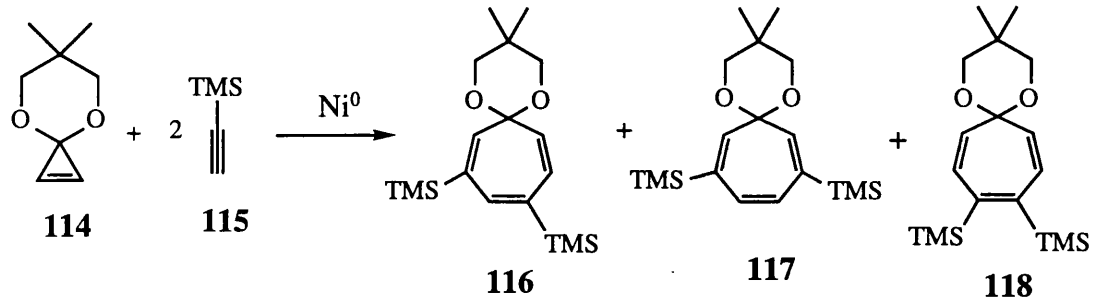
Two interrelated strategies were thus planned which fulfil these conditions. The first of these involves a novel [2+2+2] intermolecular cycloaddition between a diyne (**110**) and a cyclopropenone ketal derivative (**111**). In this manner, as shown in Scheme 41, cycloaddition is followed by electrocyclic ring opening to give an intermediate (**113**) which on deprotection of the silyl enol ether followed by 'aromatisation' through loss of methanol leads to a single step construction of the entire colchicine skeleton. It was considered that, if such a [2+2+2] cycloaddition reaction was indeed feasible, then the



Scheme 41

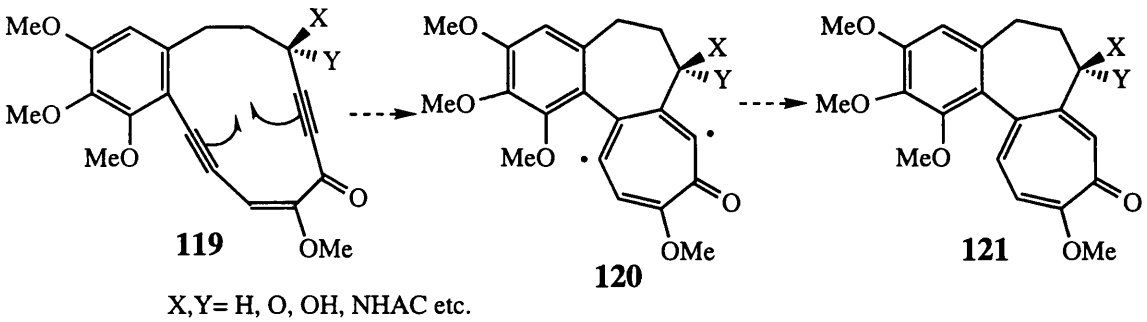
inherent problem of regioselectivity in the first step could be solved, either by a judicious selection of groups R^1 and R^2, or by the introduction of a silicon tether as indicated. In the event however, while our own model study was in progress, we were both encouraged and more probably deeply saddened by the presentation of a poster at the XIII international organometallics meeting in Bristol in September 1992 by Professor Paul Binger. This work[46], which has yet to be published, is shown in Scheme 42 and involves, in an intermolecular fashion, a similar cycloaddition between the cyclopropenone ketal (**114**) and trimethylsilyl acetylene (**115**) to give the isomeric

tropones (**116**)-(**118**). Our own preliminary study of the intramolecular variant, which was unsuccessful, will be described in section 2.2.



Scheme 42

The second strategy, which also involves potentially common diyne intermediates and also leads to concomitant formation of rings B and C, was inspired by the fascinating chemistry of the enediyne antibiotics such as calicheamicin, esperamicin and neocarzinostatin. The mode of action of the these antibiotics (*vide infra*) is the Bergman cyclisation by which the generation of highly reactive 1,4-diradicals damages DNA molecules. Since the vast majority of the work described in this thesis is devoted to this second approach, it is discussed in much more detail in the following section. It may however be encapsulated by the idea shown in Scheme 43, in which we pose the question as to the existence of a similar cycloaromatisation of the twelve-membered macrocycle (**119**) occurring to generate the tropolonyl ring C.

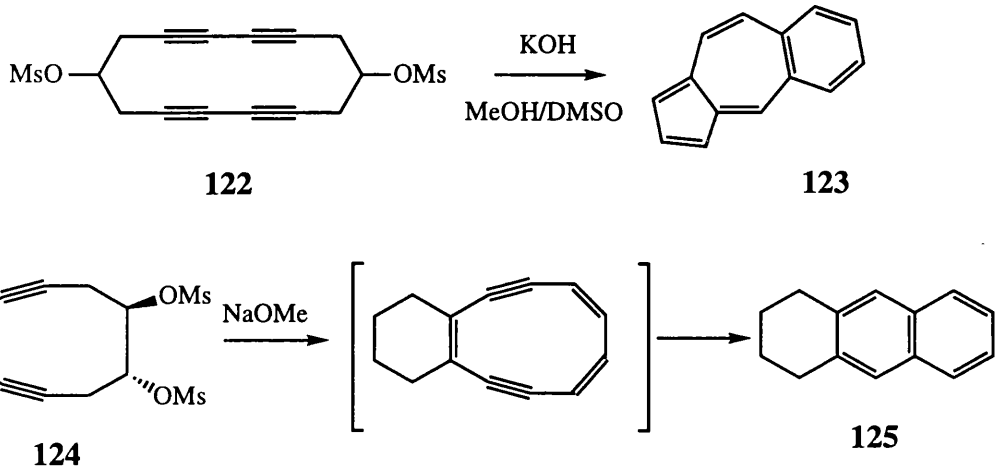


Scheme 43

2.1. The Investigation of the Cycloaromatisation Approach

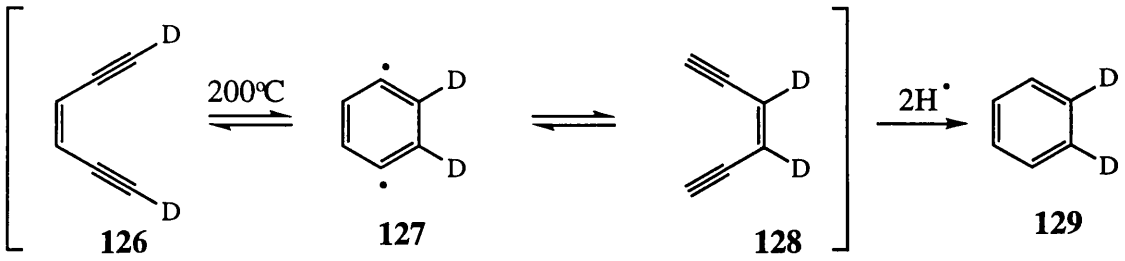
2.1.1 Strategy and Background

In 1966 Meyer and Sondheimer[47] found that a tricyclic compound (**123**) was formed when the dimesylate (**122**) was heated with base (Scheme 44). Five years later Masamune *et al*[48] reported a similar, unexpected cyclisation in which the enediyne (**124**) was transformed to the naphthalene (**125**).



Scheme 44

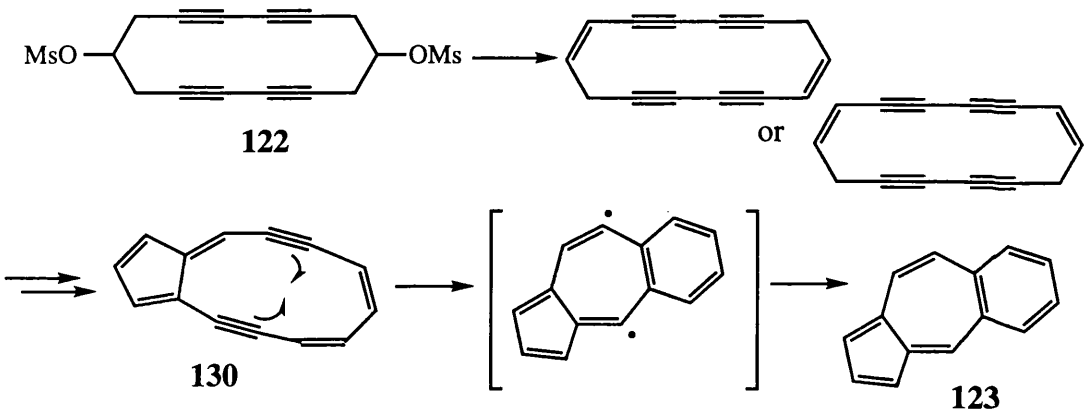
It was Bergman[49] who in 1972 elegantly demonstrated that atom scrambling occurred when deuterated *Z*-hex-3-ene-1,5-diyne (**126**) was heated at 200°C, and that deuterated benzene (**129**) was formed if a hydrogen radical source was added (Scheme



Scheme 45

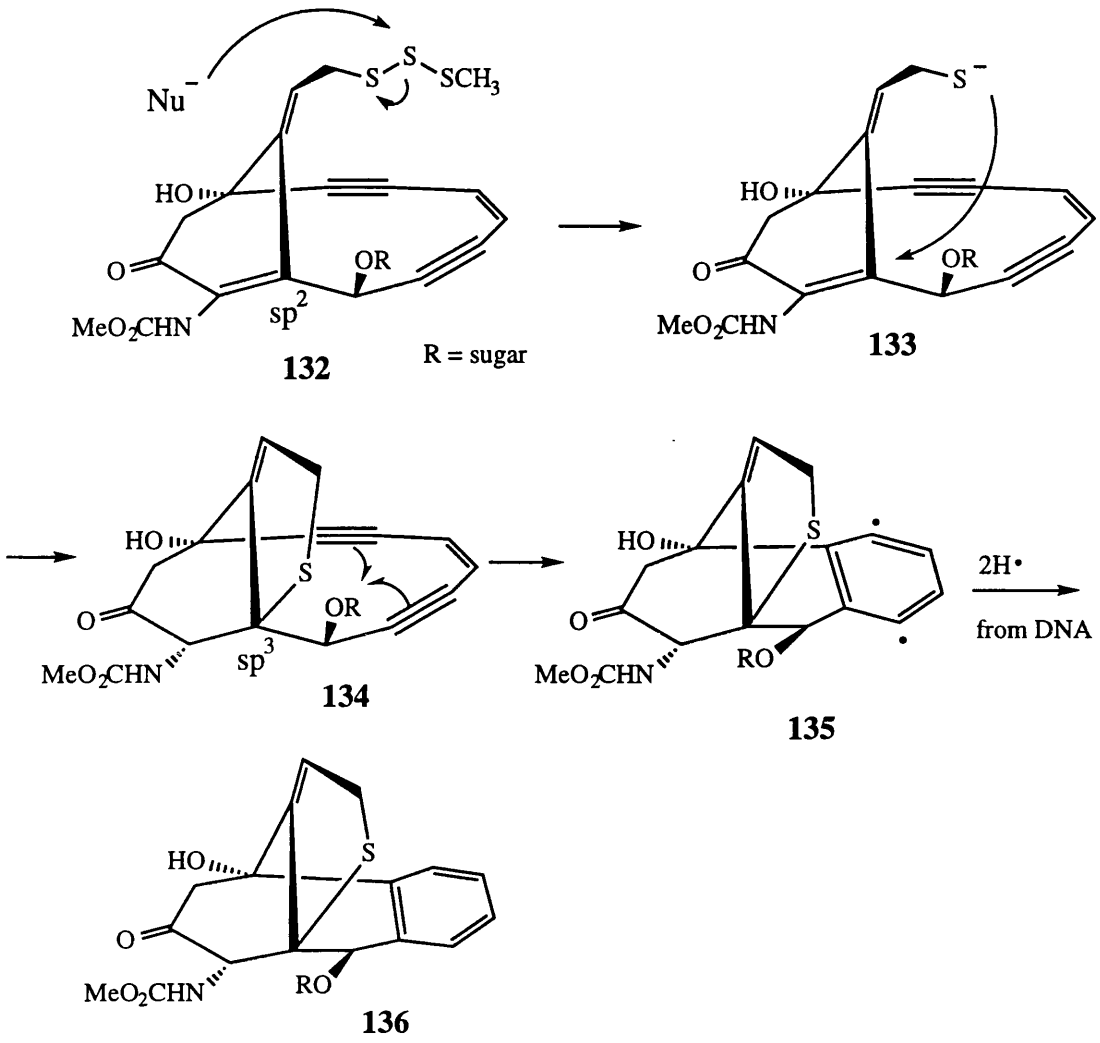
45). He then proposed that the enediyne (**126**) underwent a cycloaromatisation to form a 1,4-benzenoid diradical (**127**), which then dearomatised to the enediynes (**126** and **128**) or, in the presence of hydrogen radicals, formed benzene. Therefore, the two previous

reports of the 'mysterious' cyclisation of acetylenic compounds (**122**) and (**124**) can be ascribed to this reaction. The reaction reported by Meyer and Sondheimer may have proceeded *via* the highly conjugated diyne (**130**) (Scheme 46).



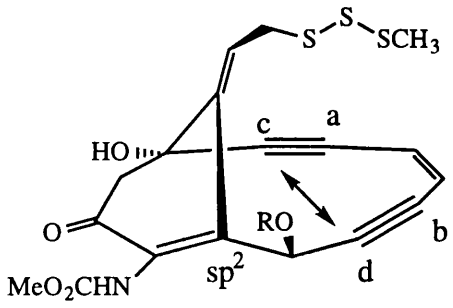
Scheme 46

In a most exciting discovery, the above type of cycloaromatisation was found to be the key process in the mode of action of the most potent antibiotics existing in nature. In the eighties, a series of bacterial products including neocarzinostatin[50], calicheamicins[51], esperamicins[52] and dynemicins[53] were discovered and their structures elucidated. Among these compounds, calicheamicin γ_1 and esperamicins were the most potent antitumour agents known at the time of discovery. This series of compounds share a very unusual structural feature, namely a *Z*-enediyne functionality as part of a macrocyclic aglycon. The mechanism[54] of action of these antibiotics on tumour cells is widely believed to be a structural change within the macrocycle followed by a Bergman cyclisation. Thus, for instance, in the case of calicheamicins (**132**), the sulfide linkage is cleaved by a nucleophile in the vicinity of DNA molecules (Scheme 47) and the resulting sulfide anion (**133**) undergoes intramolecular 1,4-addition to form the intermediate (**134**). The hybridisation of the bridgehead carbon atom therefore changes from sp^2 to sp^3 and hence facilitates the ensuing cycloaromatisation. The resultant diradical (**135**) can then abstract hydrogen atoms from the DNA helices thereby effecting double- and single-strand scissions and causing cell death.



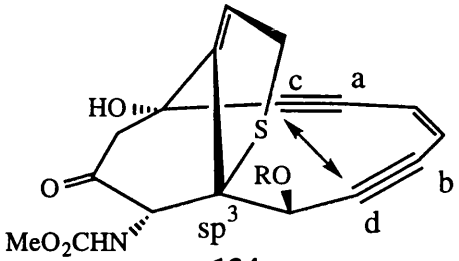
Scheme 47

The change in the hybridisation of the bridgehead carbon therefore serves as the necessary trigger for the cycloaromatisation process. One structural alteration that this hybridisation change brings about is to decrease the distance between the two triple bonds from 3.35Å to 3.16Å[55(b)] (Scheme 48). Nicolaou *et al*[55] correlated the so-called cd distance (the distance between the two alkynyl carbon atoms away from the double bond, Scheme 49) of a series of cyclic enediyne systems (**137**) with the rate of formation of the cycloaromatised products (**138**) and found that generally the shorter the cd distance, the higher the rate of cycloaromatisation. They concluded that, as a rule of thumb, 3.20-3.31Å was the limiting range for whether an enediyne would cycloaromatise spontaneously at 25°C or not.



132

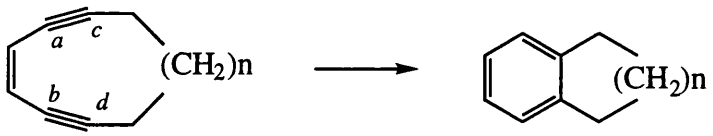
cd=3.35Å



134

cd=3.16Å

Scheme 48



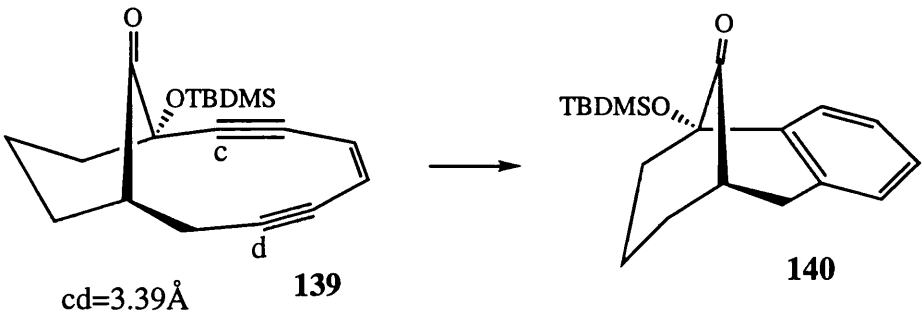
137 **138**

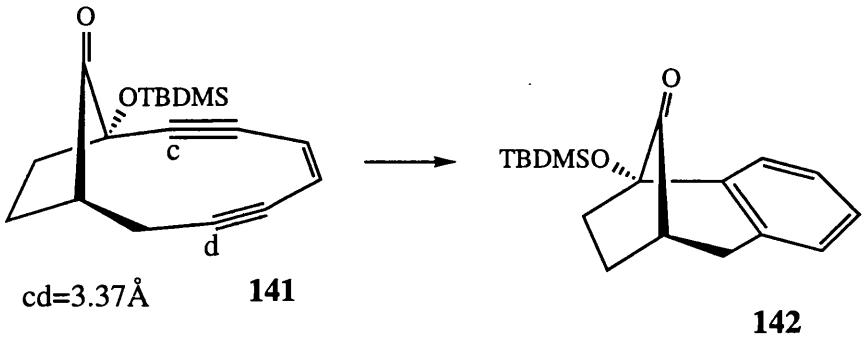
n=1-8

ring size =9-16 membered

Scheme 49

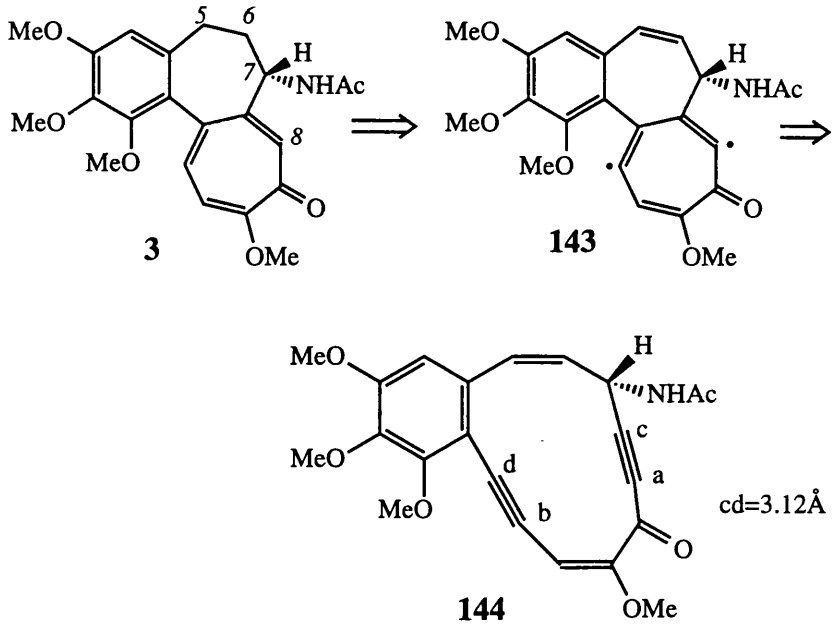
However, Magnus *et al*[54(a)] have argued that some additional factors such as the strain energy difference between the starting material and the cycloaromatised product should also be taken into consideration. They found that the cd distances of (**139**) and (**141**) (Scheme 50) were 3.39Å and 3.37Å, respectively, but that the former cyclised 650 times faster than the latter despite the similarity in the cd distances. It was reasoned that the strained, boat-shaped cyclohexanone ring was preferred for (**139**) in its ground state and that this conformation changed to chair-shaped after cycloaromatisation, thus releasing about 6 kcal of strain energy. Contrastingly, there is no such driving force in the case of (**141**).





Scheme 50

Inspired by this fascinating chemistry of enediynes, and also with an interest in preparing novel unnatural enediynes, we therefore decided to approach colchicine by using a Bergman-type cycloaromatisation to construct the tropolonyl ring C. Thus the 12-membered macrocycle (**144**) was designed as the target precursor for such a cyclisation (Scheme 51). Inspection of molecular models suggested that the introduction of an additional benzylic Z-double bond would increase the proximity of the two acetylene termini and also confer additional rigidity to the macrocyclic framework. The cd distance of the precursor (**144**) was calculated to be 3.12Å (MM2, MacroModel 4.0). Considering the precedent reported by Meyer and Sondheimer that Bergman cyclisation can give rise to a seven-membered ring (Schemes 44 and 46), we anticipated that the macrocycle (**144**), with such a short cd distance and high strain energy, would undergo very facile cycloaromatisation to the diradical (**143**).



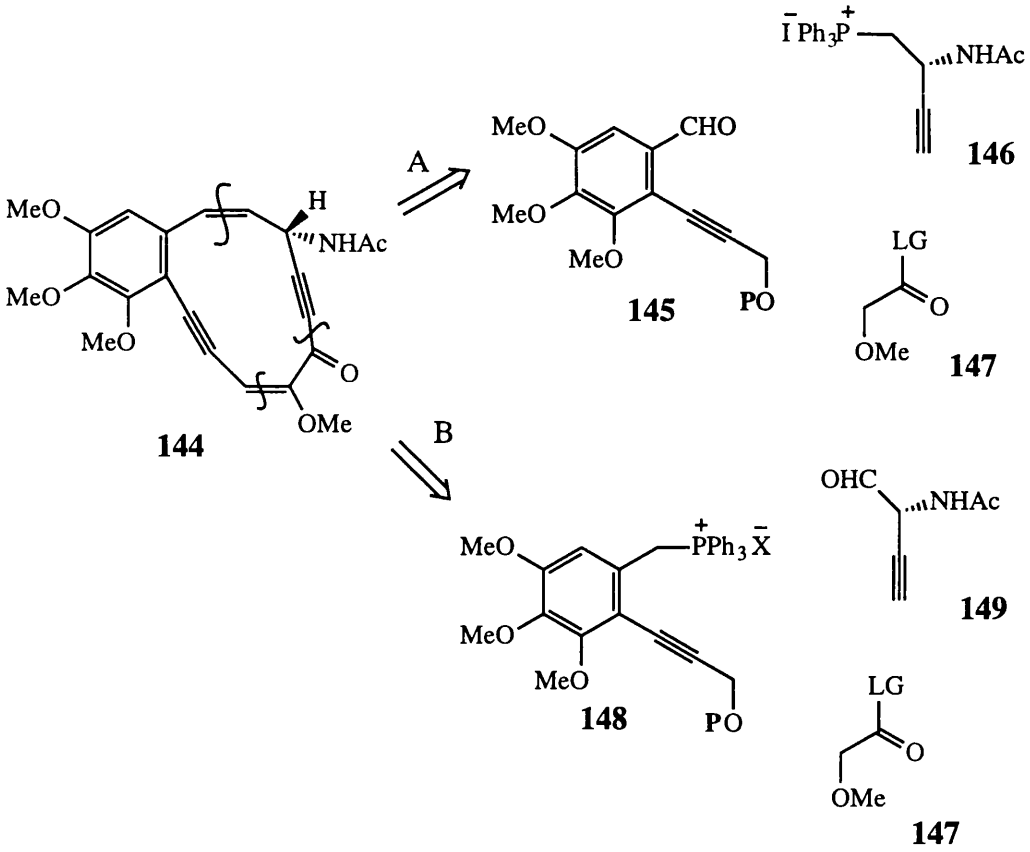
Scheme 51

As one of our preliminary objectives was to control the chirality of the C-7 stereocentre, our efforts to synthesise the macrocycle (**144**) were divided into two areas; namely the preparation of useful fragments incorporating this stereocentre and the construction of the macrocyclic skeleton. It was hoped that eventually the results of these separate investigations could be merged to constitute an efficient asymmetric synthesis of the macrocycle (**144**). However, it must be admitted that we had somewhat underestimated the task of building the macrocycle. Its elusive nature will be revealed in the following sections.

2.1.2. The Investigation of Generation of the C-7 Stereocentre

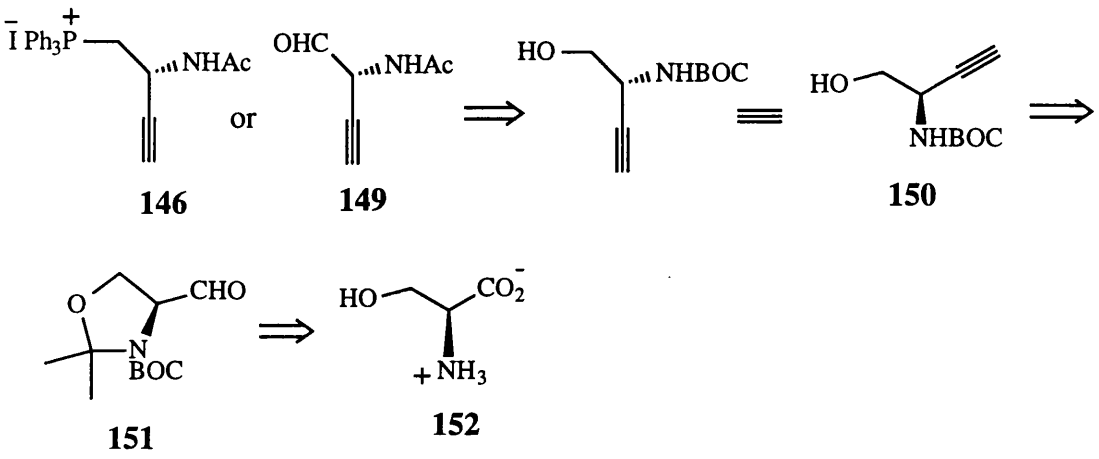
2.1.2.1. The L-Serine-Based Approach

A retrosynthetic analysis of the macrocycle (**144**) is presented in Scheme 52. Thus we planned to introduce the C-7 stereocentre by employing a four-carbon fragment (**146**) or (**149**), which could be attached to the aryl portion (**145**) or (**148**) of the macrocycle using the Wittig reaction or similar technology.



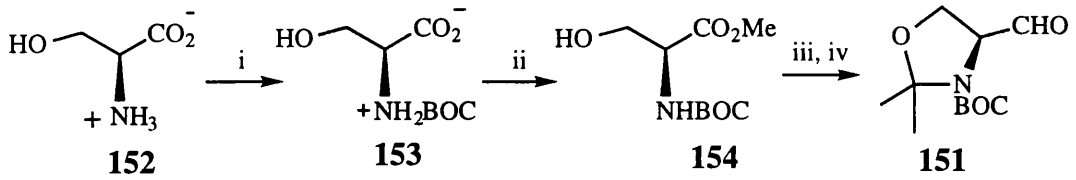
Scheme 52

It was considered that both (**146**) and (**149**) could be formed from cheap, commercially available L-serine (**152**) as shown in the route outlined in Scheme 53.



Scheme 53

One of the synthetic intermediates shown in Scheme 53 is the well-known Garner's aldehyde (**151**). The original preparation of this aldehyde by Garner and Park[56] involved the use of potentially explosive diazomethane to esterify the *N*-protected serine (**153**) (Scheme 54). We are grateful to Professor Richard Taylor and co-

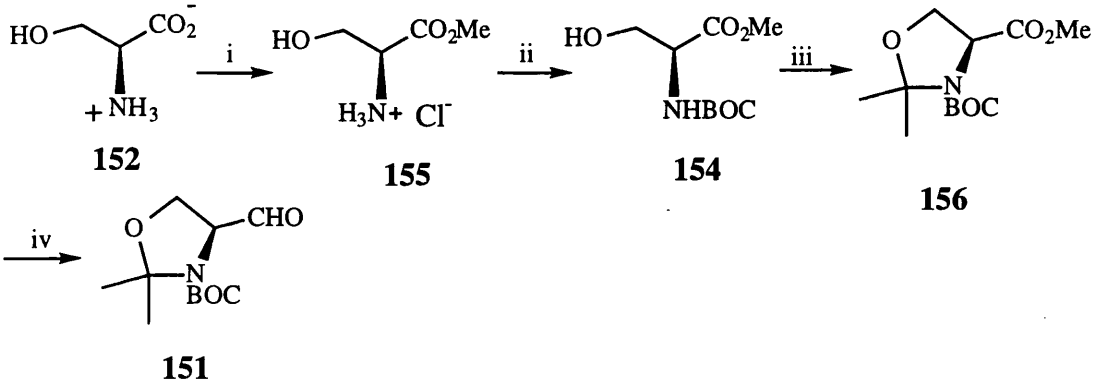


i. $(BOC)_2O$, NaOH; ii. CH_2N_2; iii. TsOH, acetone; iv. DIBAL-H, -78°C

Scheme 54

workers[57] who supplied details of a modified reaction sequence which avoided the use of diazomethane. Hence L-serine (**152**) (Aldrich) was esterified to the methyl ester (**155**) using a combination of acetyl chloride and anhydrous methanol in excellent yield (97%) (Scheme 55). The methyl ester (**155**) was then protected with di-*tert*-butyl dicarbonate ($(BOC)_2O$) and triethylamine in THF to yield the carbamate (**154**). Reaction of this carbamate with 2,2-dimethoxypropane (DMP) and catalytic boron trifluoride etherate gave rise to the doubly protected oxazole-ester (**156**) (93%). Although the pH of the reaction mixtures was not measured, base- or Lewis acid-induced racemisation was

limited as the optical rotation of the oxazole-ester (**156**) was found to be -49°, which is comparable to that reported in the literature[56] (-46.7°). The oxazole-ester was then reduced to the aldehyde (**151**) with DIBAL-H at -78°C in good yield (86%).

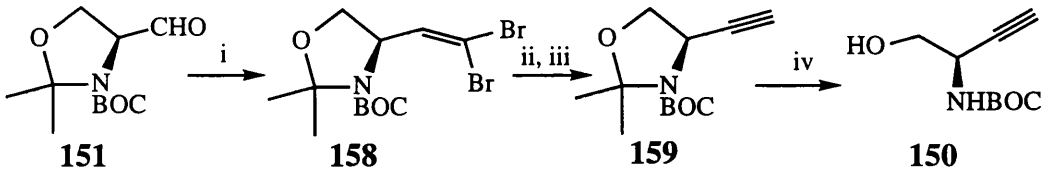


i. AcCl (10eq), MeOH, r.t. (97%); ii. $(BOC)_2O$ (1.5eq), Et_3N (2.2eq), THF, 50°C (90%); iii. DMP (2.2eq), $BF_3.Et_2O$ (10mol%), acetone, r.t. (93%); iv. DIBAL-H (1.1eq), PhMe, -78°C (86%)

Scheme 55

Garner and Park found that the ^1H NMR spectrum of the oxazole-ester (**156**) showed two sets of signals at ambient temperature probably because of the slow interconversion of the rotamers due to the BOC group. These signals merged when the probe temperature was raised to 75°C. We noted the same duplicity of signals and rather complex ^1H NMR spectra occurring to the oxazolidinyl compounds.

Nevertheless, with Garner's aldehyde (**151**) in hand, we sought to transform the formyl group to an acetylene through the use of the Corey-Fuchs protocol[58] (Scheme 56). Thus the aldehyde (**151**) was converted to the known vinyl dibromide[59] (**158**) with



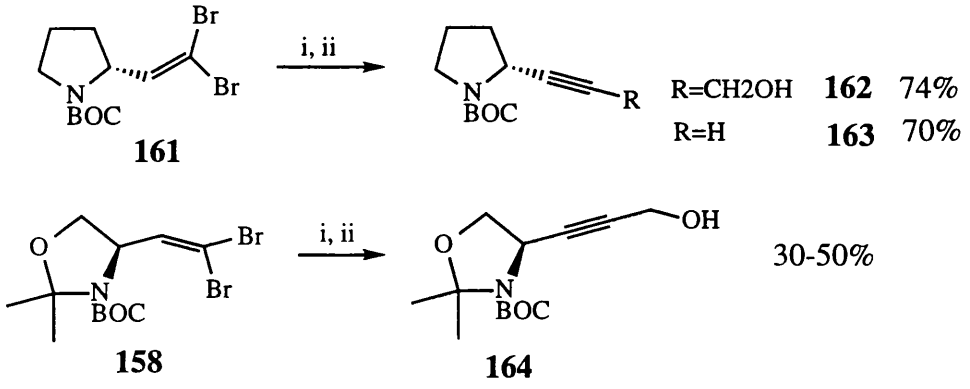
i. Ph_3P (4eq), CBr_4 (2eq), THF, 0-25°C (74%); ii. *n*-BuLi (2.2eq), THF, -78°C; iii. excess *t*-BuOH, 0°C (33%); iv. 4:6 / 1M HCl:MeOH, r.t. (59%)

Scheme 56

triphenylphosphine and carbon tetrabromide. Successful product formation was indicated by the presence in the ^1H NMR spectrum of the characteristic vinylic proton signal (doublet) at 6.45 ppm. When the dibromide (**158**) was treated with two equivalents of *n*-

butyllithium at -78°C in THF and then quenched with *t*-butanol at 0°C, the acetylene (**159**) was formed in modest yield (33%).

Chung and Wasicak[59] reported good yields when they converted the pyrrolidinyl dibromide (**161**) either to the propargylic alcohol (**162**) with *n*-butyllithium and formaldehyde or the terminal acetylene (**163**) by methanol quench (Scheme 57). However, the yield decreased quite drastically to 30-50% when the oxazolidinyl dibromide (**158**) was transformed to the alcohol (**164**) in analogous fashion. This result suggested to us that the oxazolidinyl dibromide (**158**) are unstable under such reaction conditions. Moreover, it was of interest to note a sharp increase in optical rotation was observed when the pyrrolidinyl dibromide (**161**) ($[\alpha]^{26} = -17.4°$) was converted to the acetylene (**163**) ($[\alpha]^{26} = +117.6°$). Similarly, such an increase occurred when the dibromide (**158**) ($[\alpha]^{25} = +0.23°$) was converted to the alkyne (**159**) ($[\alpha]^{25} = -144.7°$).



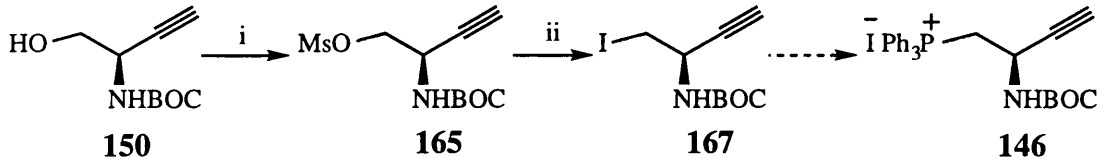
161 **158** **164**

i. *n*-BuLi (2.05eq), -78°C; ii. excess $(CH_2O)_n$ (or MeOH for **163**), -78°C

Scheme 57

The acetylene (**159**) thus obtained was deprotected to yield the alcohol (**150**) in 59% yield together with a 30% recovery of starting material (Scheme 56). A number of reagents including *p*-toluenesulfonic acid, sodium hydrogensulfate, acetic acid, copper sulfate and pyridinium *p*-toluenesulfonate were utilised in an attempt to improve the yield. However, a 6:4 / methanol:1M HCl mixture was eventually found to be the most effective, although even under these vigorous conditions the reaction still did not go to completion.

With the alcohol (**150**) in hand, we first investigated its transformation to the phosphonium salt (**146**) (Scheme 58). Whilst no methanesulfonate (**165**) was obtained when the alcohol (**150**) was reacted with methanesulfonyl chloride in the presence of pyridine and lithium chloride, a good yield (89%) was obtained by utilisation of triethylamine and methanesulfonyl chloride. Under the latter conditions, the formation of highly reactive sulfene is of course possible. Similarly, no desired product was formed



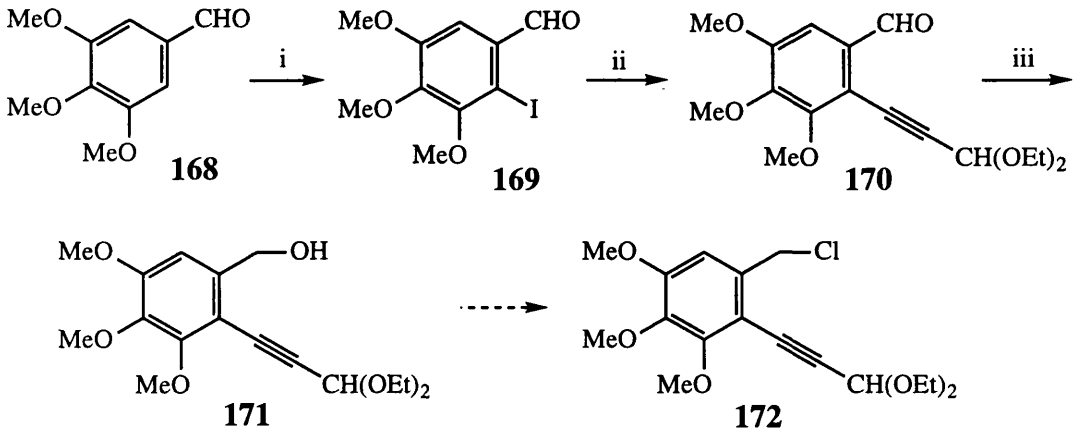
i. MsCl (1.1eq), Et_3N (1.1eq), DCM, 0°C (89%); ii. LiI (1.5eq), THF, sonication, r.t. (70%)

Scheme 58

when the methanesulfonate (**165**) was warmed with sodium iodide in acetone but the unstable iodide (**167**) was formed in 70% yield when the methanesulfonate (**165**) was sonicated with anhydrous lithium iodide in THF. The transformation of the acetylene (**159**) to the iodide (**167**) (Schemes 56 and 58) might suggest that these compounds were extremely sensitive to the reaction conditions used, and that subtle structural changes could result in great differences. In the event, this proved to be the case, and we were not too surprised to find that the iodide (**167**) did not react with triphenylphosphine in benzene or acetonitrile at room temperature and decomposed when a higher temperature was employed.

Since the formation of the phosphonium salt (**146**) was proving to be problematic, we turned our attention to the synthesis of the aldehyde (**149**) and the benzylic phosphonium salt (**148**) according to the retrosynthetic route B attained in Scheme 52. Accordingly, 3,4,5-trimethoxybenzaldehyde (**168**) was reacted under literature conditions to give the aldehyde (**169**) in excellent yield with silver trifluoroacetate and iodine (Scheme 59). A Castro/Heck-type coupling reaction[60] between the aldehyde (**169**) and commercially available propargylaldehyde diethyl acetal using palladium(II) acetate and copper(I) iodide as catalysts gave the aldehyde (**170**) in 63%

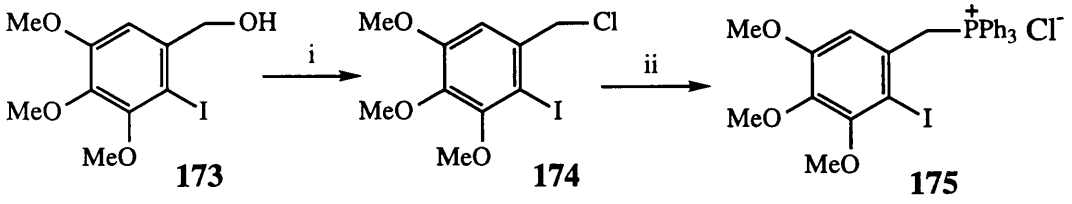
yield with a 36% recovery of starting material. As in other Heck-type palladium-mediated couplings, the active catalyst is expected to be the palladium(0) species generated *in situ* by the reduction of palladium(II) acetate. However, although this reaction worked very well on a sub-gram scale, the yield decreased to an impractical level on attempted multi-gram scale up.



i. CF_3CO_2Ag (1.0eq), I_2 (1.1eq), DCM, r.t. (98%); ii. $Pd(OAc)_2$ (5mol%), CuI (5mol%), PPh_3 (20mol%), $HC{\equiv}CCH(OEt)_2$ (1.2eq), Et_2NH, reflux (63%); iii. $NaBH_4$ (1.5eq), EtOH, 0°C (68%)

Scheme 59

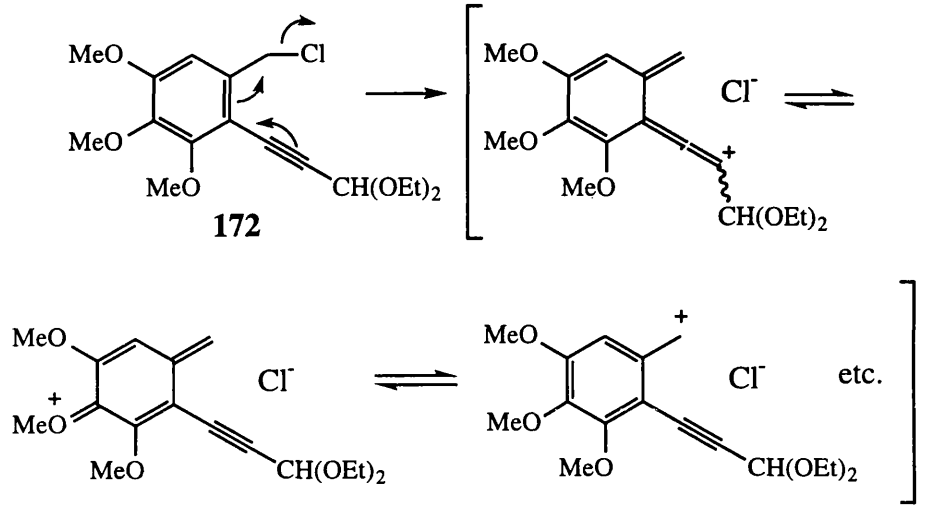
The aromatic aldehyde (**170**) could nevertheless be reduced to the alcohol (**171**) with sodium borohydride. To our surprise, all attempts to convert the alcohol (**171**) to the chloride (**172**) were unsuccessful and led to decomposition. However, the known chloride[61] (**174**) could be easily prepared from the benzyl alcohol (**173**) (Scheme 60) with either thionyl chloride or by an unusually efficient chloride anion displacement of the intermediate mesylate using methanesulfonyl chloride and triethylamine in one pot. The phosphonium salt (**175**) was then duly obtained when the chloride (**174**) was heated with triphenylphosphine in benzene.



i. $SOCl_2$, DCM (92%) or MsCl, Et_3N, DCM (41%); ii. PPh_3, PhH, 50°C (89%)

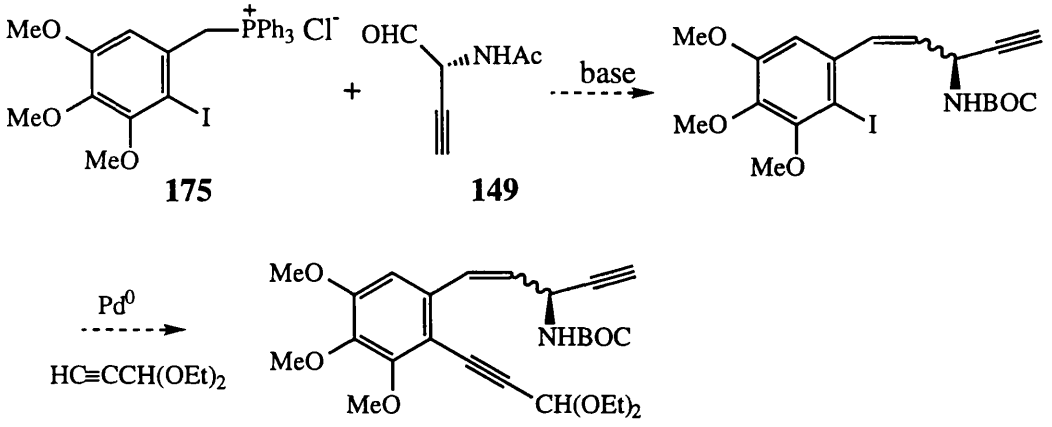
Scheme 60

These observations would suggest that the acetylenic residue *ortho* to the benzylic alcohol is, in some way, responsible for the ease of decomposition of this electron rich benzylic system. As indicated in Scheme 61, it may therefore be necessary to invoke π participation.

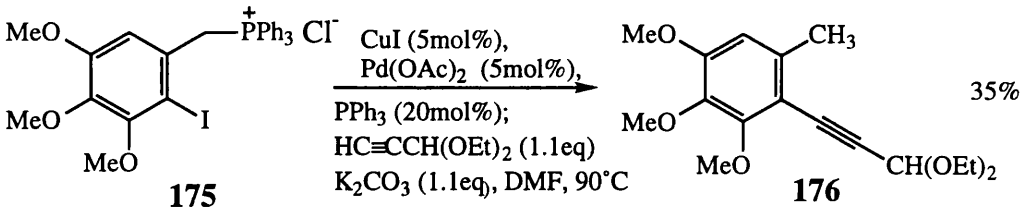


Scheme 61

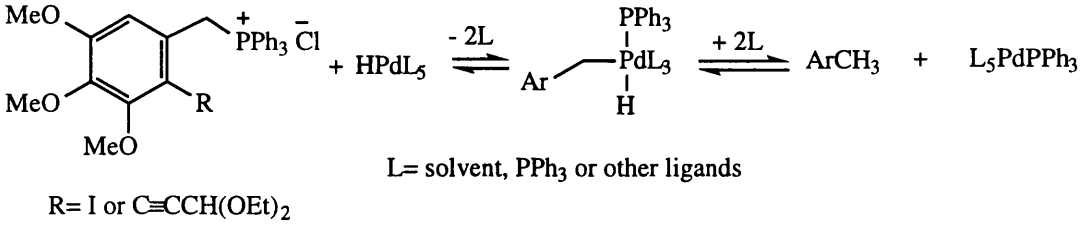
The phosphonium salt (**175**) could be, in principle, used directly as the aryl portion in retrosynthetic route B of Scheme 52 since the aryl acetylenic substituent could be incorporated after coupling of the aromatic and the acetylenic four-carbon fragments (Scheme 62). However, we were interested in finding out whether palladium coupling chemistry could be performed in the presence of phosphonium salts. Interestingly, the toluene derivative (**176**) was the only identifiable product (35% yield) found from such a coupling (Scheme 63). It is proposed that the phosphonium ion was reduced by the hydrido-palladium species present in the catalytic cycle to a toluene derivative.



Scheme 62

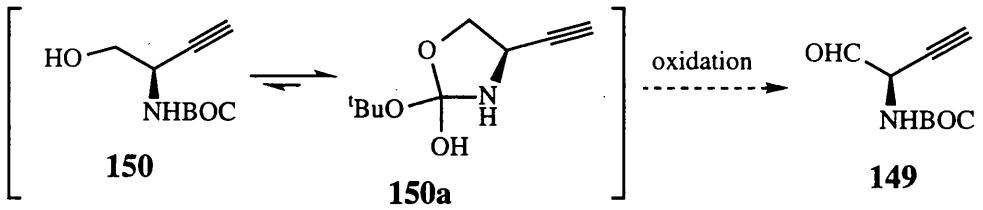


Proposed mechanism:



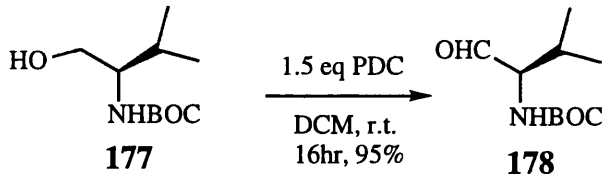
Scheme 63

Although an aryl phosphonium salt as required in Scheme 52 was prepared, oxidation of the alcohol (**150**) to the aldehyde (**149**) was completely unsuccessful. A large number of oxidants were used, including various activated DMSO-based reagents, chromium reagents, and catalytic ruthenium reagents such as tetrapropylammonium perruthenate (TPAP). In all cases the alcohol was either recovered or a large amount of 'baseline' decomposition material was formed. Curiously, the alcohol (**150**) may exist in an equilibrium with the oxazolidinyl derivative (**150a**) (Scheme 64) and thus resists



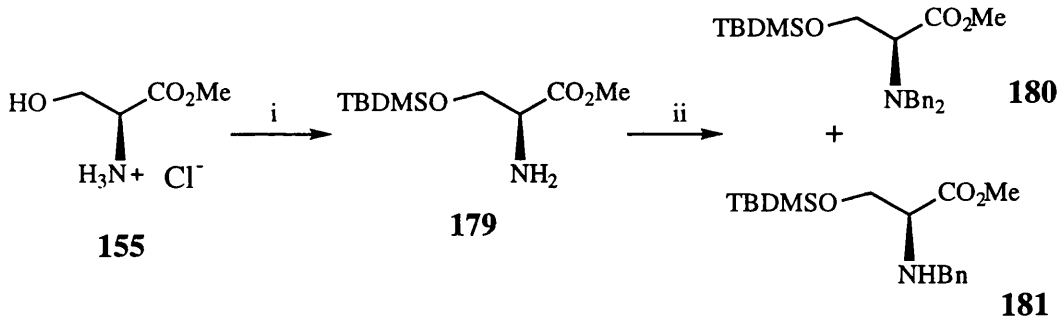
Scheme 64

oxidation. This postulate may also explain the fact that no carbonyl carbon signal was observed in the ^{13}C NMR spectrum of the alcohol (**150**) and that the proton α to the nitrogen atom gave a broad signal in ^{1}H NMR. However, as oxidation of the alcohol[62] (**177**), which possesses a similar structural motif to **150**, to the corresponding aldehyde (**178**) has been reported (Scheme 65), further investigations are certainly required to gain further insight.



Scheme 65

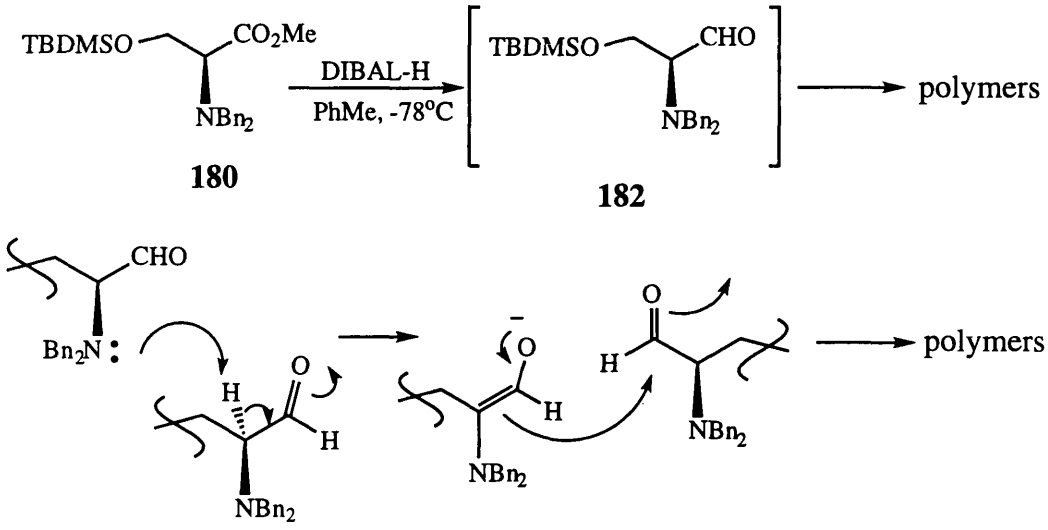
Nevertheless, one more attempt was then made to synthesise the four-carbon fragments (**146**) and (**149**) by changing the protection of the amino group from BOC to the dibenzylamino functionality. Thus the L-serine methyl ester (**155**) was *O*-protected with *t*-butyldimethylsilyl chloride (TBDMSCl) and imidazole in DMF (Scheme 66). The use of triethylamine instead of imidazole resulted in a diminished yield as triethylamine liberated the free amino group, which could then also react competitively with TBDMSCl. Imidazole was too weak a base to effect such liberation and hence it acted only as a catalyst in the silylation. The free amine (**179**) was obtained by washing the reaction mixture with sodium bicarbonate solution.



i. TBDMSCl (1.1eq), imidazole (2.2eq), DMF, r.t.; $NaHCO_3$ (80%); ii. BnBr (2.2eq), Et_3N (2.5eq), DMAP (10mol%), MeCN, 50°C (**180**, 73%; **181**, 12%)

Scheme 66

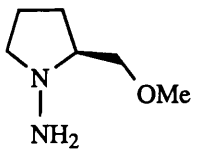
The amine (**179**) was then reacted with benzyl bromide and triethylamine in the presence of catalytic DMAP to give the dibenzylamine (**180**) and the monobenzylamine (**181**) in 73% and 12% yields, respectively. Without DMAP, the di- and monobenzylamines were obtained in 41% and 37% yields, respectively. However, when the dibenzylamine (**180**) was reduced with DIBAL-H, the desired aldehyde (**182**) was not obtained though the formation of a new compound was indicated by t.l.c.. Presumably, the aldehyde (**182**) underwent autocatalytic polymerisation during workup (Scheme 67). As a result, this L-serine-based approach was abandoned.


TBDMSO
CO2Me
NBn2
DIBAL-H
PhMe, -78°C
TBDMSO
CHO
NBn2
polymers
180
182
CHO
Bn2N:
H
O
H
NBn2
O
H
H
NBn2
O
H
NBn2
polymers

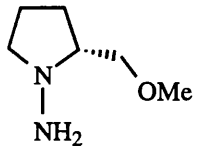
Scheme 67

2.1.2.2. The RAMP/SAMP-Based Approach

During the seventies and eighties, Enders and co-wokers pioneered the use of (*S*)- and (*R*)-1-amino-2-methoxymethylpyrrolidine (SAMP **183** and RAMP **184**) as

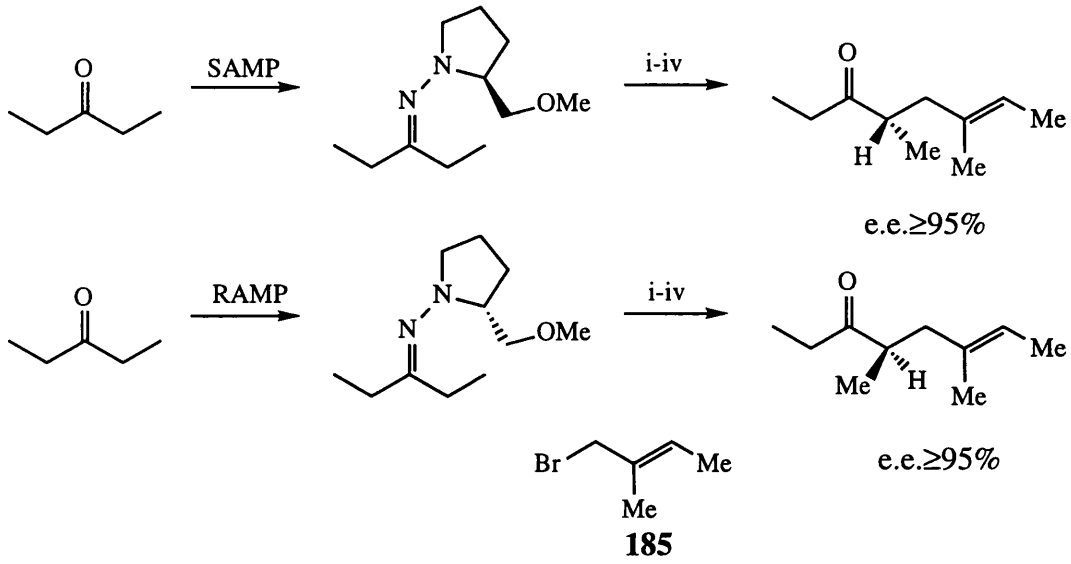


183



184

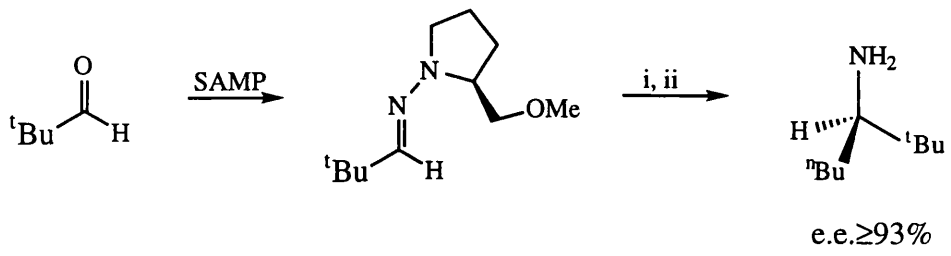
auxiliaries in asymmetric syntheses[63]. High enantiomeric excesses (e.e.) were obtained in alkylations (Scheme 68) and chiral amines could be obtained stereospecifically by nucleophilic addition to the corresponding hydrazones followed by N-N bond cleavage (Scheme 69). Denmark *et al* have also demonstrated that organocerium reagents provide higher yields in the addition step[64(a)] than organolithium reagents and that the resulting hydrazine can be cleaved under mild conditions with lithium metal in liquid ammonia[64(b)] (Scheme 70). It was noted that only 1,2-addition was observed with α,β–unsaturated SAMP hydrazone.



185

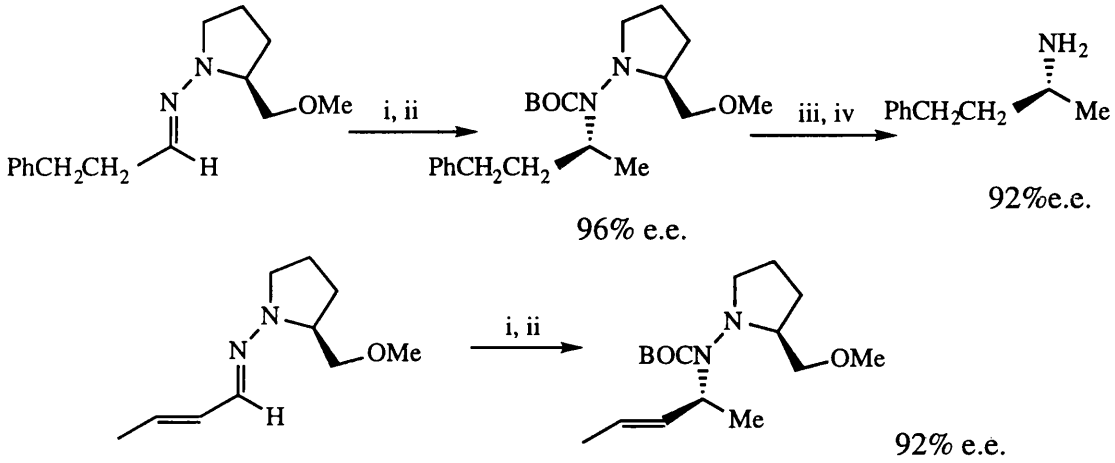
i. LDA, Et_2O, 0°C; ii. **185**, -110°C; iii. excess MeI, 60°C; iv. 3N HCl, *n*-pentane (70% over 4 steps)

Scheme 68



i. *n*-BuLi, -78°C; ii. H_2/Ni (73% over two steps)

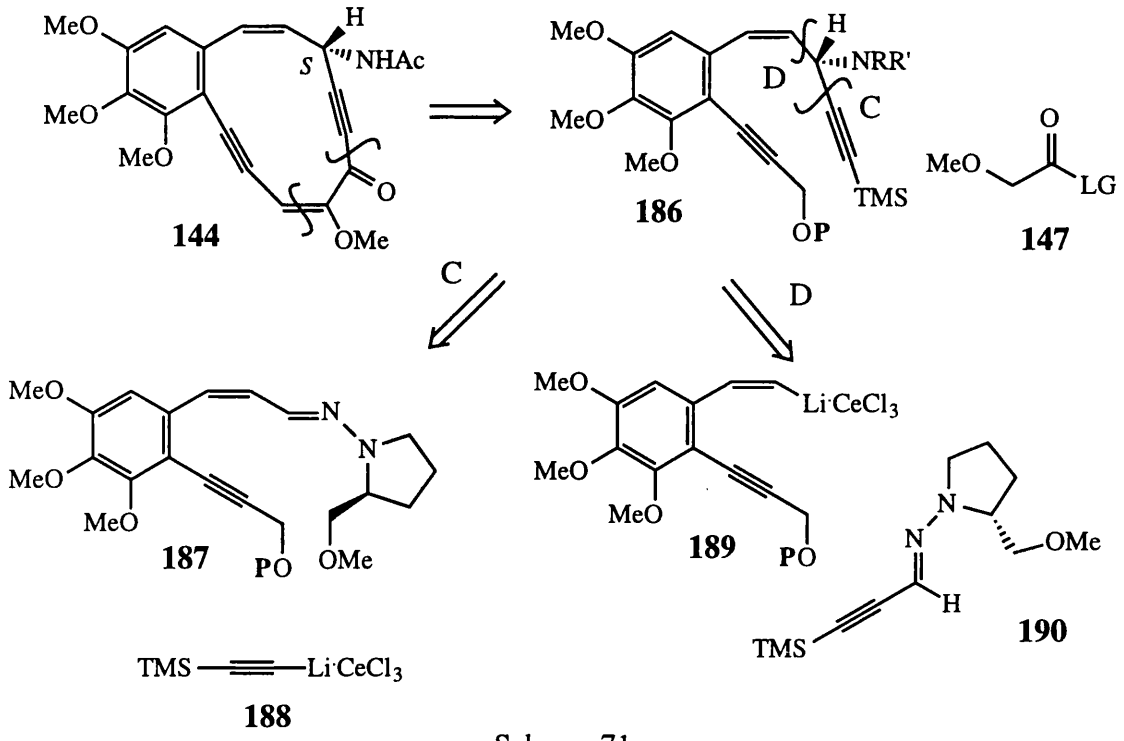
Scheme 69



i. MeLi·$CeCl_3$, -78°C; ii. $(BOC)_2O$ (~80% over 2 steps); iii. Li/NH_3; iv. NH_4Cl (84%)

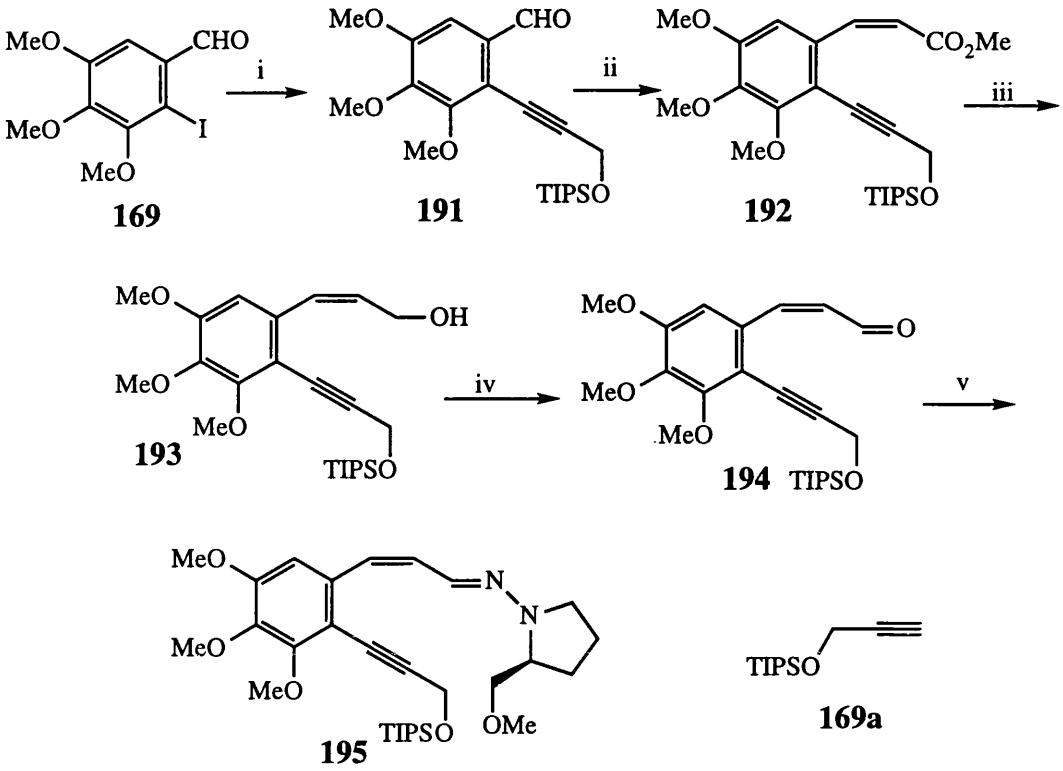
Scheme 70

Following this precedent, an attempt was made to generate the stereocentre of the macrocycle (**144**) using the SAMP/RAMP methodology. According to this retrosynthetic plan (Scheme 71), the intermediate (**186**) could be synthesised either by adding an acetylenic cerium reagent (**188**) to the SAMP hydrazone (**187**) (route C) or, alternatively, by adding the vinylic cerium reagent (**189**) to the RAMP hydrazone (**190**) (route D). SAMP and RAMP were used in routes C and D respectively so that the required *S* chirality of the stereocentre could be generated.



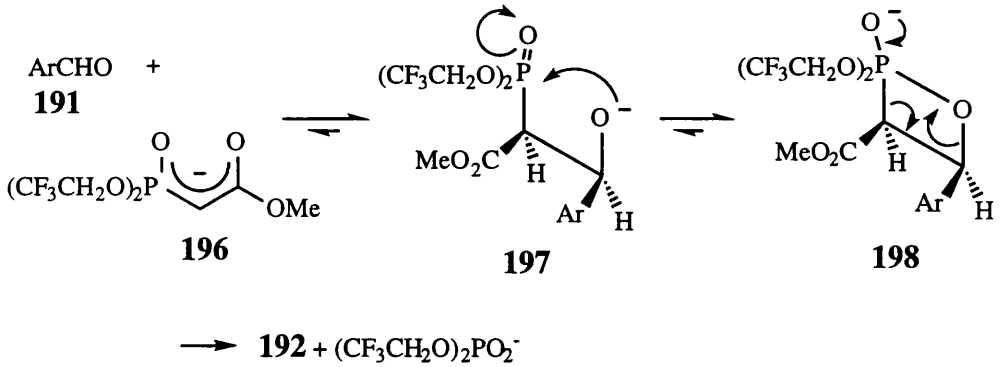
Scheme 71

In order to investigate route C, the α,β–unsaturated SAMP hydrazone (**195**) was prepared as shown in Scheme 72. Thus the iodoarene aldehyde (**169**) was coupled using the palladium methodology which had served us well before, but in this instance the known propargyl alcohol derivative[65] (**169a**) was used to give the aromatic alkyne (**191**). A few palladium catalysts and reaction conditions were tried for this coupling and the best result was obtained by using bis(triphenylphosphine)palladium(II) chloride and stirring the reaction mixture at room temperature for 4 days. The benzaldehyde (**191**) was then transformed to the *Z*-α,β–unsaturated ester (**192**) with Still's bis(trifluoroethyl)phosphonate[66] (**191a**) in good yield and stereoselectivity (>99% *Z*). The excellent *Z*-selectivity of this Horner-Emmons reaction is attributed to the highly electron-withdrawing trifluoroethyl groups[67] of the reagent (**191a**) which effect an increase in the rate of elimination of the kinetically favoured adduct (**197**) of the aldehyde (**191**) and the anion (**196**) (Scheme 73). The ester (**192**) was completely reduced with DIBAL-H to the allylic alcohol (**193**) and then re-oxidised to the aldehyde (**194**) with manganese dioxide in 76% yield over the two steps. The required SAMP hydrazone (**195**) was obtained in 70% yield by warming the aldehyde (**194**) with SAMP in benzene at 45°C.



i. $(PPh_3)_2PdCl_2$ (5mol%), CuI (5mol%), Et_2NH, **169a**, r.t. (83%); ii. $(CF_3CH_2O)_2P(O)CH_2CO_2Me$ (**191a**) (1.1eq), 18-Crown-6 (1.1eq), $KN(TMS)_2$ (1.1eq), THF, -78°C (80%); iii. DIBAL-H (2.2eq), PhMe, -78°C (91%); iv. MnO_2 (10eq), DCM, r.t. (84%); v. SAMP (1.05eq), PhH, 45°C (69%)

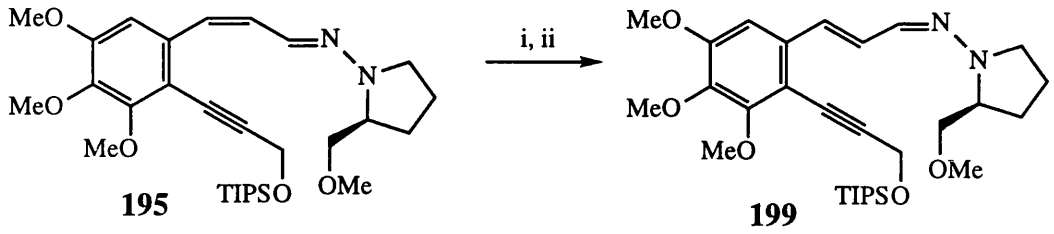
Scheme 72



Scheme 73

Although addition of nucleophiles such as acetylide anion to carbon-nitrogen double bonds is less efficient than to their carbonyl congeners, the employment of a Lewis acid has been found to boost this addition[68]. Therefore, in order to investigate the addition of the trimethylsilylacetylenic cerium reagent (**188**) (Scheme 71) to the SAMP hydrazone (**195**), two experiments were conducted. In each experiment, the organocerium reagent was prepared using the literature procedure[64(a),69] and the

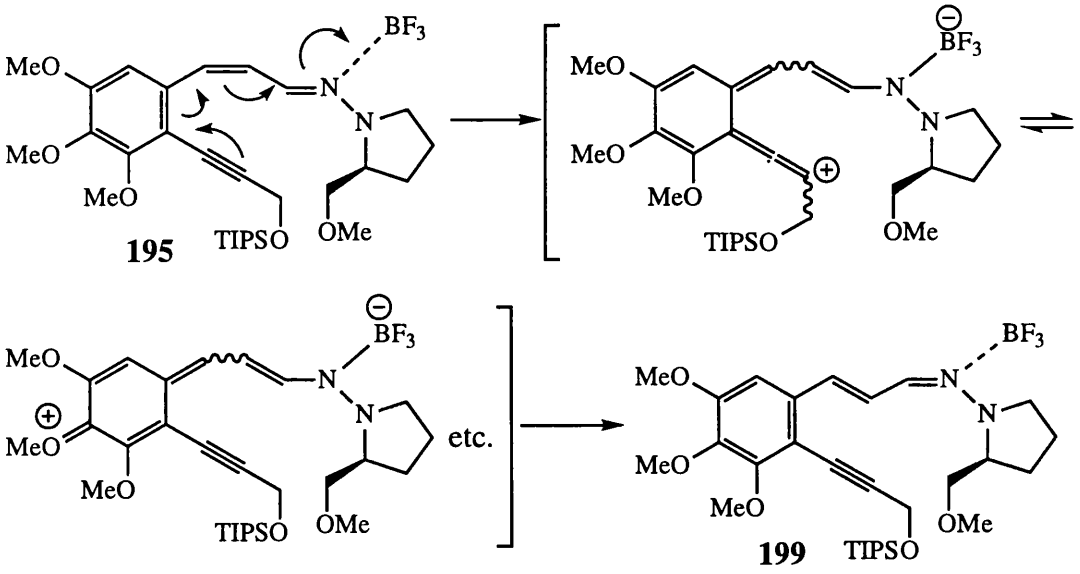
hydrazone (**195**) was added at -78°C. However, a Lewis acid, boron trifluoride etherate, was added in only one of the experiments. The control experiment without Lewis acid showed no reaction even when the temperature was raised to 40°C. The other experiment, however, as evidenced by t.l.c. did show a complete conversion of the starting material to a new compound on warming up to room temperature. Unfortunately, upon isolation and purification, the product was identified as the *E*-isomer (**199**) of the starting material (Scheme 74). Presumably, this immensely conjugated and electron-rich



i. $BF_3{\cdot}Et_2O$, THF, -78°C; ii. **188**, THF, -78°C (74%)

Scheme 74

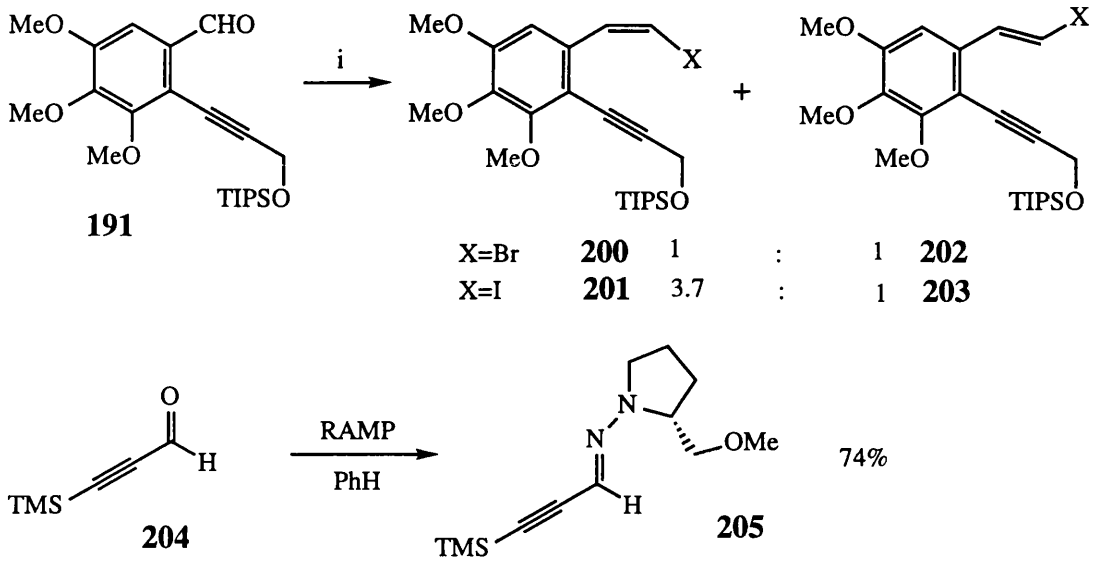
system (**195**) underwent Lewis acid-induced isomerisation instead of Lewis acid-mediated nucleophilic addition with the highly reactive organocerium reagent (Scheme 74a).



Scheme 74a

Meanwhile, the feasibility of route D in Scheme 71 was also being investigated. Thus the *Z*-vinyl halides (**200**) and (**201**) were prepared from the aldehyde (**191**) and

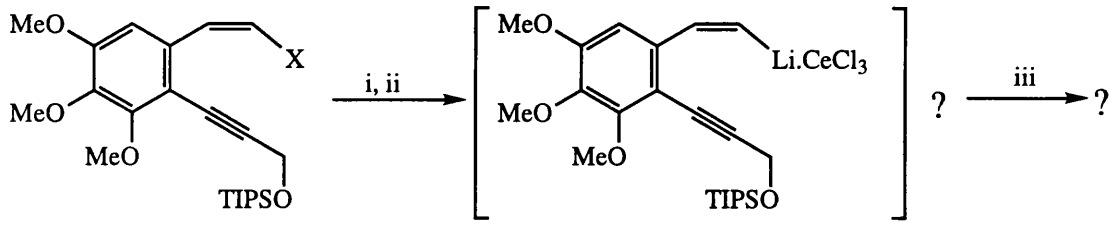
the corresponding phosphonium salts according to Stork's method[70] (Scheme 75). It was noted that the formation of the ylide was so slow that practically no Wittig reaction occurred if the base was added to the phosphonium salts at -78°C and so the addition was carried out at either 0°C or room temperature. As reported, the iodo-ylide showed a higher stereoselectivity (Z:E = 3.7:1) than the bromo analogue (Z:E ≈ 1:1). Trimethylsilylpropargylaldehyde (**204**) was then prepared by a literature procedure[71] and reacted with RAMP to give the unstable RAMP hydrazone (**205**).



i. $XCH_2PPh_3^+X^-$ (2eq), 18-crown-6 (2eq), $KN(TMS)_2$ (2eq), THF, -78°C (X=Br, 92%; X=I, 89%)

Scheme 75

Prior to addition to the RAMP hydrazone (**205**), the vinyl halides (**200**) and (**201**) were converted *in situ* to the corresponding organocerium reagents (**206**) (Scheme 76) by lithium-halogen exchange with either *n*-butyllithium or *t*-butyllithium at -78°C followed by transmetallation with anhydrous cerium(III) chloride. However, on each occasion, only unidentifiable products were formed from the addition. In all probability, the vinyl halides (**200**) and (**201**) were too unstable towards the lithiation conditions and polymerisation of the highly unsaturated molecule occurred.



200/201 **206**

i. *n*-BuLi (1eq) or *t*-BuLi (2eq), THF, -78°C; ii. $CeCl_3$, THF, -78°C; iii. **205**

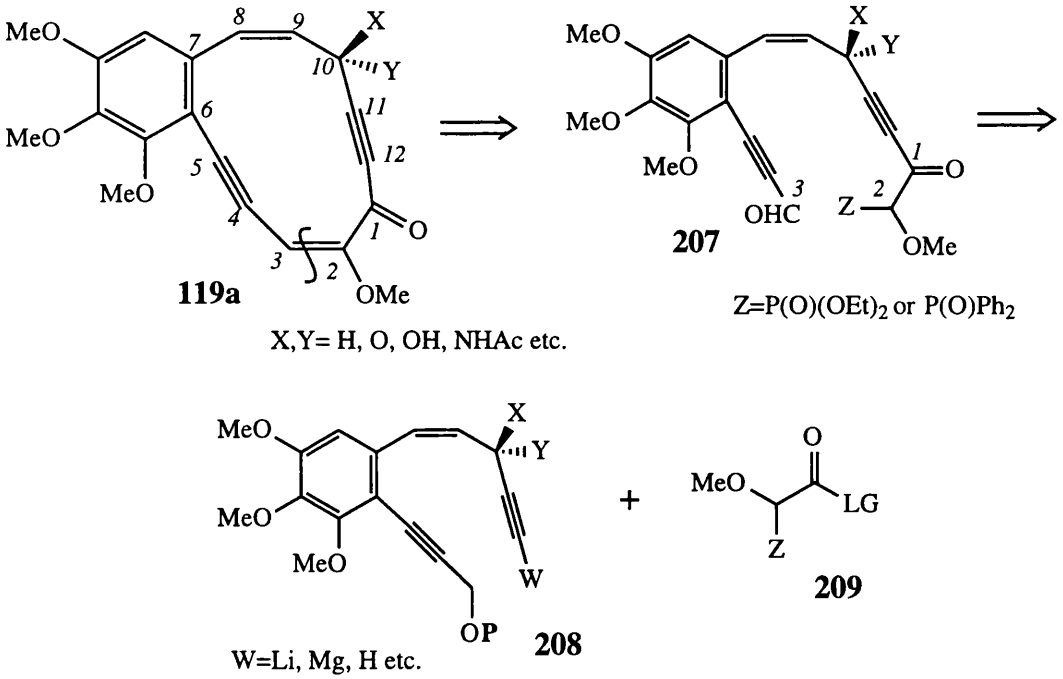
Scheme 76

The above approaches constituted the major part of our work directed towards the objective of useful building blocks in which the correct chirality of the crucial stereogenic centre was incorporated. At the same time however, as outlined below, a variety of other studies, model and otherwise, were being investigated with a view to construction of the macrocyclic enediyne framework.

2.1.3. The Construction of the Macrocyclic Framework

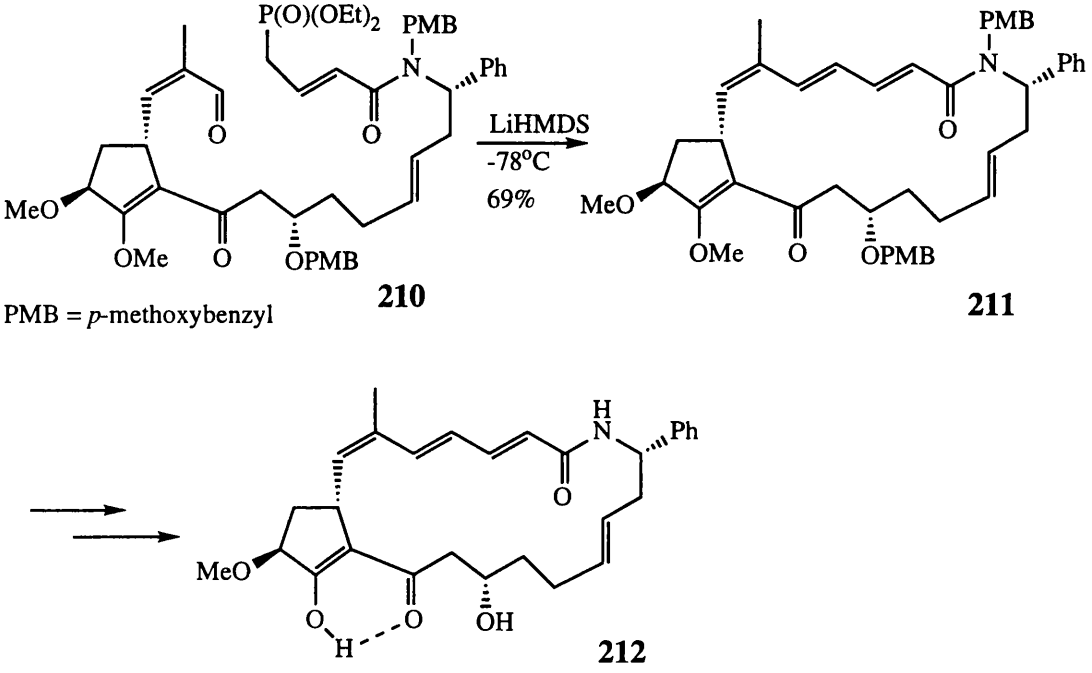
Having now described our efforts towards incorporation of the C-7 stereocentre, the work dedicated to the building of the macrocyclic framework will be discussed. As the primary objective was to assemble the 12-membered carbon skeleton, all compounds in this section are either achiral or racemic, and, apart from one exception, no attempt was made to separate stereoisomers.

A preliminary retrosynthetic analysis of the desired macrocycle incorporating the benzylic double bond is shown in Scheme 77. The aim was to form the macrocycle (**119a**) by an intramolecular olefination reaction of the Wadsworth-Horner-Emmons-type using precursor (**207**) between C-2 and C-3. In turn, precursor (**207**) could be formed by a nucleophilic attack of the acetylide anion (**208**, W=metal) on to the methoxyacetic acid derivative (**209**).



Scheme 77

Although *E*-double bonds are usually obtained from Wadsworth-Horner-Emmons olefination, we envisaged that the C2-3 double bond could be formed with the required stereochemistry from the intermediate β-hydroxyphosphonate either *via* a radical elimination protocol or because the strain of the macrocyclic framework would strongly disfavour the formation of a *E*-double bond. There are a number of precedents in which intramolecular Wadsworth-Horner olefination is employed to effect macrocyclisations[72]. For instance, in the total synthesis of (+)-Hitachimycin[72(f)] (**212**), Smith *et al* converted the phosphonate (**210**) to the macrocycle (**211**) in good yield (Scheme 78).

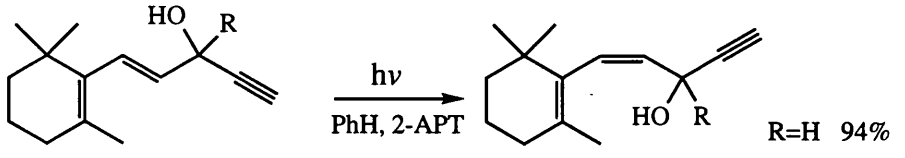


Scheme 78

In order to synthesise the acetylene (**208**, W=H), we sought to develop a method by which the benzylic *Z*-1,4-enyne moiety could be constructed efficiently. Certainly, Still's bis(trifluoroethyl)phosphonate (**191a**) could be employed to give a benzylic *Z*-double bond as previously described in Scheme 72. However, a reduction-oxidation sequence had to be carried out to form the α,β-unsaturated aldehyde (**194**) before an acetylenic group could be incorporated into the molecule. We therefore attempted to develop alternative methods in order to increase the efficiency of the formation of the *Z*-

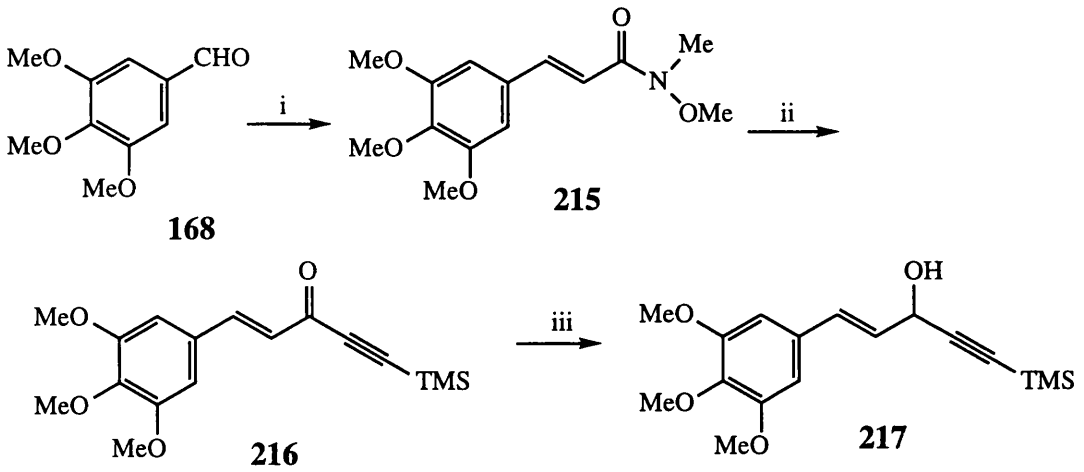
1,4-enyne moiety.

In the first instance, we investigated the feasibility of photoisomerisation of the more easily accessible benzylic *E*-double bond to the *Z*-enyne. We were particularly encouraged by a report from Okamura *et al*[73] who have described the complete conversion of the *E*-β-ionols (**213**) to the *Z*-isomers (**214**) in 9-15 hours by irradiation



213 **214**

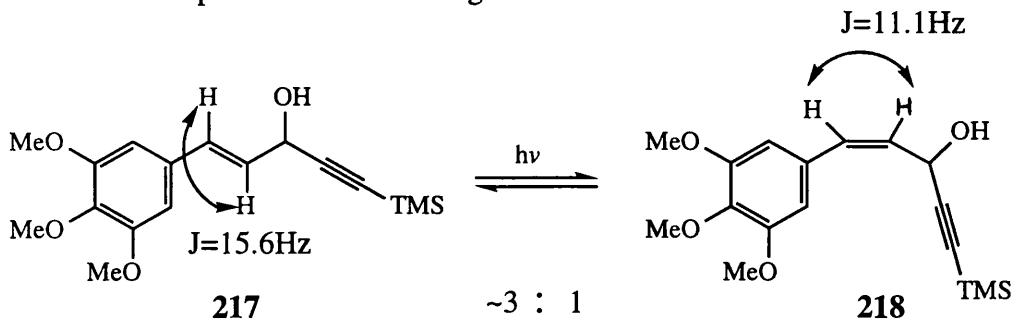
(mercury lamp) in the presence of 2-acetonaphthalene (2-APT) as a sensitiser. As the 1,4-enyne moiety of (**214**) resembled the enyne system of the fragment which we required (**208,** X or Y=OH), we considered that the benzylic *Z*-double bond might be obtained *via* a similar photoisomerisation. A model compound was therefore synthesised as shown in Scheme 79. 3,4,5-Trimethoxybenzaldehyde (**168**) was transformed into the α,β-unsaturated hydroxamate (**215**), which was then converted to the acetylenic ketone (**216**) according to Weinreb's procedure[74] in excellent overall yield. Reduction of the ketone (**216**) with DIBAL-H gave the required alcohol (**217**) for photoisomerisation studies.



i. Ph_3P=CHCONMe(OMe) (1eq), DCM, r.t. (90%); ii. TMSC≡CLi (1.5eq), THF, 0°C; 2M HCl (98%); iii. DIBAL-H (excess), PhMe, -78°C (95%)

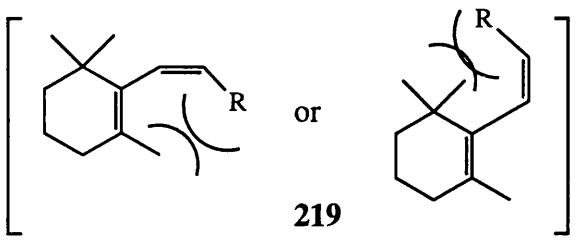
Scheme 79

A solution of the alcohol (**217**) in benzene (0.013M) was then irradiated[74a] (200W medium pressure mercury lamp) at ambient temperature under a stream of argon with 2-APT as a sensitiser. This rather low concentration was used only because of the size of the quartz photochemistry apparatus. Soon after the irradiation had commenced, generation of the *Z*-isomer (**218**) was indicated by both t.l.c. and ^{1}H NMR spectroscopy of the reaction mixture. The vinylic proton β to the aryl ring of the *E*-isomer (**217**) gave a doublet of doublets at 6.20 ppm (J=15.6 and 6.11 Hz) while a new doublet of doublets at 5.77 ppm (J=11.1 and 8.4 Hz) indicated the formation of the *Z*-isomer. An equilibrium was established when the reaction mixture was irradiated for about 36 hours and the ratio of the *E*- to *Z*-isomers was shown to be about 3:1 by ^{1}H NMR spectroscopy (Scheme 80). By comparison of the t.l.c. and crude ^{1}H NMR spectrum obtained after the equilibrium had been established with those obtained earlier, it was evident that considerable decomposition was occurring.

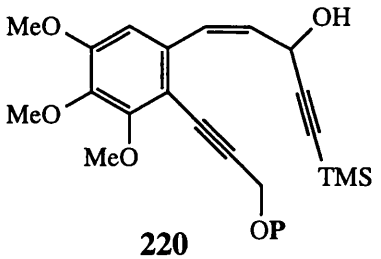


Scheme 80

Consequently, it was concluded that this method was unsuitable for further development due to the slow attainment of equilibrium, the relatively low *Z* to *E* ratio at equilibrium and the considerable decomposition that occurred during the rather long reaction time. One possible reason is proposed here for the contrasting results of the facile photoisomerisation of the β-ionols (**213**) and the rather disappointing conversion of the alcohol (**217**). Liu *et al*[75] suggested that the possible conformations of the *Z*-ionyl derivative (**219**) shown below were under severe steric hindrance and so its structure should be skewed leading to diminished conjugation between the double bonds. This



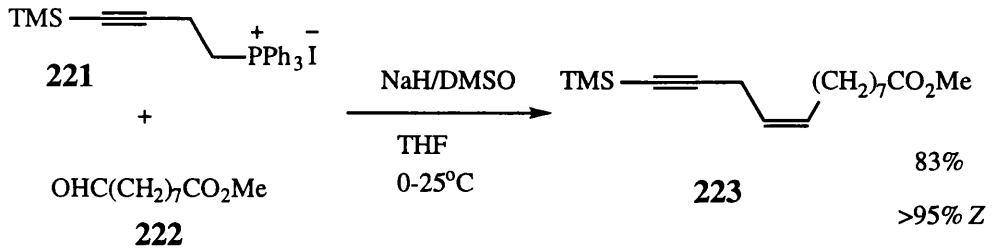
219



220

phenomenon considerably raises the S_0 energy level of the *Z*-isomer compared to the *E*-isomer. As a result, there is good discrimination in the sensitised excitation to the T_1 state between the *E*- and *Z*-isomers and the former would be converted to the latter efficiently. However, such steric hindrance is not present in the *Z*-model compound (**218**) or in the 'real' compound (**220**) and hence the S_0 energy levels of the *Z*- and *E*-isomers would be separated by a small energy gap. Amongst other factors, the absence of a good discrimination between the *Z*- and *E*-isomers during the sensitised excitation resulted in the observed equilibrium.

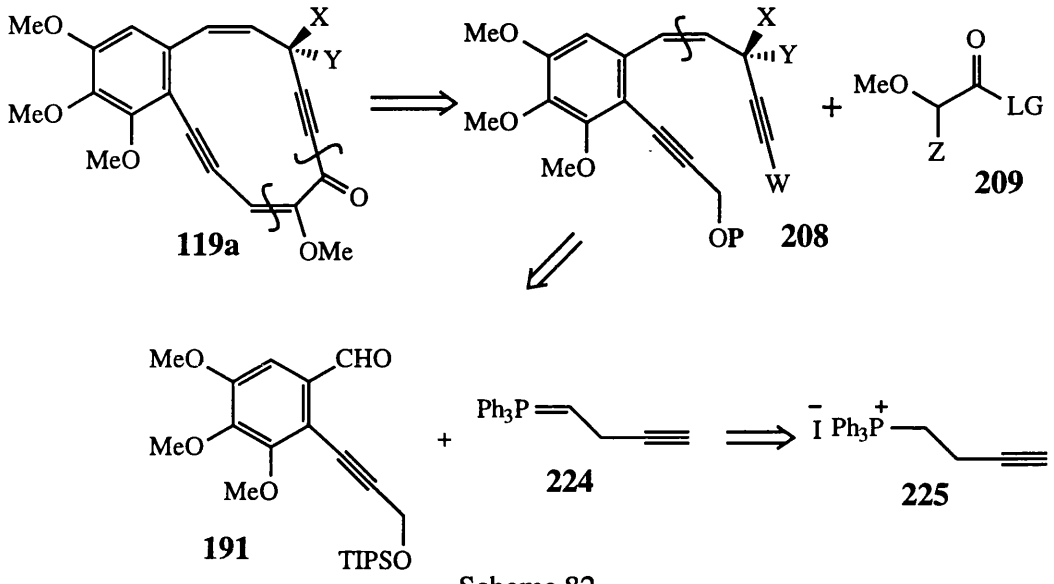
We therefore sought to form the benzylic Z-double bond required in the acetylene (**208**, W=H) using alternative methods. An obvious choice was a Wittig reaction between the aldehyde (**191**) and an unstabilised ylide with appropriate functionalities. Jones *et al*[76] have reported that the use of the Wittig reagent (**221**) in the synthesis of the 1,4-enyne (**223**) from the aldehyde (**222**) gave excellent *Z*-selectivity (Scheme 81). This reagent



Scheme 81

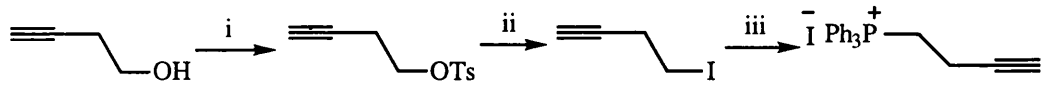
(**221**) could be very useful to us in the synthesis of the 1,4-enyne (**208**, W=TMS, X,Y=H). However, as shown in Scheme 77, since the formation of an acetylide anion

(**208**, W=metal) would be required for the coupling reaction with methoxyacetic acid derivative (**209**), the trimethylsilyl group at the acetylene terminus of reagent (**221**) was not necessary in our case. As a result, we planned to form the 1,4-enyne (**208**, W=H, X,Y=H) from a reaction between the aldehyde (**191**) and the ylide (**224**) (Scheme 82).



Scheme 82

The phosphonium salt (**225**) could be easily synthesised from the iodide (**227**) prepared by the method of Eglington and Whiting[77] (Scheme 83). Since one equivalent of base was enough to generate the ylide from the phosphonium salt (**225**) (see below), the protons α to the phosphonium group are evidently more acidic than that of the alkyne group.



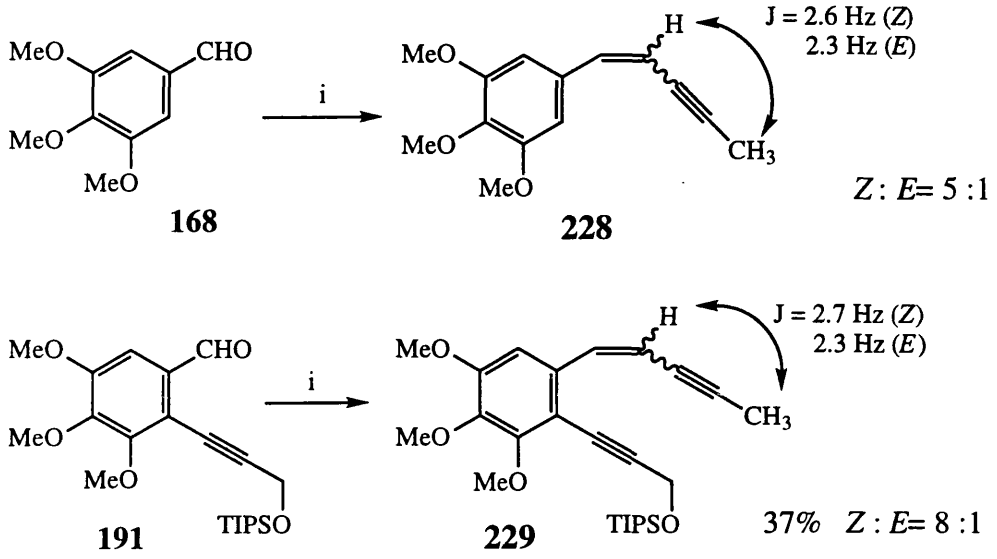
226 **227** **225**

i. TsCl (1.1eq), pyr (1.5eq), <20°C (80%); ii. NaI (1eq), acetone, reflux (81%); iii. PPh_3 (1eq), benzene, 60°C (78%)

Scheme 83

When the phosphonium salt (**225**) was treated with 3,4,5-trimethoxybenzaldehyde (**168**) or the aldehyde (**191**) according to Jones' procedure using sodium hydride in DMSO as base, a mixture of *Z*- and *E*-isomeric compounds was

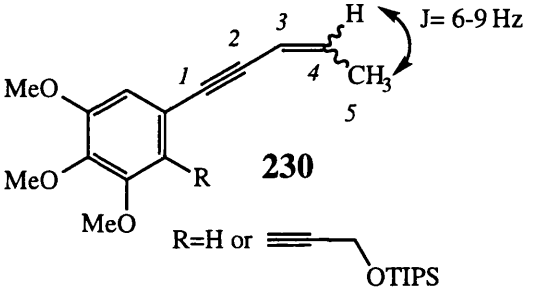
obtained (Scheme 84). The products were however shown by ^1H NMR spectroscopy to be the unexpected 1,3-enynes (**228**) and (**229**) instead of the desired 1,4-enynes, since a new methyl signal was present while no acetylenic proton signal was observed. Although the isomeric compounds (**230**) would also give very similar ^1H NMR signals, they were



i. **225** (1.2eq), NaH (1.1eq), DMSO/THF, 0-25°C

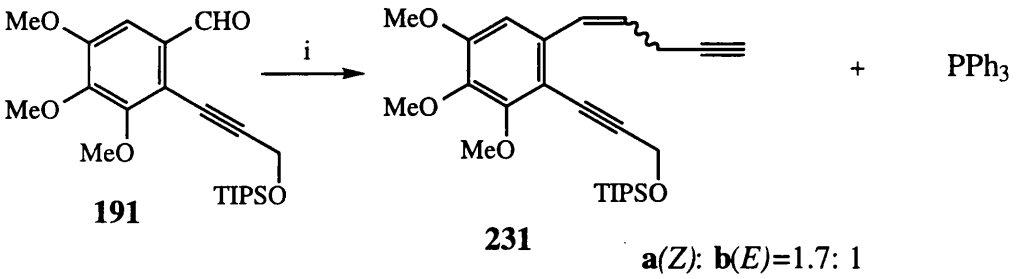
Scheme 84

excluded from the structural deduction because a long-range coupling was observed in the products between the methyl and vinylic protons (J=2.3-2.7 Hz), while the coupling constant between the C-4 and C-5 protons of compound (**230**) would be in the range of 6-9 Hz.



Fortunately, the desired product (**231**) was produced when the Wittig reaction was carried out according to Stork's procedure[70] using excess phosphonium salt (**225**) and 1.1 equivalent of KHMDS (Scheme 85). However, the *Z* to *E* ratio of the 1,4-enyne

(**231**) was shown to be only 1.7:1 by ^1H NMR spectroscopy and no improvement in stereoselectivity in favour of the formation of *Z*-isomer was obtained by varying the reaction conditions or employing co-solvents such as DMSO or 1,3-dimethyl-3,4,5,6-

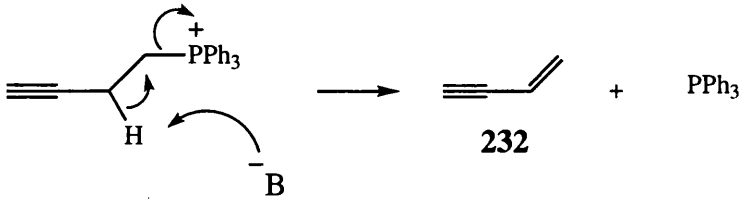


191 **231** **a**(*Z*): **b**(*E*)=1.7: 1

i. **225** (1.3eq), KHMDS (1.1eq), 18-crown-6 (1.1eq), THF, -78-25°C (30-80%)

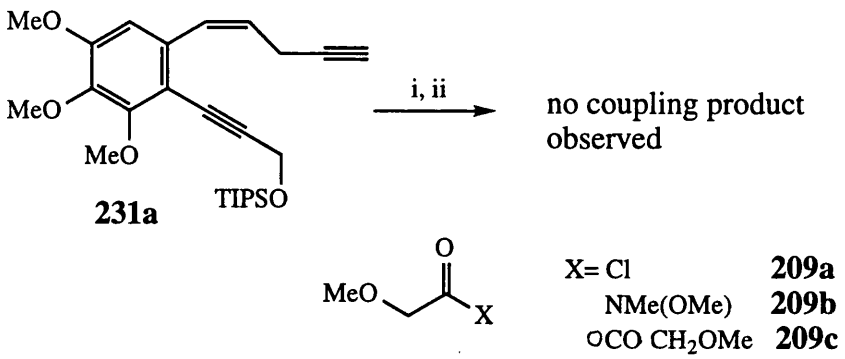
Scheme 85

tetrahydro-2(1*H*)-pyrimidinone (DMPU). Moreover, the yield of the reaction was found to vary from 30 to 80% although every effort was made to reproduce the same conditions shown in Scheme 85. Curiously, the major by-product of this reaction was found to be triphenylphosphine, which may be formed together with the volatile enyne (**232**) when strongly basic KHMDS attacks the propargylic proton of the phosphonium ion (Scheme 86). As the formation of triphenylphosphine was not observed in the generation of the 1,3-enyne (**228**) and (**229**) (Scheme 84), we assumed that sodium hydride in DMSO is probably not sufficiently basic to effect such deprotonation.



Scheme 86

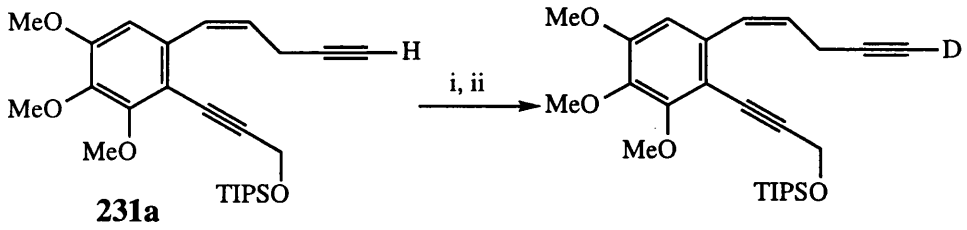
Despite the problems encountered in the Wittig step, the coupling between the *Z*-1,4-enyne (**231a**) and the methoxyacetic acid derivatives (**209a-c**) was studied (Scheme 87). In THF, a brown solution was obtained upon the addition of *n*-butyllithium to the *Z*-enyne (**231a**) at -78°C. When the methoxyacetic acid derivative (**209a**) or (**209b**) was



i. *n*-BuLi (1.1eq), THF, -78°C; ii. **209a-c**, -78-25°C

Scheme 87

added, the reaction mixture gradually turned from brown to purple, green and then light brown on warming up to room temperature. Although possible anion generation was indicated by the colour changes of the reaction mixture, no identifiable compound was obtained besides unreacted *Z*-enyne (**231a**).

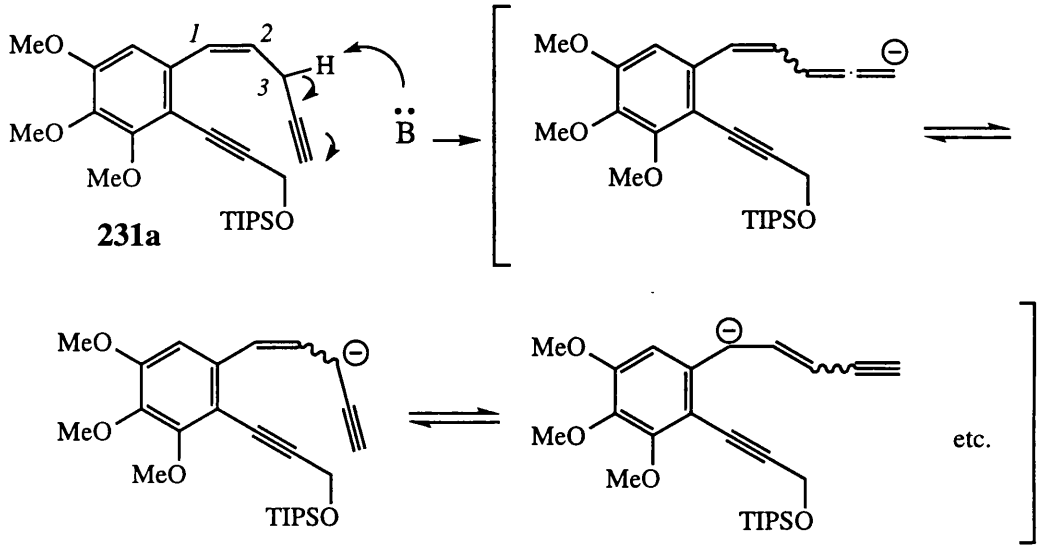


i. MeMgBr (1eq), THF, 0-25°C, ii. excess D_2O, 0°C (25% conversion)

Scheme 88

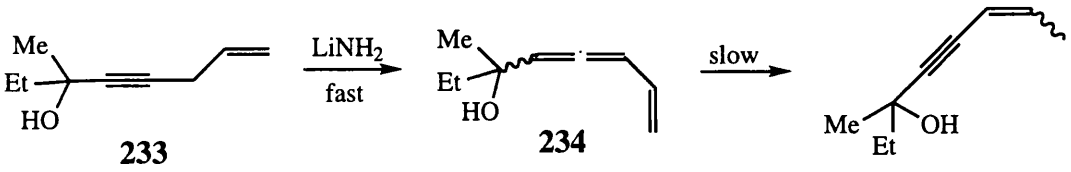
In order to study the formation of the required acetylide anion, the *Z*-enyne (**231a**) was stirred with 1 equivalent of methylmagnesium bromide in THF (Scheme 88) for 30 minutes at 0°C and then a further 30 minutes at room temperature. Upon quenching with deuterium oxide, ^1H NMR spectroscopy indicated a 25% hydrogen-deuterium exchange at the terminal alkyne group. However, when the *Z*-enyne (**231a**) was reacted, under various reaction conditions, with methylmagnesium bromide followed by methoxyacetic acid derivatives (**209a**) or (**290c**), no desired coupling product was formed although, occasionally, partial recovery of starting material was observed. We suspect that these unexpected results may stem from deprotonation at C-3 position and the

resulting mixture of anionic species may lead to subsequent side-reactions (Scheme 89). In addition, the 1,3-enyne (**229**) was not observed as a product from these reactions.



Scheme 89

Having observed the rather frustrating behaviour of the 1,4-enyne system, we attempted to account for the formation of the 1,3-enynes (**228**) and (**229**). As the purity of sodium hydride is difficult to determine, excess base might have been present when sodium hydride was used to generate the ylide. The postulate that excess base led to the formation of the 1,3-enynes (**228**) and (**229**) was further supported by the fact that the 1,3-enyne (**228**) was generated when excess KHMDS was used in the Wittig reaction between the aldehyde (**168**) and the phosphonium salt (**225**). It is known that enyne systems can rearrange through allenic species in the presence of base. For instance, a double bond relocation has been observed when the 1,4-enynol (**233**) was treated with

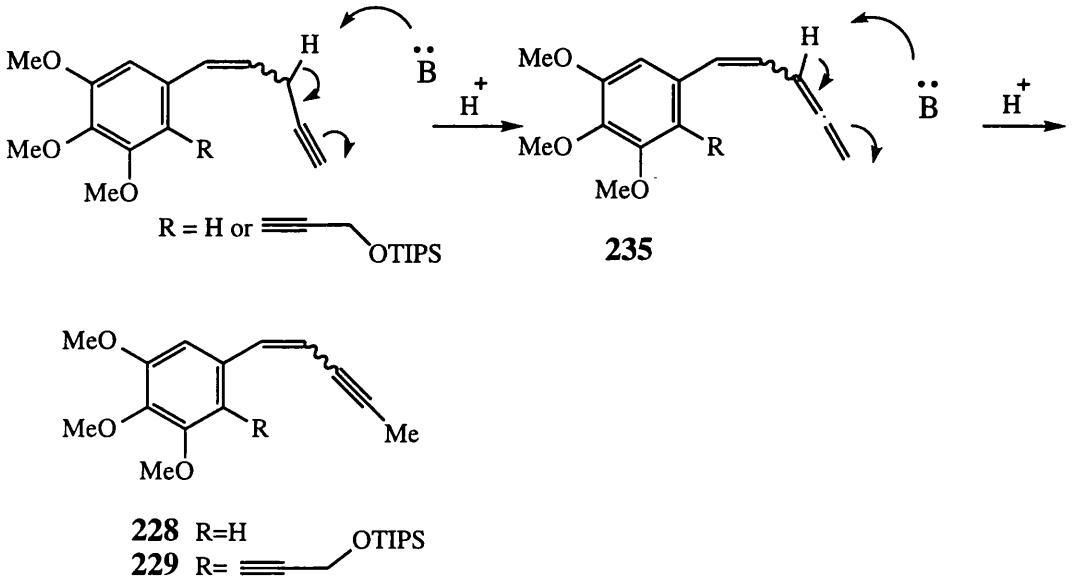


233 **234**

Scheme 90

lithium amide (Scheme 90) and the allene derivative (**234**) was found to be the

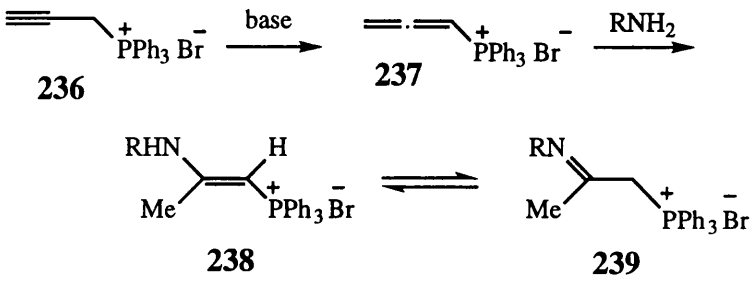
intermediate[78]. Thus, it is possible that the desired 1,4-enynes were the initial products from the Wittig reactions described in Scheme 84 but were rapidly rearranged by the additional base present to 1,3-enynes (**228**) and (**229**) through the allene derivatives (**235**) (Scheme 91).



Scheme 91

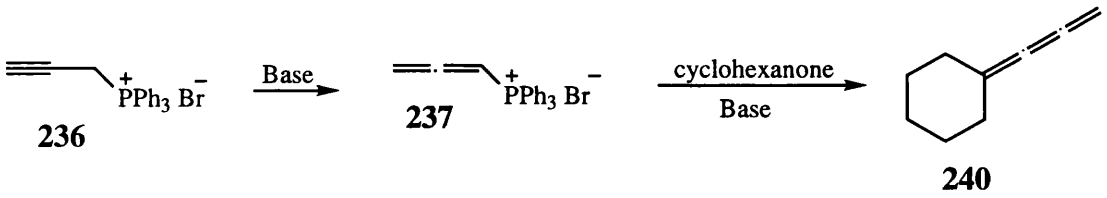
The above mechanism implies that the 1,4-enyne (**231a**) is an intermediate in the formation of the 1,3-enyne (**229**). However, according to this mechanism, the 1,3-enyne (**229**) would have been expected as a product when the 1,4-enyne (**231a**) was treated with methylmagnesium bromide and this proved not to be the case. The choice of base may be critical for the transformation of (**229**) from (**231a**) but the absence of the 1,3-enyne (**229**) from the deprotonation studies nonetheless undermines, to the same extent, the feasibility of the mechanism shown in Scheme 91.

It has been noted that the propargylphosphonium salt (**236**) rearranged in the presence of base to the allenic derivative (**237**), which further reacted with an amine to form the amino- and the imino-phosphonium salts[79] (**238**) and (**239**) as shown in Scheme 92. This result suggests that phosphonium salts possessing alkynyl functionalities may rearrange in the presence of base more rapidly than undergoing Wittig



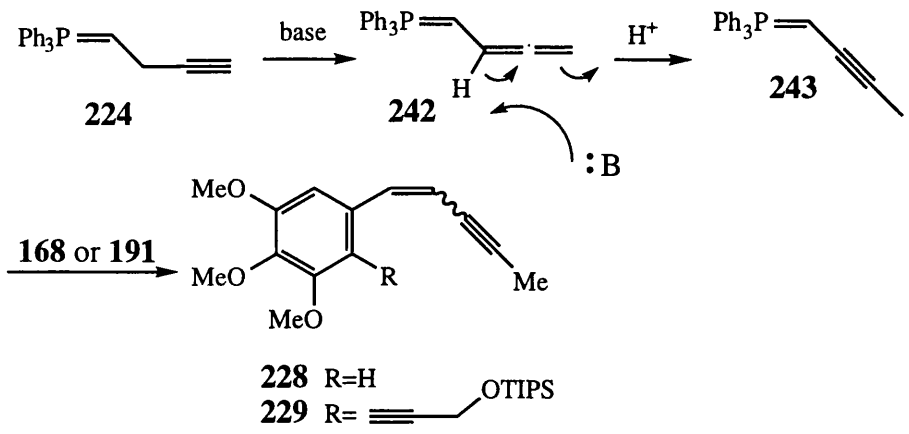
Scheme 92

reaction with carbonyl compounds. This may explain the formation of the unexpected, unstable cumulene[80] (**240**) from the reaction between the phosphonium salt (**236**) and cyclohexanone (Scheme 93).



Scheme 93

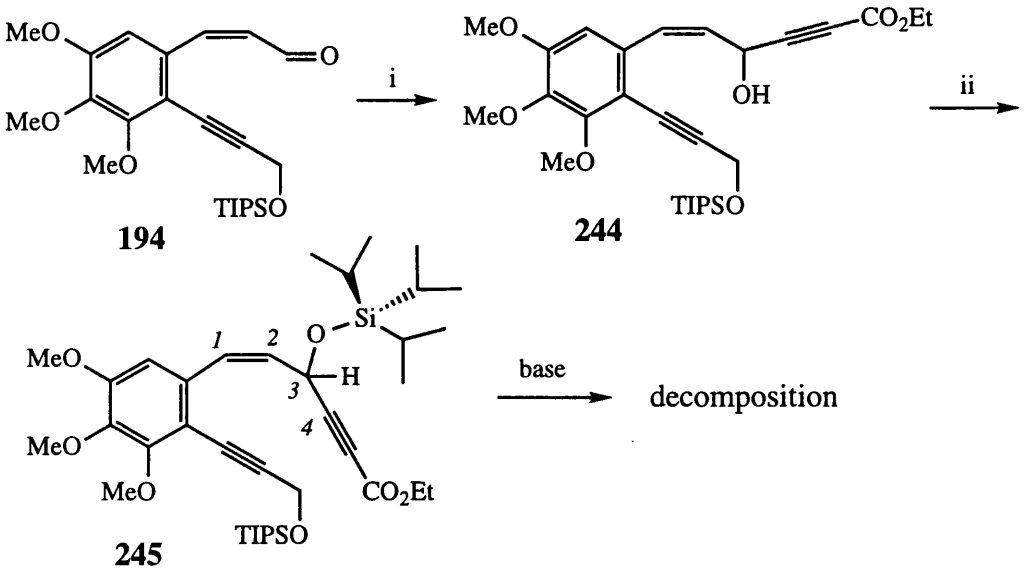
In our case, since the formation of the 1,3-enynes (**228**) and (**229**) occurred only in the presence of excess base, it is probable that it was the ylide (**224**), rather than the phosphonium salt (**225**), which underwent rearrangement. As shown in Scheme 94, the ylide (**224**) may rearrange *via* the allene derivative (**242**) to the ylide (**243**), which subsequently reacts with the aldehyde (**168**) or (**191**) to form the 1,3-enyne (**228**) or (**229**) respectively. Although this mechanism is much more speculative than the one described in Scheme 91, it can also account for the absence of the 1,3-enyne (**229**) as a product from the treatment of the 1,4-enyne (**237a**) with methylmagnesium bromide.



Scheme 94

Further investigations are certainly required in order to clarify the mechanism of formation of the 1,3-enynes (**228**) and (**229**) but their generation during the Wittig step have nevertheless highlighted the base-sensitivity of the 1,4-enyne system.

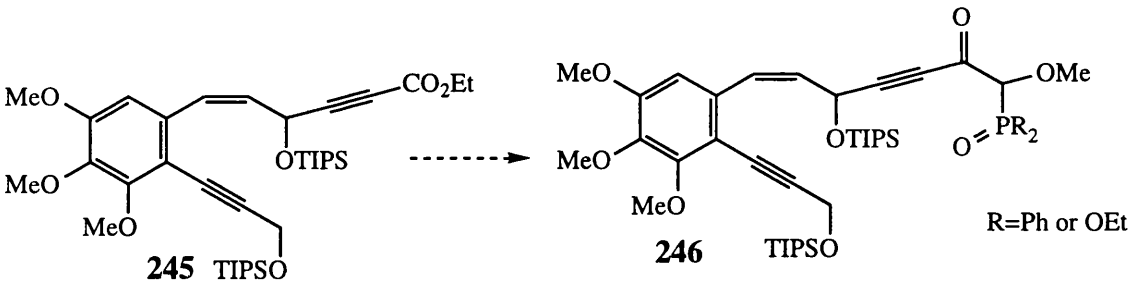
Attempts were made to overcome the problems arising from the lability of the 1,4-enyne system. To this end, the previously prepared *Z*-α,β-unsaturated aldehyde (**194**) was reacted with lithiated ethyl propiolate[80a] to form the secondary alcohol (**244**) (Scheme 95). When this alcohol was treated with TIPSCl and imidazole at room temperature, the silyl ether (**245**) was formed in only 21% yield with considerable amount of decomposition material. The yield of this protection step increased to 91% if it was carried out with triisopropylsilyl triflate and 2,6-lutidine at -78°C. Presumably, at room temperature, the alcohol (**244**) was sensitive even to the mildly basic imidazole. It was hoped that the bulk of the TIPS group, spreading like an umbrella over the C-3 atom, might exert a shielding effect on the C-3 proton and thus protect it from abstraction. However, only decomposition products were observed when the hydrolysis of the ester group of compound (**245**) was attempted.



i. $LiC{\equiv}CCO_2Et$ (2.2eq), THF, -78°C; excess NH_4Cl, -78°C (86%); ii TIPSCl (2.2eq), imidazole (4.4eq), r.t. DMF (21%) or TIPSOTf (1.3eq), 2,6-lutidine (2.5eq), DCM, -78°C (91%)

Scheme 95

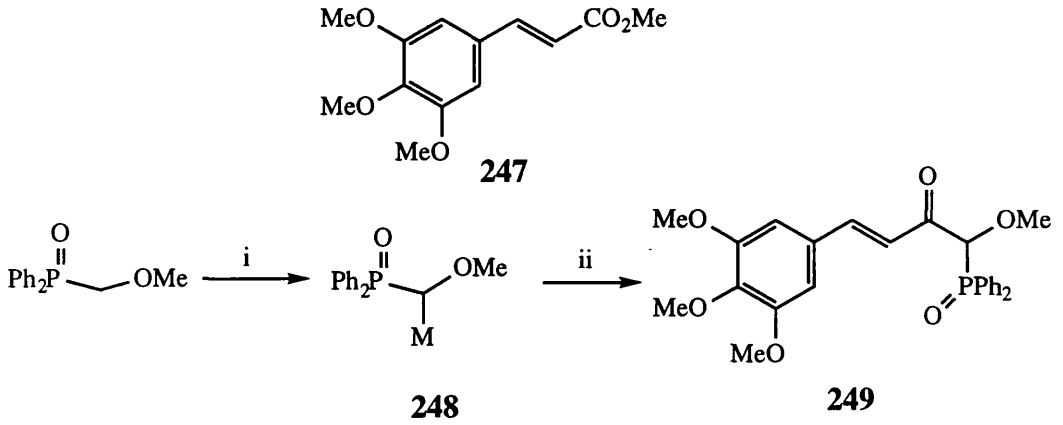
We then investigated the feasibility of a direct conversion of this ester (**245**) to the Horner-Wadsworth reagent (**246**) (Scheme 96) in order to avoid the problematic hydrolysis. It has been reported that phosphine oxide anions can be acylated with esters to



Scheme 96

form the corresponding ketones[81] and, in a model study, the known α,β-unsaturated ester[19(o)] (**247**) (Scheme 97) was treated with the phosphine oxide anion (**248**, M=Li) to form the ketone (**249**) in 18% yield. The low yield of this reaction may be caused by a deficiency of reactant as the phosphine oxide anion (**248**) is more basic than the conjugate base of the product (**249**). Nevertheless, this reaction demonstrated that the phosphine oxide anion (**248**, M=Li) could be acylated with α,β-unsaturated esters. However,

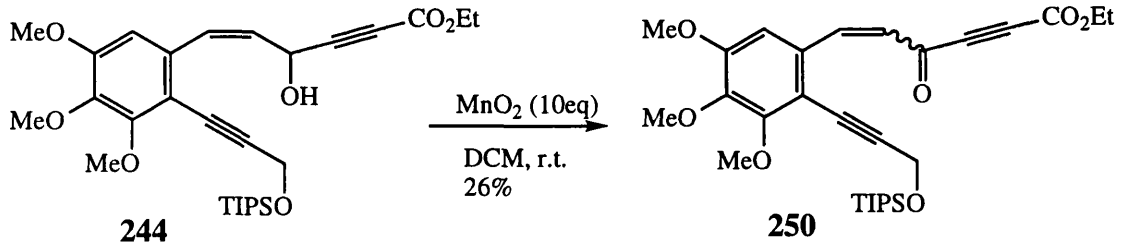
reaction of the phosphine oxide anion (**248**, M=Li) with the ester (**245**) under various conditions resulted only in decomposition. The use of the presumably less basic cerium reagent (**248**, M=Li·$CeCl_3$) was similarly unsuccessful.



i. LDA (1.2eq), THF, 0°C (M=Li); ii. **247** (1eq), 0-25°C (18%)

Scheme 97

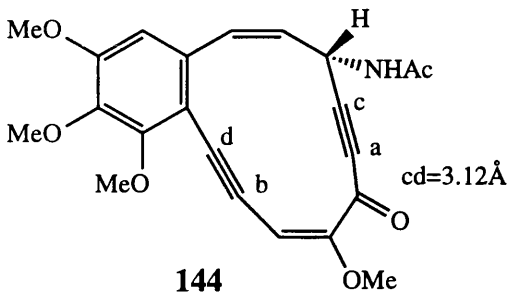
Having encountered these problems, an attempt was made to eliminate the labile C-3 protons by replacing the C-3 methylene group of the 1,4-enyne (**231a**) with an oxo group. This was achieved by oxidising the alcohol (**244**) with manganese dioxide. However, in addition to the low yield, a mixture of approximately 1:2.7 ratio of the *Z*- and *E*-ketones (**250a**) and (**250b**) was obtained as a bright yellow oil upon workup (Scheme 98). Moreover, after overnight storage at -5°C in darkness, only the *E*-ketone (**250b**) was detected by ^1H NMR spectroscopy. Apparently, this highly conjugated system can isomerise in darkness to the thermodynamically more stable *E*-isomer even at a relatively low temperature.



a (*Z*) : **b** (*E*) ≡ 1 : 2.7

Scheme 98

At this stage, it was apparent that the lability of the 1,4-enyne moiety was the major source of problems in the construction of the macrocyclic framework of **144**. Since the essence of this cycloaromatisation strategy is to construct a macrocycle which will undergo Bergman cyclisation to form the tricyclic skeleton of colchicine, structural alterations upon the target macrocycle (**144**) should be allowed as far as these alterations would not hinder the ultimate cycloaromatisation. In view of this, although we have presented arguments for deliberate incorporation of the C8-9 double bond, an examination of the analogous 12-membered macrocycle (**251**) was undertaken. Since this structure



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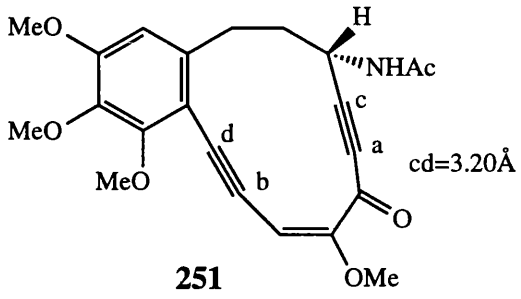
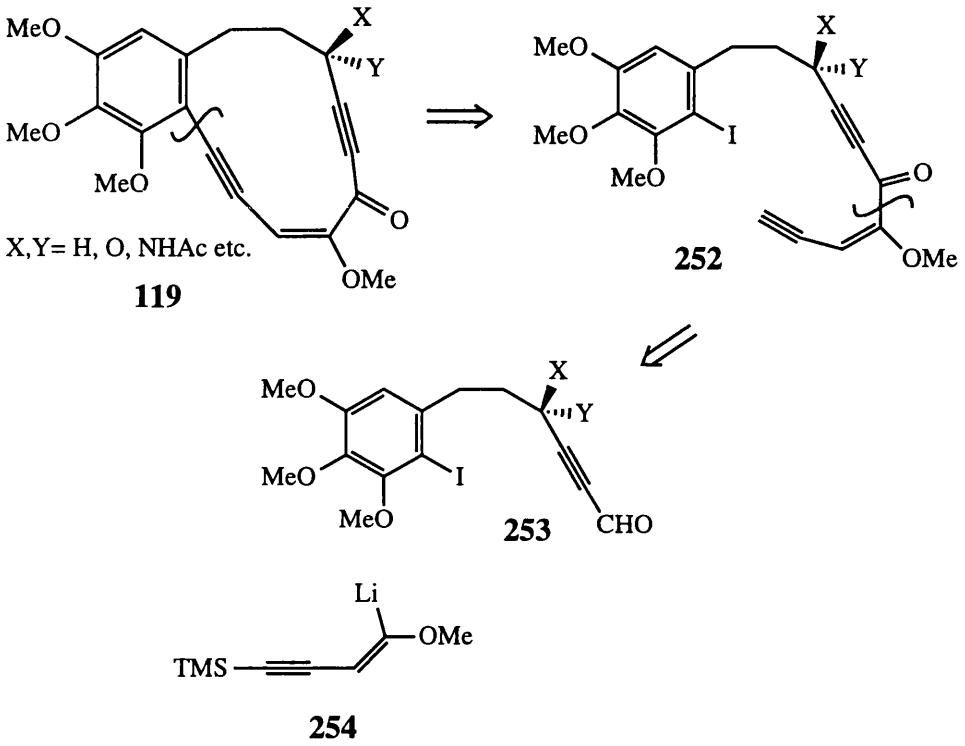


251

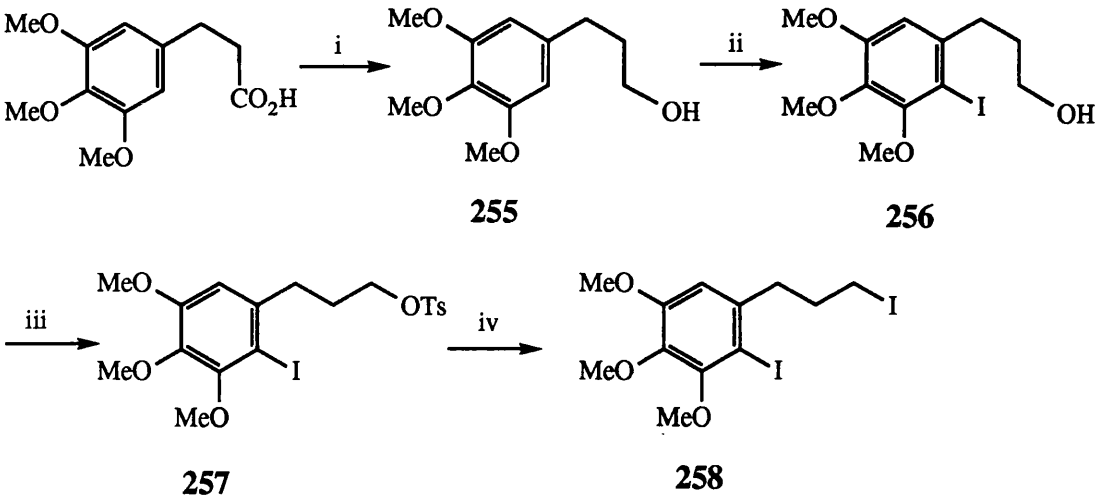
does not possess the benzylic *Z*-double bond, the previously encountered problems should not arise in the synthesis of the macrocycle (**251**). Certainly, the absence of a benzylic Z-double bond would render the macrocycle (**251**) less rigid than its analogue (**144**), as reflected by the fact that the energy of formation of the former is calculated to be 17 $kJmol^{-1}$ less than the latter (MM2, MacroModel 4.0). However, the cd distance of the compound (**251**) is calculated to be 3.20Å, which is comparable to that of the macrocycle (**144**). It is therefore highly possible that the compound (**251**) could also undergo cycloaromatisation as previously discussed. We hence decided that efforts should be made to synthesise compound (**251**) so that we could test the cycloaromatisation step and also gain more insight into the synthesis of similar macrocycles including compound (**144**) itself.

Two tactically different attempts were made to generate the macrocyclic framework of (**251**). The retrosynthetic analysis of the first is shown in Scheme 99. In this instance, the synthesis of macrocycle (**119**) is envisaged to proceed *via* an intramolecular transition metal-mediated coupling reaction between the iodoarene ring and the alkyne group of the cyclisation precursor (**252**), which in turn can be formed by a nucleophilic attack of the enyne anion (**254**) on aldehyde (**253**) followed by oxidation of the hyroxyl group.



Scheme 99

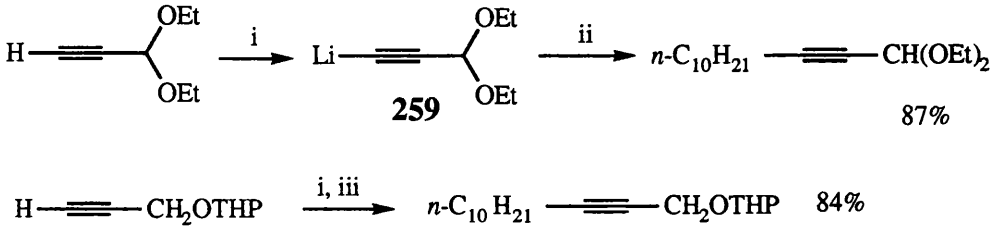
In order to prepare the aldehyde (**253**), commercially available 3-(3,4,5-trimethoxyphenyl)propanoic acid was reduced with borane-THF complex to form the alcohol[82] (**255**) almost quantitatively (Scheme 100). Iodination of the alcohol (**255**) to the iodo-alcohol (**256**) was achieved as previously described in excellent yield (90%) with silver trifluoroacetate and iodine. Conversion of the alcohol (**256**) to the iodide (**258**) was then carried out in two steps involving iodide anion displacement of the derived tosylate (**257**). Surprisingly, however, no nucleophilic displacement was



i. BH_3·THF (1.2eq), THF, 0-25°C (~100%); ii. CF_3CO_2Ag (1.0eq), I_2 (1.1eq), DCM, r.t. (90%); iii. TsCl (1.1eq), pyr (1.5eq), r.t. (74%); iv. NaI (2eq), acetone, 50°C (94%)

Scheme 100

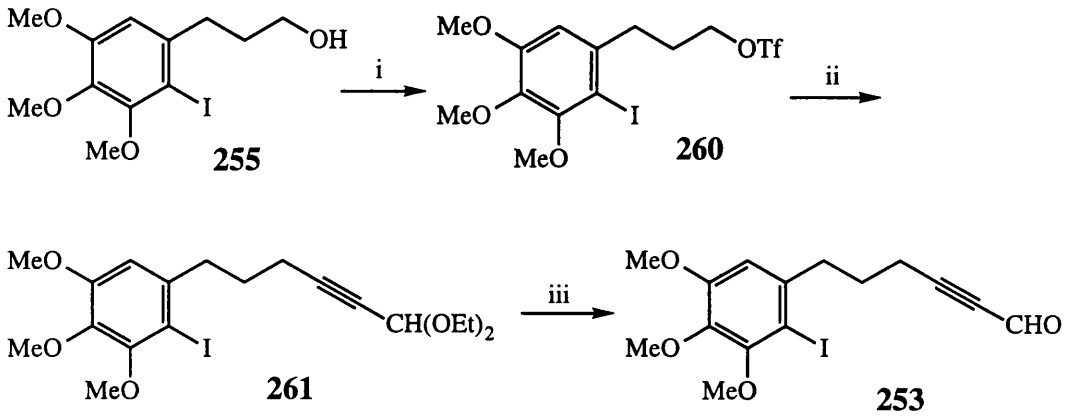
observed when either the tosylate (**257**) or the iodide (**258**) was treated with lithiated propargylaldehyde diethyl acetal (**259**), although there are precedents that alkyl halides undergo facile nucleophilic substitution with lithium acetylides in the presence of DMSO[83] (Scheme 101).



i. MeLi, THF, 0°C; ii. *n*-$C_{10}H_{21}Br$, DMSO, 0-25°C; iii. *n*-$C_{10}H_{21}Br$, DMSO, 0-25°C

Scheme 101

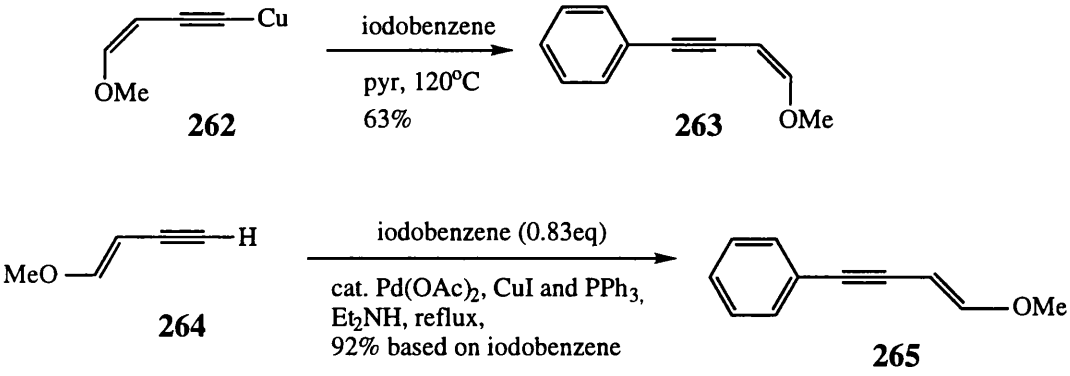
The unstable triflate (**260**) was accordingly prepared by treating the alcohol (**255**) with triflic anhydride (Scheme 102) and the crude product was then successfully converted to the acetal (**261**) by displacement with the acetylide (**259**) in 43% yield over the two steps. Upon warming with catalytic *p*-toluenesulfonic acid in aqueous acetone, the acetal (**261**) was transformed to the aldehyde (**253**, X,Y=H) in good yield (74%).



i. Tf_2O (1.15eq), pyr (1eq), DCM, 0°C; ii. **259** (2.2eq), THF, 0°C (43% over two steps); iii. $TsOH{\cdot}H_2O$ (10mol%), 1:1 / acetone:water, 55°C (74%)

Scheme 102

With the aldehyde (**253**) in hand, we turned to the incorporation of the enyne fragment (**254**). Kraus and Frazier[84] prepared the *Z*-phenylenyne (**263**) by heating the copper acetylide (**262**) with iodobenzene in pyridine at 120°C after vigorous exclusion of oxygen (Scheme 103). It was considered doubtful that the cyclisation precursor (**252**) in Scheme 99 would survive such reaction conditions. Therefore, in a model study, the *E*-enyne (**264**) was prepared according to the literature procedure[84a] and was coupled under

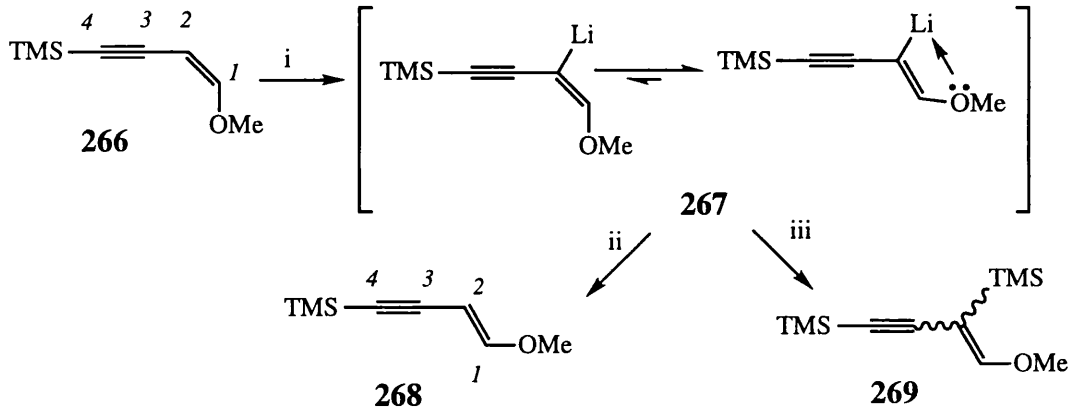


Scheme 103

milder reaction conditions with iodobenzene using palladium(II) acetate and copper(I) iodide as catalysts. Fortuitously, the *E*-phenylenyne (**265**) was obtained in good yield with retention of stereochemistry at the double bond. Although the starting enyne (**264**) was acid-sensitive, the coupling product (**265**) was, as reported by Kraus and Frazier,

sufficiently stable to be purified by silica gel column chromatography, presumably due to the higher degree of conjugation.

Moreover, Zweifel *et al*[85] reported that lithiation of the *Z*-4-trimethylsilylenyne (**266**) preferentially occurred at the C-2 position probably because the lithiated species (**267**) would be stabilised by chelation with the methoxy group as shown in Scheme 104. As a result, in order to carry out the nucleophilic attack on the aldehyde (**253**) as shown in Scheme 99, the C-2 position of the *E*-enyne (**268**) must be protected so that lithiation would occur at the C-1 position. Thus, by treating the *Z*-enyne (**266**) at -78°C with *n*-BuLi followed by TMSCl, the unstable bisprotected enyne (**269**) was formed as a colourless liquid, which readily turned brown even refrigerated. It was crucial that the quenched reaction mixture was stirred at -78°C for two hours before warming up to room temperature. Otherwise, only a black tar would be obtained upon workup.

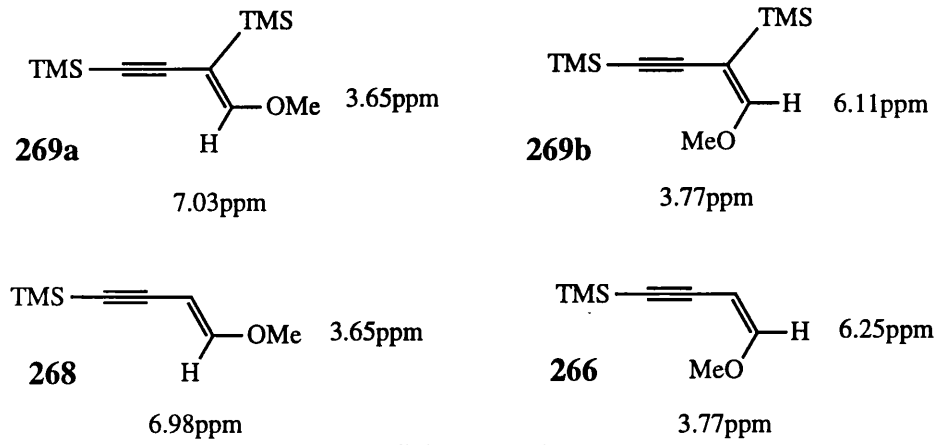


i. *n*-BuLi (1eq) -78°C, DME; ii. excess MeOH, -78°C (92%); iii. TMSCl (1.2eq), -78°C (56%)

Scheme 104

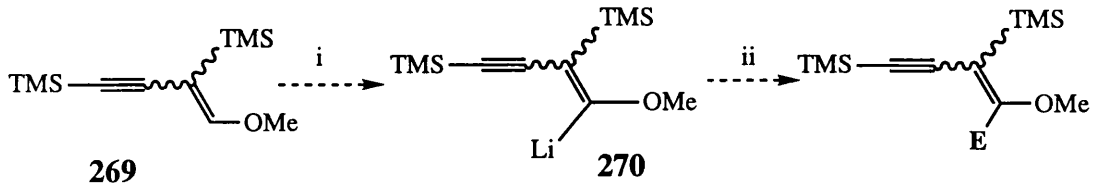
The bisprotected enyne (**269**) was found to be a mixture of *Z*- and *E*-isomers inseparable by distillation. In the ^{1}H NMR spectrum of the enyne (**269**), two vinylic proton signals were found at 7.03ppm and 6.11ppm, respectively, with a ratio of 3.5:1. A pair of methoxyl proton signals were also present at 3.65ppm and 3.77ppm, respectively, with the same ratio. After comparison with the relative chemical shifts of the methoxyl and vinylic protons of the *E*- and *Z*-enynes (**268**) and (**266**) as shown in

Scheme 105, we assumed that the desired *Z*-isomer (**269a**) was formed as the major product.



Scheme 105

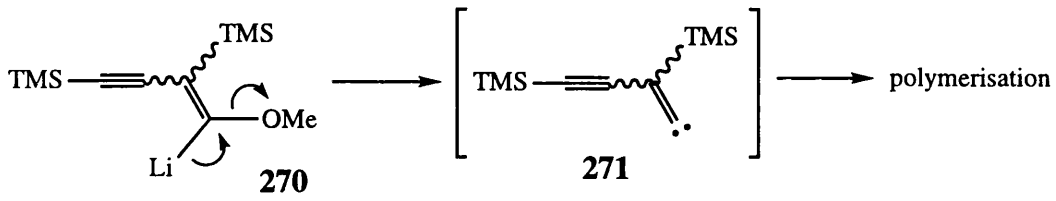
Under various reaction conditions, when the bisprotected enyne (**269**) was treated with *n*-, *s*- or *t*-butyllithium, a yellow solution was obtained indicating the probable generation of lithiated species (Scheme 106). However, on each occasion only a black tar was produced when the reaction mixture was quenched with electrophiles and then



i. BuLi (1.1eq); ii. electrophile (E), eg. NH_4Cl, TMSCl, D_2O etc.

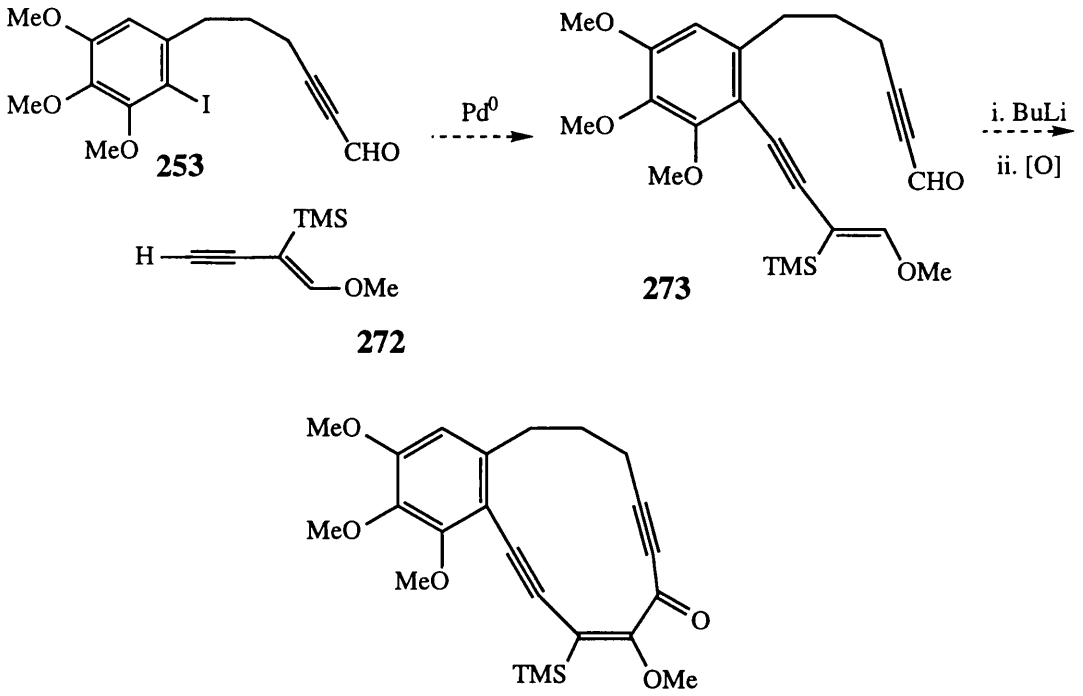
Scheme 106

warmed up to room temperature. A possible explanation may reside in the fact that the lithiated species (**270**), which is highly stabilised by the conjugated trimethylsilyethynyl and trimethylsilylethenyl groups, may not react with the electrophiles at low temperature but polymerise *via* the carbene (**271**) on warming to room temperature (Scheme 107).



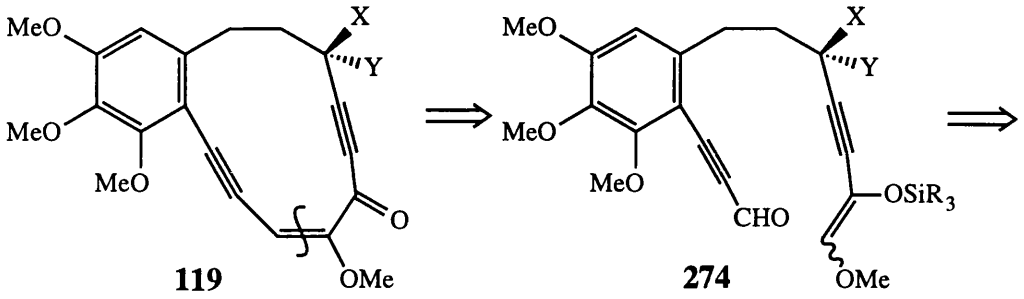
Scheme 107

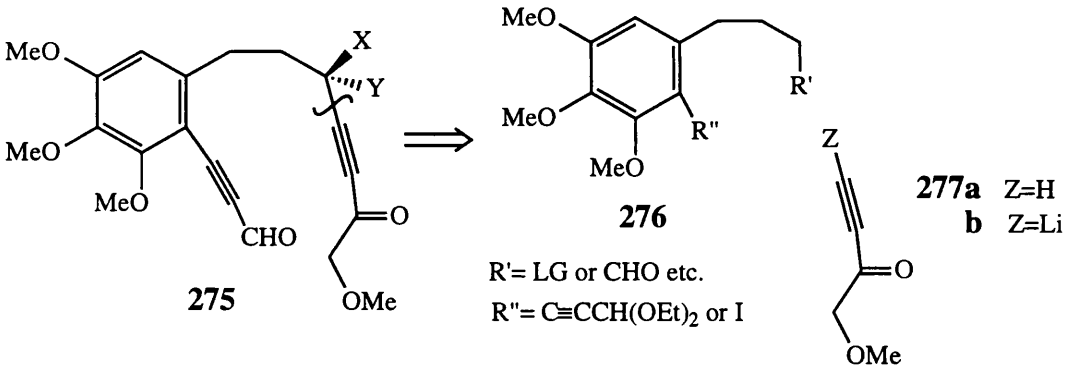
At this stage, an alteration of the synthetic plan was therefore contemplated in which the intermediate (**273**) would be formed by a palladium-mediated coupling between the aldehyde (**253**) and the monoprotected enyne (**272**) (Scheme 108). The macrocyclisation could then be achieved by an intramolecular nucleophilic addition of the lithiated enol ether to the formyl group. Therefore, in order to form the intermediate (**272**), attempts were made to achieve selective removal of the trimethylsilyl group at the acetylene terminus of the bisprotected enyne (**269**). However, the enyne (**269**) was found to be unreactive towards bases but decomposed when treated with fluoride reagents such as tetrabutylammonium fluoride or caesium fluoride. The reason for this failure of deprotection is not clear.



Scheme 108

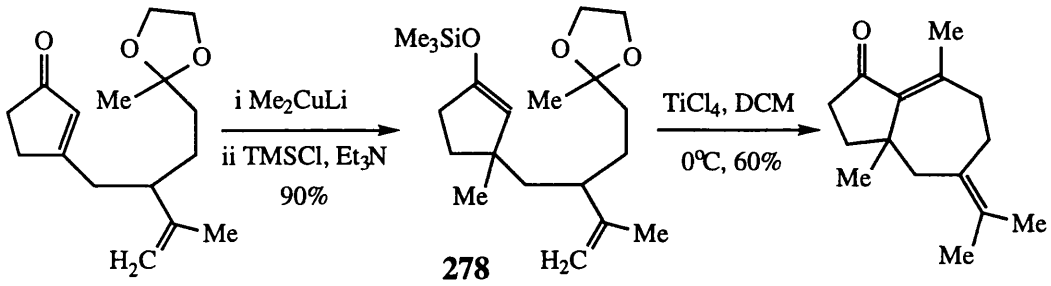
It is apparent from the previous description that the use of a preformed enol ether moiety (**269**) was inappropriate in the synthesis of the macrocycle (**119**). Hence a new retrosynthetic analysis (Scheme 109) was conceived in which the macrocycle (**119**) is formed by an intramolecular, Lewis acid-mediated aldol condensation *via* a silyl enol ether (**274**). The intermediate (**275**) can be generated by nucleophilic attack of the lithium acetylide (**277b**) on intermediate (**276**). The use of the alkynone (**277a**) could avoid the potentially problematic use of a highly unsaturated anion as previously described.





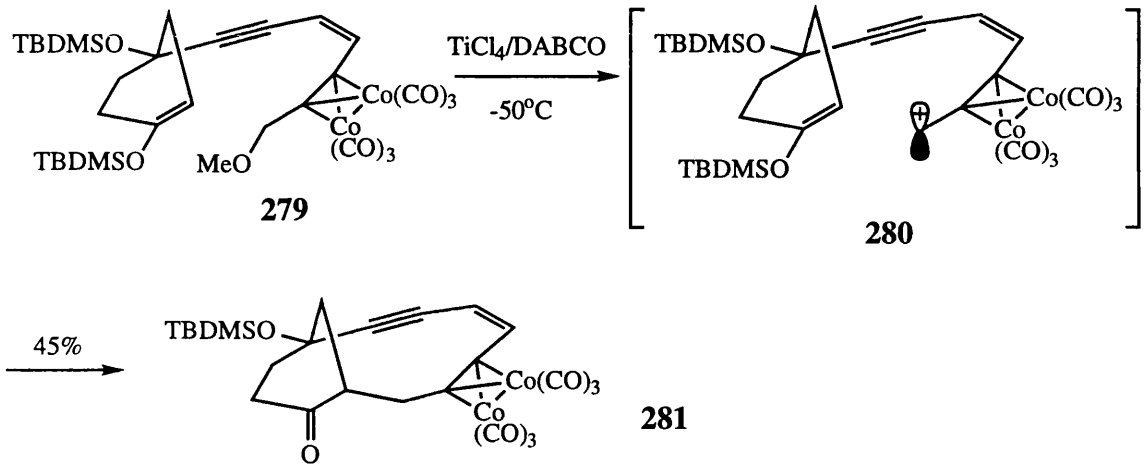
Scheme 109

The intramolecular Lewis acid-promoted aldol reaction of silyl enol ethers has been employed in the formation of a number of cyclic structures[86]. For instance, Posner *et al*[87] formed the seven-membered ring of the pseudoguaniane system from the silyl enol ether (**278**) using titanium(IV) chloride as a catalyst (Scheme 110). Magnus *et al*[54(a)] have also reported the use of titanium(IV) chloride and 4-diaza-bicyclo[2.2.2]octane (DABCO)



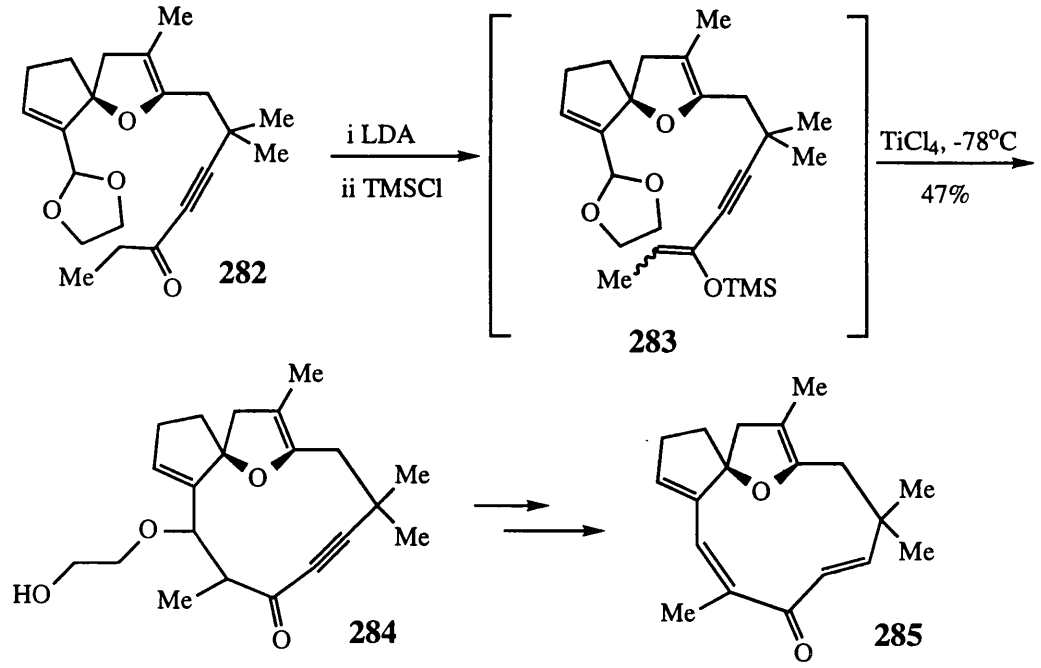
Scheme 110

to achieve the cyclisation of the dicobalthexacarbonyl alkyne complex (**279**) using the TBDMS enol ether moiety to give the ketone (**281**) through the cationic species (**280**) (Scheme 111). Moreover, in the synthesis of normethyljatrophone (**285**) (Scheme 112),



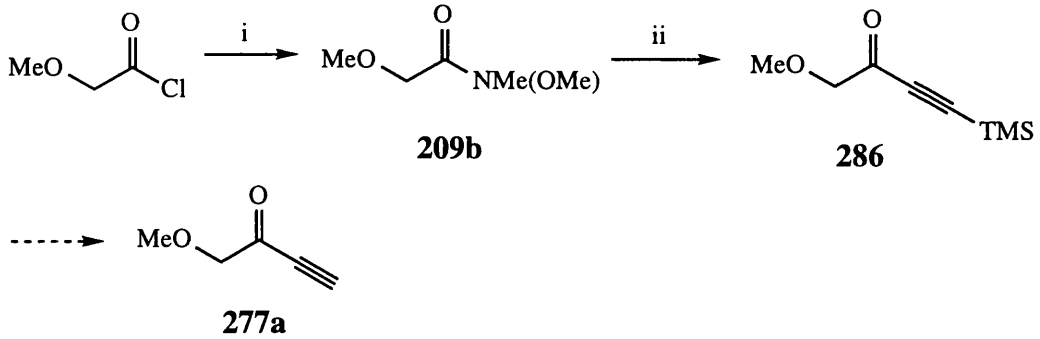
Scheme 111

Smith and co-workers[88] converted the alkynone (**282**) to the eleven-membered macrocycle (**284**) *via* the silyl enol ether (**283**) generated *in situ*. It is of interest to note that compound (**282**) possesses an α,β-unsaturated cabonyl moiety similar to that of the compound (**275**).



Scheme 112

In order to prepare the ketone (**277a**), commercially available methoxyacetyl chloride was converted to the hydroxamate (**209b**) (Scheme 113), which was treated with lithium trimethylsilylacetylide to form the alkynone (**286**) in 73% yield. No product was however obtained upon attempted removal of the trimethylsilyl group of (**286**) by

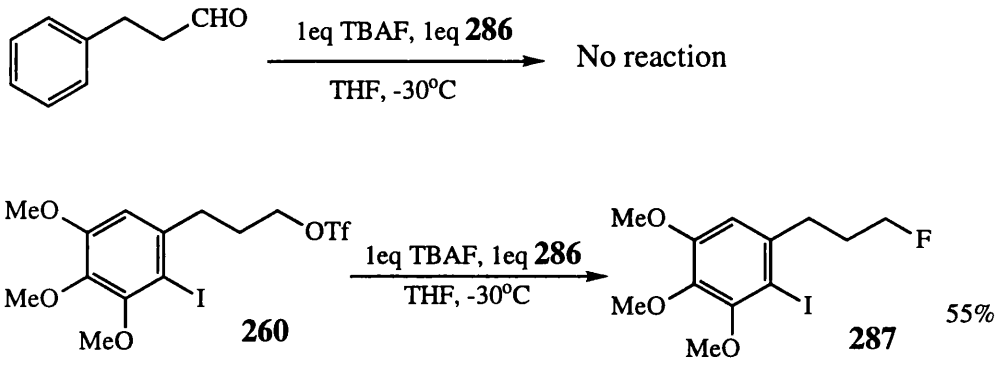


i. HNMeOMe·HCl (1.1eq), Et_3N (2.2eq), DCM, 0-25°C (78%); ii. LiC≡CTMS (1.1eq), THF, 0-25°C; H^+ (73%)

Scheme 113

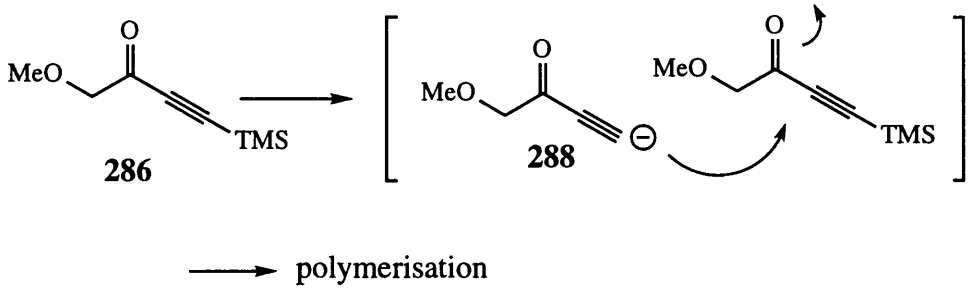
base or fluoride anion reagents presumably due to the volatility of the product (**277a**). Hence the well-documented *in situ* generation of anions by the action of tetrabutylammonium fluoride (TBAF) on silyl compounds[89] was employed. When TBAF

was added to a mixture of the alkynone (**286**) and 3-phenylpropanal at low temperature (Scheme 114), the reaction mixture turned red immediately but only decomposition of the alkynone (**286**) was observed. When the more reactive triflate (**260**) was used, the same colour change occurred and, interestingly, the fluoride (**287**) was obtained as the only identifiable product (55%). The formation of the fluoride (**287**) was indicated by a doublet of triplets in the ^1H NMR spectra with a characteristic coupling constant (47.3Hz) between the fluorine atom and the α protons.



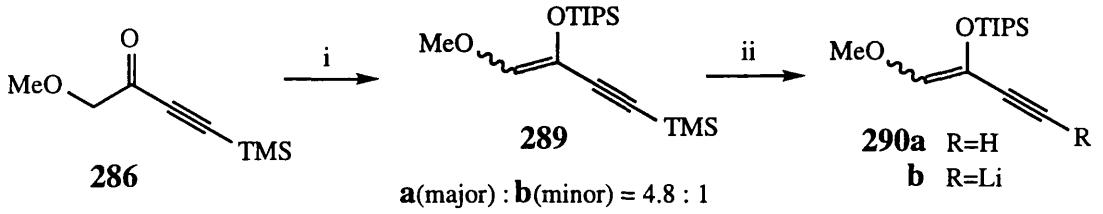
Scheme 114

The colour changes of these reactions indicated the possible generation of the 'naked' acetylide anion (**288**). However, it might undergo 1,2-addition with the parent alkynone (**286**) immediately after generation leading to polymerisation (Scheme 115). The reaction involving the triflate (**260**) showed that polymerisation occurred so rapidly that no acetylide anion (**288**) was left to compete with the more weakly nucleophilic fluoride ion.



Scheme 115

Under these circumstances, structural modifications of the alkynone (**277a**) were required in order that the resultant intermediate would be easier to handle and compatible with the addition to the compound (**276**) as shown in Scheme 109. Thus, the alkynone (**286**) was treated with triisopropylsilyl triflate (TIPSOTf) and triethylamine[90] to give the silyl enol ether (**289**) as a pair of stereoisomers in 93% overall yield with a ratio of 4.8:1 (Scheme 116). The use of 2,6-lutidine instead of triethylamine led to incomplete reaction



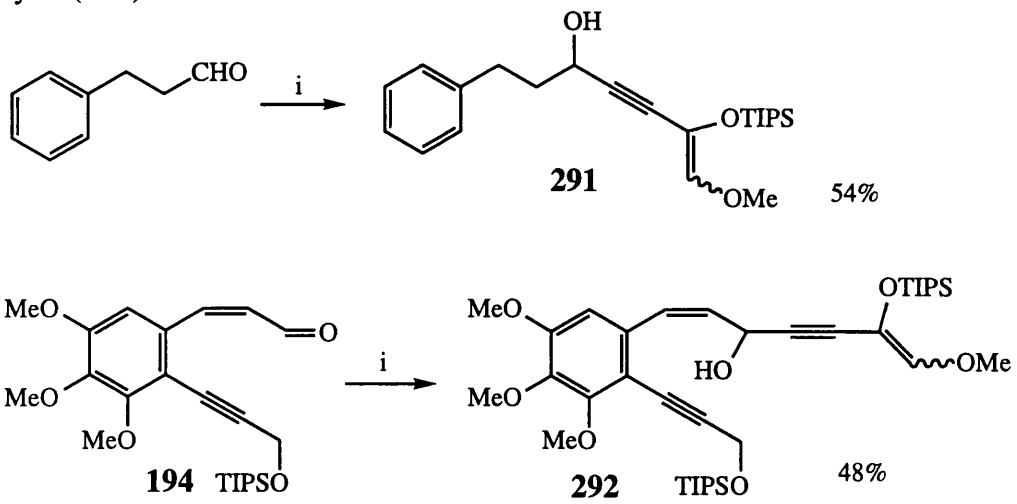
i. TIPSOTf (1.1eq), Et_3N (1.5eq), PhH, 0-25°C (93%); ii. K_2CO_3 (1.2eq), MeOH, r.t. (**290a** 86%)

Scheme 116

and a diminished yield. A TIPS group was used in the hope that the trimethylsilyl group at the acetylene terminus could be removed selectively without affecting the enol ether moiety. Indeed, when the silyl enol ether (**289a**) was treated with potassium carbonate in methanol, the trimethylsilyl group was duly removed to form the terminal alkyne (**290a**) as a non-volatile colourless liquid in good yield (86%). However, this alkyne was sensitive to silica gel chromatography and decomposed rapidly at room temperature. Hence it was used immediately after preparation. Nevertheless, the alkyne (**290a**) offered us an alternative to the alkynone (**277a**) with the additional advantage that the silyl enol ether moiety required in the subsequent cyclisation precursor (**274**) was also preformed.

The lithium acetylide (**290b**) can be generated by treating the alkyne (**290a**) with *n*-butyllithium at -78°C in THF. The addition of either 3-phenylpropanal or the α,β-unsaturated aldehyde (**194**) at -78°C provided the desired secondary alcohols (**291**) and (**292**), respectively, in about 50% yield (Scheme 117) with partial recovery of the unreacted alkyne (**290a**). Elevated temperature did not significantly improve the yields

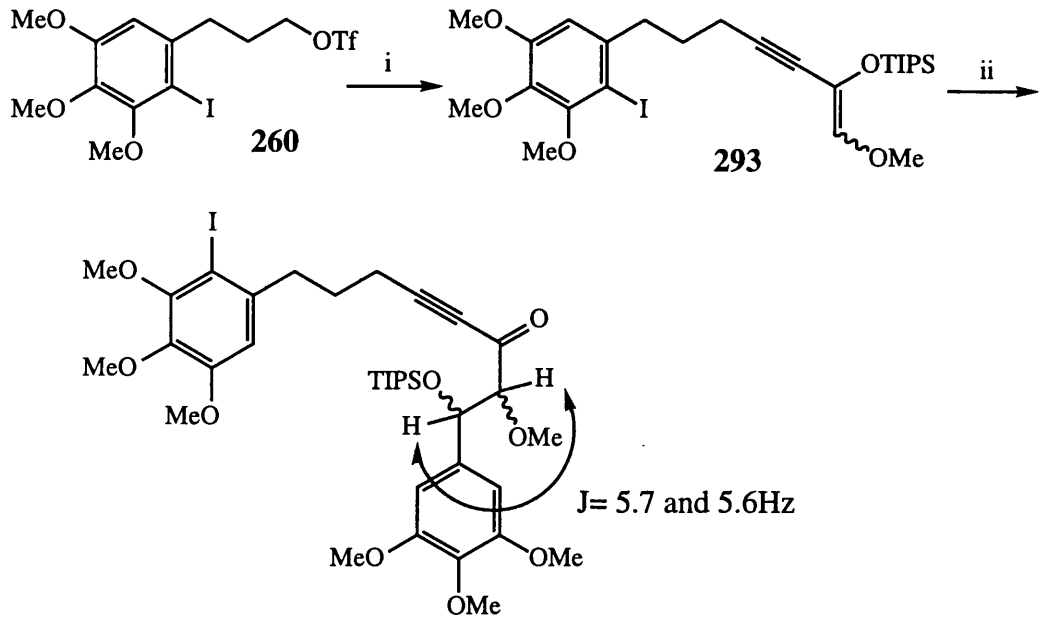
and only the expected 1,2-addition was observed in the case of the α,β-unsaturated aldehyde (**194**).



i. **290b** (1eq), THF, -78°C

Scheme 117

In order to investigate the Lewis acid-promoted aldol reaction *via* the TIPS enol ether moiety, the silyl enol ether (**293**) was prepared in 67% yield by treating the triflate (**260**) with the acetylide (**290b**) (Scheme 118). While a number of attempts using different combinations of Lewis acids and electrophiles were unsuccessful, an experiment in which compound (**293**) was reacted with titanium(IV) chloride and 3,4,5-trimethoxybenzaldehyde (**168**) in DCM at -78°C was most encouraging. The aldehyde (**168**) was chosen as a substrate because the ^{1}H NMR spectrum of the desired product would be relatively simple. Upon HPLC separation, a pair of diastereomers (**294**) with a ratio of 5 to 1 were obtained in 28% overall yield.



294 major : minor = 5 : 1

i. **290b** (1.1eq), THF, -78°C (67%); ii. **168** (1eq), $TiCl_4$ (1eq), DCM, -78°C; Na_2CO_3 (28%)

Scheme 118

The ^1H NMR spectrum showed that the TIPS group was unexpectedly retained in the products (**294**). The coupling constants between the protons of the two stereogenic centres of both diastereoisomers were shown to be about 6Hz. This is probably due to the fact that the β-hydroxyl groups of the ketones (**294**) were protected and hence they do

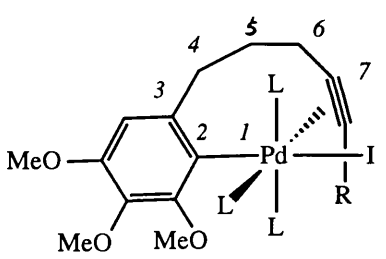
general aldol products **294**

Scheme 119

not constitute the six-membered ring formed *via* intramolecular hydrogen-bond between the carbonyl and the β-hydroxyl group (Scheme 119) as general aldol reaction products do. As a result, the relative stereochemistries of these two compounds were not determined. Nevertheless, despite the relatively low yield, this reaction demonstrated the

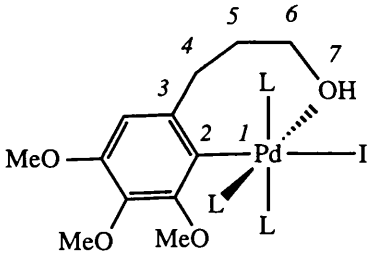
feasibility of a Lewis acid-mediated aldol reaction using a TIPS enol ether.

Encouraged by this model study, efforts were made to prepare the derivative of macrocyclisation precursor (**274**, X,Y=H) by coupling compound (**293**) with propargylaldehyde diethyl acetal using the previously described Heck/Castro-type reaction. However, despite the attempted utilisation of various palladium catalysts and reaction conditions, no desired coupling products were obtained from the silyl enol ether (**293**) or the alcohol (**256**). Partial recovery of starting material was observed if the reaction conditions were mild. It is reasoned that when palladium has inserted into the carbon-iodine bond of compounds such as (**293**) and (**256**), seven-membered cyclic species (**295**) and (**296**) may be formed. These species are so strongly chelated that the palladium atom cannot dissociate and then participate in the catalytic cycle and, as a result, no coupling occurs. Further evidence for this postulate was found during the investigation of the [2+2+2] cyclisation approach and will be discussed in section 2.2.2.



295

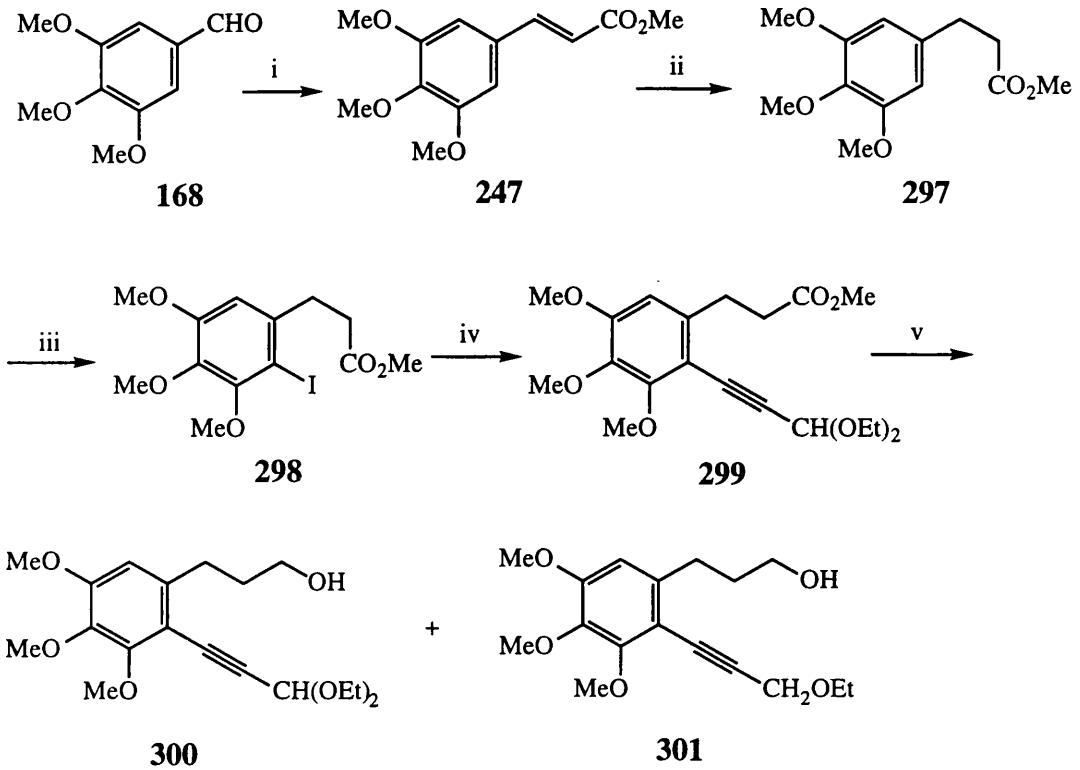
L= solvent or PPh_3



296

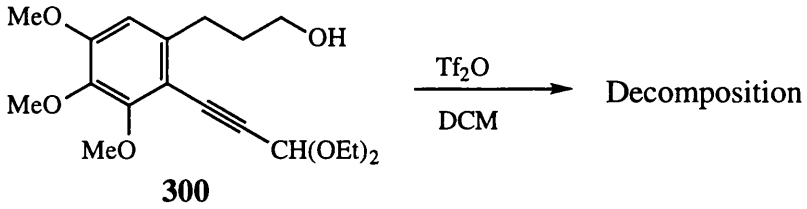
Nevertheless, the alcohol (**300**) possessing an acetylenic substituent in the aryl ring was synthesised as shown in Scheme 120. The aldehyde (**168**) was converted to the α,β-unsaturated ester (**247**) *via* a one-pot Wittig reaction in a biphasic mixture. The α,β-unsaturated ester (**247**) was then hydrogenated in excellent yield (97%) to the ester (**297**), which was transformed to the iodo-ester (**298**). The ester (**299**) was duly obtained from the palladium-catalysed coupling between the iodo-ester (**298**) and propargylaldehyde diethyl acetal. Reduction of the ester (**299**) using DIBAL-H at 0°C

generated a mixture of the desired alcohol (**300**) and the over-reduced ether (**301**) in 59% and 22% yields, respectively.



i. $MeO_2CCH_2PPh_3Br$ (1.5eq), 1M NaOH, DCM, r.t. (93%); ii. H_2, Pd/C, MeOH, r.t. (97%); iii. CF_3CO_2Ag (1eq), I_2 (1.1eq), DCM, r.t. (97%); iv. $Pd(OAc)_2$ (5mol%), CuI (5mol%), PPh_3 (20mol%), $HC{\equiv}CCH(OEt)_2$ (1.2eq), Et_2NH, reflux (75%); v. DIBAL-H (2.2eq), PhMe, 0^oC (**300** 59%, **301** 22%)

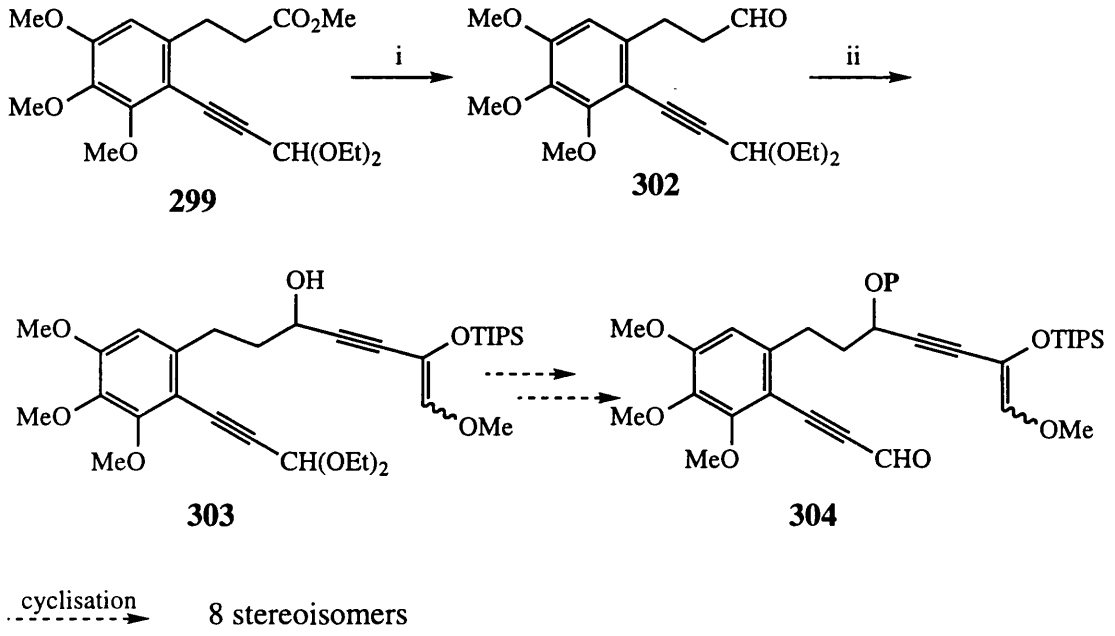
Scheme 120



Scheme 121

However, when the alcohol (**300**) was treated with triflic anhydride, an intensely purple-coloured solution was obtained and only decomposition of the starting material was observed without formation of the desired triflate (Scheme 121). Apparently, triflic anhydride preferentially reacted with the acetal group leading to polymerisation.

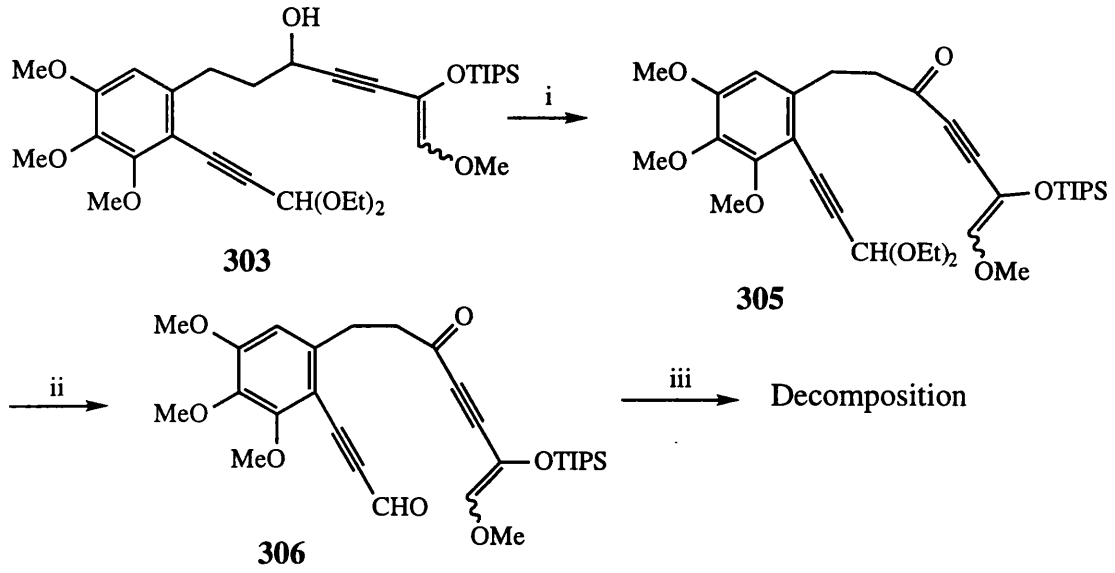
Therefore, the aldehyde (**302**) was prepared by reducing the ester (**299**) at -78°C with DIBAL-H (Scheme 122) and used as an intermediate for the incorporation of the silyl enol ether fragment. The key secondary alcohol (**303**), incorporating all the necessary carbon atoms, was then obtained in good yield by treating the aldehyde (**302**) with 1.1 equivalent of the acetylide (**290b**).



i. DIBAL-H (1.05eq), PhMe, -78°C (87%); ii. **290b** (1.1eq), THF, -78°C (83%)

Scheme 122

In order to reduce the number of isomeric products in the subsequent aldol reaction and hence the complexity of spectroscopic data, it was decided that, instead of converting to the protected alcohol (**304**), the alcohol (**303**) should be oxidised to the ketone (**305**) with manganese dioxide (Scheme 123) so that the chiral centre at the propargylic position was effectively eliminated. The keto group should not affect the subsequent cyclisation because the formyl group should react in preference to the keto group in an aldol reaction, and the silyl enol ether moiety could not react intramolecularly with the keto group because of structural constraints.



i. MnO_2 (10eq), DCM, r.t. (79% yield, 11% recovered **303**); ii. amberlyst 15 ion exchange resin (2eq in mass), acetone, 48%; iii. $TiCl_4$ (see text)

Scheme 123

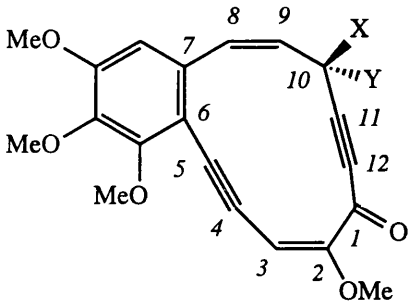
It is well-documented[86,91] that acetals can undergo Lewis acid-promoted aldol reaction with silyl enol ethers and hence attempts were made to cyclise the acetal (**305**) directly. Noyori *et al*[91(a),(b)] have reported that trimethylsilyl triflate (TMSOTf), a milder Lewis acid than titanium(IV) chloride, can be used as a catalyst in the aldol reaction between acetals and TMS enol ethers at low temperature. However, when the acetal (**305**) was treated with TIPSOTf, the corresponding reagent for the TIPS enol ether moiety, at -78°C or -55°C, no cyclisation product was observed. The acetal (**305**) decomposed rapidly even at -94°C if titanium(IV) chloride was used as Lewis acid.

Consequently, it was decided that the acetal (**305**) would be hydrolysed to form the aldehyde (**306**) as a precursor for the cyclisation. Because of the presence of the acid-sensitive silyl enol ether moiety, appropriate reagents were carefully selected to deprotect the acetal (**305**). Amberlyst 15 ion exchange resin in acetone was eventually found to be the best reagent giving the unstable aldehyde (**306**) in 48% yield (Scheme 123) while the use of other reagents such as pyridinium *p*-toluenesulfonate only led to decomposition of the starting material.

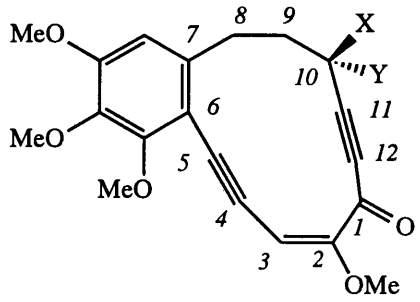
As the product (**306**) turned rapidly from pale yellow to brown even when refrigerated, it was used immediately after preparation. The utilisation of a number of Lewis acids were attempted to effect the macrocyclisation at various temperatures. When titanium(IV) chloride was used, no reaction was observed at -78°C in contrast to the analogous reaction of the acetal (**305**). On warming up to -55°C, a complete conversion of the starting material to a new compound was in evidence by t.l.c. and hence the reaction was quenched at this temperature with sodium bicarbonate solution. However, no product was isolated when the reaction mixture was warmed up to room temperature. Presumably, the product from this aldol reaction was unstable to the conditions of isolation. Nevertheless, this approach is certainly worthy of further study.

2.1.4. Concluding Remarks on the Investigation of the Cycloaromatisation Approach

The above sections constitute the major studies which were undertaken on the investigation of the cycloaromatisation approach. Although the syntheses of macrocycles, (**144**) and (**251**), have not been successfully completed, valuable information was



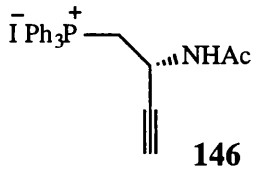
144 X=H, Y=NHAc
119a X,Y=H, O, NHAc, etc.



251 X=H, Y=NHAc
119 X,Y=H, O, NHAc, etc.

obtained through these studies about the incorporations of both the stereocentre and the macrocyclic framework. The results of these studies are briefly summarised below.

Unanticipated problems were met in the attempted incorporation of the stereocentre and the synthesis of the four-carbon fragments, (**146**) and (**149**), were not successful. Moreover, the highly unsaturated nature of the SAMP hydrazone (**195**) and



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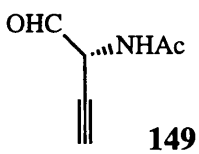
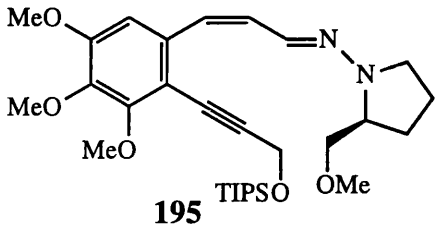


149

the vinyl halides, (**200**) and (**201**), led to the failure of the SAMP/RAMP-related approach. During the attempted synthesis of the macrocycle (**119a**), the 1,4-enyne



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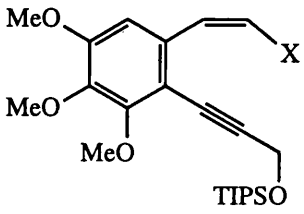
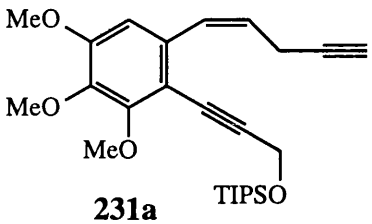
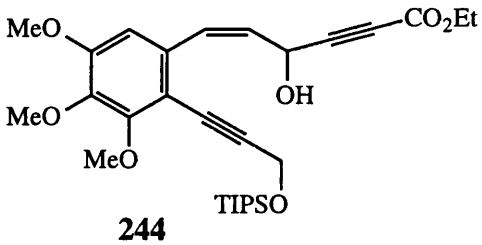


X=Br **200**
X=I **201**

systems present in both (**231a**) and (**244**) were found to be unexpectedly labile and complications resulted when elaborations of their derivatives were attempted. Furthermore, in the investigation of synthesis of the macrocycle (**119**), the use of a



231a



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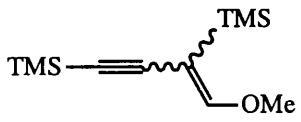
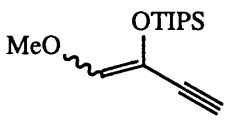
preformed *Z*-enyne fragment (**269**) for the incorporation of C2-5 was found to be problematic. However, the silyl enol ether (**290a**) has proven to be a promising

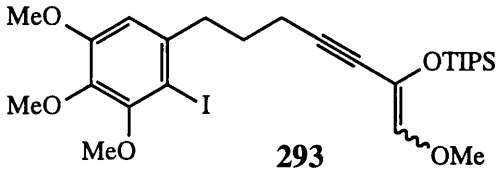


269



290a

intermediate for the incorporation of the C11-2 portion of the macrocycle. A successful titanium(IV) chloride-promoted reaction between the silyl enol ether (**293**) and 3,4,5-trimethoxybenzaldehyde demonstrated the feasibility of an aldol reaction using a TIPS enol ether but no desired cyclisation product was obtained by treatment of compound (**306**) with titanium(IV) chloride. In addition, the palladium-mediated coupling of (**293**) with propargyl diethyl acetal was unsuccessful probably because of the formation of the highly chelated complex (**295**), which prevents the palladium atom from participating the catalytic cycle.



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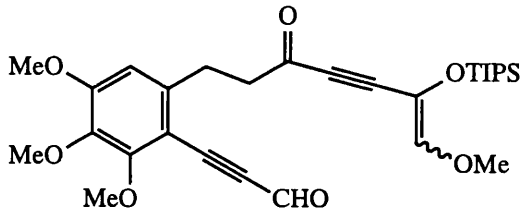

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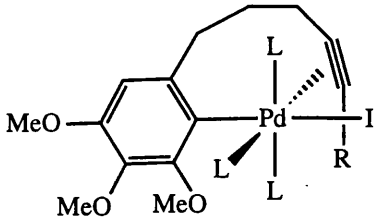


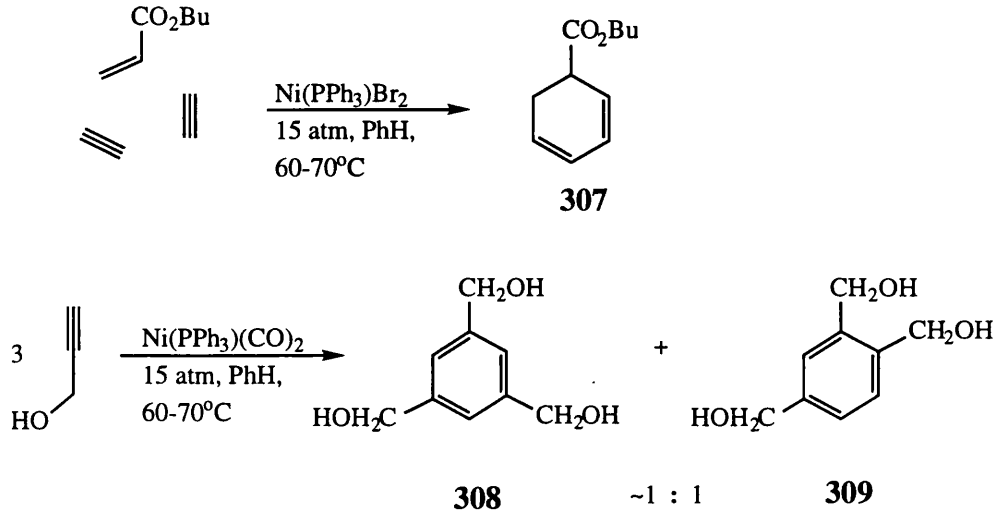
295

Amongst the other information obtained from these studies, we may conclude that the use of the silyl enol ether (**290a**) may require further elaboration in order to improve the nucleophilic addition of its lithiated derivative and the subsequent Lewis acid-promoted intramolecular aldol reaction. Moreover, the possible formation of the complex (**295**) indicates that the palladium-mediated incorporation of the C4-5 alkyne group should be carried out prior to the incorporation of the C11-12 alkyne group.

2.2. Investigation of the [2+2+2] Cycloaddition Approach

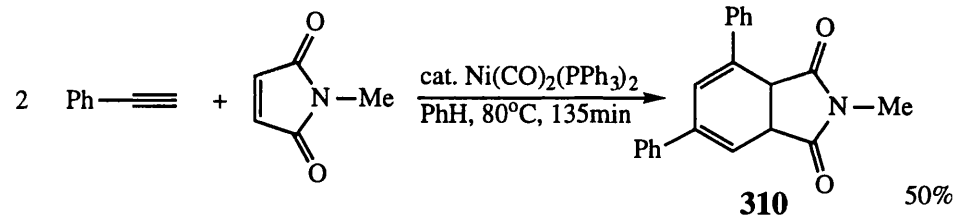
2.2.1. Background and Strategy

The generation of six-membered rings by transition metal-mediated [2+2+2] cycloaddition of alkynes and alkenes was first reported in the 1940's by Reppe and Schweckendieck[92]. They found that dibromobis(triphenylphosphine)nickel(II) promoted the cycloaddition of two molecules of acetylene and one molecule of butyl acrylate to form the cyclohexadiene derivative (**307**) (Scheme 124) and that propargyl alcohol trimerised in



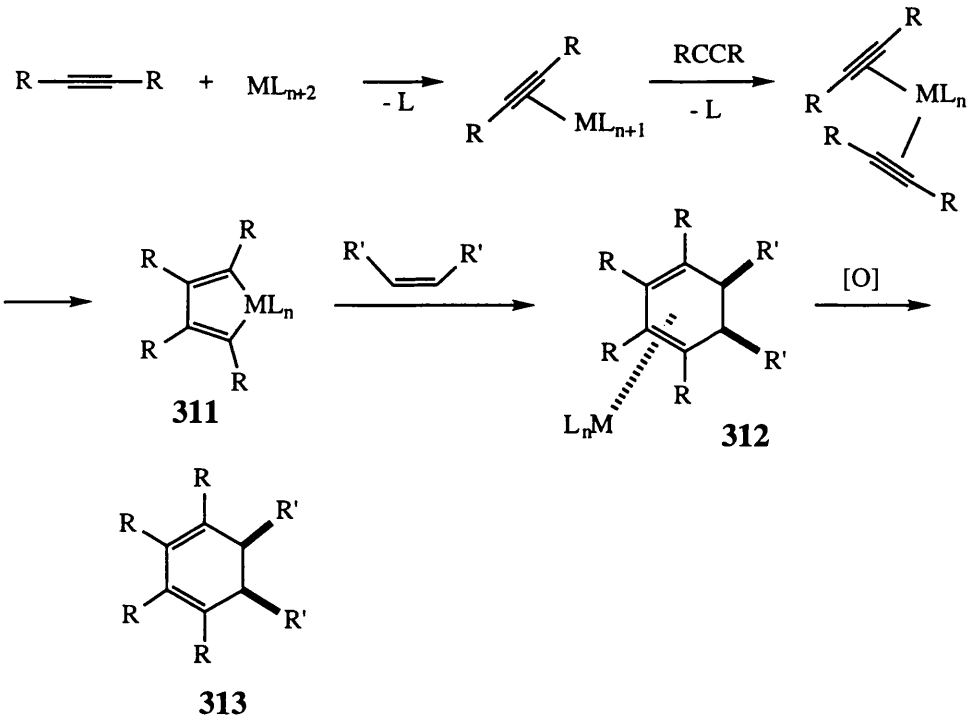
Scheme 124

the presence of dicarbonylbis(triphenylphosphine)nickel(0) to form the triols (**308**) and (**309**). Since then a number of successful similar cycloadditions have been reported. For instance, Chalk[93] achieved the highly regioselective cycloaddition of phenylacetylene and *N*-methylmaleimide with nickel(0) catalyst to form the cyclohexadiene derivative (**310**) in moderate yield (Scheme 125). Although only one product is formed in this reaction, the inherent problem of regioselectivity is encountered in most cycloadditions involving unsymmetrical components.



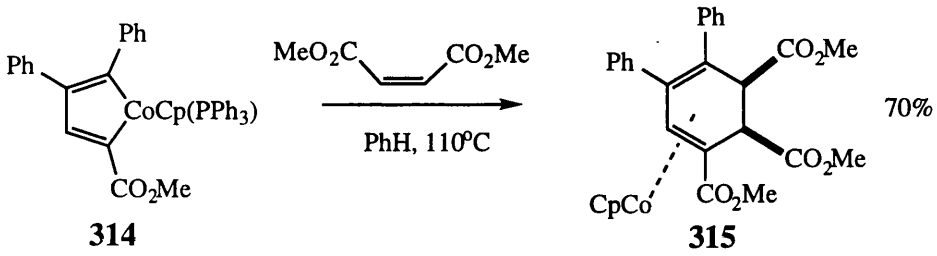
Scheme 125

The mechanism[94] of the cycloaddition varies with catalysts but it generally invloves the initial formation of a metallacyclopentadiene complex (**311**) by the metal and two alkyne molecules (Scheme 126). The complex then reacts with the alkene to provide the cyclohexadiene complex (**312**) *via* a sequence generally considered to involve alkene complexation, insertion and reductive elimination of the metal from a seven-membered ring metallacycle. This occurs with full retention of stereochemistry of the alkene component. In some cases, oxidising agents such as iodine or cerium(IV) reagents are used to release the cyclohexadiene derivative (**313**) from the complex (**312**).



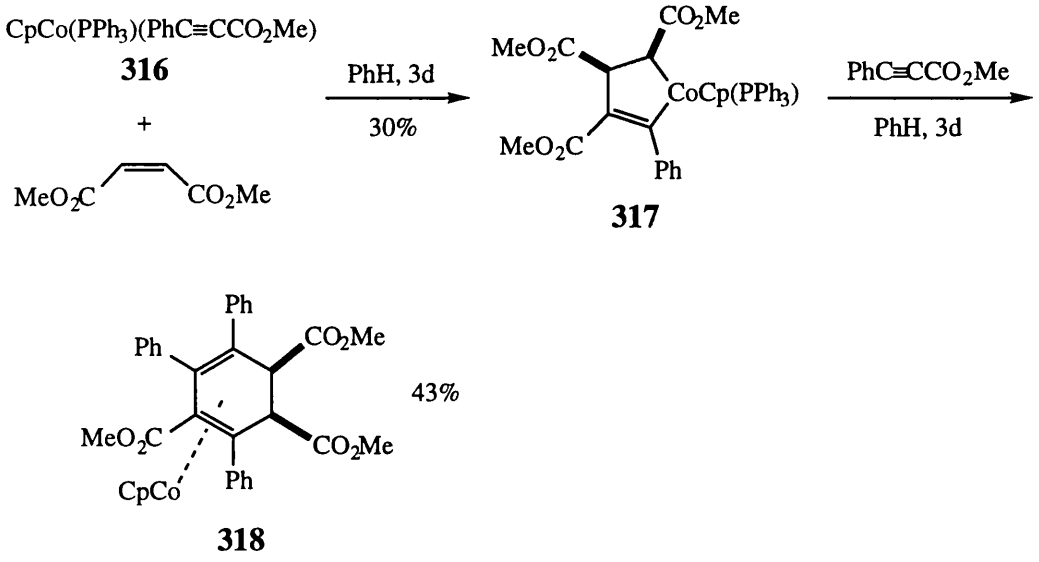
Scheme 126

However, a number of metals have been found to complex with alkenes in preference to alkynes and hence in many cases the desired cyclic products cannot be obtained from the direct addition of catalyst to a mixture of alkynes and alkenes. As a result, the stoichiometric reaction of a preformed metallacyclopentadiene complex with an alkene can also be employed. For instance, the complex (**314**) reacts with dimethyl maleate to form the cyclohexadiene complex (**315**) in good yield[95(a)] (Scheme 127). Conversely, as

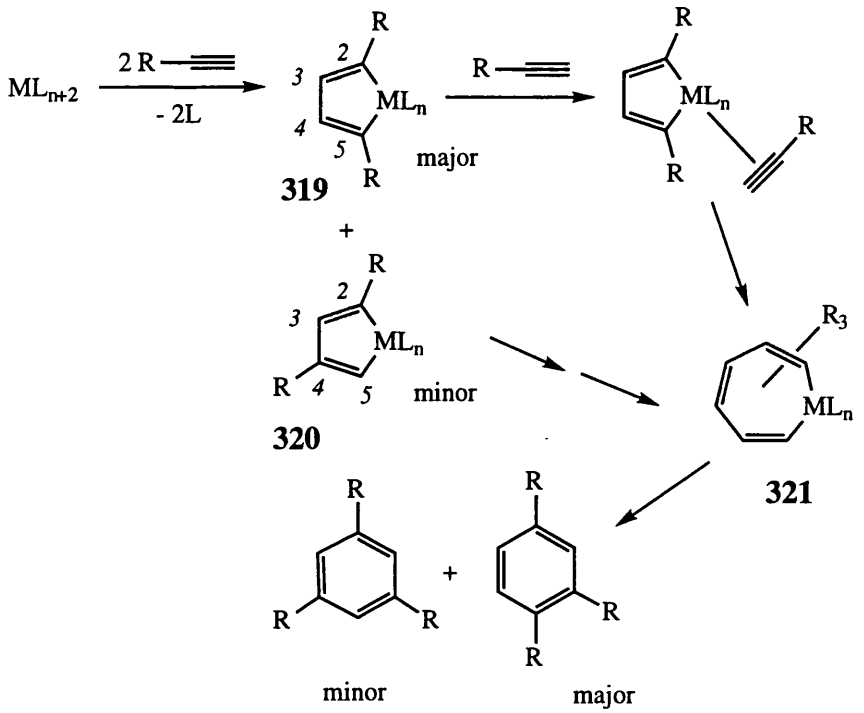


Scheme 127

Wakatsuki *et al*[95(b)] reported, the metallacyclopentene complex (**317**), which can be obtained by reacting the monoalkyne complex (**316**) with dimethyl maleate (Scheme 128), reacts stoichiometrically with another molecule of the alkyne and provides the cyclohexadiene derivative (**318**).

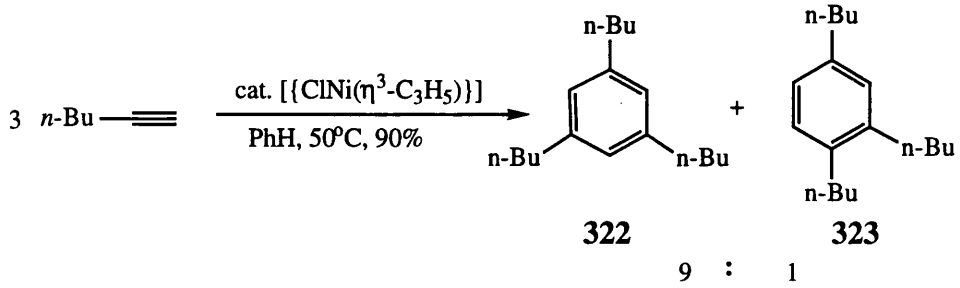


Scheme 128



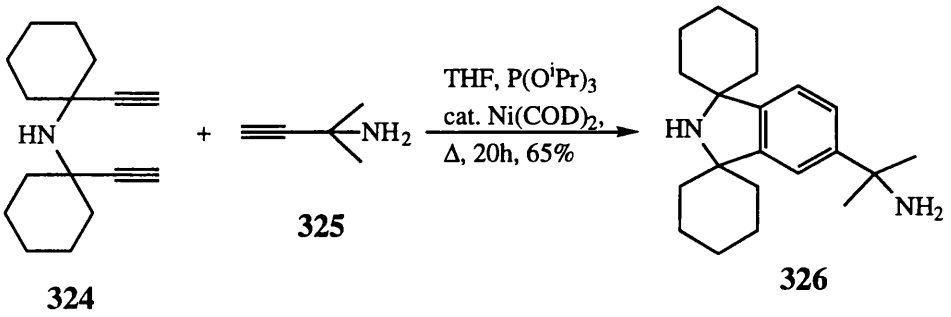
Scheme 129

The preparation of arenes by [2+2+2] cycloaddition of alkynes has also been extensively investigated. It is believed that the reaction proceeds *via* the insertion of a third alkyne molecule into the metallacyclopentadiene complexes (**319** and **320**) (Scheme 129) to form the seven-membered cyclic complex[96] (**321**). Subsequent reductive elimination of the metal forms the benzenoid products. It has been noted that the 2,5-disubstituted complex (**319**) is formed in preference to the 2,4-substituted analogue (**320**) and that 1,2,4-trisubstituted compounds are usually obtained as major products. However, some nickel(II)-based catalysts have been found to provide 1,3,5-trisubstituted benzene derivatives as major products. For instance, [{ClNi(η^3–C_3H_5)}] mediates the trimerisation of *n*-hexyne to form the arenes (**322**) and (**323**) in a 9:1 ratio[97] (Scheme 130).



Scheme 130

In addition to the intermolecular cycloaddition of 3 alkyne molecules, the tethered cycloaddition of a diyne and a monoyne has also been investigated. Thus bis(cyclooctadiene)nickel(0) ($Ni(COD)_2$) has been found to catalyse the formation of the tetracyclic compound (**326**) from the diyne (**324**) and the aminoacetylene[98] (**325**) (Scheme 131). However, in a number of cases, a selectivity problem is encountered due to the

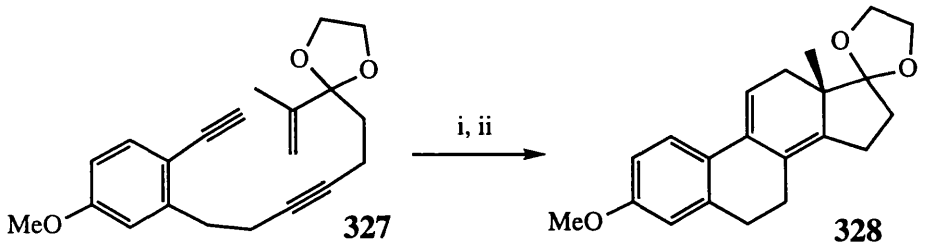


Scheme 131

competing possible trimerisation of the monoyne component. Even if a preformed metallacyclopentadiene complex of the diyne is used, the metal released upon the formation of the product may then induce the unwanted trimerisation. Therefore, disubstituted acetylenes such as bis(trimethylsilyl)acetylene or bis(trimethyltin)acetylene are frequently used as the monyne component since the trimerisations of such substrates are sterically unfavourable.

Vollhardt[96,99] and co-workers, in particular, have pioneered the use of the [2+2+2] cycloaddition technology in synthetic organic chemistry. For instance, the steroid skeleton in compound (**328**) was constructed by the cobalt-mediated intramolecular [2+2+2]

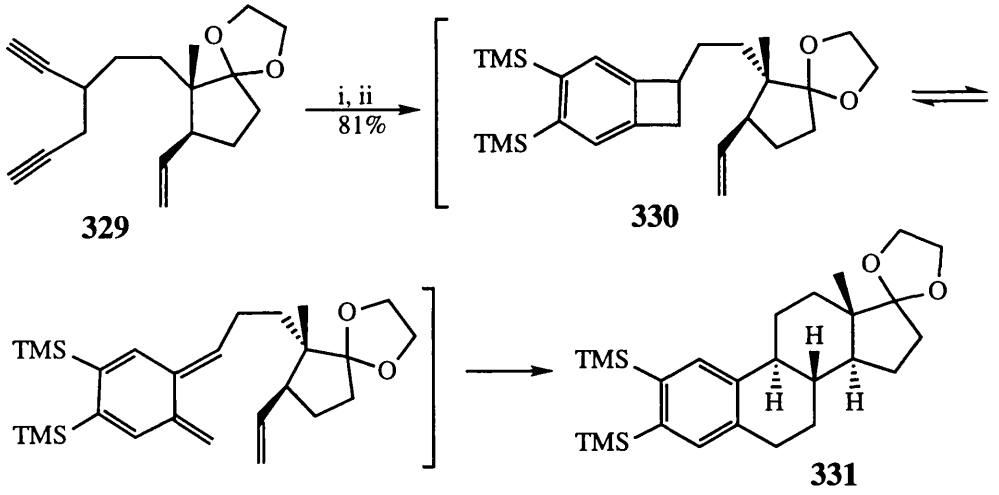
cycloaddition of the precursor (**327**) followed by decomplexation of the metal with iron(III) chloride[100] (Scheme 132).



i. isooctane, $CpCo(CO)_2$, 100°C, 48h, 65%; ii. MeCN, $FeCl_3 \cdot H_2O$, -40-0°C, 25min, 78%

Scheme 132

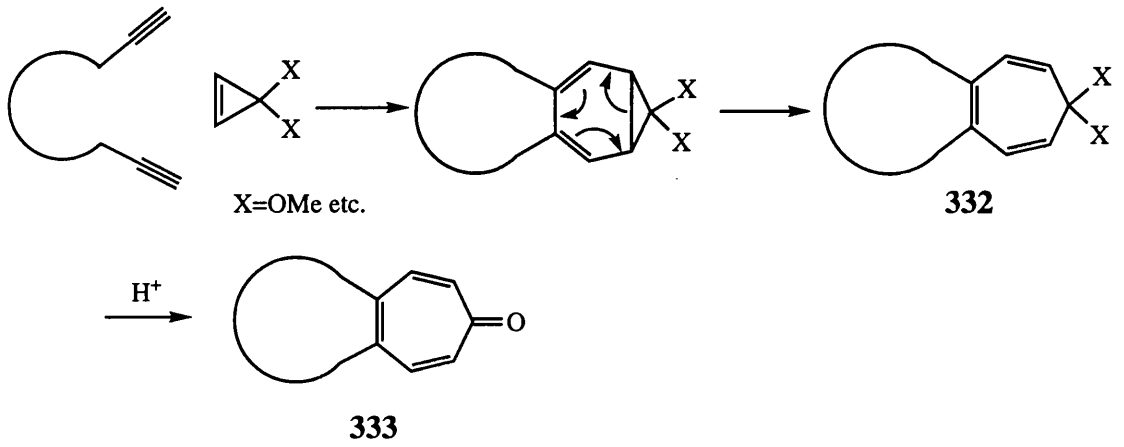
Moreover, an elegant cobalt-mediated double cycloaddition also constitutes the key step of the Vollhardt's synthesis of estrone[101]. Thus, the precursor (**329**) (Scheme 133) was transformed to the benzene derivative (**330**) *in situ* by the tethered [2+2+2] cycloaddition protocol with bis(trimethylsilyl)acetylene. Ring opening of the benzocyclobutadiene followed by a second intramolecular [2+2+2] cycloaddition of the 3 double bonds provided the product (**331**) in excellent yield.



i. TMSC≡CTMS, cat. $CpCo(CO)_2$, 41h, heating; ii. decane, 180°C, 20h, 81% overall

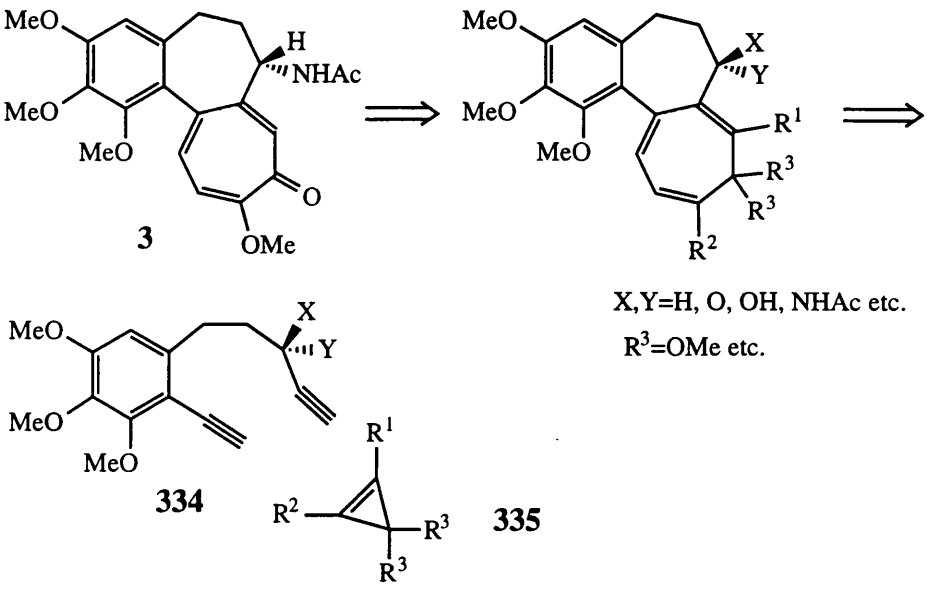
Scheme 133

Following these precedents, we envisaged that the seven-membered cyclic intermediate (**332**) could also be formed from a transition metal-mediated [2+2+2] cycloaddition of a tethered diyne and a cyclopropenone derivative as shown in Scheme 134. The ketal intermediate (**332**, X=OMe) would then be converted to the tropone (**333**) upon



Scheme 134

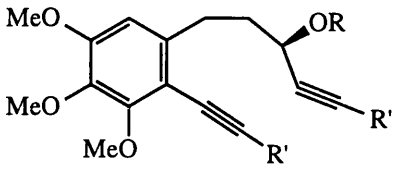
treatment of acid. If such a reaction were attainable, it implies that both rings B and C of colchicine, and of other related tropolonic alkaloids, could be generated in a single step by a similar cycloaddition of the appropriate diyne (**334**) and cyclopropenone derivative (**335**) (Scheme 135). As discussed earlier in this chapter (Scheme 41), the regioselectivity of such a cycloaddition could be enhanced by a careful selection of R^1 and R^2 groups or by employing a second intramolecular tether between the diyne and the cyclopropenone derivative. Therefore, our initial intention was to explore the feasibility of this [2+2+2] cycloaddition using a series of model studies, and to synthesise the diyne precursor (**334**) and an appropriate cyclopropenone derivative (**335**) for subsequent formation of colchicine *via* such a cycloaddition.


MeO
MeO
MeO
H
NHAc
O
OMe
3
X
Y
R1
R3
R3
R2
X,Y=H, O, OH, NHAc etc.
R3=OMe etc.
334
335

Scheme 135

2.2.2. Synthesis of the Diyne Precursor and Preliminary Studies of the Tethered [2+2+2] Cycloaddition

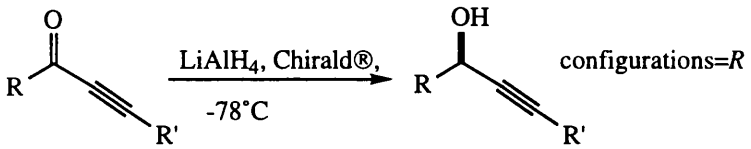
Since the C-7 acetamido group of colchicine can be introduced *via* a nucleophilic displacement of an oxygen-based leaving group with reagents such as azide anion at a later stage of the synthesis (as in Banwell's synthesis), it was decided that the protected secondary alcohol (**336b**) would be synthesised as the diyne component of the



R'=H or TMS

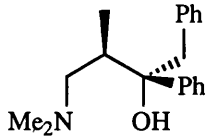
336 **a** R=H
b R=protecting group

cycloaddition. Moreover, it has been reported that α-alkynones can be reduced enantiospecifically to secondary alcohols by the use of lithium aluminium hydride with (2*S*,3*R*)-(+)-dimethylamino-1,2-diphenyl-3-methyl-2-butanol (Chirald®) as an auxiliary[102] (Scheme 136). Hence we envisaged that the alcohol (**336a**) could be generated from an α-alkynone. In this manner, our second objective of generating the C-7 stereocentre of colchicine in an asymmetric fashion can also be fulfilled.



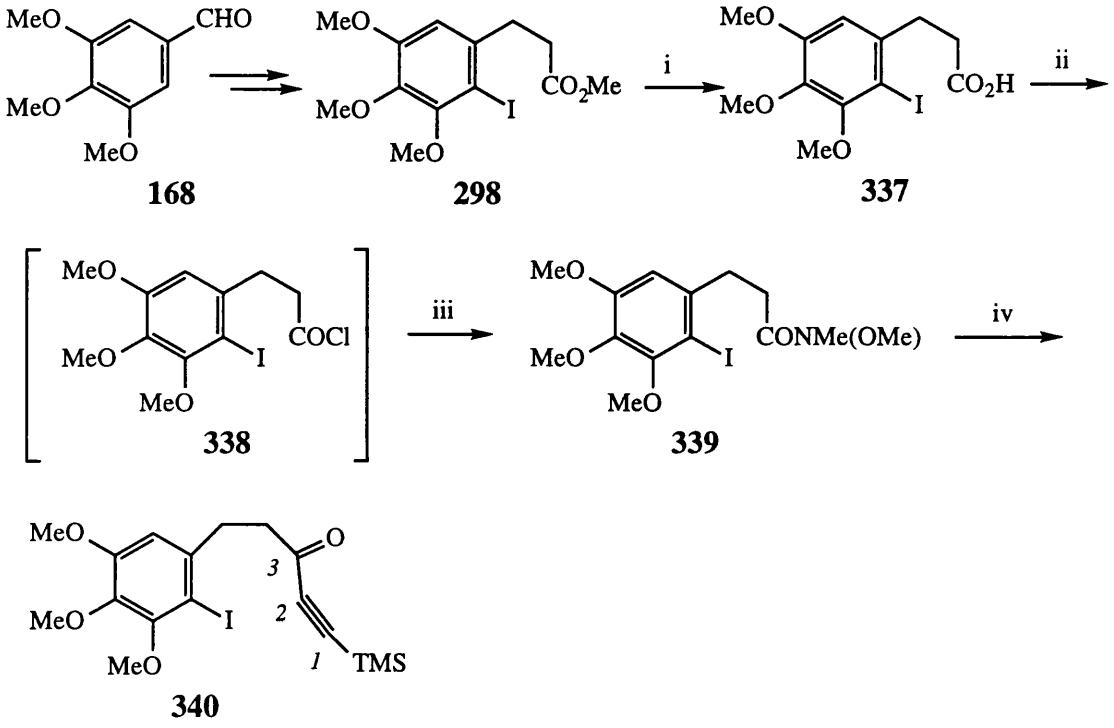
R=alkyl

R'=H, alkyl or TMS

Chirald® = 

Scheme 136

Thus, the iodo-ester (**298**) was formed from 3,4,5-trimethoxybenzaldehyde (**168**) in 3 steps as previously described in Scheme 120. The ester (**298**) was then hydrolysed in methanolic potassium hydroxide giving rise to the carboxylic acid (**337**) (Scheme 137). Heating the lithium carboxylate of the acid (**337**) with lithium trimethylsilylacetylide in THF or DME did not succeed in forming the ketone (**340**). Phosphorus oxychloride was then used to convert the acid (**337**) to its acid chloride (**338**) but a purple solution was obtained



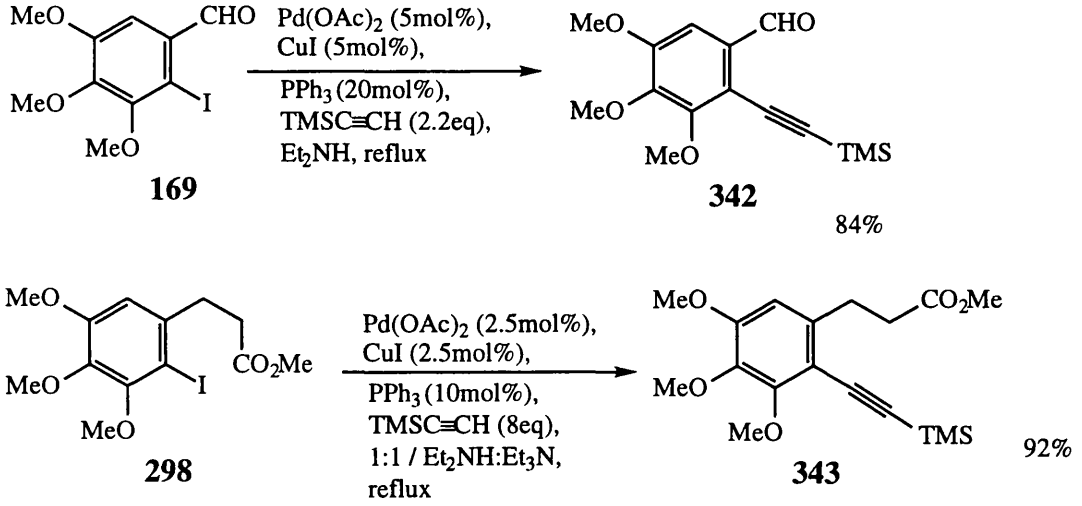
i. KOH (1.2eq), MeOH, reflux; H^+ (94%); ii. $(COCl)_2$ (1.1eq), cat. DMF, PhH, 0-25°C; iii. HNMe(OMe)·HCl (1.1eq), pyr (2.2eq), $CHCl_3$, 0-25°C (68%); iv. TMSC≡CLi (2eq), THF, 0-25°C; H^+ (69%)

Scheme 137

during the reaction and the stability of the iodine atom in this reaction was therefore doubted. Hence a much milder reaction employing oxalyl chloride with catalytic DMF was pursued. The infrared spectrum of the crude product indicated the presence of carbonyl stretching corresponding to acid chloride (1790cm^{-1}) and the absence of acid carbonyl

stretching. Various attempts including the direct addition of lithium trimethylsilylacetylide at low temperature and coupling reaction with trimethylsilylacetylene using palladium catalysts were employed in efforts to convert the acid chloride (**338**) to the ketone (**340**) but failed. Thus, the acid chloride was converted with *N,O*-dimethylhydroxylamine hydrogen chloride salt to the 'amide' (**339**), which readily reacted with lithium trimethylsilylacetylide to form the ketone (**340**). However, all attempts to couple the ketone (**340**) with trimethylsilylacetylene by Heck/Castro-type reaction failed.

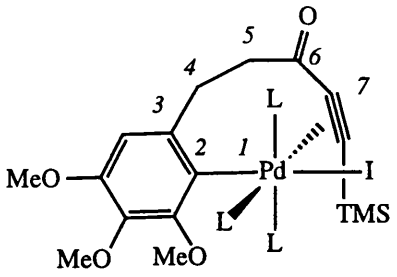
In order to investigate the reason why the coupling reaction failed, the iodobenzaldehyde (**169**) was coupled with trimethylsilylacetylene using palladium(II) acetate and copper(I) iodide as catalysts (Scheme 138). This smoothly provided the aldehyde (**342**) in 84% yield. Moreover, a similar reaction of the ester (**298**) also formed the corresponding coupling product (**343**) in high yield (92%).



Scheme 138

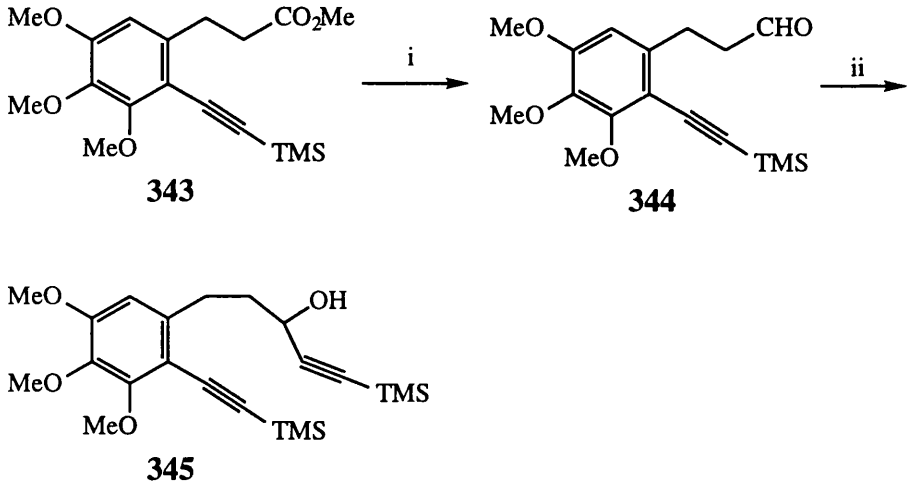
With the additional information obtained from the investigation of the cycloaromatisation approach, neither the highly electron-rich nature of the aryl system nor the C-3 carbonyl group was considered responsible for the failed palladium-mediated reaction between trimethylsilylacetylene and the ketone (**340**). As a result, the formation of

the complex (**344**), which prevents the palladium atom from participating in the catalytic cycle, is postulated.



344 L= solvent or PPh_3

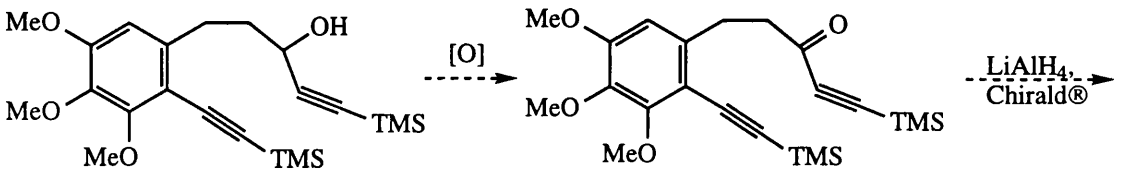
Nevertheless, the ester (**343**) was reduced with DIBAL-H at -78°C to form the aldehyde (**344**) (Scheme 139). Nucleophilic attack of lithium trimethylsilylacetylide to the



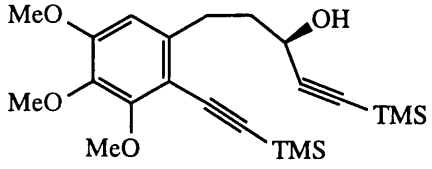
i. DIBAL-H (1.1eq), PhMe, -78°C (70%); ii. TMSC≡CLi (1.2eq), THF, 0-25°C (52%)

Scheme 139

aldehyde (**344**) then provided the racemic secondary alcohol (**345**). The protected form of this alcohol could be used as the precursor of the [2+2+2] cycloaddition or the C-7 stereocentre of colchicine could be generated subsequently as shown in Scheme 140.



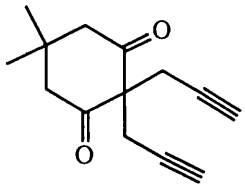
345 346



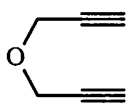
336a

Scheme 140

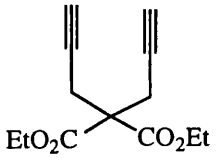
At this stage, it was deemed prudent to carry out a series of model studies in order to explore the feasibility of the [2+2+2] cycloaddition protocol of a tethered diyne and a cyclopropenone derivative. Accordingly, the known simple diynes (**347**)[103(a)], (**348**)[103(b)] and (**349**)[103(c)] were prepared. In addition, the propargyl ether (**351**) was also prepared as



347

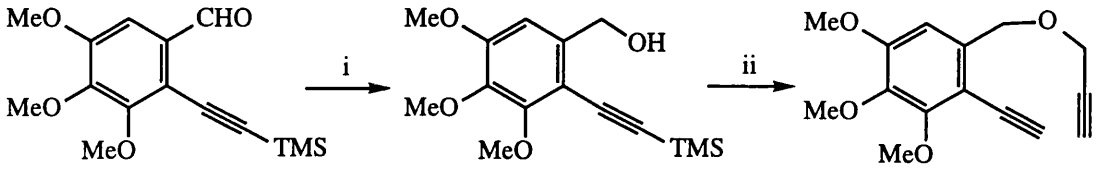


348



349

a model compound since it would provide rapid information about the cycloaddition by which a tricyclic framework analogous to that of colchicine is formed and also lead to analogue chemistry. Thus, the aldehyde (**342**) (Scheme 141) was reduced with lithium aluminium hydride to the alcohol (**350**), which was coupled with propargyl bromide by the use of sodium hydride in DMF to form the ether (**351**). Since a 'catalytic' amount of hydroxide ion might be generated by the reaction of sodium hydride with the residual water in the solvent, the TMS group of the aryl ethynyl substituent was unexpectedly removed in this step.

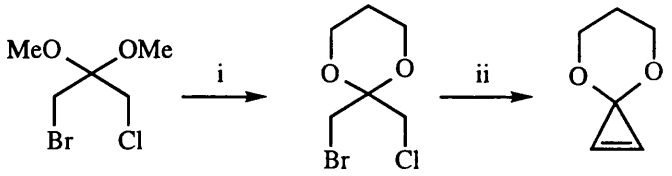


342 **350** **351**

i. $LiAlH_4$ (1eq), Et_2O, reflux (91%); ii. NaH (1.1eq), DMF, r.t.; $HC{\equiv}CCH_2Br$ (1.1eq), r.t. (69%)

Scheme 141

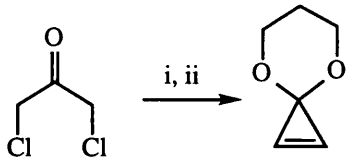
With the diynes in hand, we then sought to prepare the relatively easily accessible cyclopropenone derivative for the model studies. Boger[19(k),104] and co-workers had prepared the known cyclopropenone 1,3-propanediol ketal (**80**) from the dihaloacetone derivative (**352**) according to Breslow's procedure[105] (Scheme 142) in their formal synthesis of colchicine. Nakamura *et al*[106] have modified this method in the preparation of a number of cyclopropenone ketal derivatives by using commercially available sodamide instead of generating potassium amide *in situ* from potassium metal and ammonia. We thus prepared cyclopropenone 1,3-propanediol ketal (**80**) from 1,3-dichloroacetone by employing Nakamura's method but the yield was not significantly different from that reported by Boger's group.



352 **80**

i. $HO(CH_2)_3OH$ (1eq), cat. H_2SO_4 , 140°C (81%); ii. KNH_2 (generated *in situ*), NH_3, -50°C (~55%)

Scheme 142

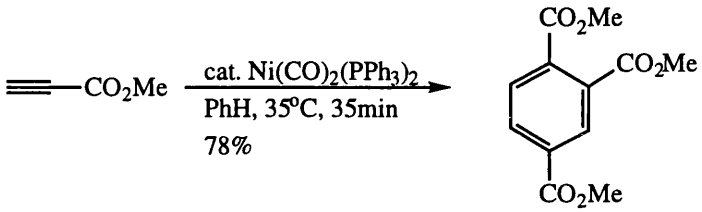


80

i. $HO(CH_2)_3OH$ (1eq), cat.TsOH, PhH, reflux (97%); ii. $NaNH_2$ (purchased, 3.5eq), NH_3, -50°C (~50%)

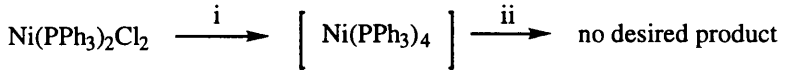
Scheme 143

Although Vollhardt *et al* have demonstrated that cobalt complexes successfully mediated various [2+2+2] cycloadditions, we decided that nickel(0) catalysts would be employed in our preliminary investigations due to a number of precedents in which nickel complexes efficiently mediate intermolecular cycloaddition of alkynes and alkenes (for instance, Schemes 124, 125, 131 and 144[107]). As we have mentioned earlier, this decision was later proven to be valid since Binger *et al* also used $Ni(COD)_2$ as a catalyst in their successful cycloaddition of trimethylsilylacetylene and the cyclopropenone ketal (**114**) (Scheme 42).



Scheme 144

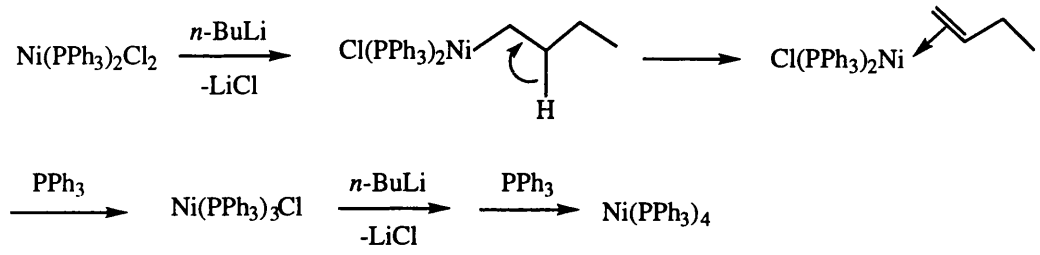
In our own studies, as summarised in Scheme 145, tetrakis(triphenylphosphine)-nickel(0) was generated *in situ* according to Smith's method[108] from dichlorobis(triphenyl-



i. *n*-BuLi (2eq), PPh_3 (2eq), THF, -78-0°C; ii. **347** or **349** (1eq) and then **80** (1eq), -78-0°C-r.t.

Scheme 145

phosphine)nickel(II) with *n*-butyllithium and triphenylphosphine, presumably *via* the mechanism outlined in Scheme 146, as a brown solution with a red tinge. The red tinge disappeared upon the addition of the diyne (**347**) or (**349**) followed by the cyclopropenone ketal (**80**). However, no desired product was formed although the reactants were consumed.



Scheme 146

In the event however, our studies in this area were curtailed both by the disclosure of Professor Binger and also by the inherent complications of regioselectivity which would inevitably surface even if the key [2+2+2] cycloaddition were successful. Since time constraints also dictated that a choice be made, the focus of our attention therefore became the cycloaromatisation which we have previously discussed.

In spite of the failure to generate a tricyclic nucleus of the colchicine framework, it is nevertheless considered that much of the chemistry which has been examined in this work will hopefully pave the way for a successful elaboration of colchicine and related analogues using transition metal-mediated reactions of acetylenes.

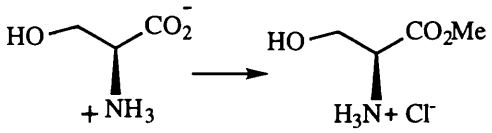
CHAPTER THREE : EXPERIMENTAL

General Procedure:

^1H NMR spectra were recorded in $CDCl_3$ at 200 MHz on a Varian XL-200, 270 MHz on a Jeol GSX 270 and 400 MHz on a Varian VXR-400. ^{13}C NMR spectra were recorded at 60 MHz and 100 MHz on a Jeol GSX 270 and Varian VXR-400, respectively. Residual protic solvents, i.e. $CHCl_3$ (δ_H=7.26 ppm; δ_C=77.0 ppm), D_2O (δ_H=4.75ppm), and C_6D_6 (δ_H=7.40ppm) were used as internal references. Coupling constants were measured in Hertz and chemical shifts in ppm relative to internal reference. Infrared spectra were recorded in wavenumbers (cm^{-1}) using sodium chloride plates on Perkin Elmer 983G and FT-IR 1600 spectrometers. Mass spectra and accurate mass measurements were recorded by EI on a VG 7070B instrument at Imperial College, on a VG 12 253 and VG ZAB-e instruments by the SERC mass spectrometry service, and by EI, CI (with NH_3 carrier gas), and FAB on a VG 7070 instrument at UCL. Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus using sealed capillary tubes. Sonication was carried out in a Sonicor SC-52 cleaning bath. Optical rotations were measured at ambient temperature on an Optical Activity AA1000 polarimeter and the concentrations are expressed in g/100ml. Microanalyses were performed at Imperial College Chemistry Department microanalytical laboratory and at UCL Chemistry Department microanalytical laboratory. HPLC separation was performed on a Partisil 5 silica gel column (250mm x 10mm), using a UV detector (254 nm). Flash column chromatography was performed on Merck Kieselgel 60 (230-400 mesh) at low positive pressure. Preparative thin layer chromatography was performed on pre-coated glass plates (Merck Kieselgel 60 F_{254}, 2mm) and visualised using ultraviolet light (254 nm). Analytical thin layer chromatography was performed on pre-coated glass backed plates (Merck Kieselgel 60 F_{254}, 0.2 mm) and visualised using ultraviolet light (254 nm), potassium permanganate, acidic ammonium molybdate and iodine, as appropriate. "Petroleum ether"

refers to petroleum ether (b.p. 40-60°C) which was distilled prior to use. Diethyl ether, tetrahydrofuran and benzene were distilled from sodium benzophenone ketyl; dichloromethane from phosphorous pentoxide; acetone from 4A molecular sieves; *N,N*-dimethylformamide, dimethoxymethane, trimethylsilyl chloride, dimethylsulfoxide, diethylamine and triethylamine from calcium hydride, pyridine from sodium hydroxide; methanol and ethanol from magnesium turnings; and toluene from sodium. Unless specified, all reactions were carried out in dry argon or nitrogen atmospheres, and removal of solvents was performed under reduced pressure (15-20mmHg). All glassware was oven-dried (120°C, 4 hours) and cooled down in a desiccator containing anhydrous calcium chloride and self-indicating silica gel prior to use. Purchased chemicals are named as indicated on the labels and used without further purification.

Preparation of (*S*)-(1-Methoxycarbonyl-2-hydroxyethyl)ammonium chloride (Methyl L-Serinate hydrogen chloride salt)[57] (155)



152 **155**

Acetyl chloride (14.9g, 0.19mol) was added to stirred anhydrous methanol (90ml) at 0°C and the resulting mixture was left stirring for 5 minutes before L-serine (7.11g, 67.7mmol) was added. The reaction mixture was then refluxed for 20 minutes and the product was obtained as a white solid (10.20g, 97%) upon the subsequent concentration.

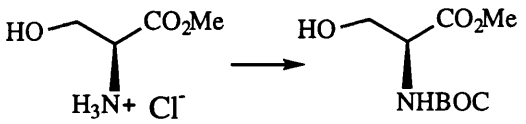
m.p. 160-162°C (dec.) (lit.[109] 163°C, dec.)

ν_{max} (film) : 3349, 2942, 1931, 1753, 1597, 1509

δ_H (270MHz, D_2O) : 4.15 (1H, m, OCH_2CH), 3.98 and 3.86 (2H, 2dd, 12.7Hz, 4.2Hz and 3.4Hz, OCH_2CH), 3.73 (3H, s, CO_2CH_3)

m/z (EI) : 120 ($[M-Cl]^+$)

Preparation of 1,1-Dimethylethyl (*S*)-(1-methoxycarbonyl-2-hydroxyethyl)carbamate[56,57] (154)



155 **154**

To a stirred suspension of the hydrogen chloride salt (**155**) (0.3g, 1.93mmol) in THF (4ml) at 0°C was added dropwise triethylamine (0.2g, 4.25mmol) followed by a solution of di-*tert*-butyl dicarbonate (0.42g, 1.93mmol) in THF (2ml). The reaction mixture was then stirred at room temperature for 6 hours, and then at 50°C for 1 hour. After concentration, the mixture was partitioned between water and diethyl ether (25ml each). The aqueous layer was extracted with diethyl ether (2x20ml) and the combined organic layers were then dried (magnesium sulfate) and concentrated to provide the title compound as a colourless oil (0.42g, 90%), which was used without further purification.

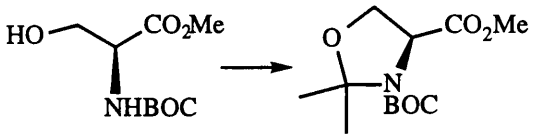
$[\alpha]_D$=-18.9° (c=1.0, MeOH) (lit.[57] -18.9°)

ν_{max} (film) : 3431 (br), 2978, 1718, 1510, 1438, 1164

δ_H (270MHz, $CDCl_3$) : 5.41 (1H, s, N*H*), 4.39 (1H, m, OCH_2CH), 3.98-3.83 (2H, m, OCH_2CH), 2.20 (1H, s, O*H*), 1.45 (9H, s, $NCO_2C(CH_3)_3$)

m/z (EI) : 189 ($[MH-OMe]^+$), 160, 146

Preparation of 3-(1,1-Dimethylethyl) 4-methyl (*S*)-2,2-dimethyl-3,4-oxazolidinedicarboxylate[56,57] (156)



154 **156**

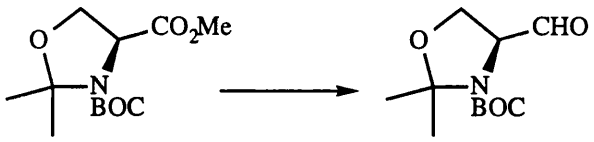
A mixture of the ester (**154**) (5g, 22.8mmol) and 2,2-dimethoxypropane (23.7g, 228mmol) in anhydrous acetone (50ml) was stirred at room temperature while boron trifluoride etherate (0.17ml) was added dropwise. The mixture was concentrated after overnight stirring at room temperature. The residue was taken up in dichloromethane (60ml) and washed with 50% sodium bicarbonate solution (40ml) and then with water (2x40ml). The organic layer was dried (magnesium sulfate), concentrated and chromatographed (30% diethyl ether / 70% petroleum ether) to afford the title compound as a yellow oil (5.49g, 93%). Complex ^{1}H NMR spectra were obtained for the oxazolidinyl compounds (**156**, **151**, **158** and **159**) due to the restricted rotation of the BOC group (see Results and Discussion).

$[\alpha]_D$=-48° (c=1.0, $CHCl_3$) (lit.[56] -46.7°)

δ_H (270MHz, $CDCl_3$) : 4.52-4.32 (1H, m, OCH_2CH), 4.20-3.95 (2H, m, OCH_2CH), 3.78 (3H, s, CO_2CH_3), 1.69-1.42 (15H, m, $O(CH_3)_2CNCO_2C(CH_3)_3$)

m/z (EI) : 244 ($[M-Me]^+$), 186

Preparation of 1,1-Dimethylethyl (*S*)-2,2-dimethyl-4-formyl-3-oxazolidinecarboxylate[56,57] (151)



156 **151**

A solution of the ester (**156**) (5.4g, 20.8mmol) in toluene (40ml) was stirred at -78°C and a solution of DIBAL-H in toluene (25% w/w, 24ml, 22.9mmol) added dropwise over 30 minutes and the reaction mixture was then further stirred for a further 2 hours. Anhydrous methanol (10ml) was added slowly at -78°C. When hydrogen gas evolution had ceased, the reaction mixture was allowed to warm to room temperature and poured into a solution of potassium sodium tartrate tetrahydrate (48.5g in 250ml of water). The resulting gelatinous mixture was vigorously stirred until it became biphasic. The aqueous layer was extracted with diethyl ether (3x80ml) and the combined organic layers were then dried (Na_2SO_4) and concentrated to a pale yellow oil, which was distilled (0.4mmHg, 82-84°C) to give the title compound as a colourless oil (4.1g, 86%).

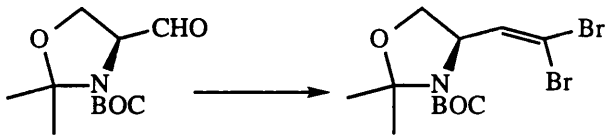
$[\alpha]_D$=-88.0° (c=1.05, $CHCl_3$) (lit.[56] -91.7°)

ν_{max} (film) : 3434, 2977, 1737, 1708, 1477, 1379, 1368, 1065

δ_H (270MHz, $CDCl_3$) : 9.60-9.54 (1H, m, C*H*O), 4.39-3.80 (2H, m, OC*H*$_2$CH), 4.56-3.41 (1H, m, OCH$_2$C*H*), 1.64-1.42 (15H, m, O(C*H*$_3$)$_2$CNCO$_2$C(C*H*$_3$)$_3$)

m/z (EI) : 216 ([M-Me]$^+$), 200

Preparation of 1,1-Dimethylethyl (*R*)-2,2-dimethyl-4-(2,2-dibromoethyl)-3-oxazolidinecarboxylate[59] (158)



151 **158**

To a stirred solution of the aldehyde (**151**) (2g, 8.73mmol) and triphenylphosphine (9.18g, 34.9mmol) in THF (40ml) at 0°C was added a solution of carbon tetrabromide (5.79g, 17.46mmol) in THF (~10ml) *via* a cannula. Pale yellow precipitate started to appear when the addition was almost complete. The reaction mixture was allowed to warm up to room temperature on complete addition, and was then left stirring for 30 minutes before filtering. The filtrate was concentrated and petroleum ether (100ml) was added to the residue. The resulting suspension was filtered and the filtrate concentrated. Then the same procedure was repeated twice until t.l.c. showed almost all triphenylphosphine oxide and unreacted triphenylphosphine were removed. The final residue was chromatographed (8% diethyl ether / 92% petroleum ether) three times to obtain the product as a white solid (2.49g, 74%).

m.p. 42-44°C

$[\alpha]_D$=+0.23° (c=1.08, MeOH)

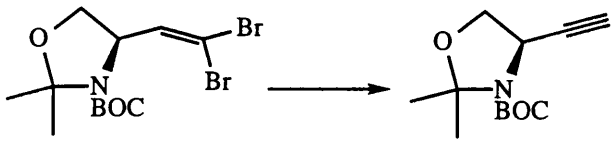
ν_{max} (film) : 1702, 1620, 1477, 1376, 1365

δ_H (270MHz, $CDCl_3$) : 6.45 (1H, d, 8.3Hz, C*H*CBr_2), 4.53-4.50 (1H, m, OCH_2CH), 4.10-3.80 (2H, m, OCH_2CH), 1.60 and 1.51 (6H, 2s, $O(CH_3)_2CN$), 1.48 (9H, s, $NCO_2C(CH_3)_3$)

m/z (FAB) : 386 ($M(^{79}Br^{81}Br)H^+$), 330, 279

Accurate mass : $C_{12}H_{20}O_3N^{79}Br^{81}Br$ (MH^+) requires 385.9789; observed 385.9750

Preparation of 1,1-Dimethylethyl (*R*)-2,2-dimethyl-4-ethynyl-3-oxazolidinecarboxylate (159)



158 **159**

A solution of the dibromide (**158**) (5.77g, 15mmol) in THF (100ml) was stirred at -78°C and *n*-butyllithium (2.5M in hexanes, 13.2ml, 33mmol) was added dropwise over 20 minutes. The reddish solution was stirred at -78°C for 40 minutes and *t*-butanol (5ml, excess) was added at 0°C. The mixture was allowed to warm up to room temperature and then concentrated. The residue was partitioned between diethyl ether and water (100ml each) and the aqueous layer was extracted with diethyl ether (3x50ml). The combined organic layers were dried (magnesium sulfate), concentrated and chromatographed (10% diethyl ether / 90% petroleum ether) to give the title compound as a colourless oil (1.12g, 33%).

$[\alpha]_D$=-144.7° (c=0.52, MeOH)

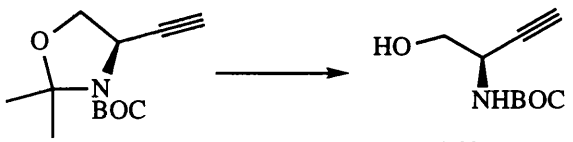
ν_{max} (film) : 3300, 2980, 1703, 1378, 1367, 1098

δ_H (270MHz, $CDCl_3$) : 4.60-4.48 (1H, m, OCH_2CH), 4.07-4.00 (2H, m, OCH_2CH), 2.27 (1H, d, 0.7Hz, C≡C*H*), 1.57 and 1.56 (6H, 2s, $O(CH_3)_2CN$), 1.50 (9H, s, $NCO_2C(CH_3)_3$)

m/z (FAB) : 226 (MH^+), 210, 206, 170

Accurate mass : $C_{12}H_{20}O_3N$ (MH^+) requires 226.1443; observed 226.1436

Preparation of 1,1-Dimethylethyl (*R*)-(1-hydroxybutyn-2-yl)carbamate (150)



159 **150**

The acetylene (**159**) (0.5g, 2.22mmol) was stirred overnight in a mixture of 6:4 / MeOH:1M HCl (10ml) at room temperature. The reaction mixture was neutralised with saturated sodium carbonate solution, and the methanol was then removed under reduced pressure. The resulting suspension was partitioned between diethyl ether and saturated sodium bicarbonate solution (30ml each). The organic layer was washed with brine (2x10ml) and the combined aqueous layers were extracted with diethyl ether (25ml). The combined organic layers were then dried (magnesium sulfate), concentrated and chromatographed (12% to 60% diethyl ether / petroleum ether) to recover unreacted starting material (0.114g, 23%) and afford the title compound as a colourless oil (0.24g, 59%).

$[\alpha]_D$=-44° (c=0.66, MeOH)

ν_{max} (film) : 3303 (br), 2978, 1693, 1515, 1368, 1253, 1167

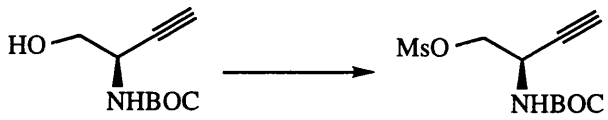
δ_H (270MHz, $CDCl_3$) : 5.50 (1H, s, N*H*), 4.55 (1H, m, OCH_2CH), 3.73 (2H, m, OCH_2CH), 2.34 (1H, d, 2.5Hz, C≡C*H*), 2.20 (1H, s, CH_2OH), 1.46 (9H, s, $NCO_2C(CH_3)_3$)

δ_C (100MHz, $CDCl_3$) : 80.69, 77.23, 72.57, 65.66, 45.23, 28.42, 28.31

m/z (FAB) : 186 (MH^+), 130

Accurate mass : $C_9H_{15}O_3N$ (MH^+) requires 186.1130; observed 186.1142

Preparation of 1,1-Dimethylethyl (*R*)-(1-methanesulfonyloxybutyn-2-yl)carbamate (165)



150 **165**

A solution of the alcohol (**150**) (0.19g, 1.0mmol) in dichloromethane (15ml) was stirred at 0°C while triethylamine (0.119, 1.1mmol) and methanesulfonyl chloride (0.13g, 1.1mmol) were added successively. The reaction mixture was stirred at 0°C for 30 minutes and then partitioned between dichloromethane and water (10ml each). The aqueous layer was extracted with dichloromethane (10ml) and the combined organic extracts were dried (magnesium sulfate), concentrated and chromatographed (80% diethyl ether / 20% petroleum ether) to obtain the product as a colourless oil (0.24g, 89%).

$[\alpha]_D$=-17.2° (c=0.96, MeOH)

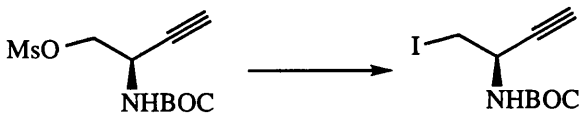
ν_{max} (film) : 3293, 2978, 1703, 1512, 1359, 1054

δ_H (270MHz, $CDCl_3$) : 4.95 (1H, s, N*H*), 4.78 (1H, m, OCH_2CH), 4.4-4.2 (2H, m, OCH_2CH), 3.07 (3H, s, CH_3SO_2), 2.38 (1H, d, 2.2Hz, C≡C*H*), 1.46 (9H, s, $NCO_2C(CH_3)_3$)

m/z (EI) : 264 (MH^+), 244

Accurate mass : $C_{10}H_{17}O_5NS$ (MH^+) requires 264.09056; observed 264.09064

Preparation of 1,1-Dimethylethyl (*R*)-(1-iodobutyn-2-yl)carbamate (167)



165 **167**

A solution of the mesylate (**165**) (0.3g, 1.14mmol) and anhydrous lithium iodide (0.54g, 2.85mmol) in THF (5ml) was sonicated in an argon atmosphere at room temperature for two days. The reaction mixture was then concentrated and partitioned between diethyl ether (20ml) and water (20ml). The ethereal layer was washed with saturated sodium bicarbonate solution and then water (20ml each). The combined aqueous layers were extracted with diethyl ether (20ml). The combined organic extracts were then dried (magnesium sulfate) and concentrated to give the product as a brown oil (0.211g, 70%), which was used immediately.

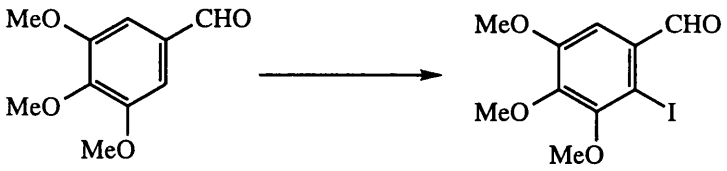
ν_{max} (film) : 3582, 1689, 1507, 1367

δ_H (270MHz, $CDCl_3$) : 4.95 (1H, s, N*H*), 4.55 (1H, m, ICH_2CH), 3.39 (2H, d, 5.1Hz, $IC\mathit{H}_2CH$), 2.41 (1H, d, 3.0Hz, C≡C*H*), 1.46 (9H, s, $NCO_2C(C\mathit{H}_3)_3$)

m/z (EI) : 296 (MH^+), 240, 196

Accurate mass : $C_9H_{15}O_2NI$ (MH^+) requires 296.0147; observed 296.0162

Preparation of 2-Iodo-3,4,5-trimethoxybenzaldehyde[110] (169)



168 **169**

3,4,5-Trimethoxybenzaldehyde (**168**) (3.66g, 18.7mmol) and silver trifluoro-acetate (4.12g, 18.7mmol) were suspended in dichloromethane (25ml). A saturated solution of iodine (5.22g, 20.6mmol) in dichloromethane was added dropwise over 2.5 hours with vigorous stirring at room temperature. The red suspension obtained at the end of addition was stirred for a further hour before filtering, and then washed successively with saturated sodium thiosulfate solution, water and saturated sodium bicarbonate solution (50ml each). The organic layer was dried (magnesium sulfate) and concentrated to give a

yellow solid, which was recrystallised from petroleum ether at -78°C to give the title compound as pale yellow needles (5.14g, 85%).

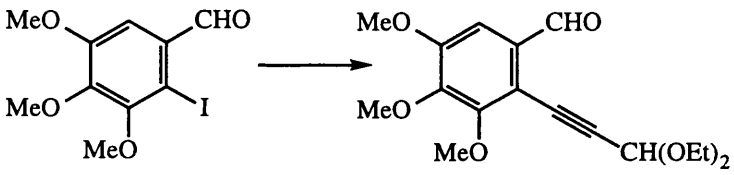
m.p. 68-69°C (lit. 66-67°C[110(a)], 66-66.5°C[110(b)])

ν_{max} (film) : 3345, 2936, 2850, 1688, 1569

δ_H (270MHz, $CDCl_3$) : 10.05 (1H, s, ArC*H*O), 7.35 (1H, s, Ar*H*), 3.97, 3.92 and 3.90 (9H, 3s, ArOCH_3)

m/z (EI) : 322 (M^+, 100%)

Preparation of 2-(3,3-Diethoxylpropynyl)-3,4,5-trimethoxybenzaldehyde (170)



169 **170**

To a stirred mixture of the aldehyde (**169**) (0.3g, 0.93mmol), palladium(II) acetate (10mg, 5mol%), copper(I) iodide (9mg, 5mol%), and triphenylphosphine (49mg, 0.19mmol) in diethylamine (10ml) at room temperature was added propargylaldehyde diethyl acetal (0.14g, 1.12mmol). The reaction mixture was gently refluxed for 4 hours and then cooled to room temperature. The reaction mixture was then pre-adsorbed on silica gel (~3g) and chromatographed (30% diethyl ether / 70% petroleum ether) to afford the title compound (0.19g, 63%) as a pale brown oil and recover unreacted starting material (0.22g, 36%).

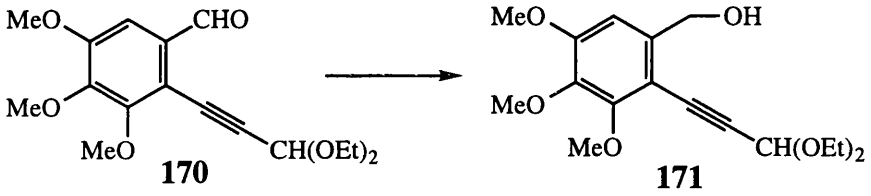
ν_{max} (film) : 2975, 2229, 1693, 1585, 1457, 1327, 1140

δ_H (270MHz, $CDCl_3$) : 10.39 (1H, s, C*H*O), 7.25 (1H, s, Ar*H*), 5.56 (1H, s, ArC≡CC*H*$(OEt)_2$), 3.97, 3.96 and 3.92 (9H, 3s, ArOC*H*$_3$), 3.80-3.60 (4H, m, $CH(OCH_2CH_3)_2$), 1.28 (6H, t, 7.1Hz, $CH(OCH_2CH_3)_2$)

m/z (EI) : 322 (M^+), 277, 249, 196

Accurate mass : $C_{17}H_{22}O_6$ (M^+) requires 322.1416; observed 322.1430

Preparation of 2-(3,3-Diethoxylpropynyl)-3,4,5-trimethoxybenzenemethanol (171)



A mixture of the aldehyde (**170**) (0.67g, 2.08mmol) and sodium borohydride (0.15g, 4.16mmol) in anhydrous ethanol (25ml) was stirred at 0°C for 30 minutes and then allowed to warm up to room temperature over 1 hour. The residual sodium borohydride was destroyed by the slow addition of potassium carbonate solution (5% w/w, 5ml) at 0°C. When hydrogen gas evolution ceased, the reaction mixture was poured into a mixture of the potassium carbonate solution (15ml) and dichloromethane (20ml). The gelatinous mixture was vigorously stirred until the phases separated. The aqueous layer was extracted with dichloromethane (2x10ml), and the combined organic extracts were then dried (magnesium sulfate), concentrated and chromatographed (80% diethyl ether / 20% petroleum ether) to give the product as a very pale yellow oil (0.46g, 68%).

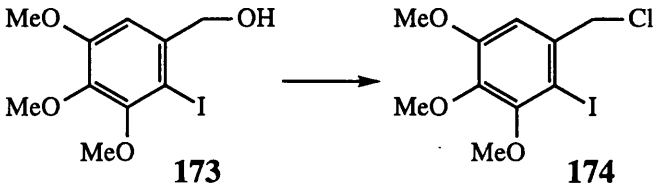
ν_{max} (film) : 3582 (br), 2937, 2178, 1648, 1591, 1332

δ_H (270MHz, C_6D_6) : 6.98 (1H, s, Ar*H*), 5.81 (1H, s, ArC≡CC*H*$(OEt)_2$), 5.00 (2H, d, 5.6Hz, ArC*H*$_2$OH), 4.14-3.79 (4H, m, $CH(OCH_2CH_3)_2$), 4.11, 3.94 and 3.54 (9H, 3s, ArOC*H*$_3$), 2.17 (1H, t, 5.6Hz, $ArCH_2OH$), 1.41 (6H, t, 7.1Hz, $CH(OCH_2CH_3)_2$)

m/z (EI) : 324 (M^+), 279, 263

Accurate mass : $C_{17}H_{24}O_6$ (M^+) requires 324.1573; observed 324.1515

Preparation of 1-Chloromethyl-2-iodo-3,4,5-trimethoxybenzene (174)



173 **174**

The title compound can be obtained by employing either the literature method[61] or the following procedure. The alcohol[61] (**173**) (0.45g, 1.39mmol) was stirred in dichloromethane (10ml) at 0°C when methanesulfonyl chloride (0.35g, 3.06mmol) and triethylamine (0.14g, 1.39mmol) were successively added. The reaction mixture was stirred at room temperature for 30 minutes and then poured into 1M HCl (10ml). The aqueous layer was extracted with dichloromethane (10ml) and the combined organic layers were dried (magnesium sulfate), concentrated and chromatographed (20% diethyl ether / 80% petroleum ether) to isolate the title compound as a white solid (0.20g, 41%).

m.p. 69-71°C (lit.[61] 72°C)

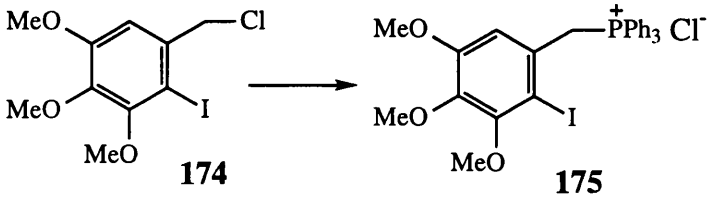
ν_{max} (film) : 3989, 3582, 2933, 1736, 1656, 1480, 1388, 1105

δ_H (270MHz, $CDCl_3$) : 6.91 (1H, s, Ar*H*), 4.70 (2H, s, ArCH_2Cl), 3.89 and 3.88 (9H, 2s, ArOCH_3)

m/z (EI) : 342 (M^+), 307

Accurate mass : $C_{10}H_{12}O_3{}^{37}ClI$ (M^+) requires 343.9490; observed 343.9488

Preparation of (2-Iodo-3,4,5-trimethoxybenzenemethyl)triphenyl-phosphonium chloride (175)



A solution of the chloride (**174**) (80mg, 0.23mmol) and triphenylphosphine (77mg, 0.28mmol) in benzene (2ml) was gently refluxed overnight. The resulting suspension was filtered and the precipitate washed with cold benzene (30ml). In this way, the product was obtained as white cubes ready for further use (0.12g, 89%).

m.p. 180-182°C (dec.)

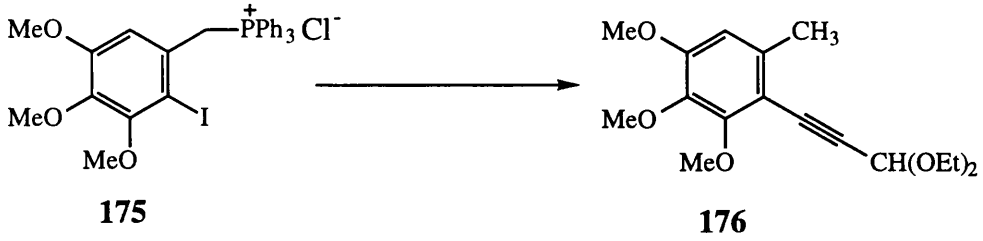
ν_{max} (film) : 3416, 1484, 1438, 1332, 1108

δ_H (270MHz, $CDCl_3$) : 7.82-7.59 (15H, m, *Ph*), 7.18 (1H, d, 2.7Hz, Ar*H*), 5.59 (2H, d, 14.2Hz, ArCH_2P), 3.83, 3.72 and 3.56 (9H, 3s, ArOCH_3)

m/z (EI) : 568 ($[M\text{-}HCl]^+$), 553

Accurate mass : $C_{28}H_{26}O_3PI$ ($[M\text{-}HCl]^+$) requires 568.0664; observed 568.0702

Preparation of 1,2,3-Trimethoxy-4-(3,3-diethoxylpropynyl)-5-methylbenzene (176)



A mixture of the phosphonium salt (**175**) (50mg, 0.083mmol), palladium(II) acetate (1mg, 5mol%), copper(I) iodide (1mg, 5mol%), triphenylphosphine (5mg,

20mol%), propargylaldehyde diethyl acetal (12mg, 0.09mmol) and anhydrous potassium carbonate (13mg, 0.09mmol) in DMF (5ml) was heated at 90°C for 4 hours. After concentration, the residue was chromatographed (20% diethyl ether / 80% petroleum ether, gradually changed to 5% methanol / 95% dichloromethane) to isolate the title compound as a brown oil (9mg, 35%).

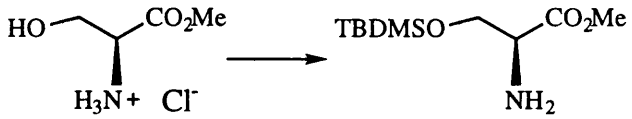
ν_{max} (film) : 2922, 1653, 1431, 1281, 1147, 1021

δ_H (270MHz, $CDCl_3$) : 6.50 (1H, s, Ar*H*), 5.55 (1H, s, ArC≡CC*H*$(OEt)_2$), 3.94, 3.85 and 3.82 (9H, 3s, ArOC*H*$_3$), 3.87-3.65 (4H, m, CH$(OCH_2CH_3)_2$), 2.38 (3H, s, ArC*H*$_3$), 1.27 (6H, t, 7.1Hz, CH$(OCH_2CH_3)_2$)

m/z (EI) : 308 (M^+), 263, 235

Accurate mass : $C_{15}H_{19}O_4$ ([M-OEt]$^+$) requires 263.1283; observed 263.1275

Preparation of Methyl (*S*)-2-amino-3-(1,1-dimethylethyldimethylsiloxy)propanoate (179)



155 **179**

A mixture of the ester (**155**) (3g, 19.3mmol), TBDMSCl (3.2g, 21.2mmol) and imidazole (2.9g, 42.5mmol) in DMF (6ml) was stirred overnight at room temperature. The resulting biphasic mixture was poured into saturated sodium bicarbonate solution (60ml) and was extracted with dichloromethane (4x20ml). The combined organic layers were washed with water (2x20ml) and then dried (magnesium sulfate), concentrated and chromatographed (2% methanol / 98% dichloromethane) to isolate the product as a pale yellow liquid (3.6g, 80%).

$[\alpha]_D$=+12° (c=1.02, methanol)

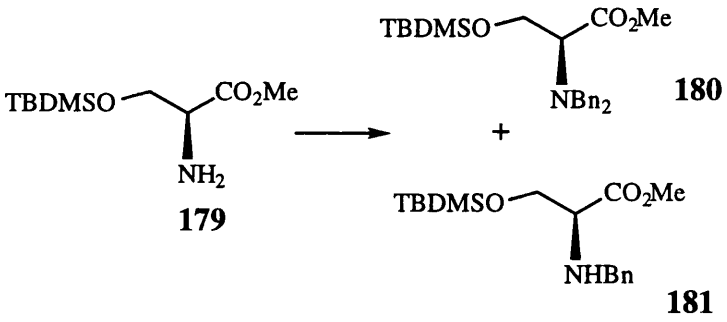
ν_{max} (film) : 3385, 2955, 2858, 1745, 1601, 1464

δ_H (270MHz, $CDCl_3$) : 3.86 and 3.76 (2H, 2dd, 4.1Hz, 9.8Hz, OCH_2CH), 3.68 (3H, s, CO_2CH_3), 3.48 (1H, t, 4.1Hz, OCH_2CH), 1.66 (2H, s, NH_2), 0.82 (9H, s, $SiC(CH_3)_3$), 0.01 and 0.00 (6H, 2s, $Si(CH_3)_2$)

m/z (EI) : 234 (MH^+), 174

Accurate mass : $C_{10}H_{24}O_3NSi$ (MH^+) requires 234.1525; observed 234.1528

Preparation of Methyl (*S*)-2-(*N*,*N*-dibenzenemethylamino)-3-(1,1-dimethylethyldimethylsiloxy)propanoate (180) and Methyl (*S*)-2-(*N*-benzylamino)-3-(1,1-dimethylethyldimethylsiloxy)propanoate (181)



A mixture of the amine (**179**) (2.5g, 10.7mmol), benzyl bromide (filtered through a short column of anhydrous active alumina, 4.4g, 25.7mmol), triethylamine (2.39g, 23.5mmol) and DMAP (0.13g, 10mol%) in anhydrous acetonitrile (20ml) was stirred overnight at 50°C. The reaction mixture was then poured into a 1:1 mixture of diethyl ether and petroleum ether and the organic layer was washed with brine and water successively (50ml each). The organic layer was dried (magnesium sulfate), concentrated and chromatographed with gradient elution (neat petrol, then 10% to 20% diethyl ether / petroleum ether) to give the dibenzylamine (**180**) (3.25g, 73%) as a colourless oil and the monobenzylamine (**181**) (0.4g, 17%) as a yellow oil.

The dibenzylamine (**180**):

$[\alpha]_D$=-45.5° (c=1.1, MeOH)

ν_{max} (film) : 3403, 2951, 2856, 1738, 1494, 1103, 837

δ_H (270MHz, $CDCl_3$) : 7.40-7.21 (10H, m, *Ph*), 4.01-3.84 (4H, m, $N(CH_2Ph)_2$), 3.74 (3H, s, CO_2CH_3), 3.70-3.65 (2H, m, OCH_2CH), 3.54 (1H, t, 6.1Hz, OCH_2CH), 0.84 (9H, s, $SiC(CH_3)_3$), -0.01 (6H, s, $Si(CH_3)_2$)

m/z (EI) : 413 (M^+), 398, 370, 354

Accurate mass : $C_{24}H_{35}O_3NSi$ (M^+) requires 413.2386; observed 413.2408

The monobenzylamine (**181**):

$[\alpha]_D$=-4.8° (c=1.2, MeOH)

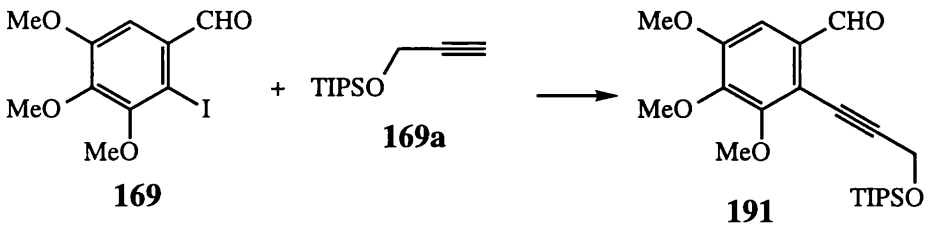
ν_{max} (film) : 3377, 2952, 2857, 1740, 1463, 1109

δ_H (270MHz, $CDCl_3$) : 7.33-7.26 (5H, m, *Ph*), 3.93-3.79 (2H, m, NCH_2Ph), 3.72-3.68 (2H, m, OCH_2CH), 3.71 (3H, s, CO_2CH_3), 3.39 (1H, t, 4.7Hz, OCH_2CH), 2.19 (1H, s, NH), 0.86 (9H, s, $SiC(CH_3)_3$), 0.02 (6H, s, $Si(CH_3)_2$)

m/z (EI) : 323 (M^+), 308, 276

Accurate mass : $C_{17}H_{29}O_3NSi$ (M^+) requires 323.1917; observed 323.1918

Preparation of 2-(3-Tris(1-methylethyl)siloxypropynyl)-3,4,5-trimethoxybenzaldehyde (191)



The aldehyde (**169**) (2g, 6.2mmol), bis(triphenylphosphine)palladium(II) dichloride (0.22g, 5mol%), copper(I) iodide (59mg, 5mol%) and the alkyne[65] (**169a**) (2g,

9.3mmol) were stirred in diethylamine (20ml) at room temperature for 4 days in a flask wrapped with aluminium foil. After concentration, the residue was taken up in diethyl ether (20ml) and washed with water (2x15ml). The organic layer was then dried (magnesium sulfate), concentrated and chromatographed (10% diethyl ether / 90% petroleum ether) to obtain the title compound (2.1g, 83%) as a pale yellow oil.

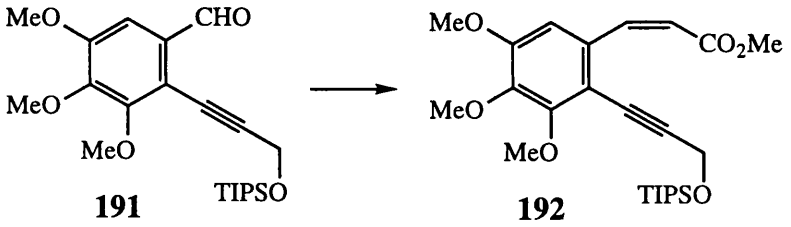
ν_{max} (film) : 3484, 2369, 1722, 1680, 1139

δ_H (270MHz, $CDCl_3$) : 10.41 (1H, s, C*H*O), 7.25 (1H, s, Ar*H*), 4.71 (2H, s, ArC≡CC*H*$_2$O), 3.96 and 3.95 (9H, 2s, ArOC*H*$_3$), 1.16-1.09 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$)

m/z (EI) : 406 (M^+), 363

Accurate mass : $C_{22}H_{34}O_5Si$ (M^+) requires 406.2166; observed 406.2174

Preparation of Methyl (*Z*)-3-(2-(3-tris(1-methylethyl)siloxypropynyl)-3,4,5-trimethoxyphenyl)prop-2-enoate (192)



191 **192**

A solution of 18-crown-6 (0.64g, 2.44mmol) and bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate (0.78g, 2.44mmol) in THF (30ml) was stirred at -78°C while potassium bis(trimethylsilyl)amide (0.5M solution in toluene, 4.9ml, 2.44mmol) was added dropwise over 15 minutes to give a yellow solution. 30 Minutes later, a solution of the aldehyde (**191**) (0.9g, 2.22mmol) in THF (15ml) cooled to -78°C was added dropwise over 15 minutes *via* a lagged cannula to form a bright yellow solution. Saturated ammonium chloride solution (10ml) was added 30 minutes later and the mixture was allowed to warm up to room temperature. Water (60ml) was added and the aqueous layer was extracted with diethyl ether (3x20ml). The combined organic layers were washed

with water (2x20ml) and then dried (magnesium sulfate), concentrated and chromatographed (20% diethyl ether / 80% *n*-hexane) to give the product (0.8g, 80%) as a pale yellow oil.

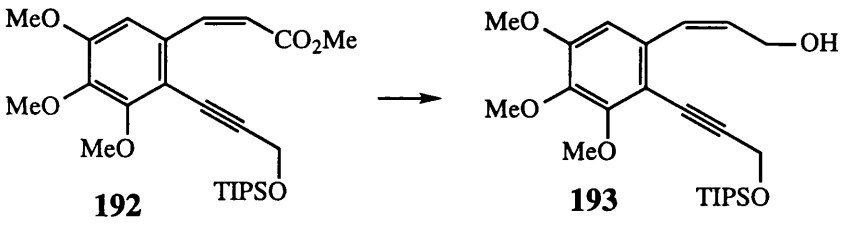
ν_{max} (film) : 2942, 2200, 1724, 1586, 1478, 1178, 1170

δ_H (270MHz, $CDCl_3$) : 7.47 (1H, s, Ar*H*), 7.37 (1H, d, 12.7Hz, ArC*H*CH), 6.06 (1H, d, 12.7Hz, ArCHC*H*), 4.77 (2H, s, ArC≡CCH_2O), 4.03, 3.99 and 3.98 (9H, 3s, ArOCH_3), 3.81 (3H, s, CO_2CH_3), 1.30-1.15 (21H, m, Si(C*H*(CH_3)$_2$)$_3$)

m/z (CI, NH_3) : 480 ($[M+NH_4]^+$), 463 (MH^+), 396

Accurate mass : $C_{25}H_{39}O_6Si$ (MH^+) requires 463.2516; observed 463.2515

Preparation of (*Z*)-3-(2-(3-Tris(1-methylethyl)siloxypropynyl)-3,4,5-trimethoxyphenyl)prop-2-enol (193)



A solution of the ester (**192**) (6.19g, 13.4mmol) in toluene (55ml) was stirred at -78°C when DIBAL-H (1.5M solution in toluene, 29.4ml, 44.2mmol) was added dropwise over 20 minutes. Anhydrous methanol (1.5ml) was added two hours later. When the reaction mixture had warmed to room temperature, it was poured into a saturated solution of potassium sodium tartrate tetrahydrate (100ml) and vigorously stirred until two layers separated. The aqueous layer was extracted with diethyl ether (2x40ml) and the combined organic layers were dried (Na_2SO_4) and concentrated to give the product as a colourless oil (5.3g, 91%).

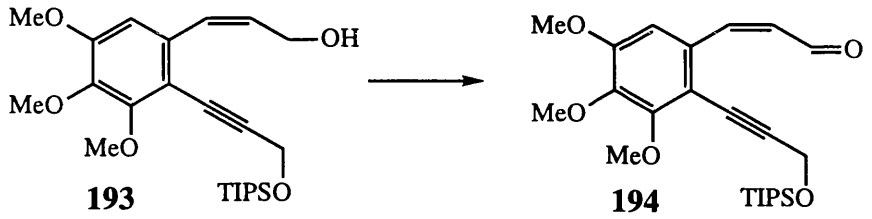
ν_{max} (film) : 3426 (br), 2937, 1718, 1558, 1478, 1104

δ_H (270MHz, $CDCl_3$) : 6.71 (1H, d, 11.6Hz, ArC*H*CH), 6.54 (1H, s, Ar*H*), 5.92 (1H, dt, 11.6Hz, 6.1Hz, ArCHC*H*), 4.66 (2H, s, ArC≡CCH_2O), 4.32 (2H, t, 6.1Hz, CH_2OH), 3.94, 3.87 and 3.86 (9H, 3s, ArOC*H*$_3$), 1.82 (1H, t, 6.1Hz, CH_2O*H*), 1.21-1.05 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$)

m/z (CI, NH_3) : 452 ($[M+NH_4]^+$), 435 (MH^+), 261

Accurate mass : $C_{24}H_{39}O_5Si$ (MH^+) requires 435.2567; observed 435.2537

Preparation of (*Z*)-3-(2-(3-Tris(1-methylethyl)siloxypropynyl)-3,4,5-trimethoxyphenyl)prop-2-enal (194)



Manganese(IV) oxide (10.64g, 122mmol) and the alcohol (**193**) (5.30g, 12.2mmol) were stirred overnight at room temperature in dichloromethane (50ml). The reaction mixture was filtered through a celite pad and the cake of manganese(IV) oxide was washed with cold and warm dichloromethane (300ml and 100ml) respectively. The filtrate was then concentrated and chromatographed with gradient elution (15% to 20% diethyl ether / petroleum ether) to give the product as a colourless oil (4.40g, 84%).

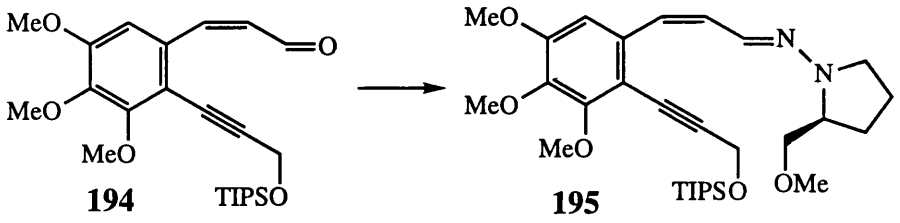
ν_{max} (film) : 2267, 1675, 1585, 1097

δ_H (270MHz, $CDCl_3$) : 7.92 (1H, d, 8.0Hz, C*H*O), 7.80 (1H, d, 11.3Hz, ArC*H*CHCHO), 6.66 (1H, s, Ar*H*), 6.19 (1H, dd, 11.3Hz, 8.0Hz, ArCHC*H*CHO), 4.67 (2H, s, ArC≡CCH_2O), 3.97, 3.91 and 3.87 (9H, 3s, ArOC*H*$_3$), 1.25-1.09 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$)

m/z (CI, NH_3) : 450 ($[M+NH_4]^+$), 433 (MH^+), 276, 259

Accurate mass : $C_{24}H_{37}O_5Si$ (MH^+) requires 433.2411; observed 433.2393

Preparation of (Z)-3-(2-(3-Tris(1-methylethyl)siloxypropynyl)-3,4,5-trimethoxyphenyl)prop-2-enal (S)-(-)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) hydrazone (195)



A solution of the aldehyde (**194**) (0.37g, 0.86mmol) in benzene (4ml) was slowly added to a stirred solution of SAMP (0.117g, 0.90mmol) in benzene (2ml) at room temperature. The yellow mixture was stirred at 45°C for 3 hours and then cooled down to room temperature. After concentration, the residue was chromatographed (30% diethyl ether / 70% *n*-hexane) to isolate the product as a yellow oil (0.32g, 69%).

$[\alpha]_D$=-48° (c=0.37, $CHCl_3$)

ν_{max} (film) : 2942, 2866, 2227, 1685, 1586, 1463, 1329, 1093

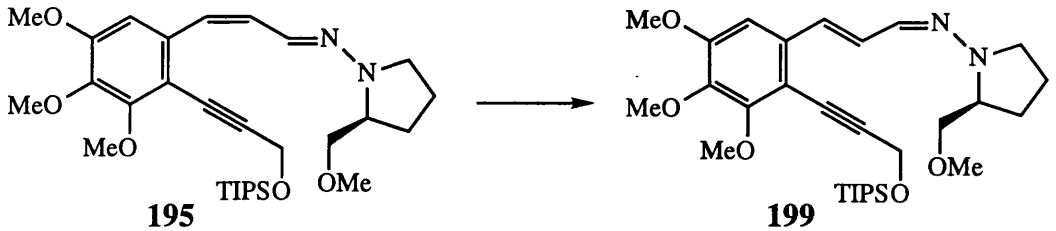
δ_H (400MHz, $CDCl_3$)[111] : 7.37 (1H, d, 9.8Hz, CHCHC*H*N), 6.77 (1H, s, Ar*H*), 6.64 (1H, d, 11.8Hz, ArC*H*CHCHN), 6.38 (1H, dd, 11.8Hz, 9.8Hz, ArCHC*H*CHN), 4.67 (2H, s, ArC≡CCH_2O), 3.94, 3.87 and 3.83 (9H, 3s, ArOCH_3), 3.66 (1H, m, $CH_2CH(CH_2OMe)$), 3.59 and 3.46 (2H, 2m, $CH(CH_2OMe)N$), 3.39 (3H, s, CH_2OCH_3), 3.35 and 2.97 (2H, 2m, NCH_2CH_2), 2.05-1.85 (4H, m, $NCH_2CH_2CH_2CH$), 1.08-1.18 (21H, m, $Si(CH(CH_3)_2)_3$)

δ_C (100MHz, $CDCl_3$) : 155.1, 153.1, 141.0, 136.4, 131.4, 129.3, 126.3, 110.1, 108.2, 95.9, 78.8, 74.5, 63.0, 61.2, 61.1, 59.2, 52.8, 56.1, 48.9, 26.8, 22.3, 18.0, 12.1

m/z (EI) : 544 (M^+), 529, 499

Accurate mass : $C_{30}H_{49}O_5N_2Si$ (MH^+) requires 545.3411; observed 545.3379

Preparation of (*E*)-3-(2-(3-Tris(1-methylethyl)siloxypropynyl)-3,4,5-trimethoxyphenyl)prop-2-enal (*S*)-(-)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) hydrazone (199)



A solution of the *Z*-hydrazone (**195**) (0.10g, 0.188mmol) in THF (2ml) was stirred at -78°C while boron trifluoride etherate (0.05ml, 0.41mmol) was added. Fifteen minutes later, this mixture was added to a stirred suspension of cerium(III) trimethylsilylacetylide reagent[69] (1.32mmol) in THF (8ml) at -78°C *via* a lagged cannula. The resulting bright yellow suspension was stirred at -78°C for 2 hours and then allowed to warm up to room temperature. It was taken up in diethyl ether (50ml) and washed with saturated sodium bicarbonate solution (3x30ml). The organic layer was dried (magnesium sulfate), concentrated and chromatographed (30% diethyl ether / 70% *n*-hexane) to give the title compound as a yellow oil (74mg, 74%).

$[\alpha]_D$=-50° (c=0.62, $CHCl_3$)

ν_{max} (film) : 2937, 1653, 1457, 1095

δ_H (400MHz, $CDCl_3$)[111] : 7.13 (1H, d, 9.0Hz, CHCHC*H*N), 7.05 (1H, d, 15.9Hz, ArC*H*CHCHN), 6.90 (1H, s, Ar*H*), 6.88 (1H, dd, 15.9Hz, 9.0Hz, ArCHC*H*CHN), 4.72 (2H, s, ArC≡CCH_2O), 3.92, 3.87 and 3.86 (9H, 3s, ArOCH_3), 3.67 (1H, m, CH_2CH(CH_2OMe)), 3.59 and 3.46 (2H, 2m, CH(CH_2OMe)N), 3.39 (3H, s,

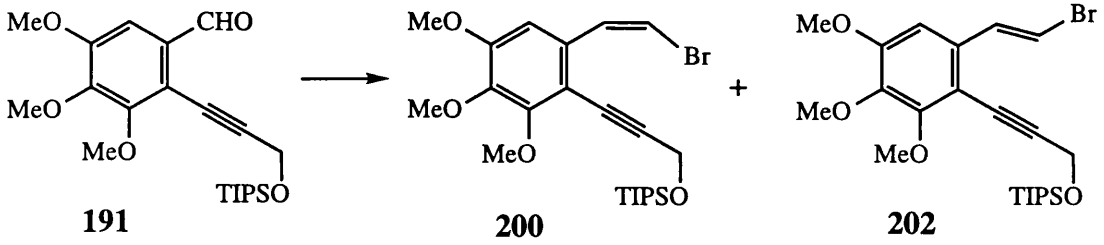
CH_2OCH_3), 3.45 and 3.03 (2H, 2m, NCH_2CH_2), 2.08-1.82 (4H, m, $NCH_2CH_2CH_2CH$), 1.22-1.04 (21H, m, $Si(CH(CH_3)_2)_3$)

δ_C (100MHz, $CDCl_3$) : 154.9, 153.8, 141.4, 135.0, 128.7, 128.1, 109.5, 102.4, 95.6, 78.7, 74.6, 63.2, 61.2, 61.1, 59.3, 55.9, 52.9, 49.1, 26.8, 22.4, 18.0, 12.1

m/z (EI) : 544 (M^+), 500

Accurate mass : $C_{30}H_{49}O_5N_2Si$ (MH^+) requires 545.3411; observed 545.3368

Preparation of (*Z*)-1,2,3-Trimethoxy-4-(3-tris(1-methylethyl)siloxypropynyl)-5-(2-bromoethen-1-yl)benzene (200) and (*E*)-1,2,3-Trimethoxy-4-(3-tris(1-methylethyl)siloxypropynyl)-5-(2-bromoethen-1-yl)benzene (202)



To a stirred suspension of (bromomethyl)triphenylphosphonium bromide (0.7g, 1.63mmol) and 18-crown-6 (0.41g, 1.55mmol) in THF (4ml) at room temperature was added dropwise potassium bis(trimethylsilyl)amide (0.5M in toluene, 3.2ml, 1.55mmol). The resulting yellow mixture was stirred at room temperature for 5 minutes and then cooled to -78°C. The aldehyde (**191**) (0.3g, 0.74mmol) in THF (2ml) was added dropwise and the reaction mixture was allowed to warm to room temperature when the addition was complete. The reaction mixture was taken up in diethyl ether (40ml) and washed with water (2x20ml). The organic layer was then dried (magnesium sulfate), concentrated and chromatographed (12% diethyl ether / 88% petroleum ether) to give the *Z*-bromide (**200**) (0.17g, 47%) and the *E*-bromide (**202**) (0.16g, 45%) respectively as pale yellow oils.

The *Z*-product (**200**) :

ν_{max} (film) : 2941, 2864, 2226, 1587, 1486, 1339

δ_H (270MHz, $CDCl_3$) : 7.46 (1H, s, Ar*H*), 7.42 (1H, d, 8.1Hz, ArC*H*CH), 6.45 (1H, d, 8.1Hz, ArCHC*H*), 4.67 (2H, s, ArC≡CCH_2O), 3.93, 3.90 and 3.89 (9H, 3s, ArOCH_3), 1.16-1.09 (21H, m, Si(C*H*(CH_3)$_2$)$_3$)

m/z (FAB) : 507 ([M(^{81}Br)+Na]$^+$), 505 ([M(^{79}Br)+Na]$^+$), 485 (M(^{81}Br)H$^+$), 483 (M(^{79}Br)H$^+$)

Accurate mass : $C_{23}H_{36}O_4BrSi$ (M(^{79}Br)H$^+$) requires 483.1566; observed 483.1537

The *E*-product (**203**) :

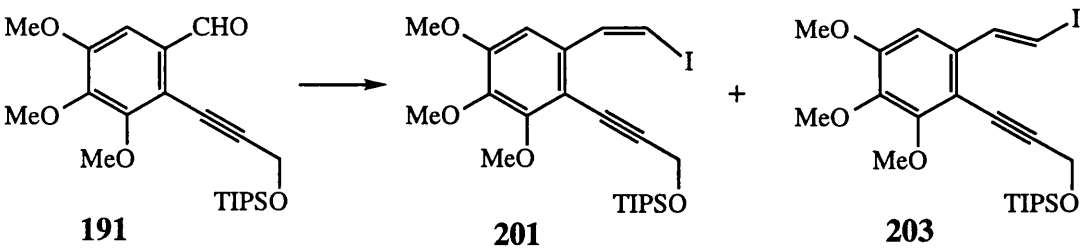
ν_{max} (film) : 2941, 2864, 2226, 1556, 1462

δ_H (270MHz, $CDCl_3$) : 7.50 (1H, d, 14.0Hz, ArC*H*CH), 6.81 (1H, d, 14.0Hz, ArCHC*H*), 6.65 (1H, s, Ar*H*), 4.70 (2H, s, ArC≡CCH_2O), 3.93, 3.88 and 3.87 (9H, 3s, ArOCH_3), 1.22-1.09 (21H, m, Si(C*H*(CH_3)$_2$)$_3$)

m/z (FAB) : 507 ([M(^{81}Br)+Na]$^+$), 505 ([M(^{79}Br)+Na]$^+$), 485 (M(^{81}Br)H$^+$), 483 (M(^{79}Br)H$^+$)

Accurate mass : $C_{23}H_{36}O_4BrSi$ (M(^{79}Br)H$^+$) requires 483.1566; observed 483.1535

Preparation of (*Z*)-1,2,3-Trimethoxy-4-(3-tris(1-methylethyl)siloxypropynyl)-5-(2-iodoethen-1-yl)benzene (201) and (*E*)-1,2,3-Trimethoxy-4-(3-tris(1-methylethyl)siloxypropynyl)-5-(2-iodoethen-1-yl)benzene (203)



The aldehyde (**191**) (0.23g, 0.57mmol) and (iodomethyl)triphenylphosphonium iodide[112] (0.6g, 1.14mmol) were reacted as described in the preparation of the bromides (**200**) and (**202**). The *Z*-iodide (**201**) (0.21g, 70%) and *E*-iodide (**203**) (57.5mg, 19%) were obtained respectively by flash column chromatography (16% diethyl ether/ 88% petroleum ether) as colourless oils.

The *Z*-product (**201**) :

ν_{max} (film) : 2941, 2228, 1554, 1486, 1407, 1334, 1095

δ_H (270MHz, $CDCl_3$) : 7.56 (1H, d, 8.3Hz, ArC*H*CH), 7.35 (1H, s, Ar*H*), 6.58 (1H, d, 8.3Hz, ArCHC*H*), 4.66 (2H, s, ArC≡CCH_2O), 3.94, 3.93 and 3.89 (9H, 3s, ArOCH_3), 1.20-1.07 (21H, m, Si(C*H*(CH_3)$_2$)$_3$)

m/z (FAB) : 553 ($[M+Na]^+$), 531 (MH^+)

Accurate mass : $C_{23}H_{35}O_4ISi$ (M^+) requires 530.1349; observed 530.1347

The *E*-product (**203**) :

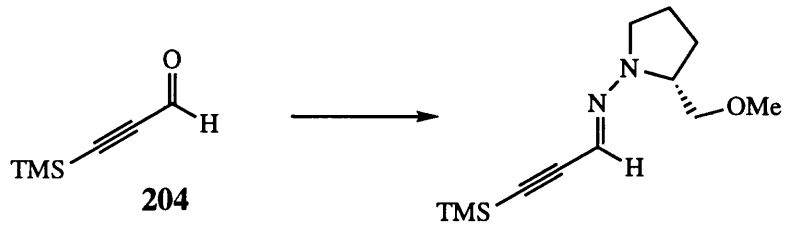
ν_{max} (film) : 2941, 2228, 1554, 1463, 1407, 1135

δ_H (270MHz, $CDCl_3$) : 7.91 (1H, d, 15.1Hz, ArC*H*CH), 6.96 (1H, d, 15.1Hz, ArCHC*H*), 6.76 (1H, s, Ar*H*), 4.80 (2H, s, ArC≡CCH_2O), 4.02, 3.98 and 3.96 (9H, 3s, ArOCH_3), 1.32-1.18 (21H, m, Si(C*H*(CH_3)$_2$)$_3$)

m/z (FAB) : 553 ($[M+Na]^+$), 531 (MH^+)

Accurate mass : $C_{23}H_{35}O_4ISi$ (M^+) requires 530.1349; observed 530.1347

Preparation of Trimethylsilylpropynal (*R*)-(+)-1-amino-2-(methoxymethyl)pyrrolidine (RAMP) hydrazone (205)



204 **205**

Trimethylsilylpropynal[71] (**204**) (0.46g, 3.65mmol) was added to neat RAMP (0.40g, 3.07mmol) stirring at 0°C. The resulting yellow liquid was allowed to warm to room temperature over 1 hour. Flash column chromatography (20% diethyl ether / 80% isohexanes) then provided the title compound (0.54g, 74%) as a colourless liquid.

$[\alpha]^{25}$=-211° (c=1.01, $CHCl_3$)

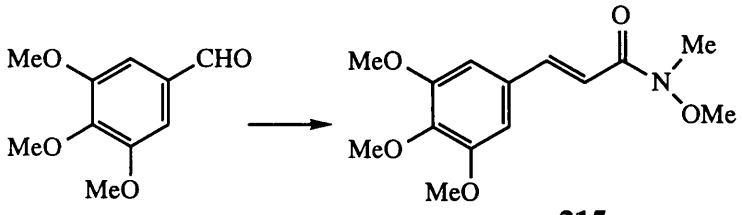
ν_{max} (film) : 2130, 1526, 1460, 1250

δ_H (270MHz, $CDCl_3$) : 6.05 (1H, s, *H*CN), 3.72 (1H, m, C*H*(CH_2OMe)), 3.57 and 3.42 (2H, 2m, CH(C*H*$_2$OMe)N), 3.27 and 2.98 (2H, 2m, NC*H*$_2$$CH_2$), 3.19 (3H, s, OC*H*$_3$), 1.99-1.52 (4H, m, $NCH_2CH_2CH_2CH$), 0.02 (9H, s, Si(C*H*$_3$)$_3$)

m/z (EI) : 239 (MH^+), 193

Accurate mass : $C_{12}H_{22}ON_2Si$ (M^+) requires 238.1502; observed 238.1501

Preparation of (*E*)-*N*-Methyl-*N*-methoxy-3-(3,4,5-trimethoxyphenyl)prop-2-enamide[113] (215)



168 **215**

A mixture of trimethoxybenzaldehyde (**168**) (3.91g, 19.9mmol) and *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidene)acetamide (7.22g, 19.7mmol) in dichloromethane (80ml) was stirred overnight at room temperature. The mixture was then adsorbed on silica gel (~25g) and chromatographed (90% diethyl ether / 10% petroleum ether) to give two fractions containing the pure title compound and the title compound contaminated with triphenylphosphine oxide, respectively. The second fraction was further purified by chromatography with gradient elution (90% to 100% diethyl ether / petroleum ether). The combined pure product was obtained as white cubes (5.0g, 90%).

m.p. 78-80°C

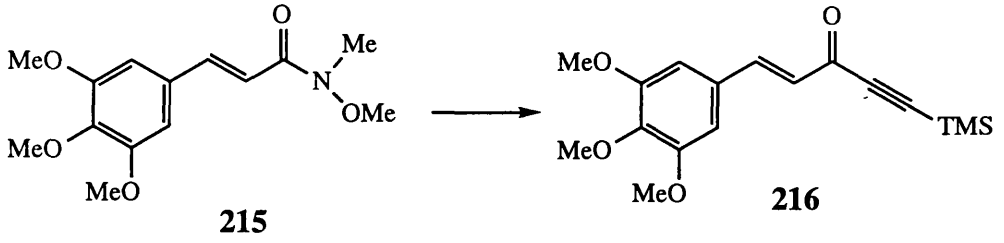
ν_{max} (film) : 3446, 1581, 1501, 1333, 1127

δ_H (270MHz, $CDCl_3$) : 7.65 (1H, d, 15.6Hz, ArC*H*CH), 6.91 (1H, d, 15.6Hz, ArCHC*H*), 6.78 (2H, s, Ar*H*), 3.90, (6H, s, *m*-ArOC*H*$_3$), 3.87, (3H, s, *p*-ArOC*H*$_3$), 3.77 (3H, s, NOC*H*$_3$), 3.31 (3H, s, NC*H*$_3$)

m/z (EI) : 281 (M^+), 251, 221

Accurate mass : $C_{14}H_{20}O_5N$ (MH^+) requires 282.1342; observed 282.1347

Preparation of (*E*)-1-Trimethylsilyl-5-(3,4,5-trimethoxyphenyl)pent-4-en-1-yn-3-one (216)



215 **216**

A solution of lithium trimethylsilylacetylide (1.61mmol) in THF was generated by adding *n*-butyllithium (2.5M in hexanes, 0.64ml, 1.61mmol) dropwise to a stirred solution of trimethylsilylacetylene (0.19g, 1.93mmol) in THF (4ml) at 0°C followed by stirring the

resulting solution at room temperature for 30 minutes. This solution was then added to a stirred solution of the amide (**215**) (0.3g, 1.07mmol) in THF (10ml) at 0°C. The reaction mixture was allowed to warm to room temperature over 30 minutes and left stirring for a further 1.5 hours. It was then poured into cold 5% HCl / ethanol (20ml) and the mixture was taken up in 1:1 / diethyl ether:dichloromethane (50ml) and washed with brine (3x50ml). After drying over magnesium sulfate, the organic layer was adsorbed on silica gel (~2g) and chromatographed (50% diethyl ether / 50% petroleum ether) to give the title compound as a yellow oil (0.36g, 98%).

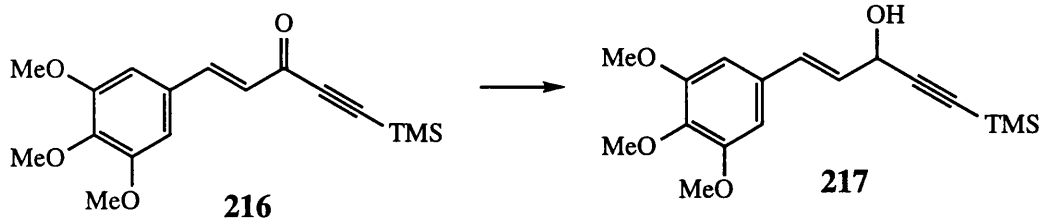
ν_{max} (film) : 3735, 2957, 2152, 1626, 1240, 846

δ_H (270MHz, $CDCl_3$) : 7.72 (1H, d, 15.9Hz, ArC*H*CH), 6.78 (2H, s, Ar*H*), 6.69 (1H, d, 15.9Hz, ArCHC*H*), 3.91, (9H, s, ArOC*H*$_3$), 0.31 (9H, s, Si(C*H*$_3$)$_3$)

m/z (EI) : 318 (M^+), 303, 287

Accurate mass : $C_{17}H_{23}O_4Si$ (MH^+) requires 319.1366; observed 319.1363

Preparation of (*E*)-1-Trimethylsilyl-5-(3,4,5-trimethoxyphenyl)pent-4-en-1-yn-3-ol (217)



A solution of the ketone (**216**) (27mg, 0.085mmol) in toluene (2.5ml) was stirred at -78°C when DIBAL-H (1.5M in toluene, 0.15ml, excess) was added dropwise. The orange solution obtained at the end of the addition was stirred at this temperature for 10 minutes. Saturated ammonium chloride solution (2.5ml) was then added and the reaction mixture was allowed to warm up to room temperature. The reaction mixture was then taken

up in diethyl ether (15ml) and washed with 1M HCl (15ml). The aqueous layer was extracted with diethyl ether (2x10ml) and the combined organic layers were dried (magnesium sulfate), concentrated and chromatographed (50% diethyl ether / 50% petroleum ether) to give the title product as a pale yellow oil (26mg, 95%).

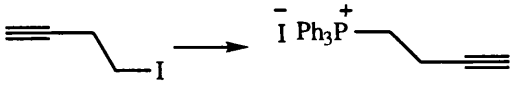
ν_{max} (film) : 3450 (br), 2958, 2170, 1584, 1508, 1248, 1127, 843

δ_H (270MHz, $CDCl_3$) : 6.66 (1H, d, 15.6Hz, ArC*H*CH), 6.62 (2H, s, Ar*H*), 6.18 (1H, dd, 15.6Hz, 6.1Hz, ArCHC*H*), 5.03 (1H, t, 6.1Hz, ArCHCHC*H*(OH)), 3.87 (6H, s, *m*-ArOC*H*$_3$), 3.84, (3H, s, *p*-ArOC*H*$_3$), 1.95 (1H, d, 6.1Hz, ArCHCHCH(O*H*)), 0.20 (9H, s, Si(C*H*$_3$)$_3$)

m/z (EI) : 320 (M^+), 318, 303, 287

Accurate mass : $C_{17}H_{24}O_4Si$ (M^+) requires 320.1444; observed 320.1449

Preparation of (But-3-yn-1-yl)triphenylphosphonium iodide (225)



227 **225**

A solution of the iodide[77] (**227**) (4.78g, 27.2mmol) and triphenylphosphine (7.13g, 27.2mmol) in benzene (8ml) was gently refluxed overnight. The white precipitate formed was filtered off and washed with cold benzene (30ml) and dried. In this way, the product (9.4g, 78%) was obtained sufficiently pure for further use but it could be further purified by recrystallisation from water to form white needles .

m.p. 142-143°C

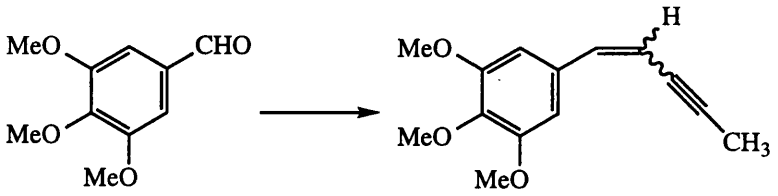
ν_{max} (film) : 3583, 1586, 1436, 1110

δ_H (200MHz, $CDCl_3$) : 7.66-7.91 (15H, m, *Ph*), 4.11-3.99 (2H, m, PC*H*$_2$CH$_2$), 2.94-2.75 (2H, m, PCH$_2$C*H*$_2$), 1.75 (1H, t, 2.7Hz, CH$_2$C≡C*H*)

m/z (FAB) : 441 (M^+), 315

Accurate mass : $C_{22}H_{20}PI$ (M^+) requires 441.0269; observed 441.0263

Preparation of (*Z*)- and (*E*)-1,2,3-Trimethoxy-5-(pent-1-en-3-yn-1-yl)benzene (228)



168 **228**

A solution of the phosphonium salt (**225**) (0.3g, 0.68mmol) and 3,4,5-trimethoxybenzaldehyde (**168**) (0.13g, 0.68mmol) in DMSO (2.2ml) and THF (3.5ml) was cooled to 0°C and was transferred *via* a lagged cannula to sodium hydride (Aldrich, 60% dispersion in mineral oil, 27mg, ~1eq) stirring at 0°C. The reaction mixture turned from yellow to brown on warming up to room temperature over 2 hours. It was then taken up in diethyl ether (20ml) and washed successively with water, 1M HCl and water again (15ml each). The organic layer was dried (magnesium sulfate), concentrated and chromatographed (35% diethyl ether/ 65% petroleum ether) to obtain the pure *Z*-product (67mg) and a mixture of both *Z*- and *E*-products (42mg, *Z*:*E*=1.3:1 by ^1H NMR) as yellow oils (69% overall, *Z*:*E*=5:1).

The *Z*-product :

ν_{max} (film) : 1603, 1572, 1509, 1128

δ_H (400MHz, $CDCl_3$) : 7.24 (2H, s, Ar*H*), 6.52 (1H, d, 11.7Hz, ArC*H*CH), 5.65 (1H, dq, 11.7Hz, 2.7Hz, ArCHC*H*), 3.91 (6H, s, *m*-ArOC*H*$_3$), 3.90 (3H, s, *p*-ArOC*H*$_3$), 2.12 (3H, d, 2.7Hz, CHC≡CC*H*$_3$)

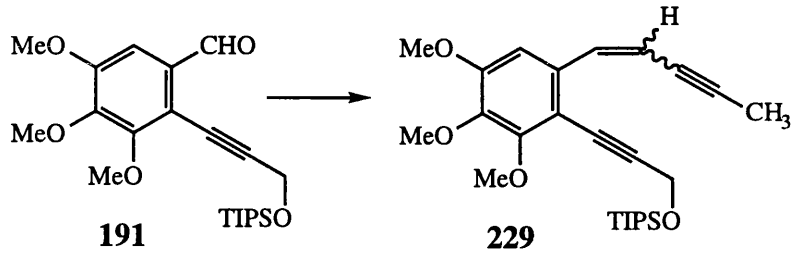
m/z (FAB) : 232 (M^+), 217, 115

Accurate mass : $C_{14}H_{16}O_3$ (M^+) requires 232.1099; observed 232.1096

The *E*-product (as in a mixture with the *Z*-product) :

δ_H (400MHz, $CDCl_3$) : 6.75 (1H, d, 16.1Hz, ArC*H*CH), 6.55 (2H, s, Ar*H*), 6.01 (1H, dq, 16.1Hz, 2.3Hz, ArCHC*H*), 3.82 (6H, s, *m*-ArOC*H*$_3$), 3.81 (3H, s, *p*-ArOC*H*$_3$), 1.99 (3H, d, 2.3Hz, CHC≡CC*H*$_3$)

Preparation of (*Z*)- and (*E*)-1,2,3-Trimethoxy-4-(3-tris(1-methylethyl)siloxypropynyl)-5-(pent-1-en-3-yn-1yl)benzene (229)



The phosphonium salt (**225**) (0.36g, 0.81mmol) and the aldehyde (**191**) (0.3g, 0.74mmol) were reacted as described in the preparation of the compound (**228**). The pure *Z*-product (80mg) and a mixture of both *Z*- and *E*-products (40mg, *Z*:*E*=2:1 by ^1H NMR) were obtained by flash column chromatography (10% diethyl ether / 90% petroleum ether) as yellow oils (36% overall, *Z*:*E*=8:1).

The *Z*-product :

ν_{max} (film) : 3311, 2215, 1488, 1463

δ_H (400MHz, $CDCl_3$) : 8.02 (1H, s, Ar*H*), 7.05 (1H, d, 12.0Hz, ArC*H*CH), 5.67 (1H, dq, 12.0Hz, 2.7Hz, ArCHC*H*), 4.66 (2H, s, ArC≡CC*H*$_2$O), 3.90, 3.88 and 3.86 (9H, 3s, ArOC*H*$_3$), 2.05 (3H, d, 2.7Hz, $CH_2C{\equiv}CCH_3$), 1.07-1.03 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$)

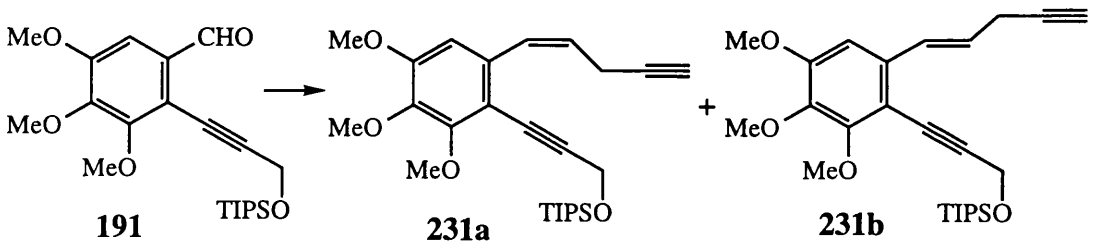
m/z (FAB) : 442 (M^+), 384

Accurate mass : $C_{26}H_{38}O_4Si$ (M^+) requires 442.2539; observed 442.2537

The *E*-product (as in a mixture with the *Z*-product) :

δ_H (400MHz, $CDCl_3$) : 7.29 (1H, d, 17.0Hz, ArC*H*CH), 6.75 (1H, s, Ar*H*), 6.06 (1H, dq, 17.0Hz, 2.3Hz, ArCHC*H*), 4.66 (2H, s, ArC≡CCH_2O), 3.90, 3.88 and 3.86 (9H, 3s, ArOCH_3), 1.99 (3H, d, 2.3Hz, $CH_2C{\equiv}CCH_3$), 1.11-1.09 (21H, m, Si(C*H*(CH_3)$_2$)$_3$)

Preparation of (*Z*)-1,2,3-Trimethoxy-4-(3-tris(1-methylethyl)siloxypropynyl)-5-(pent-1-en-4-yn-1-yl)benzene (231a) and (*E*)-1,2,3-Trimethoxy-4-(3-tris(1-methylethyl)siloxypropynyl)-5-(pent-1-en-4-yn-1-yl)benzene (231b)



To a stirred suspension of the phosphonium salt (**225**) (1.57g, 3.55mmol) and 18-crown-6 (0.80g, 3.01mmol) in THF (8ml) at 0°C was added over 5 minutes potassium bis(trimethylsilyl)amide (0.8M solution in THF, 3.76ml, 3.01mmol) and a yellowish brown mixture was obtained at the end of the addition. This mixture was immediately cooled to -78°C and a solution of the aldehyde (**191**) (1.11g, 2.74mmol) in THF (3ml) was added over 10 minutes. Having stirred at -78°C for 30 minutes, the reaction mixture was quenched with saturated ammonium chloride solution (1.5ml) and allowed to warm up to room temperature. Water (30ml) was added and the mixture was extracted with diethyl ether (2x25ml) and the combined organic layers were washed with water (2x20ml). It was then dried (magnesium sulfate), concentrated and chromatographed (10% diethyl ether /

90% petroleum ether) to give the *Z*-product (**231a**) and a mixture of both products (**231a** and **b**) as yellow oils (overall 30-80% yield, *Z*:*E*=~1.7:1, see Results and Discussion).

The *Z*-product (**231a**) :

ν_{max} (film) : 3293, 1588

δ_H (400MHz, $CDCl_3$) : 6.74 (1H, s, Ar*H*), 6.71 (1H, d, 11.2Hz, ArC*H*CH), 5.76 (1H, dt, 11.2Hz, 8.0Hz, ArCHC*H*), 4.64 (2H, s, ArC≡CCH_2O), 3.92, 3.86 and 3.85 (9H, 3s, ArOCH_3), 3.08-3.05 (2H, m, CH_2C≡CH), 2.04 (1H, t, 2.7Hz, CH_2C≡C*H*), 1.17-1.03 (21H, m, Si(C*H*(CH_3)$_2$)$_3$)

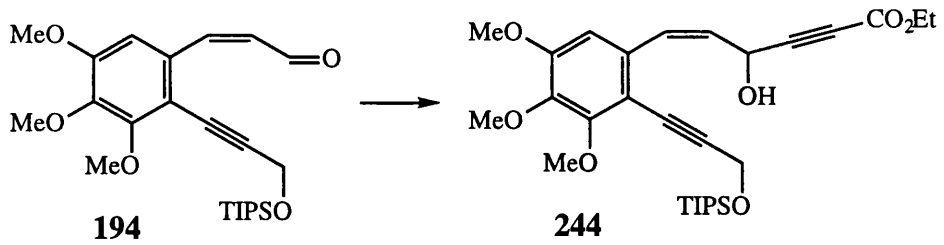
m/z (FAB) : 442 (M^+), 399

Accurate mass : $C_{26}H_{38}O_4Si$ (M^+) requires 442.2539; observed 442.2542

The *E*-product (**231b**) (as in a mixture with **231a**) :

δ_H (400MHz, $CDCl_3$) : 7.03 (1H, d, 15.6Hz, ArC*H*CH), 6.76 (1H, s, Ar*H*), 6.10 (1H, dt, 15.6Hz, 6.0Hz, ArCHC*H*), 4.68 (2H, s, ArC≡CCH_2O), 3.94 and 3.90 (9H, 2s, ArOCH_3), 3.14-3.12 (2H, m, CH_2C≡CH), 2.12 (1H, t, 2.7Hz, CH_2C≡C*H*), 1.15-1.04 (21H, m, Si(C*H*(CH_3)$_2$)$_3$)

Preparation of Ethyl (*Z*)-4-hydroxy-6-(2-(3-tris(1-methylethyl)siloxypropynyl)-3,4,5-trimethoxyphenyl)hex-5-en-2-ynoate (244)



To a stirred solution of ethyl propiolate (0.75g, 7.63mmol) in THF (15ml) at -78°C was added *n*-butyllithium (2.5M in hexanes, 3.05ml, 7.63mmol) over 5 minutes. The

resulting yellow solution was left stirring at this temperature for 15 minutes and a solution of the aldehyde (**194**) (1.5g, 3.47mmol) in THF (15ml) was then added. The reaction mixture was quenched 10 minutes later with acetic acid (1ml) and was allowed to warm to room temperature. After concentration, the mixture was partitioned between water and diethyl ether (40ml each). The aqueous layer was extracted with diethyl ether (2x15ml) and the combined organic layers were washed with water (2x20ml). The organic phase was then dried (magnesium sulfate), concentrated and chromatographed (40% diethyl ether / 60% petroleum ether) to give the title compound as a red oil (1.61g, 87%).

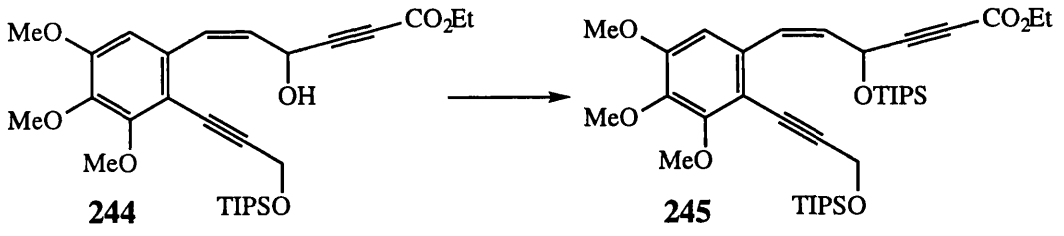
ν_{max} (film) : 3546 (br), 2942, 2233, 1713, 1588, 1246, 1137, 1099

δ_H (200MHz, $CDCl_3$) : 6.81 (1H, d, 11.2Hz, ArC*H*CH), 6.71 (1H, s, Ar*H*), 5.81 (1H, dd, 11.2Hz, 8.9Hz, ArCHC*H*), 5.75 (1H, dd, 8.9Hz, 5.4Hz, ArCHCHC*H*(OH)), 4.64 (2H, s, ArC≡CCH_2O), 4.22 (2H, q, 6.67Hz, OCH_2CH3), 3.88, 3.87 and 3.86 (9H, 3s, ArOCH_3), 2.50 (1H, d, 5.4Hz, ArCHCHCH(O*H*)), 1.27 (3H, t, 6.67Hz, OCH_2CH_3), 1.25-1.06 (21H, m, Si(C*H*(CH_3)2)3)

m/z (FAB) : 529 ($[M-H]^+$), 487, 441, 357

Accurate mass : $C_{29}H_{41}O_7Si$ ($[M-H]^+$) requires 529.2622; observed 529.2626

Preparation of Ethyl (*Z*)-4-(3-tris(1-methylethyl)siloxy)-6-(2-(3-tris(1-methylethyl)siloxypropynyl)-3,4,5-trimethoxyphenyl)hex-5-en-2-ynoate (245)



Triisopropylsilyl triflate (TIPSOTf) (1.2g, 3.89mmol) and 2,6-lutidine (distilled from sodium hydroxide, 0.80g, 7.48mmol) were added successively to a stirred solution of the alcohol (**244**) (1.61g, 3.04mmol) in dichloromethane (40ml) at -78°C. The reaction mixture was quenched with saturated ammonium chloride solution (2ml) 4 hours later and then allowed to warm to room temperature. The reaction mixture was partitioned between water (40ml) and dichloromethane (10ml) and the aqueous layer was extracted with dichloromethane (2x20ml). The combined organic layers were washed with water (2x20ml) and then dried (magnesium sulfate), concentrated and chromatographed (40% diethyl ether / 60% petroleum ether) to give the title compound as a colourless oil (2.01g, 91%).

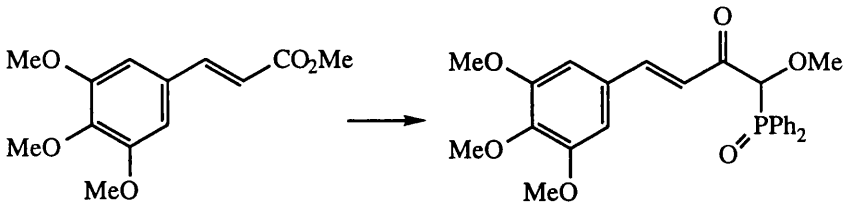
ν_{max} (film) : 2842, 2355, 2338, 1709

δ_H (200MHz, $CDCl_3$) : 6.79 (1H, 11.1Hz, ArC*H*CH), 6.70 (1H, s, Ar*H*), 5.79 (1H, dd, 11.1Hz, 8.1Hz, ArCHC*H*), 5.31 (1H, d, 8.1Hz, ArCHCHC*H*(OTIPS)), 4.64 (2H, s, ArC≡CCH_2O), 4.21 (2H, q, 7.2Hz, OCH_2CH3), 3.92, 3.89 and 3.87 (9H, 3s, ArOCH_3), 1.28 (3H, t, 7.2Hz, OCH_2CH_3), 1.13-1.04 (42H, m, Si(C*H*(CH_3)$_2$)$_3$)

m/z (FAB) : 685 (M^+), 644, 513, 403

Accurate mass : $C_{38}H_{61}O_7Si_2$ (M^+) requires 685.3956; observed 685.3972

((*E*)-1-Methoxy-2-oxo-4-(3,4,5-trimethoxyphenyl)but-3-en-1-yl)diphenylphosphine oxide (249)



247 **249**

To a stirred solution of diisopropylamine (0.11g, 1.13mmol) in THF (2ml) at 0°C was added dropwise *n*-butyllithium (2.5M in hexanes, 0.39ml, 0.97mmol) and the

resulting solution was left stirring at 0°C for 30 minutes. A solution of (methoxymethyl)diphenylphosphine oxide (0.2g, 0.81mmol) in THF (3.5ml) was then added dropwise to give an orange-coloured solution. Having stirred at 0°C for 10 minutes, this solution was cooled to -78°C and the ester (**247**) (0.20g, 0.81mmol) in THF (1ml) was added dropwise. The reaction mixture was allowed to warm up to room temperature on complete addition and left stirring overnight. It was then partitioned between diethyl ether and saturated ammonium chloride solution (20ml each) and the organic layer was washed successively with saturated ammonium chloride solution and water (10ml each). The organic layer was dried (magnesium sulfate), concentrated and chromatographed with gradient elution (50% to 90% diethyl ether / petroleum ether, and then neat EtOAc) to recover the unreacted phosphine oxide (87mg, 44%) and isolate the product as a yellow, foam-like solid (67mg, 18%).

m.p. 57-59°C

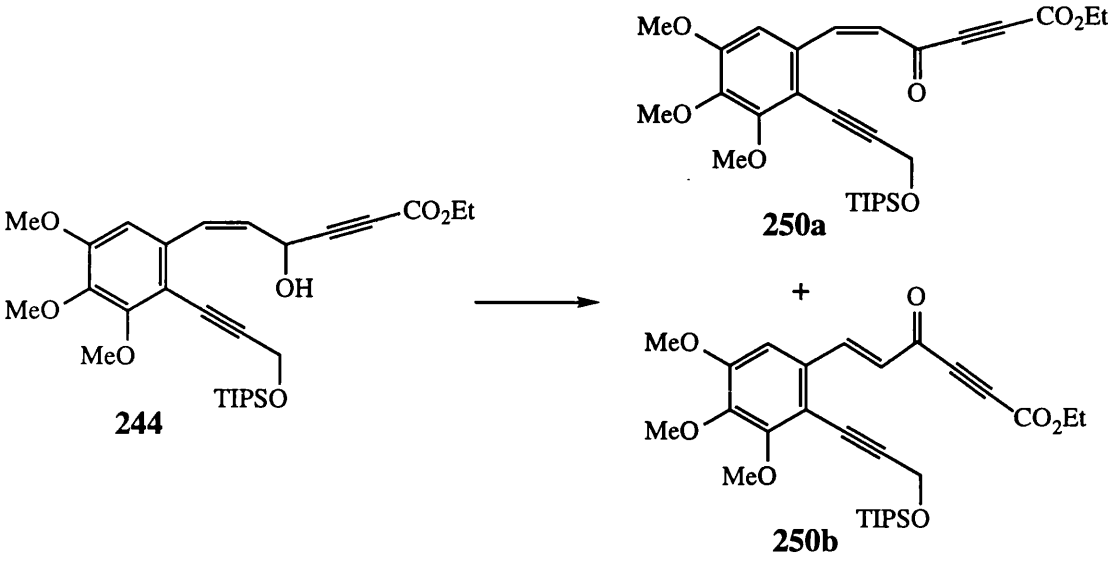
ν_{max} (film) : 3428, 2360, 1605, 1580, 1127

δ_H (200MHz, $CDCl_3$) : 7.95-7.46 (10H, m, *Ph*), 7.59 (1H, 15.8Hz, ArC*H*CH), 7.09 (1H, d, 15.8Hz, ArCHC*H*), 6.76 (2H, s, Ar*H*), 4.83 (1H, d, 14.8Hz, PC*H*OMe), 3.87 (9H, s, ArOC*H*$_3$), 3.41 (3H, s, CHOC*H*$_3$)

m/z (FAB) : 467 (MH^+), 183

Accurate mass : $C_{26}H_{28}O_6P$ (MH^+) requires 467.1624; observed 467.1620

Preparation of Ethyl (*Z*)-4-oxo-6-(2-(3-tris(1-methylethyl)siloxypropynyl)-3,4,5-trimethoxyphenyl) hex-5-en-2-ynoate (250a) and Ethyl (*E*)-4-oxo-6-(2-(3-tris(1-methylethyl)siloxypropynyl)-3,4,5-trimethoxyphenyl)hex-5-en-2-ynoate (250b)



A mixture of the alcohol (**244**) (0.3g, 0.57mmol) and manganese(IV) oxide (0.25g, 2.85mmol) in dichloromethane (5ml) was stirred overnight at room temperature. The reaction mixture was filtered through a celite pad and the cake of manganese(IV) oxide was washed with dichloromethane (60ml). The filtrate was concentrated and chromatographed with gradient elution (20% to 40% diethyl ether / petroleum ether) to recover the unreacted alcohol (0.16g, 53%) and to give the inseparatable products (**250a** and **b**) as a bright yellow oil (26% overall, *Z*:*E*=~1:2.7). However, after overnight storage at -5°C, all the *Z*-product isomerised to the *E*-product.

The *E*-product (**250b**) :

ν_{max} (film) : 2943, 2866, 1719, 1635, 1584, 1244, 1098

δ_H (200MHz, $CDCl_3$) : 8.34 (1H, 16.3Hz, ArC*H*CH), 6.90 (1H, s, Ar*H*), 6.78 (1H, d, 16.3Hz, ArCHC*H*), 4.71 (2H, s, ArC≡CCH_2O), 4.32 (2H, q, 7.1Hz, OCH_2CH3), 3.94,

3.93 and 3.90 (9H, 3s, ArOC*H*$_3$), 1.35 (3H, t, 7.1Hz, OCH$_2$C*H*$_3$), 1.13-1.08 (42H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$)

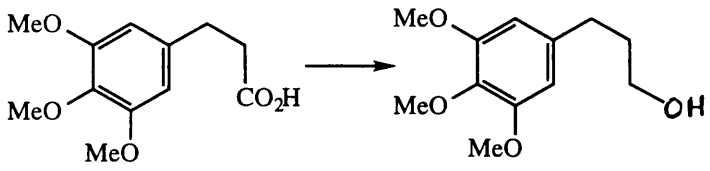
m/z (FAB) : 529 (MH^+), 486, 455, 429

Accurate mass : $C_{29}H_{40}O_7SiNa$ ([M+Na]$^+$) requires 551.2441; observed 551.2446

The *Z*-product (**250a**) (as in a mixture with the *E*-product) :

δ_H (200MHz, $CDCl_3$) : 7.49 (1H, 12.6Hz, ArC*H*CH), 7.24 (1H, s, Ar*H*), 6.30 (1H, d, 12.6Hz, ArCHC*H*), 4.67 (2H, s, ArC≡CC*H*$_2$O), 4.24 (2H, q, 6.4Hz, OC*H*$_2$CH$_3$), 3.93, 3.92 and 3.90 (9H, 3s, ArOC*H*$_3$), 1.31 (3H, t, 6.4Hz, OCH$_2$C*H*$_3$), 1.13-1.08 (42H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$)

Preparation of 3-(3,4,5-Trimethoxyphenyl)propan-1-ol[82] (255)



255

To a stirred solution of 3-(3,4,5-trimethoxyphenyl)propionic acid (8g, 33.3mmol) in THF (150ml) at 0°C was added dropwise borane-THF complex (1.0M in THF, 40ml, 40.0mmol) over 15 minutes. When hydrogen gas evolution had subsided, the mixture was stirred at room temperature for 1 hour. The residual borane was then destroyed by the slow addition of 1:1 / water:THF (10ml) at 0°C. After warming up to room temperature, the reaction mixture was concentrated and partitioned between dichloromethane and water (100ml each). The aqueous layer was extracted with dichloromethane (2x30ml) and the combined organic layers were washed with water (3x30ml). Upon drying (magnesium sulfate) and concentration, the crude product (7.6g, ~100%) was obtained as a colourless oil, which was shown by ^{1}H NMR spectroscopy to be sufficiently pure for further use.

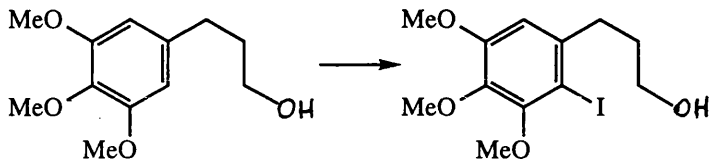
ν_{max} (film) : 3477 (br), 2940, 1723, 1590, 1509, 1461, 1421, 1239, 1126

δ_H (200MHz, $CDCl_3$) : 6.42 (1H, s, Ar*H*), 3.84 (6H, s, *m*-ArOC*H*$_3$), 3.81 (3H, s, *p*-ArOC*H*$_3$), 3.69 (2H, t, 6.4Hz, $ArCH_2CH_2CH_2$), 2.66 (2H, t, 7.3Hz, $ArCH_2CH_2$), 1.92-1.85 (2H, m, $ArCH_2CH_2CH_2$)

m/z (FAB) : 226 (M^+), 181

Accurate mass : $C_{12}H_{18}O_4$ (M^+) requires 226.1205; observed 226.1207

Preparation of 3-(2-Iodo-3,4,5-trimethoxyphenyl)propan-3-ol (256)



255 **256**

To a stirred suspension of the alcohol (**255**) (7.6g, 33.3mmol) and silver trifluoroacetate (7.35g, 33.3mmol) in dichloromethane (50ml) at room temperature was added dropwise a solution of iodine (8.46g, 33.3mmol) in dichloromethane (220ml) over 1.5 hours. The red suspension obtained at the end of the addition was filtered and the filtrate was washed successively with saturated sodium thiosulfate solution (2x100ml) and water (2x200ml). The organic layer was then dried (magnesium sulfate), concentrated and chromatographed with gradient elution (50% to 60% EtOAc / petroleum ether) to provide the title compound as a pale yellow oil (10.5g, 90%).

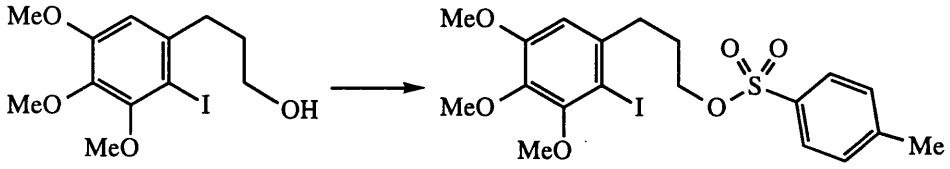
ν_{max} (film) : 3409 (br), 2836, 1561, 1478, 1386, 1104

δ_H (200MHz, $CDCl_3$) : 6.66 (1H, s, Ar*H*), 3.86 and 3.84, (9H, 2s, ArOC*H*$_3$), 3.72 (2H, t, 6.4Hz, $ArCH_2CH_2CH_2$), 2.82 (2H, t, 7.0Hz, $ArCH_2CH_2$), 1.89-1.81 (2H, m, $ArCH_2CH_2CH_2$)

m/z (FAB) : 352 (M^+), 307, 226

Accurate mass : $C_{12}H_{17}O_4I$ (M^+) requires 352.0172; observed 352.0173

Preparation of 3-(2-Iodo-3,4,5-trimethoxyphenyl)prop-3-yl 4-methylbenzenesulfonate (257)



256 **257**

To a stirred solution of *p*-toluenesulfonyl chloride (0.13g, 0.69mmol) and pyridine (74mg, 0.94mmol) in dichloromethane (3ml) at room temperature was added dropwise a solution of the alcohol (**256**) (0.22g, 0.63mmol) in dichloromethane (2ml). Having stirred for 2 days, the reaction mixture was diluted with dichloromethane (10ml) and washed successively with 1M HCl (10ml) and water (2x10ml). The organic layer was then dried (magnesium sulfate), concentrated and chromatographed with gradient elution (15% to 50% EtOAc / petroleum ether) to give the product as a colourless solid (0.24g, 74%).

m.p. 87-89°C

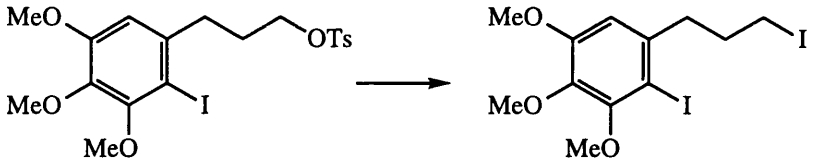
ν_{max} (film) : 2937, 1561, 1478, 1356, 1176

δ_H (200MHz, $CDCl_3$) : 7.81 (2H, d, 8.5Hz, Ar*H* α to SO_3), 7.35 (2H, d, 8.5Hz, Ar*H* β to SO_3), 6.63 (1H, s, Ar*H* α to OMe), 4.06 (2H, t, 6.1Hz, $ArCH_2CH_2CH_2$), 3.84 and 3.83 (9H, 2s, $ArOCH_3$), 2.77 (2H, t, 7.5Hz, $ArCH_2CH_2$), 2.44 (3H, s, *p*-$ArCH_3$), 1.96-1.92 (2H, m, $ArCH_2CH_2CH_2$)

m/z (FAB) : 506 (M^+), 380

Accurate mass : $C_{19}H_{23}O_6IS$ (M^+) requires 506.0260; observed 506.0251

Preparation of 1-(3-Iodoprop-1-yl)-2-iodo-3,4,5-trimethoxybenzene (258)



257 **258**

A solution of the tosylate (**257**) (0.17g, 0.34mmol) and anhydrous sodium iodide (0.1g, 0.68mmol) in acetone (5ml) was refluxed for 2 hours and then cooled down to room temperature. After concentration, the reaction mixture was partitioned between water and dichloromethane (10ml each) and the aqueous layer was extracted with dichloromethane (2x8ml). The combined organic layers were washed with water (10ml) and then dried (magnesium sulfate). The title compound was given as a yellow oil (0.15g, 94%) upon concentration.

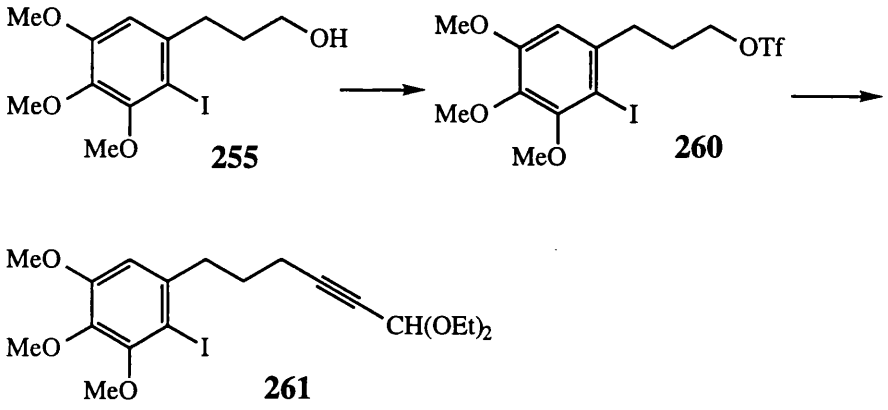
ν_{max} (film) : 2934, 1559, 1481, 1387, 1101

δ_H (200MHz, $CDCl_3$) : 6.68 (1H, s, Ar*H*), 3.86, 3.85 and 3.84 (9H, 3s, ArOC*H*$_3$), 3.21 (2H, t, 6.7Hz, $ArCH_2CH_2CH_2$), 2.84 (2H, t, 7.5Hz, $ArCH_2CH_2$), 2.13-2.05 (2H, m, $ArCH_2CH_2CH_2$)

m/z (FAB) :462 (M^+), 336, 307, 208

Accurate mass : $C_{12}H_{16}O_3I_2$ (M^+) requires 461.9189; observed 461.9191

Preparation of 3-(2-Iodo-3,4,5-trimethoxyphenyl)prop-1-yl 2,2,2-trifluoromethanesulfonate (260) and 6-(2-Iodo-3,4,5-trimethoxyphenyl)hex-2-ynal diethyl acetal (261)



To a stirred solution of triflic anhydride (0.28g, 0.98mmol) in dichloromethane (3ml) at 0°C was added dropwise a solution of the alcohol (**255**) (0.3g, 0.85mmol) and pyridine (69µl, 0.85mmol) in dichloromethane (4ml) over 20 minutes. The resulting greyish purple solution was stirred at 0°C for 30 minutes and was then washed with water (2x10ml). The organic layer was dried (magnesium sulfate) and concentrated to give the triflate (**260**) as a dark brown liquid (0.33g).

δ_H (200MHz, $CDCl_3$) : 6.64 (1H, s, Ar*H*), 4.58 (2H, t, 6.8Hz, $CH_2CH_2CH_2OTf$), 3.87, 3.85 and 3.84 (9H, 3s, $ArOCH_3$), 2.87 (2H, t, 8.6Hz, $ArCH_2CH_2$), 2.17-2.10 (2H, m, $ArCH_2CH_2CH_2$)

To a stirred solution of propargylaldehyde diethyl acetal (0.19g, 1.52mmol) in THF (5ml) at 0°C was added *n*-BuLi (2.5M in hexanes, 0.61ml, 1.52mmol) and the yellow solution thus obtained was stirred at this temperature for 15 minutes. The triflate (**260**) (0.33g, 0.69mmol) in THF (2ml) was then added dropwise to the acetylide solution and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was taken up in diethyl ether (30ml) and washed with water (3x20ml). The organic layer was

dried (magnesium sulfate), concentrated and chromatographed (10% EtOAc / 90% petroleum ether) to provide the acetal (**261**) as a yellow oil (0.17g, 43% over two steps).

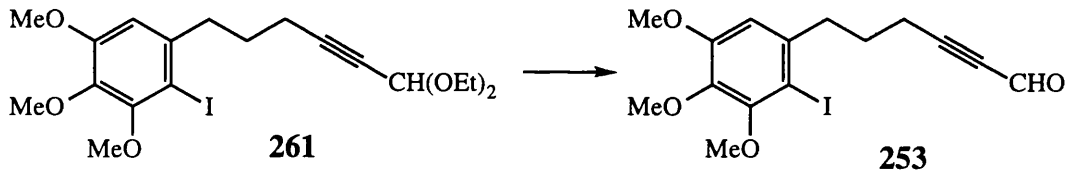
ν_{max} (film) : 2974, 2241, 1564, 1480, 1387, 1331

δ_H (200MHz, $CDCl_3$) : 6.65 (1H, s, Ar*H*), 5.28 (1H, s, C≡CC*H*$(OEt)_2$), 3.86 and 3.84 (9H, 2s, ArOC*H*$_3$), 3.82-3.53 (4H, m, CH(OC*H*$_2$CH$_3$)$_2$), 2.82 (2H, t, 7.5Hz, ArC*H*$_2$CH$_2$), 2.31 (2H, t, 6.9Hz, ArCH$_2$CH$_2$C*H*$_2$), 1.85-1.77 (2H, m, ArCH$_2$C*H*$_2$CH$_2$), 1.23 (6H, t, 7.1Hz, CH(OCH$_2$C*H*$_3$)$_2$)

m/z (EI) : 462 (M^+), 417, 335, 307, 290

Accurate mass : $C_{19}H_{27}O_5I$ (M^+) requires 462.0903; observed 462.0911

Preparation of 6-(2-Iodo-3,4,5-trimethoxyphenyl)hex-2-ynal (253)



A solution of the acetal (**261**) (0.16g, 0.35mmol) and *p*-toluenesulfonic acid hydrate (6.7mg, 10mol%) in a mixture of acetone and water (3ml each) was stirred at 55°C for 3 hours and then cooled down to room temperature. After removal of acetone, the reaction mixture was extracted with dichloromethane (3x5ml) and the combined organic layers were washed successively with saturated sodium bicarbonate solution and water (10ml each). The organic layer was then dried (magnesium sulfate), concentrated and chromatographed (40% diethyl ether / 60% petroleum ether) to give the title compound as a pale yellow oil (0.10g, 74%).

ν_{max} (film) : 2937, 2277, 2201, 1666, 1564, 1478

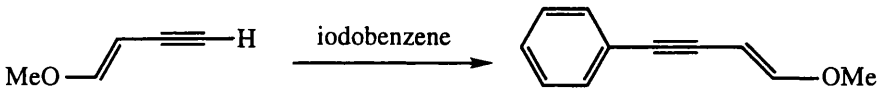
δ_H (200MHz, $CDCl_3$) : 9.20 (1H, d, 0.8Hz, C*H*O), 6.63 (1H, s, Ar*H*), 3.86 and 3.85 (9H, 2s, ArOC*H*$_3$), 2.88-2.81 (2H, m, $ArCH_2CH_2CH_2$), 2.48 (2H, t, 7.0Hz, $ArCH_2CH_2$), 1.95-1.80 (2H, m, $ArCH_2CH_2$)

m/z (FAB) : 388 (M^+), 357, 307, 290, 262

Accurate mass : $C_{15}H_{17}O_4I$ (M^+) requires 388.0172; observed 388.0184

Elemental Analysis : Calc. C (46.5%), H (4.4%); Found C (47.0%), H (4.7%)

Preparation of (*E*)-(4-Methoxy-3-buten-1-ynyl)benzene (265)



264 **265**

To a stirred mixture of *E*-1-methoxy-1-buten-3-yne[84a] (**264**) (4.82g, 58.8mmol), palladium(II) acetate (45mg, 0.2mmol), copper(I) iodide (40mg, 0.2mmol), and triphenylphosphine (0.44g, 1.7mmol) in diethylamine (60ml) at 0°C was added dropwise iodobenzene (10g, 49mmol). The reaction mixture was gently refluxed for 30 minutes and then cooled down to room temperature. After adsorbing on silica gel (~30g), the reaction mixture was chromatographed (3% diethyl ether / 97% petroleum ether) to isolate the title compound (7.14g, 92% based on iodobenzene) as a colourless oil, which readily turned brown at room temperature.

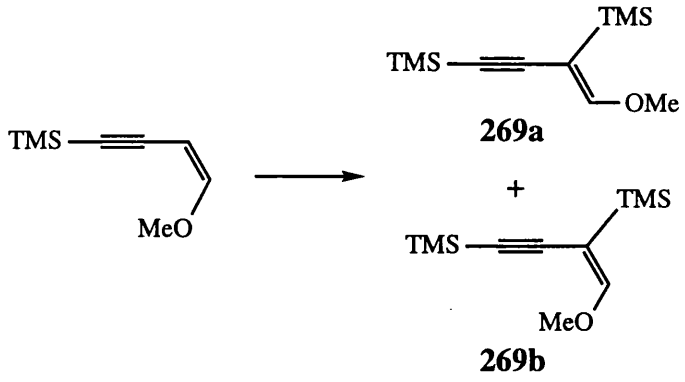
ν_{max} (film) : 2935, 2835, 2203, 1623, 1594, 1299, 1214

δ_H (270MHz, $CDCl_3$) : 7.34 (5H, m, *Ph*); 6.98 (1H, d, 12.7Hz, C*H*CHOMe); 5.09 (1H, d, 12.7Hz, CHC*H*OMe); 3.65 (3H, s, CHCHOC*H*$_3$)

m/z (EI) : 158 (M^+), 129

Accurate mass : $C_{11}H_{10}O$ (M^+) requires 158.0732; observed 158.0741

Preparation of (*Z*)-1-Methoxy-2,4-bis(trimethylsilyl)but-1-en-3-yne (269a) and (*E*)-1-Methoxy-2,4-bis(trimethylsilyl)but-1-en-3-yne (269b)



To a stirred solution of (*Z*)-1-methoxy-4-trimethylsilylbut-1-en-3-yne[85] (**266**) (1g, 6.49mmol) in DME (15ml) at -78°C was added dropwise *n*-BuLi (2.38M in hexanes, 3.0ml, 7.15mmol) to give a yellow solution, which turned brown after stirring at this temperature for 15 minutes. TMSCl (0.95g, 8.76mmol) was then added dropwise to provide a wine-red solution. After stirring at -78°C for 2 more hours and the colour had changed to purple, the reaction mixture was allowed to warm up to room temperature. The resulting yellow suspension was left stirring for 30 minutes and then filtered. The pale brown precipitate was washed with DME (10ml). The filtrate was concentrated and filtered again through glass wool. Distillation (2.5mmHg, 72-76°C) afforded an inseparable mixture of the products as a colourless liquid (0.82g, 56%). The ratio of the *Z*- and *E*-products was shown by ^{1}H NMR spectroscopy to be 3.5:1. This mixture decomposed rapidly and hence was used freshly after preparation.

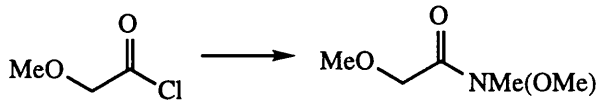
ν_{max} (film) : 2959, 2123, 1593, 1248, 815

δ_H (200MHz, $CDCl_3$) : *major product* (**269a**) 7.03 (1H, s, C*H*OMe), 3.65 (3H, s, CHOC*H*$_3$), 0.15 (9H, s, CH(OMe)C(Si(C*H*$_3$)$_3$)), 0.14 (9H, s, C≡CSi(C*H*$_3$)$_3$)

minor product (**269b**) 6.11 (1H, s, C*H*OMe), 3.77 (3H, s, CHOC*H*$_3$), 0.17 (9H, s, CH(OMe)C(Si(C*H*$_3$)$_3$)), 0.16 (9H, s, C≡CSi(C*H*$_3$)$_3$)

m/z (EI) : 226 (M^+), 211, 197

Preparation of *N*-Methoxy-*N*-methyl-2-methoxyacetamide (209b)



209b

To a stirred suspension of methoxyacetyl chloride (10g, 92.1mmol) and *N,O*-dimethylhydroxylamine hydrogen chloride salt (9.43g, 96.7mmol) in dichloromethane (120ml) at 0°C was added dropwise pyridine (15.4g, 0.19mmol). The resulting dense white suspension was occasionally hand-shaken during the addition in order to maintain stirring. When the addition was complete, the mixture was stirred at 0°C for 30 minutes and then at room temperature for 1 hour. After dilution with dichloromethane (50ml), the reaction mixture was washed successively with water (50ml) and brine (2x50ml). The organic layer was dried (sodium sulfate) and concentrated to give a brown liquid. This was then distilled (15mmHg, 87-9°C) to give the title compound as a pale yellow liquid (9.55g, 78%).

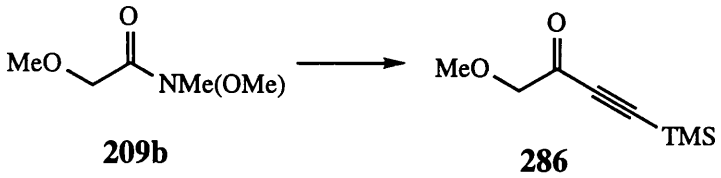
ν_{max} (film) :1838, 1761, 1679, 1449

δ_H (200MHz, $CDCl_3$) : 4.20 (2H, s, CH_2OMe), 3.67 (3H, s, $NOCH_3$), 3.45 (3H, s, CH_2OCH_3), 3.18 (3H, s, NCH_3)

m/z (EI) : 133 (M^+), 103

Accurate mass : $C_5H_{11}O_3N$ (MH^+) requires 134.0817; observed 134.0827

Preparation of 1-Methoxy-4-trimethylsilylbut-3-yn-2-one (286)



209b **286**

To a stirred solution of trimethylsilylacetylene (5.54g, 56.4mmol) in THF (40ml) at 0°C was added dropwise *n*-BuLi (2.3M in hexanes, 23.4ml, 53.8mmol). After stirring at this temperature for 30 minutes, this mixture was added dropwise over 90 minutes to a stirred solution of the amide (**209b**) in THF (100ml) at 0°C. When the addition was complete, the mixture was further stirred at 0°C for 1 hour and then poured into cold 5% HCl / ethanol (500ml). After stirring at 0°C for 30 minutes, the mixture was taken up in 1:1 / diethyl ether:dichloromethane (400ml) and then washed with brine (3x200ml). The organic layer was dried (magnesium sulfate), concentrated and chromatographed (8% diethyl ether / 92% petroleum ether) to give the product as a yellow liquid (6.71g, 73%).

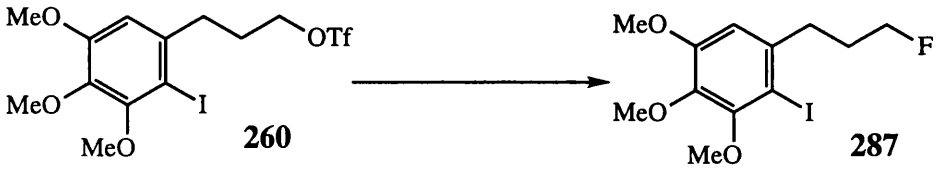
ν_{max} (film) : 2961, 1694, 2200, 1253

δ_H (200MHz, $CDCl_3$) : 4.17 (2H, s, CH_2OMe), 3.45 (3H, s, CH_2OCH_3), 0.25 (9H, s, $Si(CH_3)_3$)

m/z (EI) : 170 (M^+), 150, 140, 125

Accurate mass : $C_8H_{14}O_2Si$ (M^+) requires 170.0763; observed 170.0762

Preparation of 1-(3-Fluoroprop-1-yl)-2-iodo-3,4,5-trimethoxybenzene (287)



The triflate (**260**) was prepared from the alcohol (**256**) (0.31g, 0.88mmol) and triflic anhydride (0.29g, 1.32mmol) as a dark brown liquid as previously described. To a solution of the triflate (**260**) and the ketone (**286**) (0.14g, 0.82mmol) in THF (20ml) stirred at -30°C was added TBAF (1.1M in THF, 0.75ml, 0.82mmol) over 10 minutes to give a red solution. The reaction mixture was left stirring at this temperature for a further 40 minutes and then quenched with saturated ammonium chloride solution (1ml). After warming up to room temperature, the reaction mixture was diluted with diethyl ether (20ml) and washed with water (2x20ml). The organic layer was then dried (magnesium sulfate), concentrated and chromatographed (40% diethyl ether / 60% petroleum ether) to give the title compound as a pale yellow oil (0.17g, 55%).

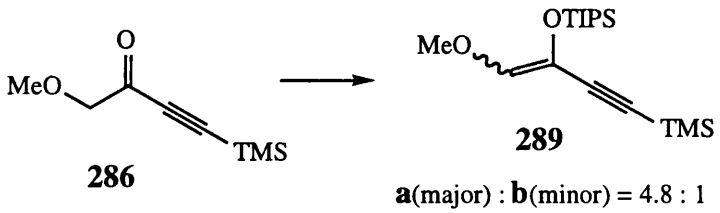
ν_{max} (film) : 2936, 1560, 1481, 1427, 1388

δ_H (200MHz, $CDCl_3$) : 6.64 (1H, s, Ar*H*), 4.49 (2H, dt, 5.8Hz, 47.3Hz, $ArCH_2CH_2CH_2$), 3.86, 3.84 and 3.83 (9H, 3s, $ArOCH_3$), 2.83 (2H, t, 6.1Hz, $ArCH_2CH_2$), 2.07-1.82 (2H, m, $ArCH_2CH_2CH_2$)

m/z (EI) : 354 (M^+), 307

Accurate mass : $C_{12}H_{17}O_3F$ (MH^+) requires 355.0206; observed 355.0203

Preparation of 1-Methoxy-2-tris(1-methylethyl)siloxy-4-trimethylsilylbut-1-en-3-yne (289a0 and (289b)



To a stirred solution of triethylamine (0.18g, 1.77mmol) and the ketone (**286**) (0.20g, 1.18mmol) in benzene (5ml) at 0°C was added dropwise TIPSOTf (0.40g, 1.30mmol). The reaction mixture was left stirring at room temperature for 45 minutes and then taken up in diethyl ether (20ml) and washed with water (2x20ml). The organic layer was dried (magnesium sulfate), concentrated and chromatographed (2% diethyl ether / 98% petroleum ether) to give respectively the pure major product (**289a**) and a mixture of the both products as colourless oils (0.33g overall, 93%). The ratio of the major : minor products was shown to be 4.8:1 by ^1H NMR spectroscopy.

The major product (**289a**) :

ν_{max} (film) : 2945, 2867, 2139, 1754, 1694, 1652, 1464, 844

δ_H (200MHz, $CDCl_3$) : 5.89 (1H, s, C*H*OMe), 3.63 (3H, s, CHOC*H*$_3$), 1.18-1.06 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 0.14 (9H, s, Si(C*H*$_3$)$_3$)

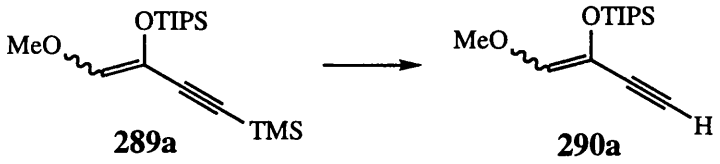
m/z (EI) : 326 (M^+), 283, 268

Accurate mass : $C_{17}H_{34}O_2Si_2$ (M^+) requires 326.2097; observed 326.2098

The minor product (**289b**) (as in a mixture with the major product) :

δ_H (200MHz, $CDCl_3$) : 7.37 (1H, s, C*H*OMe), 3.40 (3H, s, CHOC*H*$_3$), 1.18-1.06 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 0.17 (9H, s, Si(C*H*$_3$)$_3$)

Preparation of 1-Methoxy-2-tris(1-methylethyl)siloxybut-1-en-3-yne (290a)



289a **290a**

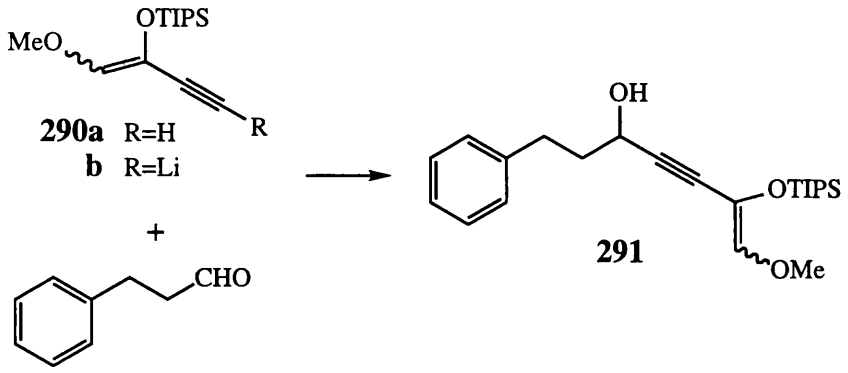
A suspension of the enyne (**289a**) (0.112g, 0.34mmol) and anhydrous potassium carbonate (57mg, 0.41mmol) in anhydrous methanol (2.5ml) was stirred at room temperature for 1 hour and then filtered. The filtrate was concentrated and partitioned between diethyl ether and water (10ml each). The organic layer was dried (magnesium sulfate) and concentrated to give the title compound as a yellow oil (74mg, 86%), which was used immediately.

ν_{max} (film) : 3312, 2944, 2867, 2093, 1655, 1463, 1341, 1230, 1136

δ_H (200MHz, $CDCl_3$) : 5.90 (1H, s, C*H*OMe), 3.64 (3H, s, CHOC*H*$_3$), 2.95 (1H, s, C≡C*H*), 1.18-1.06 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$)

m/z (EI) : 254 (M^+), 237, 211

Preparation of 1-Phenyl-6-tris(1-methylethyl)siloxy-7-methoxyhept-6-en-4-yn-3-ol (291)



290a R=H
b R=Li
+
291

The acetylide (**290b**) was generated by the addition of *n*-butyllithium (2.3M in hexanes, 0.13ml, 0.30mmol) to a stirred solution of the alkyne (**290a**) (77mg, 0.30mmol)

in THF (2ml) at -78°C. This solution was stirred at -78°C for 15 minutes and 3-phenylpropanal (41mg, 0.3mmol) was then added. The reaction mixture was left stirring at -78°C for 80 minutes and then quenched with saturated ammonium chloride solution (0.5ml). After warming up to room temperature, the reaction mixture was partitioned between diethyl ether and water (10ml each) and the organic layer was washed with water (10ml). The organic layer was then dried (magnesium sulfate), concentrated and chromatographed with gradient elution (2% to 30% diethyl ether / petroleum ether) to recover the ketone (**290a**) (20mg, 26%) and give the title compound as a pale yellow oil (63mg, 54%).

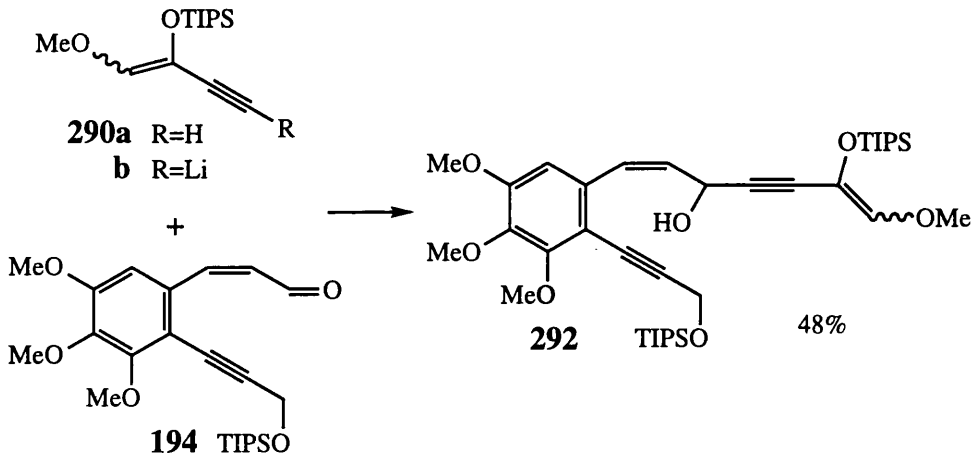
ν_{max} (film) : 3406 (br), 2944, 2866, 2208, 1656, 1342, 1229, 1134

δ_H (200MHz, $CDCl_3$) : 7.28-7.21 (5H, m, *Ph*), 5.87 (1H, s, C*H*OMe), 4.51-4.41 (1H, m, $CH_2CH_2CH(OH)$) 3.64 (3H, s, $CHOCH_3$), 2.78 (2H, t, 7.7Hz, $ArCH_2CH_2$), 2.07-1.95 (2H, m, $ArCH_2CH_2$), 1.67 (1H, d, 13.1Hz, $CH_2CH_2CH(OH)$), 1.18-1.06 (21H, s, $Si(CH(CH_3)_2)_3$)

m/z (FAB) : 388 (M^+), 371, 345

Accurate mass : $C_{26}H_{41}O_5Si$ (M^+) requires 388.2434; observed 388.2430

Preparation of (*Z*)-1-(2-(3-Tris(methylethyl)siloxypropynyl)-3,4,5-trimethoxyphenyl)-6-tris(1-methylethyl)siloxy-7-methoxyhepta-1,6-dien-4-yn-3-ol (292)



The alkyne (**290a**) (77mg, 0.28mmol) was lithiated with *n*-butyllithium (2.3M in hexanes, 0.12ml, 0.28mmol) to form the acetylide (**290b**) and then reacted with the aldehyde (**194**) (0.12g, 0.28mmol) as described in the preparation of the alcohol (**291**). The title compound was isolated using flash column chromatography with gradient elution (2% to 15% and then 35% diethyl ether / petroleum ether) as a yellow oil (92mg, 48%) along with recovered alkyne (**290a**) (9mg, 12%).

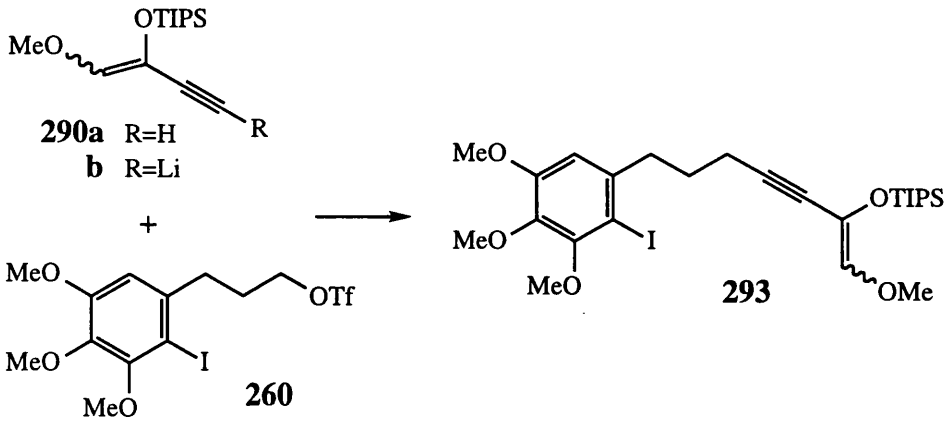
ν_{max} (film) : 3444 (br), 2943, 2866, 2210, 1656, 1589, 1464

δ_H (200MHz, $CDCl_3$) : 6.79 (1H, s, Ar*H*), 6.76 (1H, d, 11.3Hz, ArC*H*CH), 5.86 (1H, s, C*H*OMe), 5.79 (1H, dd, 11.3Hz, 8.6Hz, ArCHC*H*CH(OH)), 5.26 (1H, dd, 4.9Hz, 8.6Hz, ArCHCHC*H*(OH)), 4.65 (2H, s, ArC≡CCH_2O), 3.94, 3.87 and 3.86 (9H, 3s, ArOCH_3), 3.63 (3H, s, CHOCH_3), 2.10 (1H, d, 4.9Hz, ArCHCHO*H*), 1.17-1.06 (42H, m, Si(C*H*(CH_3)$_2$)$_3$)

m/z (FAB) : 686 (M^+), 669, 655

Accurate mass : $C_{38}H_{62}O_7Si_2$ (M^+) requires 686.4034; observed 686.4038

Preparation of 1-(6-Tris(1-methylethyl)siloxy-7-methoxyhept-6-en-4-yn-1yl)-2-iodo-3,4,5-trimethoxybenzene (293)



Solutions of the triflate (**260**) (1.42mmol) in THF (3ml) and acetylide (**290b**) (1.56mmol) in THF (15ml) were prepared respectively as previously described. The former solution was added dropwise to the latter at -78°C and the resulting mixture was stirred at -78°C for 30 minutes and then at room temperature for 30 minutes. The reaction mixture was taken up in diethyl ether (50ml) and then washed with water (3x30ml). The organic layer was dried (magnesium sulfate), concentrated and chromatographed with gradient elution (3% to 10% diethyl ether / petroleum ether) to recover the alkyne (**290a**) (92mg, 23%) and give the product as a brown oil (0.56g, 67%).

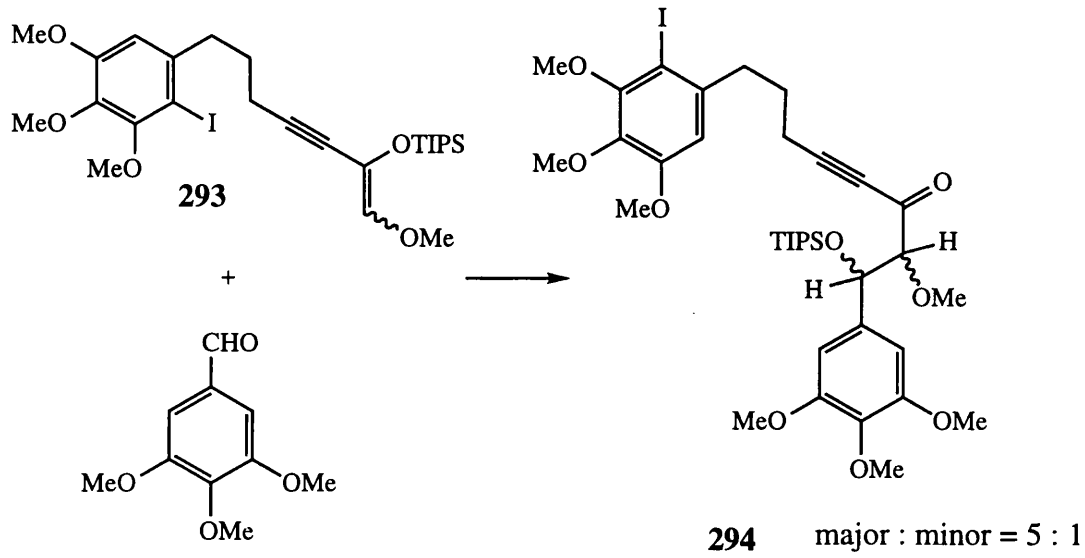
ν_{max} (film) : 2219, 1655, 1480, 1132, 1008, 883

δ_H (200MHz, $CDCl_3$) : 6.63 (1H, s, Ar*H*), 5.79 (1H, s, C*H*OMe), 3.86 and 3.84 (9H, 2s, ArOC*H*$_3$), 3.60 (3H, s, CHOC*H*$_3$), 2.84-2.77 (2H, m, $ArCH_2CH_2CH_2$), 2.35 (2H, t, 7.0Hz, $ArCH_2CH_2$), 1.82-1.73 (2H, m, $ArCH_2CH_2$), 1.16-1.05 (21H, s, $Si(CH(CH_3)_2)_3$)

m/z (FAB) : 588 (M^+), 545, 461

Accurate mass : $C_{26}H_{41}O_5Si$ (M^+) requires 588.1768; observed 588.1773

Preparation of 1-(3,4,5-Trimethoxyphenyl)-1-tris(1-methylethyl)siloxy-2-methoxy-8-(2-iodo-3,4,5-trimethoxyphenyl)oct-4-yn-3-one (294)



To a stirred solution of the silyl enol ether (**293**) (0.24g, 0.41mmol) and 3,4,5-trimethoxybenzaldehyde (80mg, 0.41mmol) in dichloromethane (8ml) at -78°C was added dropwise titanium(IV) chloride (77mg, 0.41mmol) to give a dark brown solution. Saturated sodium carbonate solution (1ml) was added 10 minutes later and the reaction mixture was allowed to warm to room temperature. It was then partitioned between dichloromethane and water (20ml each) and the aqueous layer was extracted with dichloromethane (15ml). The combined organic layers were dried (magnesium sulfate), concentrated and chromatographed (20% EtOAc / 80% petroleum ether). The fractions containing the products were combined and subjected to HPLC separation (20% EtOAc / 80% *n*-hexane, 2ml/min) to provide the pure major product and a mixture of both products as pale yellow oils (overall 90mg, 28%). The ratio of the major to minor products was shown by ^1H NMR spectroscopy to be 5:1.

The major product :

ν_{max} (film) : 2209, 1682, 1589, 1127

δ_H (400MHz, $CDCl_3$) : 6.62 (1H, s, *H*ArCH$_2$CH$_2$), 6.59 (2H, s, *H*ArCH(OTIPS)), 4.97 (1H, d, 5.6Hz, C*H*(OMe)), 3.85, 3.84, 3.83 and 3.80 (18H, 4s, ArOC*H*$_3$), 3.78 (1H, d, 5.6Hz, C*H*(OTIPS)), 3.37 (3H, s, CH(OC*H*$_3$)), 2.80-2.76 (2H, m, ArCH$_2$CH$_2$C*H*$_2$), 2.37 (2H, t, 7.0Hz, ArC*H*$_2$CH$_2$CH$_2$), 1.85-1.75 (2H, m, ArCH$_2$C*H*$_2$CH$_2$), 1.03-0.9 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$)

δ_C (100MHz, $CDCl_3$) : 12.39, 17.92, 18.73, 28.03, 39.90, 56.07, 56.17, 59.15, 60.73, 60.86, 60.97, 76.10, 80.96, 87.91, 92.75, 97.13, 104.34, 108.92, 135.87, 137.50, 139.18, 140.52, 152.76, 153.15, 153.59, 187.48

m/z (FAB) : 807 ($[M+Na]^+$), 353

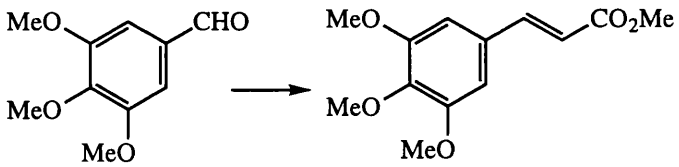
Accurate mass : $C_{36}H_{53}O_9SiNa$ ($[M+Na]^+$) requires 807.2401; observed 807.2404

Elemental Analysis : Calc. C (55.1%), H (6.8%); Found C (55.3%), H (6.8%)

The minor product (as in a mixture with the major product) :

δ_H (200MHz, $CDCl_3$) : 6.64 (1H, s, *H*ArCH$_2$CH$_2$), 6.60 (2H, s, *H*ArCH(OTIPS)), 5.06 (1H, d, 5.7Hz, C*H*(OMe)), 3.87, 3.85, 3.84 and 3.82 (18H, 4s, ArOC*H*$_3$), 3.80 (1H, d, 5.7Hz, C*H*(OTIPS)), 3.34 (3H, s, CH(OC*H*$_3$)), 2.83-2.79 (2H, m, ArCH$_2$CH$_2$C*H*$_2$), 2.43 (2H, t, 7.2Hz, ArC*H*$_2$CH$_2$CH$_2$), 1.90-1.78 (2H, m, ArCH$_2$C*H*$_2$CH$_2$), 1.02-0.97 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$)

Preparation of (*E*)-Methyl 3-(3,4,5-trimethoxyphenyl)prop-2-enoate[19(o)] (247)



168 **247**

(Carbomethoxymethyl)triphenylphosphonium bromide (19.1g, 46.0mmol) and 3,4,5-trimethoxybenzaldehyde (**168**) (6.0g, 30.6mmol) were vigorously stirred overnight in a mixture of 1M NaOH(aq) (60ml) and dichloromethane (60ml) at room temperature. The organic layer was washed with water (3x30ml) and dried (magnesium sulfate) and concentrated. The residue was chromatographed (20% petroleum ether / 80% dichloromethane) giving the title compound as a white solid (7.50g, 97%, >99% *E*). This was sufficiently pure for further use but it could be recrystallised from diethyl ether and a minute amount of dichloromethane at -78°C to give large white needles.

m.p.94-96°C (lit. 95.5-97°C)

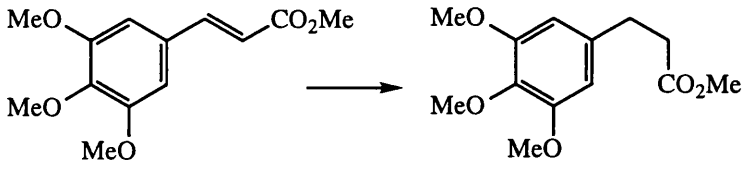
ν_{max} (film) : 1692, 1286, 1130

δ_H (270MHz, $CDCl_3$) : 7.61 (1H, d, 16.0Hz, ArC*H*CH), 6.74 (2H, s, Ar*H*), 6.35 (1H, d, 16.0Hz, ArCHC*H*), 3.89 (3H, s, *p*-ArOC*H*$_3$), 3.88 (6H, s, *m*-ArOC*H*$_3$), 3.81 (3H, s, CO_2CH_3)

m/z (EI) : 252 (M^+); 237 ($[M-Me]^+$)

Elemental analysis : C(61.9%), H (6.3%); Found C (61.9%), H (6.5%)

Preparation of Methyl 3-(3,4,5-trimethoxyphenyl)propanoate[114] (297)



247 **297**

The ester (**247**) (0.625g, 2.48mmol) was dissolved in methanol (25ml) with slight warming under argon. Palladium (5%) on activated carbon (ca. 20mg) was added and a balloon reservoir was used to give a positive pressure of hydrogen. In order to speed up the reaction, another balloon reservoir was attached 3 hours later. The reaction mixture was left stirring at room temperature overnight. It was then filtered and the filtrate was concentrated

to give the product (0.610g, 95%) as a colourless oil, which crystallised to a colourless solid on standing at room temperature.

m.p. 47-48°C (lit. oil)

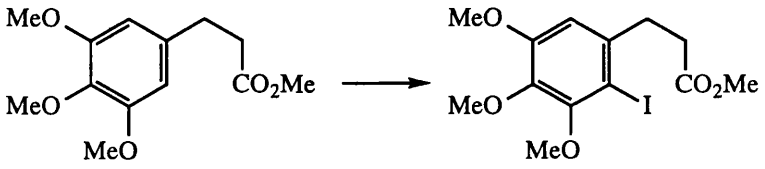
ν_{max} (film) : 2947, 1736, 4590, 1507, 1010

δ_H (270MHz, $CDCl_3$) : 6.41 (2H, s, Ar*H*), 3.83 (6H, s, *m*-ArOC*H*$_3$), 3.81 (3H, s, *p*-ArOC*H*$_3$), 3.68 (3H, s, CO_2CH_3), 2.89 (2H, t, 7.8Hz, $ArCH_2CH_2$), 2.62 (2H, t, 7.8Hz, CH_2CH_2)

m/z (EI) : 254 (M^+); 181

Elemental analysis : Calc.C (61.2%), H (7.1%); Found C (61.4%), H (7.3%)

Preparation of Methyl 3-(2-iodo-3,4,5-trimethoxyphenyl)propanoate (298)



297 **298**

The ester (**297**) (1.441g, 5.67mmol) was reacted with silver trifluoroacetate (1.25g, 5.67mmol) and iodine (1.59g, 6.26mmol) as previously described. The crude product was purified by flash column chromatography (35% diethyl ether / 65% petroleum ether) to give the title compound as a colourless oil (1.94g, 90%).

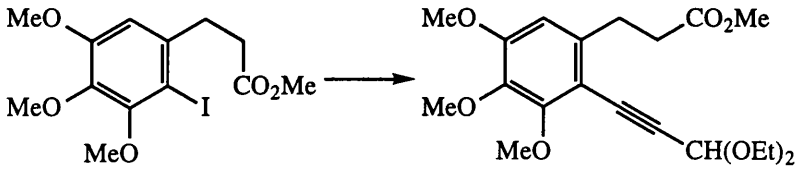
ν_{max} (film) : 2930, 1736, 1560, 1104, 1007

δ_H (270MHz, $CDCl_3$) : 6.68 (1H, s, Ar*H*), 3.86, 3.84 and 3.83 (9H, 3s, ArOC*H*$_3$), 3.69 (3H, s, CO_2CH_3), 3.05 (2H, t, 7.6Hz, $ArCH_2CH_2$) 2.62 (2H, t, 7.6Hz, $ArCH_2CH_2$)

m/z (EI) : 380 (M^+), 307, 253

Elemental analysis : Calc. C (41.0%), H (4.5%); Found (C 41.2%), H (4.3%)

Preparation of Methyl 3-(2-(3,3-diethoxypropynyl)-3,4,5-trimethoxyphenyl)propanoate (299)



298 **299**

To a stirred mixture of the ester (**298**) (0.3g, 0.79mmol), palladium(II) acetate (8.9mg, 5mol%), copper(I) iodide (7.5mg, 5mol%), and triphenylphosphine (41mg, 0.16mmol) in diethylamine (10ml) at room temperature was added propargylaldehyde diethyl acetal (0.12g, 0.95mmol). The reaction mixture was gently refluxed for 3.5 hours and then concentrated to a brown sludge. Flash-column chromatography (20% diethyl ether / 80% petroleum ether) then provided the title compound (0.23g, 75%) as a pale brown oil.

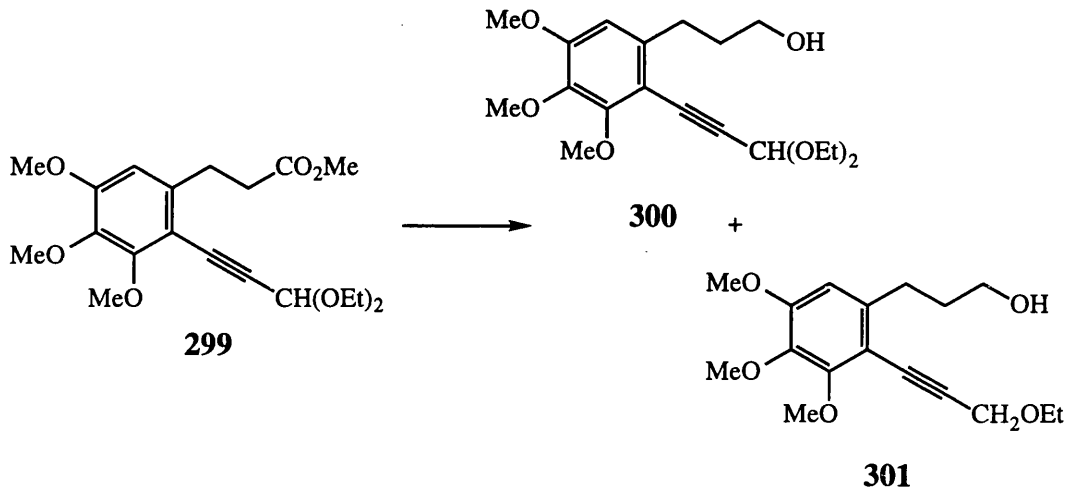
ν_{max} (film) : 2976, 2227, 1737, 1494, 1050

δ_H (270MHz, $CDCl_3$) : 6.54 (1H, s, Ar*H*), 5.53 (1H, s, ArC≡CC*H*$(OEt)_2$), 3.94, 3.85 and 3.83 (9H, 3s, ArOC*H*$_3$), 3.85-3.65 (4H, m, $CH(OCH_2CH_3)_2$), 3.04 (2H, t, 7.8Hz, ArC*H*$_2$$CH_2$), 2.65 (2H, t, 7.8Hz, $ArCH_2CH_2$), 1.27 (6H, t, 7.1Hz, $CH(OCH_2CH_3)_2$)

m/z (EI) : 380 (M^+), 349, 335

Accurate mass : $C_{20}H_{28}O_7$ (M^+) requires 380.1835; observed 380.1849

Preparation of 3-(2-(3,3-Diethoxypropynyl)-3,4,5-trimethoxyphenyl)propan-1-ol (300) and 3-(2-(3-Ethoxypropyn-1-yl)-3,4,5-trimethoxyphenyl)propan-1-ol (301)



To a stirred solution of the ester (**299**) (1.35g, 3.56mmol) in toluene (40ml) at 0°C was added dropwise DIBAL-H (1.5M in toluene, 5.9ml, 8.90mmol) to give a yellow solution. The reaction mixture was quenched 20 minutes later with ethanol (3ml) and then poured into saturated potassium sodium tartrate tetrahydrate solution (150ml). After stirring vigorously for 2 hours, the aqueous layer was extracted with diethyl ether (2x50ml). The combined organic layers were dried (magnesium sulfate), concentrated and chromatographed (60% EtOAc / 40% petroleum ether) to provide respectively the desired product (**300**) (0.75g, 59%) and the over-reduced product (**301**) (0.24g, 22%) as pale yellow oils.

3-(2-(3,3-Diethoxypropynyl)-3,4,5-trimethoxyphenyl)propan-1-ol (300) :

ν_{max} (film) : 3424 (br), 2975, 2226, 1595, 1565, 1493, 1325, 1103, 1049

δ_H (200MHz, $CDCl_3$) : 6.52 (1H, s, Ar*H*), 5.53 (1H, s, ArC≡CC*H*$(OEt)_2$), 3.85, 3.83 and 3.82 (9H, 3s, ArOC*H*$_3$), 3.83 and 3.69 (4H, 2q, 7.1Hz, CH$(OCH_2CH_3)_2$), 3.67 (2H, t, 6.6Hz, $ArCH_2CH_2CH_2OH$), 2.83 (2H, t, 7.6 Hz, $ArCH_2CH_2$), 1.90-1.83 (2H, m, $ArCH_2CH_2$), 1.26 (6H, t, 7.1Hz, $CH(OCH_2CH_3)_2$)

m/z (EI) : 352 (M^+), 307

Accurate mass : $C_{19}H_{28}O_6Na$ ($[M+Na]^+$) requires 375.1784; observed 375.1787

3-(2-(3-Ethoxypropynyl)-3,4,5-trimethoxyphenyl)propan-1-ol (301) :

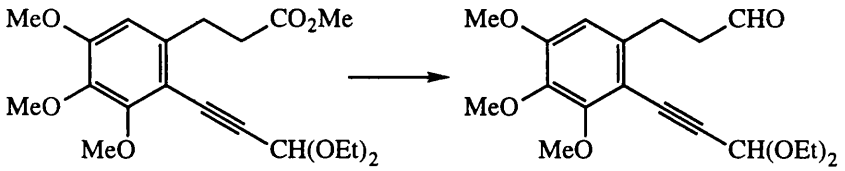
ν_{max} (film) : 3417 (br), 2936, 2224, 1595, 1493

δ_H (200MHz, $CDCl_3$) : 6.52 (1H, s, Ar*H*), 4.42 (2H, s, ArC≡C*CH*$_2$OEt), 3.94, 3.84 and 3.83 (9H, 3s, ArO*CH*$_3$), 3.71-3.61 (4H, m, CH_2CH_2OH + $CH_2OCH_2CH_3$), 2.83 (2H, t, 7.8Hz, Ar*CH*$_2$CH$_2$), 1.91-1.84 (3H, m, $ArCH_2CH_2CH_2O$*H*), 1.25 (3H, t, 7.0Hz, $CH_2OCH_2CH_3$)

m/z (EI) : 308 (M^+), 264, 219, 181

Accurate mass : $C_{17}H_{24}O_5Na$ ($[M+Na]^+$) requires 331.1521; observed 331.1525

Preparation of 3-(2-(3,3-Diethoxypropynyl)-3,4,5-trimethoxyphenyl)propanal (302)



299 **302**

To a stirred solution of the ester (**299**) (1.13g, 2.98mmol) in toluene (20ml) at -78°C was added dropwise DIBAL-H (1.5M in toluene, 2.1ml, 3.15mmol) to give a yellow solution. The reaction mixture was quenched 20 minutes later by slow addition of ethanol (3ml). When hydrogen gas evolution had ceased, the reaction mixture was allowed to warm up to room temperature and then poured into saturated potassium sodium tartrate tetrahydrate solution (100ml). After vigorously stirring for 1.5 hours, the aqueous layer was extracted with diethyl ether (2x30ml). The combined organic layers were dried

(magnesium sulfate), concentrated and chromatographed (60% diethyl ether / 40% petroleum ether) to provide the product (0.91g, 87%) as a yellow oil.

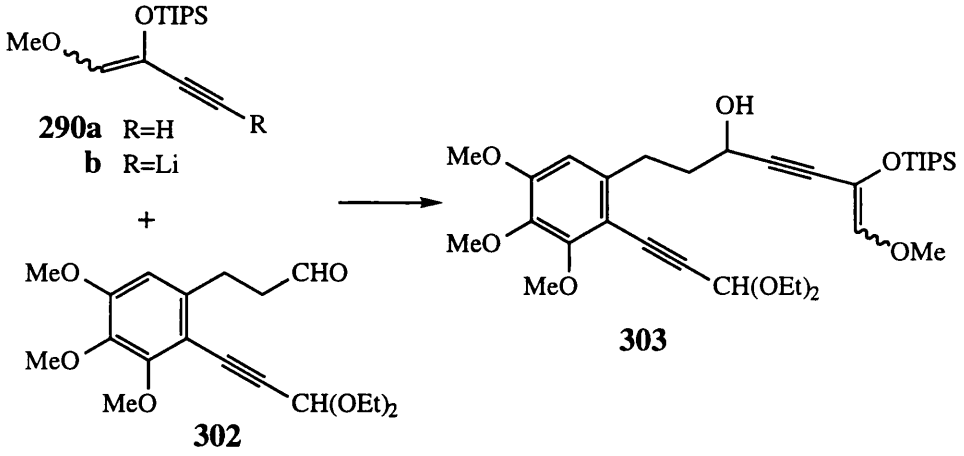
ν_{max} (film) : 2976, 2936, 2725, 2226, 1724, 1595, 1494, 1408

δ_H (200MHz, $CDCl_3$) : 9.81 (1H, d, 0.8Hz, C*H*O), 6.52 (1H, s, Ar*H*), 5.52 (1H, s, ArC≡CC*H*$(OEt)_2$), 3.93, 3.85 and 3.82 (9H, 3s, ArOC*H*$_3$), 3.79 and 3.68 (4H, 2q, 7.1Hz, $CH(OCH_2CH_3)_2$), 2.99 (2H, t, 7.0Hz, ArCH_2CH_2), 2.84 (2H, dt, 7.0Hz, 0.8Hz, $ArCH_2CH_2$), 1.25 (6H, t, 7.1Hz, $CH(OCH_2CH_3)_2$)

m/z (EI) : 350 (M^+), 305, 277

Accurate mass : $C_{19}H_{26}O_6Na$ ($[M+Na]^+$) requires 373.1627; observed 373.1623

Preparation of 1-(2-(3,3-Diethoxypropynyl)-3,4,5-trimethoxyphenyl)-6-tris(1-methylethyl)siloxy-7-methoxyhept-6-en-4-yn-3-ol (303)



To a stirred solution of the acetylide (**290b**) (0.95mmol) in THF (5ml) at -78°C was added dropwise a solution of the aldehyde (**302**) (0.3g, 0.86mmol) in THF (3ml). Having stirred at -78°C for 20 minutes, the reaction mixture was quenched with saturated ammonium chloride solution (0.5ml) and allowed to warm up to room temperature. It was then taken up in diethyl ether (20ml) and washed with water (2x15ml). The organic layer

was dried (magnesium sulfate), concentrated and chromatographed (60% diethyl ether / 40% petroleum ether) to give the product as a pale yellow oil (0.43g, 83%).

ν_{max} (film) : 3444 (br), 2941, 2886, 2041, 2227, 1653, 1595

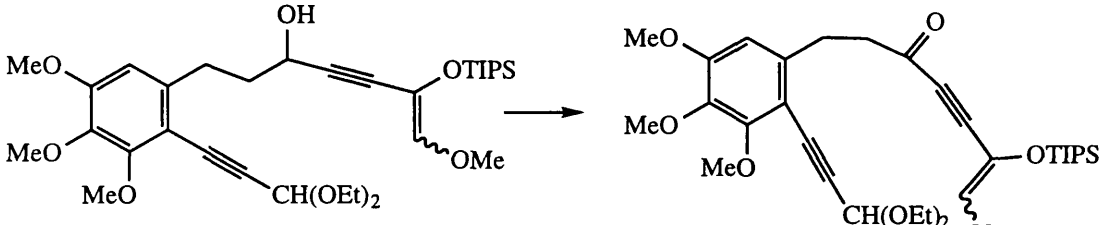
δ_H (200MHz, $CDCl_3$) : 6.52 (1H, s, Ar*H*), 5.84 (1H, s, C*H*OMe), 5.52 (1H, s, ArC≡CC*H*$(OEt)_2$), 4.52-4.43 (1H, m, $ArCH_2CH_2CH$), 3.94, 3.85 and 3.83 (9H, 3s, $ArOCH_3$), 3.62 (3H, s, $CHOCH_3$), 3.87-3.58 (4H, m, $CH(OCH_2CH_3)_2$), 2.90-2.75 (2H, m, $ArCH_2CH_2$), 2.60 (1H, d, 6.6Hz, $CH_2CH_2CH(OH)$), 2.1-1.8 (2H, m, $ArCH_2CH_2$), 1.26 (6H, t, 7.0Hz, $CH(OCH_2CH_3)_2$), 1.20-1.07 (21H, m, $Si(CH(CH_3)_2)_3$)

m/z (FAB) : 627 ($[M+Na]^+$), 587, 575, 559

Accurate mass : $C_{33}H_{52}O_8SiNa$ ($[M+Na]^+$) requires 627.3329; observed 627.3325

Elemental Analysis : Calc. C (65.5%), H (8.6%); Found C (65.0%), H (8.4%)

Preparation of 1-(2-(3,3-Diethoxypropynyl)-3,4,5-trimethoxyphenyl)-6-tris(1-methylethyl)siloxy-7-methoxyhept-6-en-4-yn-3-one (305)



303 **305**

A mixture of the alcohol (**303**) (0.213g, 0.35mmol) and manganese(IV) oxide (0.61g, 7mmol) in dichloromethane (5ml) was stirred overnight at room temperature The reaction mixture was then filtered through a celite pad and the cake of manganese(IV) oxide was washed with warm dichloromethane (40ml). The filtrate was concentrated and

chromatographed (50% diethyl ether / 50% petroleum ether) to recover the starting material (19mg, 9%) and give the title compound as a yellow oil (0.17g, 79%).

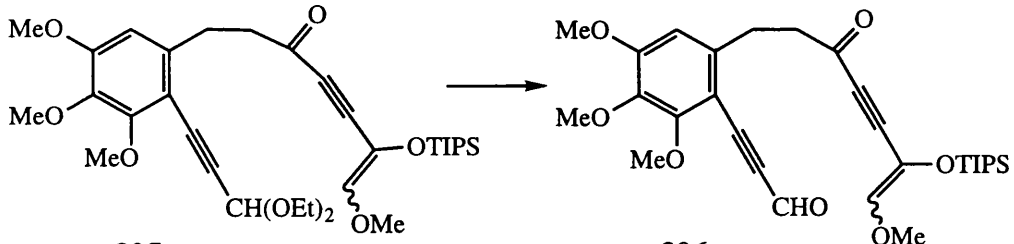
ν_{max} (film) : 2941, 2226, 2166, 1667, 1626, 1595

δ_H (200MHz, $CDCl_3$) : 6.65 (1H, s, Ar*H*), 6.21 (1H, s, C*H*OMe), 5.53 (1H, s, ArC≡CC*H*$(OEt)_2$), 3.93, 3.83 and 3.82 (9H, 3s, ArOC*H*$_3$), 3.74 (3H, s, CHOC*H*$_3$), 3.85-3.66 (4H, m, CH$(OCH_2CH_3)_2$), 3.05 (2H, t, 6.6Hz, ArCH_2CH_2), 2.88 (2H, t, 6.6Hz, ArCH_2CH_2), 1.25 (6H, t, 7.0Hz, CH$(OCH_2CH_3)_2$), 1.20-1.05 (21H, m, Si$(CH(CH_3)_2)_3$)

m/z (FAB) : 625 ($[M+Na]^+$), 597, 557

Accurate mass : $C_{33}H_{50}O_8SiNa$ ($[M+Na]^+$) requires 625.3173; observed 625.3176

Preparation of 1-(2-(3-Oxopropynyl)-3,4,5-trimethoxyphenyl)-6-tris(1-methylethyl)siloxy-7-methoxyhept-6-en-4-yn-3-one (306)



305 **306**

A mixture of the ketone (**305**) (0.51g, 0.84mmol) and amberlyst 15 ion exchange resin (Aldrich, 1.0g) was stirred in acetone (10ml) at room temperature for 45 minutes and then filtered. The filtrate was diluted with diethyl ether (40ml) and washed with water (3x25ml). The organic layer was then dried (magnesium sulfate), concentrated and chromatographed (50% diethyl ether / 50% petroleum ether) to give the product (0.21g, 48%) as a yellow oil, which turned rapidly to brown at room temperature and hence was used immediately.

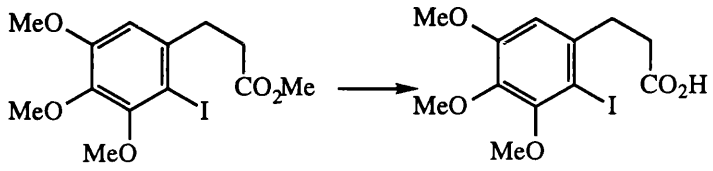
ν_{max} (film) : 2943, 2867, 2176, 1656, 1652, 1622, 1591

δ_H (400MHz, $CDCl_3$) : 9.47 (1H, s, C*H*O), 6.61 (1H, s, Ar*H*), 6.26 (1H, s, C*H*OMe), 4.01, 3.90 and 3.84 (9H, 3s, ArOC*H*$_3$), 3.77 (3H, s, CHOC*H*$_3$), 3.12 (2H, t, 7.3Hz, ArCH$_2$C*H*$_2$), 2.91 (2H, t, 7.3Hz, ArC*H*$_2$CH$_2$), 1.11 (18H, s, Si(CH(C*H*$_3$)$_2$)$_3$), 1.09 (3H, s, Si(C*H*(CH$_3$)$_2$)$_3$)

m/z (FAB) : 551 ([M+Na]$^+$), 485

Accurate mass : $C_{29}H_{40}O_7SiNa$ ([M+Na]$^+$) requires 551.2441; observed 551.2445

Preparation of 3-(2-Iodo-3,4,5-trimethoxyphenyl)propanoic acid (337)



298 **337**

Methyl 3-(2-iodo-3,4,5-trimethoxy)phenylpropionate (**298**) (1.936g, 5.09mmol) was refluxed with potassium hydroxide (0.43g, 7.65mmol) in methanol (20ml) for 1 hour. The solvent was removed and the residue dissolved in water. After acidifying to pH3.5, the mixture was extracted with *tert*-butyl methyl ether (3x20ml). The combined organic layers were dried (magnesium sulfate) and concentrated to afford the title compound (1.742g, 94%) as a white solid.

m.p. 118-121°C

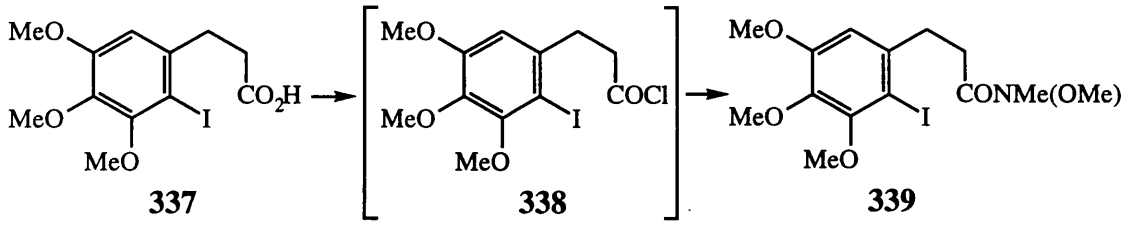
ν_{max} (film) : 2937, 1798, 1481, 1389, 1105

δ_H (270MHz, $CDCl_3$) : 6.70 (1H, s, Ar*H*), 3.87, 3.85 and 3.84 (9H, 3s, ArOC*H*$_3$), 3.06 (2H, t, 7.6Hz, ArC*H*$_2$CH$_2$), 2.68 (2H, t, 7.6Hz, ArCH$_2$C*H*$_2$)

m/z (EI) : 366 (M$^+$), 307, 240

Elemental analysis : Calc. (C 39.3%), H (4.1%); Found C (39.5%), H (4.1%)

Preparation of *N*-Methyl-*N*-methoxy-3-(2-iodo-3,4,5-trimethoxyphenyl)propanamide (339)



3-(2-Iodo-3,4,5-trimethoxyphenyl)propanoic acid (**337**) (2.604g, 7.11mmol) was dissolved in benzene (50ml) with slight warming and stirred at 0°C. Oxalyl chloride (0.139g, 7.82mmol) and a drop of DMF were then added successively. The mixture was concentrated when carbon monoxide evolution had ceased. In order to remove the residual DMF, and benzene (10ml) was added to the residue and the mixture was concentrated again . The infrared spectrum of the residue showed a prominent absorbance at 1790cm^{-1} and indicated the absence of acid stretching signal. The acid chloride (**338**) thus obtained was dissolved in ethanol-free chloroform (20ml), which was prepared by washing the commercial chloroform with water twice, drying (magnesium sulfate) overnight and finally distilling over molecular sieves just before the reaction. *N,O*-Dimethylhydroxylamine hydrogen chloride salt (0.782g, 7.82mmol) was stirred in the acid chloride solution at 0°C and pyridine (1.32g, 15.64mmol) was added with evolution of white fumes. The reaction mixture was then stirred at room temperature for 1 hour. After concentration, the residue was partitioned between 1:1 / diethyl ether:dichloromethane and brine (50ml each). The organic layer was dried (sodium sulfate) and concentrated. The residue was chromatographed with gradient elution (50% to 100% diethyl ether / petroleum ether) giving the title compound (1.98g, 68%) as a colourless solid.

m.p. 66-69°C

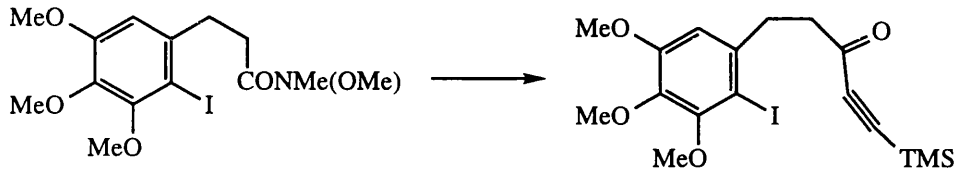
ν_{max} (film) : 1650, 1562, 1480

δ_H (270MHz, $CDCl_3$) : 6.73 (1H, s, Ar*H*), 3.86, 3.84 and 3.83 (9H, 3s, ArOC*H*$_3$), 3.63 (3H, s, CONOC*H*$_3$), 3.18 (3H, s, CONC*H*$_3$), 3.06 (2H, t, 7.3Hz, ArC*H*$_2$CH$_2$), 2.71 (2H, t, 7.3Hz, C*H*$_2$CON)

m/z (EI) : 409 (M^+), 282

Accurate mass : $C_{14}H_{21}O_5IN$ ($[MH]^+$) requires 410.0465; observed 410.0460

Preparation of 1-Trimethylsilyl-5-(2-iodo-3,4,5-trimethoxyphenyl)pent-1-yn-3-one (340)



339 **340**

Trimethylsilylacetylene (76mg, 0.11ml, 2.0eq) was stirred in THF (1ml) at 0°C while *n*-butyllithium (2.5M solution in hexanes, 0.23ml, 0.72mmol) was added dropwise and the resulting mixture was stirred at 0°C for 30 minutes, and then at room temperature for 15 minutes. To a stirred solution of *N*-methyl-*N*-methoxy-3-(2-iodo-3,4,5-trimethoxy)phenylpropanamide (**339**) (0.20g, 0.48mmol) in THF (2ml) at 0°C was added dropwise the lithiated trimethylsilylacetylene solution and the mixture was stirred at room temperature for 45 minutes. The reaction mixture was then poured into ice-cooled 5% HCl / ethanol (10ml). 1:1/ Diethyl ether:dichloromethane (20ml) was added and the resulting solution was washed with brine (2x15ml). The organic layer was dried (magnesium sulfate), concentrated and chromatographed (25% diethyl ether / 75% petroleum ether) to give the title compound (0.15g, 69%) as a pale yellow liquid.

ν_{max} (film) : 2150, 1676, 1583, 1560, 1481

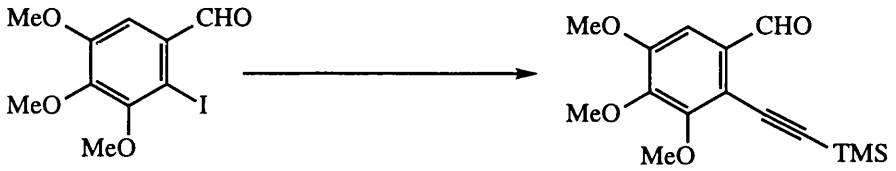
δ_H (270MHz, $CDCl_3$) : 6.67 (1H, s, Ar*H*), 3.86, 3.84 and 3.83 (9H, 3s, ArOC*H*$_3$), 3.08 (2H, t, 7.6Hz, ArC*H*$_2$CH$_2$), 2.88 (2H, t, 7.6Hz, ArCH$_2$C*H*$_2$), 0.24 (9H, s, Si(C*H*$_3$)$_3$)

δ_C (60MHz, $CDCl_3$) : 186.07, 153.58, 153.13, 140.55, 138.45, 109.12, 101.74, 98.38, 87.67, 60.87, 60.66, 56.08, 45.42, 34.96, -0.80

m/z (EI) : 446 (M^+); 319

Accurate mass : $C_{17}H_{23}O_4ISi$ (M^+) requires 446.0410; observed 446.0419

Preparation of 2-(Trimethylsilylethynyl)-3,4,5-trimethoxybenzaldehyde (342)



169 **342**

A mixture of 2-iodo-3,4,5-trimethoxybenzaldehyde (**169**) (0.15g, 0.41mmol), palladium(II) acetate (4.6mg, 5mol%), triphenylphosphine (24mg, 20mol%), copper(I) iodide (57mg, 5mol%) and trimethylsilylacetylene (89mg, 0.90mmol) in diethylamine (4ml) was gently refluxed for 1.5 hours and then cooled to room temperature. After filtering and the filtrate concentrating down to a brown oil, the reaction mixture was extracted with 1:9 / EtOAc:petroleum ether (ca. 5ml). The extracted material was then chromatographed (same solvent as extraction) to provide the product (0.22g, 84%) as crimson needles.

m.p. 70-71°C

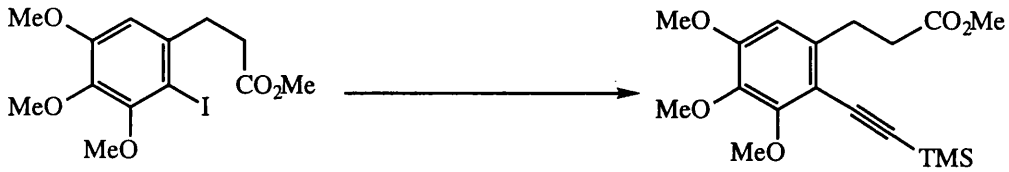
ν_{max} (film) : 2954, 2147, 1691, 1582, 849

δ_H (270MHz, $CDCl_3$) : 10.42 (1H, s, ArC*H*O), 7.23 (1H, s, Ar*H*), 3.98, 3.96 and 3.92 (9H, 3s, ArOC*H*$_3$), 0.28 (9H, s, Si(C*H*$_3$)$_3$)

m/z (EI) : 292 (M^+); 277, 219

Accurate mass : $C_{15}H_{20}O_4Si$ ($[MH]^+$) requires 293.1209; observed 293.1204

Preparation of Methyl 3-(2-(trimethylsilylethynyl)-3,4,5-trimethoxyphenyl)propanoate (343)



298 **343**

A mixture of methyl 3-(2-iodo-3,4,5-trimethoxyphenyl)propionate (**298**) (2.00g, 5.26mmol), palladium(II) acetate (30mg, 2.5mol%), triphenylphosphine (0.14g, 10mol%), copper(I) iodide (25mg, 2.5mol%) and trimethylsilylacetylene (4.5g, 46.3mmol) in a mixture of 1:1 / triethylamine:diethylamine (10ml) was gently refluxed for 3.5 hours and then cooled down to room temperature. The resulting brown suspension was filtered and the filtrate adsorbed on silica gel. Flash column chromatography (1:3 / diethyl ether:petroleum ether) then provided the title compound (1.69g, 92%) as a pale yellow oil.

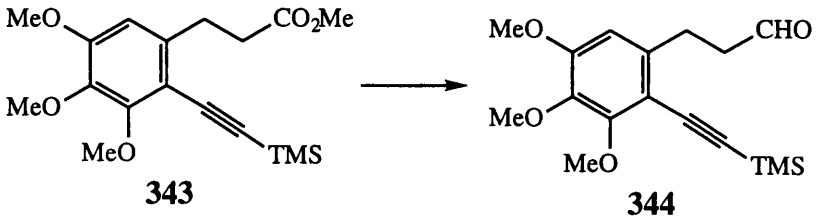
ν_{max} (film) : 2956, 2149, 1738, 1129, 843

δ_H (270MHz, $CDCl_3$) : 6.53 (1H, s, Ar*H*), 3.95, 3.84 and 3.82 (9H, 3s, ArOC*H*$_3$), 3.67 (3H, s, CO2C*H*$_3$), 3.02 (2H, t, 7.4Hz, ArC*H*$_2$CH$_2$), 2.65 (2H, t, 7.4Hz, ArCH$_2$C*H*$_2$), 0.25 (9H, s, Si(C*H*$_3$)$_3$)

m/z (EI) : 350 (M^+); 277

Elemental Analysis : Calc. C (61.7%), H (7.4%); Found (C 61.6%), H (7.8%)

Preparation of 3-(2-(Trimethylsilylethynyl)-3,4,5-trimethoxyphenyl)propanal (344)



343 **344**

A solution of the ester (**343**) (0.30g, 0.86mmol) in toluene (10ml) was stirred at -78°C and DIBAL-H (1.5M in toluene, 0.63ml, 0.95mmol) was added dropwise. Methanol (0.5ml) was slowly added 30 minutes later and the reaction mixture was allowed to warm up to room temperature. It was then poured into 1M HCl (20ml) and extracted with diethyl ether (3x10ml). The combined organic layers were dried (magnesium sulfate), concentrated and chromatographed (30% diethyl ether / 70% petroleum ether) to afford the title compound as a colourless oil (0.19g, 70%), which solidified at room temperature.

m.p. 37-38°C

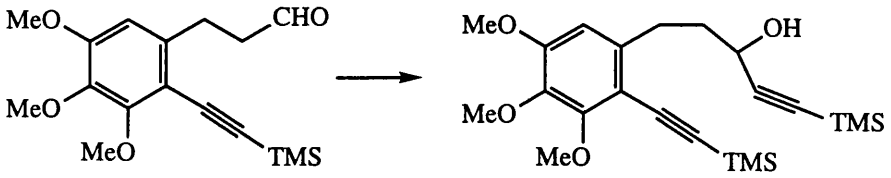
ν_{max} (film) : 2959, 2150, 1725, 1594, 1493, 1129, 843

δ_H (270MHz, $CDCl_3$) : 9.82 (1H, s, C*H*O), 6.51 (1H, s, Ar*H*), 3.94, 3.84 and 3.82 (9H, 3s, ArOC*H*$_3$), 2.98 (2H, t, 7.2Hz, ArC*H*$_2$CH$_2$), 2.80 (2H, t, 7.2Hz, ArCH$_2$C*H*$_2$), 0.23 (9H, s, Si(C*H*$_3$)$_3$)

m/z (EI) : 321 (M^+); 305, 290, 277, 205

Accurate mass : $C_{17}H_{25}O_4Si$ (M^+) requires 321.1522; observed 321.1526

Preparation of 1-Trimethylsilyl-5-(2-(trimethylsilylethynyl)-3,4,5-trimethoxyphenyl)pent-1-yn-3-ol (345)



344 **345**

A solution of the aldehyde (**344**) (92mg, 0.29mmol) in THF (2ml) was stirred at 0°C and a solution of lithium acetylide in THF (3ml), which was prepared from trimethylsilylacetylene (34mg, 0.34mmol) and *n*-BuLi (2.3M in hexanes, 0.13ml, 0.3mmol) as previously described, was added dropwise. Saturated ammonium chloride solution (0.5ml) was added 15 minutes later. The mixture was then taken up in diethyl ether (20ml) and washed with water (3x10ml). The organic layer was then dried (magnesium sulfate), concentrated and chromatographed (50% diethyl ether / 50% petroleum ether) to afford the product as a colourless oil (63mg, 52%).

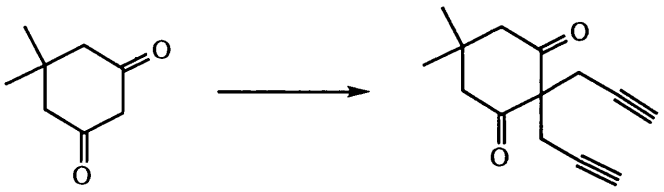
ν_{max} (film) : 3476 (br), 2958, 2151, 1594, 1493

δ_H (270MHz, $CDCl_3$) : 6.51 (1H, s, Ar*H*), 4.31 (1H, m, $CH_2CH(OH)$), 3.94, 3.84 and 3.82 (9H, 3s, $ArOCH_3$), 2.79-2.95 (2H, m, $ArCH_2CH_2$), 2.09-1.91 (2H, m, $ArCH_2CH_2$), 0.25 and 0.16 (18H, 2s, $2xSi(CH_3)_3$)

m/z (FAB) : 418 (M^+); 403, 277

Accurate mass : $C_{22}H_{34}O_4Si_2$ (M^+) requires 418.1996; observed 418.1991

Preparation of 2,2-Di(prop-2-ynyl) dimedone[103(a)] (347)



347

A suspension of propargyl chloride (0.32g, 4.28mmol), dimedone (0.3g, 2.14mmol) and anhydrous potassium carbonate (0.42, 4.28mmol) was gently refluxed in acetone (30ml) for 20 hours and then cooled down to room temperature. The reaction mixture was filtered and the filtrate concentrated. Flash column chromatography (30% diethyl ether / petroleum ether) then provided the title compound as a white solid (0.21g, 44%).

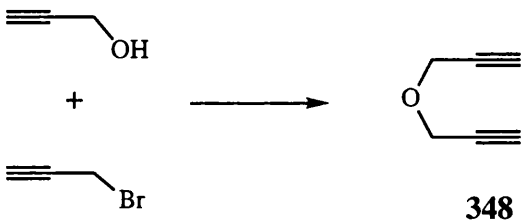
m.p. 82-4°C (lit. 83-4°C)

ν_{max} (film) : 3285, 2958, 1732, 1700

δ_H (270MHz, $CDCl_3$) : 2.69 (4H, s, 2xMe_2CCH_2), 2.68 (4H, d, 2.7Hz, 2x$CH_2C{\equiv}CH$), 2.07 (2H, t, 2.7Hz, $C{\equiv}CH$), 1.06 (6H, s, 2xCH_3)

m/z (EI) : 276 (M^+); 177, 133

Preparation of 3,3'-Oxybis-1-propyne[103(b)] (348)



348

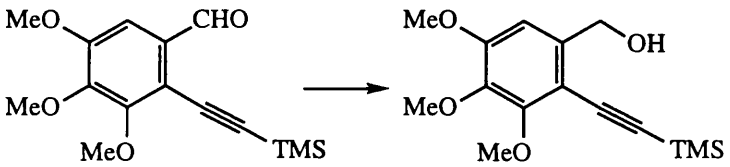
To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 0.42g, 11.7mmol) DMF (10ml) at 0°C was added dropwise propargyl alcohol (0.6g, 10.7mmol). The resulting mixture was stirred at room temperature for 30 minutes before propargyl

bromide (80% solution in toluene, 1.62g, 11.7mmol) was added dropwise. Having stirred overnight at room temperature, the reaction mixture was diluted with diethyl ether (50ml) and then washed with water (3x30ml). The ethereal layer was then dried (magnesium sulfate) and concentrated (600 mmHg). The residue was distilled (20 mmHg, ambient temperature, collected in an ice-cooled bath) to provide the title compound as a colourless liquid (0.2g, 21%).

δ_H (270MHz, $CDCl_3$) : 4.22 (4H, d, 2.7Hz, 2xCH_2C≡CH), 2.40 (2H, 2.7Hz, 2xCH_2C≡C*H*)

m/z (EI) : 93 ($[M-H]^+$), 73, 55

Preparation of 2-Trimethylsilylethynyl-3,4,5-trimethoxybenzenemethanol[115] **(350)**



342 **350**

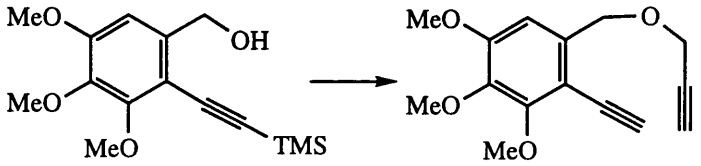
2-(Trimethylsilylethynyl)-3,4,5-trimethoxybenzaldehyde (**342**) (0.18g, 0.70mmol) was dissolved in diethyl ether (2ml) and added dropwise to a stirred suspension of lithium aluminium hydride (0.027g, 0.70mmol) in diethyl ether (5ml) at 0°C. When the addition was complete, the temperature was slowly raised to gentle reflux. The mixture was then cooled down to room temperature and slowly added to 2M HCl (20ml). The resulting mixture was extracted with diethyl ether (20ml), and the organic layer was washed with water (2x20ml) and dried (magnesium sulfate). After concentration, the title compound (0.187g, 91%) was given as a pale yellow oil. This material was used without further purification.

ν_{max} (film) : 3412 (br), 2925, 1597, 1463, 1265, 1126

δ_H (270MHz, $CDCl_3$) : 6.76 (1H, s, Ar*H*), 4.74 (2H, d, 4.4Hz, CH_2OH), 3.97, 3.89 and 3.85 (9H, 3s, $ArOCH_3$), 2.21 (1H, t, 4.4Hz, CH_2OH), 0.27 (9H, s, $Si(CH_3)_3$)

m/z (FAB) : 294 (M^+), 277

Preparation of 2-Ethynyl-3,4,5-trimethoxybenzenemethyl prop-2-ynyl ether (351)



350 **351**

A solution of 2-(trimethylsilylethynyl)-3,4,5-trimethoxybenzenemethanol (**350**) (0.116g, 0.40mmol) in DMF (2ml) was added dropwise to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 17mg, 0.44mmol) in DMF (2ml) at 0°C. The mixture was allowed to warm to room temperature after the addition was complete. Propargyl bromide (80% solution in toluene, 0.064g, 0.44mmol) was then added and the mixture was stirred at room temperature for 3 hours. The reaction mixture was then partitioned between diethyl ether (20ml) and water (20ml) and the ethereal layer was further washed with water (2x20ml) and dried ($MgSO_4$). After concentration, the residue was chromatographed (1:9 / EtOAc:petroleum ether) to give the title compound as a pale yellow oil (0.071g, 69%).

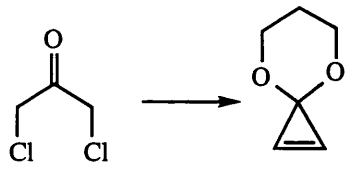
ν_{max} (film) : 3282, 2940, 2130, 1595, 1491, 1126

δ_H (270MHz, $CDCl_3$) : 6.81 (1H, s, Ar*H*), 4.71 (2H, s, $ArCH_2O$), 4.25 (2H, d, 2.5Hz, $OCH_2C{\equiv}CH$), 3.96, 3.88 and 3.85 (9H, 3s, $ArOCH_3$), 3.42 (1H, s, $ArC{\equiv}CH$), 2.47 (1H, t, 2.5Hz, $OCH_2C{\equiv}CH$)

m/z (EI) : 260 (M^+), 205

Accurate mass : $C_{15}H_{16}O_4$ (M^+) requires 260.1049; observed 260.1050

Preparation of Cyclopropenone 1,3-propanediol ketal[104,105,106] (80)



80

1,3-Dichloroacetone (10g, 78.7mmol) and trimethylene glycol (6.58g, 86.6mmol) in benzene (50ml) were refluxed in a Dean-Stark apparatus for 4 hours. After cooling down, the reaction mixture was concentrated to a dark brown solid, which was dissolved in dichloromethane (100ml) and washed successively with saturated sodium bicarbonate solution (2x50ml) and water (50ml). Upon concentration, 1,3-dichloroacetone 1,3-propanediol ketal was given as a light brown solid (14.1g, 97%), which was used immediately without further purification.

ν_{max} (film) : 2970, 2874, 1488, 1430, 1243, 1212, 1129, 1108, 1028

δ_H (270MHz, $CDCl_3$) : 3.97 (4H, t, 5.6Hz, OCH_2CH2CH_2O), 3.80 (4H, s, $2xCH_2Cl$), 1.80 (2H, q, 5.6Hz, $OCH_2CH_2CH_2O$)

Liquid ammonia (~100ml) was condensed in a 3-necked flask cooled to -78°C containing stirred sodamide (95% assay from Aldrich, 7.48g, 0.18mol). A solution of 1,3-dichloroacetone 1,3-propanediol ketal (9.66g, 52.2mmol) in diethyl ether (70ml) was added dropwise over about 30 minutes. When the addition was complete, the reaction mixture was stirred at -50°C for 3 hours and then cooled down to -78°C. Solid ammonium chloride (4 g) was then added and the reaction mixture was diluted with diethyl ether (50ml). The cooling bath was removed and ammonia was allowed to evaporated off overnight. The resulting mixture was filtered and the filtrate was concentrated and distilled

(0.5 mmHg, 82-84°C) to give the product as a colourless liquid (2.86g, 49%), which readily turned yellow even refrigerated.

ν_{max} (film) : 2984, 2869, 1605, 1432

δ_H (270MHz, $CDCl_3$) : 7.85 (2H, s, C*H*C*H*), 4.02 (4H, t, 5.4Hz, OC*H*$_2$CH2C*H*$_2$O, 1.85 (2H, q, 5.4Hz, OCH$_2$C*H*$_2$CH$_2$O)

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