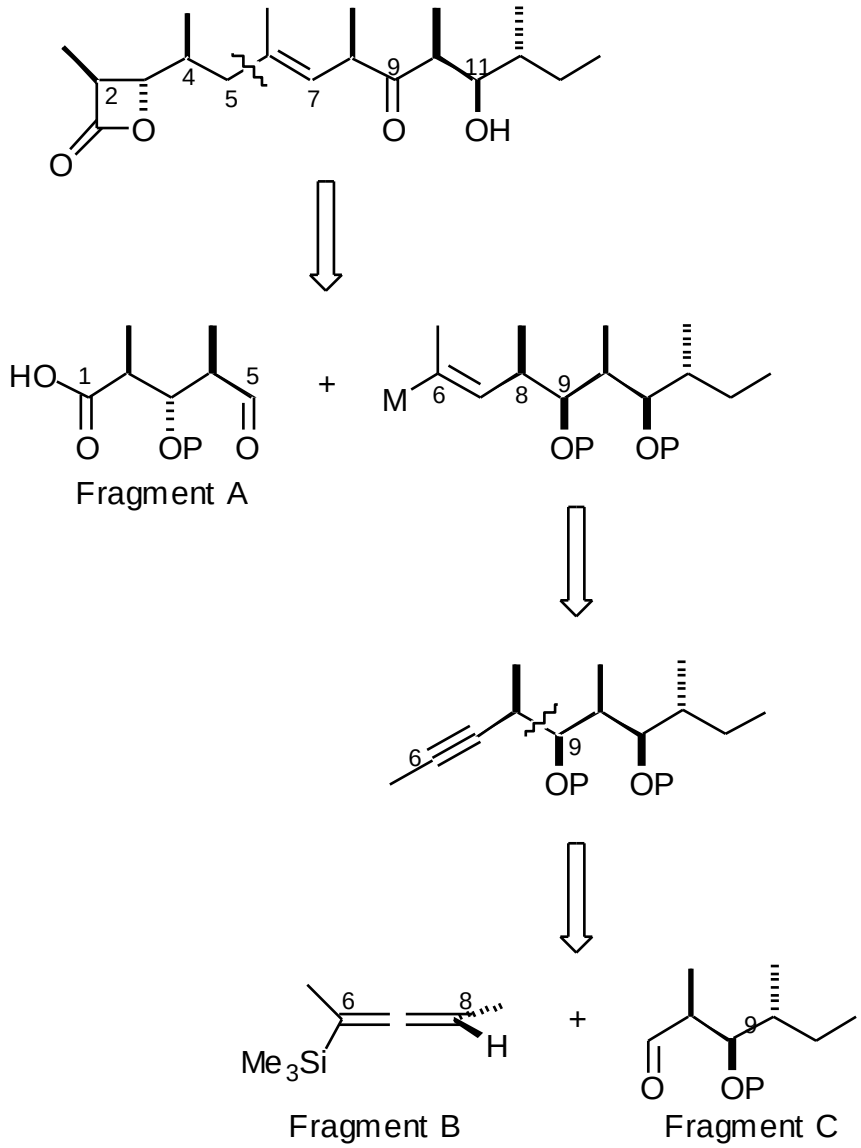
Chapter 2
Previous Work

2.1 Retrosynthetic Analysis

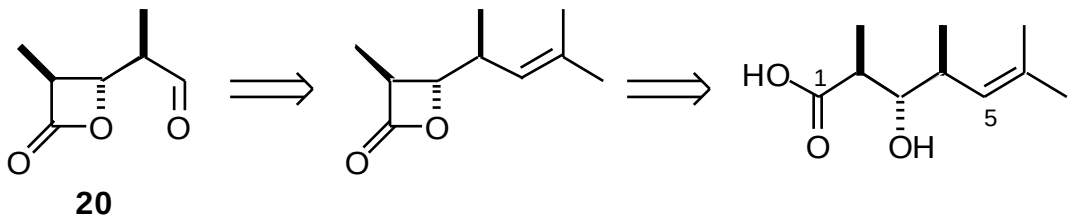
Work has been in progress in the Fleming group on and off for almost two decades towards the synthesis of ebelactone-a using silicon-controlled chemistry.[108] Our retrosynthetic analysis is shown in scheme 2.1. The target molecule is taken back to three small fragments A, B and C, each of which is synthesised separately in enantiopure form and then joined together, the convergent nature of the synthesis leading, we hope, to high efficiency. Fragments A, B and C have all been synthesised already, and fragments B and C have been successfully combined. An unsuccessful attempt was made by Williams to couple this with fragment A. This project concerns work towards solving this problem and completing a total synthesis of ebelactone-a.

2.2 Synthesis of the Fragments

Throughout the work, this basic retrosynthetic strategy has not changed, so the work relating to each of fragments A, B and C will be described separately, followed by details of the couplings of B to C, of the coupled product of B and C to A, and finally of the transformations necessary after joining A, B and C.



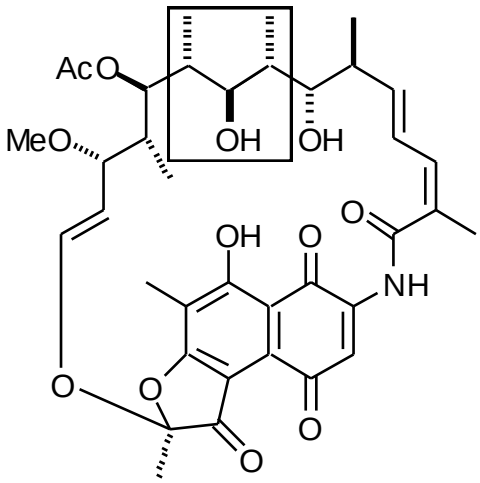
Scheme 2.1



Scheme 2.2

2.2.1 Fragment A

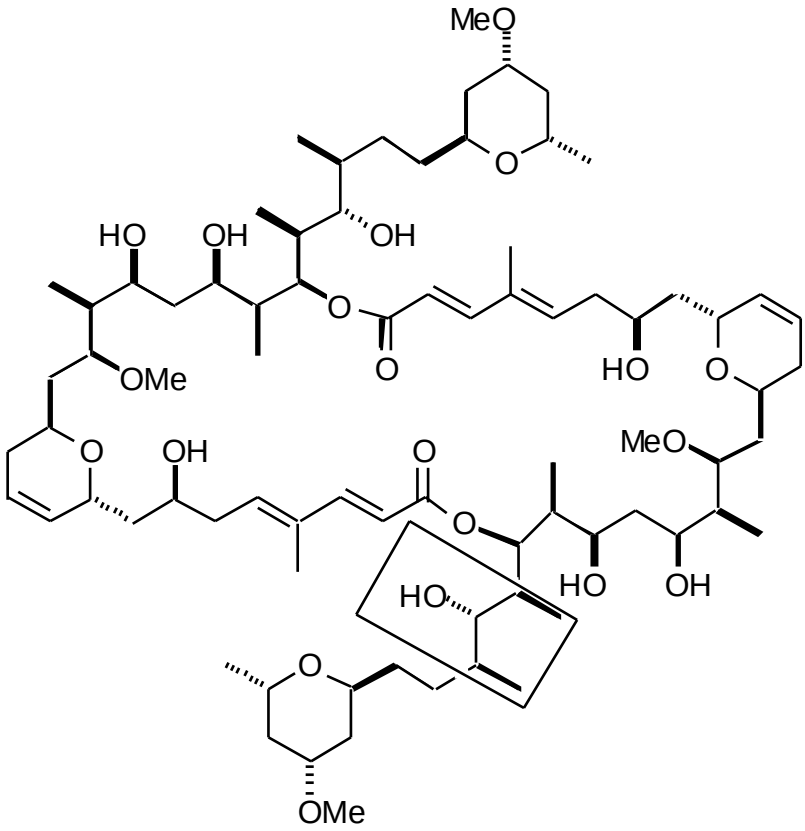
Fragment A **20**, whether viewed with the lactone open or closed and with the aldehyde functionality explicit or masked as an alkene, contains carbon atoms 1 to 5 of ebelactone-a (scheme 2.2). The *anti-anti* relationship of the three stereogenic centres is a common feature of many natural products, such as rifamycin (figure 2.1a),[109] calyculin A,[110] swinholide A,[111] muamvatin[112] and aplyronine A (figure 2.1b).[113] It is generally regarded as the most difficult of all the stereotriads to construct,[114] but there are in fact many methods in the literature of setting up this system.[115]



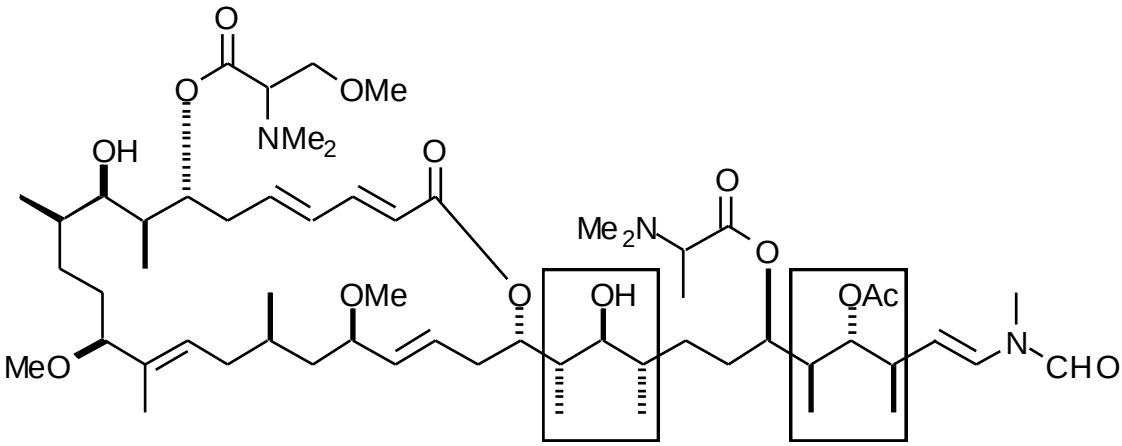
Rifamycin S

Figure 2.1a

In the early 1980's, Parker[116] began with the commercially available and (then) cheap diethyl glutaconate **21** and treated this with a silylcuprating reagent to give the β-silyl diethyl ester **22** (scheme 2.3). The idea was that on alkylation twice (with LDA followed by methyl iodide) the silyl group would direct the in-coming methyl groups *anti* to itself on both sides, in accordance with the known behaviour of β-silyl enolates (see chapter 1), and that this would establish the *anti-anti* arrangement required. As a vinylogous β-dicarbonyl compound, ester



Swinholide A

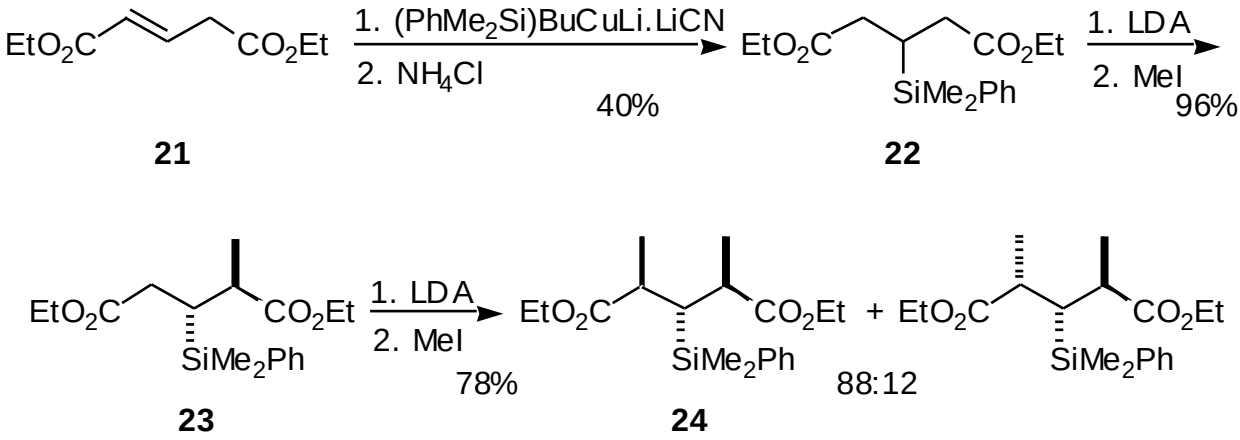


Aplyronine A

Figure 2.1b

21 is significantly acidic, so it was not surprising that in the silylcupration with dimethyl(phenyl)silylcuprate a large proportion of starting material was routinely recovered

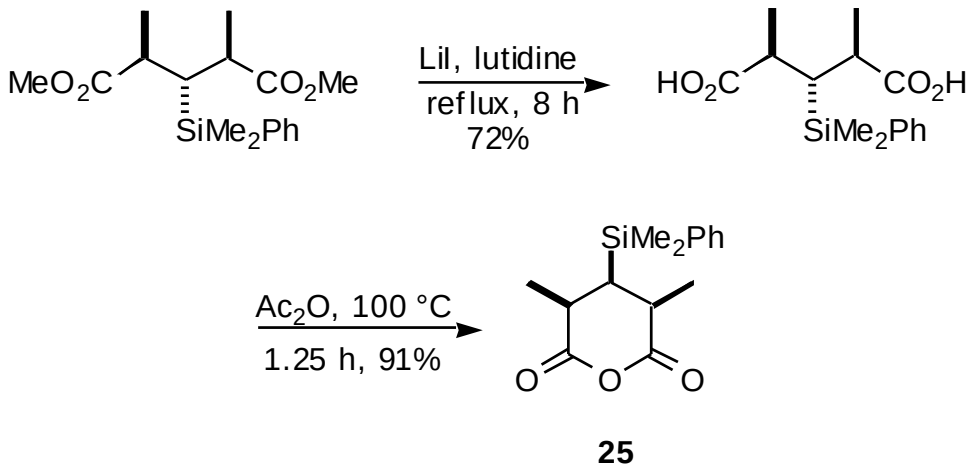
(due to formation of the enolate, which deprotonates the starting material, leading to a maximum yield of 50%). However, some of the desired product was obtained, and deprotonation was found to be slightly less of a problem when the mixed butylsilylcuprate was employed—and using this also reduced the amount of dimethyl(phenyl)silyllithium wasted. However, it did mean that the enolate formed from the conjugate addition had to be protonated, the starting material separated by distillation and recycled, and the enolate of the unmethylated diester formed in a separate stage. The yield of the silylcupration step taking into account the recovered starting material was 75%.



Scheme 2.3

The first methylation proceeded with high diasterioselectivity and in high yield to give diester **23**, but the second achieved only 86% diastereoisomeric excess, took place in lower yield and required high dilution, a large excess of methyl iodide and a long reaction time to produce diester **24**. Bazin[117] tried transesterifying diethyl ester **22** to give the dimethyl ester, and this took place efficiently (77% yield), but the methylations of this were no better. (Advantages of methyl esters over ethyl esters for this work are the range of conditions under which hydrolysis can take place and the greater simplicity of the NMR signals for the purposes of estimating the diastereoisomeric excess.) Nevertheless, since the *anti-anti* triad generally does present difficulties, and as this use of the directing properties of silicon seemed quite neat, it was thought worth proceeding with this general route.

It was necessary to move from the *meso* system of **24** to the homochiral system of fragment A; in other words, to differentiate the two ends of the molecule. In principle, there were many possible methods.[118] Enzymatic methods were available, such as monohydrolysis of the diester to give an ester-acid;[119] reduction to the diol, diester formation and monohydrolysis to the ester-alcohol;[120] or complete hydrolysis to the diacid followed by mono-esterification to give the ester-acid.[121] However, although the possibility of using an enzyme system was explored,[122] further effort was not invested in these possibilities at that time, since it was felt that a great deal of work would have to be done to find an enzyme for which the diester was a substrate, and also that the low water solubility (due to the large hydrophobic silyl group) would lead to difficulties. This left either reducing the diester to the diol and then mono-protecting with a chiral protecting group;[123] or else forming the cyclic anhydride and selectively opening with a chiral amine,[124] a chiral alcohol (or alcohol with a chiral catalyst),[125] or a chiral reducing agent.[126] These two basic approaches were briefly explored in work towards fragment A.

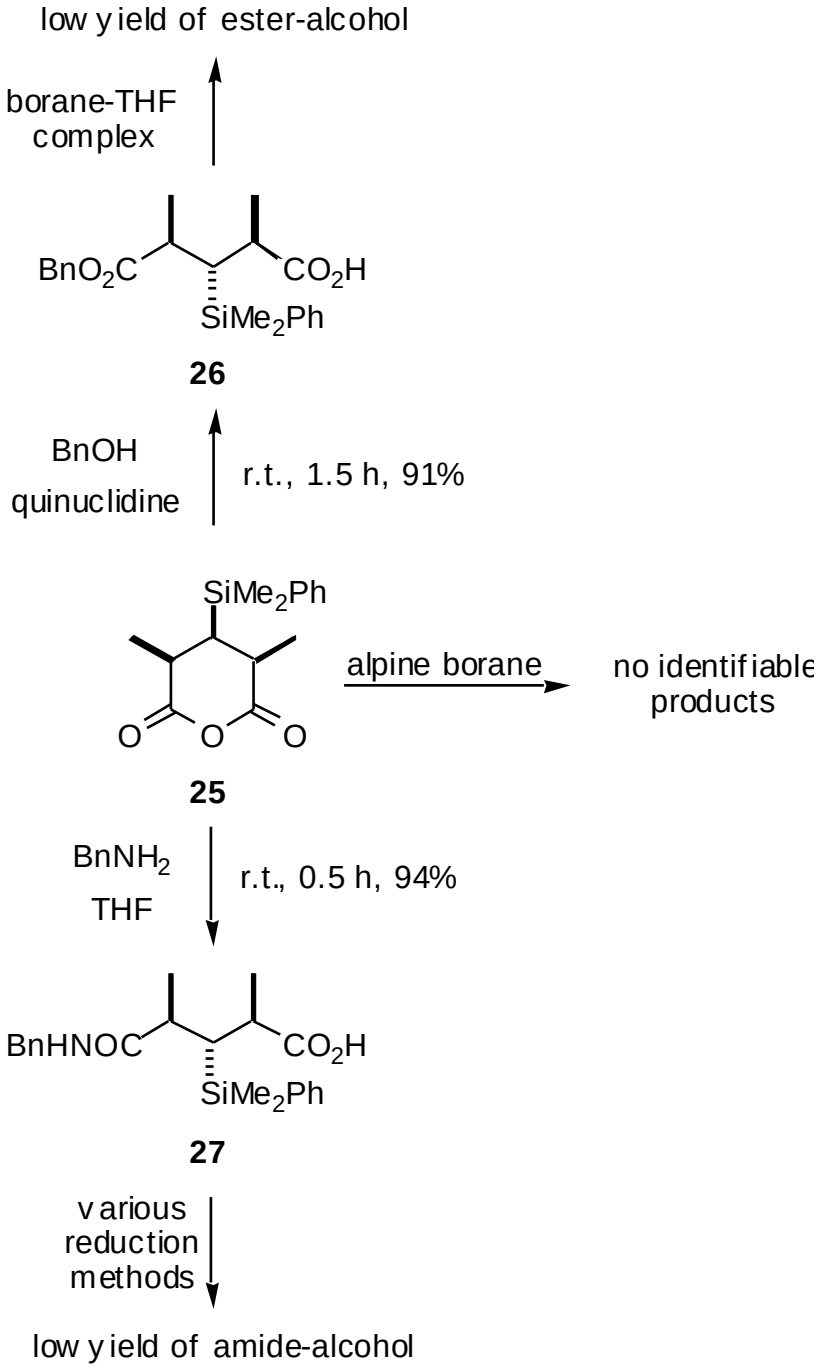


25

Scheme 2.4

First, Bazin made the cyclic anhydride **25** using fairly vigorous conditions (100 °C), and there was concern that equilibration might have led to a more stable diastereoisomer forming (scheme 2.4). However, the NMR showed that the anhydride formed was *meso,* and he was able to show that he had not obtained the other *meso* anhydride, so the stereochemistry was

proved. He treated it with benzyl alcohol and quinuclidine to form the ester-acid **26** (scheme 2.5). Since the anhydride **25** is *meso*, clearly the ester-acid will be racemic, but it would be expected that if the reaction were performed in the presence of a chiral catalyst [e.g., a cinchona alkaloid such as quinine or quinidine rather than the achiral quinuclidine (figure 2.2)], an enantiomerically enriched product might be formed. The idea from here was to



Scheme 2.5

reduce the acid to an alcohol with a borane reducing agent, and then by standard transformations (in an order to be determined, and almost certainly involving the use of protecting groups) perform a silyl-to-hydroxy conversion, hydrolyse the benzyl ester, form the lactone and oxidise the remaining hydroxyl group to the aldehyde of fragment A. This plan was spoiled by the low yield of the attempted selective reduction of acid **26** by borane-THF complex, and this route had to be abandoned.

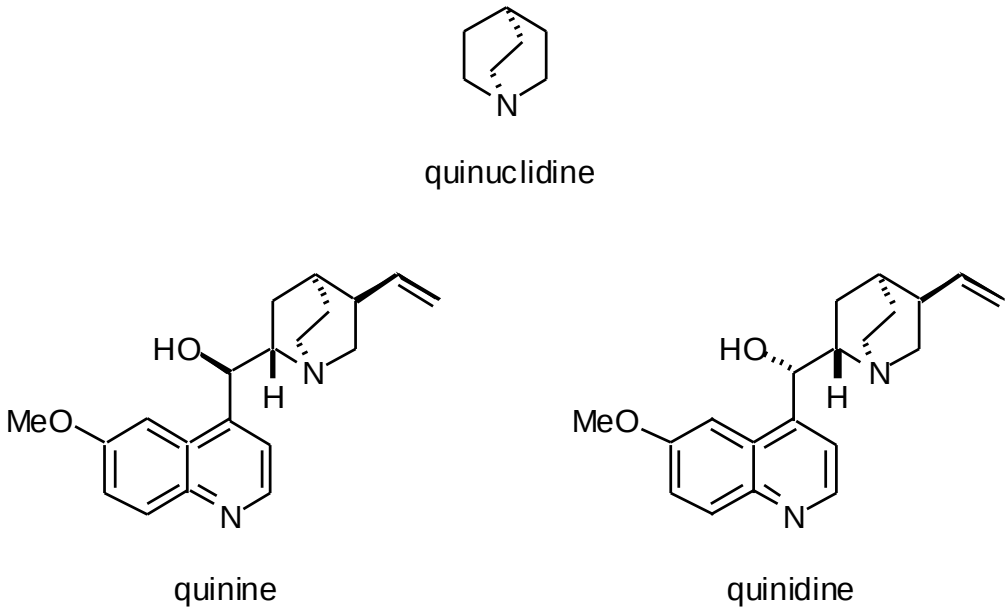
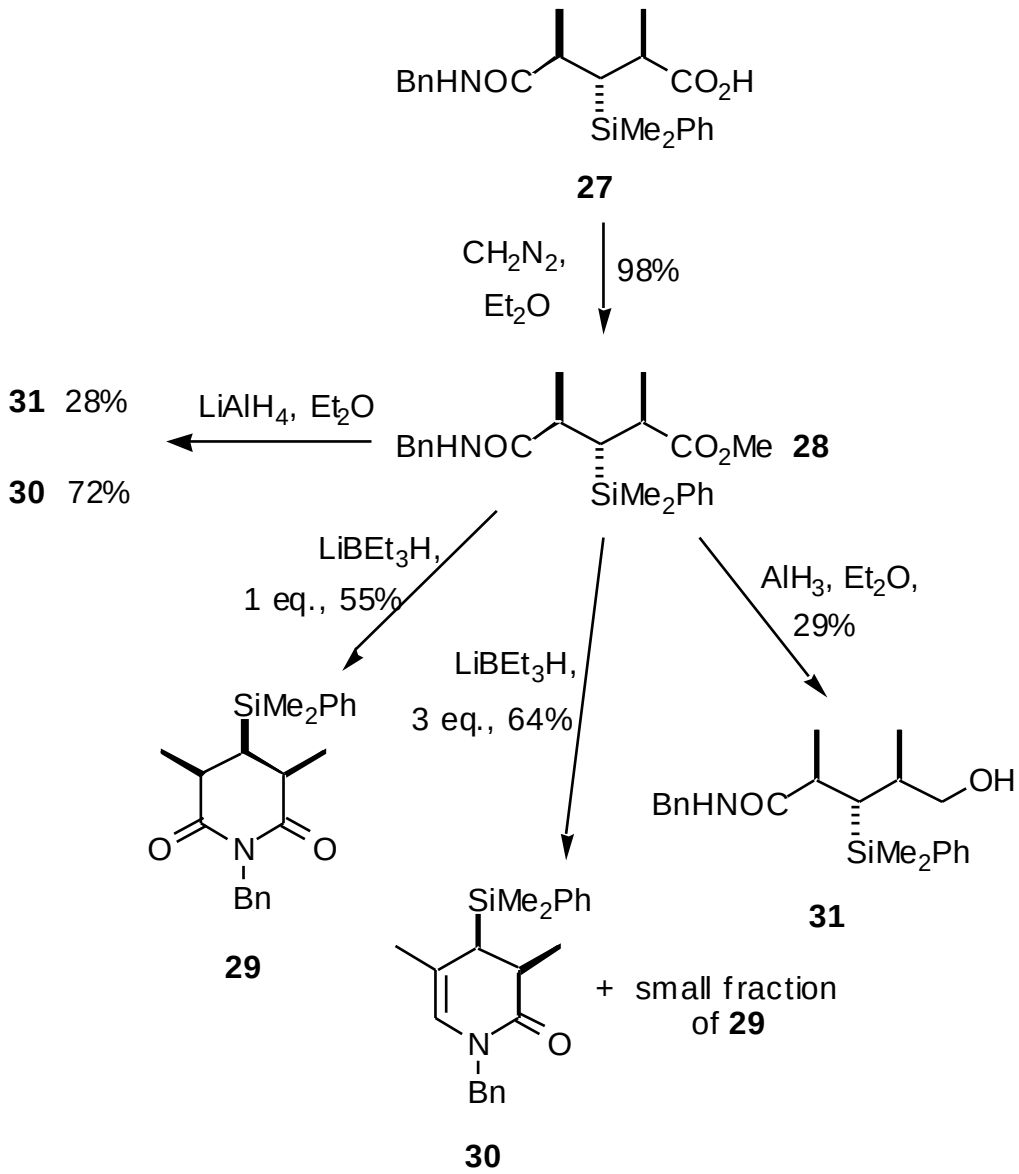


Figure 2.2

Going back to the cyclic anhydride **25**, two possibilites remain. Selective reduction with alpine borane was attempted, but this led to a complex mixture of products (scheme 2.5). Chiral amine attack to give a chiral imide was tested (using benzylamine), but in this case also problems were encountered at the reduction stage. However, it is supposed to be easier to reduce an ester in the presence of a secondary amide than it is an acid, so the acid **27** was methylated with diazomethane (98% yield) to give ester **28** before reduction was attempted. However, lithium triethylborohydride led either to intramolecular cyclisation to the imide **29** or to the unsaturated lactam **30**, and alane, although leading to the desired alcohol **31** (thanks to its combination of high reducing power and low basicity) did so in unsatisfactory yield.

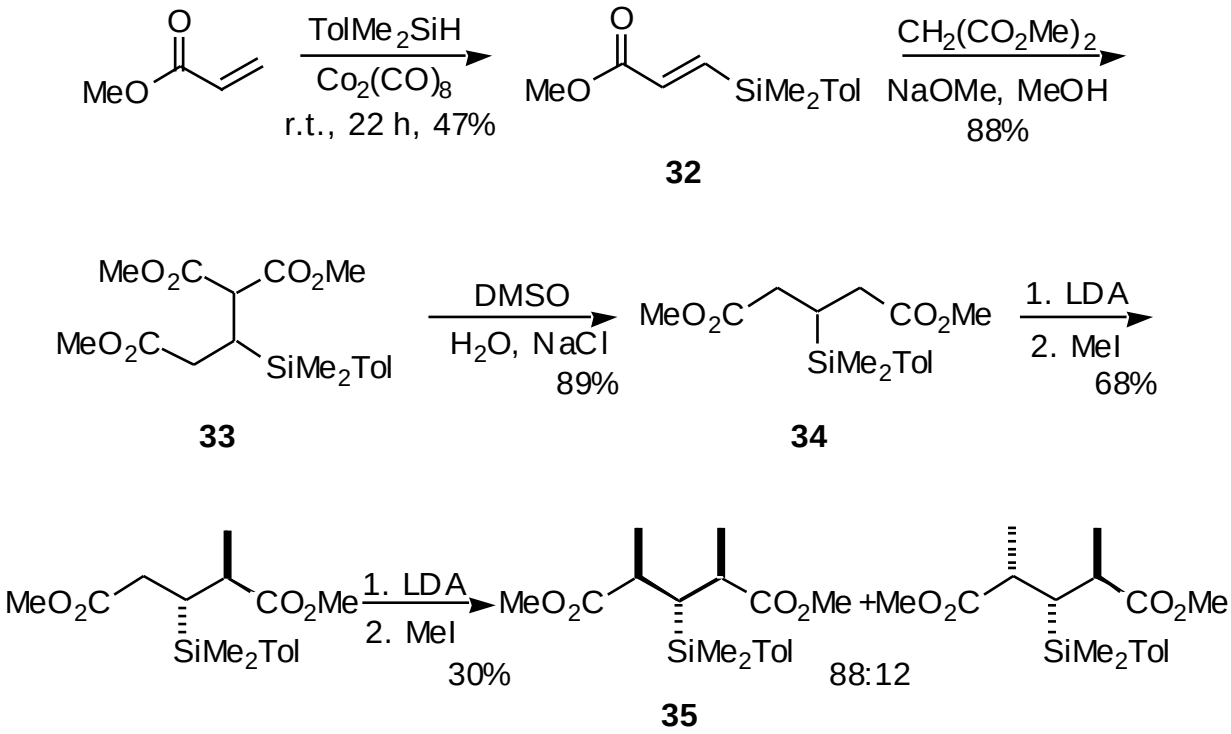
Lithium aluminium hydride reduction led to mainly the lactam **30**, together with a low yield of the desired alcohol **31**. It seemed that although the cyclic anhydride opened the door to many routes, none was showing immediate promise (scheme 2.6).



Scheme 2.6

By the time Zwicky[127] and Jank[128] came on the scene, diethyl glutaconate **21** had risen considerably in price, and this combined with the problems encountered with the silylcupration step as described above led to the development of a different route to a β-silyl diester. 4-Tolyldimethylsilane (formed by lithium aluminium hydride reduction of dimethyl-

4-tolylsilyl chloride or from 4-tolylmagnesium bromide and dimethylchlorosilane) was coupled with methyl acrylate using dicobalt octacarbonyl to give the unsaturated ester **32** (scheme 2.7).[129,130]

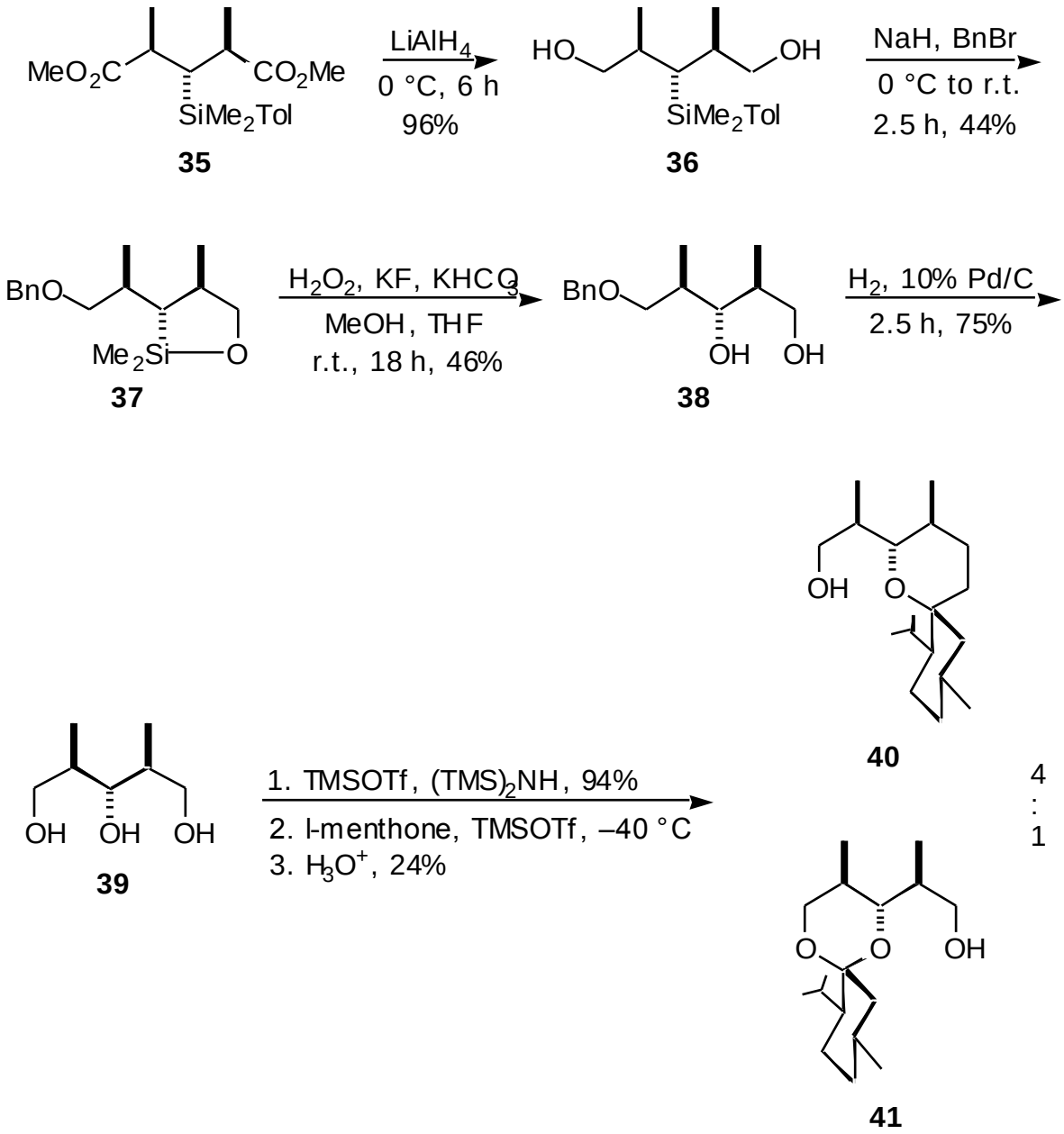


Scheme 2.7

The tolyldimethylsilyl group has the advantage of a greater likelihood of leading to crystalline products and also the greater ease of removal;[131] this group could not be introduced by the previous method, since it has not proved possible to form the silylcuprate of this silyl group. The ester **32** was obtained in acceptable yield, and conjugate addition of dimethyl malonate[132] gave the triester **33**, which was decarboxylated by the Krapcho method[133] to give the diester **34**, analogous to diester **22**. This diester was then methylated twice with LDA and methyl iodide, with low yield and similar diastereoselectivity to the dimethyl(phenyl)silyl case. Unfortunately none of the compounds in this series crystallised.

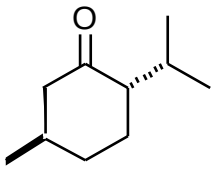
The remaining untried method of differentiation was now employed; i.e., formation of the *meso* triol **39** and then selective protection of one end of this with a chiral protecting group. Many methods are in principle available for selective protection of the triol.[115] It

turned out that the best way of transforming the dimethyl ester **35** into the triol was first to reduce the diester to the diol **36**, then to form the benzyl ether **37** by treatment with sodium hydride and benzyl bromide, next to perform the silyl-to-hydroxy conversion using potassium fluoride and hydrogen peroxide to give the diol **38** and finally to remove the benzyl group with hydrogen on palladium-carbon. These steps were carried out in low overall yield to give the triol **39** (scheme 2.8).[127]



Scheme 2.8

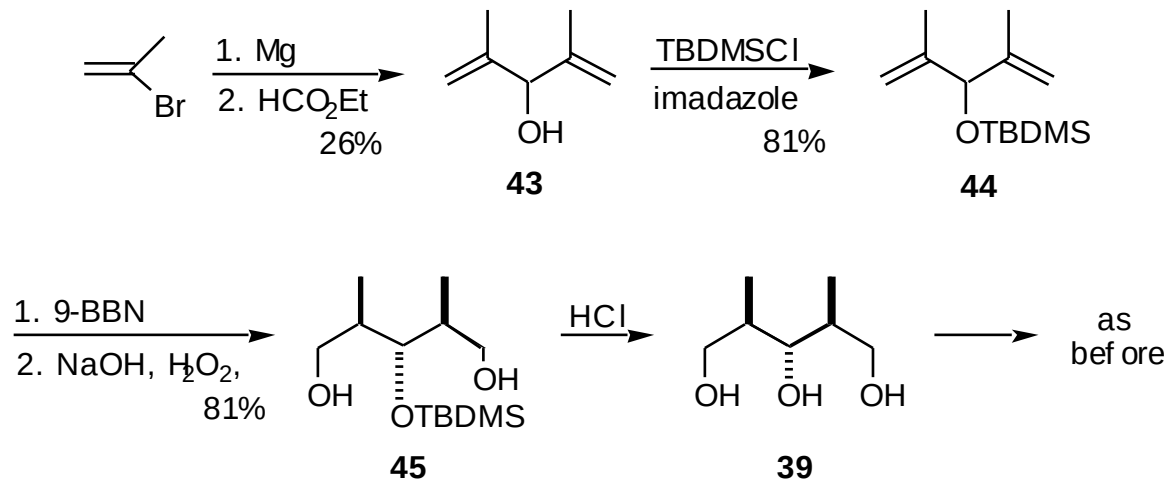
Following Oku and Harada,[134] the triol was converted to its tris(trimethylsilyl)ether using trimethylsilyl triflate and hexamethyldisilazane and then immediately distilled and treated with l-menthone **42** (figure 2.3) and trimethylsilyl triflate. Chromatography gave a 4:1 ratio of what were assumed by analogy to be the diastereoisomeric ketals **40** and **41** respectively. The major isomer could in principle be converted into fragment A and the minor isomer recycled.



l-menthone
42

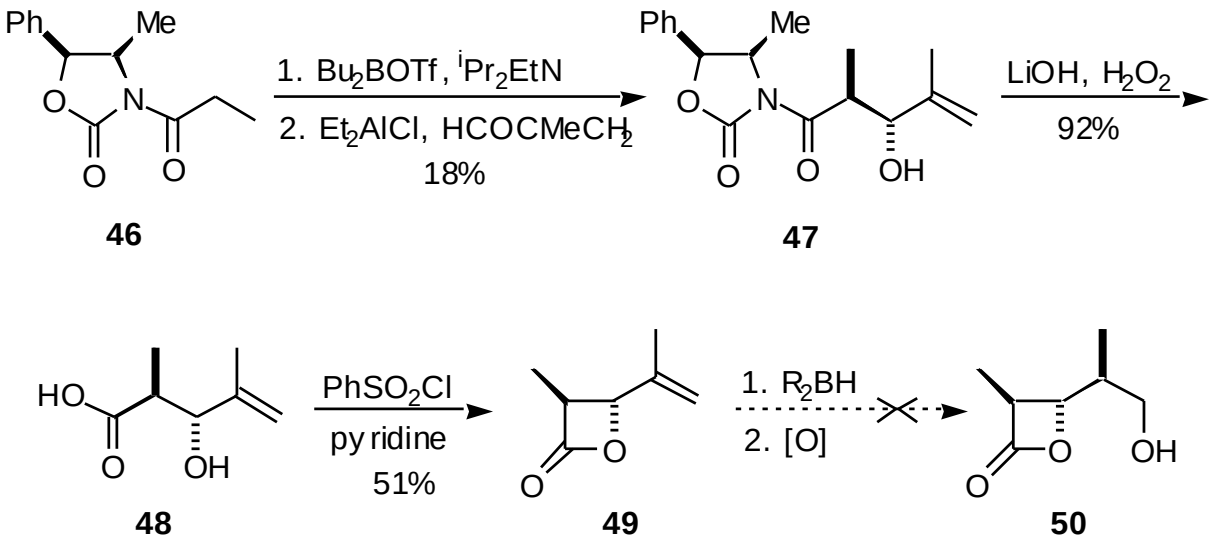
Figure 2.3

Following Harada, an alternative, quicker and more efficient route (not utilising silicon chemistry) to the triol **39** was pursued by Jank. (Now that the compound had been obtained by silicon chemistry, a more convenient supply of this was needed in order to proceed with the desymmetrisation work.) (Since this work was carried out, another route to the triol has been published.[123d]) Ethyl formate was treated with isopropenyl Grignard to give the dienol **43** in



Scheme 2.9

very poor yield (scheme 2.9). (The low yield was due to experimental error.) Following Corey,[135] this was then treated with TBDMS chloride and imidazole in DMF to give the silyl ether **44**. Hydroboration with 9-BBN[136] followed by oxidation led to diol **45**, which was deprotected in aqueous acid, giving the triol **39**. Formation of the tris(trimethylsilyl)ether and subsequent ketalisation with l-menthone gave the same diastereoisomers Zwicky had made. The problem with this approach is the difficulty of separating the menthone diastereoisomers. Jank tried transforming them into 3,5-dinitrobenzoate ester derivatives, which he hoped would crystallise and hence aid purification, but without success.



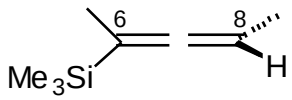
Scheme 2.10

Williams[137] developed two non-silicon-based approaches to fragment A. The first began with aldol reaction of the enol triflate of the easily-synthesised imide **46** containing one of Evans' chiral auxiliaries with methacrolein to give the *anti* aldol adduct **47** in poor yield (scheme 2.10). This was hydrolysed with lithium hydroperoxide to give the hydroxy acid **48** and recovered chiral auxiliary, and then lactonisation with benzenesulfonyl chloride in pyridine gave the lactone-alkene **49**. Hydroboration followed by oxidation was expected to give the alcohol **50**, which could in principle be oxidised to fragment A, but when formation of the alcohol was attempted (in the racemic series) severe problems were encountered. The β-lactone is susceptible to attack by hydroxide ion, and simple treatment of lactone **49** with

borane-DMS complex followed by sodium hydroxide and hydrogen peroxide predictably opened the lactone. Varying the reaction conditions and precise reagents, including employing more bulky hydroborating agents (9-BBN and thexylborane) led to small quantities of the desired product, but the route was abandoned due to the low yield and number of side-products contaminating the desired lactone-alcohol **50**.

Williams pursued a second non-silicon-based method to fragment A, and this was repeated in the work described in this thesis (see chapter 4).

2.2.2 Fragment B



51

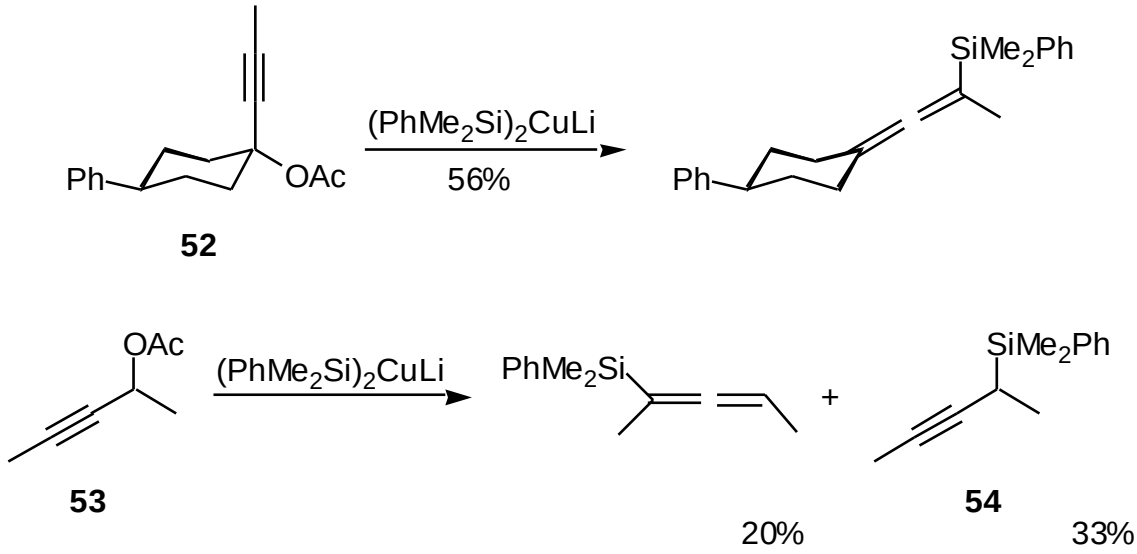
Figure 2.4

Carbons 6 to 8 of ebelactone-a come from the allenylsilane **51** (fragment B). The original silicon-based plan for the synthesis of this fragment was to attack an alkyne possessing a leaving group on the propargylic position with the dimethyl(phenyl)silylcuprate reagent. Terrett[138] had previously found that treatment of propargyl acetates with the silylcuprate reagent led to allenylsilanes in a stereospecifically *anti* sense (scheme 2.11).

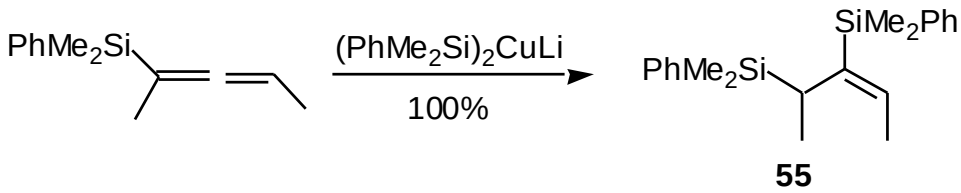
Tertiary acetates (such as **52**) give allenylsilanes in good yield, but in the case of secondary acetates (such as **53**), the products of direct attack, propargylsilanes (**54**), are formed too. However, it was observed that sometimes the silylcuprate reagent formed an addition product with the product allenylsilane, giving a product such as **55** with two silyl groups (scheme 2.12).

This was the beginning of the study of silylcuprate addition to allenes taken up by Pulido[139] and used in some of the work described in this thesis (see chapter 5). However, for the purposes of the construction of fragment B, it was clear that the allenylsilane required

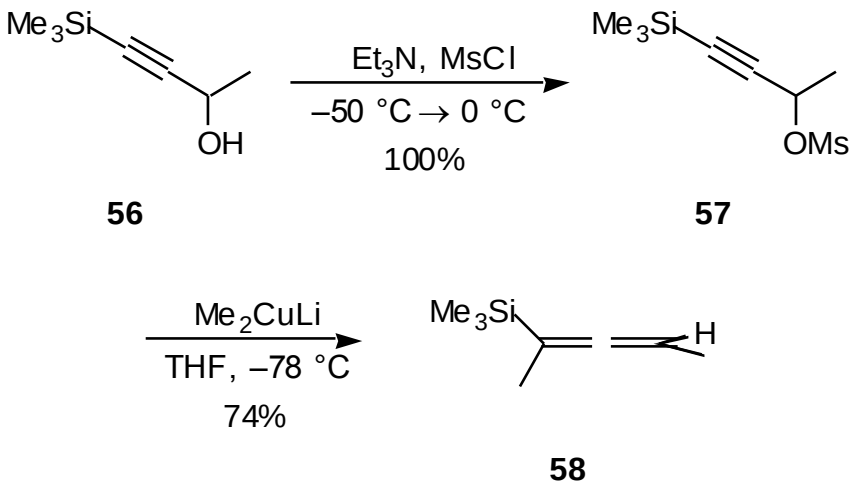
might be susceptible itself to silylcuprate attack, so a modification of this approach was necessary.



Scheme 2.11



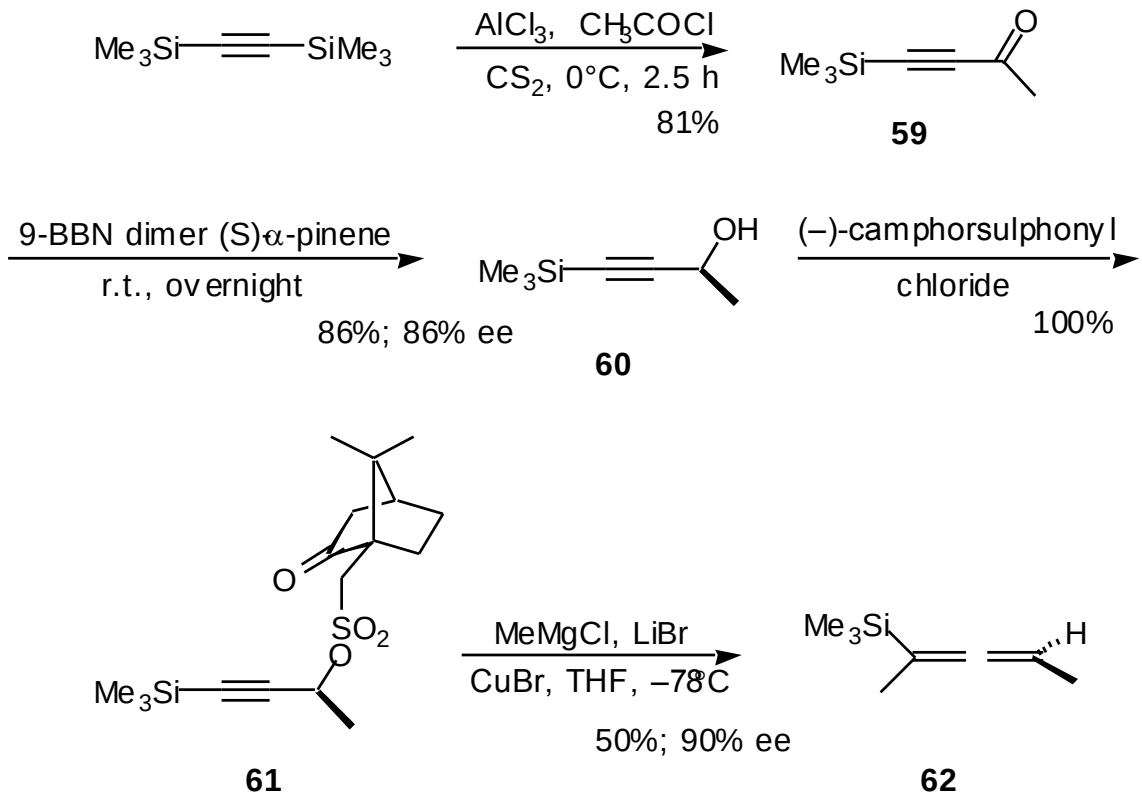
Scheme 2.12



Scheme 2.13

Takaki[140] synthesised the allene **58** in good yield by means of a modification of Vermeers' procedure[141] from the propargylic alcohol **56** with the silicon already in the molecule [as trimethylsilyl rather than dimethyl(phenyl)silyl] *via* S_N2' attack of methyl cuprate on the mesylate **57** (scheme 2.13).

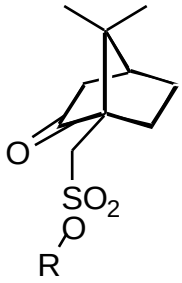
Bazin repeated this work and improved the yield by using conditions and reagents reported by Danheiser and others,[142,143] notably using methylmagnesium chloride in place of methyl cuprate. (Cuprates are known to racemise allenes, and though obviously this was not a problem in the racemic synthesis, it would be in the homochiral series.) He then developed a simple and efficient synthesis of the optically active allenylsilane **62** (scheme 2.14).



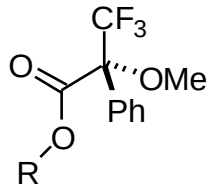
Scheme 2.14

Bazin found that the propargylic ketone **59** was best made by Birkofer's Friedel Crafts acylation reaction on bis(trimethylsilyl)acetylene,[144] though it is in fact now commercially available.[145] Reduction with freshly-made neat alpine borane according to the procedure of Brown and Midland[146,147] gave the alcohol **60** in good yield, and the enantiomeric purity was

determined by forming the camphorsulfonate ester **61** and found to be 86% ee (Mosher's ester[148] formation was incomplete and gave unreliable results) (see figure 2.5). Using (–)-camphorsulfonyl chloride led to the required diastereoisomer being the less soluble of the two, and so made recrystallisation easier. Since this work was carried out, alternative methods of asymmetric reduction of propargylic ketones have been developed.[149]



(–)-camphorsulfonate ester



Mosher's ester

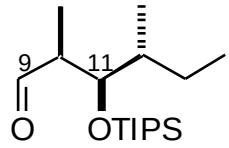
Figure 2.5

Buckle[150] repeated this synthesis and was able by repeated recrystallisation to improve the diastereoisomeric excess of the camphorsulfonate ester to >99%. It was found that as expected camphorsulfonate was a good enough leaving group to form the allene under the reaction conditions, so the mesylate derivative could be avoided altogether and the allenylsilane **62** formed in one step by Danheiser's[141-143,151] method. The optical purity was found to be 98% by chiral GLC.[152] Other routes to highly enantiomerically enriched allenylsilanes from optically active propargylic alcohols have been developed since this work was carried out.[153]

2.2.3 Fragment C

Carbons 9 to 12 of ebelactone-a are a common feature of many natural products, such as oleandomycin (figure 2.7),[154] and methods are available in the literature for its synthesis.[115a,b]

The first attempt by the Fleming group at a synthesis of this fragment was carried out by Ware[105] from the chiral *anti-anti*-lactone **64** (scheme 2.15).



63

Figure 2.6

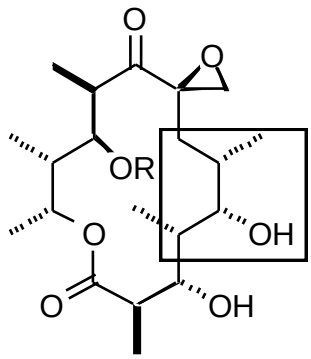


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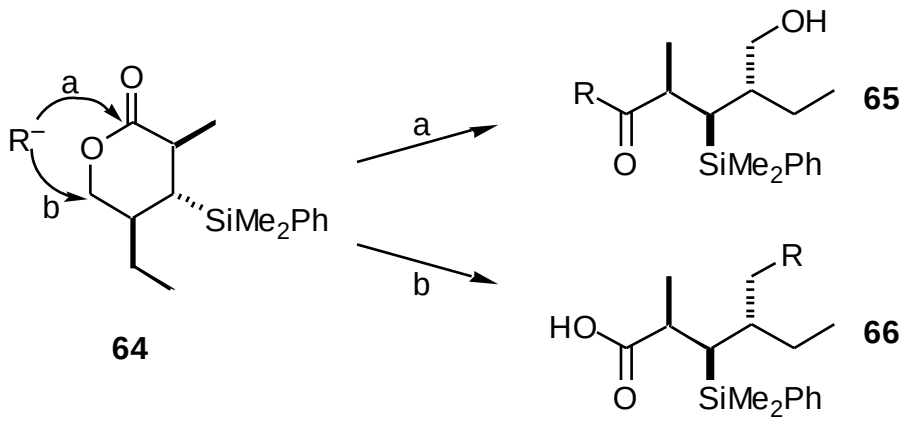
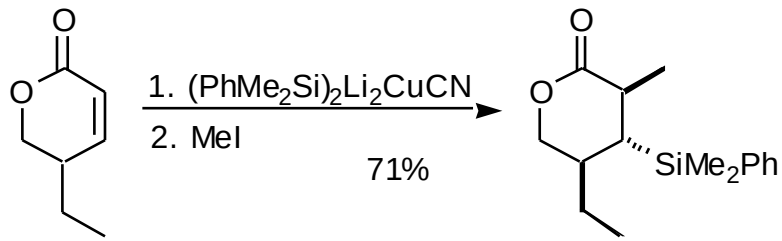
Figure 2.7



64

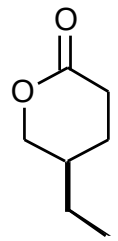
Scheme 2.15

It was envisaged that by some means lactone **64** could be opened either in sense *a* giving ketone **65** or in sense *b* giving acid **66**, either of which might be seen to be precursors to fragment C. The racemic lactone **64** was readily synthesised by Ware with very high diastereoselectivity by conjugate addition of the dimethyl(phenyl)silylcuprate reagent to the unsaturated lactone **67** (figure 2.8), followed by methylation with methyl iodide (scheme 2.16).



67 **64**

Scheme 2.16



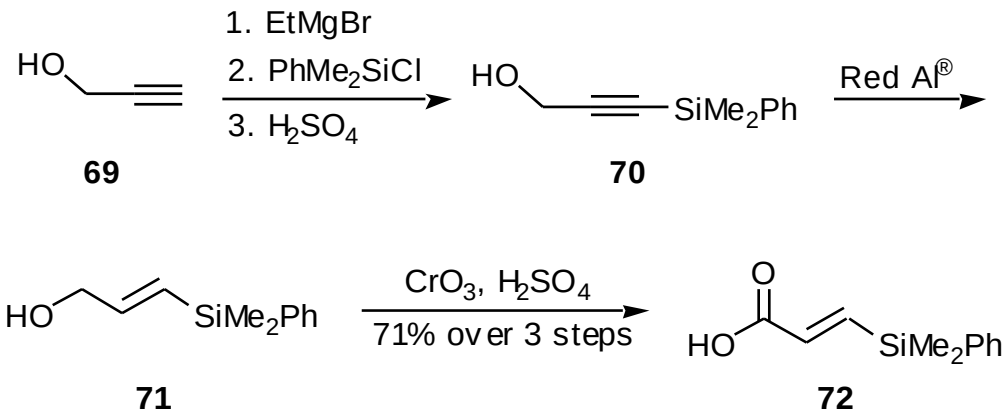
68

Figure 2.8

The saturated lactone **68** (figure 2.8) has been synthesised in enantiomerically pure form,[155] so it ought to be possible to obtain enantiomerically pure lactone **64** from this by straightforward chemistry. Unfortunately, when Ware tried to open the racemic lactone she was unable to do so in acceptable yield, though she tried sixteen different methods, including methoxymethylamine, various secondary amines, benzylamine and sodium hydroxide (path *a*); and iodide, selenide, thiocyanate and various sulfur-based nucleophiles (path *b*). The best

results were obtained with some of the amines she tried, but the reactions were not clean, and harsh conditions would be required for hydrolysis of the resultant amides. In addition, there was evidence for epimerisation α to the carbonyl group in the ring-opened products—disastrous from the point-of-view of the synthesis. Hence this route was abandoned for the time being, though the work has recently been looked at again by Mandal[156] who has considered further methods of opening the lactone, so far without success.

An open-chain route was begun by Ware and completed by Archibald.[157] It began with the synthesis of unsaturated acid **72** from propargyl alcohol **69** by an adaptation of Denmark's synthesis (scheme 2.17).[158] (Other routes to this acid had been tried but had led either to a mixture of *E* and *Z* diastereoisomers or to the presence of the saturated acid as a contaminant.)

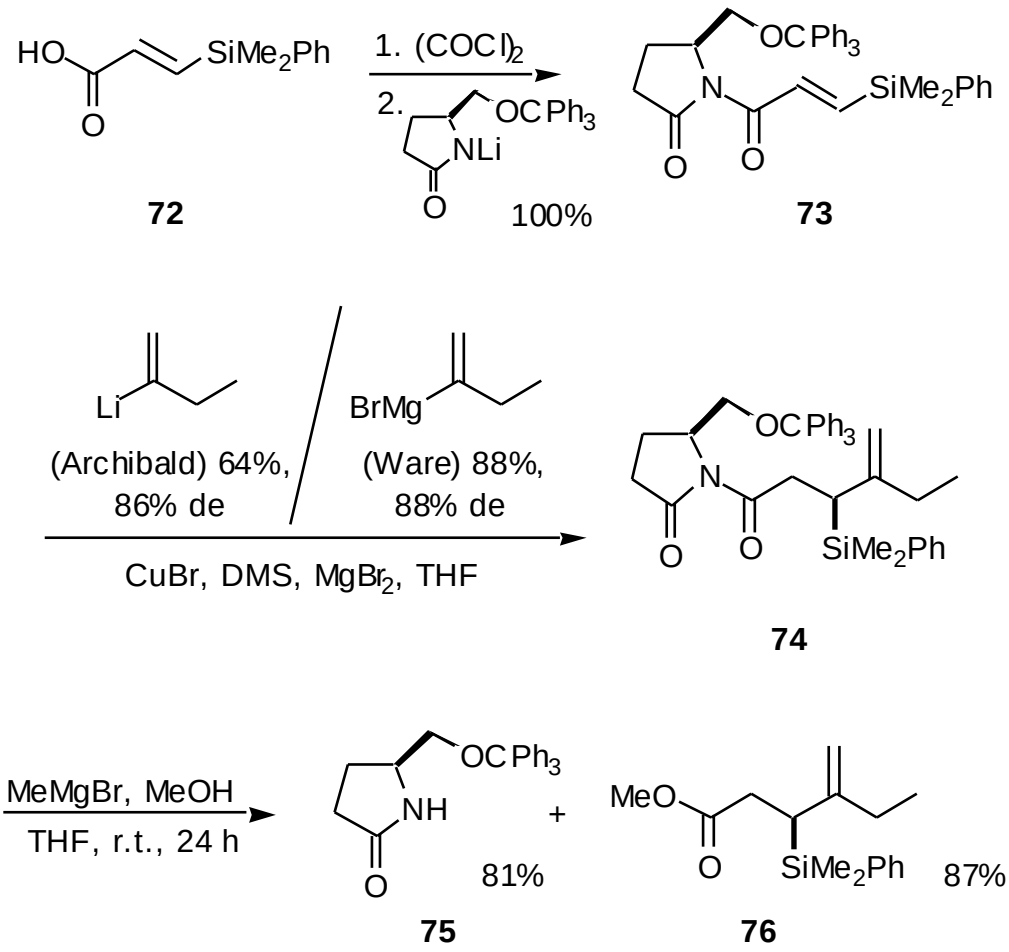


Scheme 2.17

Silylation gave the silylacetylene **70**, which on reduction with Red Al®[159] gave the *E*-alcohol **71** exclusively. This was readily oxidised to give the unsaturated acid **72**. Koga's chiral auxiliary[160] was attached to this in quantitative yield to give the chiral imide **73**, which underwent vinyl Grignard (Ware) or vinyllithium (Archibald) conjugate attack (scheme 2.18). Kindon[161,162] had previously found that conjugate addition to unsaturated chiral silyl imides took place in some cases with good diastereoselectivity.

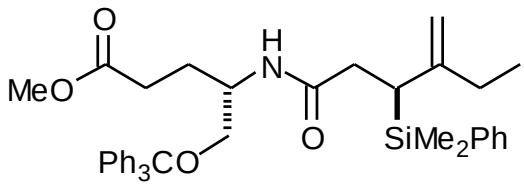
Both nucleophiles led to good yields and similar diastereoselectivities (though the vinyllithium was easier to prepare since, following Denmark,[163] the Bond modification[164] of the Shapiro reaction[165] could be employed, and this avoided the troublesome use of volatile 2-

bromobutene). However, it was unfortunately not possible to improve the diastereoisomeric excess by chromatography or by recrystallisation, since the imide **74** was not crystalline. The best cleavage conditions turned out to be magnesium methoxide formed *in situ* from methyl magnesium bromide and methanol, since this did not lead to the ring-opened side product **77**



Scheme 2.18

(figure 2.9), which was seen under alternative conditions (e.g. lithium methoxide hydrolysis, where protons were evidently present). Interestingly, Mwaniki[166] has since found that ring-opened products such as **77** can generally be treated with base to regenerate the chiral auxiliary and the required cleavage product. This presumably takes place *via* deprotonation at nitrogen and recyclisation to the imide. Thus the unstable (to isomerisation) ester **76** was obtained.

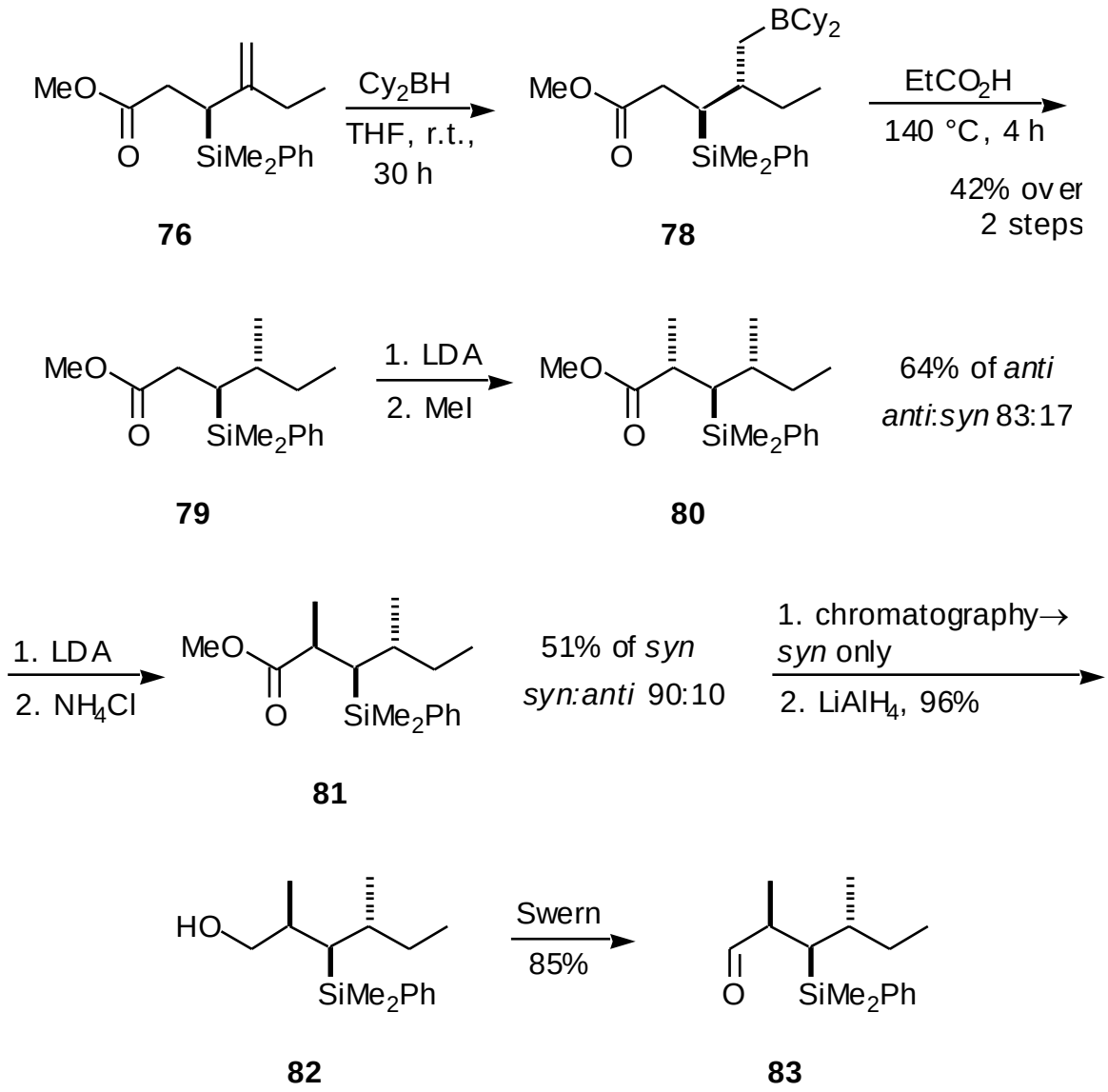


77

Figure 2.9

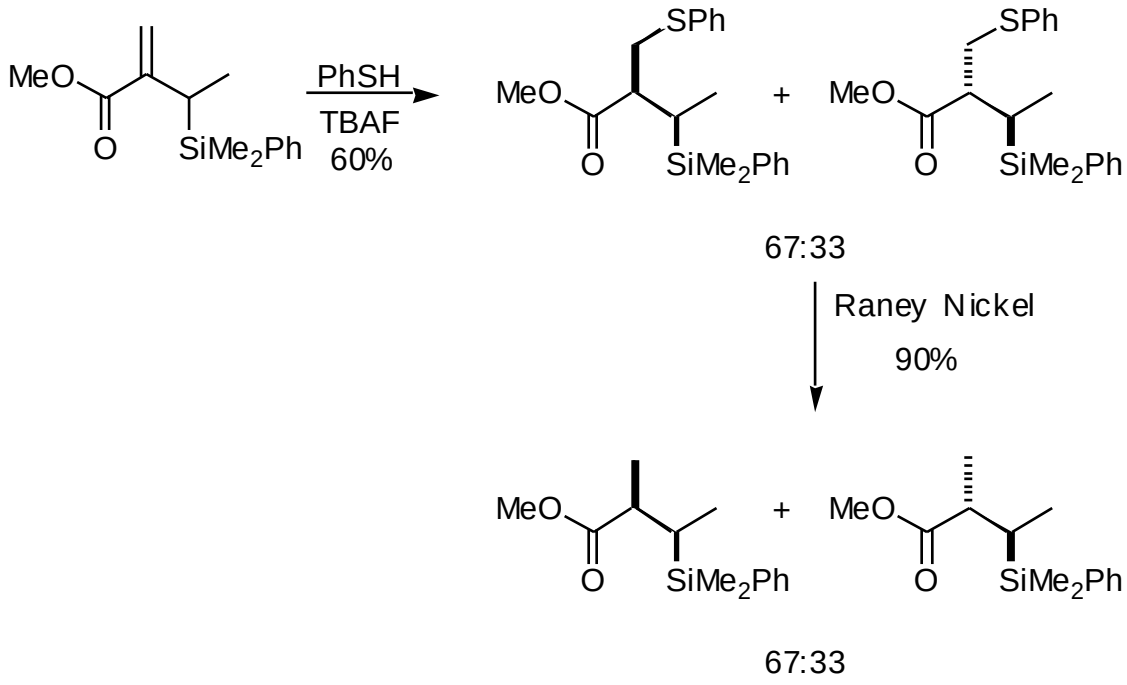
The double bond at C12 needs to be reduced diastereoselectively, but hydrogenation of ester **76** proved to be unselective, and attempted hydrogenation at the previous imide stage simply removed the trityl group and isomerised the double bond. Therefore hydroboration was explored. The ester **76** was successfully hydroborated with cyclohexylborane (though the reaction was slow) leading to the CH_2BR_2 group going *anti* to the silyl group in the product **78**, as expected and required (scheme 2.19). Removal of the boron group caused problems when both protodeboronation and iododeboronation were tried in a model series and on borane **78** itself. Both gave low yields and many side products, and using different boronating agents led to no improvement. Tonoletti[167] looked at mercury-deboronation, but without success. Hence cyclohexylborane was retained as the boronating agent, and propionic acid was used for the protodeboronation step, since this was the easiest way of performing the transformation on a large scale. The yield was never good.

The methylation of ester **79** proceeded well to give a mixture of the *anti* **80** and *syn* **81** esters (83:17), which could be separated by chromatography (scheme 2.19). The *syn* ester **81** is the required product, and in principle deprotonation (with LDA) at the α position of this mixture of esters, followed by reprotonation, ought to give predominantly the *syn* product. However, it has generally been found to be impossible to form the enolate in open chain systems where the α position is already substituted,[168] and so several alternative ideas were explored. These involved putting in on C10 not a methyl group but a methylene group. Then conjugate attack of an appropriate nucleophile should give the desired enolate, protonation of which ought to lead predominantly to this group going *syn* to the silyl group. The attacking nucleophile group would then need to be removed to give ester **81**. An obvious choice of

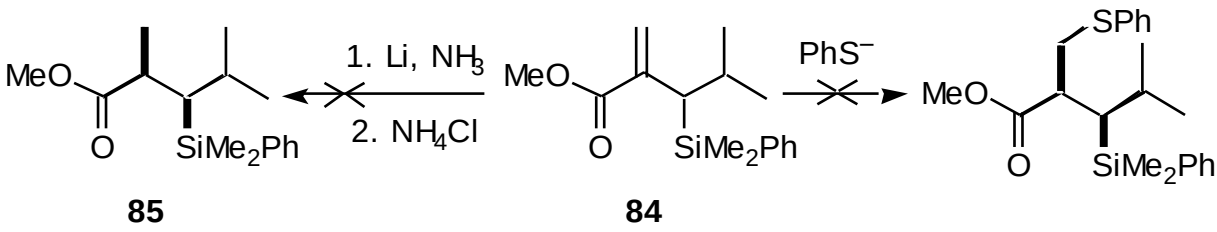


Scheme 2.19

nucleophile would be thiophenol, since the sulfur group could be removed by treatment with Raney Nickel. Kilburn obtained promising results in the model series (scheme 2.20),[169] but when Archibald tried a substrate **84** with a bulkier isopropyl group replacing the methyl group in Kilburn's model, it proved impossible to add the thiophenolate anion (scheme 2.21). Archibald also briefly considered the possibility of reducing the unsaturated ester **84** to the saturated ester **85** by means of liquid ammonia,[170] but this was unsuccessful. Happily, however, none of this complicated procedure was necessary, since Archibald was surprised to find that deprotonation of ester **80** was not problematic at all!



Scheme 2.20



85 **84**

Scheme 2.21

The *anti* ester **80** was deprotonated with LDA (scheme 2.19) and then reprotonated to give a mixture predominating in the *syn* isomer now (*syn*:*anti* 90:10), and chromatography gave the pure *syn* ester **81**. This ratio is not quite as good as hoped, the probable reason being that for precisely the same reason that the enolate **86** (figure 2.10) protonates such as to afford the *syn* product, this *syn* ester will be more easily deprotonated than will the *anti*. We would therefore expect total deprotonation of the *syn* ester but possibly incomplete deprotonation of the *anti*, and this will reduce the *syn*:*anti* ratio of the products. Reduction of the *syn* ester **81**

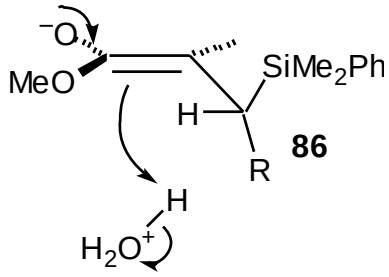
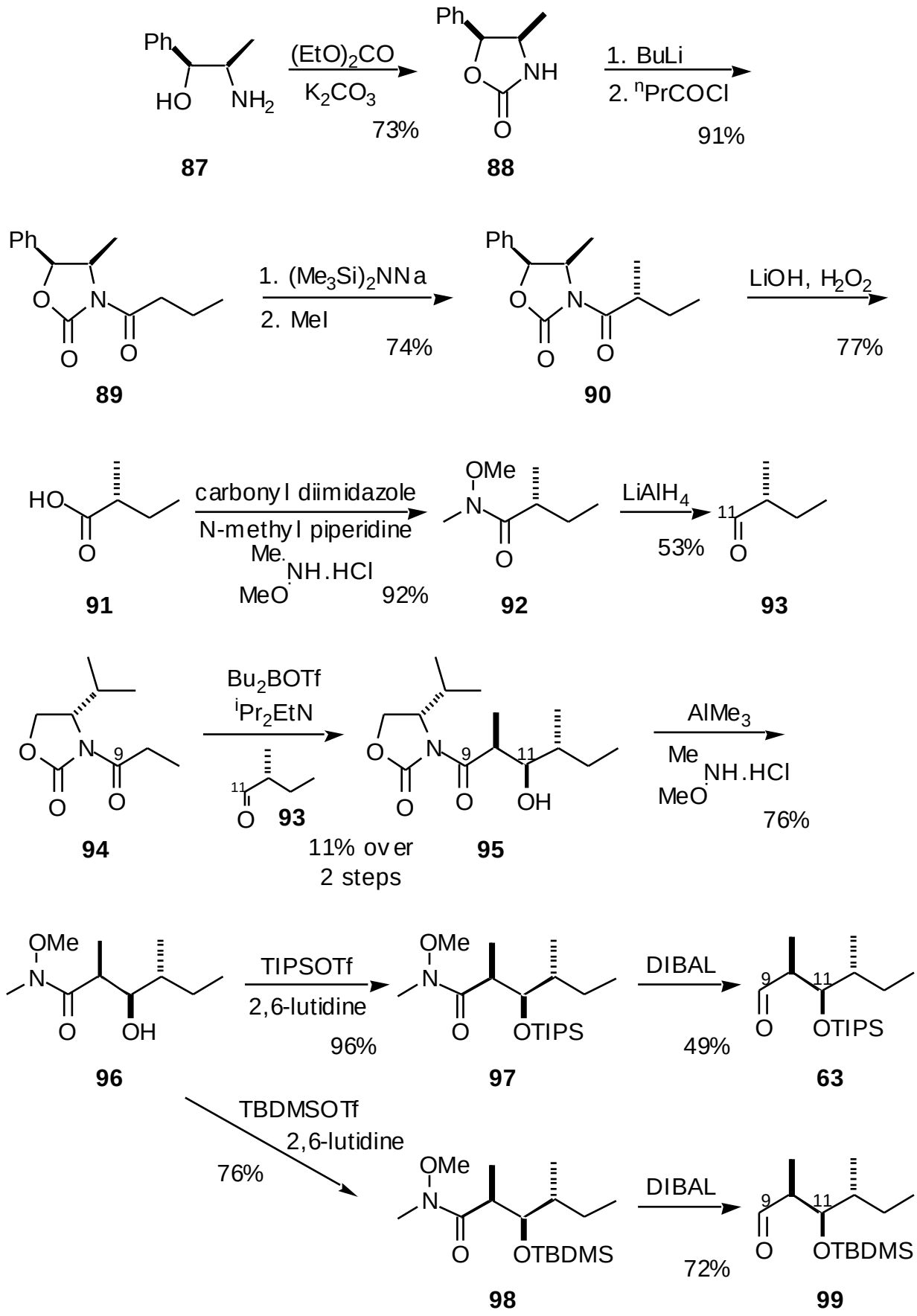


Figure 2.10

with lithium aluminium hydride gave the alcohol **82** which was oxidised by the Swern procedure[171] to give homochiral fragment C **83** (analogous, by silyl-to-hydroxy conversion, to structure **63**).

By this stage in the work, the aim of synthesising fragment C by silicon chemistry had been realised, and further quantities were needed in order to explore other aspects of the ebelactone-a synthesis, so Williams successfully prepared fragment C using the methodology of Evans' chiral auxiliaries (scheme 2.22).[137] This time, C11 was given an oxygen substituent rather than silicon (see section 2.3.1 for the reason for this), and versions containing two different protecting groups, OTIPS and OTBDMS, were synthesised so that their performance in the coupling of fragments B and C could be compared (see section 2.3.1). The synthesis began with auxiliary **88**, made according to a well-established procedure[172] in good yield from (1*S*,2*R*) norephedrine **87** and diethyl carbonate. This was *N*-butyrylated with butyryl chloride in excellent yield to give imide **89**, and then methylated (also in good yield) using sodium bis(trimethylsilyl)amide and methyl iodide according to Evans' procedure[173] to give the methylated product **90** with a diastereoisomeric excess of 82%. (The stereoselectivity is readily explained in figure 2.11, where the bulky phenyl and methyl groups prevent approach of the methyl iodide on to the top surface.) Reductive removal of the auxiliary to give aldehyde **93** or the corresponding alcohol were troublesome due to the volatility of the products. Therefore, lithium hydroperoxide was employed to regenerate the auxiliary (in 87% yield)[174] and to give the relatively involatile acid **91**. In the next step, the Weinreb amide[175] **92** was formed in excellent yield by carbonyldiimidazole coupling of *N*,*O*-


Ph
HO
NH2
(EtO)2CO
K2CO3
73%
87
Ph
O
NH
O
88
1. BuLi
2. nPrCOCl
91%
Ph
O
N
O
O
89
1. (Me3Si)2NNa
2. MeI
74%
90
LiOH, H2O2
77%
HO
O
91
carbonyl diimidazole
N-methyl piperidine
Me
NH.HCl
MeO
92%
OMe
N
O
92
LiAlH4
53%
11
O
93
O
N
9
O
O
94
Bu2BOTf
iPr2EtN
11
O
93
11% over
2 steps
OH
95
AlMe3
Me
NH.HCl
MeO
76%
OMe
N
O
OH
96
TIPSOTf
2,6-lutidine
96%
OTIPS
97
DIBAL
49%
9
11
O
OTIPS
63
TBDMSOTf
2,6-lutidine
76%
OTBDMS
98
DIBAL
72%
OTBDMS
99

Scheme 2.22

dimethylhydroxylamine and the acid.[176] The aldehyde **93** was then obtained cleanly by lithium aluminium hydride reduction. This was then combined with the boron enolate of imide **94**, formed by propionylation of another Evans auxiliary (this time made from l-valine) in an aldol reaction to give the aldol adduct **95** in reasonable yield. (The stereoselectivity is rationalised by means of figure 2.12. The chair transition structure is favoured, with the alkyl chain of the aldehyde occupying an equatorial position. Of the two possible structures which can be drawn, this one is favoured by putting the isopropyl group on the oxazolidine ring *exo* to the chair.) Protection of the alcohol, followed by Weinreb amide formation was problematic, so the Weinreb amide **96** was formed first in good yield by transamination of the

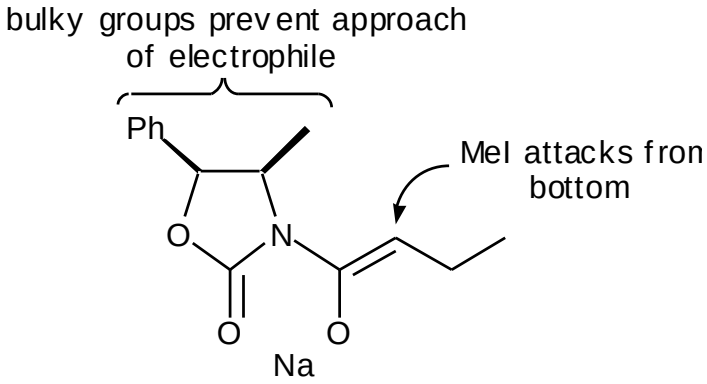


Figure 2.11

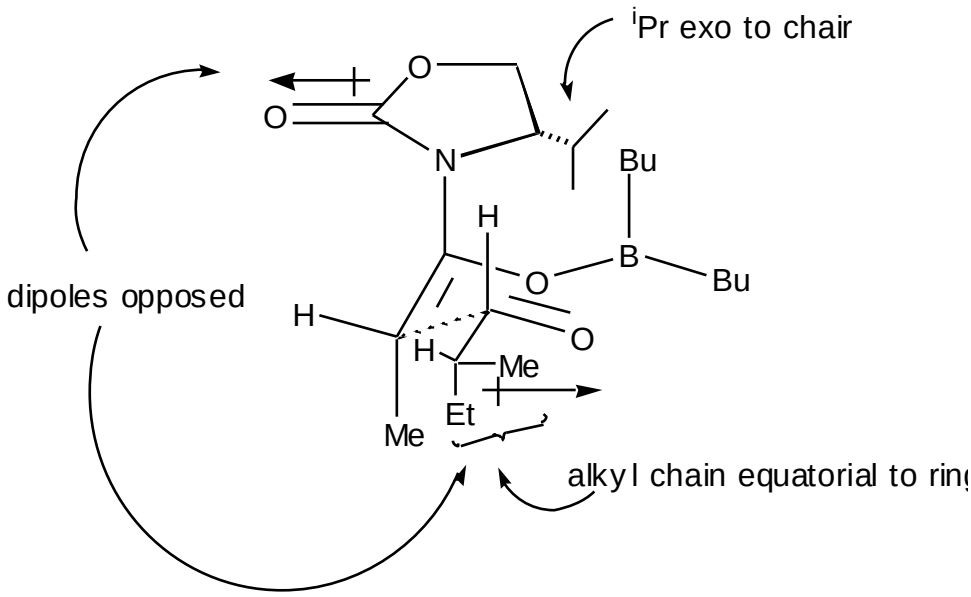
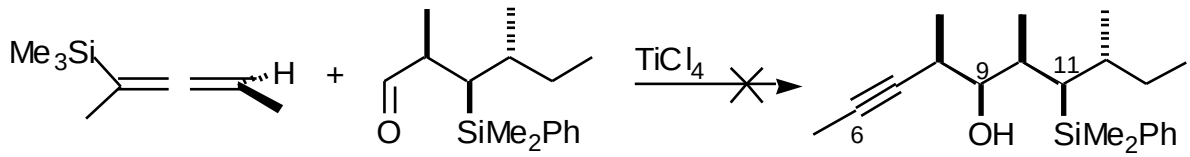


Figure 2.12

aldol adduct **95**, and this was then protected with either TBDMS triflate or TIPS triflate (in excellent and good yield respectively) to give the two silyl ethers **98** and **97** respectively. Lithium aluminium hydride reduction of these ethers led to low yields of impure aldehydes, but DIBAL reduction gave highly pure product aldehydes **99** and **63** (scheme 2.22).

2.3 Joining the Fragments Together and Completing the Synthesis

2.3.1 Coupling of Fragments B and C



51 **83** **100**

Scheme 2.23

Initially allenylsilane fragment B **51** was envisaged to attack the silicon version of fragment C **83** to give the coupled product of B and C **100**, as shown in scheme 2.23, and fragment C **83** was synthesised accordingly. The stereoselectivity was anticipated to be as shown in the product, leading to the methyl at C8 and the hydroxyl at C9 both lying *syn* to the methyl at C10 of fragment C. This should be controlled by three factors. Firstly by the known[140,177-182] stereochemical behaviour of allenylsilanes in S_E2' reactions, where the carbon-silicon bond that breaks is oriented *anti* to the carbon-carbon bond which forms; secondly, by the Cram selectivity[183] arising from the stereogenic centre of the α carbon of the aldehyde; and thirdly, by the known preference for *syn* products observed by Danheiser[177]and ascribed to the allenylsilane attacking the face of the aldehyde which puts the bulky chain of fragment C away from the methyl group on the allenylsilane in the favoured anticlinal transition structure of an *anti* S_E2' process. (A synclinal transition state is also a possibility, however.[184]) These three factors are illustrated in figure 2.13.

The relatively large difference in size of the groups on the α carbon of the aldehyde ought to make the Cram selectivity good, and the favoured product from this is the same as that favoured by the *anti* selectivity of the S_E2' reaction of the allenylsilane. Hence the two components are matched, and this ought to lead to a highly diastereoselective reaction. Therefore, if fragment C **83** is not of especially high enantiomeric purity, fragment B **51** ought to react faster with the correct enantiomer to give the desired product.

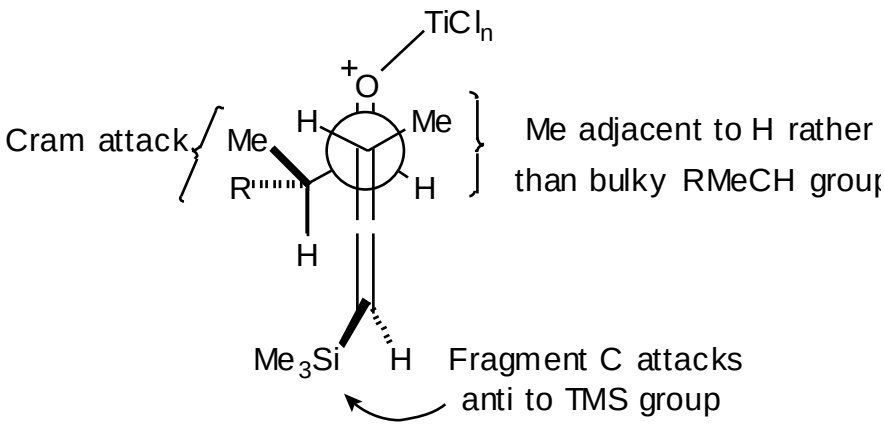
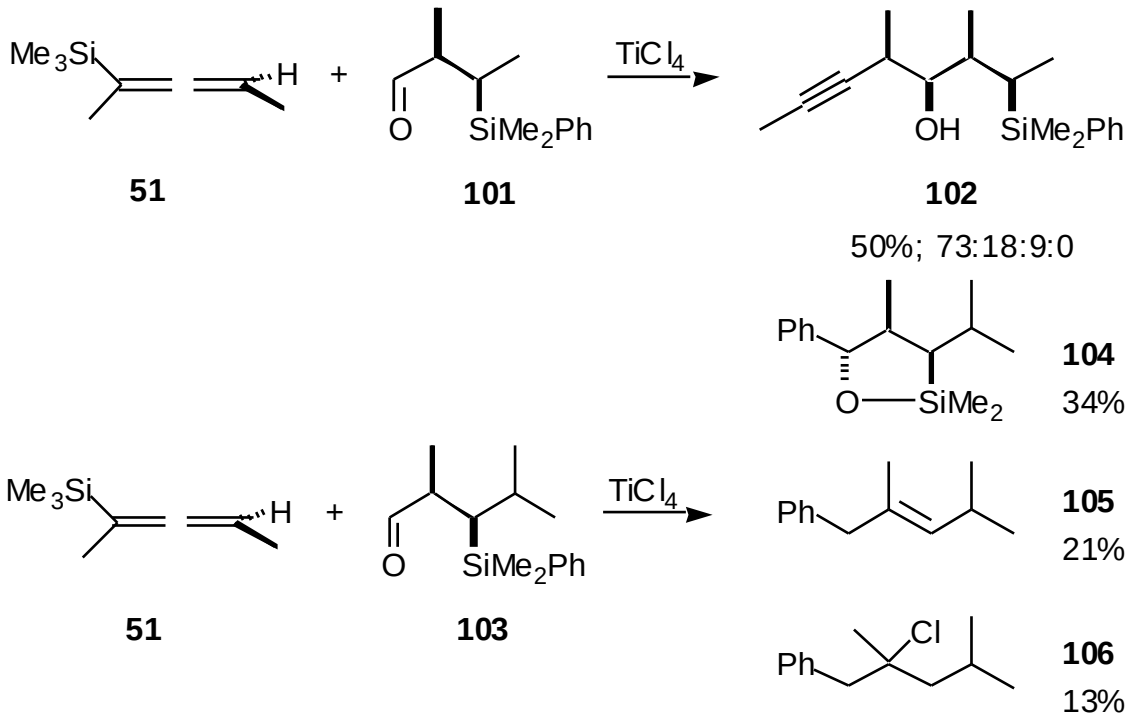
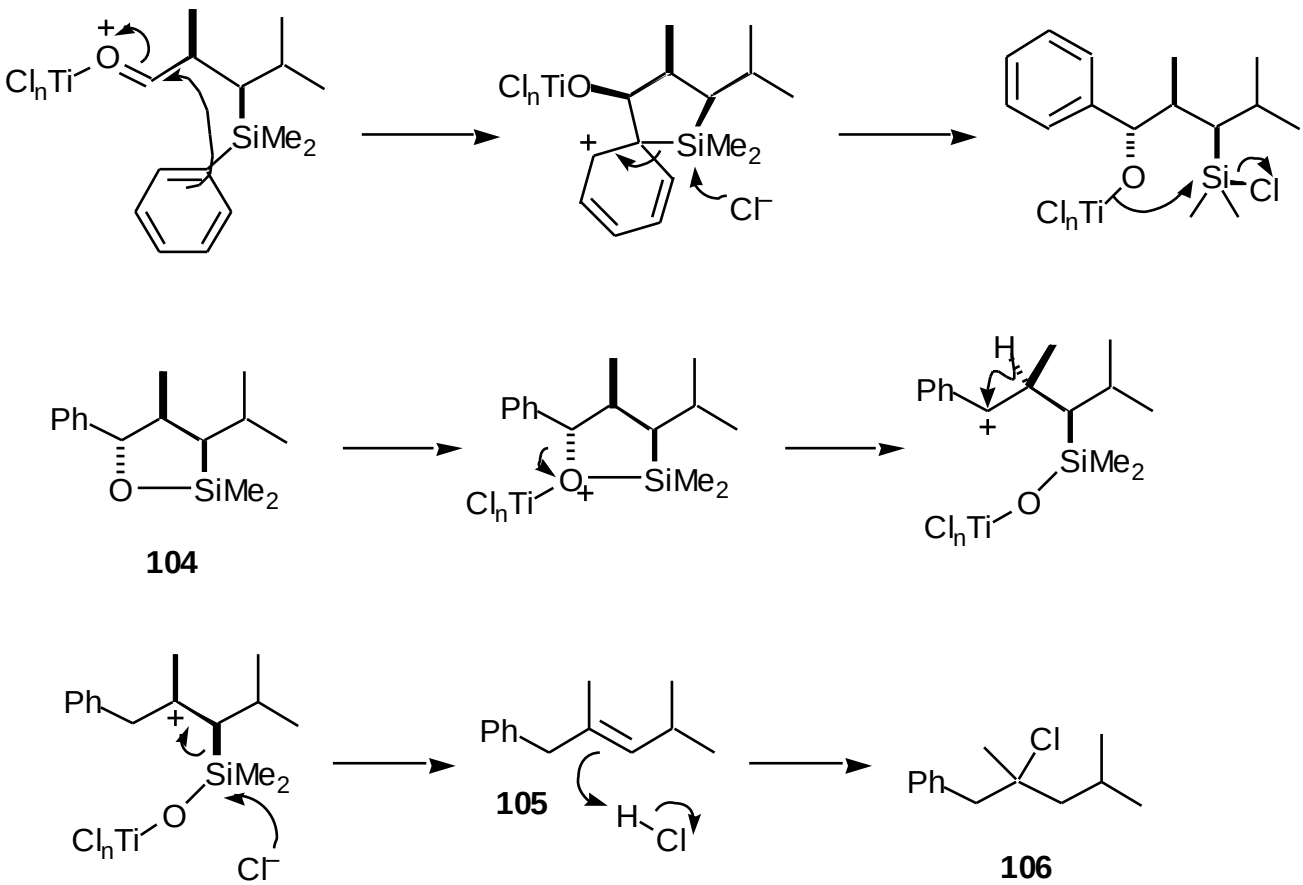


Figure 2.13

In the late 1980's, Takaki[140] reacted his racemic version of fragment B with different aldehydes in the presence of titanium(IV) chloride. He showed that the *syn* alcohols were the major products. Buckle found the same result when he reacted fragment B **51** itself with isobutyraldehyde and obtained 95:5 *syn*:*anti*. However, when closer analogues to fragment C were tried, a serious problem was encountered. Treatment of model aldehyde **101** with fragment B gave the expected product **102** in good diastereoisomeric excess—remarkably, given that both components were racemic—but simply replacing the methyl group in aldehyde **101** with isopropyl (to make a closer analogue **103** to fragment C) led to none of the desired product at all, but instead to three decomposition products **104**, **105** and **106** of the aldehyde (scheme 2.24).[185]



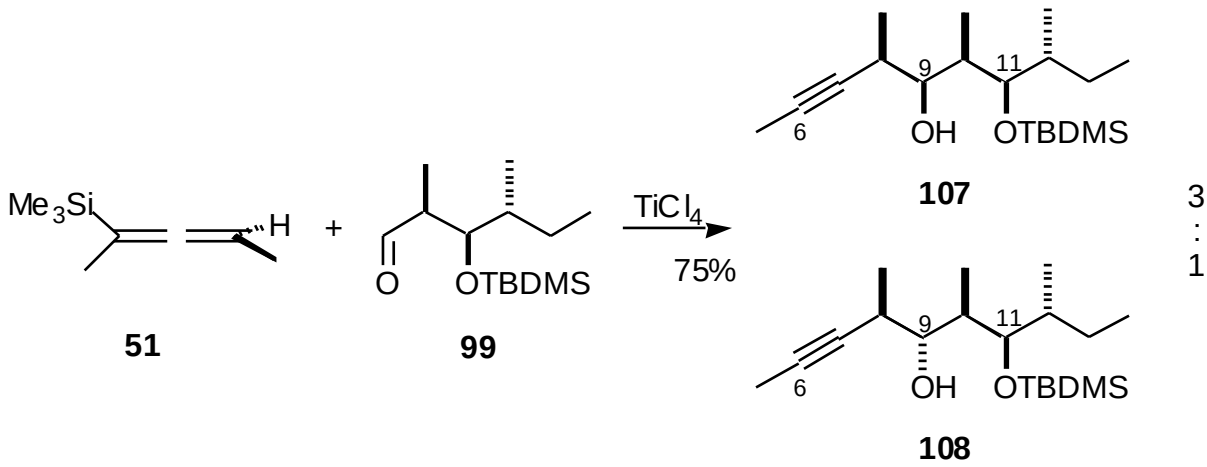
Scheme 2.24



Scheme 2.25

It was apparent that in the presence of the Lewis acid, intramolecular attack of the phenyl group on the aldehyde was now taking place faster than the desired intermolecular reaction (see scheme 2.25). For this reason, this route had to be modified: fragment C could now not contain the dimethyl(phenyl)silyl group—silyl-to-hydroxy conversion would need to take place *before* the coupling of fragments B and C.

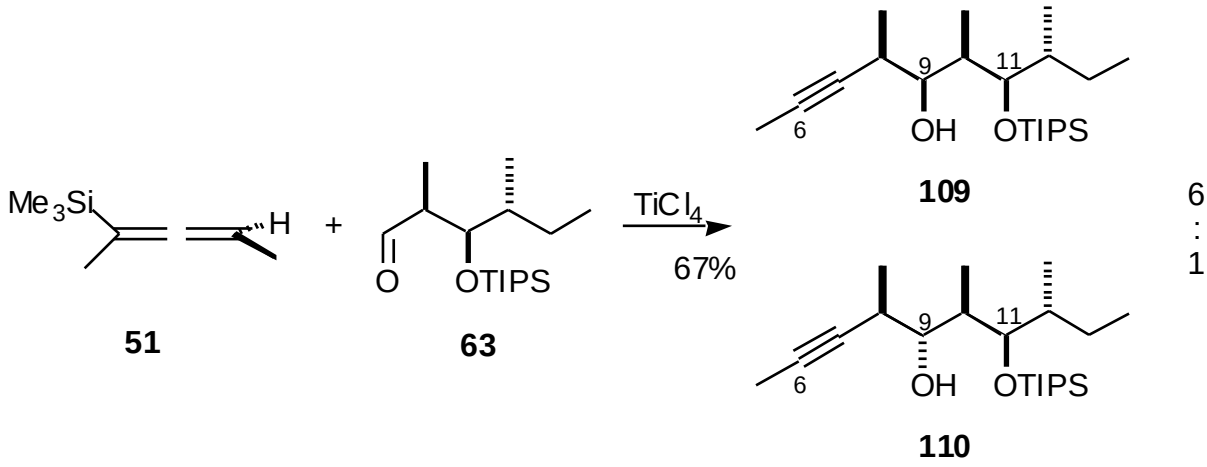
The advantage of having the oxygen functionality at C11 masked as a silyl group was that no chelation would take place in the coupling reaction: chelation would lead to a favouring of the undesired anti-Cram product and hence a mismatching, leading to a less diastereoselective reaction. Since it was now necessary to carry an oxygen atom on C11 through the coupling, a bulky protecting group would be required to ensure that chelation was minimised. Trialkylsilyl ethers are known to be effective for this for either steric or electronic (π-withdrawing) reasons.[186] Hence, after testing in the model series, Archibald made the homochiral TBDMS ether **99** from the β-silyl ester **81**, and found that coupling with fragment B (98% ee) was successful this time, giving alcohols **107** and **108** in a 3:1 ratio (scheme 2.26).



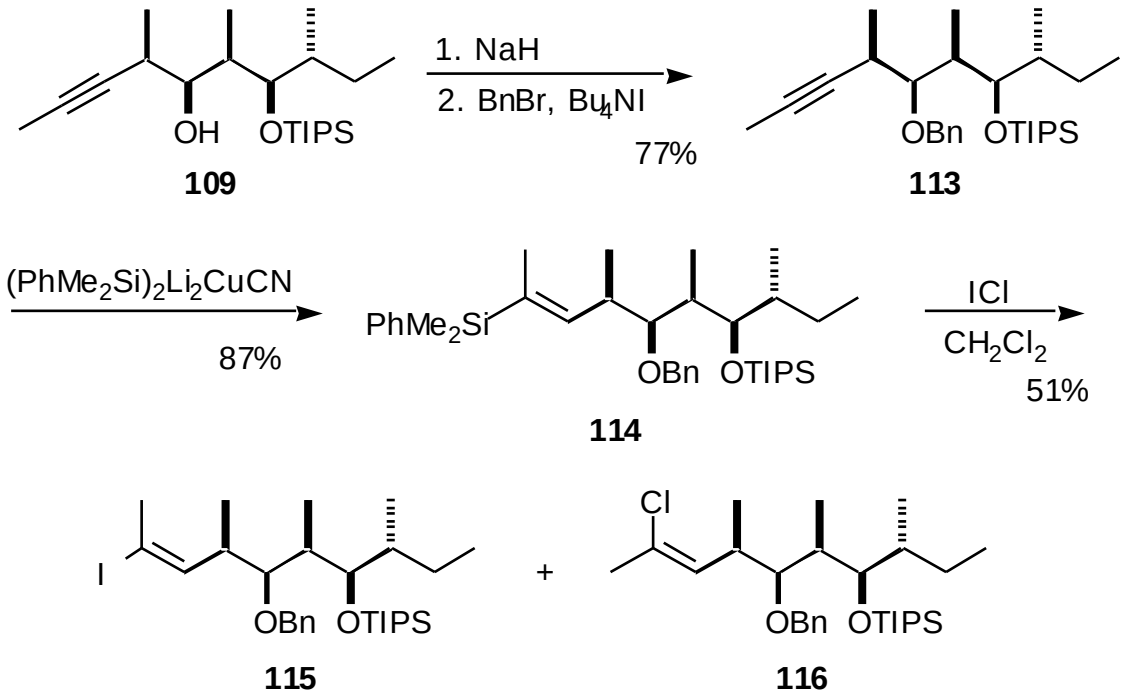
Scheme 2.26

This selectivity was rather disappointing for a matched system, and the likely problem was that the TBDMS group was insufficiently bulky to prevent some chelation. The C9 carbon eventually will be oxidised on the way to ebelactone-a, but carrying a mixture of diastereoisomers through numerous steps would be complicated and is to be avoided if

possible. Hence, when Williams repeated this work she made, in addition to the TBDMS ether **99**, the TIPS ether **63** so that their performances in the coupling reaction could be compared. TIPS is a bulkier group, and so ought to lead to a lower proportion of the chelation-controlled *anti* alcohol. This turned out to be the case, with a 6:1 ratio being obtained in the case of the TIPS ether (scheme 2.27).



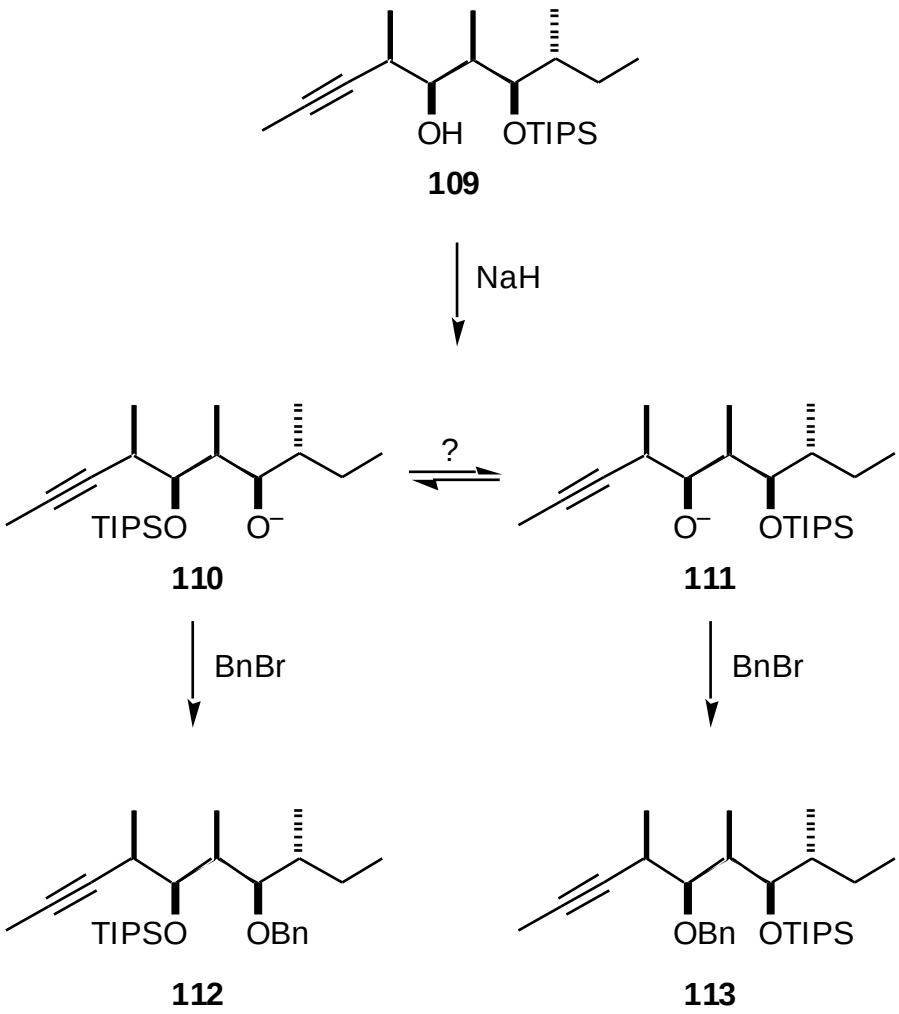
Scheme 2.27



Scheme 2.28

Even this ratio was quite poor in comparison with literature examples where chelation was prevented completely,[187] but at least an improvement had been made. (The stereochemistry of these products has not been determined; they are assigned by analogy with previous work.)

Williams took the alcohol **109** on to the benzyl ether **113** in good yield following Czernecki's[188] procedure (scheme 2.28). This step proceeds *via* the alkoxide ion **111**, and it is known that when alkoxide ions are formed β to silyl groups, the silyl group can swap from one oxygen to the other (**110** × **111**) (scheme 2.29). Hence, it was not certain whether benzyl ether **112** or **113** was in fact formed, but provided (as seemed likely from the NMR) only one or other of these was produced (and not both), and that it could be established at some point which, it could in principle be sorted out at a later stage in the synthesis. An alternative



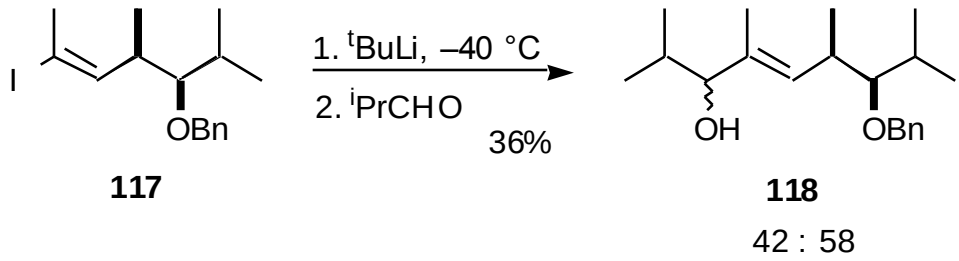
Scheme 2.29

benzylation procedure, such as that of Bundle[189] using benzyltrichloroacetimidate and a catalytic quantity of triflic acid under neutral conditions, would also be a possibility, as this avoids the oxy-anion intermediate.

Silylcupration[190] of the acetylene **113** led to the stable (indefinitely at +4 °C) vinylsilane **114** in good yield, and treatment with iodine monochloride[191] at –78 °C in the dark led to a mixture of the desired vinyl iodide **115** and the vinyl chloride by-product **116** in a ratio of about 12:1. The stereochemistry of the double bonds were determined by NOE difference experiments and by consideration of the NMR spectra of the products of protodehalogenation. This chemistry is further developed in work described in this thesis (see chapter 3).

2.3.2 Coupling of Fragment A to the Product of Coupling Fragments B and C

Archibald has modelled the coupling of vinyl iodide **115** to fragment A by forming the vinyllithium species from vinyl iodide **117** with t-butyllithium, and treating this with isobutyraldehyde, successfully obtaining diastereoisomeric alcohols **118** in low yield (scheme 2.30).



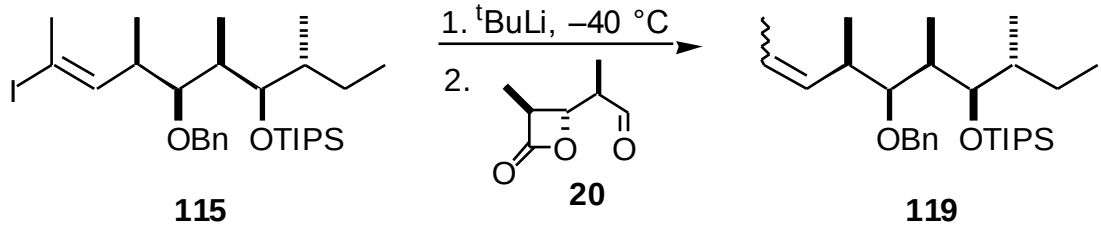
117 **118**

42 : 58

Scheme 2.30

Williams followed this precedent using vinyl iodide **115** (containing some vinyl chloride **116**, which ought not to react) and fragment A **20**, but very sadly none of the desired alcohol **120** was obtained—only the alkene **119**, indicating that though the vinyl lithium species had formed, it was quenched by a proton before it could react with the aldehyde (scheme 2.31).

This was probably due simply to the small scale of the reaction, necessitated by the very limited quantities of fragment A available at the time.

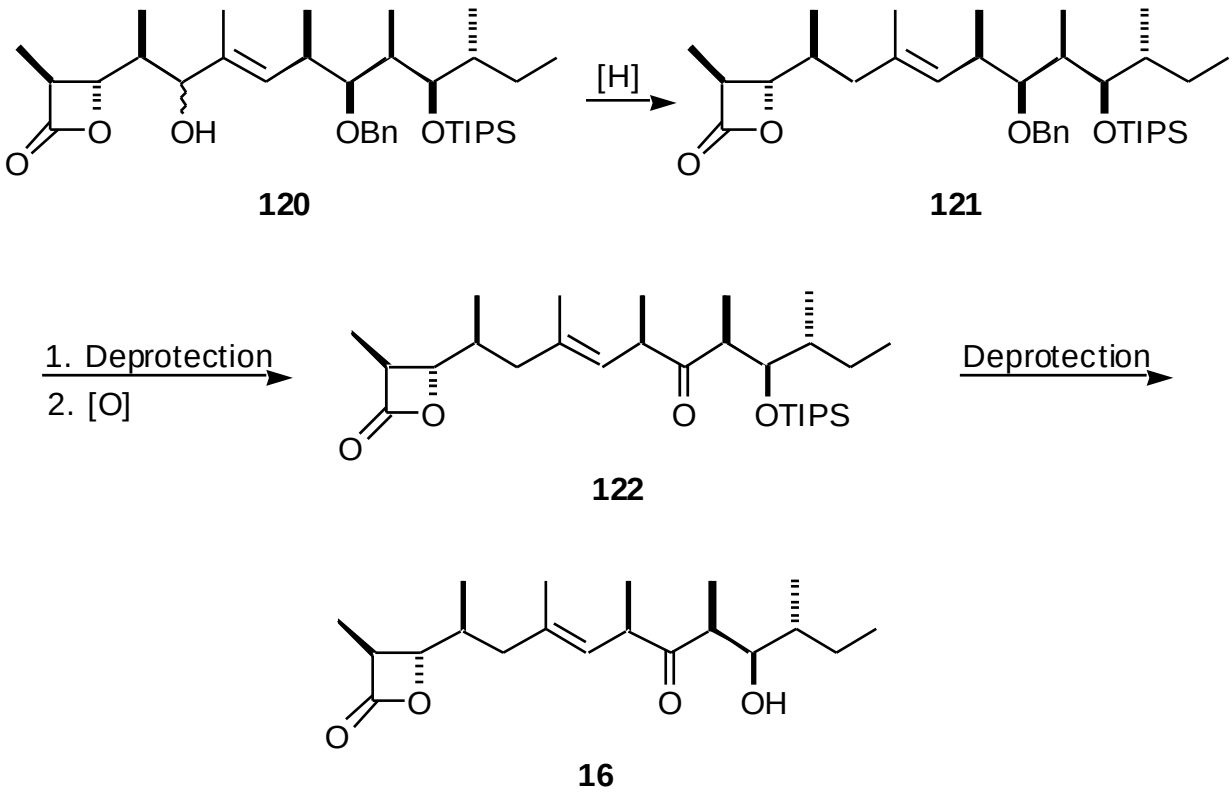


115 **20** **119**

Scheme 2.31

An alternative method of achieving this coupling is developed in the work described in this thesis (chapter 3).

2.3.3 Final Transformations

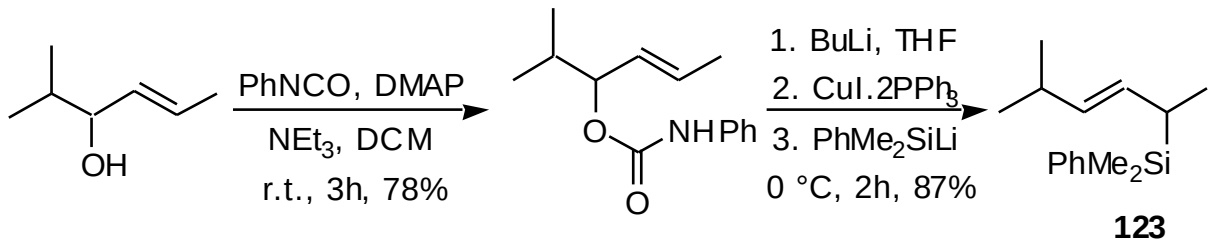


120 **121** **122** **16**

Scheme 2.32

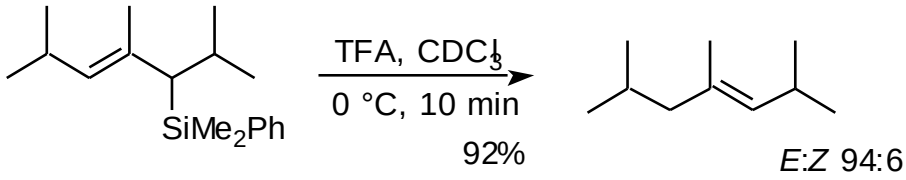
Once the final coupling (discussed above) is achieved and alcohol **120** obtained, all that will remain to be done will be removal of the hydroxyl at C5 (with retention of the double bond position and geometry) to give alkene **121**; deprotection at C9, followed by oxidation to the ketone **122**; and deprotection at C10 to give ebelactone-a **16** (scheme 2.32). (Whether the lactone functionality can be carried through these steps, or whether it needs to be opened and protected in some way remains to be investigated.)

Model work has been carried out with regard to the first step, that of reducing the allylic alcohol without shifting the double bond or losing the *E*-geometry. The strategy, developed by Thomas,[192-194] involves formation of the *N*-phenylcarbamate of the alcohol and S_N2' displacement of this with dimethyl(phenyl)silylcuprate nucleophile, leading to the allylsilane, protodesilylation of which gives the alkene. The function of the carbamate, besides its leaving group property, is that the silylcuprate can be built onto the nitrogen and delivered to the other end of the allylic system intramolecularly, thus ensuring inversion of the allyl system. This method has been tried in a model series by Higgins (scheme 2.33) and used in Winter's synthesis of a prostaglandin intermediate,[195] and it is developed in the work described in this thesis (see chapter 3).



Scheme 2.33

In the formation of the allylsilane **123**, the double bond has shifted, but we expect protodesilylsation to restore the position and geometry we require (see scheme 2.34). There is precedent for this from work by Higgins (see figure 2.14) in a similar substitution pattern to our system.[196,197]



Scheme 2.34

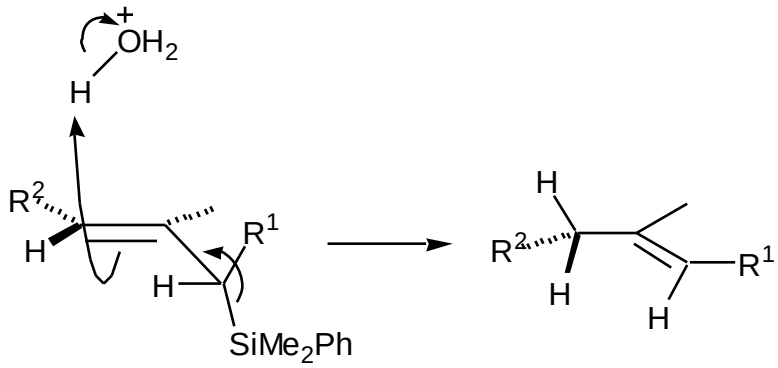


Figure 2.14