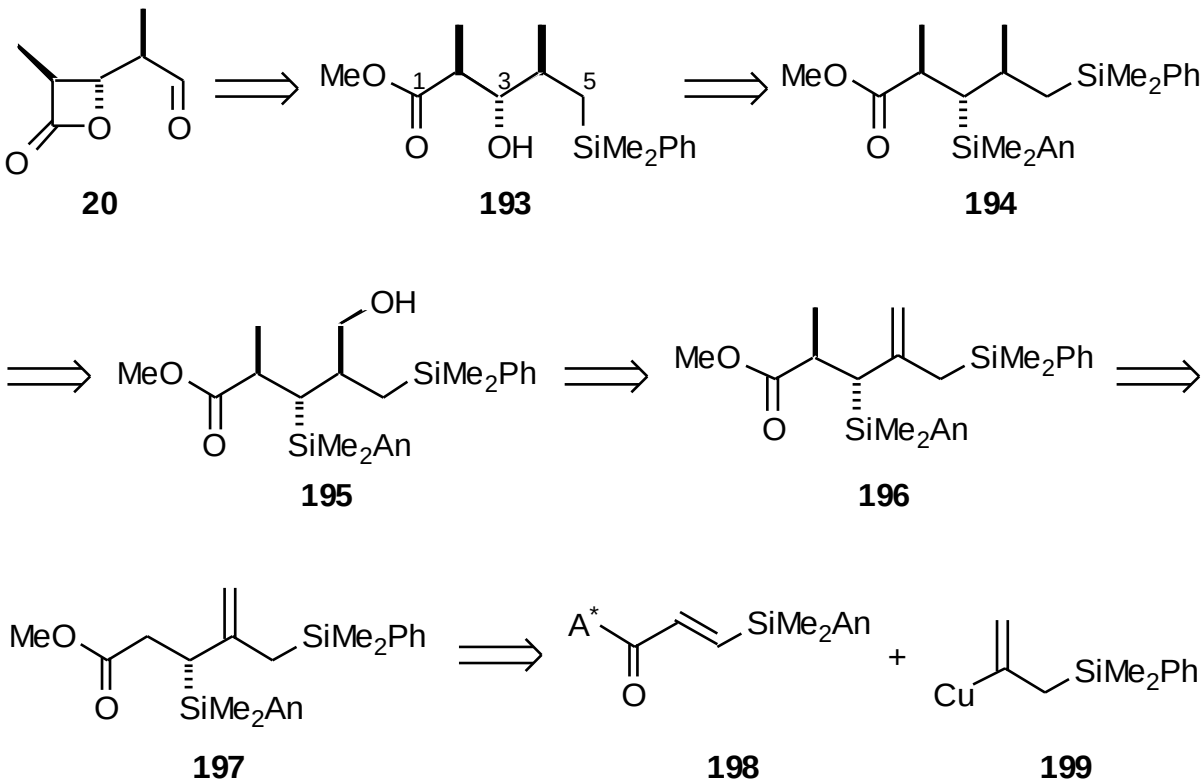
Chapter 5

A New Route to Fragment A

5.1 Introduction

Since we were encountering difficulties in repeating the aldol reaction in Williams' route to fragment A (see chapter 4), we decided to pursue an alternative, silicon-based, route. The retrosynthesis we chose to use is outlined in scheme 5.1.

Retrosynthetically, the β-lactone of fragment A **20** is opened to give the hydroxyester **193** with the aldehyde masked as a dimethyl(phenyl)silyl group (the aldehyde can be formed



Scheme 5.1 [An = 4-methoxyphenyl (anisyl)]

from the silyl group by silyl-to-hydroxy conversion followed by oxidation—see chapter 1). The secondary alcohol at C3 also comes from a silyl group, and we chose to differentiate these positions by using the dimethyl(4-methoxyphenyl)silyl [hereafter referred to as "dimethyl(anisyl)silyl"] group at C3 in ester **194**; we expected that it would be possible to oxidise this group selectively in the presence of the dimethyl(phenyl)silyl group, since the methoxy group activates the aromatic ring towards electrophilic substitution [the first step in the silyl-to-hydroxy conversion (see chapter 1)]. The relative rates of protodesilylation of anisyl, tolyl and phenyl in two different acids are given in figure 5.1,[131] and suggest that there would be a sufficiently large difference in reactivity between the two silyl groups in ester **194** for it to be possible to convert the dimethyl(anisyl)silyl group selectively in the presence of the other. This would be the first time that two silyl groups in a molecule have been separately transformed to hydroxy groups.

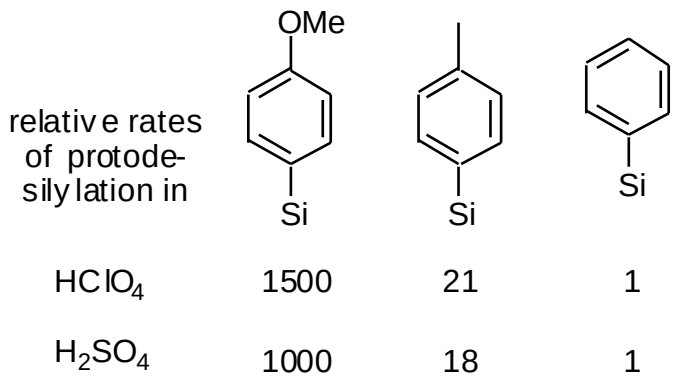
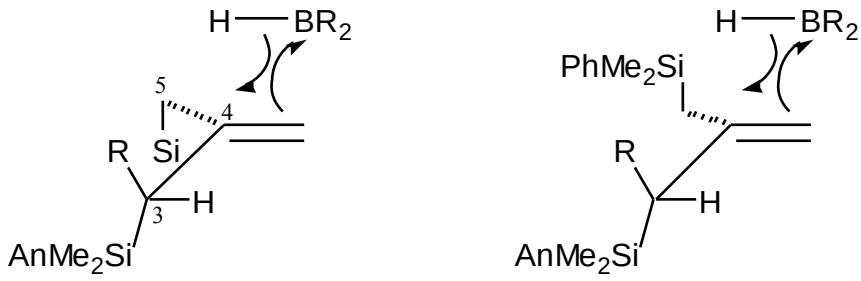


Figure 5.1

The methyl group at C4 can be obtained stereoselectively from allylsilane **196** by a hydroboration-oxidation process followed by reduction (perhaps by a radical method). The silyl group on C3 ought to direct the methyl group at C4 *anti* to itself (see chapter 1), but this reaction has never been done before with a second silyl group [the dimethyl(phenyl)silyl] β to the carbon bearing the positive charge in the intermediate. We were aware that there would be a risk that the steric bulk of the dimethyl(anisyl)silyl group on the lower face (see figure 5.2) would cause the other silyl group (on C5) to adopt a position preferentially on the upper face

(conformation **II**), thereby leading to a loss of stereoselectivity (i.e., the hydroboration taking place on both faces of the double bond with little to distinguish between them). The only way to discover whether this is likely to be a problem is actually to try it.



I **II**

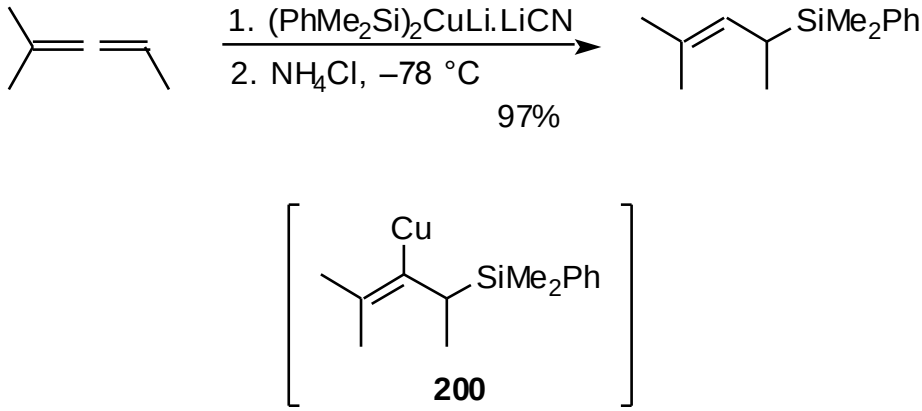
Figure 5.2 (Si = $PhMe_2Si$ in I)

Methylation of ester **197** with LDA followed by methyl iodide is expected to set up the methyl group at C2 of ester **196** with good selectivity (the selectivity of this reaction is known to be improved when, as in this case, a γ-δ-double bond is present—the reason for this is not known). This ester **197** can be made from treatment of carbonyl compound **198** with vinylcuprate **199**, in which the chiral auxiliary A^* leads to a diastereoselective reaction, resulting in enantiomerically enriched ester **197** once the chiral auxiliary has been cleaved off. We were familiar with Oppolzer's sultams (see chapter 4), and had some available from the other route to fragment A; furthermore, alkylcuprates have frequently been added to *N*-β-(silyl)enoylsultams (notably by Oppolzer—see below), so we chose to use this methodology once again. We intended to make vinylcuprate **199** by silylcupration of allene (see below).

5.2 Silylcupration of Allenes

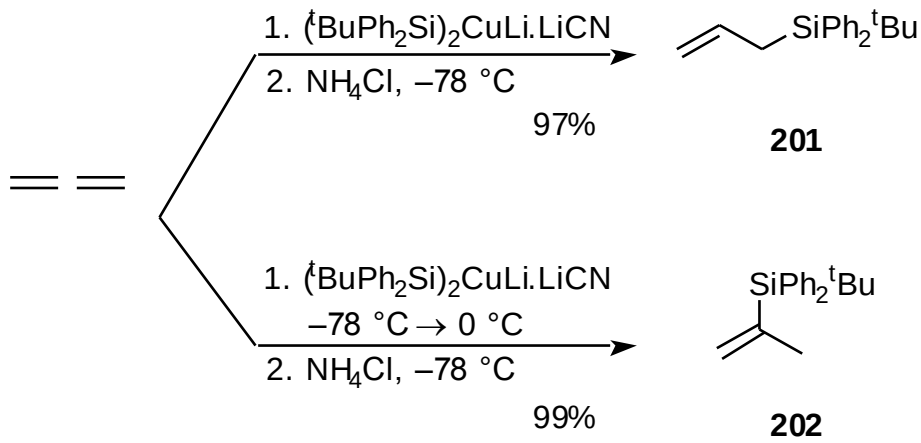
Silylcuprates are known to undergo addition to allenes, frequently with high regio- and stereospecificity (e.g., see scheme 5.2, where the intermediate cuprate **200** is quenched by a

proton).[301] The orientation of silylcupration (whether the copper goes to the end or the middle of the allenyl system) determines whether the product is an allylsilane or a vinylsilane, and this is dependent on the structure of the allene and in some cases the conditions of the reaction. For



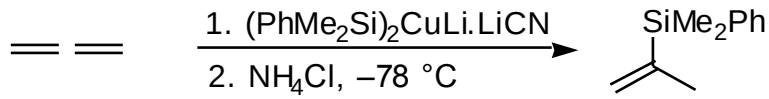
Scheme 5.2

example, with allene itself it has been shown that bis(t-butyldiphenylsilyl)cuprate can give either the allylsilane **201** or the vinylsilane **202**, depending on the temperature at which the reaction is performed (scheme 5.3).[302] Presumably vinylsilane **202** is produced at the higher temperature because the allylcuprate from which it is formed is the thermodynamic product—the allylsilane **201** is kinetically favourable because the silyl group experiences less steric congestion on adding to the terminal carbon atom than it would on adding to the middle one.



Scheme 5.3

With the less bulky dimethyl(phenyl)silyl group, silylcupration gives *only* the vinylsilane **203**, regardless of the temperature at which the reaction is performed. It appears that, now, the kinetic preference for allylsilane formation is less marked, owing to the smaller silyl group (scheme 5.4).[139]



203

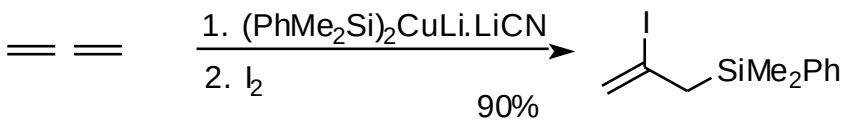
Scheme 5.4

It is possible to trap the cuprate intermediate with other electrophiles besides the proton, and it is found that vinylsilane-containing compounds **204** are the major products with most electrophiles (e.g., methyl iodide, acetyl chloride, ethylene oxide, enones, etc.) (scheme 5.5).

204

205

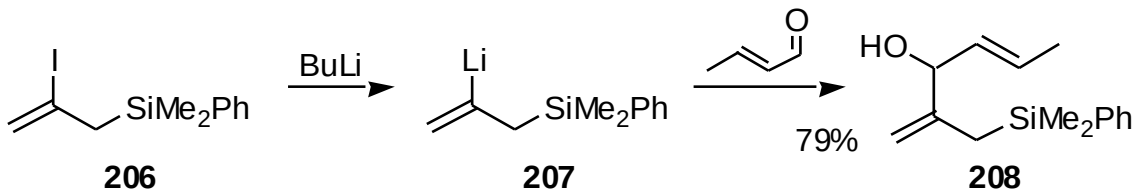
Scheme 5.5 (E^+ = Electrophile)



206

Scheme 5.6

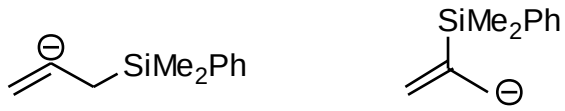
The two notable exceptions are bromine, which gives a mixture of **204** and **205**, and iodine, which gives exclusively the vinyl iodide **206** in excellent yield (scheme 5.6).



206 **207** **208**

Scheme 5.7

It is possible to treat vinyl iodide **206** with butyllithium to form the vinyllithium **207**, and then react this with electrophiles (e.g., methyl iodide, crotonaldehyde, etc.) to form allylsilane-containing products (such as **208**) in good yields (e.g., scheme 5.7). Hence, *via* the vinyl iodide, one can access the synthon **209** to complement the synthon **210**, available from silylcupration of allene (figure 5.3).

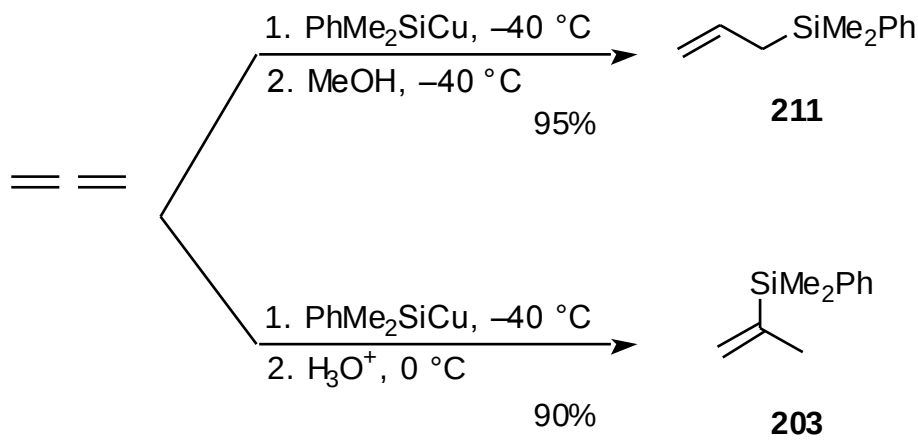


209 **210**

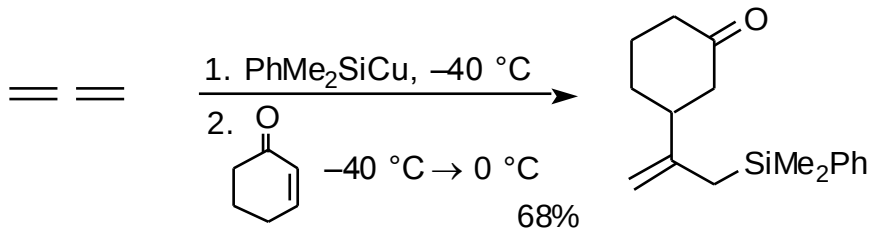
Figure 5.3

More recently, Pulido has reported that the dimethyl(phenyl)silylcopper reagent prepared from one equivalent of dimethyl(phenyl)silyllithium with one equivalent of copper(I) cyanide gives, on reaction with allene, either the vinylsilane **203** or the allylsilane **211**, depending on the temperature of the quenching, in an analogous manner to the bis(t-butyldiphenylsilyl)cuprate reaction (scheme 5.8).[303] He has successfully trapped the vinylcopper with electrophiles, such as methyl iodide, acetyl chloride and ethylene oxide (e.g., see scheme 5.9).

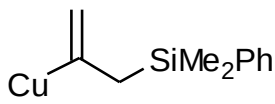
Since the vinylcuprate **199** (figure 5.4) we require is this same species, we chose to use Pulido's method to prepare it.



Scheme 5.8



Scheme 5.9

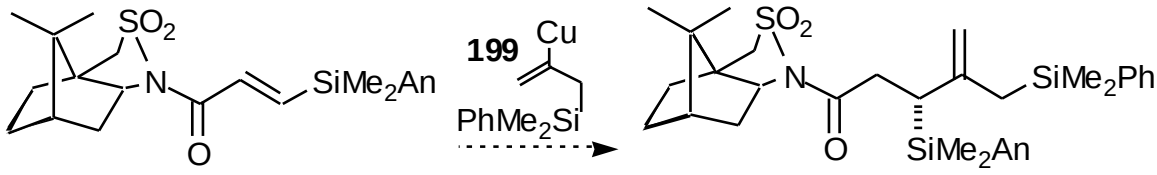


199

Figure 5.4

5.3 Nucleophilic Addition to *N*-β-(Silyl)enoylsultams

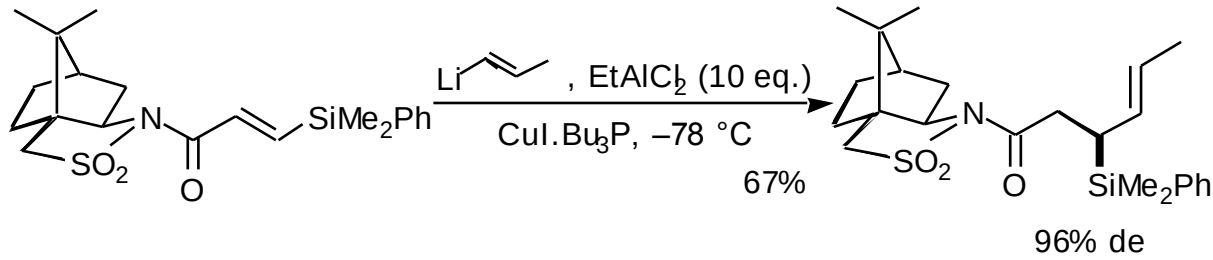
We needed to prepare the *N*-β-(silyl)enoylsultam **212** in order to react it with the vinylcuprate nucleophile **199** previously discussed (section 5.2), thereby establishing the first stereogenic centre of fragment A (at C3) in sultam **213** (scheme 5.10).



212 **213**

Scheme 5.10

Nucleophilic addition reactions of *N*-β-(silyl)enoylsultams are known to proceed with excellent diastereoisomeric excesses and good yields (e.g., scheme 5.11).[304-306] A wide variety of nucleophiles are effective. The sense of attack has been rationalised by means of the proposed transition structure given in figure 5.5.



Scheme 5.11

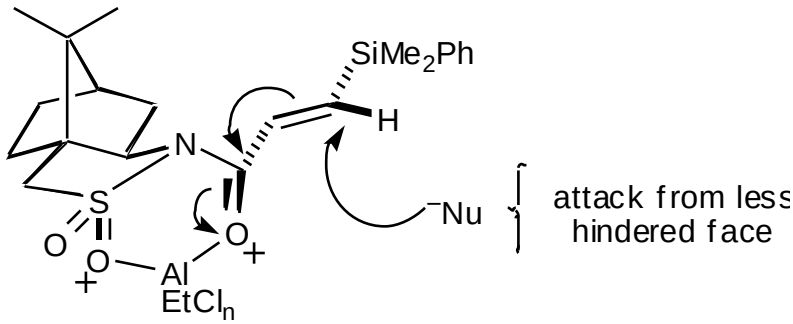


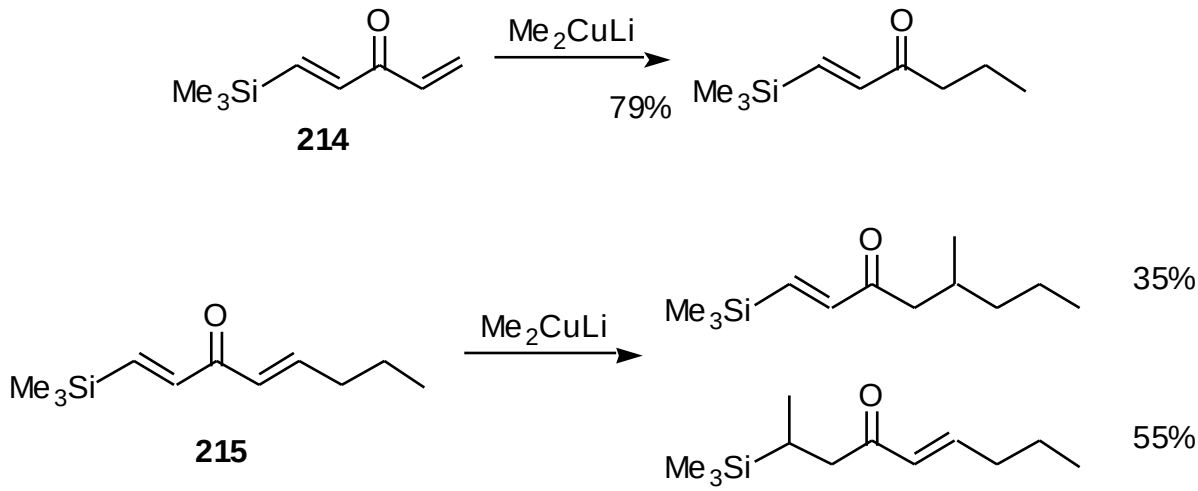
Figure 5.5

The Lewis acid (ethylaluminium dichloride) coordinates between the oxygen of the carbonyl group and one of those from the SO_2 group, locking the π-system into a position where an

incoming nucleophile prefers to attack from below to avoid the bulk of the sultam methyl groups on the upper surface.

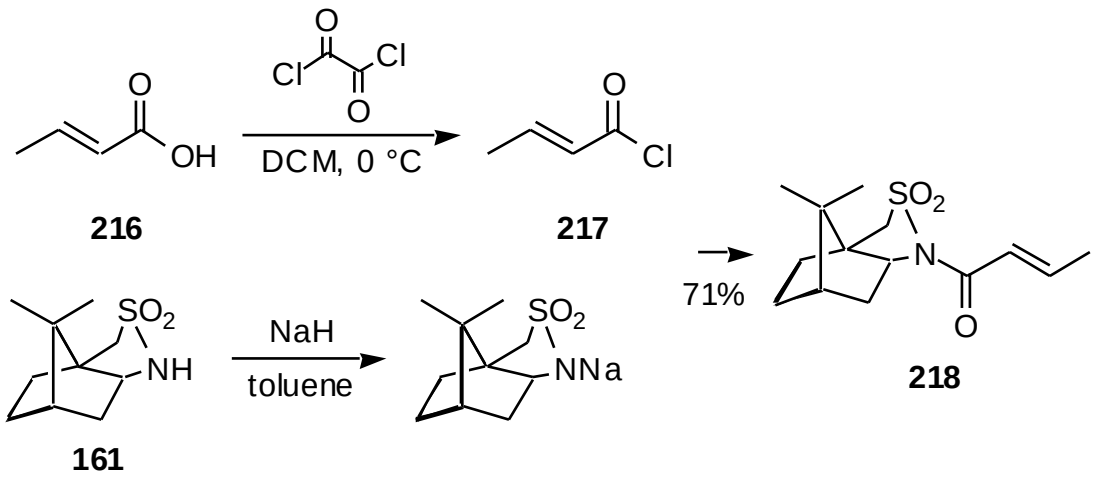
5.4 Model Reactions on Crotonylsultam 218

5.4.1 Allene Methodology



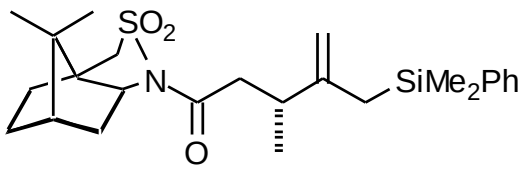
Scheme 5.12

Before investing the time necessary to synthesise the required *N*-β-(silyl)enoylsultam **212**, we decided to experiment with the allene ∅ vinylcuprate methodology in a simpler substrate with similar reactivity. Fleming has investigated the electrophilic properties of β-silylenones and found that the effect of a silyl group on the β position of an enone is comparable with that of an alkyl group (see scheme 5.12).[306] Methylcuprate reaction with dienone **214** gave attack exclusively at the unsubstituted double bond, while the dienone **215** suffered attack more or less equally on both sides. Hence, we felt that crotonylsultam would be a reasonable model for us to use simply to see whether we could perform the desired nucleophilic addition reaction, since the methyl group on the double bond ought to have an effect similar to that of a silyl group.



Scheme 5.13

Crotonylsultam **218** was prepared by deprotonation of (+)-camphorsultam **161** with sodium hydride in toluene followed by addition of crotonyl chloride **217**, freshly prepared by treatment of crotonic acid **216** with oxalyl chloride in dichloromethane at 0 °C. The preparation of the acid chloride had to be carried out carefully, since crotonyl chloride is volatile—in initial attempts, all of the material was lost on the high vacuum pump. A large excess of acid chloride was prepared, and only brief evaporation (to remove the dichloromethane and excess oxalyl chloride) was permitted before dissolving the material in toluene and adding to the deprotonated sultam. Pure crotonylsultam **218** was obtained in good yield after recrystallisation from methanol (scheme 5.13).

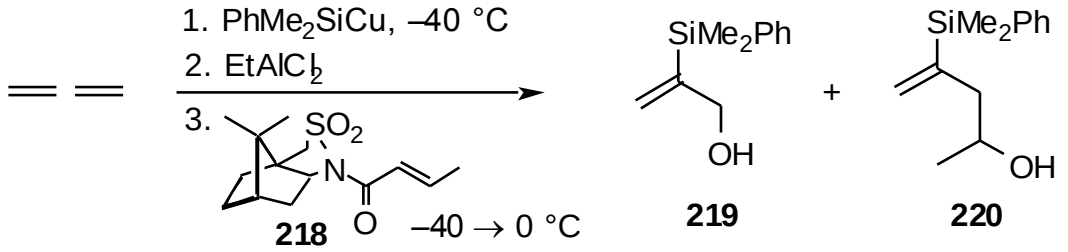


221

Figure 5.6

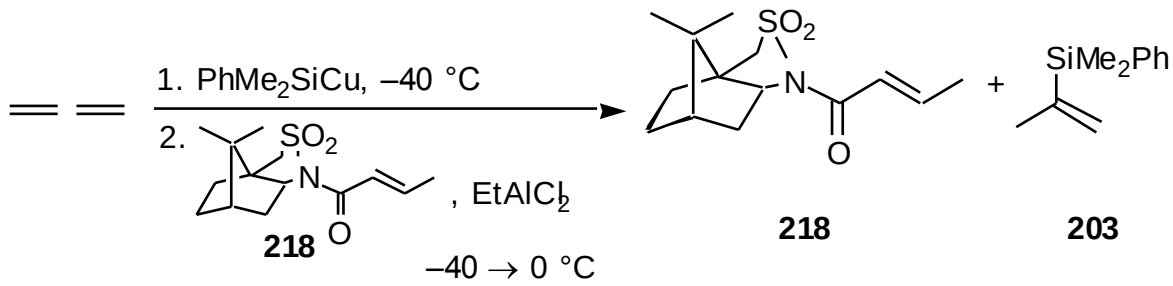
Following Pulido's procedure, we treated allene with the dimethyl(phenyl)silylcopper reagent, and then added the Lewis acid (ethylaluminium dichloride) at –40 °C, followed by the

crotonylsultam **218** in THF, obtaining on work-up only the alcohols **219** and **220** (scheme 5.14). None of the desired sultam **221** was isolated (figure 5.6).



Scheme 5.14

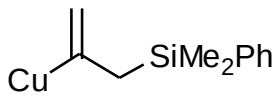
Alcohol **219** is formed unremarkably from oxidation of the allylcopper, suggesting that this copper species did indeed form. The alcohol **220** appears to be the result of nucleophilic addition of the allylcopper to acetaldehyde (produced, perhaps, either by retroaldol reaction from the crotonyl residue, or from the enolate of acetaldehyde, well known[307] to be produced in basic solutions of THF), but rather surprising.



Scheme 5.15

It is possible that in this procedure the addition of the ethylaluminium dichloride *before* the crotonylsultam converts the cuprate into an organoaluminium derivative, and that this has different reactivity from the desired cuprate. Hence, we tried changing the order of addition from that given by Oppolzer,[304] pre-mixing the sultam and the ethylaluminium dichloride before adding the silylcopper reagent, again at –40 °C. This time, the only products of the reaction were the starting material (crotonylsultam **218**) and the *vinyl*silane **203** (scheme 5.15).

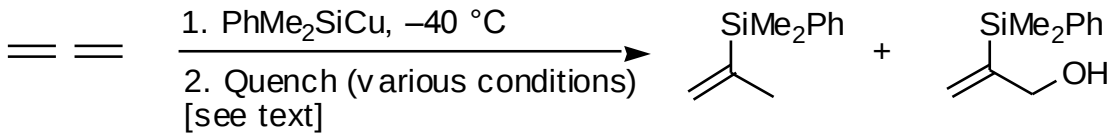
We were not expecting to see any of the vinylsilane in this reaction, since we understood from Pulido's work that it would be the allylsilane-vinylcopper species **199** which was present under these conditions (figure 5.7). Protonation of this should have given the *allyl*silane **211**.



199

Figure 5.7

Hence, we sought to reproduce Pulido's result in the protonation reactions of the products of silylcupration of allene with the dimethyl(phenyl)silylcopper reagent. To our surprise, we found that under no conditions were we able to obtain the allylsilane **211**. Regardless of the temperature at which the quenching took place (–78 °C, –40 °C or 0 °C), or how slowly it was carried out, the vinylsilane **203** was always the major product (the alcohol **219**, formed by oxidation, was generally present, but none of the desired allylsilane **211** was observed). Deliberately quenching at "high" (room) temperature—we thought that Pulido might possibly have reported his results the wrong way round—led to the same vinylsilane **203** (together with the alcohol **219**) (scheme 5.16).



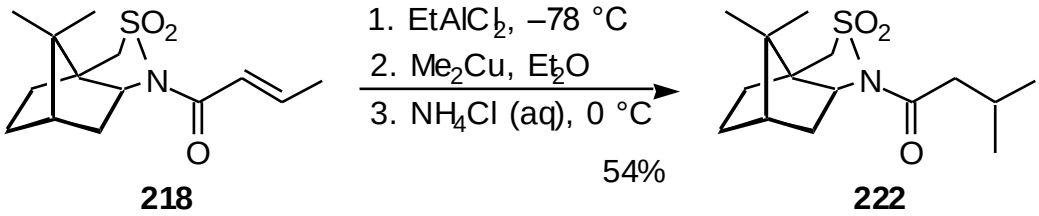
203 **219**

Scheme 5.16

Thus, in our hands we have not been able to utilise this methodology. We could probably have formed the required vinylcuprate *via* the vinyl iodide-vinyllithium-vinylcuprate route

previously described (see section 5.2), but we chose instead to use Sweeney's straightforward method for the synthesis of this nucleophile (see below).

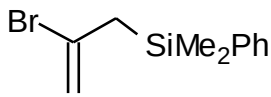
5.4.2 Alternative Route to the Vinylcuprate 199



218 **222**

Scheme 5.17

We first verified that our reagents and procedure were adequate for the nucleophilic addition to the crotonylsultam by trying the reaction with methylcuprate. Pre-mixing the sultam with ethylaluminium dichloride at –78 °C, followed by addition of methylcuprate, gave on work-up the sultam **222** cleanly and in reasonable yield (scheme 5.17).

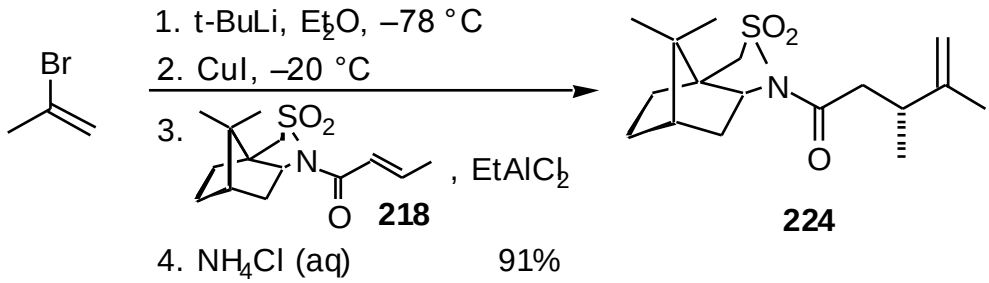


223

Figure 5.8

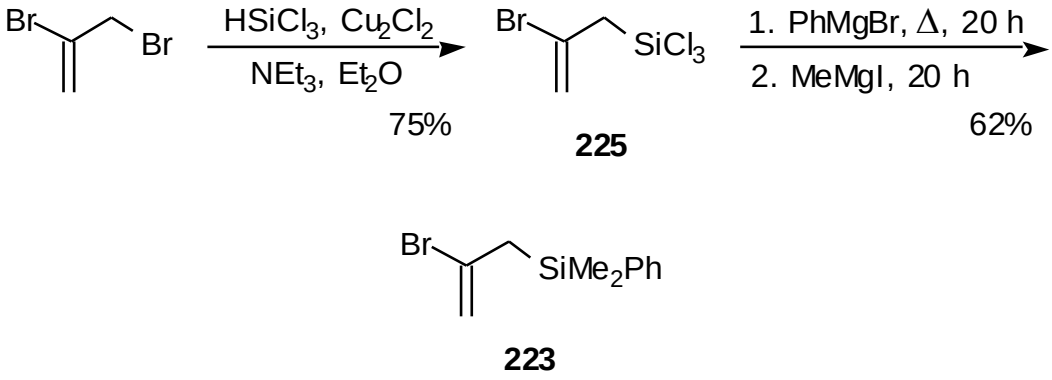
Sweeney's method[308] (see below) leads to the vinyl bromide **223** (figure 5.8); this can be readily transformed into the vinylcuprate **199** by successive treatment first with t-butyllithium at –78 °C to give the vinyllithium (**207**), followed by copper(I) iodide at –20 °C. We practised this sequence, starting out with 2-bromopropene, and then combined the isopropenylcuprate formed with crotonylsultam **218**, pre-complexed with ethylaluminium dichloride, and obtained sultam **224** smoothly in excellent yield (scheme 5.18). Hence, we had some

confidence that if we could pursue Sweeney's method without encountering any difficulties, then the allylsilane-sultam **213** would be within our grasp.



Scheme 5.18

Sweeney's method[308] is shown in scheme 5.19, and starts with readily available, though expensive, 2,3-dibromopropene. We repeated this work to prepare the vinyl bromide **223**. 2,3-Dibromopropene is mixed with trichlorosilane and catalytic copper(I) chloride in basic ether solution.[309] After stirring for 1 day, the copper(I) chloride is filtered off, and silyl chloride **225** is obtained in good yield. This silyl chloride is fairly moisture-sensitive, and is taken through straight away to the next step.

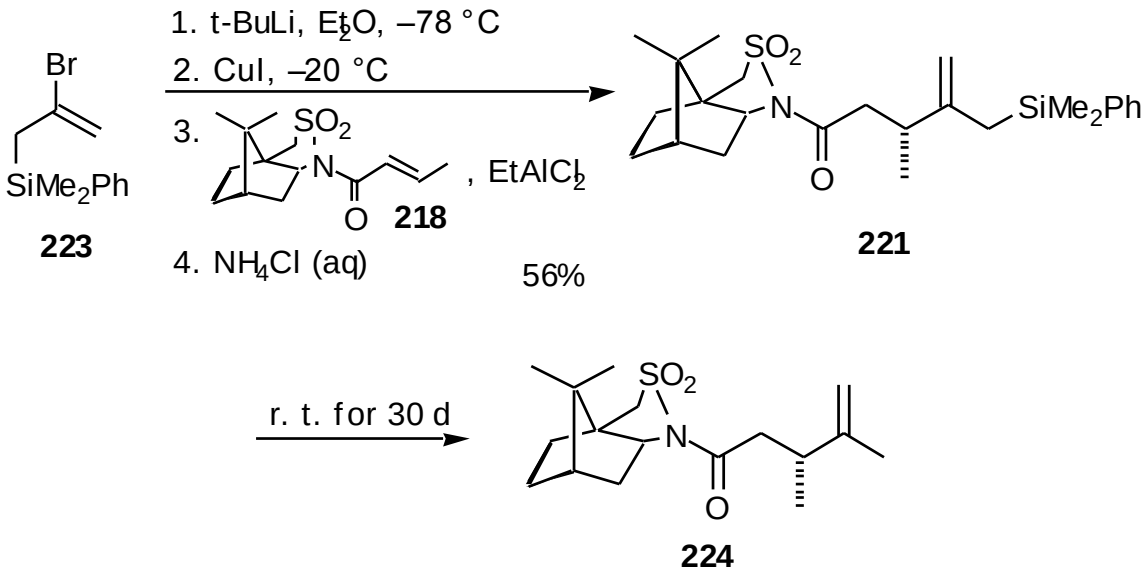


Scheme 5.19

Phenylmagnesium bromide is added to the silyl chloride **225**, and the mixture refluxed overnight. After one day, two equivalents of methylmagnesium iodide are added. This simple procedure leads, after a further day's stirring and simple work-up, to the required vinyl

bromide **223** in good yield and excellent purity after column chromatography. The vinyl bromide is a colourless liquid, indefinitely stable at +5 °C.

Forming the vinylcuprate **199** from this vinyl bromide, and reacting this with crotonylsultam **218** under the same conditions as before, afforded the desired sultam **221** in reasonable yield (scheme 5.20), together with an inseparable mixture of the familiar vinylsilane **203** and the allylsilane **211** (figure 5.9).



Scheme 5.20

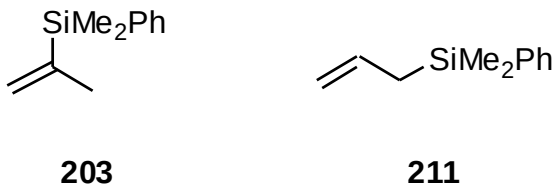


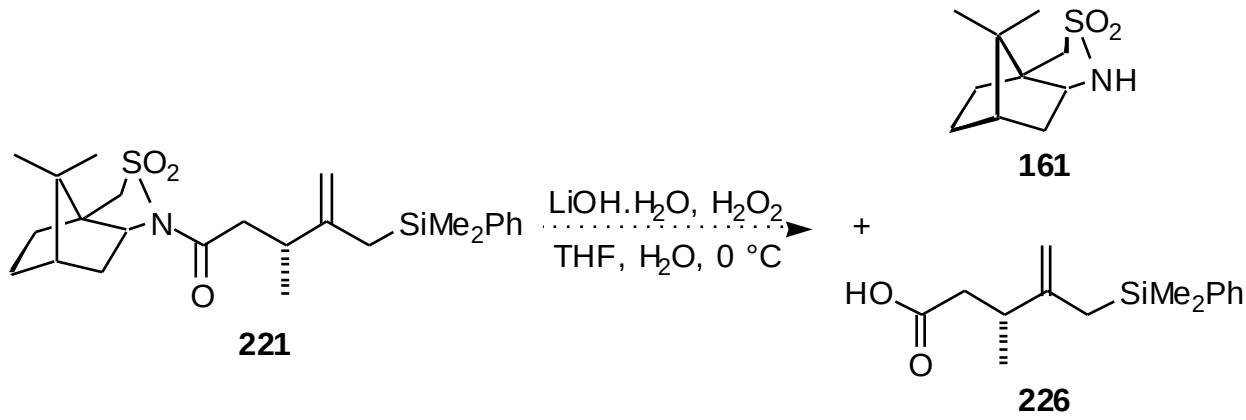
Figure 5.9

Though we obtained the sultam **221** in pure form, it did prove to be unstable with respect to protodesilylation, forming sultam **224** (identical to that prepared from isopropenylcuprate and crotonylsultam earlier) on standing for several weeks at room temperature. We were aware of the danger of this happening; in the quenching of the reaction

we always used *basic* saturated ammonium chloride solution, so as to discourage protodesilylation, but it seems that the tertiary silicon-stabilised carbocation intermediate is sufficiently stable to make the process favourable.

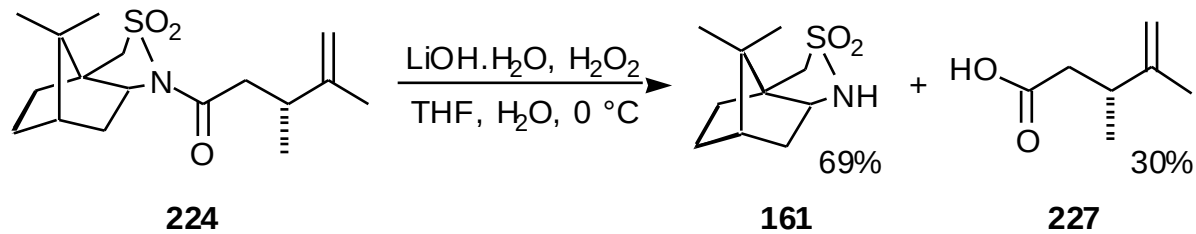
This made us less hopeful about the synthesis of the target sultam **213**, in which such a cation would be silicon-stabilised twice-over. However, we did not know how serious this problem would be, and felt that the compounds were still worth trying to make.

Our plan prior to this result had been to cleave the sultam **221** to give the sultam **161** and the carboxylic acid **226** (scheme 5.21), so we carried out a brief model series of experiments.



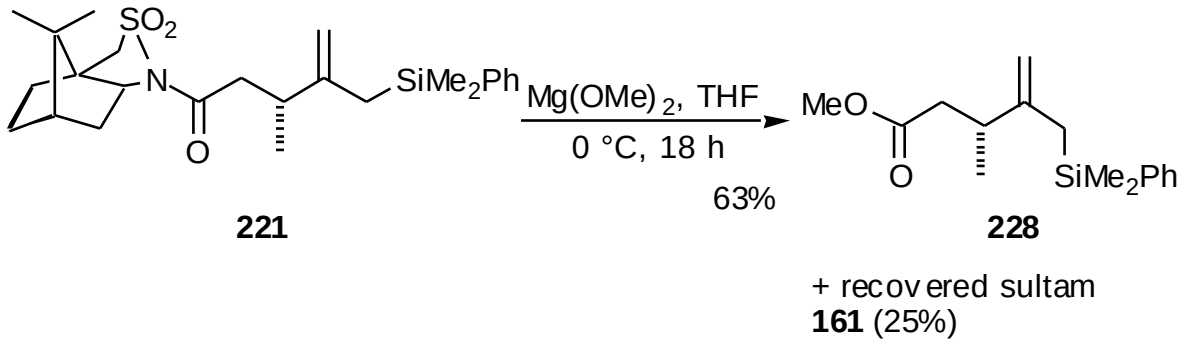
Scheme 5.21

Treating sultam **224** with lithium hydroxide and hydrogen peroxide in 3:1 THF:water for one day led to a good recovery of the sultam **161** but a low yield of acid **227** (scheme 5.22).



Scheme 5.22

Clearly, with the allylsilane functionality being so acid-sensitive, acid **226**, if formed, will protodesilylate itself, so this method would be a bad method of sultam cleavage. Instead, we chose to use magnesium methoxide under anhydrous conditions. Methylmagnesium iodide is added to methanol in THF at 0 °C, and the magnesium methoxide formed *in situ* cleaves the sultam group from the sultam **221**.[137] Freshly-prepared sultam **221** was treated under these conditions and gave the methyl ester **228** cleanly in good yield. The ester is a stable compound in the absence of acid (scheme 5.23).



Scheme 5.23

5.5 Synthesis of *N*-β-(Silyl)enoylsultam 212

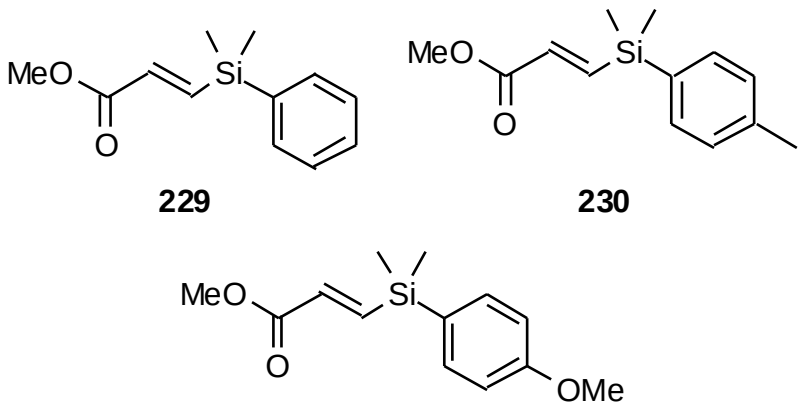
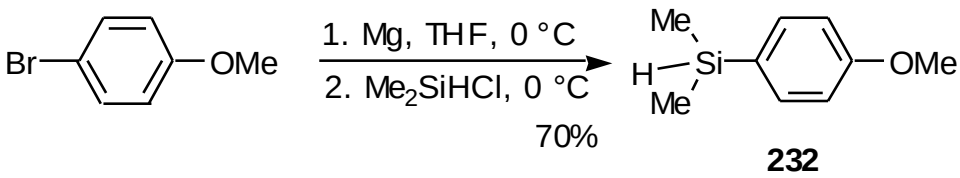


Figure 5.10

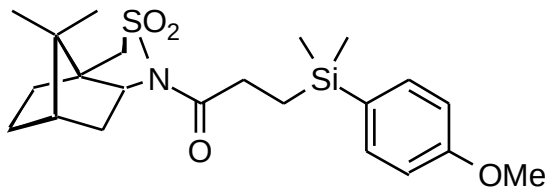
Esters **229** and **230** have previously been made by others (see chapter 2),[127] so synthesis of ester **231** posed no new challenge (figure 5.10). Following Zwicky's procedure,[127] the Grignard reagent was prepared from 4-bromoanisole and combined with chlorodimethylsilane to give the known silane **232**[310] in good yield (scheme 5.13).



232

Scheme 5.24

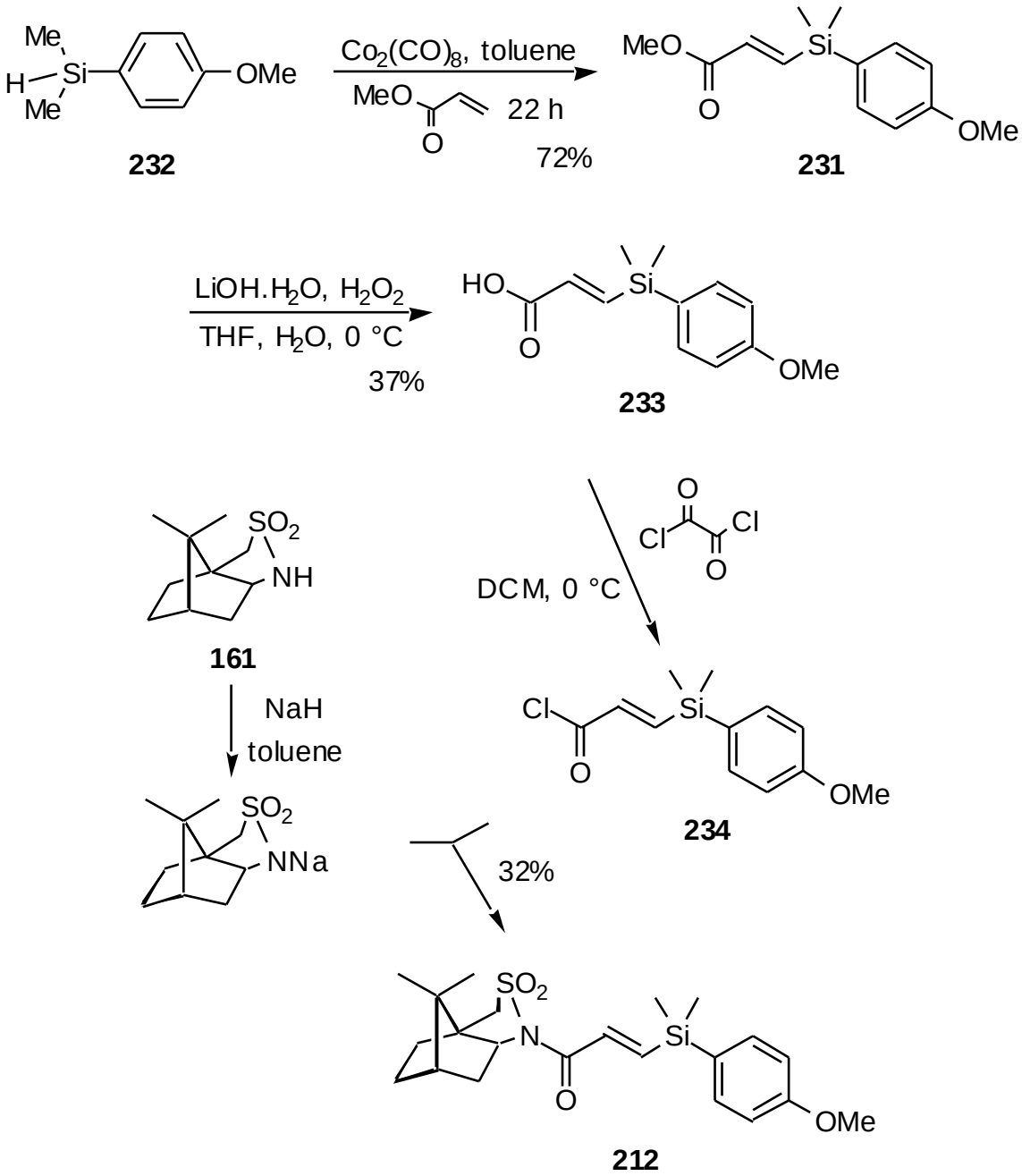
Dicobalt octacarbonyl-catalysed reaction of this silane with methyl acrylate in toluene for one day gave the crude acrylate **231** in good yield (scheme 5.25).[130] [Purification was postponed until after the next step (hydrolysis), so that advantage could be taken of the ease of removal of non-acidic impurities from the carboxylic acid product.]



235

Figure 5.11

The mechanism of this hydrosilation reaction is thought to be oxidative addition of $R_3SiCo(CO)_n$ to the C=C bond, followed by elimination of $HCo(CO)_n$.[130] Methyl acrylate is reduced to methyl propionate, and so a large excess of methyl acrylate is employed to avoid the reduction of significant quantities of the product ester **231**, leading to the saturated silyl ester **235** (figure 5.11). We saw no evidence for the formation of any of this in our reactions (NMR), which was fortunate, as it would have been difficult to separate from the unsaturated material.



Scheme 5.25

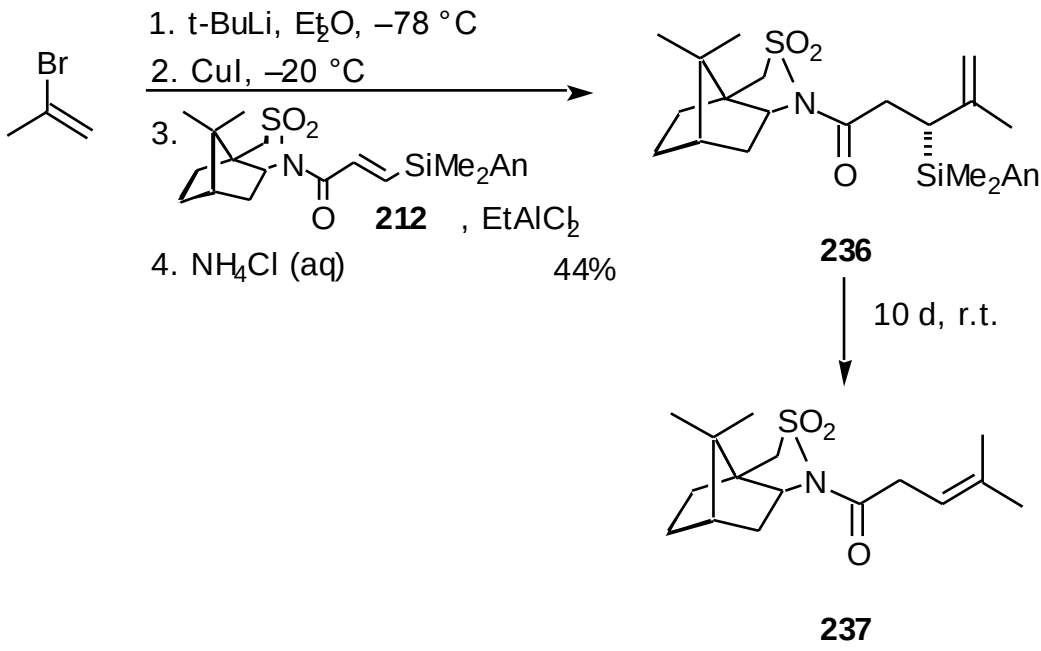
The dicobalt octacarbonyl reagent needs careful handling, since, besides its toxicity, it is rather water-sensitive. We weighed out the compound and added it to scrupulously dry silane **232** in a glove-box; the reaction is fairly vigorous, giving rise to brown fumes, and 1 g of silane was the maximum scale of reaction that we were happy to perform. The removal of the

inorganic products during the work-up is significantly easier if, after quenching the reaction with water, it is allowed to stir vigorously in air overnight.

Hydrolysis of the ester **231** with lithium hydroxide and hydrogen peroxide in 3:1 THF:water for several days gave the carboxylic acid **233**, which was purified in the work-up by washing out any organic impurities with ether before acidifying and extracting the acid with ether. This accounts for the low yield of pure acid, since the accumulated impurities of the previous two steps are removed during this process. The acid could be recrystallised with difficulty from light petroleum, but the crystals produced slowly decreased in purity over time, presumably because the acid protodesilylates itself.

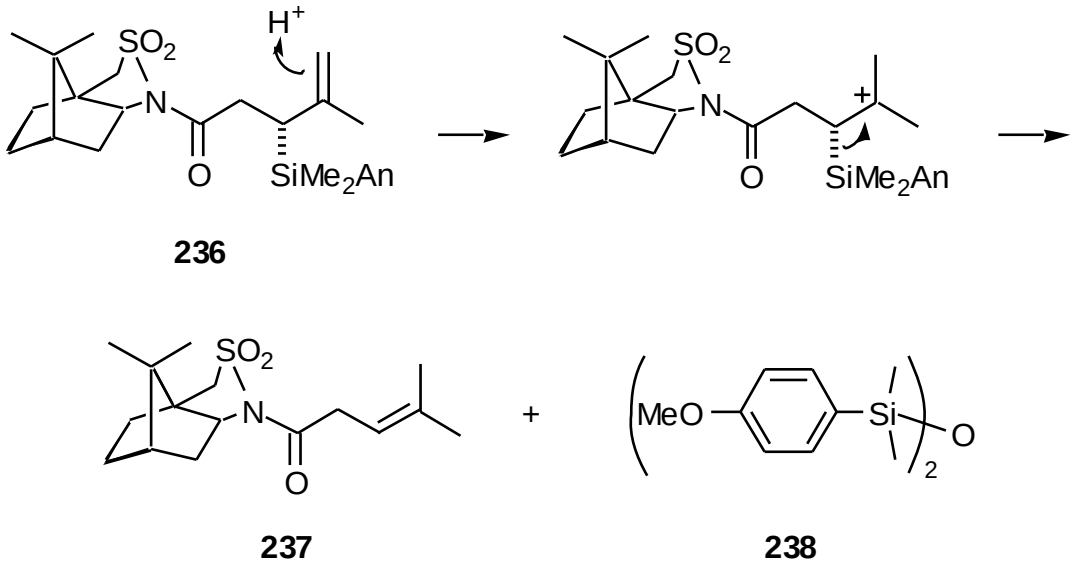
Treatment of freshly-prepared acid **233** with oxalyl chloride in dichloromethane at 0 °C gave the acid chloride **234**, which was not isolated but immediately combined with deprotonated (+)-camphorsultam **161** (prepared as described in chapter 4) in toluene to give the required sultam **212** in low yield (scheme 5.25). Attempts to improve this yield were unsuccessful. The material is easily recrystallised from methanol to give a stable product.

5.6 Reaction of Vinylcuprate 199 with Sultam 212



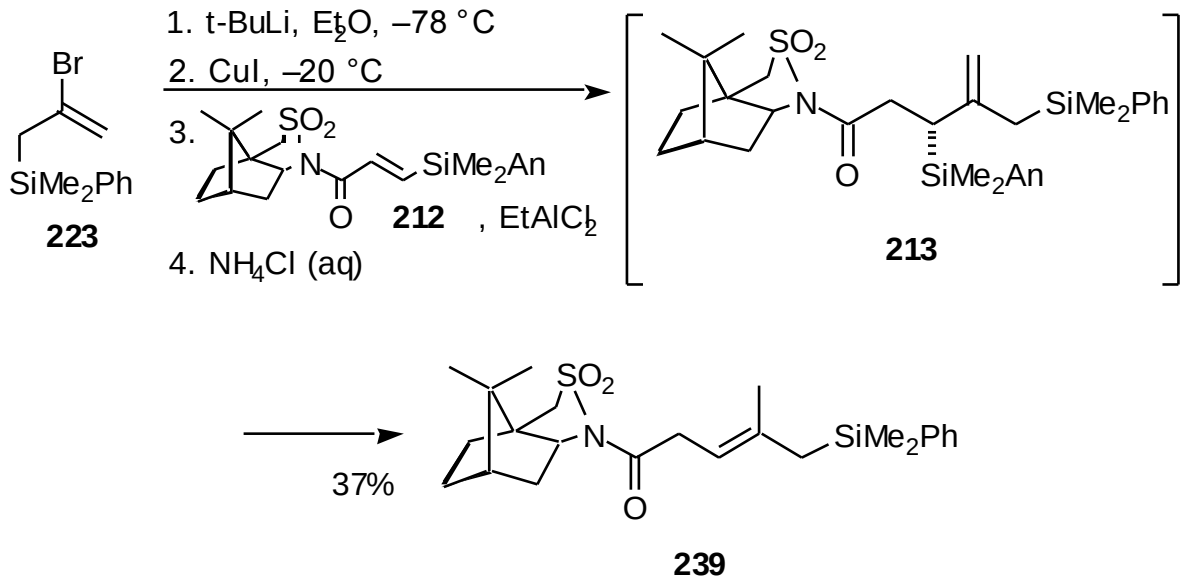
Scheme 5.26

We initially tried isopropenylcuprate addition to this sultam **212** by the same procedure we used on crotonylsultam **218** (see section 5.4.2), and obtained sultam **236** in low yield (scheme 5.26). This material was easily protodesilylated, so that after ten days at room temperature, sultam **237** and disiloxane **239** were the only products (scheme 5.27).



236 **237** **238**

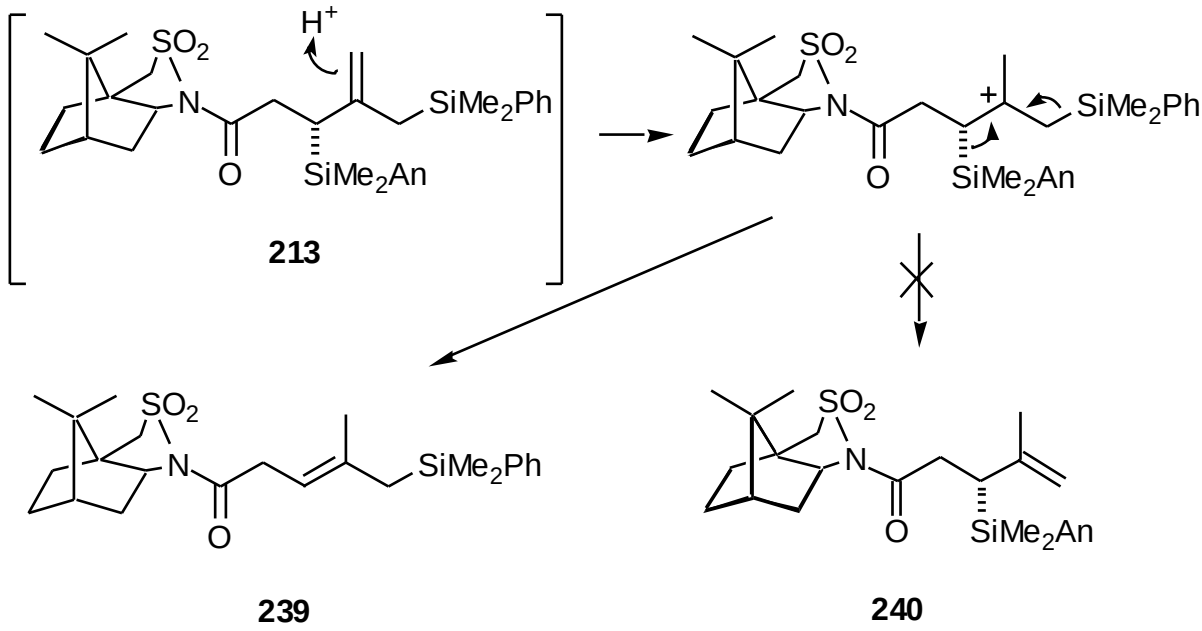
Scheme 5.27



223 **213** **239**

Scheme 5.28

This was a discouraging result, as it called into question whether the product sultam **213** of our desired reaction between vinylcuprate **199** and sultam **212** would also prove too susceptible to protodesilylation. On trying the reaction, we indeed found our fears realised, and the only product (in low yield) was the sultam **239**, formed by the desired reaction followed by protodesilylation, in which the dimethyl(anisyl)silyl group had been removed (scheme 5.28).

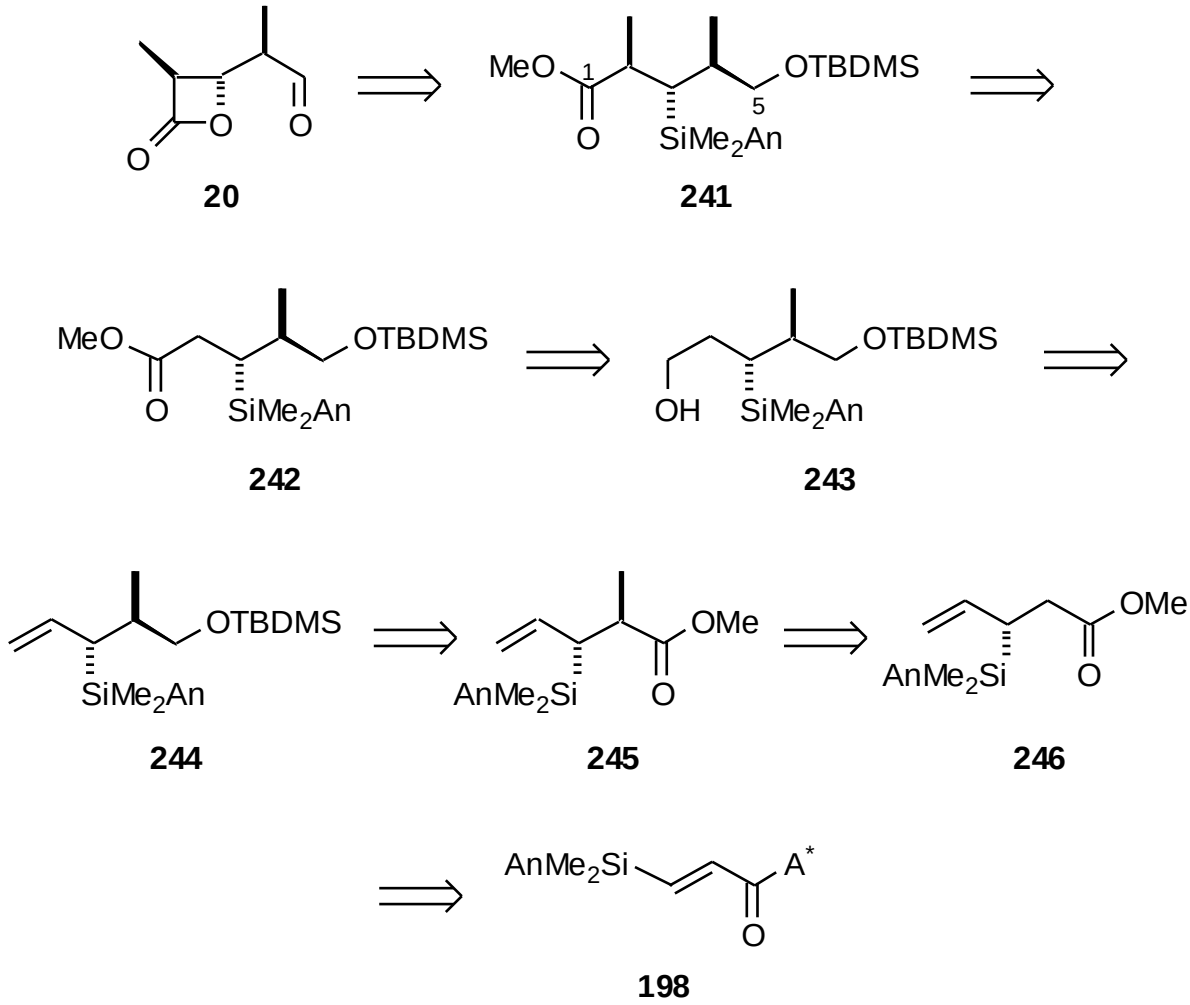


Scheme 5.29

None of isomer **240** [in which the dimethyl(phenyl)silyl group is lost] was obtained, no doubt because of the greater thermodynamic stability of the trisubstituted double bond in sultam **239** as compared with the disubstituted double bond of sultam **240**, rather than any difference between the anisyl and phenyl groups (scheme 5.29).

This result effectively closed off this entire route, and we had to think again how we could make fragment A, preferably using the sultam **212** which we had already taken considerable trouble over preparing.

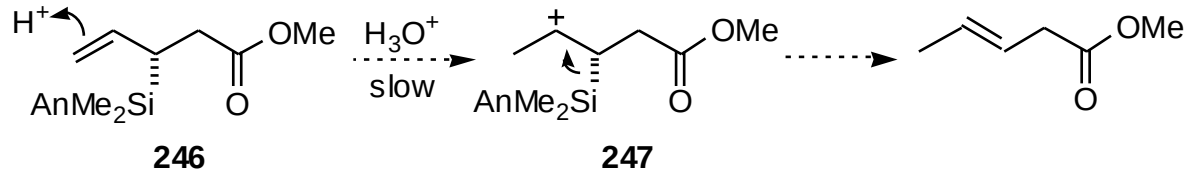
5.7 Another Synthesis of Fragment A



Scheme 5.30

This time we took fragment A **20** back retrosynthetically to the ester **241**, with the aldehyde at C5 latent as a silyl ether-protected alcohol. Disconnection of the methyl group at C2 gave ester **242**, which could come from oxidation of primary alcohol **243**, made by hydroboration-oxidation of allylsilane **244**. This allylsilane could be formed by TBDMS ether protection of the primary alcohol formed by reduction of ester **245**, formed from ester **246** by α-methylation with LDA and methyl iodide. Ester **246** could be obtained from the sultam derivative derived from vinylcuprate addition to the enantiomer of sultam **212** (scheme 5.30). Hence, we had a new synthetic route, distinguished from the previous one by using an

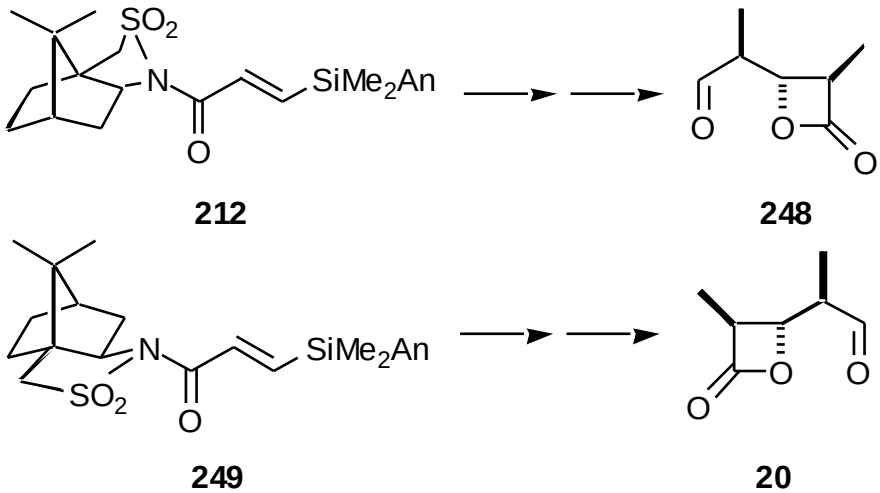
unsubstituted vinylcuprate nucleophile in place of a substituted one: this will certainly remove the potential for an allylsilane such as **246** to undergo protodesilylation, since protonation gives a cation **247** which is only secondary (rather than tertiary, or tertiary and β-silicon-stabilised, as before) (scheme 5.31).



246 **247**

Scheme 5.31

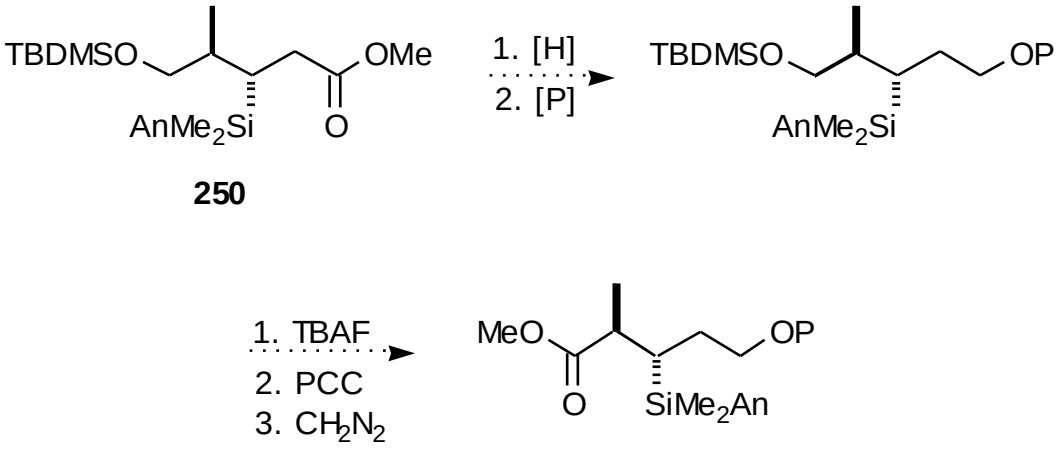
Using sultam **212**, this route would lead to the enantiomer **248** of fragment A (scheme 5.32). It would be possible to modify the synthesis so as to swap around the functional groups on the end of ester **250** (the enantiomer of **242**) and to arrive at the correct enantiomer (scheme 5.33). Due to the limited time available at this stage of the work, we decided that we would use the sultam **212** already prepared, so as to work towards a synthesis of the enantiomer **248** of fragment A; subsequent workers can then synthesise the enantiomer **249** of sultam **212** and repeat the steps in the enantiomeric series to make fragment A **20** itself (scheme 5.32).



212 **248**

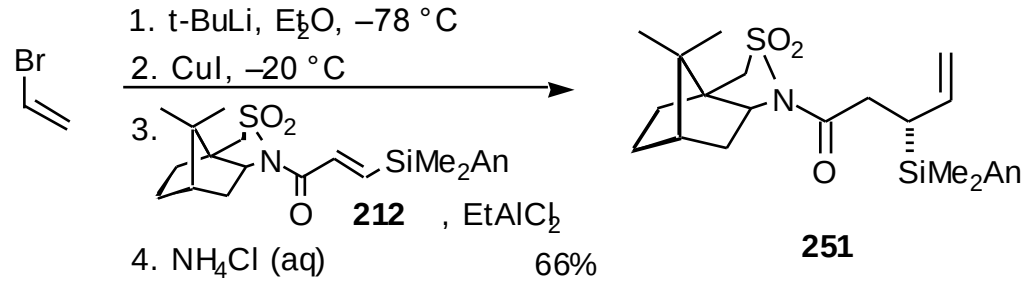
249 **20**

Scheme 5.32

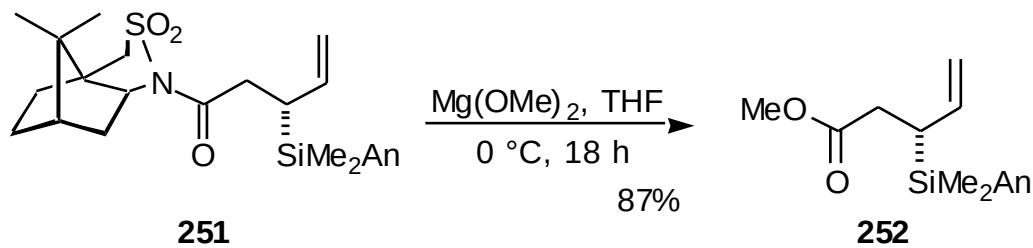


Scheme 5.33

Treatment of sultam **212** with vinylcuprate proceeded smoothly under the same conditions as earlier to give sultam **251** in good yield (scheme 5.34).

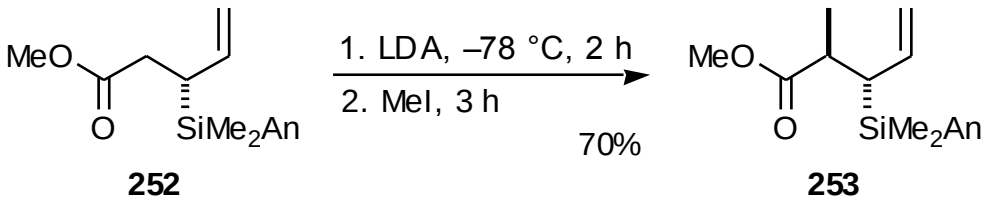


Scheme 5.34



Scheme 5.35

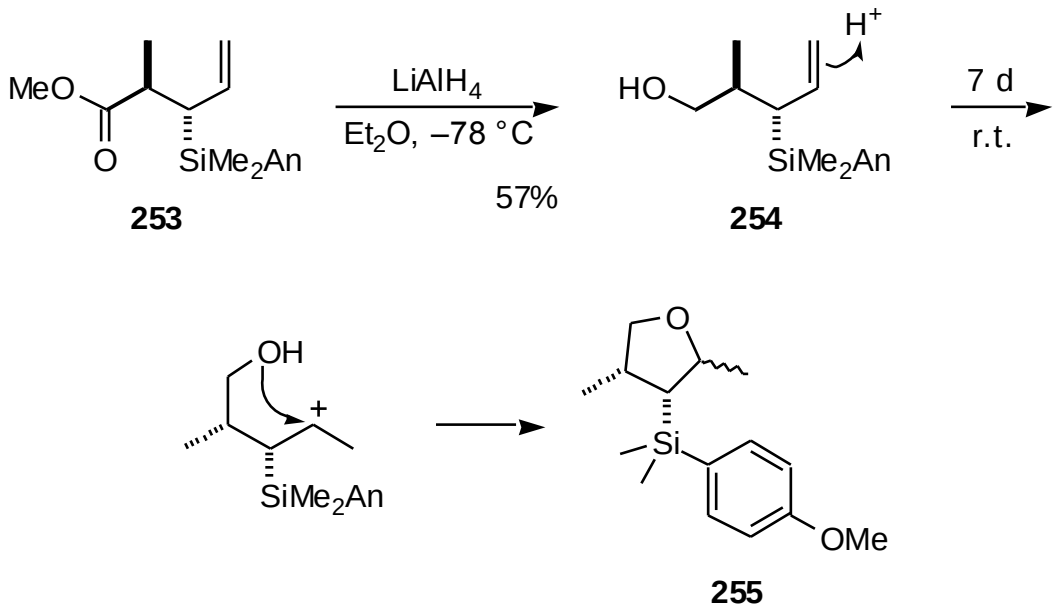
This product was easily recrystallised from methanol. The methyl ester **252** was formed in good yield with magnesium methoxide in THF (see earlier) (scheme 5.35), and this was subjected to methylation by addition of LDA in THF at –78 °C, followed by methyl iodide (scheme 5.36).[157]



252 **253**

Scheme 5.36

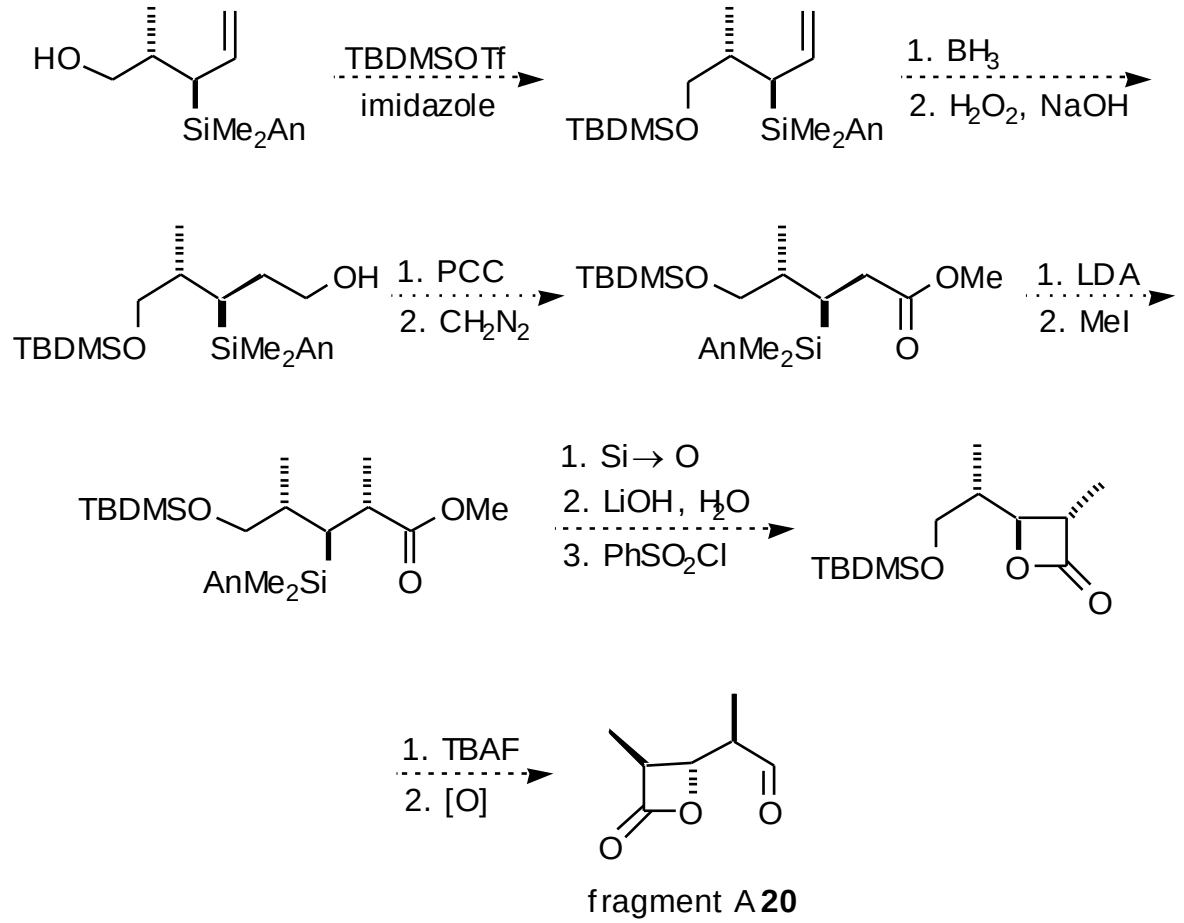
The α-methylated ester **253** was formed in good yield and excellent diastereoisomeric purity [no *syn* diastereoisomer was seen (NMR)]. (We expected the diastereoselectivity of this step to be good, because of the presence of the C=C bond—see earlier.) (See chapter 1 for an explanation of the β-silicon effect on α-methylation of β-silylesters.)



253 **254** **255**

Scheme 5.37

Reduction of the ester **253** with lithium aluminium hydride in ether at –78 °C led to the alcohol **254** in low yield. This alcohol cyclised to give the tetrahydrofuran **255** in a reaction having precedence with similar compounds (scheme 5.37).[311] (The protonation is probably assisted by delivery from the hydroxyl group.) There was insufficient time available to resynthesise more material to pursue this synthetic route, but there is little doubt that if the alcohol **254** were protected (TBDMS triflate in imidazole) immediately it was formed, this isomerisation could be prevented and the sequence continued.



Scheme 5.38

With this route successful up to this stage, the plan for a synthesis of fragment A is on a firm basis, with all of the steps in scheme 5.38 likely to work well. It is now being carried forward by Amit Mandal.