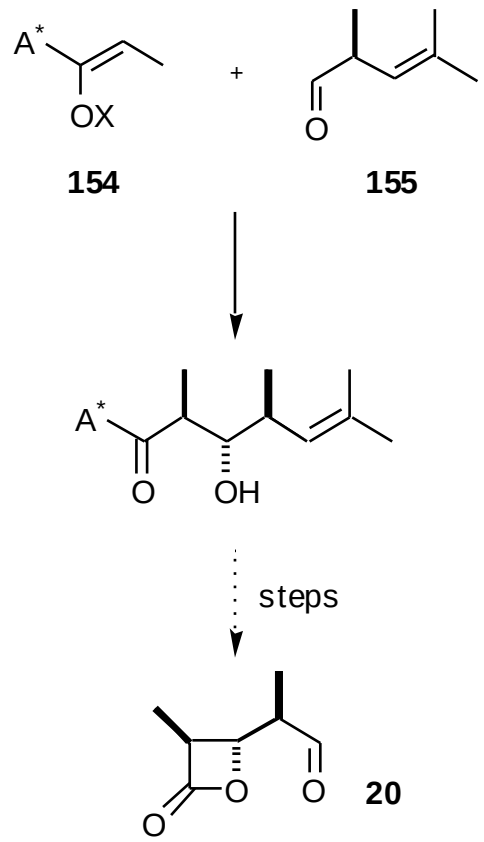
Chapter 4

Fragment A and the Model Coupling Reaction

4.1 Introduction

When Williams began working on the ebelactone project, previous workers had largely established that silicon-based methods could be used to solve the stereochemical problems of



Scheme 4.1

fragment A, but no efficient route to the fragment had been developed. Hence, in order to move the work on to the stage where the target molecule could be put together, she developed a non-silicon-based route to fragment A. It was necessary to repeat this work in order to attempt the Nozaki-Kishi reaction developed in the model series (chapter 3) on fragment A itself.

Williams viewed fragment A **20** as the product of an *anti* aldol reaction between enolate **154** and aldehyde **155**, the double bond in the aldehyde portion acting as a masked aldehyde functionality (scheme 4.1). This double bond can be cleaved by ozonolysis at a later stage in the reaction. (The two methyl groups on the double bond are there to improve this step, and they also contribute bulk to the intermediates in the sequence.) This method relies on the directing power of the chiral auxiliary A* to override the natural Cram-selectivity of the aldehyde.

Many methods of performing *anti* aldol reactions of this kind are available in the literature (see below).

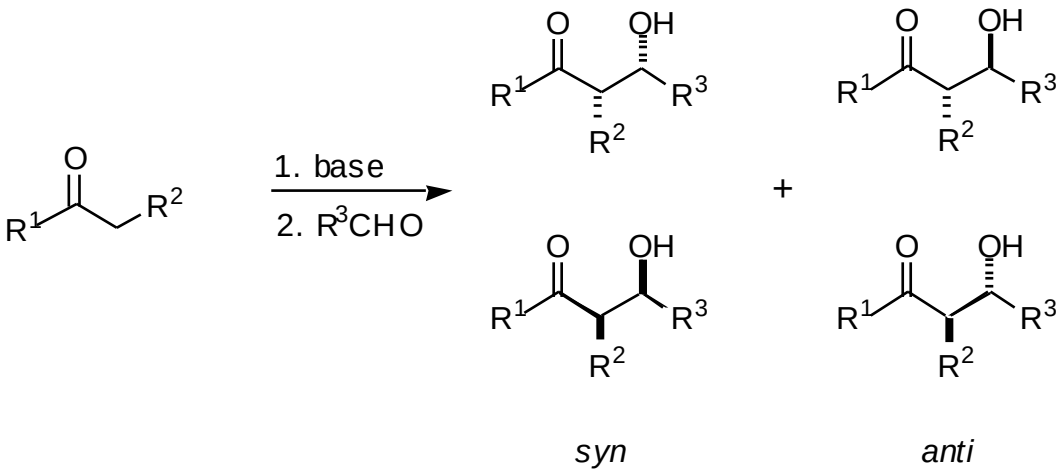
4.2 The Aldol Reaction

4.2.1 Introduction

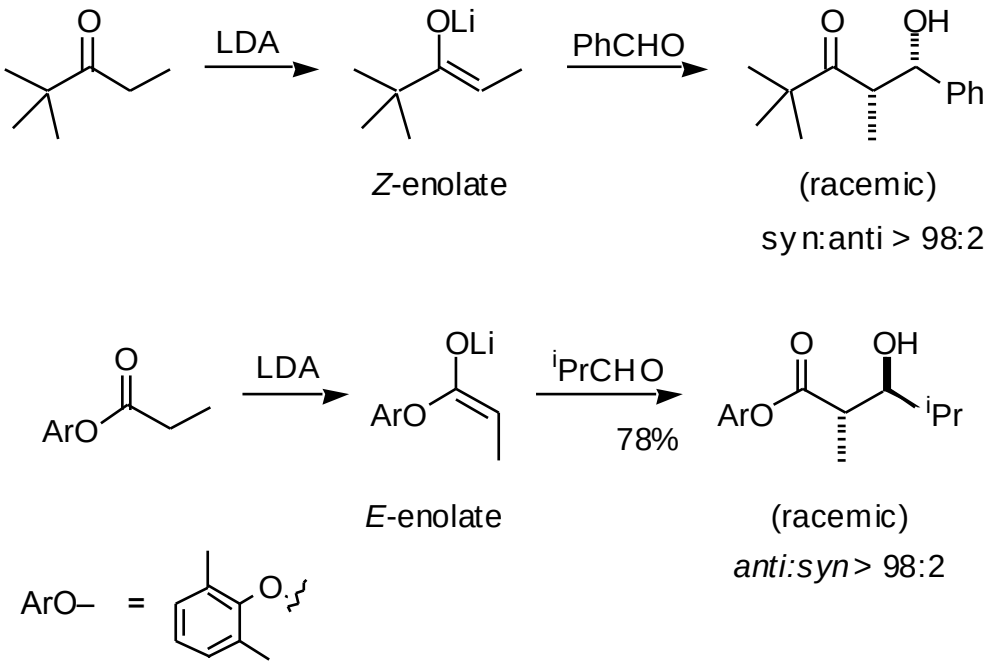
In the past, aldol reactions were performed under protic conditions, so that the enolate was formed reversibly. However, nowadays it is much more common to use a strong non-nucleophilic base to form the enolate quantitatively before combining it with the electrophilic component, as this results in a massive improvement in reaction control. Instead of forming an often complex mixture of products, frequently including much self-condensation of the starting materials, very often only one enantiomer is formed if chiral aldehydes or chiral enolates—or both—are employed. Much work has been directed in recent years towards stereocontrolled aldol reactions,[259-269] and only a very brief summary of some of this work can be given here.

2.2 Achiral Enolates with Achiral Aldehydes

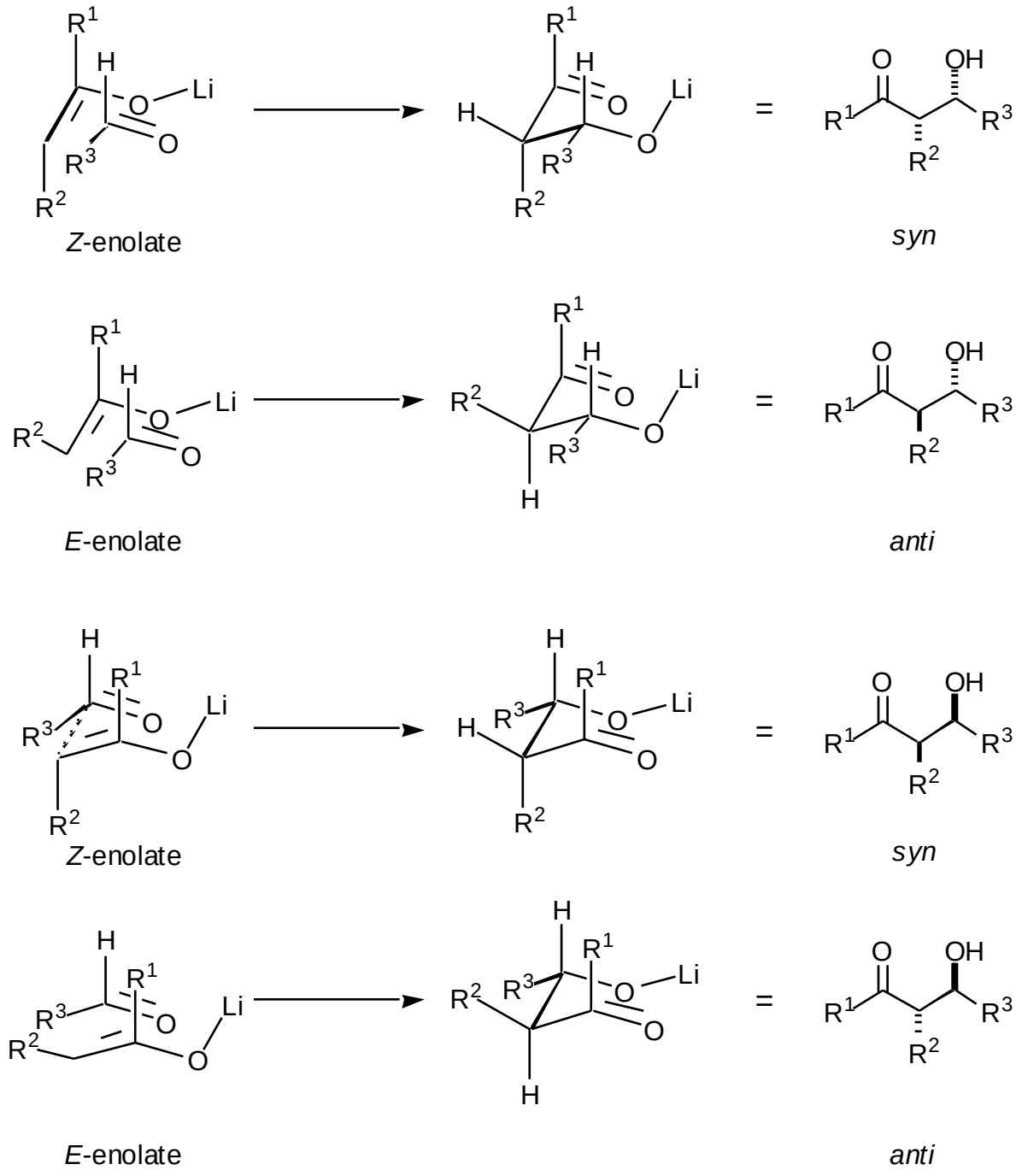
In the achiral situation, four diastereoisomers are possible: two enantiomeric *syn* diastereoisomers, and two enantiomeric *anti* diastereoisomers (scheme 4.2). The precise product(s) formed in any particular aldol reaction depend(s) not only on R^1, R^2 and R^3 but



Scheme 4.2



Scheme 4.3



Scheme 4.4

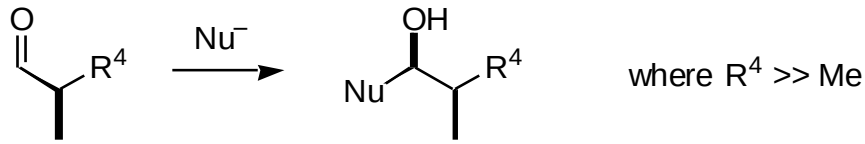
also on the nature of the base and any metal ions present. As is well-known, it has been found[270] that provided that R^1 is bulky enough and that the metal chelates in the transition structure, then, with lithium or boron, the *syn*/*anti* diastereoselectivity is largely dependent on the geometry of the enolate, *Z*-enolates giving *syn* products and *E*-enolates giving *anti*

products (e.g., scheme 4.3).[271,272] (Throughout this thesis, we refer to the geometry of an enolate as *Z* or *E* on the basis of the convention that the oxygen group derived from the carbonyl group is designated as having the higher priority regardless of the nature of the other substituents, in accordance with common practice.)

The outcomes are readily rationalised in terms of the Zimmerman-Traxler chair-like transition structures shown in scheme 4.4,[270] involving coordination between the two oxygen atoms and the metal centre. The chief steric interaction is that between R^1 and R^3. This is minimised in all the structures drawn in scheme 4.4 by positioning R^3 equatorial in the chair.

Since *Z*- and *E*-enolates can usually be produced at will (in particular, with LDA, ketones frequently give the *Z*-enolate while esters give the *E*-enolate), the relative stereochemistry of aldol reactions is largely a solved problem.

4.2.3 Achiral Enolates with Chiral Aldehydes



Scheme 4.5

For achiral nucleophiles attacking aldehydes possessing a stereogenic centre α to the carbonyl group, Cram's rule[273] predicts diastereoselectivity as shown in scheme 4.5, but for aldol reactions with achiral enolates, the diastereoisomeric excesses are not generally good, and are heavily dependent on the precise nature of the enolate. The situation is much improved by using chiral *enolates* as well; i.e., moving to *double* asymmetric synthesis.

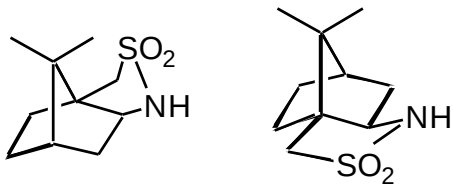
4.2.4 Chiral Enolates with Chiral Aldehydes

There are many examples of highly enantioselective aldol reactions involving chiral enolates with chiral aldehydes, and much work has been done establishing the effects of

particular features in the reactants. Notably, when the stereochemical preferences are "matched", very high enantiomeric excesses are frequently seen.[259-269]

Asymmetric aldol reactions readily provide *syn* aldols, but the *anti* unit is considerably more difficult to engineer. Methods in the literature include using boron, titanium or tin(II) enolates bearing chiral ligands;[274] the use of metal enolates formed from chiral carbonyl compounds;[275] and the Mukaiyama aldol reaction.[276] This latter category of reaction consists of aldol processes where a Lewis acid acts as a catalyst. The difficulties associated with establishing the *anti-anti* stereotriad have been described earlier (chapter 2). Williams chose to use the Mukaiyama aldol reaction, with Oppolzer's sultam providing the chirality in the enolate unit (A^* in scheme 4.1). This nicely complements the use of the sultam to produce the chiral aldehyde unit for the aldol reaction (though opposite sultam enantiomers are required) (see below).

4.3 Oppolzer's Sultams as Chiral Auxiliaries



Oppolzer's sultams

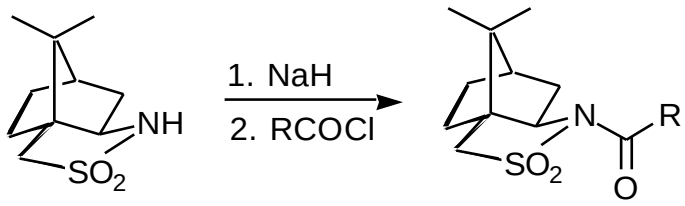
Figure 4.1

4.3.1 Introduction

Since they were first prepared in 1984,[277] Oppolzer's sultams (figure 4.1) have been very widely used, with great success, as chiral auxiliaries, controlling Diels-Alder reactions, hydrogenations, osmium(IV) oxide-catalysed bishydroxylations, hydride additions, alkylations, aminations and many more classes of reactions with very high

stereoselectivity.[278] The application to aldol reactions is of particular relevance here and is described below.

They are prepared from the readily available enantiomeric camphorsulfonic acids,[279,280] and the *N*-acyl sultam derivatives are easily formed by deprotonation with sodium hydride and reaction with the appropriate acid chloride (scheme 4.6).[281]

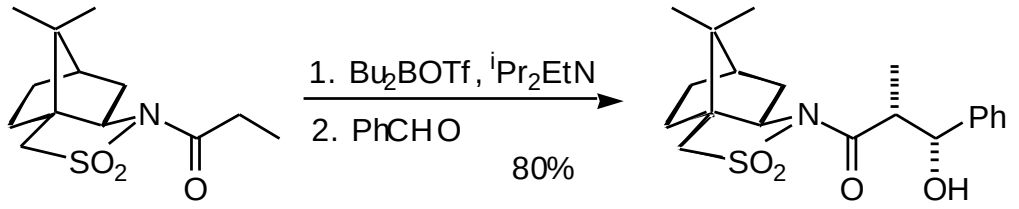


Scheme 4.6

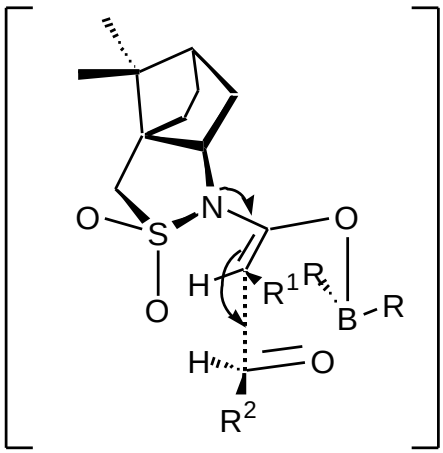
Enolates are obtained from *N*-acyl sultams by treatment with an appropriate base and a silylating agent. Alternatively, bromination of an α,β-unsaturated-*N*-acyl sultam at the γ-position (easily achieved with *N*-bromosuccinimide) affords the possibility of S_N' attack at the α-position, thus setting up a stereogenic centre here (the sultam auxiliary controlling the sense) with loss of bromide ion (see section 4.3.3). Both of these uses of the sultam auxiliary are exploited in Williams' synthesis of fragment A, and are described in more detail below.

4.3.2 *Syn* and *Anti* Methodology

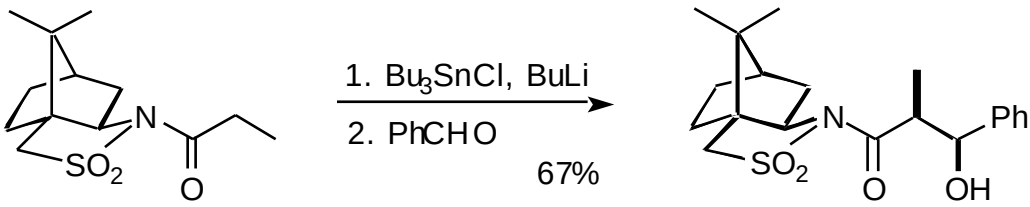
Oppolzer's sultams have been extensively used as chiral auxiliaries for aldol chemistry by directing the approach of a (chiral or achiral) aldehyde towards the enolate containing the auxiliary. Both *syn*[282] and *anti*[283] aldol methodology are available, as illustrated by examples in schemes 4.7 (*syn*) and 4.8 (*anti*). The difference lies in the different transition structures associated with the processes. In each case, a *Z*(O)-enolate is formed from the acyl sultam, but in the *anti* procedure there is no chelation between the oxygen of the aldehyde and either that of the enolate or those of the SO_2 group. Hence, there is no Zimmerman-



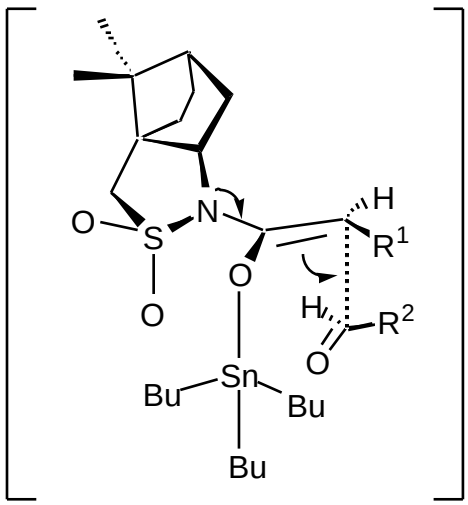
syn:other *syn*:*antis* 99:1:0



chelation of boron between enolate and aldehyde oxygens only

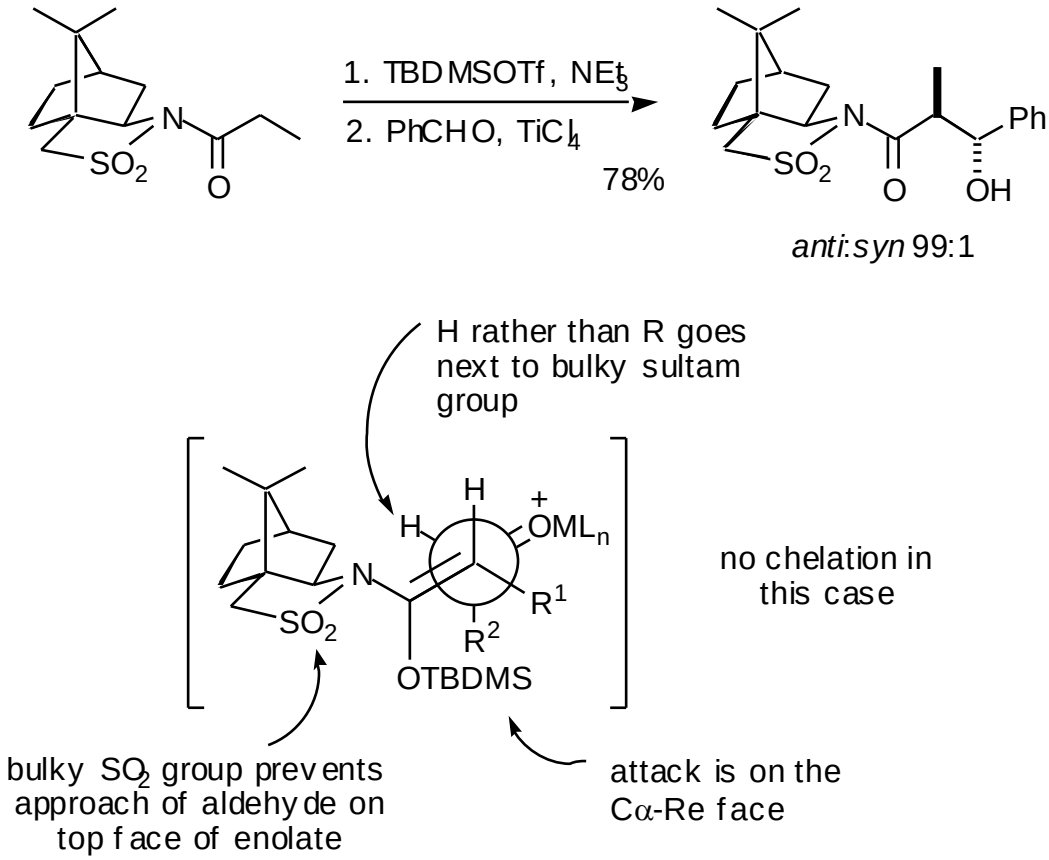


syn:other *syn*:*antis* 85:7:7



chelation of tin to oxygen of sultam auxiliary as well as to enolate and aldehyde oxygens

Scheme 4.7



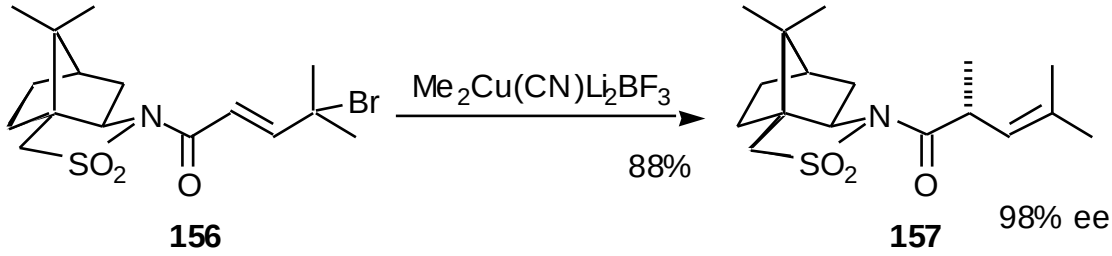
Scheme 4.8

Traxler transition structure (see section 4.2.2), and instead of the expected *syn* product, the product is *anti*, in excellent enantioselectivity.

In the *syn* methodology, either *syn* diastereoisomer is available from the same sultam enantiomer, depending on whether a boron or a tin compound is used as the Lewis acid. Boron's maximum covalency of four means that having formed the boron enolate it can coordinate only to the aldehyde oxygen, forming a classical Zimmerman-Traxler transition structure; tin's capacity for greater coordination allows a different transition structure to form, in which one of the SO_2 oxygen atoms is also coordinated to the tin. This leads to the opposite *syn* diastereoisomer.

Williams used the *anti* methodology to set up C2 and C3 of ebelactone, as described below.

4.3.3 The S_N' Reaction



Scheme 4.9

Bloch has found that γ-bromo-α,β-unsaturated-*N*-acyl sultams (e.g., compound **156**, scheme 4.9) undergo S_N' allylic substitution with high regio- and stereoselectivity when treated with organocuprate reagents, producing α-substituted-β,γ-unsaturated sultams with high enantiomeric excesses.[284]

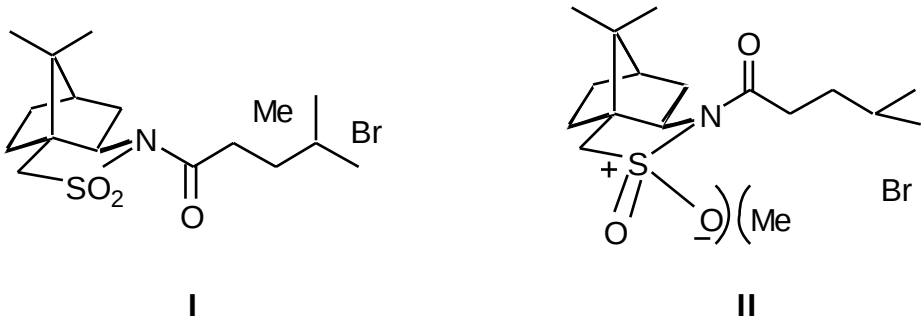


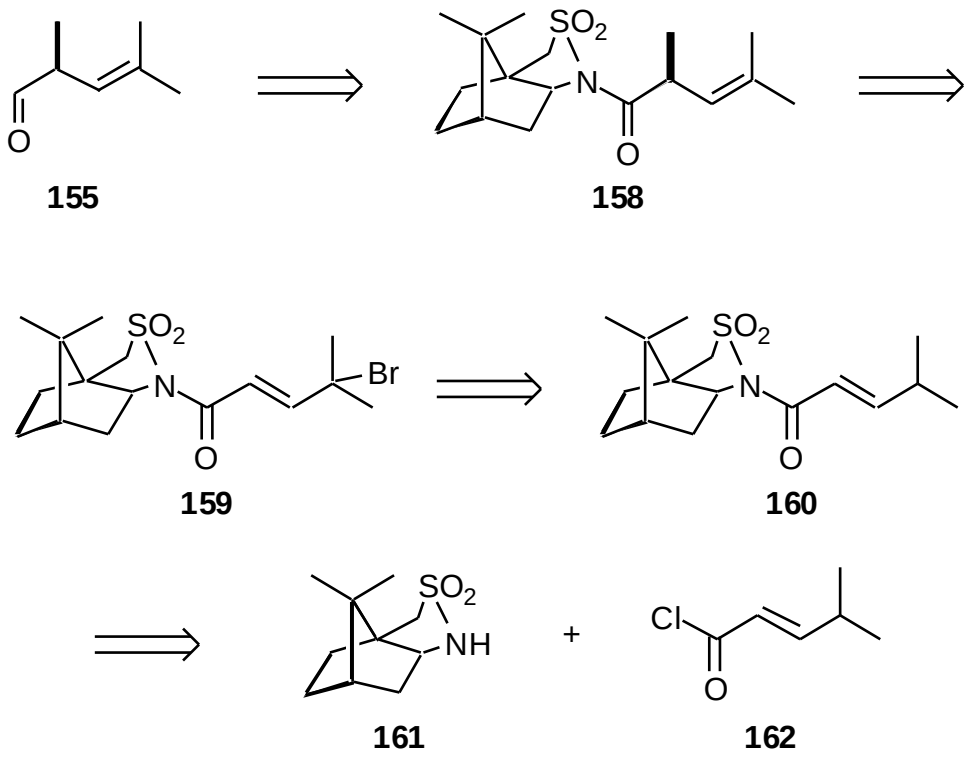
Figure 4.2

The stereoselectivity is rationalised if transition structure **II** has higher energy than **I** (figure 4.2) due to the steric repulsion between the substituents on the quaternary γ-carbon centre and the SO_2 group, addition of the methylcuprate then taking place from the less-hindered side of the double bond in transition structure **I**. (Initial attack on the α carbon is in fact thought to be by copper rather than methyl as shown, so this argument is a simplification of the actual situation.)

Williams used this methodology to set up C4 in ebelactone (see below).

4.4 Synthesis of Aldehyde 155

The required aldehyde **155** for the aldol reaction can be made from the enantiomer (**158**) of sultam **157** in scheme 4.9, and we can make this by the same method using the enantiomer (**159**) of the bromosultam **156**. This sultam **159** is made by bromination of sultam **160**, formed by joining sultam **161** to acid chloride **162**. Hence, these are the two materials which initially needed to be made (scheme 4.10).

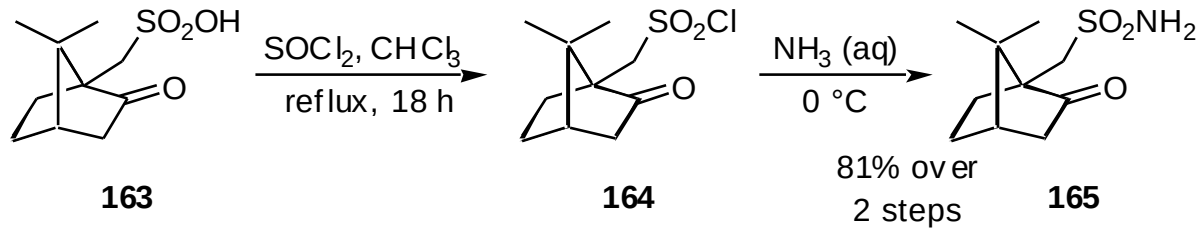


155 **158** **159** **160** **161** **162**

Scheme 4.10

(7*R*)-(+)-2,10-Camphorsultam **161** was synthesised by the (revised) method of Davis *et al.*[279,280] starting from (1*R*)-(–)-camphorsulfonic acid, in which isolation of the camphorsulfonyl chloride intermediate **164** is not attempted. Procedures involving isolation or even washing with cold water of the chloride[285,286] easily run into the problem of

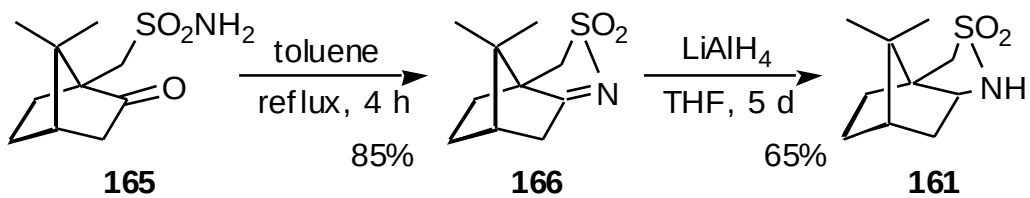
hydrolysis back to the acid. Instead, we used the method employing thionyl chloride as the chlorinating agent rather than phosphorus(V) chloride, since this has the advantage that no aqueous work-up is needed (scheme 4.11). (The sulfonyl chloride is in fact commercially available, though expensive, and there are other good routes to it in the literature.[287])



163 **164** **165**

Scheme 4.11

Thionyl chloride was added dropwise to camphorsulfonic acid **163** in chloroform, and then the solution was refluxed overnight, adequate precautions being taken to remove safely the hydrogen chloride and sulfur dioxide gases produced. [Before use, we filtered the (distilled) chloroform through silica to remove the ethanol with which it is contaminated.] The resulting brown solution of camphorsulfonyl chloride **164** was added slowly to concentrated ammonia solution at 0 °C by means of a dropping funnel. This step was slightly problematic, since ammonia vapour from the flask tended to react instantly with the chloride while it was still running down the stem of the dropping funnel, rapidly clogging it up and preventing reaction of the rest of the chloride. For this reason, a steady but slow addition was necessary, with vigorous stirring of the mixture in the flask. We obtained crude sulfonamide **165** in good yield over two steps (scheme 4.11).



165 **166** **161**

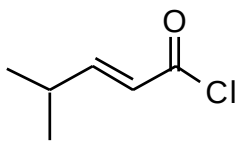
Scheme 4.12

The sulfonamide **165** was contaminated chiefly with a considerable quantity of the sulfonimine **166**, but as this is the product of the next reaction this was no problem, and the entire material was treated with Amberlyst 15 ion exchange resin,[288] in refluxing toluene, removing the water produced by means of a Dean-Stark apparatus. Dehydration took place in 85% yield to give the sulfonimine **166**, which was recrystallised from ethanol to give a pure material (scheme 4.12).

Reduction of the sulfonimine **166** to the sultam **161** by lithium aluminium hydride proved to be troublesome. Even after very careful drying of the sulfonimine, its reaction with the lithium aluminium hydride proved just too vigorous to be carried out using a Soxhlet apparatus as described in the published procedure.[279,280] As soon as the THF solvent extracted any of the sulfonimine into the bottom of the flask (containing the lithium aluminium hydride), there was such violent effervescence that reaction contents were carried right up the apparatus, so that lithium aluminium hydride ended up even in the condenser connected to the top of the Soxhlet. Starting material was recovered time after time.

Eventually, this method was abandoned and a straightforward mixing of lithium aluminium hydride, THF and sulfonimine **166** at room temperature was tried. This proved to be a very slow but effective method, giving yields over 60% after about five days of stirring.

It is necessary to carry out the work-up carefully. The literature method involves adding dilute hydrochloric acid "cautiously", but we were concerned about the potentially hazardous nature of this. Using methanol caused problems in the extraction of the sultam, but water proved to be acceptable, provided it was added dropwise with cooling in ice, acid being added once all the lithium aluminium hydride was quenched.

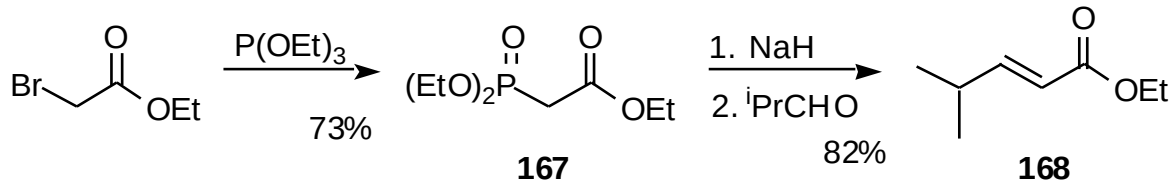


162

Figure 4.3

Next, the acid chloride **162** was made (figure 4.3), ready for coupling to the (+)-sultam. This is prepared from the acid **171**, which in turn comes from the methyl ester **170** (see below).

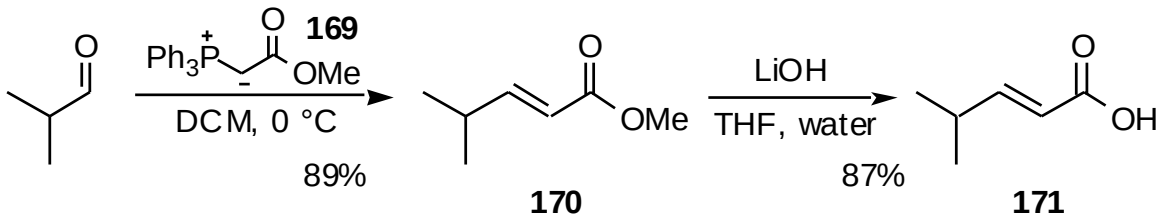
Williams had previously prepared the *ethyl* ester **168** by a Wittig-Horner reaction using the ylid generated from triethylphosphonoacetate **167** (previously prepared by the Arbusov reaction from ethyl bromoacetate and triethyl phosphite,[289] but in fact commercially available) and isobutyraldehyde (scheme 4.13).[137,290]



Scheme 4.13

An attempt to repeat the second step of this procedure using commercially available triethyl phosphonoacetate failed, the yield of α,β-unsaturated ester **168** being negligible. In accordance with group precedent,[291] the main product after distillation was the triethyl phosphonoacetate starting material **167**.

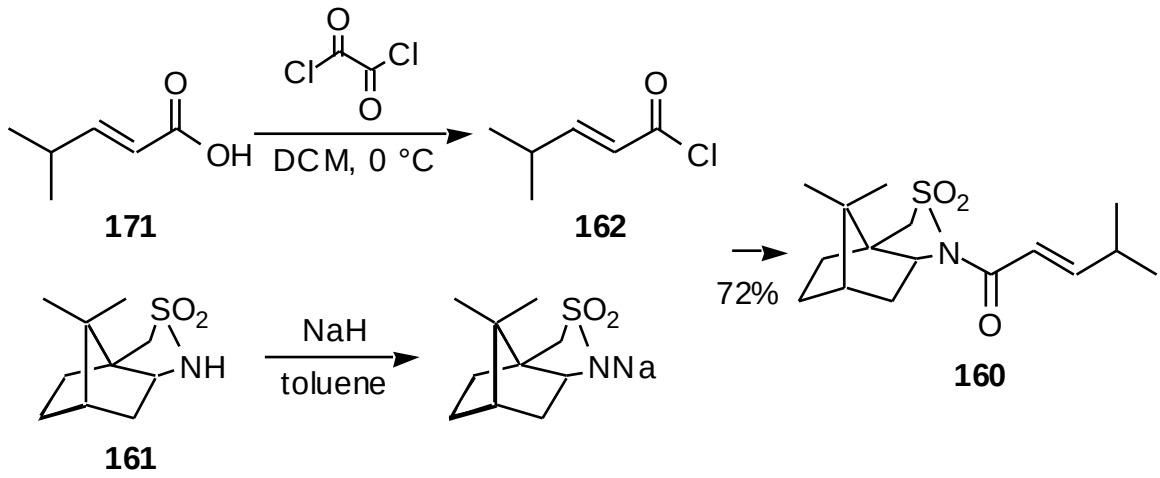
An alternative method was tried using the commercially available carbomethoxy-methylenetriphenylphosphorane Wittig reagent **169**[292] to form the corresponding *methyl* ester **170** from the same aldehyde (scheme 4.14). Simply adding isobutyraldehyde to the ylid in dichloromethane at 0 °C gave the methyl ester **170** in good yield.



Scheme 4.14

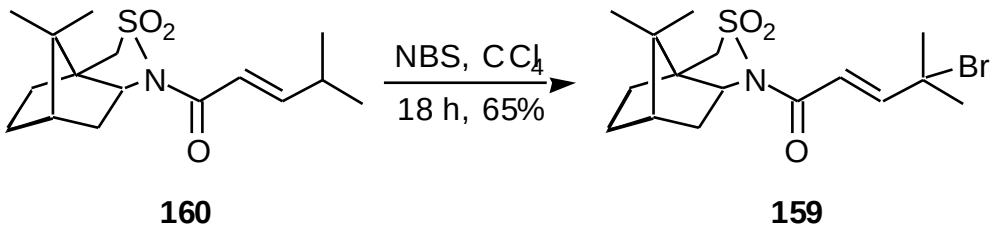
Hydrolysis of this ester to the acid was difficult, however. A 3:1 THF:water mixture containing lithium hydroxide was used, but very vigorous stirring was needed to mix the two layers totally. TLC showed one lower-running spot after about five days usually, especially if a large excess of lithium hydroxide was employed. The acid **171** was isolated in 87% yield.

Conversion to the acid chloride **162** was accomplished with oxalyl chloride in dichloromethane at 0 °C (scheme 4.15).



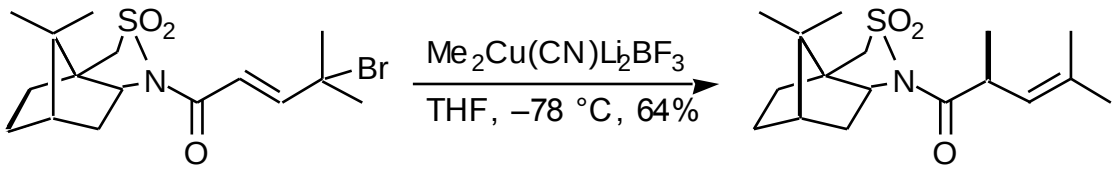
Scheme 4.15

This ceased to be problematic once care was taken to exclude *all* air at all stages of the process, especially by removing the dichloromethane and excess oxalyl chloride on high vacuum so that the need to transfer to a rotary evaporator was eliminated. The acid chloride **162** was not isolated, but immediately coupled to the sultam **161** by addition in toluene solution to the deprotonated sultam (scheme 4.15).[281] The yield for this step was consistently an improvement on Williams' 60%.



Scheme 4.16

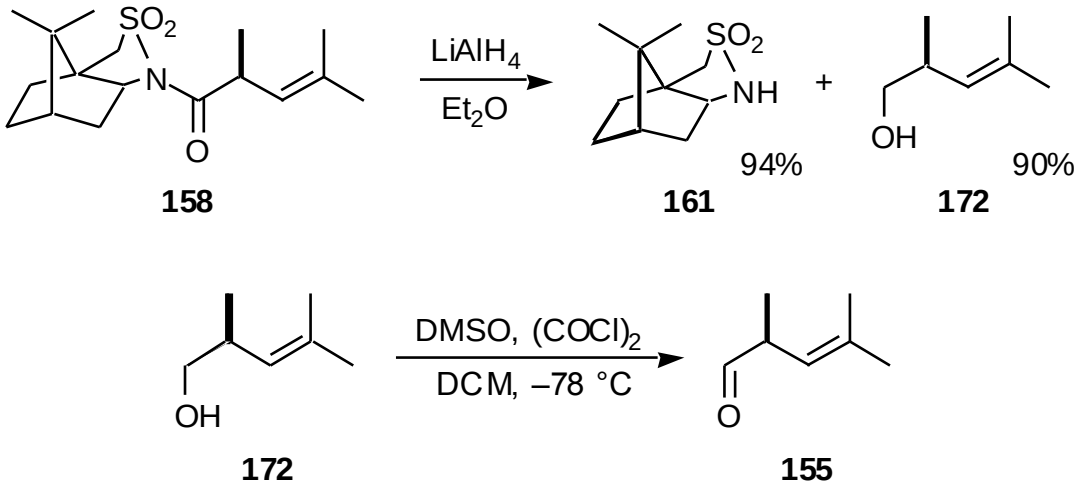
The substrate for the S_N' reaction is the bromide **159**, and this was readily formed from the sultam **160** by treatment with *N*-bromosuccinimide in refluxing carbon tetrachloride overnight. Recrystallisation from ethanol gave the pure bromide **159** in reasonable yield (scheme 4.16).[284]



159 **158**

Scheme 4.17

The S_N' reaction described in section 4.3.3 sets up the stereogenic centre α to the carbonyl group, and this will become C4 of ebelactone. [This reaction is simply the mirror image of Bloch's (scheme 4.9).[284]] Addition of the bromide **159** in THF to methylcuprate (formed from methyllithium and copper(I) cyanide) and boron trifluoride diethyletherate in THF gave, after 1.5 hours, an acceptable yield of the methylated sultam **158**, which could be recrystallised with difficulty from ethanol and water (scheme 4.17). There was no evidence in the ^{1}H NMR spectrum for the epimer at the α carbon.



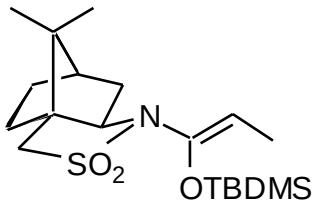
158 **161** **172**

172 **155**

Scheme 4.18

Williams established that the best route from methylated sultam **158** to the required aldehyde **155** is to cleave off the sultam with lithium aluminium hydride and then oxidise the resulting alcohol. Treatment of the methylated sultam **158** with lithium aluminium hydride in ether at –78 °C gave the sultam **161** (94% recovery) and the alcohol **172** as a colourless, relatively volatile liquid in 90% yield (scheme 4.18). She then used the Swern method of oxidation[171,293] to obtain the required aldehyde **155**, which is not isolated but taken immediately into the aldol reaction. We repeated this step (see below).

4.5 The Aldol Reaction

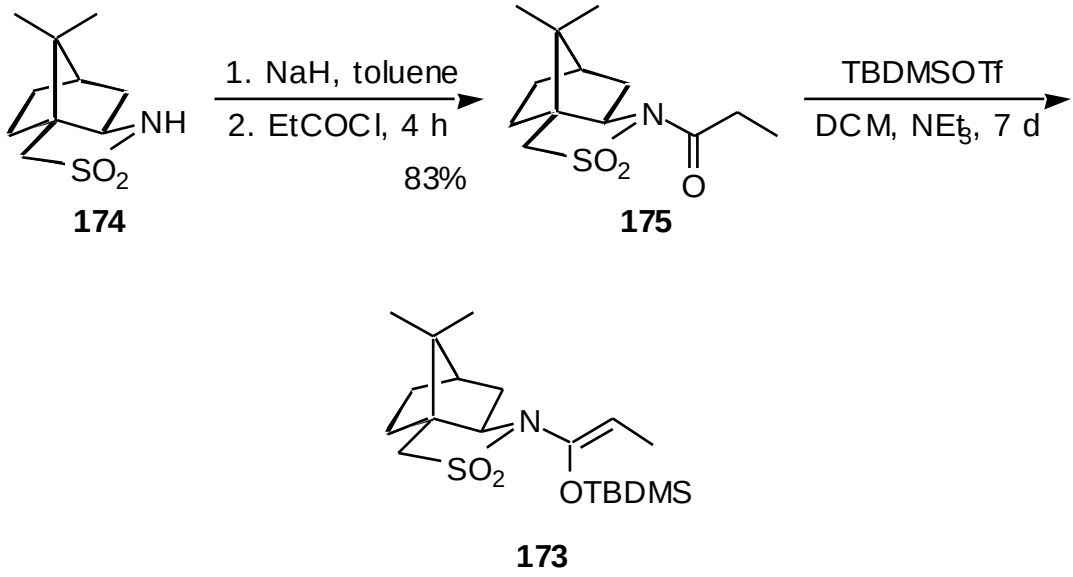


173

Figure 4.4

The required *Z*(O)-enolate **173** (figure 4.4) comes from (–)-camphorsultam **174**, the opposite enantiomer to the one needed for the synthesis of the aldehyde **155**. Hence, we made this sultam from (+)-camphorsulfonic acid in an exactly similar way (see section 4.4). Treatment of this with sodium hydride in toluene followed by addition of propionyl chloride gave the propionyl sultam **175**, the precursor to the enolate **173**, in good yield after easy recrystallisation from methanol (scheme 4.19).[281]

Treatment of propionyl sultam **175** with TBDMS triflate and triethylamine in dichloromethane at room temperature led, after about a week, to a deep red solution of the silylketene acetal **173**. Oppolzer warned that this silylketene acetal is "rapidly hydrolysed on exposure to air",[283] and Williams experienced difficulties here. The procedure is to



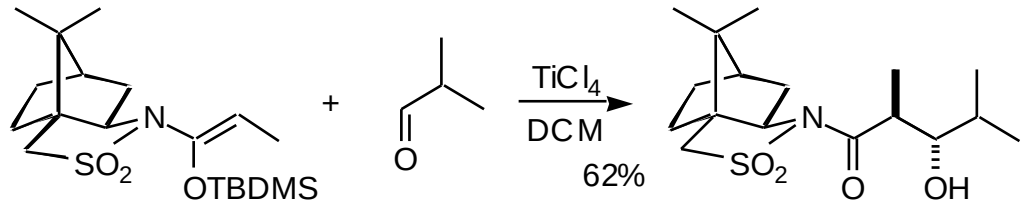
Scheme 4.19

evaporate off the dichloromethane, excess TBDMS triflate and triethylamine to give a dark red solid. Trituration of this with pentane and evaporation of the solvent leads to a pale cream solid which can be dissolved in dichloromethane and used straight away in the aldol reaction. Williams found that the initial evaporation had to be carried out under high vacuum rather than by transferring the flask to a rotary evaporator, otherwise hydrolysis took place. She also experienced problems with the quality of the TBDMS triflate, finding that larger excesses were sometimes needed.[137]

On repeating this work, we too ran into the same problem of hydrolysis of the silylketene acetal, leading to recovered starting material (propionyl sultam **175**) on working up the aldol reaction. In fact, work on this aldol reaction consumed more time than any other piece of work described in this thesis. The aldehyde **155** is not isolated, but dissolved in dichloromethane and cooled to –78 °C before addition of titanium(IV) chloride, followed, after 2 minutes, by the silylketene acetal in dichloromethane. After 5 minutes, the reaction is quenched at –78 °C with saturated ammonium chloride solution.

We decided to work first on a trial reaction using isobutyraldehyde in place of aldehyde **155**. This was freshly distilled and carefully dried before addition of titanium(IV) chloride followed by the silylketene acetal **173**, but again propionyl sultam starting material was

recovered time after time. We experimented with the length of time allowed for the silylketene acetal to form. The solution begins to turn pink within minutes of mixing the starting materials, and after one day a red colour is observed. 5-7 days later, the solution is deep red—Williams reported that this was evidence of silylketene acetal formation. Using material that had been left 7-10 days resulted in a successful reaction with isobutyraldehyde and the formation of aldol adduct **176** in acceptable yield, and a small quantity (9%) of recovered sultam **175** (scheme 4.20).



173 **176**

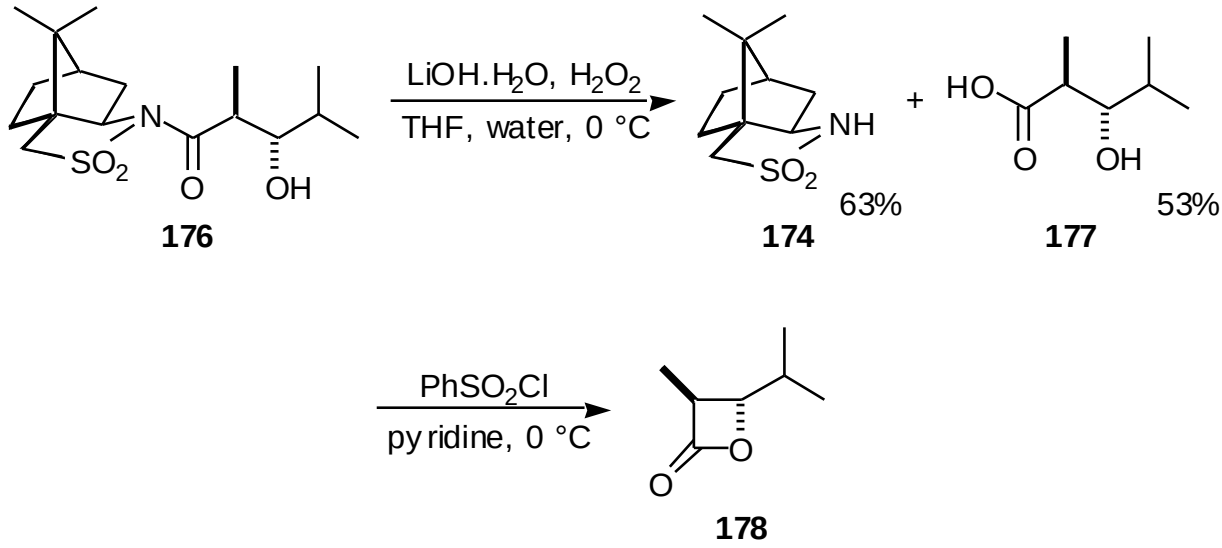
Scheme 4.20

TBDMS triflate[294] is dispensed in ordinary bottles, but fuming is violent on opening the bottle. A septum cannot be used to seal the bottle under an argon atmosphere, because it is rapidly attacked by the triflate: after a few days, the septum is black and holes start to appear. The best solution is on opening a fresh bottle to transfer the entire contents immediately by syringe, under argon, into a flask sealed with a glass tap, and then to store the flask in the dark until needed. Material which has turned even faintly yellow should not be used in this reaction—clearly the presence of any triflic acid (the product of hydrolysis) would be disastrous in the aldol reaction.

Removal of the TBDMS triflate (b.p. 66 °C /12 mmHg) and triethylamine under vacuum must be carried out thoroughly. Heating led to less pure-looking silylketene acetal after trituration (it should be a cream colour). Sometimes high vacuum (0.1 mmHg) was needed for up to 5 hours to obtain completely dry material.

We hydrolysed the aldol product **176** with lithium hydroxide and hydrogen peroxide in THF and water at 0 °C to give recovered sultam **174** and the known hydroxy acid **177** (the

NMR data matched that in the literature[295,296]) both in reasonable yield (scheme 4.21). (Chromatography is not necessary, since extraction of the basic solution obtained at the end of the reaction gives the sultam, and acidification of the remaining aqueous solution, followed by extraction, yields the carboxylic acid in a pure form.)



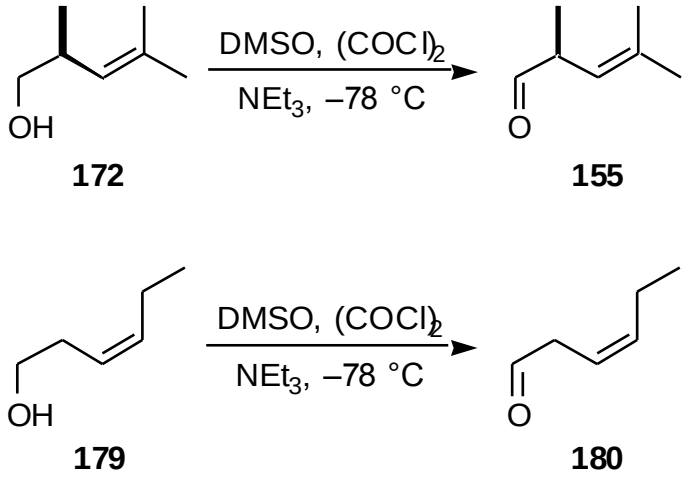
Scheme 4.21

Finally, treating the hydroxy acid **177** with benzenesulfonyl chloride, according to Adam's procedure,[78] gave the lactone **178**, mixed with pyridine that had not been completely removed by the acid washes in the work-up.

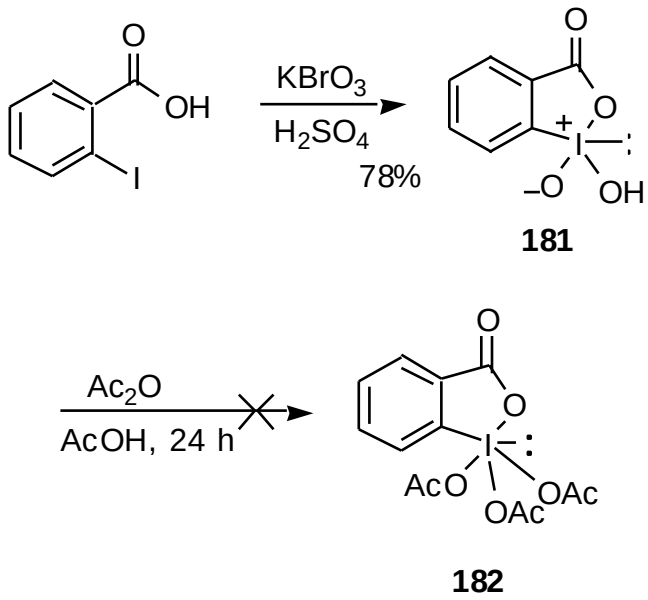
With this experience in hand, we attempted again the aldol reaction with aldehyde **155**. Unfortunately, we still achieved no success (propionyl sultam recovered), so we turned to the possibility that the problem lay with the oxidation of alcohol **172**.

Following Williams, we had used the Swern oxidation to form the aldehyde.[171,293] Dimethyl sulfoxide in dichloromethane [neat dimethyl sulfoxide frequently freezes (*sic*) in the syringe] is added dropwise to oxalyl chloride in dichloromethane at –78 °C, followed by the alcohol **172** in dichloromethane (again dropwise), and then triethylamine. Stirring at –78 °C, warming to room temperature, adding water and then working up led to material that was not isolated but taken straight through into the aldol reaction.

We decided to practise these conditions using readily available *Z*-hex-3-en-1-ol **179**. We found the reaction to be variable, the turning yellow of the contents of the reaction flask at any point during the course of the reaction being, we think, a bad sign in terms of the quality of the aldehyde produced. The NMR spectrum of the freshly-prepared aldehyde was found to be complicated, with no evidence of the desired product (scheme 4.22).



Scheme 4.22

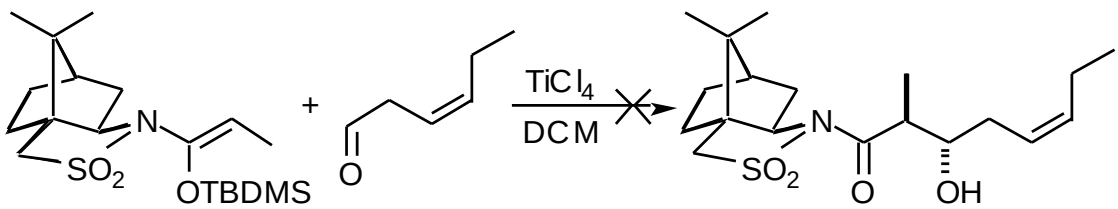


Scheme 4.23

Williams had used both the Swern and the Dess-Martin oxidation procedures to prepare aldehyde **155**, though without comparing their relative effectiveness, since the aldehyde was isolated only once for characterisation purposes. The Dess-Martin reagent is well-known to be a reliable method for mild oxidation of alcohols to aldehydes, so we set about preparing some.[297-299] It, too, is highly air-, moisture- and temperature-sensitive. We had no problem preparing the oxide **181** intermediate by heating potassium bromate(V), sulfuric acid and 2-iodobenzoic acid, but were unable successfully to acylate this with acetic anhydride and acetic acid; oxide **181** starting material only was obtained (scheme 4.23).

Presumably the problem was caused by water creeping into the reaction at some stage. Rather than spending time on this, we purchased some Dess-Martin reagent[300] to try in the oxidation.

The procedure for using the Dess-Martin reagent is simple. It is weighed out in a glove-box, dissolved in dry dichloromethane at 0 °C, and the alcohol **179** in dichloromethane is added. The mixture is allowed to warm to room temperature and stirred for 2 hours. On work-up, we obtained a solution containing the pure aldehyde **180** (NMR). Owing to its volatility, we did not seek to isolate it, but instead immediately took it into the aldol reaction to see whether we could carry out the aldol successfully with an aldehyde that we had prepared. Unfortunately, only propionyl sultam **175** was obtained once again (scheme 4.24).

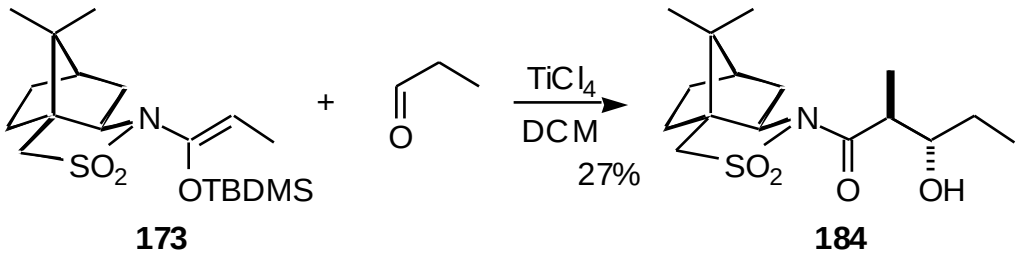


173 **180** **183**

Scheme 4.24

It appeared that the titanium(IV) chloride had deteriorated in quality, and we wondered whether this might account for the failure of this aldol reaction. We had run out of pure isobutyraldehyde, but on trying the reaction with propionaldehyde instead, and using the same

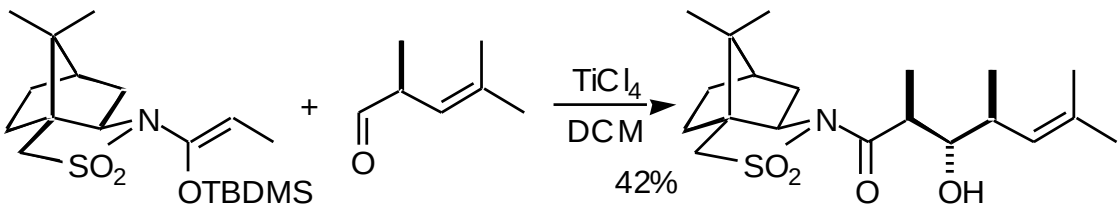
titanium(IV) chloride, we obtained some aldol adduct **184**, albeit in low yield. Hence, we concluded that there was a problem with the aldehyde **180**, though the low yield did suggest that this was not all that was amiss (scheme 4.25).



173 **184**

Scheme 4.25

On returning to the Swern method of oxidation, some samples of aldehyde were prepared which did perform in the aldol reaction, and by this means a small quantity of adduct **185** was prepared, but the aldol reaction was exceedingly unreliable and quite unsatisfactory, the maximum yield obtained (assuming 100% formation of silylketene acetal and aldehyde) was 42% (scheme 4.26). This does, however, compare favourably with Williams' yield of 32%—it should also be noted that she was not able completely to separate the aldol adduct **185** from the propionyl sultam starting material **175**, whereas we found that chromatography in 2:1 light petroleum-ether gave effective separation, and the propionyl sultam was recovered in 45% yield.

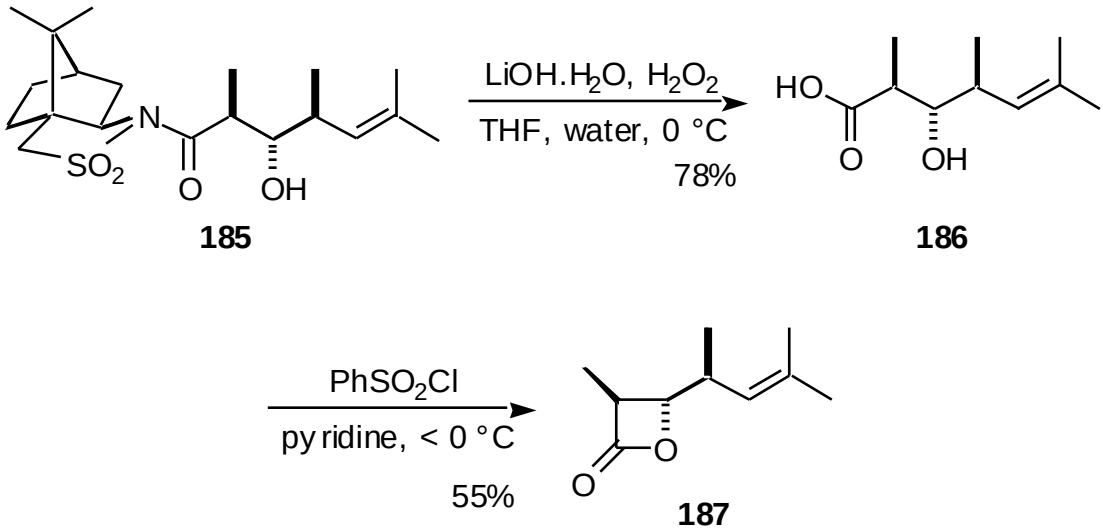


173 **155** **185**

Scheme 4.26

We tried the aldol reaction with isobutyraldehyde again but using zinc chloride as the Lewis acid in place of titanium(IV) chloride, but only propionyl sultam starting material was recovered. Neither did we obtain any of the desired product by carrying out the reaction with addition of no Lewis acid at all, simply relying on the TBDMS triflate present to perform this function. Oppolzer does report, however, that good yields are obtained with this latter method only in the case of aromatic aldehydes.[283] Time did not allow us to spend longer on this work.

4.6 Final Steps

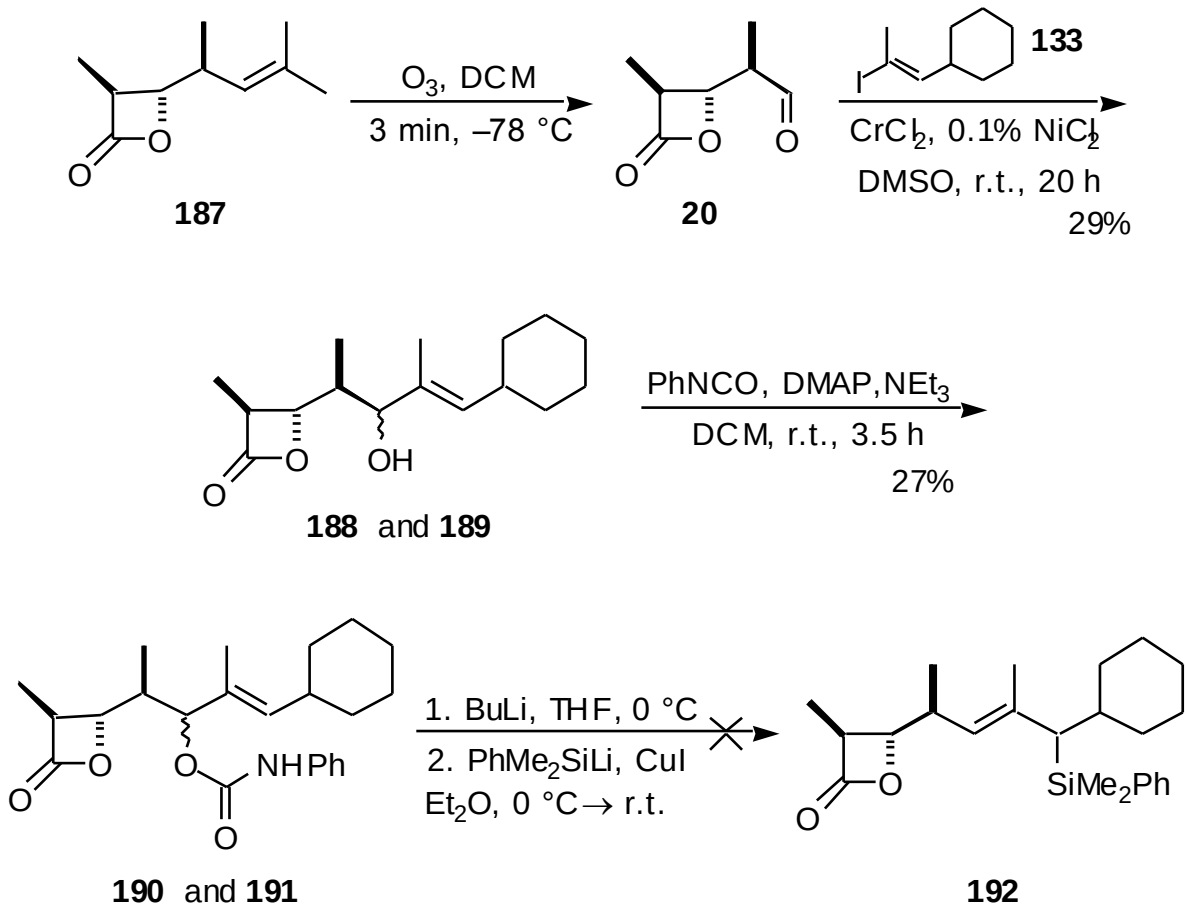


Scheme 4.27

The limited quantity of pure aldol adduct **185** obtained was treated with lithium hydroxide and hydrogen peroxide in THF and water at 0 °C to give the sultam **174** (89% recovery) and the acid **186** in good yield (78%) (scheme 4.27). Lactonisation was achieved by keeping the hydroxy acid **186** with benzenesulfonyl chloride in pyridine in the freezer for 5 days.[78] On work-up, repeated washings with dilute hydrochloric acid are necessary to remove all of the pyridine (Williams had traces of pyridine remaining in her product). This does not appear to threaten the stability of the lactone. The lactone **187** had a ^{1}H NMR spectrum

matching Williams' precisely; in particular, the ^3J coupling of 4.1 Hz between the two hydrogens in the ring proving the *trans* geometry of the lactone.

Finally, reaction of this lactone-alkene **187** with ozone in dichloromethane at –78 °C gave fragment A **20** (scheme 4.29). Williams performed this step by blowing ozone over the surface of the solution, and reaction took 1 hour, but we found that by bubbling the ozone through the liquid, transformation was complete in less than three minutes. The reaction is readily monitored visually: the appearance of a blue coloration indicates the presence of excess ozone, and indicates that the flask can be flushed with argon and dimethyl sulfoxide (just a few drops) be added before allowing the reaction to warm to room temperature. Once again, the NMR spectrum matched Williams'.



Scheme 4.29

We did not attempt to isolate this sensitive molecule, but instead added it immediately to freshly-prepared vinyl iodide **133** in dimethyl sulfoxide (prepared from vinylsilane **132**—see chapter 3). Chromium(II) chloride and a trace of nickel(II) chloride were added (Nozaki-Kishi conditions—also see chapter 3), and the mixture stirred overnight (scheme 4.29). A 2:3 mixture of alcohols **188** and **189** was formed in low yield, thereby verifying the feasibility of the Nozaki-Kishi reaction as a means of coupling a vinyl iodide to fragment A itself. The C=O absorption in the infra-red spectrum at 1811 cm^{-1} showed us that the β-lactone was intact, and the NOESY spectrum verified that the configuration of the double bond was unchanged (figure 4.5). Hence, the conditions of this reaction are clearly compatible with the sensitive β-lactone functionality.

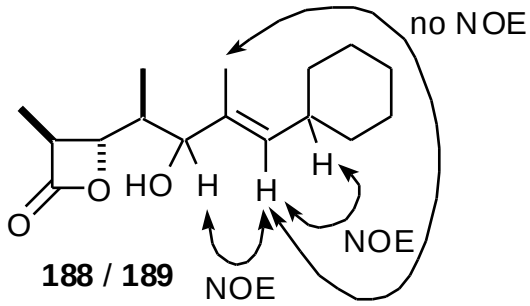


Figure 4.5

Although the carbamate methodology was found not to be a successful method for the allylic reduction which needs now to be done, we decided to see whether the carbamate could be formed from the mixture of alcohols under the usual conditions without disruption of the lactone. Hence, we treated the mixture of alcohols **188** and **189** for 3.5 hours with phenyl isocyanate, DMAP and triethylamine in dichloromethane, as we had done in the model series (chapter 3), and obtained a 2:3 mixture of carbamates **190** and **191** (scheme 4.9). Again, the infra-red C=O stretch was at 1826 cm^{-1}, showing that the β-lactone was still intact, and a NOESY spectrum confirmed that the double bond configuration was unchanged by the reaction conditions, as expected. We were not surprised, however, that when we attempted the silylcupration reaction on this carbamate mixture we obtained none of the desired allylic

alcohol **192**: the model work we had carried out (chapter 3) had prepared us to expect this result.