Chapter 4

Alternatives and AMPTD

4 Alternatives and AMPTD

This chapter contains various concepts that were studied and subsequently abandoned during investigations towards APTO and AETD. At the end of the chapter preliminary studies into the application of the synthetic strategy to the preparation of another analogue, AMPTD are reported.

4.1 Increased Steric Demand of Ester

Hydrolysis of the C_1 methyl ester (Figure 4.1) was a side reaction in the AD of alkene ***E*-23** (see Chapter 3, page **Error! Bookmark not defined.**). Hydrolysis of this group was also detected in the trans-esterification reaction to remove the *p*-methoxybenzoyl protecting group of oxazolidine **67** (see Chapter 2, page **Error! Bookmark not defined.**) due to advanticious water. The hydrolysis in the AD was later overcome by using a buffer and accelerating the AD using less sterically demanding ligands. Rigorous drying techniques were used to minimise hydrolysis in the trans-esterification reaction. However an alternative solution to this problem was first considered. It was proposed that hydrolysis could be reduced by increasing the steric demand of the C_1-ester protecting group because sterically hindered esters are hydrolysed with more difficulty.[60]

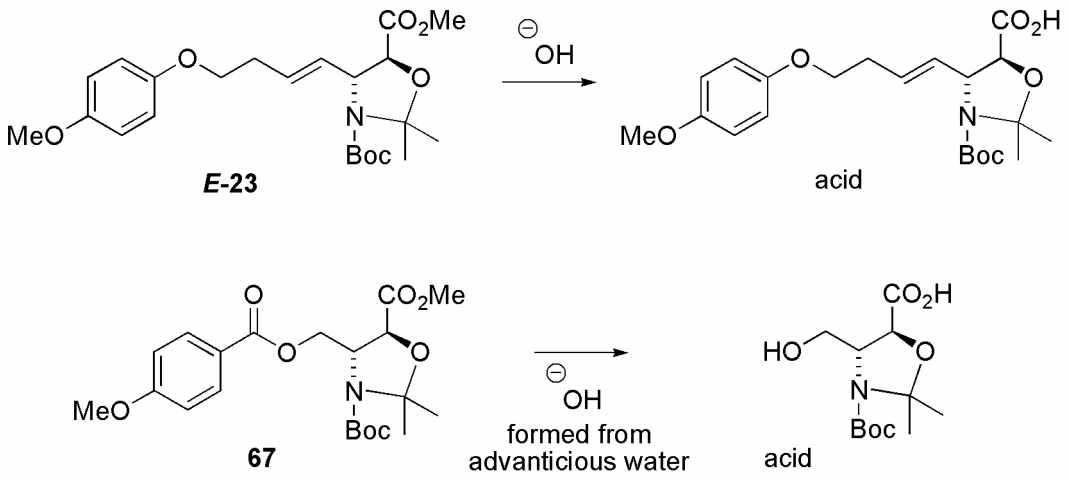


Figure 4.1 Hydrolysis of the C_1 methyl ester.

Different sized esters have been found to react with different regio- and enantio-selectivity in the AA[30] and with different enantio-selectivity in the AD.[32] Bodkin[36] studied the effect of increasing the steric demand of the ester in alkenes **115**, **116** and **117** (Figure 4.2). As the size of the ester substituent (R) was increased the regio-selectivity was found to decrease while the enantio-selectivity remained high (Figure 4.3). The yield was also found to decrease with increased ester size.

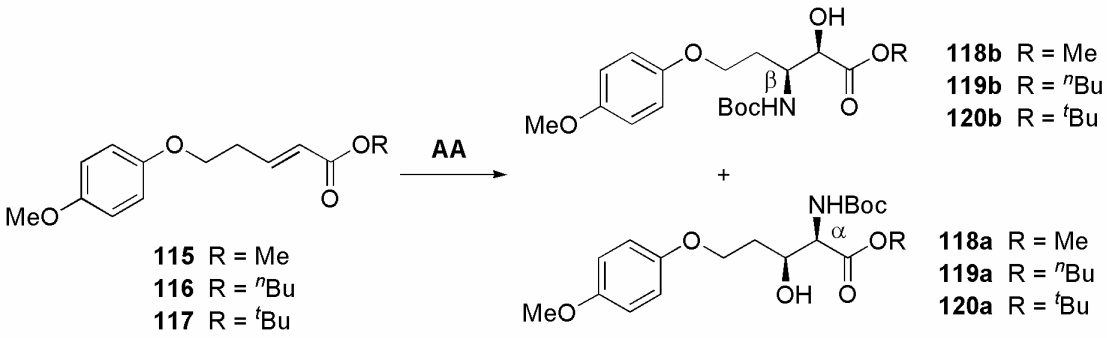


Figure 4.2 Bodkin's ester steric demand studies.

Entry	R	Ligand	Regio-selectivity α : β	Major product	Yield*	% ee*
1	Me	$(DHQ)_2PHAL$	1 : 20	**118b**	78	97
2	^{n}Bu	$(DHQ)_2PHAL$	1 : 9	**119b**	64	99
3	^{t}Bu	$(DHQ)_2PHAL$	1 : 6	**120b**	36	95

* = of major product

Figure 4.3 Bodkin's results.

It was decided that the effect of increasing the steric demand of the C_1-ester protecting group on the selectivity of the AA must be determined by performing the reaction on ethyl ester ***E*-121** and *tert*-butyl ester ***E*-122**.

Ethyl ester **121**[61] and *tert*-butyl ester **122** were prepared from allyl compound **39** by cross metathesis with ethyl acrylate and *tert*-butyl acrylate respectively (Figure 4.4). Ethyl ester **121** (Figure 4.5, entry 2) and *tert*-butyl ester **122** (entry 3) were formed in higher yield than methyl ester **28**, formed previously (entry 1), but with lower (*E*)-selectivity. The isomers were easily separated by flash chromatography and pure (*E*)-alkenes were reacted in the AA.

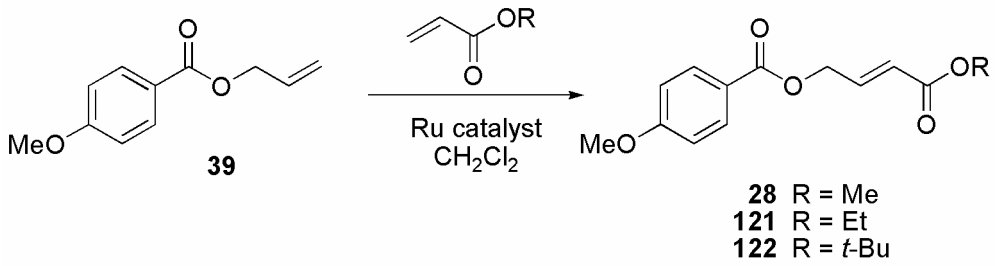


Figure 4.4 Preparation of esters.

Entry	R	Ester	Yield (%)*	*E* : *Z*§
1	Me	**28**	65	*E* only
2	Et	**121**	86	11 : 1
3	*t*-Bu	**122**	84	11 : 1

***** = combined yield; **§** = ratio was determined from isolated products

Figure 4.5 Results of cross metatheses.

AA of ethyl ester ***E*-121** and *tert*-butyl ester ***E*-122** using $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ ligands were performed (Figure 4.6). Ethyl ester ***E*-121** reacted with decreased regio-selectivity (Figure 4.7, entry 3, 4) compared to methyl ester ***E*-28** (entry 1, 2). The observed regio-selectivity was in agreement with the findings of Chuang et al. (entry 5).[61] *tert*-Butyl ester ***E*-122** reacted in the presence of $(DHQD)_2PHAL$ to form aminoalcohol products in very low yield with reversed regio-selectivity (entry 6) however by-product **123**[82] (Figure 4.8) was identified as the major product in the reaction. It was proposed that this compound formed under the basic reaction conditions by trans-esterification of the *p*-methoxybenzoyl ester of the starting material or the product with the solvent, propanol. By-product **123** was also identified as the major product in the reaction using DHQ_2PHAL (Figure 4.7, entry 7). Other more polar by-products were isolated from the reaction. There are two possible explanations for the observed reversal in regio-selectivity. The first is that *tert*-butyl ester may be too large to allow effective interaction of the substrate with the PHAL ligands and that reaction is occurring independently from the ligand. The second is that preferential trans-esterification of the β-aminoalcohol product is occurring to form by-product **123**. The reaction was repeated using the less sterically demanding ligand, DHQD-CLB, and

β-aminoalcohol **126** was isolated in good yield but with low regio-selectivity (entry 8). Only trace by-product **123** was isolated in this case.

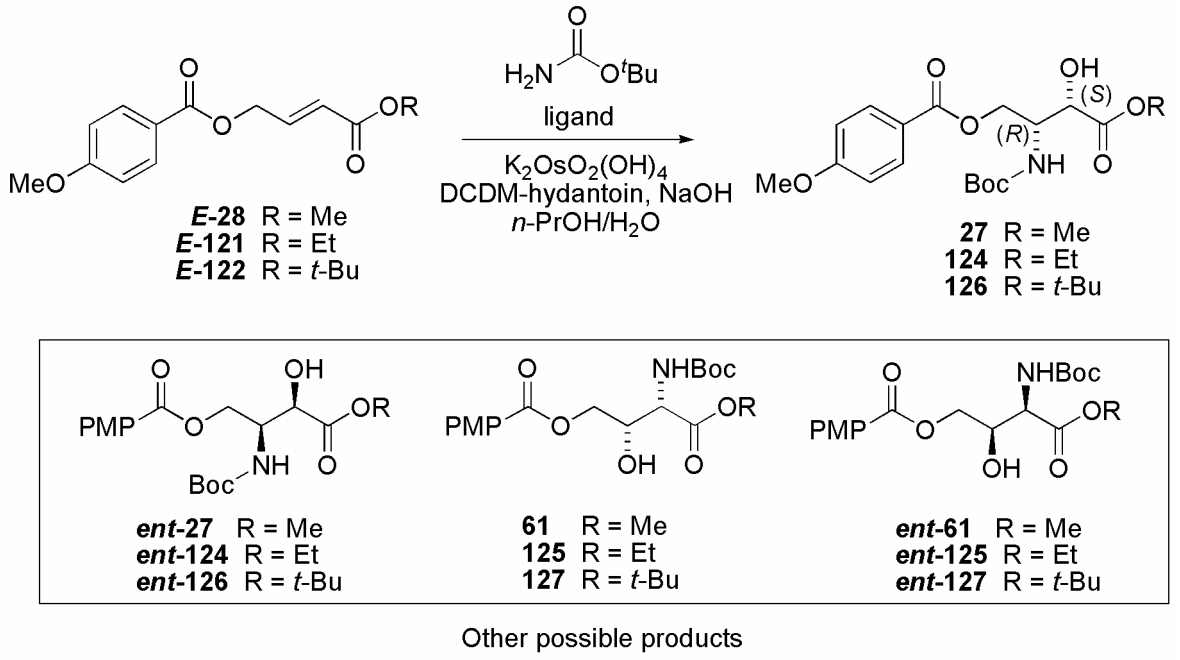


Figure 4.6 AA with alternative esters.

Entry	Ester	Ligand	Major AA product	Yield (%)	Regio α : β	%ee	**123** (%)
1	***E*-28**	$(DHQD)_2PHAL$	**27**	84	β-only	97*	-
2		$(DHQ)_2PHAL$	***ent*-27**	70	β-only	98*	-
3	***E*-121**	$(DHQD)_2PHAL$	**124**[61]	§	1.0 : 5.6	§	-
4		$(DHQ)_2PHAL$	***ent*-124**	§	1.0 : 5.9	§	-
5[#]		$(DHQ)_2PHAL$	***ent*-124**	59	1.0 : 7.0	§	-
6	***E*-122**	$(DHQD)_2PHAL$	**127**	1	8.4 : 1.0	§	45
7		$(DHQ)_2PHAL$	***ent*-127**	§	§	§	major
8		DHQD-CLB	**126**	67	1.0 : 1.8	§	trace

* = determined by Hung Duong; **§** = not determined; **#** = results of Chuang et al.[61] using *t*-BuOCONHCl as the nitrogen source

Figure 4.7 Results of the AA with alternative esters.

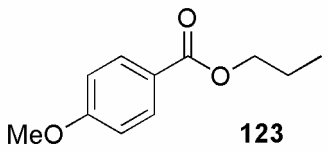


Figure 4.8 By-product **123**.

It was decided that any potential benefit of using larger ester groups to reduce hydrolysis in the AD was outweighed by the loss of regio-selectivity observed in the AA of these substrates and this approach was abandoned. The problems of hydrolysis were overcome by using a buffer in conjunction with less sterically demanding ligands in the AD and by using rigorous drying techniques in the de-protection of the *p*-methoxybenzoyl ester.

4.2 Bi-directional AA Substrate

A symmetrical bis-C3 building block (**128** in Figure 4.9) has been used by Wang and co-workers[62] as a substrate for an AD. The use of this bi-directional substrate enhanced the efficiency of their synthesis, allowing for better atom economy along with improved enantio-selectivity. The major products of the AD were diastereomeric which allowed for more effective separation and purification. Wang and co-workers chose a hydroquinone group because it can tolerate extreme reaction conditions such as strong acid and base and can be readily removed using CAN.

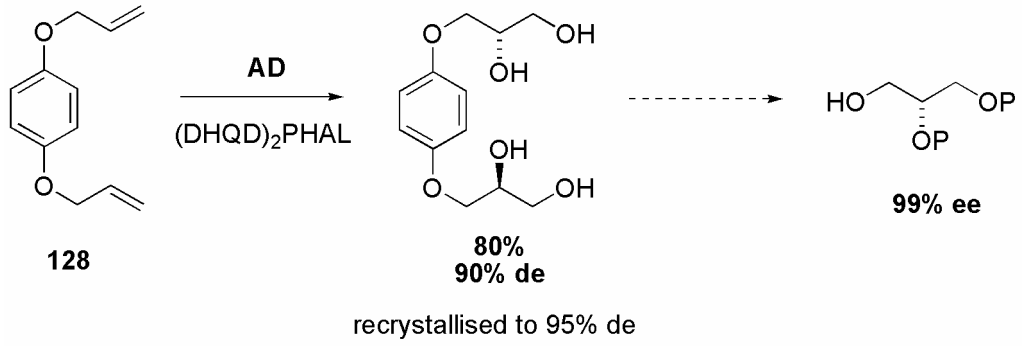


Figure 4.9 AD reaction with bi-directional substrate.

Assuming both arms of a bi-directional substrate reacted independently, the use of such a substrate can improve the atom economy of a synthesis while boosting

the ee of the product. It was proposed that a bi-directional substrate involving a naphthalene group (**129** in Figure 4.10) could be an improved substrate for the AA. The naphthalene directing group was chosen for its structural homology with benzoate ***E*-28** used in the previous system. It was thought the naphthalene aromatic group would be appropriately placed for good substrate-catalyst interaction and removal of the group was envisaged using CAN.

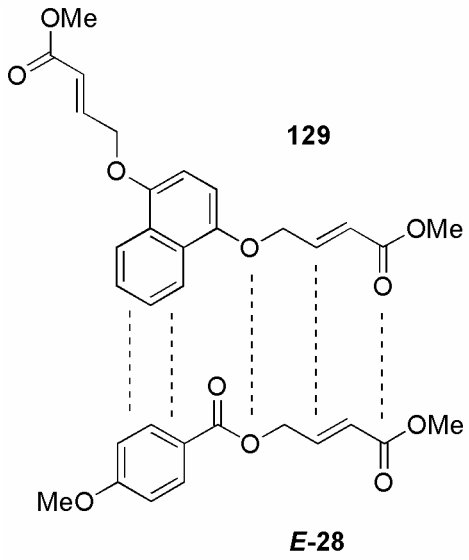


Figure 4.10 Structural homology between bi-directional substrate **129** and mono-directional substrate ***E*-28**.

The theoretical improvement to the ee of the product was calculated (Figure 4.11). If the reaction occurs using a mono-directional substrate to give products (2*S*,3*R*) : (2*R*,3*S*) in a 9 : 1 ratio then the product would be formed with an 80% ee by definition. The products of this reaction are enantiomeric and hence would be inseparable by flash chromatography. The sample may be enriched in one enantiomer by recrystallisation or separation of the enantiomers may be achieved using chiral HPLC. Assuming that each arm of bi-directional substrate **129** reacts independently of each other with the same selectivity (9 : 1) then reaction of the first arm would give (2*S*,3*R*)-compound **130A** and (2*R*,3*S*)-compound **130B** in a ratio of 9 : 1 and subsequent reaction of the second arm would give (2*S*,3*R*),(2'*S*,3'*R*)-compound **131AA** and (2*S*,3*R*),(2'*R*,3'*S*)-compound **131AB** and (2*R*,3*S*),(2'*R*,3'*S*)-compound **131BB** in a ratio of 81 : 18 : 1. Compound **131AB** is diastereomeric to compound **131AA** and should be separable by conventional

methods while compound **131BB** is enantiomeric to compound **131AA** and would be separable by chiral HPLC or enriched by recrystallisation. After a non-chiral separation, a mixture of **131AA** and **131BB** would be obtained in a ratio of 81 : 1. This mixture now has a greatly enhanced ee of 97.5% compared to the mono-directional product which had an ee of 80%. Use of this method would lead to enhanced selectivity at the expense of overall yield.

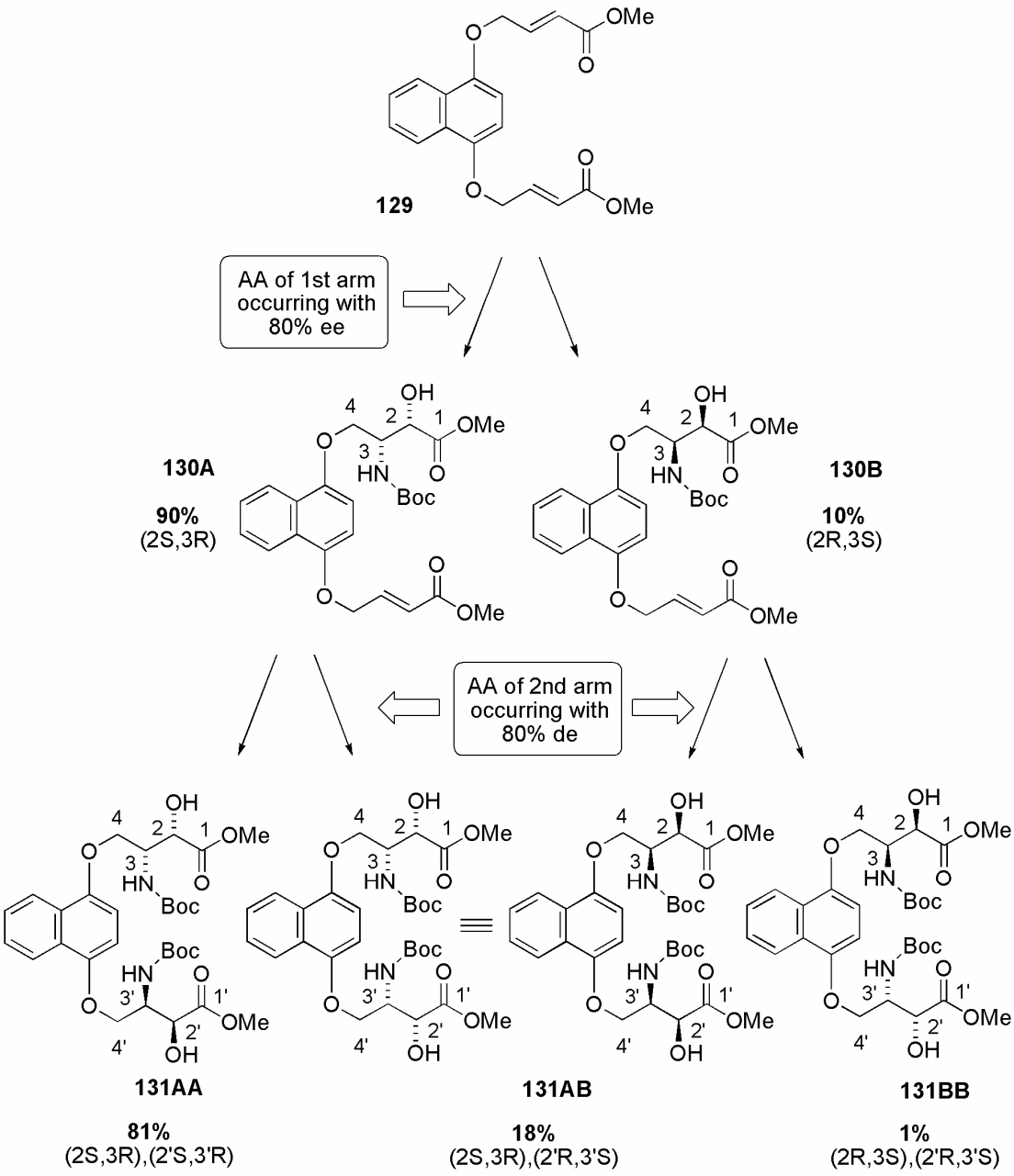


Figure 4.11 Statistical outcome of AA reaction with bi-directional substrate.

Synthesis of bi-directional AA substrate **129** was carried out. Reduction of 1,4-naphthoquinone **132** using freshly purchased sodium dithionite gave 1,4-naphthalenediol **133** (Figure 4.12). To avoid reoxidation during handling, the product was used immediately in the next step. Allylation of **133** gave allyl species **134** in excellent overall yield. Initially the experiment was attempted using old sodium dithionite and the reaction was very messy and produced only 3% of **134** over the two steps. The use of fresh sodium dithionite is crucial to the success of the reaction. Cross metathesis of allyl species **134** with methyl acrylate gave bi-directional substrate **129** in moderate yield. Immediate purification in the dark was necessary to avoid decomposition. Significant quantities of dimer **135**, thought to form after dimerisation of allyl species **134**, were isolated from the reaction. Further exposure of dimer **135** to the reaction conditions may convert it to the more thermodynamically stable species **129**. The reaction may be improved by use of higher reaction temperatures using toluene as the solvent.

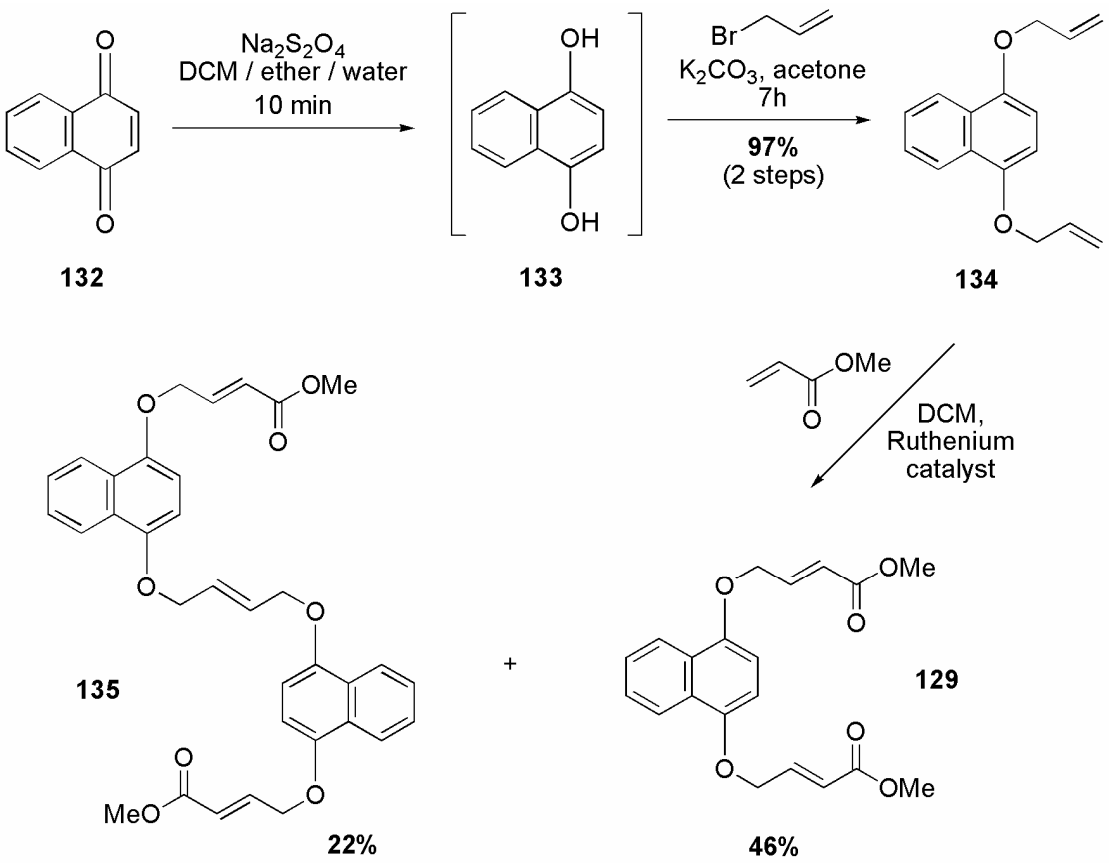


Figure 4.12 Preparation of bi-directional substrate.

The AA of bi-directional substrate **129** formed an inseparable mixture of products. The ^{1}H NMR spectra of the product mixture contained two broad doublets, one at 5.48 ppm, typical of an α-aminoalcohol N-H and another at 5.06 ppm, typical of a β-aminoalcohol N-H which indicated the formation of regio-isomers (see Chapter 2, **Error! Reference source not found.**). The three possible regio-isomers that could form in the reaction are the desired product **β,β-136** (Figure 4.13), and its regio-isomers **α,β-136** and **α,α-136**. The relative integration of the α-aminoalcohol N-H and β-aminoalcohol N-H peaks was 1 : 2.4 indicating a large proportion of material was converted to **α,β-136** and **α,α-136**. These products were not easily separable from **β,β-136**.

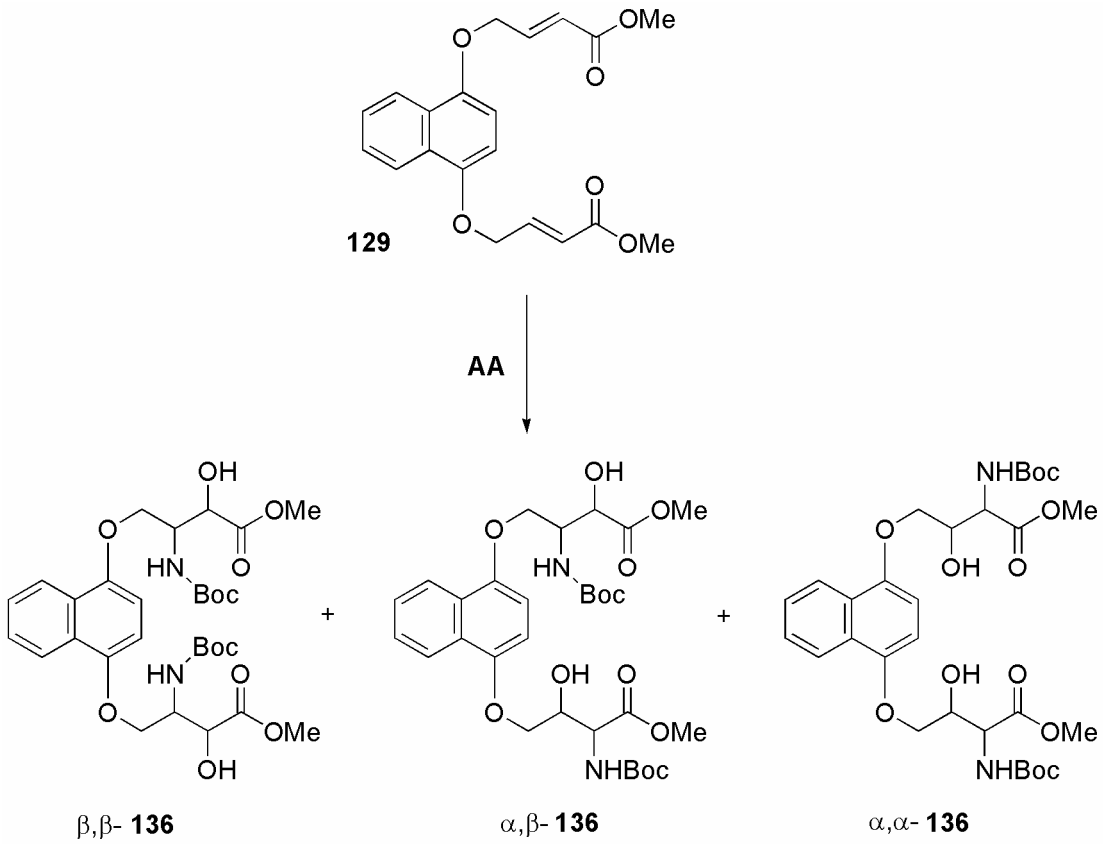


Figure 4.13 AA with bi-directional substrate.

The presence of binding groups in the substrate for the AA has been found to have a large effect on the regio-selectivity and enantio-selectivity of the reaction.[36] It is possible that after the first arm of bi-directional substrate **129** has reacted, the compound interacts differently with the catalyst causing a loss in regio-selectivity in reaction of the second arm. Alternatively the naphthalene group may not be an

effective directing group for the reaction and each arm may have reacted with poor selectivity.

It was decided that the potential increase in ee of the product could not warrant the difficult separation and loss in yield. Better results may have been obtained using a less sterically demanding ligand however this was not pursued further.

4.3 Methyl carbamate

Methyl carbamate was considered as an alternative nitrogen source for the AA. It was thought the resulting product may react with greater success in subsequent reactions, such as the Julia olefination or the oxazolidine formation, due to decreased steric effects. Its final de-protection could be effected under mild conditions for example using $Li^{+-}SPr$[31] or sodium hydrogen telluride.[33]

The AA using methyl carbamate (Figure 4.14) and $(DHQD)_2PHAL$ proceeded smoothly to form β-aminoalcohol **137** in good yield (Figure 4.15, entry 1) while reaction using $(DHQ)_2PHAL$ gave the opposite enantiomer ***ent*-137** (entry 2). Formation of α-aminoalcohol was not observed in either case.

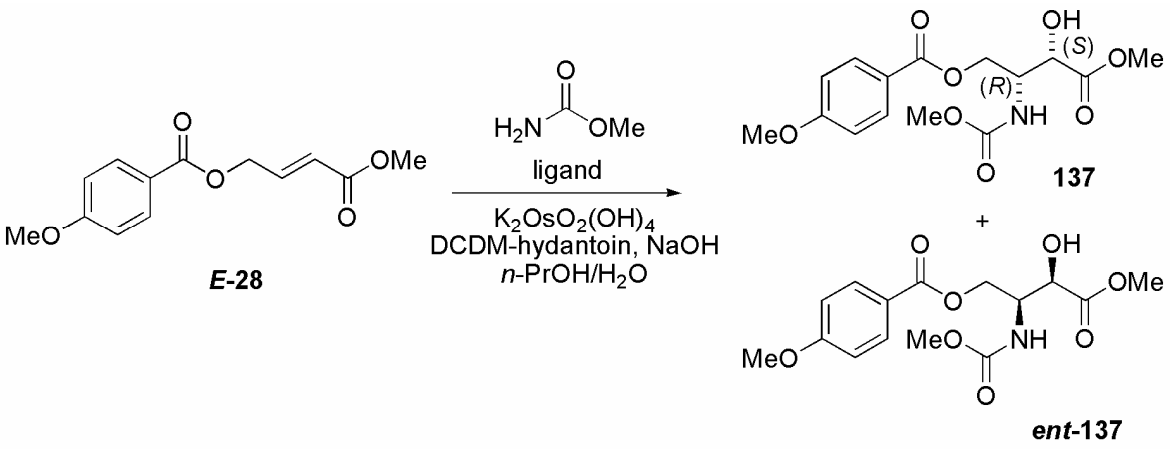


Figure 4.14 AA with methyl carbamate.

The absolute stereochemistry was not confirmed using Mosher's method but was assigned by analogy with the *tert*-butyl carbamate compound **27**. The optical rotation of β-aminoalcohol **137** was of similar intensity and the same sense as β-aminoalcohol **27** while that of the enantiomer ***ent*-137** was of the opposite sense. The % ee of the products were not determined but were predicted to be

high because it has generally been found to improve as the carbamate gets smaller.[30] Analytical chiral HPLC would be necessary to determine the % ee of the products.

Entry	Ligand	Yield (%)	Regio-selectivity	Major enantiomer*
1	$(DHQD)_2PHAL$	67	β-only	**137**
2	$(DHQ)_2PHAL$	43	β-only	***ent*-137**

***** = predicted by the AD mnemonic, optical rotations were of the same sense and similar magnitude to those of the analogous *tert*-butyl compounds

Figure 4.15 Results of the AA with methyl carbamate.

Protection of β-aminoalcohol **137** as oxazolidine **138** proceeded with similar complications as were encountered with the *tert*-butyl analogue **27** (see Chapter 2, page **Error! Bookmark not defined.**). Oxazolidine **138** was formed in moderate yield with significant amounts of intermediate **139** and by-product **140** isolated from the reaction mixture (Figure 4.16). It was interesting to note that by-product **140** appeared to exist as two isomers with some duplicating of peaks in the NMR. It is suspected that both diastereoisomers of the compound were formed with one as the major component. As for the *tert*-butyl series, this reaction may be improved by using 2,2-DMP as the source of the protecting group.

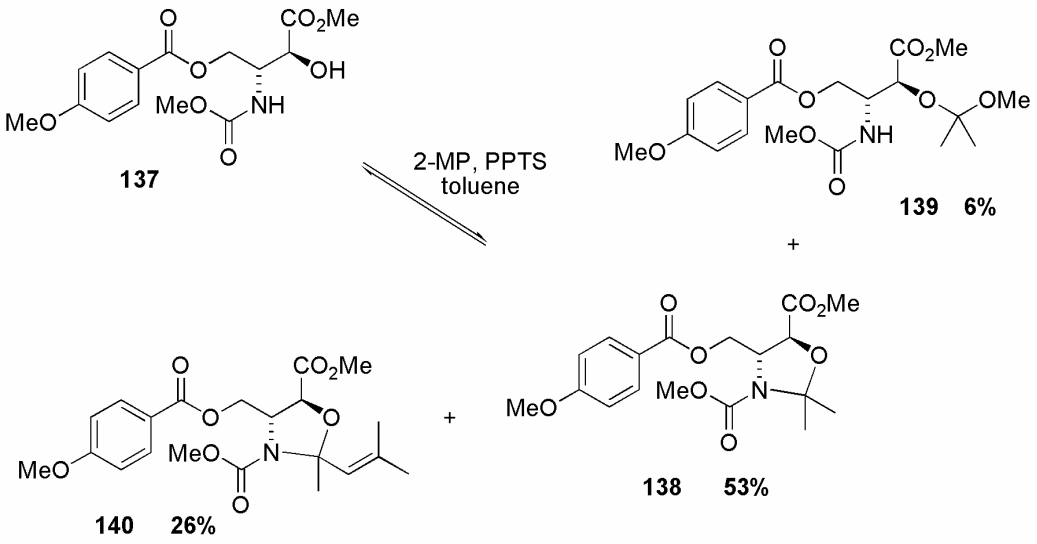


Figure 4.16 Protection as oxazolidine.

Deprotection of the *p*-methoxybenzoyl group of **138** proceeded well to give alcohol **141** in good yield (Figure 4.17). Subsequent oxidation using Dess-Martin periodinane gave aldehyde **142** which was purified and isolated in good yield. The synthesis may benefit by omitting the purification at this step and proceeding with crude aldehyde. Julia olefination of purified aldehyde **142** with PT-sulfone **26** formed alkene **143** which was isolated in reasonable yield however it was hard to remove unidentified contaminants of similar polarity. The *E* : *Z* ratio of alkene **143** (2.4 : 1) was slightly lower than that with the *tert*-butyl system (2.7 : 1 - see Chapter 2, page **Error! Bookmark not defined.**). Subsequent isomerisation enhanced the ratio to 3.9 : 1 but this was not as much as was seen with the *tert*-butyl system (6.5 : 1 - see Chapter 2, page **Error! Bookmark not defined.**). This may be due to the decreased steric interactions between the alkene substituents on the methyl carbamate compound.

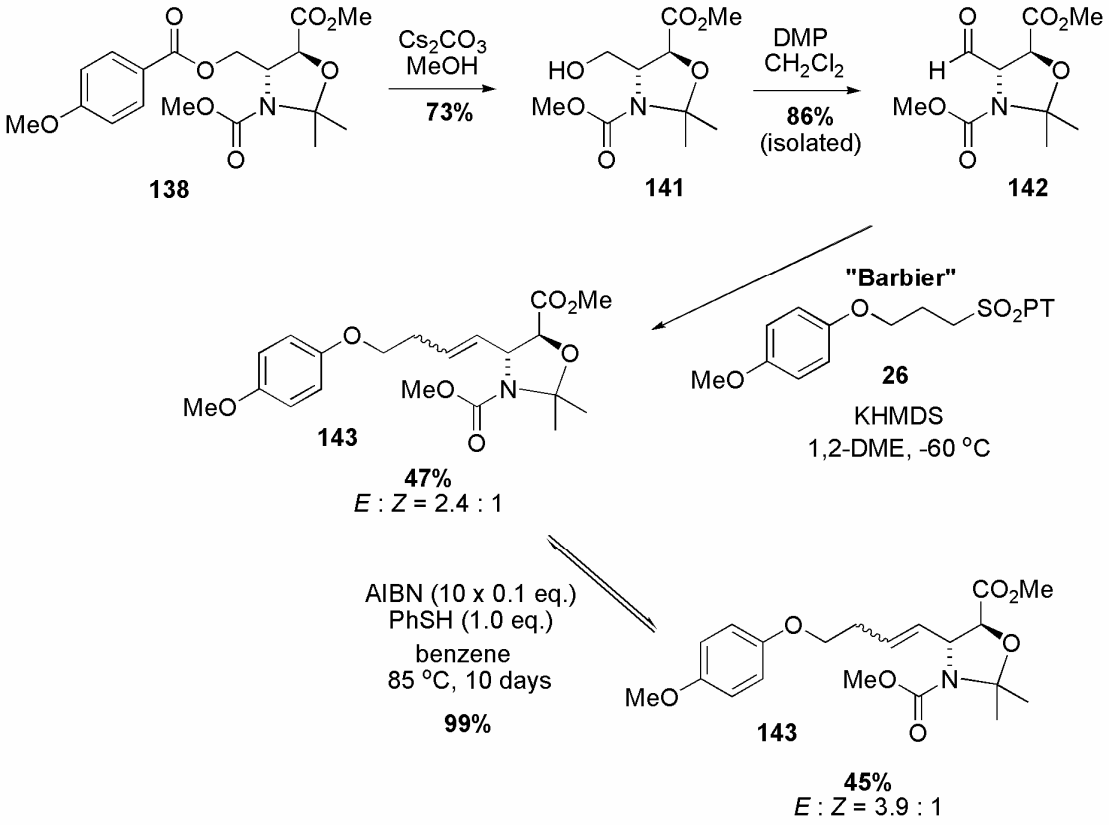


Figure 4.17 Elaboration to Julia olefination.

The use of methyl carbamate appears to be comparable to the *tert*-butyl carbamate system however it was decided to persevere with the *tert*-butyl system because of the higher *E* : *Z* ratios obtained in the isomerisation.

4.4 Alternative Julia Olefination

Before the use of alkene isomerisation to enhance the ratio of (*E*)-alkene ***E*-23** an alternative Julia olefination with reversed fragment substitution was investigated in the hope of obtaining better (*E*)-selectivity. The *E* : *Z* selectivity in the Julia olefination has been found to be quite substrate specific[47] and it was proposed that if the functional groups of the fragments were reversed a different selectivity may be observed. That is, if aldehyde **144** (Figure 4.18) and sulfone **145** were used instead of the original aldehyde **24** and sulfone **26**.

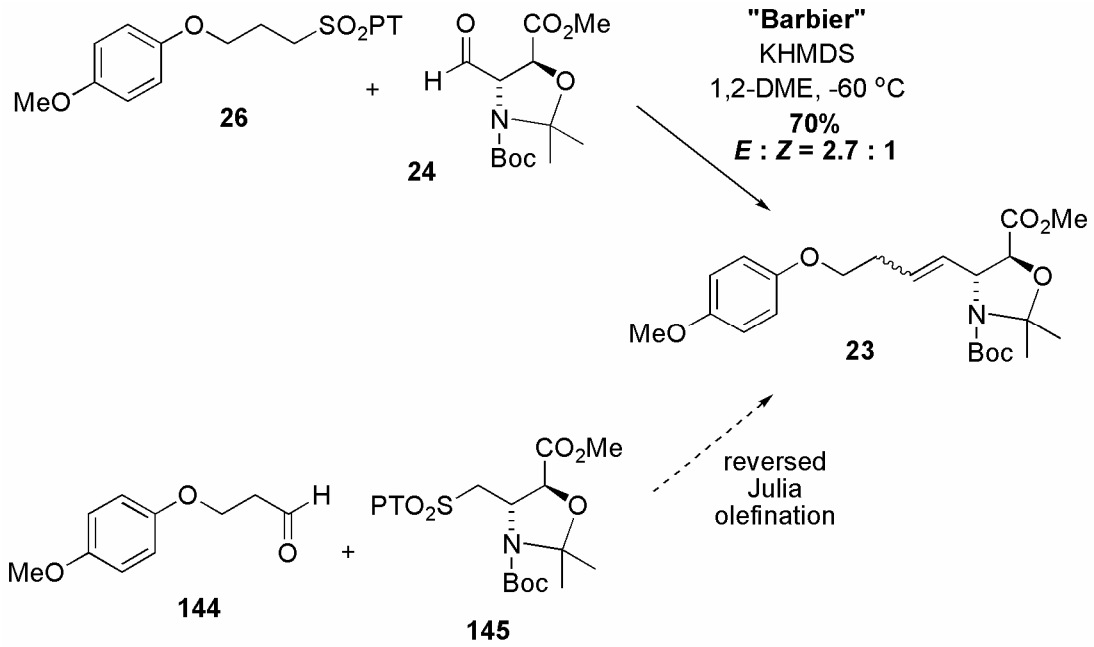


Figure 4.18 Original and proposed reversed Julia olefination.

Aldehyde **144**[71] was prepared by oxidation of alcohol **85** (synthesised in Chapter 2, page **Error! Bookmark not defined.**) using Dess-Martin periodinane (Figure 4.19). It was stored in a freezer for months without decomposition.

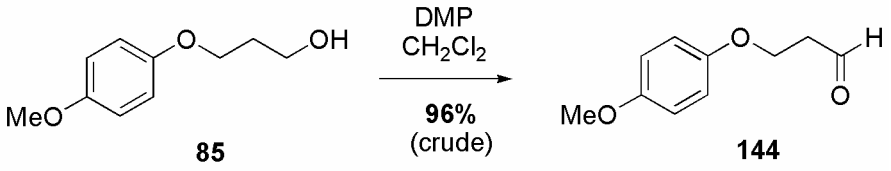


Figure 4.19 Preparation of aldehyde **144**.

The PT-sulfone of TBDMS protected compound **64** was synthesised to test the applicability of the reaction since this material had been previously abandoned (Figure 4.20). Mitsunobu reaction between alcohol **64** (synthesised in Chapter 2, page **Error! Bookmark not defined.**) and PTSH gave thio-ether **146** which was subsequently oxidised to sulfone **147** in good overall yield.

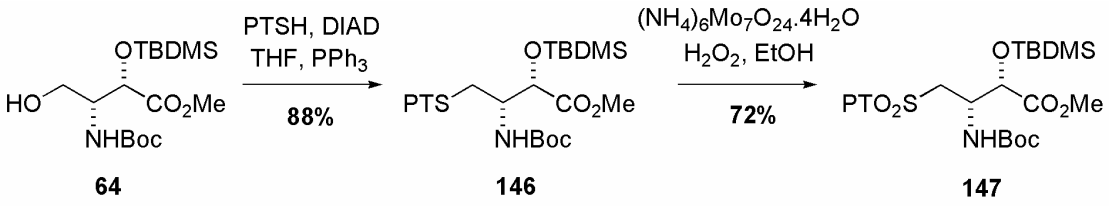


Figure 4.20 Synthesis of sulfone **147**.

Julia olefination of PT-sulfone **147** with isobutyraldehyde **88** failed to afford alkenes **148** using the reaction conditions that were found to be the best for the previous system (Figure 4.21). Only trace unreacted sulfone was visible in the crude ^{1}H NMR spectra and it appeared that sulfone **147** had undergone side reactions to form unidentified by-products. It was suspected that the intermediate β-alkoxysulfone **149** may have cyclised to form lactone by-products **150** (Figure 4.22).

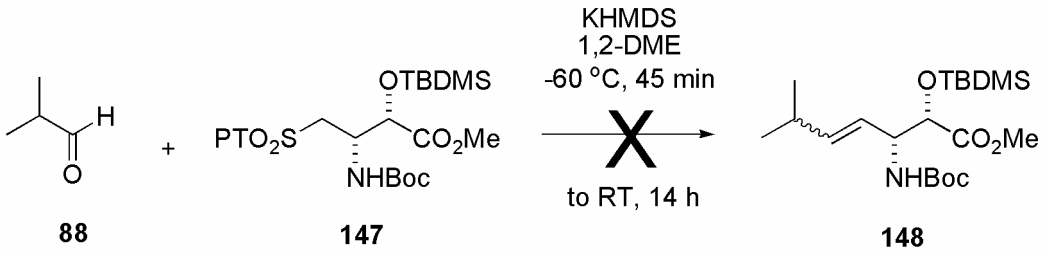


Figure 4.21 Model reversed Julia olefination.

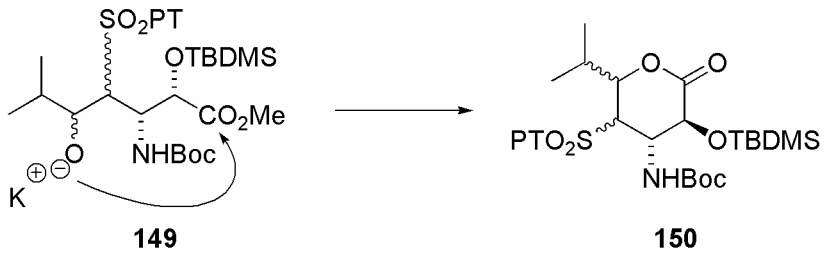


Figure 4.22 Proposed lactonisation.

It was proposed that this lactonisation would not be possible with oxazolidine protected PT-sulfone **145** since the ring would fix the reactive groups in a *trans*-relationship. PT-sulfone was similarly prepared from alcohol **73** (synthesised in Chapter 2, page **Error! Bookmark not defined.**) via thio-ether **151** in good overall yield (Figure 4.23).

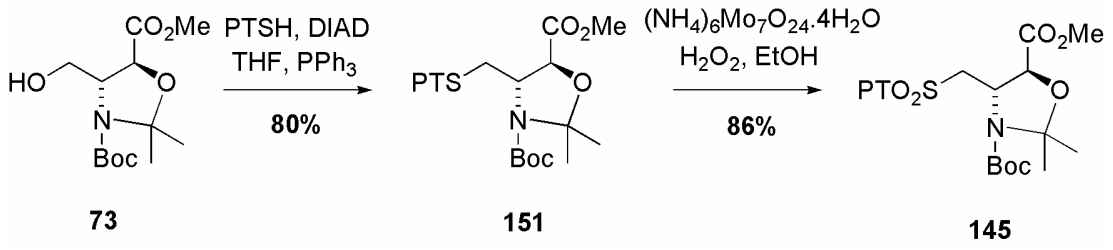


Figure 4.23 Synthesis of sulfone **145**.

Julia olefination of PT-sulfone **145** with isobutyraldehyde **88** gave alkenes **152** in low yield with some inseparable impurities (Figure 4.24). Significant amounts of unreacted sulfone **145** were recovered from the reaction mixture while no unreacted isobutryaldehyde was recovered. This reaction may give better results using premetallation conditions because no evidence of self-condensation of sulfone **145** was observed. The *E* : *Z* ratio of alkene **152** was 2 : 1 which was the same as was obtained for the original model system (see Chapter 2, page **Error! Bookmark not defined.**). The low (*E*)-selectivity observed is in agreement with Blakemore's summary of selectivity (see Chapter 2, page **Error! Bookmark not defined.**) for reaction of an aliphatic sulfone and an aliphatic aldehyde via path **A**. The model study suggested that a low (*E*)-selectivity would be observed with the reversed system.

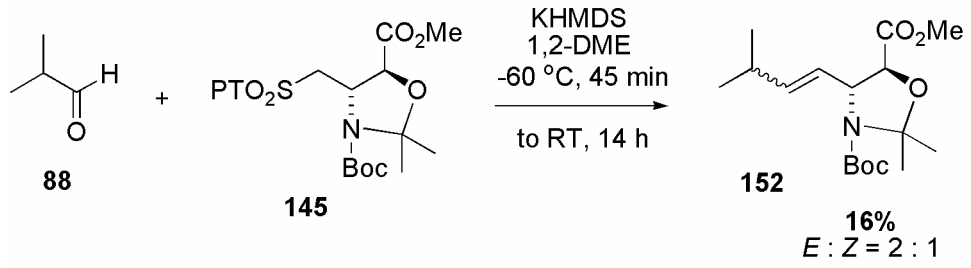


Figure 4.24 Model reversed Julia olefination.

Julia olefination between PT-sulfone **145** and aldehyde **144** failed to form alkene **23** (Figure 4.25). Trace unreacted sulfone **145** was recovered while no

aldehyde **144** was recovered. By-product **153**[72,73] was isolated as the major product of the reaction and other unidentified by-products were observed.

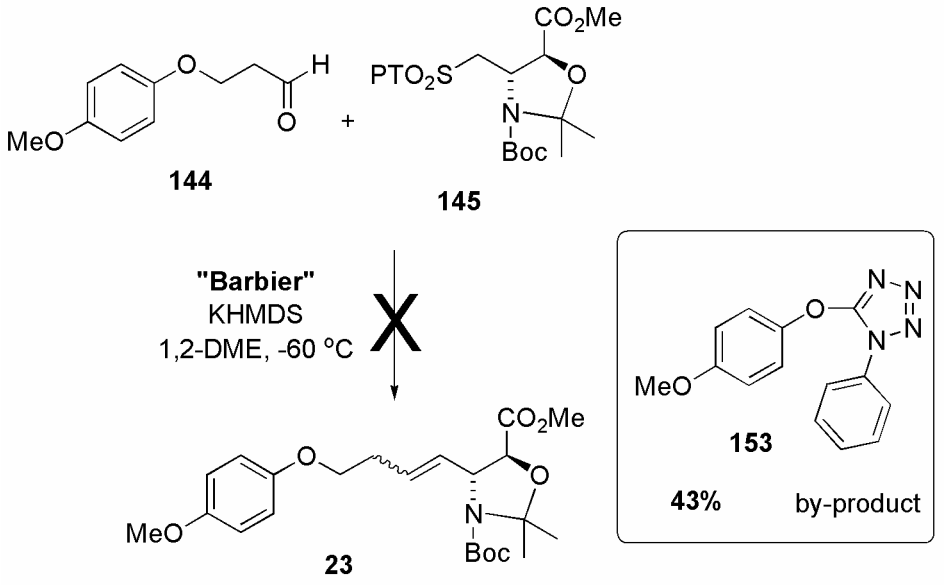


Figure 4.25 The reversed Julia olefination.

By-product **153** is thought to be formed by β-elimination of aldehyde **144** (Figure 4.26) and attack by the resulting phenolate anion **154** on the *ipso*-position of PT-sulfone **145** followed by elimination of the sulfone moiety. This reversed Julia olefination was abandoned due to the incompatibility of the aldehyde fragment with the reaction conditions.

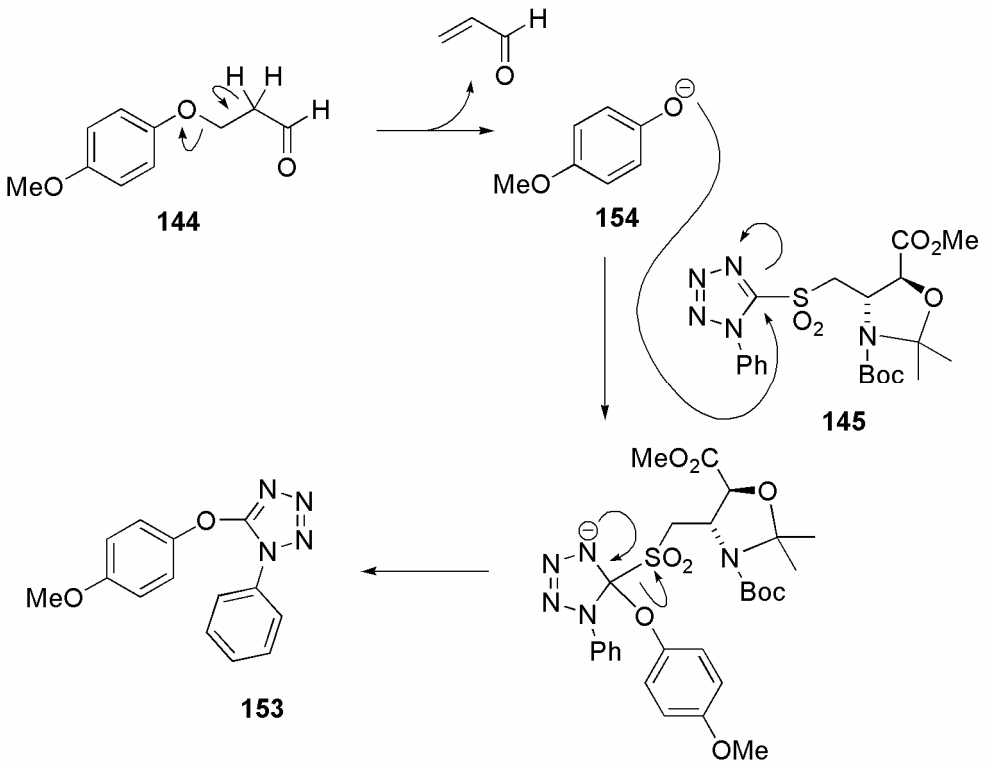


Figure 4.26 Formation of by-product **153**.

Blakemore[47] has observed that generally electron rich aldehydes react via path **C** (see Chapter 2, **Error! Reference source not found.**) to form alkenes with good (*E*)-selectivity. This suggests a reversed Julia olefination for the formation of alkene **18** involving benzaldehyde **155** and aliphatic sulfone **156** may give good (*E*)-selectivity (Figure 4.27). Future studies should include this reaction and the analogous reaction towards AETD. Care in the preparation of sulfone **156** would need to be taken and buffering of the oxidation step may be required.

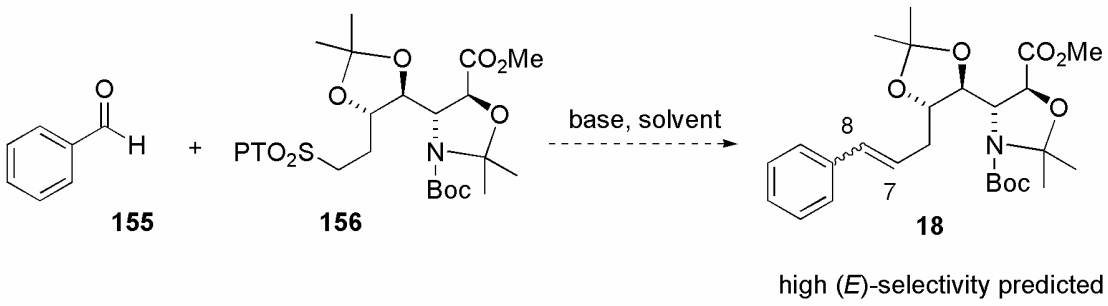


Figure 4.27 Proposed reversed Julia olefination for the final step.

4.5 Additional Alkene Isomerisations

Before carrying out the isomerisation on alkene **23** the procedure was tested on alkene **28**. A sample of alkene **28** with an *E* : *Z* of 1 : 10 was isomerised overnight to give a sample with an *E* : *Z* of 18 : 1 (Figure 4.28). The alkene was recovered in essentially quantitative yield. This system worked very well as alkene **28** is a good radical acceptor.

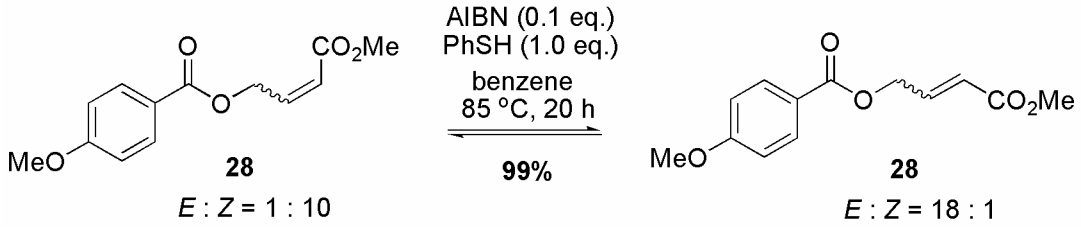
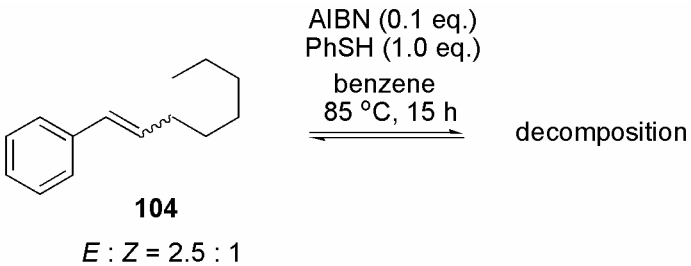


Figure 4.28 Isomerisation of alkene **28**.

It was proposed that alkene **18** (see **Error! Reference source not found.**) and diene **30** (see **Error! Reference source not found.**) may be good radical acceptors because of the neighbouring unsaturation in these compounds. Before committing material to this step, isomerisation of model products, alkene **104** and diene **114** was investigated (Figure 4.29). Alkene **104** decomposed completely under the reaction conditions. The ^{1}H NMR of the crude product contained broad aromatic and heptane-like peaks. It was suspected that polymerisation had occurred. Model diene **114** also decomposed completely under the reaction conditions. Diene **114** was since found to be quite unstable decomposing rapidly on the bench (two days) and in the freezer (one week). The diene may undergo polymerisation or Diels Alder reactions. Shorter reaction time and lower temperature may provide better results with these systems. Alternative isomerisation methods may prove more successful.



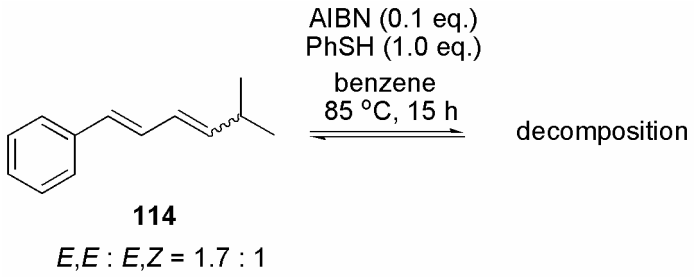


Figure 4.29 Isomerisation of alkene **104** and diene **114**.

4.6 Application of the Synthesis to AMPTD

Initial studies into the application of the synthetic strategy to the synthesis of protected AMPTD ***E*-36** were made. The two differences between this compound and protected APTO ***E*-18** and protected AETD ***E*-30** are that it has a chiral methyl group at the C_6 position and contains different substitution in the aromatic tail. It was envisaged that the chiral methyl group could be installed by coupling sulfone **31** with aldehyde **24** in the Julia olefination and elaboration of the alkene product **32** to reach aldehyde **33** (Figure 4.30). A Wittig olefination between aldehyde **33** and phosphonium salt **34** was proposed to form protected AMPTD **36**. The syntheses of sulfone **31** and phosphonium salt **34** were undertaken.

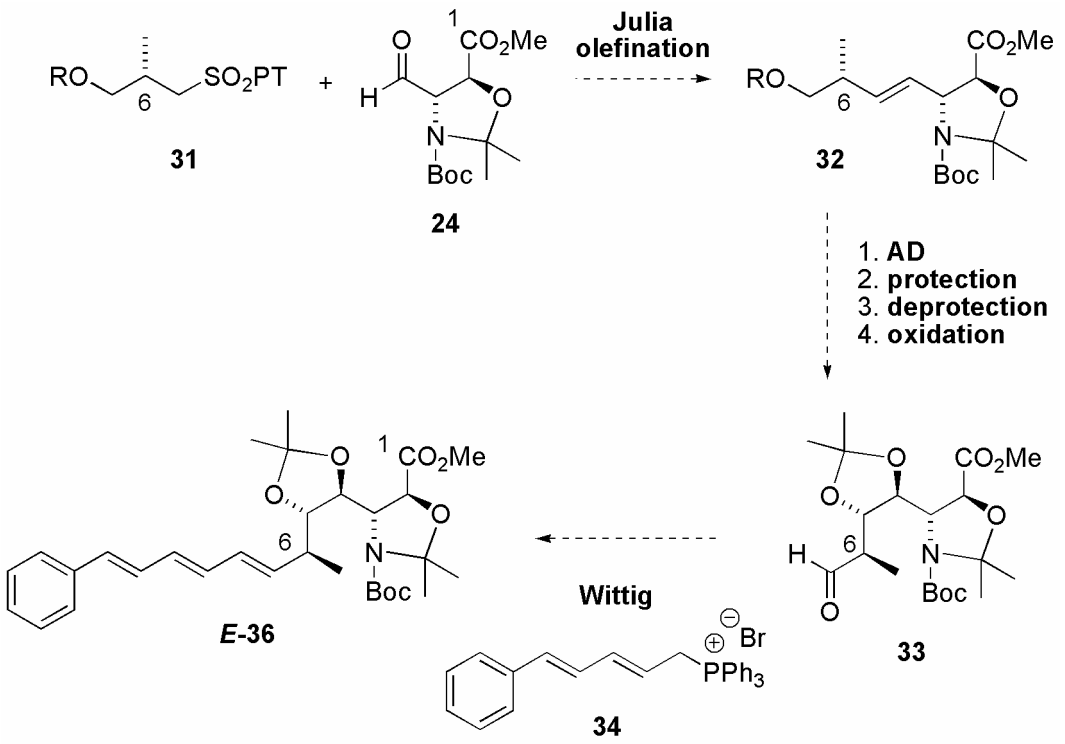


Figure 4.30 Proposed synthesis of protected AMPTD **36**.

Horner-Wadsworth-Emmons reaction of *trans*-cinnamaldehyde **157** with methyl diethylphosphonoacetate **52** gave diene **158**[83,84] with complete (*E*)-selectivity (Figure 4.31). DIBAL-H was used successfully to reduce ester **158** to alcohol **159**[83,85,86,87]. Use of alternative reagents, lithium aluminium hydride or lithium borohydride led to extensive decomposition. Bromine substitution using phosphorus tribromide gave pure bromo-compound **160**[83] which displayed similar instability as bromo-compound **112** (see Chapter 3, **Error! Reference source not found.**). Bromo-compound **160** was combined with triphenylphosphine to give phosphonium salt **34**[85] in excellent overall yield. The salt was stored under reduced pressure over potassium hydroxide before subsequent use.

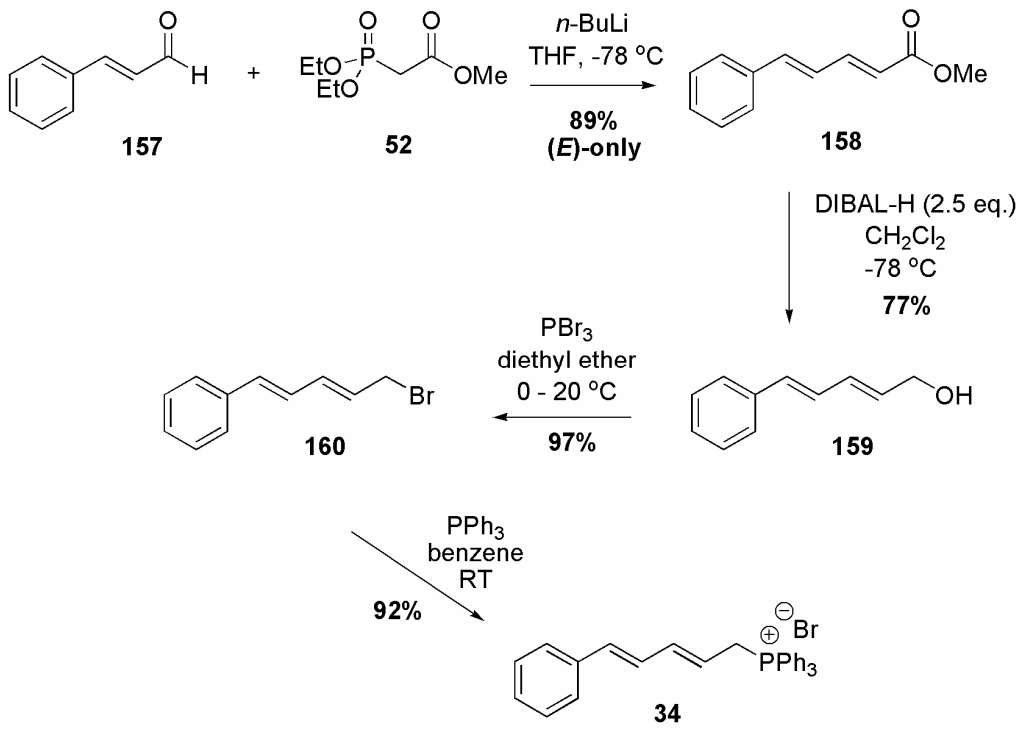


Figure 4.31 Preparation of phosphonium salt **34**.

Hetero-aromatic sulfone **31**[91] was synthesised in four steps from commercially available (+)-methyl (*S*)-3-hydroxy-2-methylpropionate **161** (Figure 4.32). Protection of **161** as TBDMS-ether **162**[89,90] and subsequent reduction using DIBAL-H gave alcohol **163**[90] in excellent overall yield. Mitsunobu reaction between alcohol **163** and PTSH gave thio-ether **164**[91]. The use of potassium dihydrogen phosphate as a buffer in the oxidation step was necessary to prevent loss of the TBDMS group and give sulfone **31** in good yield.

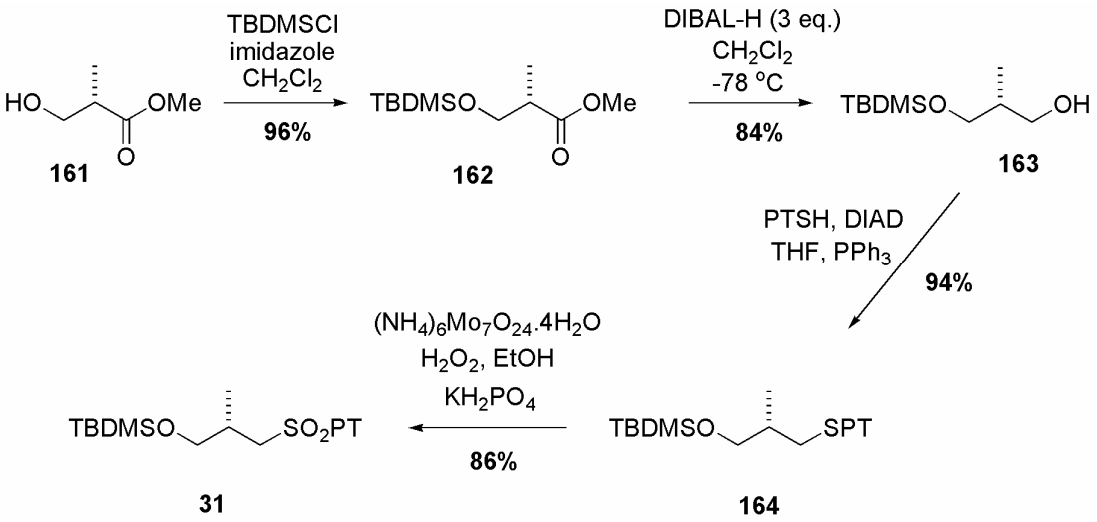


Figure 4.32 Preparation of sulfone **31**.

Initial studies into the Julia olefination have been made. These reactions are not optimised and future work should include this. A model Julia olefination between sulfone **31** and isobutryaldehyde **88** (Figure 4.33) gave alkene **165** with an *E* : *Z* of 1.9 : 1.

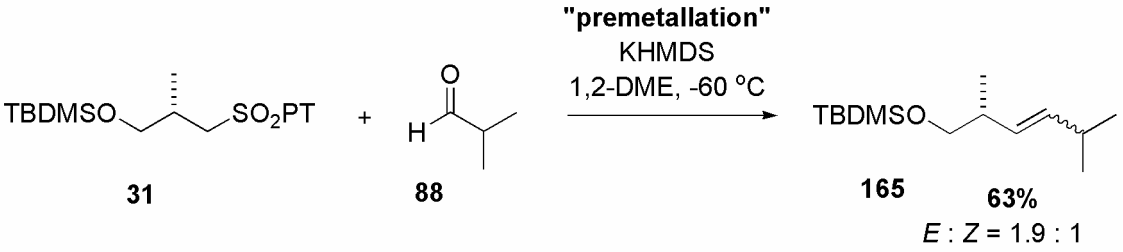


Figure 4.33 Model Julia olefination.

Julia olefination between sulfone **31** and aldehyde **24** gave alkene **32** with an *E* : *Z* of 1 : 1.5 (Figure 4.34). The product was hard to visualise by TLC with poor UV activity and poor staining with anisaldehyde, ninhydrin, permanganate, iodine, vanillin or molybdenum. The Julia olefination to form alkene **32** was performed once using premetallation conditions and the reaction should be optimised. Use of Barbier conditions may improve the outcome of the reaction. It was interesting to note that the reaction favoured (*Z*)-alkene ***Z*-32**.

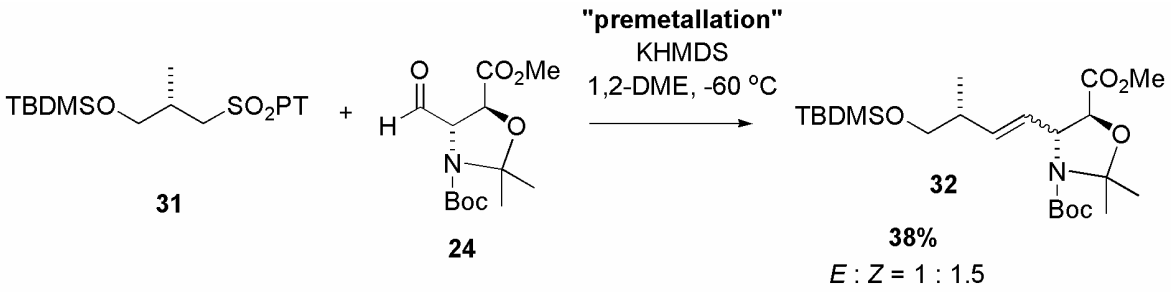


Figure 4.34 Julia olefination.

Isomerisation of alkene **32** should be investigated in order to improve the *E* : *Z* ratio of the product. It was proposed that isomerisation of this compound would work better than that of alkene **23** (see Chapter 2, **Error! Reference source not found.**) because of the increased sterics that the C_6 chiral methyl brings to the alkene.

Application of the synthetic strategy to the synthesis of AMPTD looks promising. Further studies into the olefination and subsequent isomerisation must be performed before full elaboration to protected AMPTD ***E*-36** can be completed.