Part 3: Towards the synthesis of (-)-Dysibetaine

Chapter 1: Introduction

1.1 (-)-Dysibetaine

New molecules are regularly discovered in nature that show interesting characteristics and biological activity. These biologically active molecules provide synthetic challenges to organic synthetic chemists as well as the potential for new drug candidates.

(-)-Dysibetaine **1** was isolated from the marine sponge *Dysidea herbacea* collected from Yap, Micronesia.[1] The structure of (-)-dysibetaine **1** was published in 1999 by Sakai and to date five groups have published total syntheses.

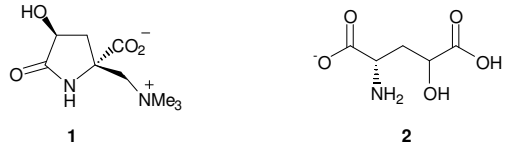
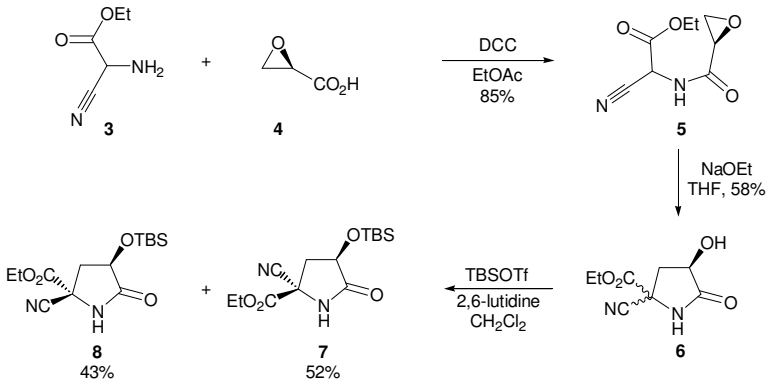


Figure 1. Dysibetaine and 4-hydroxyglutamate

The *Dysidea herbacea* was extracted to obtain only 3.1 mg of **1** from 200 g of the marine sponge. This corresponds to 0.0016% by weight of (-)-dysibetaine **1**. The compound was characterised by spectroscopic methods and its structure confirmed by X-ray crystallography. However the absolute configuration could not be determined at this stage. It was suggested by Sakai that **1** may have been formed from 4-hydroxyglutamate **2** which gives the depicted stereochemistry.

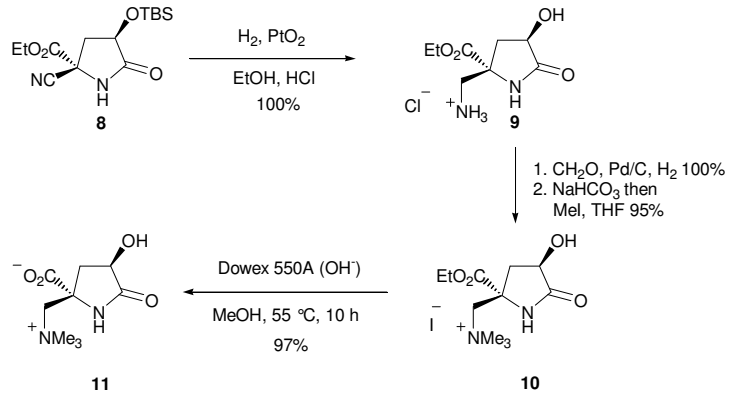
The first total synthesis was published in 2001 by Snider.[2] Intramolecular alkylation of a glycidamide was used to construct the pyrrolidinone ring **6**. The first step involved amide coupling with (*R*)-glycidic acid **4** and ethyl

amino(cyano)acetate **3** using DCC to form **5** (Scheme 1). The (*R*)-glycidic acid **4** was prepared from (*S*)-serine following the procedure by Larchevêque.[3] Intramolecular alkylation of **5** gave the pyrrolidinone **6** and protection of the alcohol with TBS allowed separation of the two diastereomers **7** and **8** by flash column chromatography.



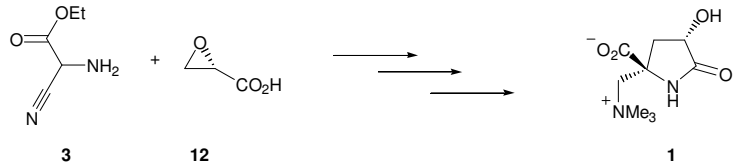
Scheme 1. Snider synthesis of R,R-dysibetaine

Hydrogenation of the nitrile over PtO_2 and HCl gave the hydroxy amine hydrochloride **9** in quantitative yield (Scheme 2). Methylation of **9** using aqueous formaldehyde and Pd/C under Clarke-Eschweiler conditions followed by neutralisation using $NaHCO_3$ and reaction with MeI gave **10**. Saponification of **10** in methanol provided the *R,R*-dysibetaine **11** in seven steps with an overall yield of 20%.



Scheme 2. Snider synthesis of R,R-dysibetaine

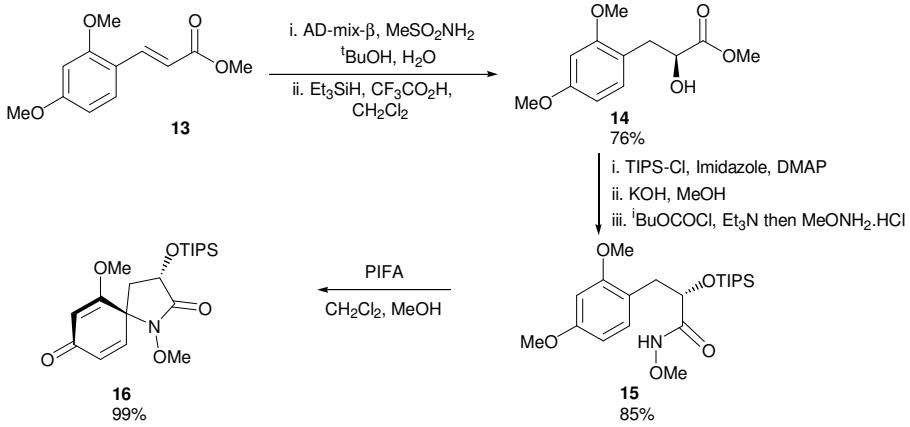
The *R,R*-dysibetaine **11** product was found to have an optical rotation similar in magnitude but opposite in sign compared to the natural product **1**. This indicated that the absolute configuration of the natural product was *S,S*-dysibetaine **1**.



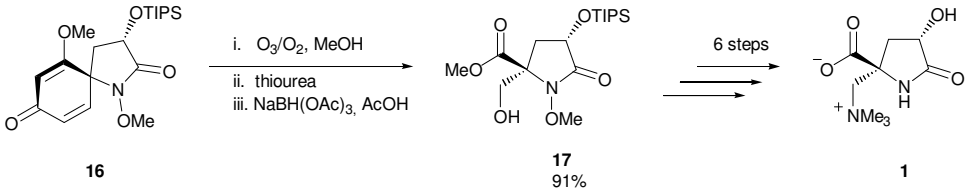
Scheme 3. Snider synthesis of S,S-dysibetaine

An identical sequence of reactions was used to prepare **1** from *S*-glycidic acid **12** and ethylamino(cyano)acetate **3** (Scheme 3). The optical rotation obtained with the synthetic *S,S*-dysibetaine was $[\alpha]_D$ = -7.1° and was very close to the reported natural product with an $[\alpha]_D$ = -7.3°. This paper established the absolute stereochemistry of the natural product.

In 2004, the Wardrop group reported the total synthesis of (-)-dysibetaine **1** using a nitrenium ion cyclisation to introduce the pyrrolidinone ring **16** (Scheme 4) followed by a dienone cleavage to form **17** (Scheme 5).[4] The synthesis involved 13 steps and gave an overall yield of 12%.

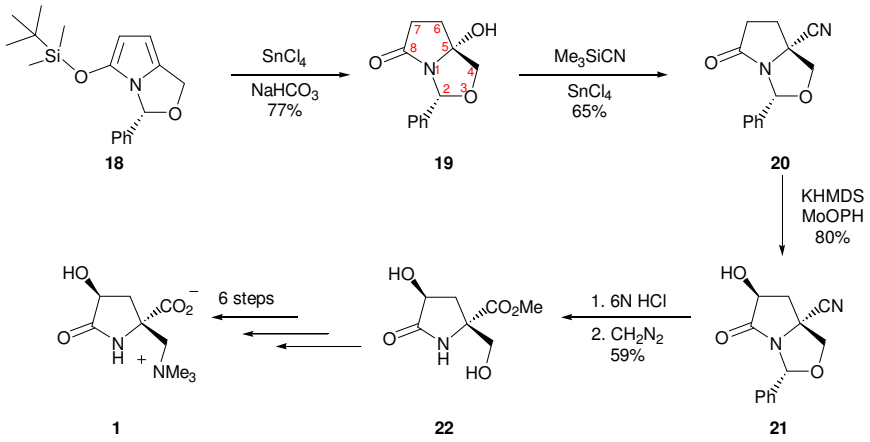


Scheme 4. Wardrop synthesis of (-)-dysibetaine



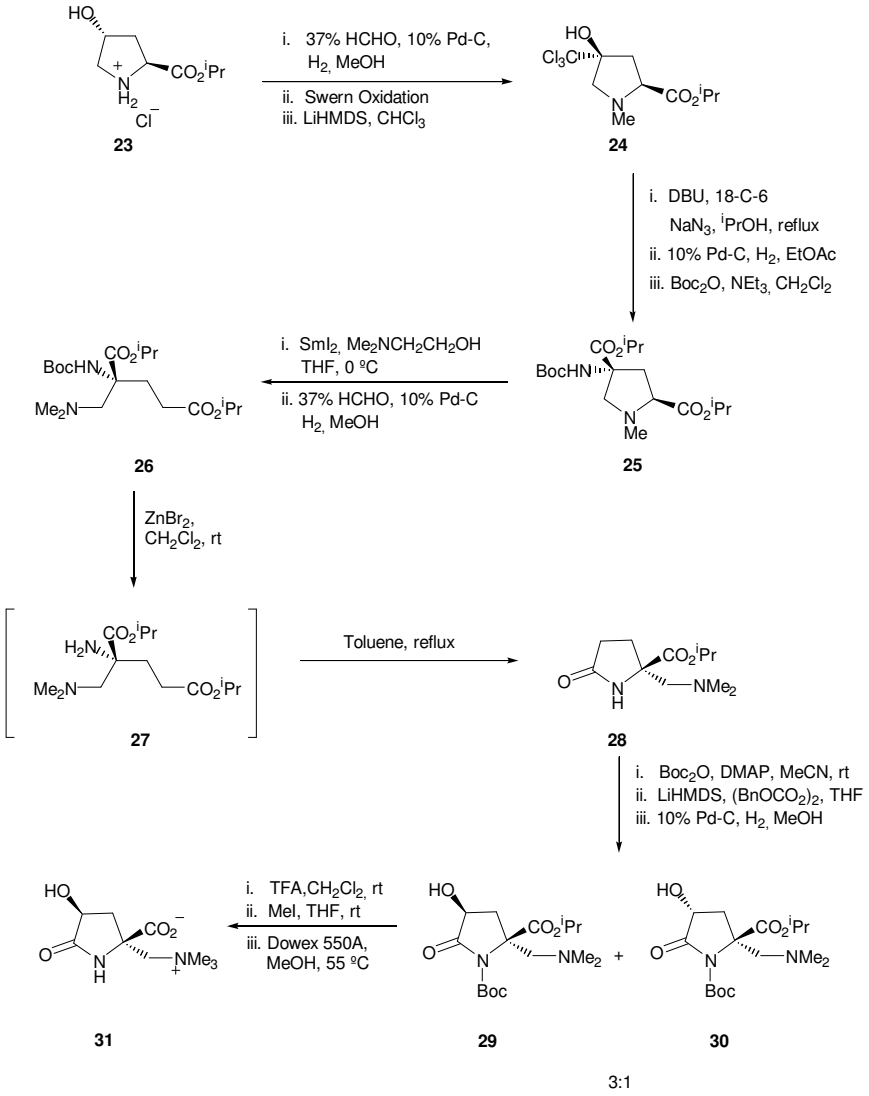
Scheme 5. Wardrop synthesis of (-)-dysibetaine

Langlois also reported the total synthesis of (-)-dysibetaine **1** in 2004.[5] In this case the pyrrolidone ring was introduced from initially a siloxy pyrrole **18** (Scheme 6). The double protonation in the first step is believed to occur due to slow hydrolysis of the complex between the siloxypyrrole **18** and $SnCl_4$. This was followed by trapping of the iminium ion with a hydroxide ion which gave **19**. The hydroxy group at C^5 could be converted to nitrile group by reaction with trimethylsilylcyanide in the presence of $SnCl_4$ to produce **20** as one diastereomer in 65% yield. The introduction of the hydroxy group at C^7 was investigated and found that deprotonation followed by reaction with the molybdenum peroxide complex MoOPH gave the desired diastereomer **21** in the highest yield. (–)-Dysibetaine **1** was produced in eleven steps from **18** with an overall yield of 5%.



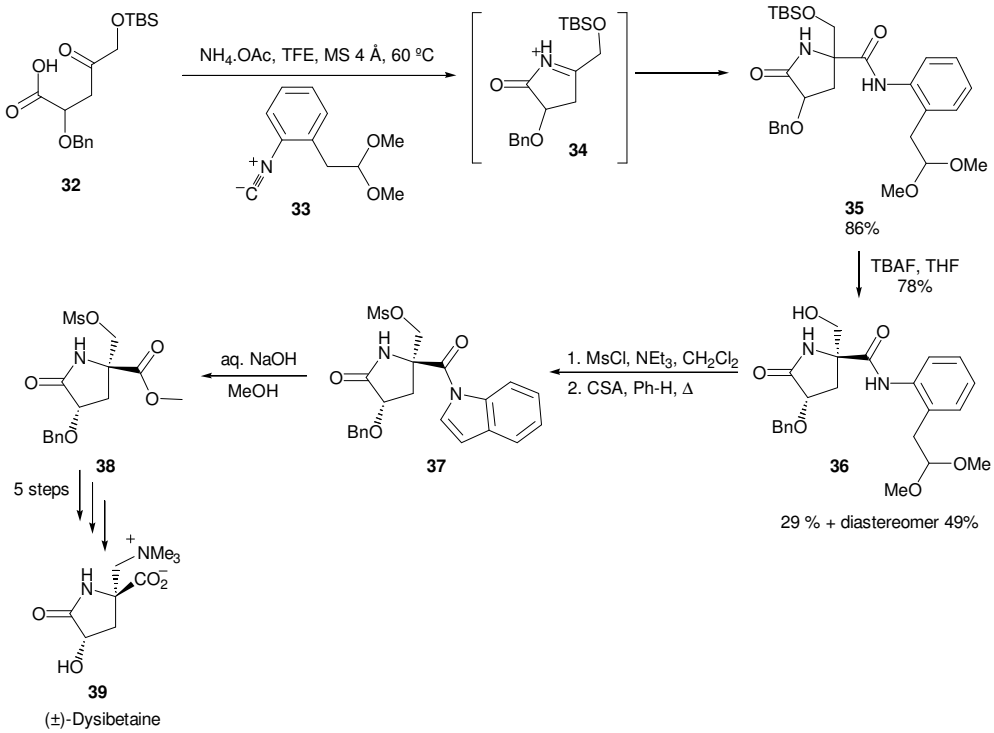
Scheme 6. Langlois synthesis of (-)-dysibetaine

Honda published the synthesis of (-)-4-*epi*-dysibetaine **31** in 2007.[6] The key reaction in this synthesis was the samarium iodide reductive carbon-nitrogen bond cleavage of a proline derivative **25** to give **26** which was then deprotected to form **27** which cyclised to produce the pyrrolidinone **28** (Scheme 7). Unfortunately when the alcohol was introduced α to the carbonyl of **28** the major product was the undesired hydroxy compound **29**. Alcohol **29** was converted to (-)-4-*epi*-dysibetaine **31**. The synthesis was completed in 15 steps and gave an overall yield of 18%.



Scheme 7. Honda synthesis of (-)-4-epi-dysibetaine

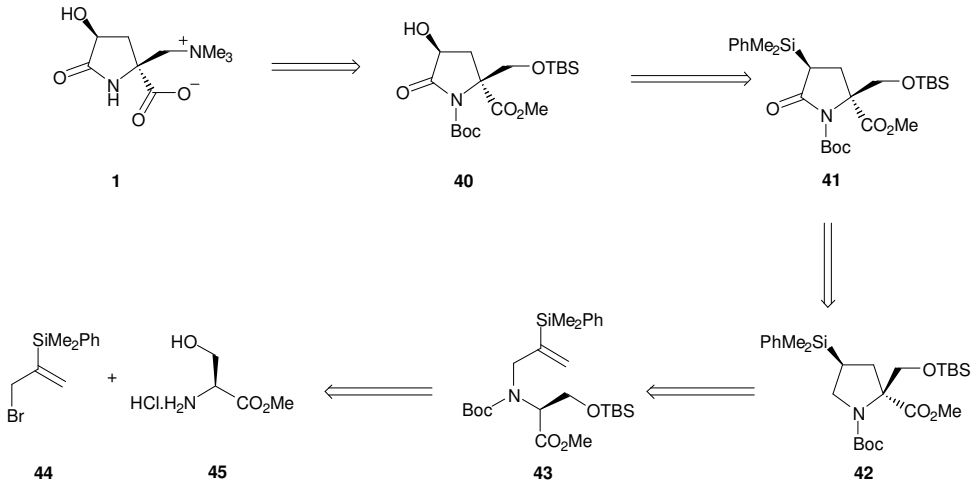
In 2008, a racemic total synthesis was published by Kobayashi.[7] The pyrrolidinone ring **35** was formed by an Ugi 4-centered 3-component reaction (Scheme 8). The TBS group was removed using TBAF and the diasteroemers were separated at this stage by silica column chromatography to give a single racemic diastereomer **36**. The isocyanide **33** was chosen as it could be converted to an acylindole **37** which was easily hydrolysed to the methyl ester **38**. The racemic dysibetaine **39** could then be formed *via* several functional group interchanges. The racemic synthesis was completed in 16 steps with an overall yield of 9% from commercially available materials. Kobayashi has recently reported the asymmetric synthesis of (-)-dysibetaine **1** with the isocyanate **33** and a derivative of L-malic acid to introduce the desired chirality at the hydroxyl group.[8] This produced the natural product **1** in 11 steps with an 11% overall yield.



Scheme 8. Kobayashi synthesis of (±)-dysibetaine

1.2 Proposed Retrosynthesis

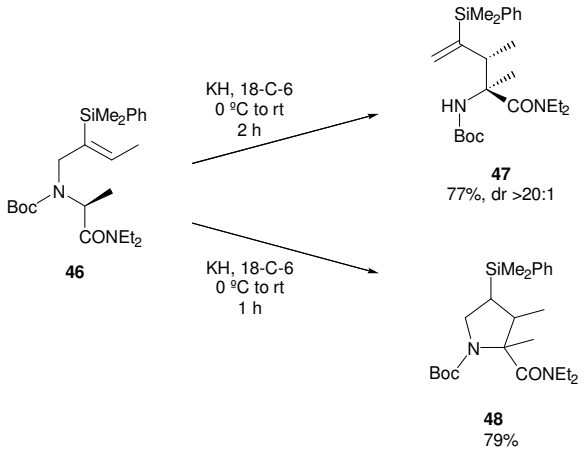
Our proposed retrosynthesis is outlined below (Scheme 9) and it was envisaged that the natural product **1** could be synthesised *via* several functional group interchanges from **40** which have precedence in the literature. The compound **40** could be formed from a Fleming oxidation of **41**. Oxidation of **42** to introduce the pyrrolidine carbonyl using a RuO_2 catalyst would provide compound **41**. It was envisaged that compound **42** could be formed from compound **43** *via* an aza-[2,3]-Wittig cyclisation protocol which had been developed in our group. Compound **43** would be made by coupling bromo allyl silane **44** with serine methyl ester hydrochloride salt **45** followed by protection of the amine and alcohol.



Scheme 9. Proposed Retrosynthesis

1.3 Previous Research

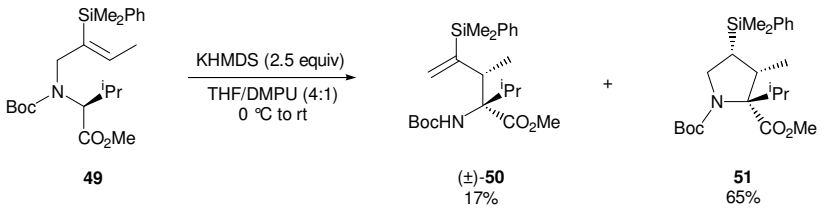
The aza-[2,3]-Wittig rearrangement has been an on-going project within the Anderson group for a number of years. In 2002 our group published an example of the rearrangement reaction that formed the quaternary amino acid derivative **47** (Scheme 10).[9] The precursor is deprotonated at the carbon α to the amide **46** followed by the rearrangement to give the racemic compound **47** after workup in 77% yield with a *dr* >20:1 (Scheme 10). This work was repeated by Davies, however the rearrangement product **47** was not observed and only the cyclised pyrrolidine **48** was obtained in 79% yield.[10] Attempts to reproduce the formation of **47** were unsuccessful.



Scheme 10. Aza-[2,3]-Wittig rearrangement and aza-[2,3]-Wittig rearrangement cyclisation

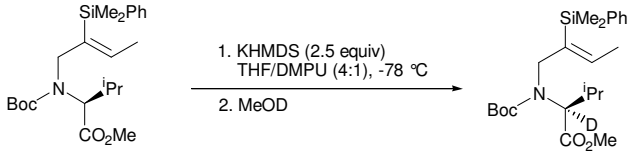
The pyrrolidine product **51** was also obtained in 65% yield; the base used in this reaction was KHMDS (Scheme 11). A small amount of the rearranged product **50** was also obtained under these conditions. The reaction temperature was investigated and it was found that only the pyrrolidine product **51** was obtained at temperatures from -40 °C to 0 °C. A deuterium quench experiment at -78 °C to investigate whether deprotonation was occurring at the carbon α to

the ester of **49** was found to give 90% incorporation in the product **52** (Scheme 12). The deuterated product **52** exhibited a specific rotation of -25.7 10^{-1} deg cm^2 g^{-1} compared to the protonated precursor **49** of -39.5 10^{-1} deg cm^2 g^{-1}. This showed the precursor **49** was being deprotonated at these low temperatures and suggested the stereochemistry had to some degree been maintained.



49 (±)-**50** 17% **51** 65%

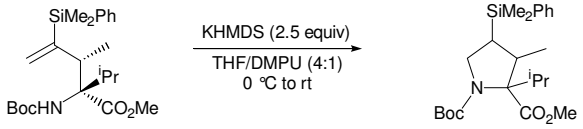
Scheme 11. Aza-Wittig Rearrangement & cyclisation



49 **52** 90%

Scheme 12. Deuterium Experiment

The isolated rearrangement product **50** was resubjected to the reaction conditions and the pyrrolidine **51** was obtained in 92% yield (Scheme 13). This suggested that the initial [2,3] rearrangement product **50** was an intermediate in the formation of the pyrrolidine **51**.

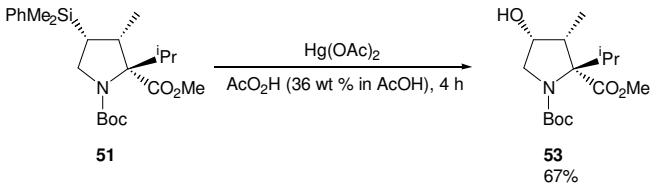


50 **51** 92%

Scheme 13. Formation of the pyrrolidine from **50**.

Previous work has also shown that the $SiMe_2Ph$ group could be converted to a hydroxyl group *via* Fleming oxidation conditions. It was found that the desired alcohol **54** was obtained using mercury acetate and peracetic acid as the

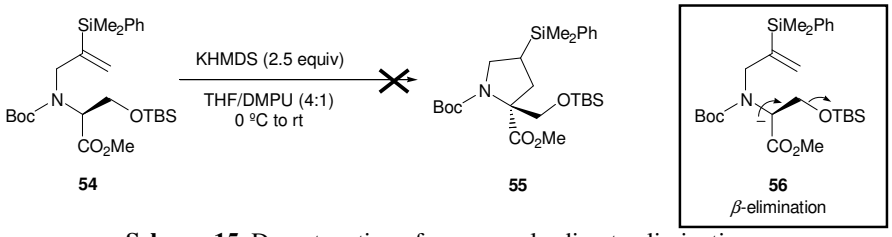
oxidant (Scheme 14). The alcohol **54** was obtained in an unoptimised yield of 67%. This was important as we required the Fleming oxidation to introduce the alcohol into our proposed retrosynthesis.



51 **53** 67%

Scheme 14. Fleming oxidation of cyclised product **51**

We decided to investigate whether this methodology could be used in natural product synthesis of (-)-dysibetaine **1**. An initial investigation into the synthesis of dysibetaine using the aza-[2,3]-Wittig cyclisation using the precursor **54** was unsuccessful and led to degradation, believed to be due to β-elimination **56**, rather than the desired cyclisation to **55** (Scheme 15).[11]



54 **55** **56** β-elimination

Scheme 15. Deprotonation of precursor leading to elimination

A potential method to avoid β-elimination would be to mask the alcohol and ester group as a β-lactone. This would hopefully avoid the potential for elimination as the anion orbital and the leaving group are held orthogonal by the 4-membered ring **57** (Figure 2). Generally elimination occurs *via syn-* or *anti*-parallel arrangement of the orbitals and these eliminations are termed "allowed". Thus by using the conformationally restricted β-lactone, which holds the orbitals orthogonal this would avoid elimination.

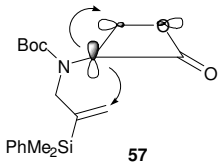
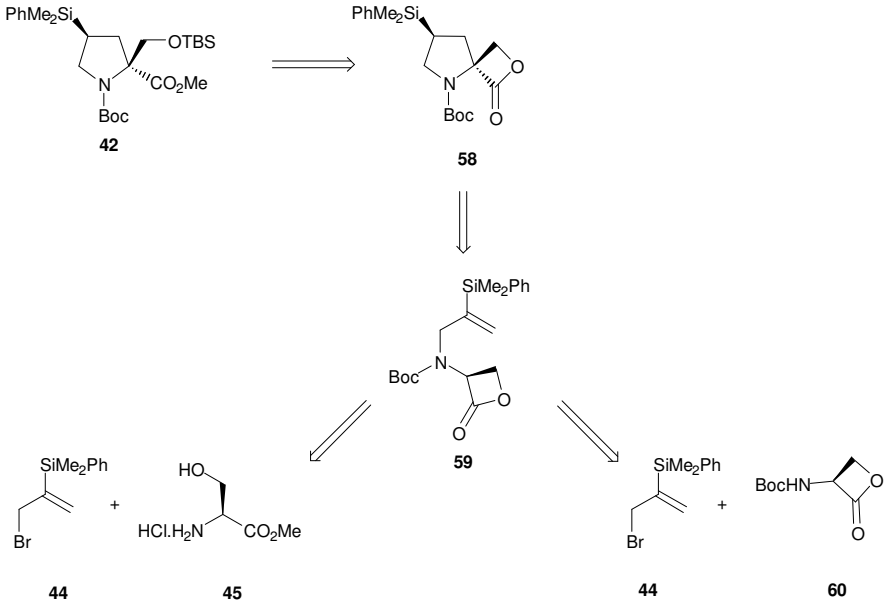


Figure 2. Deprotonated β-lactone in proposed aza-[2,3]-Wittig Rearrangement/Cyclisation

Therefore our revised retrosynthesis would involve the preparation of β-lactone **59** as our precursor for the aza-[2,3]-Wittig cyclisation to form **58** (Scheme 16). The compound **59** was also chosen to avoid the possibility of β-elimination under aza-[2,3]-Wittig cyclisation conditions. The β-lactone **59** could be prepared by reaction of the bromoallyl silane **44** with **60** or by coupling **44** with the L-Serine methyl ester hydrochloride **45** followed by several functional group interchanges.



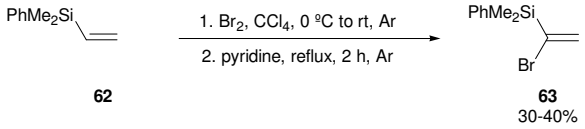
Scheme 16. Revised retrosynthesis

Chapter 2: Results & Discussion

2.1 Route to β-lactone precursor

As discussed earlier in chapter 1.3 (Scheme 16), we decided to investigate the synthesis of the precursor **59** using the bromoallyl silane **44**, which had been previously synthesised in the group, with the Boc-protected β-lactone **60**. This would give the desired precursor **59** in the minimum number of steps.

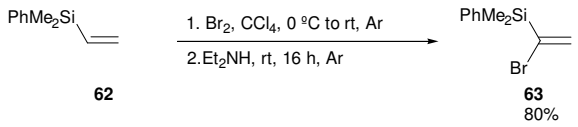
The initial reaction involved the bromination of dimethylphenylvinylsilane **62** followed by elimination using pyridine to give **63** (Scheme 17). The literature reports the yield of 62% for **63** using pyridine at reflux to eliminate HBr.[12] However, using this method only 30-40% yield was obtained. A possible reason for the lower yield may be due to the fact that the HBr.pyridine salt is soluble at reflux and could have been reacting with the dibromide intermediate reducing our yield.



62 **63** 30-40%

Scheme 17

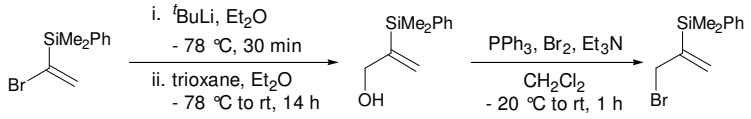
A literature investigation into similar elimination reactions used dry diethylamine at rt to eliminate the HBr.[13] This was attempted on the dibromide intermediate and the HBr.Et_2NH salt precipitated. The salt was removed by filtration and the yield had increased to 80% for the desired (1-bromovinyl)phenyl dimethyl silane **63** (Scheme 18).



62 **63** 80%

Scheme 18

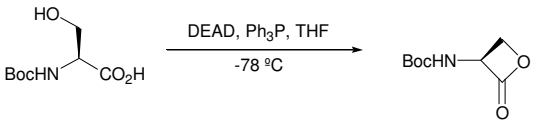
The synthesis of 1-(bromomethylvinyl) dimethylphenylsilane **44** was synthesised by methodology developed in the Anderson group (Scheme 19).[14] Bromo vinyl silane **63** was converted to allylic alcohol **64** *via* halogen lithium exchange followed by reaction with trioxane and gave **64** in 60% yield (lit.[12] 63%). Alcohol **64** was converted to bromide **44** in 69% yield (lit.[14] 95%) using triphenyl phosphine, bromine and triethylamine. The overall yield for the two steps was 41%.



63 **64** 60% **44** 69%

Scheme 19

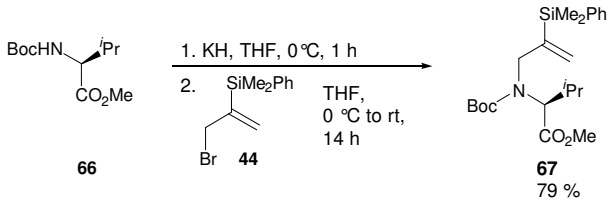
The next step in this synthesis would require the preparation of β-lactone **60,** previously synthesised by Vederas.[15] Treatment of N-Boc-Serine **65** under Mitsonobu conditions provided **61** in 61% yield (Lit.[15] 72%) (Scheme 20).



65 **60** 61%

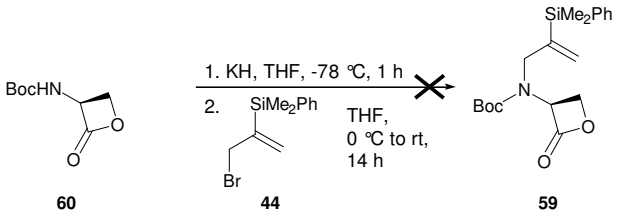
Scheme 20

Thus, we had the two compounds which we desired to react to give **59**. Previous work on the aza-[2,3]-Wittig rearrangement had achieved this by deprotonating Boc-protected amine **66** followed by nucleophilic attack on bromo allyl silane **44** to give **67** (Scheme 21).[10]



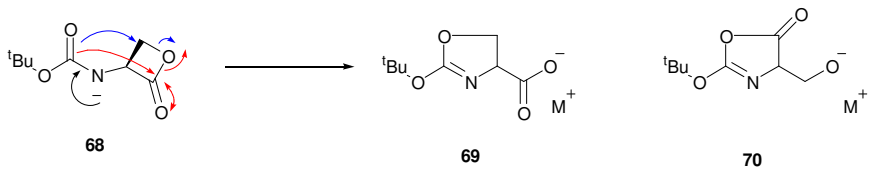
Scheme 21

Following previous conditions in the group, β-lactone **60** was deprotonated with KH and a solution of **44** in THF was added (Scheme 22). However after work-up, a proton NMR spectrum of the crude product showed only the unreacted **44**. The reaction was repeated several times but the desired compound **59** was never formed. β-Lactone **60** appeared to degrade and was removed during the aqueous work up. This could be due to the formation of the intermediates **69** and **70** (Scheme 23) which could easily be hydrolysed on workup to produce Boc-D/L-serine which is soluble in water.[15]



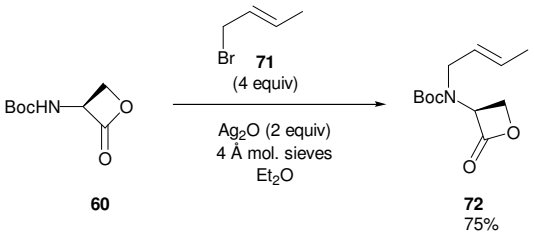
Scheme 22

Previously in the group, compounds which had been difficult to couple had the Boc group removed to allow S_N2 reaction to occur followed by reprotection with Boc anhydride. A literature search on the chemistry of serine derived β-lactones such as **60** suggested that deprotection to the primary amine would lead to degradation.[16]



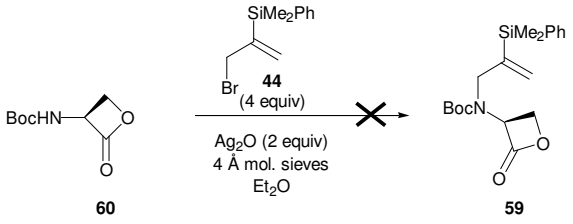
Scheme 23

In 1991, Beaulieu showed that **60** could be coupled with crotyl bromide **71** in a 75% yield (Scheme 24).[17] This was of interest to us as a base was not formally required which could avoid ring opening, and the electrophile was an allylic bromide like **44**.



Scheme 24

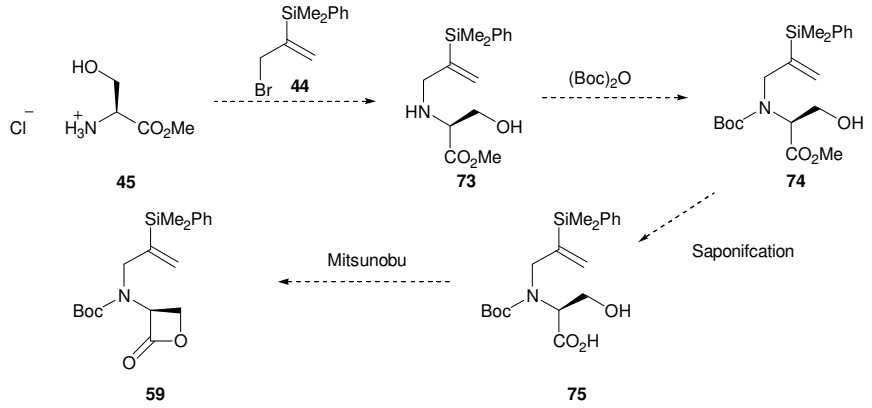
Unfortunately when **60** and **44** were subjected to identical conditions no reaction was observed (Scheme 25). Both **61** and **44** were isolated after workup, recovered in 98% and 70% respectively, and we believe sterics due to the $SiMe_2Ph$ group could be the reason no reaction was observed.



Scheme 25

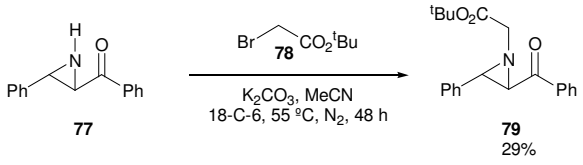
Thus having tried several different conditions to couple the two compounds, attention shifted to an alternative route using serine methyl ester hydrochloride **45**. This would involve reacting **44** with amine of **45** as the first step, followed by Boc protection of secondary amine **73** to give **74** (Scheme 26). The ester

could then undergo saponification to give acid **75** which could react *via* a Mitsunobu reaction to give β-lactone **59**.

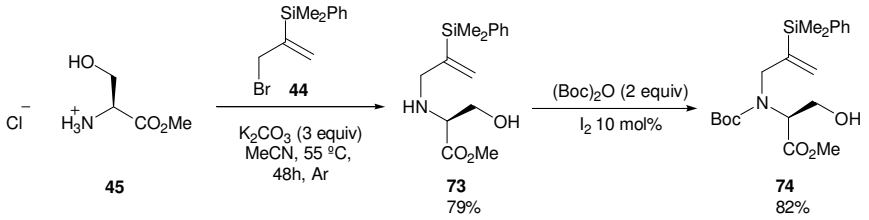


Scheme 26

In 1995, Coldham reported the coupling of aziridine **77** with *t*-butyl bromoacetate **78** in the presence of potassium carbonate in acetonitrile (Scheme 27) to give N-alkylated aziridine **79** in 29% yield.[18] Using these conditions and an excess of K_2CO_3, serine methyl ester **45** was reacted with **44** to give **73** in 79% yield (Scheme 28). Secondary amine **73** was protected with neat Boc_2O and catalytic iodine using conditions developed by Adapa to yield **74** in 82%.[19] The ^1H NMR of **74** was broad and therefore **74** was subjected to variable temperature ^1H NMR to resolve the compound. The broad signals for **74** are most likely due to N-Boc protection and this was later verified by functional group transformations.

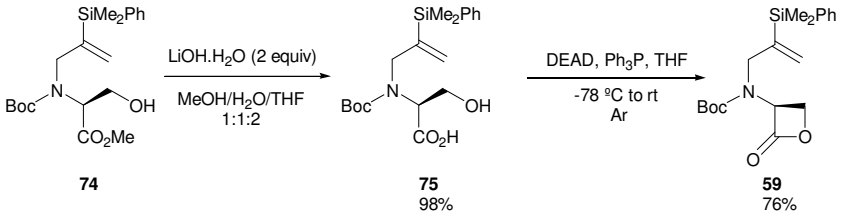


Scheme 27



Scheme 28

With the Boc-protected amine **74** prepared we were able to convert the ester to acid **75** *via* saponification with LiOH in an aqueous solution of methanol and THF to give **75** in 98% yield (Scheme 29). The acid was converted to β-lactone precursor **59** using the same conditions as described earlier (Scheme 20) and gave **59** in a 76% yield. β-Lactone **59** was characterized by the distinctive IR stretch at 1834 cm^{-1} which is indicative for C=O bonds of β-lactones. Mass spectrometry also confirmed the structural assignment.

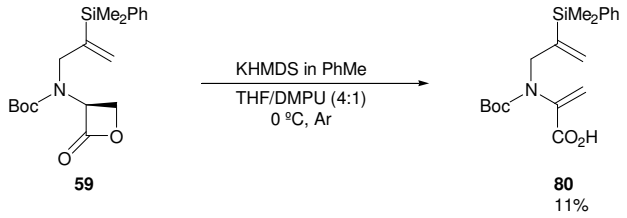


Scheme 29

2.2 Investigation into the aza-[2,3]-Wittig cyclisation using precursor 59

With **59** in hand, the standard aza-[2,3]-Wittig cyclisation reaction protocol developed in our group was attempted. β-Lactone **59** was dissolved in THF/DMPU (4:1) at 0 °C and deprotonated with a solution of KHMDS in toluene (Scheme 30). The reaction was monitored by tlc and showed that after 2 h the β-lactone had been consumed. The reaction was quenched and

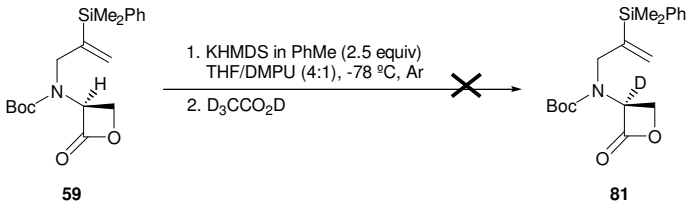
purification by silica gel column chromatography was attempted. However the only product isolated was **80** in 11% yield.



Scheme 30

This suggested under these conditions that the deprotonated β-lactone of **59** would prefer to ring open *via* β-elimination rather than cyclise to **58**. This was disappointing as the reason for selecting the β-lactone **59** was precisely to avoid this possibility occurring.

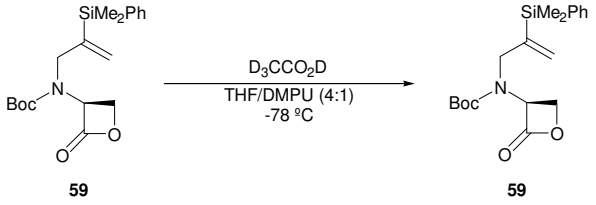
Thus we decided to investigate whether deprotonation had occurred at the desired α carbon on **59**. The β-lactone **59** was deprotonated at -78 °C with KHMDS and after 30 min d_4-Acetic acid was added to quench the reaction (Scheme 31). The reaction was warmed to rt and solvent was removed under vacuum. However the deuterated β-lactone **81** was not observed. It appeared that the compound had degraded on warming to rt.



Scheme 31

Possibly the degradation had occurred due to excess KHMDS and d^4-Acetic acid. The deuterium quench was repeated using KH and d_4-Acetic acid with only 1.5 equiv but again deuterated β-lactone **81** was not observed. The crude

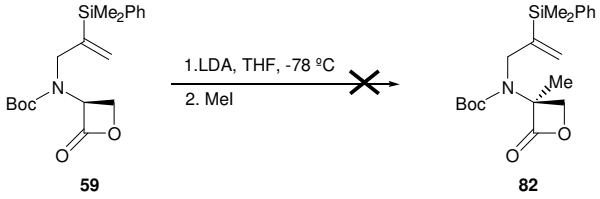
material was subjected to variable temperature ^{1}H NMR in attempt to distinguish rotamers however the NMR at 90 °C suggested **59** had degraded under these conditions. Therefore we decided to check the stability of β-lactone **59** in the presence of d_4-acetic acid. Compound **59** was cooled to -78 °C in THF/DMPU and 1 equiv of d^4-acetic acid was added (Scheme 32). The reaction was warmed to rt and the standard work up was performed. Unreacted β-lactone **59** was recovered in 88% yield. This suggested that degradation was due to deprotonation.



59 **59**

Scheme 32

Thus far the deuterium quenches had been unsuccessful. Therefore we decided to attempt to quench the deprotonation of **59** with MeI (Scheme 33). Unfortunately the desired compound **82** was not observed.

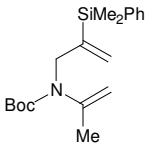


59 **82**

Scheme 33

After purification by silica gel column chromatography two compounds could be identified. As discussed earlier, acid **80** was obtained in 8% yield and could have formed due to elimination. However the other compound **83,** isolated in only 3% yield, was more difficult to explain (Figure 3). A potential explanation may be that methylated product **82** was formed and decarboxylation somehow

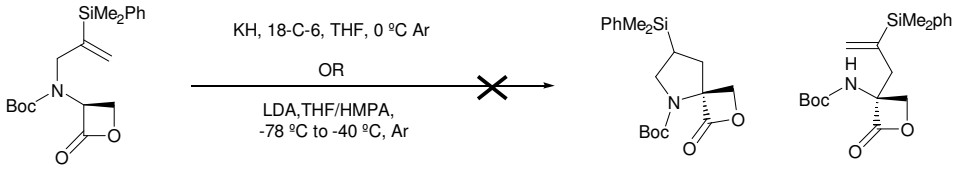
led to **83**. Decarboxylation of β-lactones is unusual but known in the literature.[20]



83

Figure 3

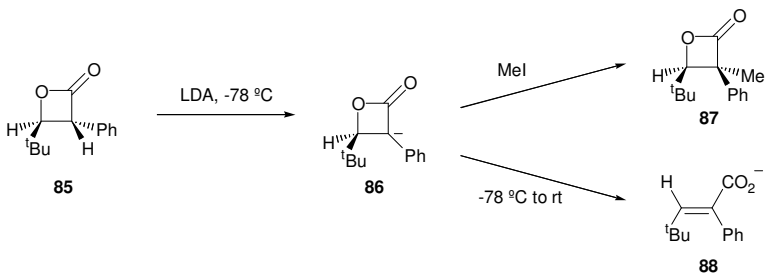
Other aza-[2,3]-Wittig rearrangement conditions which had previously been developed in the group were also attempted. The reaction using KH and 18-C-6 at 0 °C or LDA at -78 °C to -40 °C, did not generate the rearranged **84** or cyclised products **58** (Scheme 34). This was verified by mass spectrometry. Thus **59** had degraded under these conditions.



59 **58** **84**

Scheme 34

This was disappointing as in 1980 Mulzer had shown that it is possible to deprotonate at the α carbon of β-lactone **85** using LDA in THF at -78 °C.[21] Enolate **86** that formed was reacted with a variety of electrophiles such as alkyl halides, aldehydes and acid chlorides (Scheme 35). However on warming the enolate **86** to rt, β-elimination occurred to form acrylic acid anion **88** quantitatively. The enolate anion **86** has additional stabilisation from the Ph group. The enolate **57** is less stabilized, and therefore more reactive which could explain β-elimination occurring so readily.

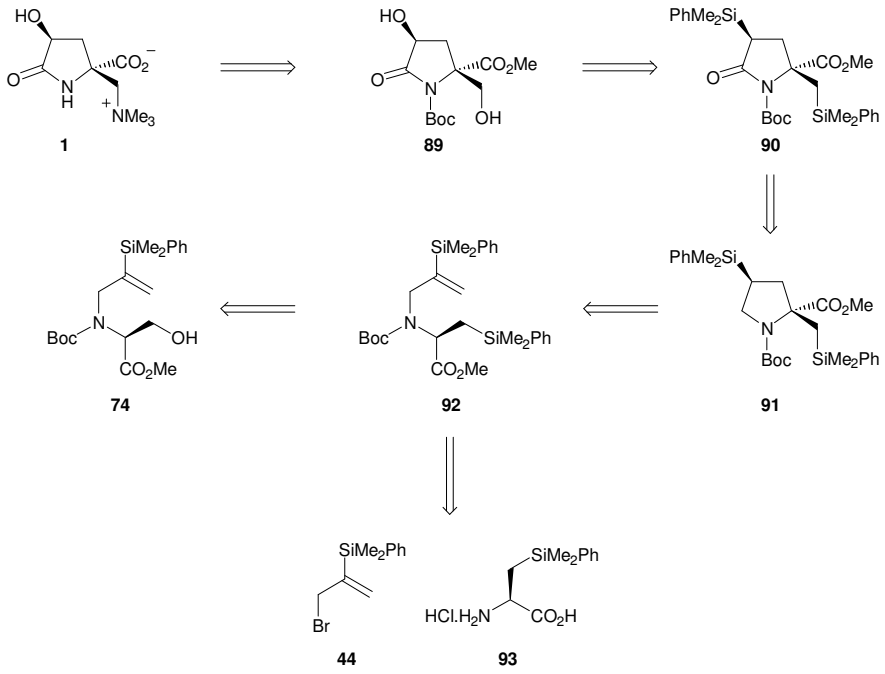


Scheme 35

In 1987, Vederas published that at temperatures greater than -30 °C N-protected β-lactones rapidly undergo "forbidden" elimination to the acid.[15] In our group it had been discovered that the aza-[2,3]-Wittig rearrangement would not occur at temperatures below -40 °C.[10] Thus there was only a small window of opportunity of approximately 10 °C where the possibility of the rearrangement product **58** might occur. Unfortunately this was never observed which suggests the ring opening to **80** occurred faster than rearrangement to **84**. Therefore we decided to investigate an alternative route.

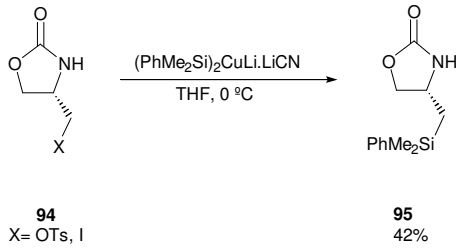
2.3 Alternative aza-[2,3]-Wittig rearrangement cyclisation precursor towards Dysibetaine

Our previous retrosynthesis (Scheme 9) had involved introducing the alcohol **40** from pyrrolidinone **41** *via* a Fleming oxidation. Thus we decided to mask the primary alcohol as a $SiMe_2Ph$ group as well (**92**). This would avoid the problem of elimination and would allow us the possibility to introduce both alcohols in **89** *via* a double Fleming oxidation at a later stage from **90** (Scheme 36).



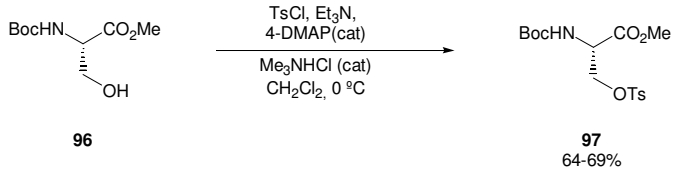
Scheme 36

Ruthenium oxidation would still be used to introduce the carbonyl to form pyrrolidinone **90**. Pyrrolidine **91** would be formed *via* the aza-[2,3]-Wittig cyclisation using precursor **92**. The precursor could be formed either by converting alcohol **74** to a $SiMe_2Ph$ *via* a S_N2 reaction or by coupling **44** with silyl amino acid **93**.



Scheme 37

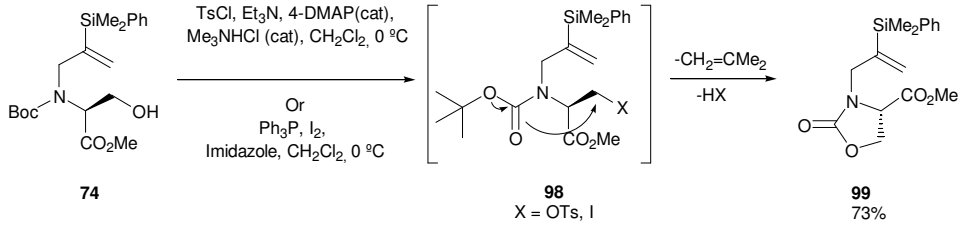
As we had compound **74** prepared we wished to investigate the possibility of converting alcohol **74** to a $SiMe_2Ph$ group. In 1998 Sibi demonstrated that the reaction of **94** with $LiCu(SiMe_2Ph)_2$.LiCN produced **95** (Scheme 37).[22]



96 **97**
64-69%

Scheme 38

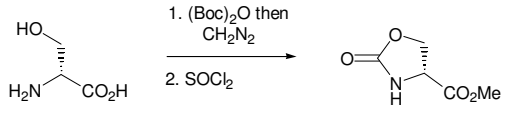
Therefore we decided to investigate converting alcohol **74** to a good leaving group using conditions developed by Jackson (Scheme 38).[23] However when our substrate **74** was subjected to these conditions we did not obtain the tosylated product **98**. Instead the oxazolidinone compound **99** was obtained in 73% (Scheme 39). Conversion of alcohol **74** to iodide **98** was also attempted using conditions by Koert,[24] however the same product **99** was obtained. It is believed that the desired compound **98** was formed but intramolecular cyclisation leads to compound **99**.



74 **98**
X = OTs, I
99
73%

Scheme 39

This type of reaction had previously been reported by Shirahama in 1995 when it was used to produce desired oxazolidinone **100** from D-serine **101** (Scheme 40).[25] Due to time constraints this approach was halted.

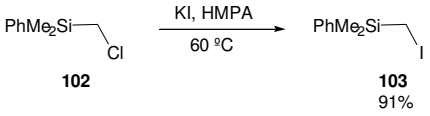


100 **101**

Scheme 40

We decided to investigate the alternative synthesis of **92** using the silyl amino acid **93** which is known in the literature.[26] However due to time constraints we

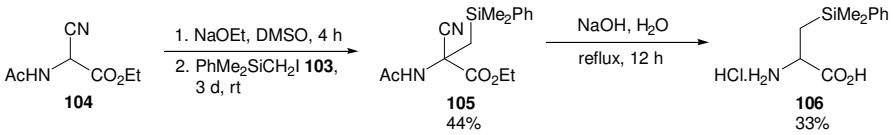
decided to synthesise the racemic silyl amino acid **106**.[27] This involved preparation of **103** *via* a Finkelstein reaction from the commercially available $PhMe_2SiCH_2Cl$ **102** (Scheme 41). The reaction gave the desired compound in 91% yield (lit.[28] 99%).



102 **103** 91%

Scheme 41

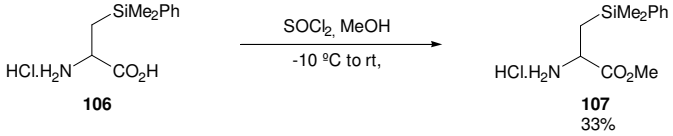
Silyl amino acid **106** was prepared by deprotonation of ethyl acetamidocyanoacetate **104**, followed by addition of **103**. The reaction was stirred for 3 days to give **105** in 44% yield (lit.[27] 44%) (Scheme 42). Amino acid **106** was obtained by saponification and decarboxylation of **105** in 33% yield (lit.[27] 70%, contaminated with inorganics).



104 **105** 44% **106** 33%

Scheme 42

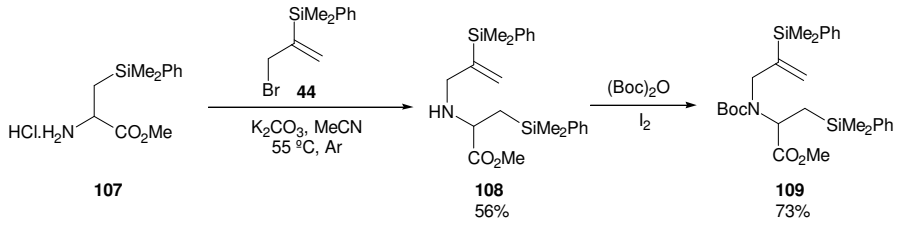
The silyl amino acid **106** was converted to methyl ester **107** using thionyl chloride and methanol in only 33% yield (Scheme 43).[29] This was quite low and may be due to amino acid **106** being contaminated with inorganics.



106 **107** 33%

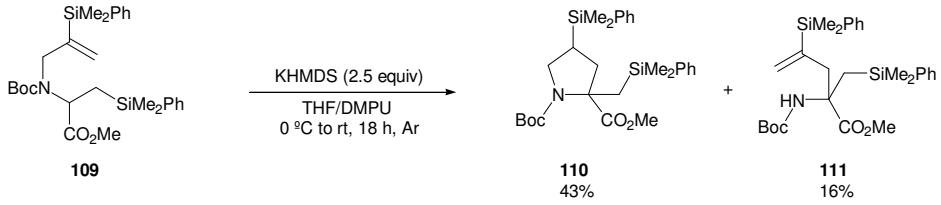
Scheme 43

Aza-[2,3]-Wittig precursor **109** was then prepared *via* an analogous route as **74**. Amino acid methyl ester **107** was reacted with bromoallyl silane **44** in the presence of K_2CO_3 in MeCN to give **108** in 56% yield, followed by Boc protection to give **109** in 73% yield (Scheme 44).



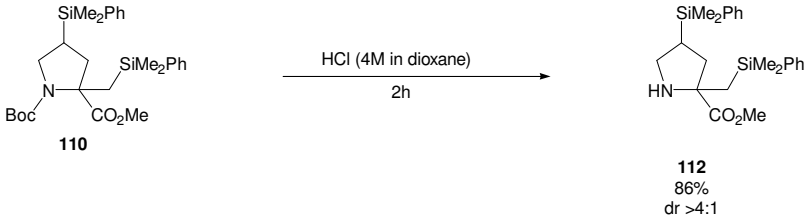
Scheme 44

With the desired precursor **109** in hand, we subjected it to the standard aza-[2,3]-Wittig cyclisation protocol (Scheme 45). The precursor **109** was deprotonated at 0 °C using KHMDS and warmed to rt overnight. Two products were obtained using the unoptimised conditions; the desired pyrrolidine **110** and the rearranged product **111**. The pyrrolidine **110** was the major product with 43% yield. Rearranged product **111** was obtained in 16% yield.



Scheme 45

Attempts to characterise pyrrolidine **110** by ^{1}H and ^{13}C NMR were ambiguous due to rotamers. The ^{1}H NMR showed no alkene protons were present which would coincide with compound **110.** Previously when rotamers had occurred we had characterised the compound using variable temperature NMR. A suitable ^{13}C NMR was obtained at 90 °C, however the ^{1}H NMR was still ambiguous. Therefore a small amount of the pyrrolidine **110** was deprotected using HCl in dioxoane to obtain **112** (Scheme 46). The pyrrolidine **112** was obtained in 86% yield and with a diasteromeric ratio of >4:1 determined by ^{1}H NMR.



Scheme 46

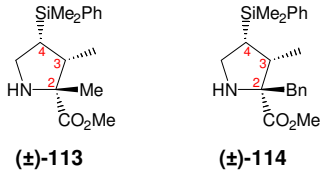


Figure 4

Previous research by Davies into the relative stereochemistry of the cyclised products **113** and **114** had been assigned 2R*, 3R*, 4R* (Figure 4).[10] Therefore we tentatively suggest that the major diastereomers relative stereochemistry for **112** is probably 2R*, 4R* (Figure 5).

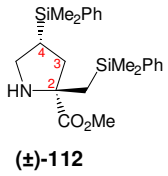
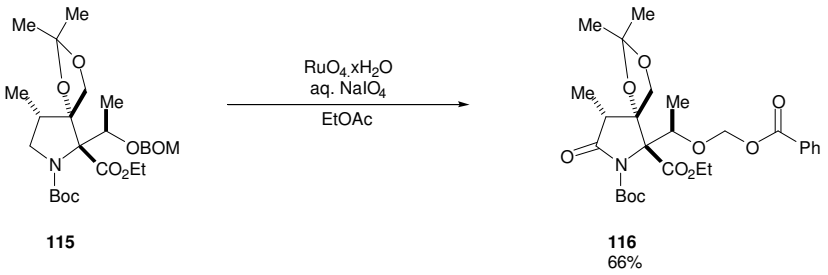


Figure 5

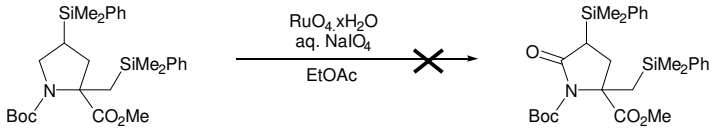
This was very encouraging as it suggested that dysibetaine scaffold can be formed using aza-[2,3]-Wittig conditions. We decided to investigate the next step in our synthesis which would involve converting the pyrrolidine **110** to pyrrolidinone **117**. This would use conditions developed by Yoshifuji using RuO_4 and $NaIO_4$. [30] These conditions had previously been used by Donohoe in the synthesis of pyrrolidinone core of KSM-2690 B (Scheme 47).[31] These conditions gave the desired pyrrolidinone **116** in 66% yield however the oxidation at the benzylic position of the BOM group also occurred.



115 **116**
66%

Scheme 47

The pyrrolidine **110** was dissolved in EtOAc and added to an aqueous solution of RuO_4 and $NaIO_4$ at rt (Scheme 48). The reaction was monitored using tlc and after 4 h the reaction still showed **110** present. Consequently the reaction was heated to 40 °C overnight. The tlc of the reaction after 20 h suggested that the pyrrolidine **110** was still present; therefore the reaction was quenched. The ^{1}H NMR was ambiguous and no clear compound could be assigned. The mass spectrometry of the crude compound showed that the desired compound **117** was not present and suggested **110** was still present.



110
43%

117

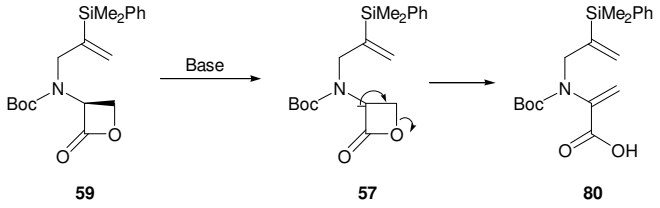
Scheme 48

This result was disappointing and suggested that further investigation into the oxidation reaction to introduce the carbonyl was required. Unfortunately, due to lack of material and time, further investigation of the oxidation of pyrrolidine **110** did not occur.

Chapter 3: Conclusion

3.1 Conclusion

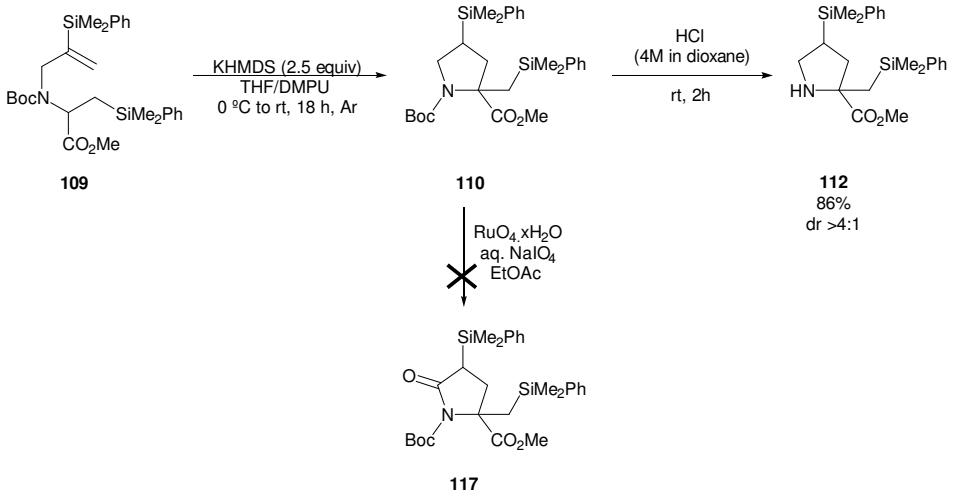
An investigation in order to ascertain the feasibility of the aza-[2,3]-Wittig rearrangement/cyclisation protocol in the synthesis of (-)-dysibetaine was explored. The precursor **59** was proposed as a possible suitable substrate (Scheme 49). However **59** did not under go aza-[2,3]-Wittig rearrangement or cyclisation. Instead the β-lactone enolate **57** led to degradation *via* β-elimination. Unfortunately the stability of the enolate **57** was temperature dependent and established that the β-elimination to **80** was favoured over aza-[2,3]-Wittig rearrangement/cyclisation.



59 **57** **80**

Scheme 49

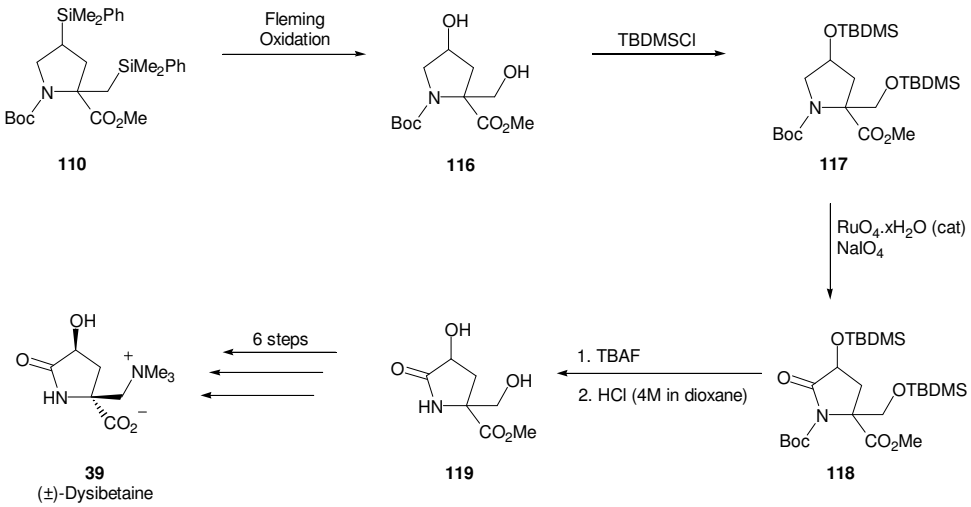
The precursor **109** was investigated as it would avoid β-elimination by using a $SiMe_2Ph$ group as a masked alcohol. Precursor **109** was treated to standard aza-[2,3]-Wittig rearrangement/cyclisation protocol and gave pyrrolidine **110** in 43% (Scheme 50). The diastereoselective ratio could not be determined at this stage due to rotamers. Therefore the pyrrolidine **110** was deprotected to give **112**. The pyrrolidine **112** proved the formation of **110** and gave dr >4:1.



Scheme 50

The formation of **110** illustrated the feasibility of the aza-[2,3]-Wittig reaarangement/cyclisation as a method to introduce the pyrrolidine ring in the synthesis of (-)-dysibetaine. Unfortunately the attempted oxidation to pyrrolidinone **115** was unsuccessful and due to a lack of time and material no further investigation was performed.

To complete the synthesis of dysibetaine the oxidation of the pyrrolidine ring **110** would need to be further investigated. If the oxidation of **110** to **115** continued to be unsuccessful, an option would be to react **110** under Fleming oxidation conditions to obtain the diol **116** (Scheme 51). Protection of the diol **116** with TBDMSCl would give **117** which could be oxidised using RuO_4 as a catalyst and sodium periodate to give **118**.[32] Global deprotection of **118** would give **119** which is an intermediate in the Langlois synthesis of (-)-dysibetaine. Hopefully the diastereomers could be separated and assigned at some stage. The synthesis could then be completed in 6 steps to give racemic (±)-dysibetaine **39**.


SiMe2Ph
SiMe2Ph
N
Boc
CO2Me
110
Fleming
Oxidation
OH
OH
N
Boc
CO2Me
116
TBDMSCl
OTBDMS
OTBDMS
N
Boc
CO2Me
117
RuO4.xH2O (cat)
NaIO4
OTBDMS
OTBDMS
O
N
Boc
CO2Me
118
1. TBAF
2. HCl (4M in dioxane)
OH
O
HN
OH
CO2Me
119
6 steps
OH
O
HN
+
NMe3
CO2−
39
(±)-Dysibetaine

Scheme 51

Chapter 4: Experimental

4.1 General Experimental Details

All experimental procedures were performed under an atmosphere of dry, oxygen free argon. All glassware was oven dried and flame dried prior to use. Cooling to 0 °C was achieved using an ice-water bath. Cooling to temperatures below 0 °C was achieved by using dry ice/acetone mixtures. All reactions were monitored by thin layer chromatography using Merck 5554 $60F_{254}$ silica gel coated plates. Visualisation was achieved using ultraviolet light and then either potassium permanganate or anisaldehyde. Flash column chromatography was performed using Merck silica gel 60 as the stationary phase and Fisher, certified or specified grade solvents.

Purification of Solvents and Reagents:

Commercial solvents and reagents were used as supplied or purified in accordance with standard procedures, as described below.

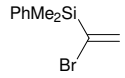
Solvents were either dried by passing through activated alumina (THF, diethyl ether, toluene, hexane and pentane) or distilled and dried using: Et_3N (CaH_2), Et_2NH (CaH_2), $^iPr_2NH$ (CaH_2), DCM (CaH_2), DMSO (CaH_2), HMPU (CaH_2), DMPU (CaH_2). When necessary DMF, Et_3N, $^iPr_2NH$, HMPU and DMPU were stored under Ar and over 4Å molecular sieves (activated by heating (250 ºC) under vacuum (0.1 mbar) for 24 h.

Characterisation:

Specific rotations were determined on a Jasco DIP-370 digital polarimeter and $[\alpha]_D$ values are reported in 10^{-1}deg cm^2 g^{-1} and concentration (*c*) in g per 100 mL. Infrared spectra are recorded on a Perkin-Elmer 157G and all values are given in cm^{-1}. All NMR spectra were recorded on Bruker AV(III)400, AV400, DPX400 or JEOL EX270 spectrometer. The chemical shifts were recorded relative to the solvent standard or tetramethylsilane. NMR spectra were recorded using $CDCl_3$ (δ_H = 7.27, δ_C = 77.1 ppm) or d^6-DMSO (δ_H = 2.52, δ_C = 39.52 ppm). Multiplicities for coupled signals are denoted as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. All resonances that were recorded were in parts per million (ppm). The NMR spectra were obtained at room temperature unless otherwise stated. Those run at high temperature were recorded on the Jeol EX-270 or Bruker-AV400 in deuterated DMSO. All coupling constants (*J*) were recorded in Hertz (Hz). Elemental analysis was performed by the School of Chemistry, University of Nottingham on an Exeter Analytical CE-440 elemental analyser. Mass spectra were acquired on a Micromass LC-TOF, using electron impact electrospray (ES^+) techniques. Melting points are uncorrected and were recorded on a Gallenkamp melting point apparatus.

4.2 Experimental Procedures

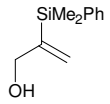
(1-Bromovinyl)phenyl dimethyl silane (63)[12,13]



63

To a solution of dimethylphenylvinylsilane (10.0 mL, 55.0 mmol, 1.00 equiv) in CCl_4 (60 mL) cooled to 0 °C in an atmosphere of argon was slowly added a solution of bromine (2.82 mL, 55.0 mmol, 1.00 equiv) in CCl_4 (20 mL + 10 mL). The reaction was warmed to rt over 1 h. The reaction was washed with saturated aq. $NaHCO_3$ solution containing sodium sulifite (3 x 50 mL) and brine (3 x 20 mL). The organic phase was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to obtain a clear oil of the dibromide (17.0 g). The dibromide was diluted with Et_2NH (40 mL) and stirred overnight at rt. The suspension obtained was filtered and the filtrate was washed with 5% aq. HCl solution (3 x 20 mL) and H_2O (3 x 20 mL). The organic phase was dried ($MgSO_4$), filtered and solvent removed *in vacuo* to obtain the crude (1-Bromovinyl)phenyl dimethyl silane as a yellow oil (10.6 g). Purification by silica gel column chromatography (Hexane) gave **63** as a clear oil (10.6 g, 80%, lit.[12] 62%); Rf 0.58 (Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (2H, m, *m*-H-Ph) 7.42 (3H, m, *o/p*-H-Ph) 6.37 (1H, d, *J*=1.6, CCH_2) 6.18 (1H, d, *J*=1.6, CCH_2) 0.51 (6H, s, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7 (Cq), 135.2 (Cq), 134.1(CH), 131.5 (CH_2), 129.8 (CH), 128.0 (CH), -3.41 (SiCH_3).

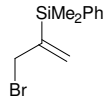
2-(Dimethylphenylsilane) prop-2-en-1-ol (64)[14]



64

Bromo vinyl silane **63** (2.16 g, 8.94 mmol, 1.00 equiv) was converted *via* the literature procedure to alcohol **64** (1.00 g, 60% lit.[14] 63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (2H, m, *m*-H-Ph), 7.40-7.35 (3H, m, *o/p*-H-Ph), 5.93 (1H, m, C=CH_2), 5.50 (1H, m, C=CH_2), 4.25 (2H, d, *J*=4.8, CCH_2OH), 0.43 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9 (Cq), 137.6(Cq), 133.9(CH), 129.2 (CH), 127.9 (CH), 124.7 (CH_2), 66.5 (CH_2OH), -3.0 ($SiCH_3$).

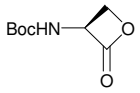
1-(Bromomethylvinyl) Dimethylphenylsilane (44)[14]



44

Alcohol **64** (1.39 g, 7.23 mmol, 1.00 equiv) was converted *via* the literature procedure to give **44** (1.27g, 69%, lit.[14] 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (2H, m, m-H-Ph), 7.39 (3H, m, *o/p*-H-Ph), 6.04 (1H, dt, *J*=2.0, 1.6, C=CH_2), 5.58 (1H, dt, *J*=2.0, 0.8, C=CH_2), 4.10 (2H, dd, *J*=1.6, 0.8, CH_2Br), 0.49 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3 (Cq), 137.5 (Cq), 134.6 (CH), 131.7 (CH_2), 130.1 (CH), 128.6 (CH), 38.2 (CH_2Br), -2.0 ($Si(CH_3)_2$).

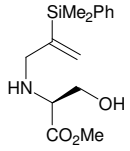
N-(tert-Butoxycarbonyl)-L-Serine β-lactone (60)[15]



60

N-(tert-Butoxycarbonyl)-L-serine (1.50 g, 7.31 mmol, 1.00 equiv) was converted *via* the literature procedure to give **60** as an off-white solid (836 mg, 61%, lit.[15] 72%); m.p. 115 °C (Lit.[15] m.p. 120 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (1H, brs, NH), 5.12 (1H, m, NCH), 4.44 (2H, m, NCHCH_2O), 1.46 (9H, s, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5 (C=O-lactone) 154.6 (C=O-Boc), 81.4 (OC(CH$_3$)$_3$), 66.6 (CH_2O), 59.5 (NCH), 28.2 (OC(CH$_3$)$_3$).

2-(2-Dimethylphenylsilanyl)allylamino-3-hydroxy propionic methyl ester (73)

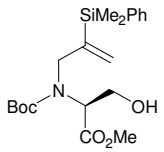


73

A suspension of K_2CO_3 (3.44 g, 24.9 mmol, 3.00 equiv), (L)-serine methyl ester hydrochloride salt (1.93 g, 12.5 mmol, 1.50 equiv) and **44** (2.12 g, 8.31 mmol, 1.00 equiv) in MeCN (60 mL) was heated to 50 °C overnight. The reaction was cooled to rt and solvent was removed *in vacuo*. The residue was partitioned between Et_2O (35 mL) and saturated aq. $NaHCO_3$ solution (35 mL). The two phases were separated and the aqueous was extracted with Et_2O (2 x 25 mL). The organic phases were combined, dried ($MgSO_4$), filtered and

solvent removed under vacuum to obtain a yellow oil. Purification by silica gel column chromatography (30% EtOAc/hexanes) gave **73** as a pale yellow oil (1.92 g, 79%); Rf 0.21 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ -34.5 (c 3.7, CH_2Cl_2); IR ν_{max} (solution in $CHCl_3$) 3502, 3021, 2957, 1736 (C=O), 1602, 1458, 1428, 1405, 1251, 1231, 1222, 1210, 1202, 1197, 1178, 1111, 1053, 941, 835, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (2H, m, *m*-H-Ph), 7.37 (3H, m, *o/p*-H-Ph), 5.88 (1H, m, C=CH_2), 5.53 (1H, m, C=CH_2), 3.72 (3H, s, OCH_3), 3.65 (1H, dd, *J*=10.8, 4.4, CHCH_2OH), 3.49 (1H, dd, *J*=10.8, 6.4, CHCH_2OH), 3.42 (1H, dt, *J*=14.0, 1.2, NCH_2), 3.29 (1H, dd, *J*=6.4, 4.4, NCH(CO_2Me)CH_2), 3.23 (1H, dt, *J*=14.0, 1.6, NCH_2) 2.4-1.7 (2H, brs, NH/OH) 0.41 (6H, d, *J*=2.0, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) 173.4 (C=O), 148.0 (Cq), 138.0 (Cq), 133.8 (*m*-CH), 129.1 (*p*-CH), 128.0 (*o*-CH), 127.2 (CH_2), 62.3 (CH_2OH), 61.9 (NCHCO_2Me), 53.3 (NCH_2), 52.1 (OCH_3), -2.96 (Si$(CH_3)_2$); m/z (ES^+) 294 (100%, MH^+); HRMS $C_{15}H_{24}NO_3Si$ calcd. 294.1520, found 294.1532 Anal. calcd. for $C_{15}H_{23}NO_3Si$ C 61.40, H 7.90, N 4.77, found C 61.55, H 7.90, N 4.56%.

2-*tert*-Butoxycarbonyl-[2-(Dimethylphenylsilanyl)allyl]amino-3-hydroxy propionic acid methyl ester (74)

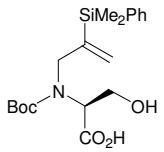


74

To a magnetically stirred mixture of **73** (2.96 g, 10.1 mmol, 1.00 equiv) and Boc_2O (4.61 g, 21.1 mmol, 2.10 equiv) in an atmosphere of argon was added iodine (256 mg, 1.01 mmol, 10 mol%) and stirred at rt overnight. The crude

reaction was diluted with Et_2O (25 mL) and washed with saturated aq. $NaHCO_3$ solution (3 x 25 mL) and brine (3 x 20 mL). The organic phase was dried ($MgSO_4$), filtered and the solvent was removed under vacuum (6.35 g). Purification by silica column chromatography (30% EtOAc/hexanes) gave **74** as a pale yellow oil (3.26 g, 82%); Rf 0.39 (30% EtOAc/hexanes); $[\alpha]_D^{21}$ -13.6 (c 4.0, CH_2Cl_2); IR ν_{max} (solution in $CHCl_3$) 3690, 3567, 3011 (CH), 2981(CH), 1812, 1732 (C=O-ester), 1685 (C=O-Boc), 1603, 1456, 1428, 1409, 1369, 1334, 1252, 1161, 1120, 1076, 1043, 932, 837 cm^{-1}; ^1H NMR (270 MHz, d^6-DMSO at 90 °C) δ 7.58-7.50 (2H, m, *m*-H-Ph), 7.42-7.36 (3H, m, *o/p*-H-Ph), 5.87 (1H, d, *J*=2.1, C=CH$_2$), 5.46 (1H, d, *J*=1.9, C=CH$_2$), 4.55 (1H, t, *J*=5.4, NCH(CO$_2$Me)CH$_2$OH), 4.23-4.16 (1H, brs, OH), 4.10 (1H, d, *J*=17.3, NCH$_2$), 3.96 (1H, d, *J*=17.5, NCH$_2$), 3.83 (1H, dd, *J*=11.1, 5.4, CHCH$_2$OH), 3.72 (1H, dd, *J*=11.1, 5.2, CHCH$_2$OH), 3.64 (3H, s, OCH$_3$), 1.37 (9H, s, C(CH$_3$)$_3$), 0.40 (6H, s, Si(CH$_3$)$_2$); ^{13}C NMR (100 Hz, $CDCl_3$) δ 171.1 (CO$_2$Me), 156.2 (O(CO)N), 145.7 (Cq), 137.1 (Cq), 133.8 (*m*-CH), 129.3 (*p*-CH), 127.9 (*o*-CH), 125.7 (C=CH$_2$), 80.9 (OC(CH$_3$)$_3$), 62.0 (NCH(CO$_2$Me)CH$_2$), 61.7 (CH$_2$OH), 53.0 (NCH$_2$), 52.2 (OCH$_3$), 28.2 (C(CH$_3$)$_3$), -3.3 (SiCH$_3$)$_2$); m/z (ES^+) 416 (100%, MNa^+); HRMS $C_{20}H_{31}NNaO_5Si$ calcd. 416.1864, found 416.1862

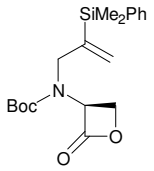
2-{tert-butoxycarbonyl-[2-(Dimethylphenylsilanyl)-allyl]-amino}-3-hydroxy propionic acid (75)



75

To a solution of **74** (2.29 g, 5.82 mmol, 1.00 equiv) in MeOH/H_2O/THF (100 mL, 1:1:2) was added LiOH.H_2O (489 mg, 11.7 mmol, 2.00 equiv) and stirred at rt. The reaction was stirred until **74** had been consumed by TLC (30% EtOAc/hexanes). 1M HCl (50 mL) solution was added to the reaction and extracted with EtOAc (3 x 25 mL). The organic phase was dried ($MgSO_4$), filtered and solvent removed under vacuum to obtain **75** as a pale yellow oil. (2.16 g, 98%); $[\alpha]_D^{20}$ -2.03 (c 2.9, CH_2Cl_2); IR ν_{max} (solution in $CHCl_3$) 3694, 3606, 3514, 3011 (CH), 2980 (CH), 1699 (C=O), 1603, 1456, 1428, 1409, 1369, 1253, 1160, 1111, 1081, 1043, 934, 910, 836, 821 cm^{-1}; ^1H NMR (270 MHz, d^6-DMSO at 90 °C) δ 7.57-7.50 (2H, m, *m*-H-Ph), 7.42-7.32 (3H, m, *o/p*-H-Ph), 5.92 (1H, d, *J*=2.2, C=CH$_2$), 5.45 (1H, d, *J*=2.0, C=CH$_2$), 4.2-4.0 (1H, m, NCH(CO_2H)CH_2OH), 4.09 (1H, d, *J*=17.3, NCH$_2$), 3.94 (1H, d, *J*=17.5, NCH$_2$), 3.84 (1H, dd, *J*=11.1, 5.2, CH$_2$OH), 3.70 (1H, dd, *J*=11.1, 6.2, CH$_2$OH), 1.38 (9H, s, C(CH$_3$)$_3$), 0.40 (6H, s, Si(CH$_3$)$_2$); ^{13}C NMR (100 MHz, d^6-DMSO at 80 °C) δ 171.8 (CO_2CH_3), 155.3 (O(C=O)N), 146.2 (Cq), 137.9 (Cq), 134.1 (*m*-CH), 129.4 (*p*-CH), 128.2 (*o*-CH), 125.3 (C=CH$_2$), 79.6 (OC(CH$_3$)$_3$), 65.2 (NCH(CO_2Me)CH_2), 60.8 (CH$_2$OH), 51.6 (NCH$_2$), 28.4 (OC(CH$_3$)$_3$), -2.5 (Si(CH$_3$)$_2$), -2.8 (Si(CH$_3$)$_2$); m/z (ES^+) 402 (100%, MNa^+); HRMS $C_{19}H_{29}NNaO_5Si$ calcd. 402.1707, found 402.1702

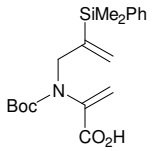
[2-(Dimethylphenylsilanyl)-allyl]-(2-oxo-oxetan-3-yl)carbamic acid (59)



59

To a solution of Ph_3P (1.92 g, 7.31 mmol, 1.00 equiv) in THF (50 mL) cooled to -78 °C under argon was added diethyl azodicarboxylate (1.15 mL, 7.31 mmol, 1.00 equiv) and stirred for 20 min at -78 °C. A solution of the **75** (2.77 g, 7.31 mmol, 1.00 equiv) in THF (25 mL) was added slowly over 30 min and the reaction was stirred for 1 h at -78 °C before slowly to rt overnight. The solvent was removed *in vacuo* to obtain a pale yellow solid. Purification by silica gel column chromatography (20% EtOAc/hexanes) gave **59** as a pale yellow oil (2.0 g, 76%); Rf 0.44 (20% EtOAc/hexanes) $[\alpha]_D^{21}$ -2.69 (c 4.2, CH_2Cl_2): IR ν_{max} (solution in $CHCl_3$) 3692, 3497, 3009 (CH), 2981 (CH), 1834 (C=O-β-lactone) 1758, 1704 (C=O-Boc), 1478, 1455, 1428, 1412, 1370, 1332, 1306, 1253, 1159, 1111, 1054, 1005, 938, 909, 896, 856, 836 cm^{-1}; ^1H NMR (270 MHz, d^6-DMSO at 80 °C) δ 7.56-7.50 (2H, m, *m*-H-Ph), 7.42-7.36 (3H, m, *o/p*-H-Ph), 5.78 (1H, q, *J*=2.1, C=CH_2), 5.51 (1H, q, *J*=1.6, C=CH_2), 4.95 (1H, t, *J*=5.8, NCHCH_2O), 4.31 (2H, d, *J*=5.8, NCHCH_2O), 3.99 (2H, t, *J*=1.6, NCH_2), 1.41 (9H, s, C(CH_3)$_3$), 0.42 (6H, d, *J*=2.2, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) 169.2 (C=O-lactone), 145.6 (Cq), 133.8 (*m*-CH), 129.4 (*p*-CH), 128.0 (*o*-CH), 127.4 (C=CH_2), 80.0 (OC(CH_3)$_3$) 65.7 (NCHCH_2O), 64.7 (NCHCH_2O), 53.2 (NCH_2), 28.1 (OC(CH_3)$_2$), -3.2 (Si(CH_3)$_2$), -3.7 (Si(CH_3)$_2$); m/z (ES^+) 384 (100%, MNa^+); HRMS $C_{19}H_{27}NNaO_4Si$ calcd. 384.1602, found 384.1597.

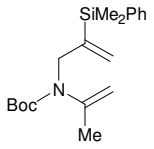
2-(*tert*-Butoxycarbonyl-[2-(Dimethylphenylsilanyl)allyl]-amino)-acrylic acid (80)



80

To a stirred solution of **59** (82 mg, 0.23 mmol, 1.00 equiv) (dried by azeotrope from toluene) in THF/DMPU (1 mL) at 0 °C under Ar was added KHMDS (0.5 M in toluene; 1.10 mL, 0.57 mmol, 2.50 equiv). The reaction was warmed to rt overnight and quenched with aq. saturated NH_4Cl solution (2.4 mL). The reaction was extracted with Et_2O (3 x 3 mL). The organic phase was combined, washed with brine (2 x 8 mL), dried ($MgSO_4$), and solvent removed under vacuum. Product obtained by silica gel column chromatography (EtOAc) to give **80** as an oil (9 mg, 11%); IR ν_{max} (solution in $CHCl_3$) 3692, 3514, 3009, 2961, 2929, 2856, 1710 (C=O), 1626, 1477, 1455, 1428, 1393, 1370, 1344, 1253, 1163, 1135, 1112, 1088, 927, 910, 885 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (2H, m, *m*-H-Ph), 7.37-7.34 (3H, m, *o/p*-H-Ph), 5.80 (1H, d, *J*=2.0, $NCH_2C=CH_2$), 5.73 (1H, s, $NC(CO_2H)=CH_2$), 5.53 (1H, d, *J*=1.6, $NCH_2C=CH_2$), 5.26 (1H, s, $NC(CO_2H)=CH_2$), 4.16 (2H, s, NCH_2C), 1.41 (9H, s, $OC(CH_3)_3$), 0.39 (6H, s, $Si(CH_3)_2$); m/z (ES^+) 384 (100%, MNa^+); HRMS $C_{19}H_{27}NNaO_4Si$ calcd. 384.1607, found 384.1602.

[2-(Dimethylphenylsilanyl)allyl]isopropenyl-carbamic acid *tert*-butyl ester (83)

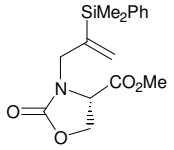


83

To a solution of **59** (200 mg, 0.55 mmol, 1.00 equiv) (dried by azeotrope from toluene) in THF (1 mL) at -78 °C under Ar was slowly added a solution of LDA [prepared from $^{i}Pr_2NH$ (0.12 ml, 0.83 mmol, 1.50 equiv) and $^{n}BuLi$ (2.5M solution in hexanes; 0.33 mL, 0.83 mmol, 1.50 equiv) in THF (1 mL) at 0 °C for 30 min].The reaction was warmed to -60 °C and then cooled to -78 °C. Methyl iodide (118 mg, 0.83 mmol, 1.50 equiv) was added and the reaction was warmed to rt overnight. The reaction was quenched with aq. saturated NH_4Cl solution (2 mL) and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 3 mL). The organic layers were combined, dried ($MgSO_4$) and solvent removed under vacuum. Purification by silica gel column chromatography (20% EtOAc/hexanes) gave **83** as an oil (6 mg, 3%); Rf 0.74 (20% EtOAc/hexanes); IR ν_{max} (solution in $CHCl_3$) 3691, 3607, 3455, 3070 (Ar-CH), 3008 (Ar-CH), 2962(Alk-CH), 2928 (Alk-CH), 2856, 1692 (C=O-Boc), 1650, 1603, 1505, 1477, 1454, 1428, 1391, 1383, 1368, 1348, 1327, 1293, 1250, 1166, 1110, 1096, 1047, 958, 931, 910, 860 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.50 (2H, m, *m*-H-Ph), 7.38-7.32 (3H, m, *o/p*-H-Ph), 5.71 (1H, q, *J*=2.0, C=CH_2), 5.49 (1H, q, *J*=2.0, $NCH_2C=CH_2$), 4.65 (1H, s, $NC(CH_3)=CH_2$), 4.60 (1H, d, *J*=1.2, $NC(CH_3)=CH_2$), 4.10 (2H, t, *J*=1.8, $NCH_2C=CH_2$), 1.94 (3H, d, *J*=0.8, $NC(CH_3)=CH_2$), 1.44 (9H, s, $OC(CH_3)_3$), 0.41 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0 (C=O), 145.8

($NCH_2\underline{C}=CH_2$), 145.5 ($N\underline{C}(CH_3)=CH_2$), 137.4 (C), 133.9 (*m*-CH), 129.2 (*p*-CH), 127.9 (*o*-CH), 124.5 ($NCH_2C=\underline{C}H_2$), 106.4 ($NC(CH_3)=\underline{C}H_2$), 80.0 ($O\underline{C}(CH_3)_3$), 54.1 ($N\underline{C}H_2C$), 28.3 ($OC(\underline{C}H_3)_3$), 21.8 ($NC(\underline{C}H_3)=CH_2$), -3.2 ($Si(\underline{C}H_3)_2$); m/z ($ES^+$) 354 (100%, MNa^+); HRMS $C_{19}H_{29}NNaO_2Si$ calcd. 354.1860, found 354.1848.

3-[2-(Dimethylphenylsilanyl)allyl]-2-oxo-oxazolidine-4-carboxylic acid methyl ester (99)

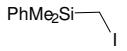


99

To a solution of Ph_3P (491 mg, 1.87 mmol, 1.20 equiv) and imidazole (319 mg, 4.68 mmol, 3.00 equiv) in DCM (7 mL) cooled to 0 °C under Ar was added iodine (476 mg, 1.87 mmol, 1.20 equiv). The solution was stirred for 5 min at 0 °C before a solution of **74** (614 mg, 1.56 mmol, 1.00 equiv) in DCM (3 mL) was added slowly over 10 min. The reaction mixture was stirred with exclusion of light for 4 h and quenched with aq. saturated $Na_2S_2O_3$ solution (20 mL). The two phases were separated and the aqueous was extracted with Et_2O (3 x 20 mL). The organic phases were combined, washed with brine (3 x 20 mL), dried ($MgSO_4$) and solvent removed *in vacuo* to obtiain an off-white residue. Purification by silica gel column chromatography (30% EtOAc/hexanes) gave **99** as a yellow oil (362 mg, 73%); Rf 0.35 (30% EtOAc/hexanes); $[\alpha]_D^{22}$ -46.8 (c 4.1, CH_2Cl_2); IR ν_{max} (solution in $CHCl_3$) 3696, 3606, 3066, 3050 (Ar-CH), 3005 (Ar-CH), 2958 (Alk-CH), 1761 (C=O), 1602, 1479, 1438, 1427, 1413, 1364, 1252, 1240, 1170, 1111, 1085, 1064, 999, 952, 837 cm^{-1}; ^1H NMR (400

MHz, $CDCl_3$) δ 7.54-7.51 (2H, m, *m*-H-Ph), 7.40-7.36 (3H, m, *o/p*-H-Ph), 5.78 (1H, m, C=CH_2), 5.67 (1H, m, C=CH_2), 4.56 (1H, dt, *J*=14.8, 1.4, NCH_2), 3.99 (1H, dd, *J*=8.8, 3.6, NCH(CO_2Me)CH_2O), 3.72 (3H, s, OCH_3), 3.69 (1H, dd, *J*=9.6, 3.6, NCH(CO_2Me)CH_2O), 3.62 (1H, d, *J*=14.8, NCH_2), 3.37 (1H, dd, *J*=9.2, 8.8, NCH(CO_2Me)CH_2O), 0.50 (3H, s, Si(CH_3)$_2$), 0.42 (3H, s, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2 (CO_2Me), 156.9 (N(C=O)O), 144.6 (Cq), 137.3 (Cq), 133.6 (*m*-CH), 130.3 (C=CH_2), 129.4 (*p*-CH), 128.1 (*o*-CH), 63.9 (NCH(CO_2Me)CH_2O), 55.6 (NCH(CO_2Me)CH_2O), 52.7 (OCH_3), 48.8 (NCH_2C), -3.3 (Si(CH_3)$_2$), -4.4 (Si(CH_3)$_2$); m/z (ES^+) 342 (48%, MNa^+); HRMS $C_{16}H_{21}NNaO_4Si$ calcd. 342.1132, found 342.1121; Anal. calcd. for $C_{16}H_{21}NO_4Si$ C 60.16, H 6.63, N 4.38, found C 59.90, H 6.63, N 4.26%.

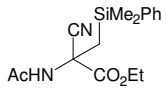
Dimethyl(iodomethyl)phenyl silane (103)[28]



103

$PhMe_2SiCH_2Cl$ (5.00 g, 27.1 mmol, 1.00 equiv) was converted *via* the literature procedure to obtain **103** as a yellow oil (6.84 g, 91%, lit.[28] 99%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (2H, m, *m*-H-Ph), 7.45-7.35 (3H, m, *o/p*-H-Ph), 2.20 (2H, s, SiCH_2I), 0.46 (6H, s, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ136.8 (*i*-C), 133.7 (CH), 129.6 (CH), 128.0 (CH), -2.9 (Si(CH_3)$_2$), -13.6 (SiCH_2I).

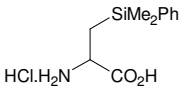
Ethyl-2-acetamido-2-cyano-3-(Dimethylphenylsilyl) propionate (105)[27]



105

Ethyl acetamidocyanoacetate (5.03 g, 29.5 mmol, 1.20 equiv) and $PhMe_2SiCH_2I$ **103** (6.80 g, 24.6 mmol, 1.00 equiv) was converted *via* the literature procedure to give **105** (4.16 g, 44%, lit.[27] 44%); Rf 0.31 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (2H, m, *m*-H-Ph), 7.45 (3H, m, *o/p*-H-Ph), 5.73 (1H, brs, NH), 4.20 (1H, dq, *J*=10.4, 7.2, OCH_2CH_3), 4.07 (1H, dq, *J*=10.8, 7.2, OCH_2CH_3), 1.94 (1H, d, *J*=14.8, $SiCH_2C$), 1.65 (1H, d, *J*=14.8, $SiCH_2C$), 1.63 (3H, s, $(CO)CH_3$), 1.30 (3H, t, *J*=7.2, OCH_2CH_3), 0.55 (3H, s, $SiCH_3$), 0.41 (3H, s, $SiCH_3$); ^{13}C NMR (100 Hz, $CDCl_3$) δ 169.2 ($N(CO)CH_3$), 167.2 (CO_2Et), 136.4 (Cq), 133.9 (*m*-CH), 130.3 (*p*-CH), 128.6 (*o*-CH), 117.4 (C≡N), 63.6 (OCH_2CH_3), 54.4 (Cq), 25.0 ($SiCH_2C$), 22.1 ($COCH_3$), 13.8 (OCH_2CH_3), -2.6 ($SiCH_3$), -3.0 ($SiCH_3$).

2-Amino-3-(dimethylphenylsilanyl)-propionic acid (106)[27]

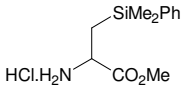


106

Compound **105** (637 mg, 2.00 mmol, 1.00 equiv) was converted *via* the literature procedure to amino acid **106** (170 mg, 33%, lit.[27] 70% contaminated with inorganics); ^{1}H NMR (400 MHz, d^6-DMSO) δ 7.56-7.51 (2H, m, *m*-H-Ph), 7.36-7.31 (3H, m, *o/p*-H-Ph), 3.18 (1H, dd, *J*=11.2, 4.8, $NCH(CO_2H)CH_2$), 1.16 (1H, dd, *J*=14.0, 11.2, $SiCH_2CH$), 1.00 (1H, dd, *J*=14.0, 4.8, $SiCH_2CH$), 0.35 (3H, s, $SiCH_3$), 0.30 (3H, s, $SiCH_3$); ^{13}C NMR (100 MHz, d^6-DMSO) δ 170.9 (C=O), 140.5 (Cq), 133.9 (*m*-CH), 129.1 (*p*-

CH), 128.1 (*o*-CH), 52.8 (N<u>C</u>H(CO_2H)CH_2), 19.9 (Si<u>C</u>H_2CH), -1.3 (Si<u>C</u>H_3), -2.0 (Si<u>C</u>H_3).

2-Amino-3-(dimethylphenylsilanyl)-propionic acid methyl ester hydrochloride (107)

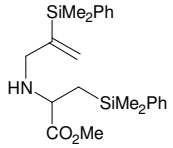


107

To MeOH (50 mL) cooled to 0 °C in an argon atmosphere was added thionyl chloride (2.10 mL, 28.7 mmol, 10.0 equiv). The reaction was stirred for 10 min at before a suspension of the **106** (744 mg, 2.87 mmol, 1.00 equiv) in MeOH (20 mL) was added. The reaction was stirred at 0 °C for 1 h and then warmed to rt overnight. Solvent was removed *in vacuo* to obtain a yellow residue. The residue was partitioned between 2M KOH (20 mL) and Et_2O (20 mL). The two phases were separated and the aqueous phase was extracted with Et_2O (2 x 20 mL). The organic phases were combined and washed with H_2O (3 x 20 mL). The organic phase was acidified with 2M HCl. The aqueous phase was concentrated *in vacuo* and freeze dried to obtain **107** as an off white solid (306 mg, 39%); IR ν_{max} (solution in $CHCl_3$) 3692, 3600, 3050 (CH), 2961 (CH), 1752 (C=O), 1602, 1511, 1442, 1428, 1253, 1188, 1115, 925, 838 cm^{-1}; ^{1}H NMR (400 MHz, d^6-DMSO) δ 8.5-8.2 (3H, brs, N<u>H</u>$_3^+$), 7.50 (2H, m, *m*-<u>H</u>-Ph), 7.38 (3H, m, *o/p*-<u>H</u>-Ph), 3.90 (1H, m, NC<u>H</u>(CO_2Me)CH_2), 3.42 (3H, s, OC<u>H</u>$_3$), 1.35 (2H, m, CHC<u>H</u>$_2$Si), 0.35 (3H, s, SiC<u>H</u>$_3$), 0.29 (3H, s, SiC<u>H</u>$_3$); ^{13}C NMR (100 MHz, d^6-DMSO) δ 170.6 (C=O), 137.7 (C), 133.8 (*m*-CH), 129.8 (*p*-CH), 128.4 (*o*-CH), 52.7 (OCH_3), 50.6 (N<u>C</u>H(CO_2Me)CH_2), 18.8 (Si<u>C</u>H_2CH), -1.9

($SiCH_3$), -2.8 ($SiCH_3$); m/z (ES^+) 221 (100% M-HCl-CH_3) 260 (74%, MNa^+-HCl); HRMS $C_{12}H_{19}NNaO_2Si$ calcd. 260.1077, found 260.1075.

3-(Dimethylphenylsilanyl)-2-[2-(dimethylphenylsilanyl)allylamino]-propionic acid methyl ester (108)

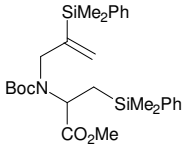


108

A suspension of **107** (362 mg, 1.32 mmol, 1.00 equiv), **44** (506 mg, 1.98 mmol, 1.50 equiv) and K_2CO_3 (548 mg, 3.96 mmol, 3.00 equiv) in MeCN (25 mL) was heated to 55 °C overnight. The reaction was cooled to rt and solvent was removed under vacuum. The residue was partitioned between Et_2O (20 mL) and saturated aq. $NaHCO_3$ solution (10 mL). The two phases were separated and the aqueous was extracted with Et_2O (2 x 10 mL). The organic phases were combined, dried ($MgSO_4$), filtered and solvent removed *in vacuo* to obtain a yellow oil. Purification by silica gel column chromatography (5% EtOAc/hexanes) gave **108** as a pale yellow oil. (302 mg, 56%); Rf 0.23 (5% EtOAc/hexanes); IR ν_{max} (solution in $CHCl_3$) 3691, 3071, 3011, 2958, 2929, 2873, 1731 (C=O), 1602, 1459, 1428, 1376, 1304, 1251, 1175, 1113, 1045, 997, 937, 909 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (4H, m, *m*-H-Ph), 7.35 (6H, m, *o/p*-H-Ph), 5.81 (1H, m, C=CH_2), 5.44 (1H, m, C=CH_2), 3.49 (3H, s, OCH_3), 3.23 (1H, d, *J*=14.4, NCH_2), 3.20 (1H, t, *J*=8.0, NCH(CO_2Me)CH_2), 3.03 (1H, d, *J*=14.0, NCH_2), 1.17 (1H, dd, *J*=14.4, 7.6, CHCH_2Si), 1.10 (1H, dd, *J*=14.4, 7.6, CHCH_2Si), 0.37 (6H, d, *J*=1.2, CH_2=CSi(CH_3)$_2$), 0.30 (6H, d, *J*=8.0, CH_2Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5 (C=O), 148.0

(Cq), 138.7 (Cq), 138.1 (Cq), 134.0 (*m*-CH), 133.6 (*m*-CH), 129.0 (CH), 128.9 (CH), 127.8 (CH), 127.7 (CH), 126.3 ($C=CH_2$), 58.0 ($NCH(CO_2Me)CH_2$), 52.5 (NCH_2C), 51.3 (OCH_3), 21.2 ($CHCH_2Si$), -2.1 ($Si(CH_3)_2$), -2.8 ($SiCH_3$), -3.0 ($SiCH_3$); m/z (ES^+) 412 (100%, MH^+); HRMS $C_{23}H_{34}NO_2Si$ calcd. 412.2123, found 412.2104.

2-{*tert*-Butoxycarbonyl-[2-(dimethylphenylsilanyl)-allyl]-amino}-3-(dimethylphenylsilanyl) propionic acid methyl ester (109)

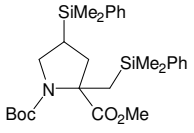


109

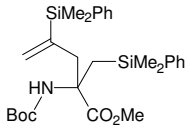
To **108** (300 mg, 0.73 mmol, 1.00 equiv) and Boc_2O (318 mg, 1.46 mmol, 2.00 equiv) stirred in an argon atmosphere at rt was added iodine (19 mg, 0.07 mmol, 10 mol%) and stirred overnight. The reaction was diluted with Et_2O (15 mL) and washed with saturated aq. $NaHCO_3$ solution containing sodium sulfite (3 x 10 mL) and brine (2 x 10 mL). The organic phase was dried ($MgSO_4$), filtered and solvent removed under vacuum to obtain a yellow oil. Excess Boc_2O was removed by stirring the crude reaction product in $^nPrNH_2$ in Et_2O (0.2 M, 4 mL) overnight and solvent was removed under vacuum. Purification by silica gel column chromatography (10% EtOAc/hexanes) gave **109** as a pale yellow oil (274 mg, 73%); Rf 0.41 (10% EtOAc/hexanes); IR ν_{max} (solution in $CHCl_3$) 3071, 3011 (CH), 2956 (CH), 1739 (C=O-ester), 1683 (C=O-Boc), 1602, 1454, 1428, 1395, 1367, 1327, 1163, 1112, 1064, 998, 929, 908, 836, 821 cm^{-1}; ^1H NMR (270 MHz, d^6-DMSO at 90 °C) δ 7.53-7.42 (4H, m, *m*-H-Ph), 7.42-7.30 (6H, m, *o/p*-H-Ph), 5.61 (1H, q, *J*=2.4, $C=CH_2$), 5.40 (1H, q,

J=2.5, C=C$\underline{H}_2$), 4.40-4.28 (1H, m, NC$\underline{H}$), 3.89 (1H, dt, *J*=17.4, 1.6, NC$\underline{H}_2$C), 3.70 (1H, *J*=17.5, 1.6, NC$\underline{H}_2$C), 3.50 (3H, s, OC$\underline{H}_3$), 1.45 (1H, dd, *J*=14.7, 9.6, NCHC$\underline{H}_2$Si), 1.36 (9H, s, C(C$\underline{H}_3$)$_3$), 1.11 (1H, dd, *J*=14.7, 5.6, NCHC$\underline{H}_2$Si), 0.37 (6H, d, *J*=1.2, Si(C$\underline{H}_3$)$_2$), 0.28 (6H, d, *J*=2.6, Si(CH$_3$)$_2$); ^{13}C NMR (67.9 MHz, d^6-DMSO at 90 °C) δ 172.3($\underline{C}$O$_2$Me), 154.9 (O($\underline{C}$=O)N), 146.3 ($\underline{C}$=CH$_2$), 138.8 (C), 137.8 (C), 134.1 (CH), 133.8(CH), 129.6 (CH), 129.4 (CH), 128.3 (CH), 128.2 (CH), 125.2 (C=$\underline{C}$H$_2$), 79.9 (O$\underline{C}$(CH$_3$)$_3$), 56.3 (N$\underline{C}$H), 51.9 (N$\underline{C}$H$_2$), 49.8 (OCH$_3$), 28.5 (C($\underline{C}$H$_3$)$_3$), 17.8 (Si$\underline{C}$H$_2$) , -2.0 (Si($\underline{C}$H$_3$)$_2$), -2.8 (Si($\underline{C}$H$_3$)$_2$); m/z (ES$^+$) 534 (100%, MNa$^+$); HRMS $C_{28}H_{41}NO_4Si$ calcd. 534.2466, found 534.2446.

4-(Dimethylphenylsilanyl)-2-[(dimethylphenylsilanyl)-methyl]-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (110) and 2-tert-Butoxycarbonylamino-4-(dimethylphenylsilanyl)-2-[(dimethyl-phenyl silanyl)-methyl]-pent-4-enoic (111)



110



111

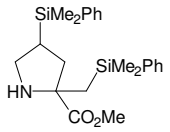
To a stirred solution of **109** (100 mg, 0.20 mmol, 1.00 equiv) (dried by azeotrope with toluene) in THF/DMPU (4:1, 1 mL) at 0 °C in an argon atmosphere was slowly added KHMDS (0.5 M solution in toluene: 0.98 mL, 0.49 mmol, 2.50 equiv). The reaction was slowly warmed to rt and stirred overnight. The reaction was quenched with aq. saturated NH_4Cl solution (2 mL) and extracted with Et_2O (3 x 5 mL). The organic phases were combined, washed with brine (2 x 10 mL), dried ($MgSO_4$) and solvent was removed under

vacuum to obtain a clear oil. Purification by silica gel column chromatography (15% EtOAc/hexanes) gave **110** (43 mg, 43%) and **111** (16 mg, 16%).Data for **110**; Rf 0.34 (10% EtOAc/hexanes); IR ν_{max} (solution in $CHCl_3$) 3011 (Ar-CH), 2956 (Alk-CH), 1732 (C=O-ester), 1686 (C=O-Boc), 1427, 1392, 1368, 1252, 1160, 1113, 999, 909, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.50 (2H, m, Ph-H), 4.00-3.90 (0.6H, m, $NC\underline{H}_2$), 3.78-3.70 (0.4H, m, $NC\underline{H}_2$), 3.70-3.62 (3H, m, $OC\underline{H}_3$), 3.17-3.05 (1H, m, $NC\underline{H}_2$), 2.10-1.55 (5H, m, Alk-CH), 1.50-1.40 (9H, m, $OC(C\underline{H}_3)_3$), 0.30-0.10 (12H, m, $SiC\underline{H}_3$); ^{13}C NMR (100 MHz, d^6-DMSO at 90 °C) δ 175.2 ($\underline{C}O_2Me$), 153.6 (O($\underline{C}$=O)N), 140.2 (Cq), 137.2 (Cq), 134.0 (CH), 133.9 (CH), 133.7 (CH), 129.7 (CH), 129.6 (CH), 129.2 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 79.4 ($O\underline{C}(CH_3)_3$), 68.6 (Cq), 55.1 ($N\underline{C}H_2$), 52.3 ($O\underline{C}H_3$), 50.7, 28.6 ($OC(\underline{C}H_3)_3$), 23.0 ($\underline{C}H_2SiMe_2Ph$), -0.37 ($Si\underline{C}H_3$), -0.66 ($Si\underline{C}H_3$), -0.99 ($Si\underline{C}H_3$), -1.45 ($Si\underline{C}H_3$), -4.3 ($Si\underline{C}H_3$), -4.4 ($Si\underline{C}H_3$); m/z (ES^+) 534 (100%, MNa^+), 512 (20%, MH^+); HRMS $C_{28}H_{41}NNaO_4Si_2$ calcd. 534.2466, found 534.2463.

Data for **111**; Rf 0.59 (10% EtOAc/hexanes); IR ν_{max} (solution in $CHCl_3$) 3420 (N-H), 3010 (Ar-CH), 2958 (Alk-CH), 1707 (C=O), 1496, 1441, 1428, 1392, 1367, 1334, 1250, 1165, 1112, 1084, 1021, 955, 909, 874 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 -7.41 (4H, m, *m*-$\underline{H}$-Ph), 7.35-7.29 (6H, m, *o/p*-$\underline{H}$-Ph), 5.70 (1H, brs, C=$C\underline{H}_2$), 5.58 (1H, brs, N$\underline{H}$), 5.46 (1H, brs, C=$C\underline{H}_2$), 3.31 (1H, d, *J*=15.2, $CC\underline{H}_2C(SiMe_2Ph)=CH_2$), 3.19 (3H, s, $OC\underline{H}_3$), 2.55 (1H, d, *J*=15.2, $CC\underline{H}_2C(SiMe_2Ph)=CH_2$), 2.24 (1H, d, *J*=14.8, $CC\underline{H}_2Si$), 1.42 (9H, s, $OC(C\underline{H}_3)_3$), 1.35 (1H, d, *J*=14.8, $CC\underline{H}_2Si$), 0.32 (6H, brs, $Si(C\underline{H}_3)_2$), 0.23 (6H, d, *J*=6.8, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1 ($\underline{C}O_2Me$), 153.7 (O($\underline{C}$=O)N), 145.6 ($\underline{C}$=CH_2), 138.6 (Cq), 138.3 (Cq), 134.0 (*m*-CH), 133.8 (*m*-

CH), 130.5 (C=$\underline{C}H_2$), 128.9 (CH), 127.7 (CH), 79.1 (O$\underline{C}(CH_3)_3$), 61.9 (BocHN$\underline{C}$), 51.9 (O$\underline{C}H_3$), 43.6 (NC$\underline{C}H_2$C(SiMe$_2$Ph)=CH$_2$), 28.5 (OC($\underline{C}H_3)_3$), 26.0 (NC$\underline{C}H_2$SiMe$_2$Ph), -1.8 (Si$\underline{C}H_3$), -2.6 (Si$\underline{C}H_3$), -2.7 (Si$\underline{C}H_3$), -3.0 (Si$\underline{C}H_3$); m/z (ES$^+$) 534 (100%, MNa$^+$); HRMS $C_{28}H_{41}NNaO_4Si_2$ calcd. 534.2466, found 534.2469.

4-(Dimethylphenylsilanyl)-2-[(dimethylphenylsilanyl)-methyl]-pyrrolidine-2-carboxylic acid methyl ester (112)



112

To **110** (30 mg, 0.06 mmol, 1 equiv), was added HCl (4 M in dioxane, 0.50 mL, 30.0 equiv) and stirred for 2 h. Solvent was removed *in vacuo* and the residue partitioned between DCM (5 mL) and saturated aq. $NaHCO_3$ solution (5 mL). The two phases were separated and the aqueous was extracted with DCM (3 x 2 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried ($MgSO_4$), and solvent removed *in vacuo* to obtain **112** as a yellow oil (21 mg, 86%); IR ν_{max} (solution in $CHCl_3$) 3350, 3071, 3053 (Ar-CH), 3009 (Ar-CH), 2956 (Alk-CH), 1722 (C=O), 1487 (Alk-CH), 1427, 1409, 1252, 1193, 1173, 1113, 999, 910, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.40 (4H, m, *m*-$\underline{H}$-Ph), 7.40-7.30 (6H, m, *o/p*-$\underline{H}$-Ph), 3.43 (3H, s, OC$\underline{H}_3$), 3.12 (1H, dd, *J*=10.0, 8.8, NC$\underline{H}_2$), 2.81 (1H, t, *J*=10.0, NC$\underline{H}_2$), 2.60-2.30 (1H, brs, N$\underline{H}$), 2.32 (1H, dd, *J*=12.0, 6.8, NCC$\underline{H}_2$), 1.50-1.25 (4H, m, alk-C$\underline{H}$), 0.28 (6H, s, SiC$\underline{H}_3$), 0.25 (3H, s, SiC$\underline{H}_3$), 0.24 (3H, s, SiC$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6 ($\underline{C}O_2$Me), 139.3 (Cq), 137.8 (Cq), 133.7 (Ar-CH), 129.1 (Ar-

CH), 128.9 (Ar-CH), 127.8 (Ar-CH), 127.7 (Ar-CH), 69.2 (NCq), 52.0 (O<u>C</u>H_3), 48.3 (CH_2), 42.0 (CH_2), 28.4 (Si<u>C</u>H_2), 25.9 (SiCH), -1.68 (Si<u>C</u>H_3), -2.0 (Si<u>C</u>H_3) -4.4 (Si<u>C</u>H_3), -4.6 (Si<u>C</u>H_3); m/z (ES^+) 412 (100%, MH^+); HRMS $C_{23}H_{34}NO_2Si_2$ calcd. 412.2123, found 412.2132.

Chapter 5: References

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