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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.

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. 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 PtO₂ 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 NaHCO₃ 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.

\[ \text{Scheme 3. Snider synthesis of } S,S\text{-dysibetaine} \]

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 \([\alpha]_D = -7.1^\circ\) and was very close to the reported natural product with an \([\alpha]_D = -7.3^\circ\). 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%.

\[ \text{Scheme 4. Wardrop synthesis of } (-\)-dysibetaine} \]
Langlois also reported the total synthesis of (-)-dysibetaine 1 in 2004. 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 siloxypyrrrole 18 and SnCl₄. This was followed by trapping of the iminium ion with a hydroxide ion which gave 19. The hydroxy group at C⁵ could be converted to nitrile group by reaction with trimethylsilylcyanide in the presence of SnCl₄ to produce 20 as one diastereomer in 65% yield. The introduction of the hydroxy group at C⁷ 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 5. Wardrop synthesis of (-)-dysibetaine

Scheme 6. Langlois synthesis of (-)-dysibetaine
Honda published the synthesis of (-)-4-epi-dysibetaine 31 in 2007. 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 diastereomers 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 \textit{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.

\textbf{Scheme 8.} Kobayashi synthesis of \((\pm\))-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 RuO₂ 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](image-url)
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). The precursor is deprotonated at the carbon $\alpha$ 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. Attempts to reproduce the formation of 47 were unsuccessful.

\[
\begin{align*}
\text{Scheme 10. Aza-[2,3]-Wittig rearrangement and aza-[2,3]-Wittig rearrangement cyclisation}
\end{align*}
\]

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 $\alpha$ 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.

\[
\text{Scheme 11. Aza-Wittig Rearrangement & cyclisation}
\]

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.

\[
\text{Scheme 12. Deuterium Experiment}
\]

Previous work has also shown that the SiMe\(_2\)Ph 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.

**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).\(^{11}\)

**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.
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 $\beta$-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 $\beta$-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.

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$_2$NH 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).
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%.

\[
\text{Scheme 19}
\]

The next step in this synthesis would require the preparation of \(\beta\)-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).

\[
\text{Scheme 20}
\]

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).\(^{10}\)
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

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 re-protection 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
In 1991, Beaulieu showed that 60 could be coupled with crotyl bromide 71 in a 75% yield (Scheme 24).\textsuperscript{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.

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$_2$Ph group could be the reason no reaction was observed.

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.

![Diagram of chemical reactions]

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.\(^\text{18}\) Using these conditions and an excess of K\(_2\)CO\(_3\), serine methyl ester 45 was reacted with 44 to give 73 in 79% yield (Scheme 28). Secondary amine 73 was protected with neat Boc\(_2\)O and catalytic iodine using conditions developed by Adapa to yield 74 in 82%.\(^\text{19}\) The \(^1\)H NMR of 74 was broad and therefore 74 was subjected to variable temperature \(^1\)H 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.

![Diagram of chemical reactions]

Scheme 27
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 \(\beta\)-lactone precursor 59 using the same conditions as described earlier (Scheme 20) and gave 59 in a 76% yield. \(\beta\)-Lactone 59 was characterized by the distinctive IR stretch at 1834 cm\(^{-1}\) which is indicative for C=O bonds of \(\beta\)-lactones. Mass spectrometry also confirmed the structural assignment.

### 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. \(\beta\)-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 \(\beta\)-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](image)

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

Thus we decided to investigate whether deprotonation had occurred at the desired \( \alpha \) carbon on 59. The \( \beta \)-lactone 59 was deprotonated at -78 °C with KHMD 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 \( \beta \)-lactone 81 was not observed. It appeared that the compound had degraded on warming to rt.

![Scheme 31](image)

Possibly the degradation had occurred due to excess KHMD 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 \( \beta \)-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.

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.

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.\textsuperscript{20}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure3.png}
\caption{Figure 3}
\end{figure}

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.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{scheme34.png}
\caption{Scheme 34}
\end{figure}

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

\section*{2.3 Alternative aza-[2,3]-Wittig rearrangement cyclisation precursor towards Dysibetaine}

Our previous retrosynthesis (Scheme 9) had involved introducing the alcohol \textsuperscript{40} from pyrrolidinone \textsuperscript{41} \textit{via} a Fleming oxidation. Thus we decided to mask the primary alcohol as a SiMe\textsubscript{2}Ph group as well (\textsuperscript{92}). This would avoid the problem of elimination and would allow us the possibility to introduce both alcohols in \textsuperscript{89} \textit{via} a double Fleming oxidation at a later stage from \textsuperscript{90} (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$_2$Ph via a S$_N$2 reaction or by coupling 44 with silyl amino acid 93.

As we had compound 74 prepared we wished to investigate the possibility of converting alcohol 74 to a SiMe$_2$Ph group. In 1998 Sibi demonstrated that the reaction of 94 with LiCu(SiMe$_2$Ph)$_2$.LiCN produced 95 (Scheme 37).
Therefore we decided to investigate converting alcohol 74 to a good leaving group using conditions developed by Jackson (Scheme 38). 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, however the same product 99 was obtained. It is believed that the desired compound 98 was formed but intramolecular cyclisation leads to compound 99.

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). Due to time constraints this approach was halted.

We decided to investigate the alternative synthesis of 92 using the silyl amino acid 93 which is known in the literature. However due to time constraints we
decided to synthesise the racemic silyl amino acid 106. This involved preparation of 103 via a Finkelstein reaction from the commercially available PhMe₂SiCH₂Cl 102 (Scheme 41). The reaction gave the desired compound in 91% yield (lit. 99%).

Scheme 41

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

Scheme 42

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

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 K₂CO₃ in MeCN to give 108 in 56% yield, followed by Boc protection to give 109 in 73% yield (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.

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.
Previous research by Davies into the relative stereochemistry of the cyclised products 113 and 114 had been assigned 2R*, 3R*, 4R* (Figure 4).  
Therefore we tentatively suggest that the major diastereomers relative stereochemistry for 112 is probably 2R*, 4R* (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 RuO₄ and NaIO₄. These conditions had previously been used by Donohoe in the synthesis of pyrrolidinone core of KSM-2690 B (Scheme 47). These conditions gave the desired pyrrolidinone 116 in 66% yield however the oxidation at the benzylic position of the BOM group also occurred.
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.

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 (-)-dysiabetaine was explored. The precursor 59 was proposed as a possible suitable substrate (Scheme 49). However 59 did not undergo 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.

The precursor 109 was investigated as it would avoid β-elimination by using a SiMe₃Ph 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.
The formation of 110 illustrated the feasibility of the aza-[2,3]-Wittig rearrangement/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. 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.
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 60F254 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$_3$N (CaH$_2$), Et$_2$NH (CaH$_2$), $i$Pr$_2$NH (CaH$_2$), DCM (CaH$_2$), DMSO (CaH$_2$), HMPU (CaH$_2$), DMPU (CaH$_2$). When necessary DMF, Et$_3$N, $i$Pr$_2$NH, HMPU and DMPU were stored under Ar and over 4Å molecular sieves (activated by heating (250 °C) 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 $10^{-1}\text{deg cm}^2\text{g}^{-1}$ 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$_3$ ($\delta_H = 7.27, \delta_C = 77.1$ ppm) or d$_6$-DMSO ($\delta_H = 2.52, \delta_C = 39.52$ 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)\textsuperscript{12,13}

\[
\begin{array}{c}
\text{PhMe}_2\text{Si} \\
\text{Br}
\end{array}
\]

To a solution of dimethylphenylvinylsilane (10.0 mL, 55.0 mmol, 1.00 equiv) in CCl\textsubscript{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\textsubscript{4} (20 mL + 10 mL). The reaction was warmed to rt over 1 h. The reaction was washed with saturated aq. NaHCO\textsubscript{3} solution containing sodium sulfite (3 x 50 mL) and brine (3 x 20 mL). The organic phase was dried (MgSO\textsubscript{4}), filtered and the solvent removed \textit{in vacuo} to obtain a clear oil of the dibromide (17.0 g). The dibromide was diluted with Et\textsubscript{2}NH (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\textsubscript{2}O (3 x 20 mL). The organic phase was dried (MgSO\textsubscript{4}), filtered and solvent removed \textit{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.\textsuperscript{12} 62%); Rf 0.58 (Hexane); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.60 (2H, \textit{m}, \textit{m}-H-Ph) 7.42 (3H, \textit{m}, \textit{o/p-H-Ph}) 6.37 (1H, \textit{d}, \textit{J}=1.6, CCH\textsubscript{2}) 6.18 (1H, \textit{d}, \textit{J}=1.6, CCH\textsubscript{2}) 0.51 (6H, \textit{s}, SiCH\textsubscript{3}); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 136.7 (Cq), 135.2 (Cq), 134.1(CH), 131.5 (CH\textsubscript{2}), 129.8 (CH), 128.0 (CH), -3.41 (SiCH\textsubscript{3}).

University Of Nottingham
2-(Dimethylphenylsilane) prop-2-en-1-ol (64)\(^{14}\)

![Chemical Structure of 2-(Dimethylphenylsilane) prop-2-en-1-ol (64)](image)

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\(_3\)) \(\delta\) 7.54 (2H, m, \text{m-H-Ph}), 7.40-7.35 (3H, m, \text{o/p-H-Ph}), 5.93 (1H, m, \text{C=CH}_2), 5.50 (1H, m, \text{C=CH}_2), 4.25 (2H, d, \text{J=4.8, CCH}_2\text{OH}), 0.43 (6H, s, Si(CH\(_3\))\(_2\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 149.9 (Cq), 137.6 (Cq), 133.9 (CH), 129.2 (CH), 127.9 (CH), 124.7 (CH\(_2\)), 66.5 (CH\(_2\)OH), -3.0 (SiCH\(_3\)).

1-(Bromomethylvinyl) Dimethylphenylsilane (44)\(^{14}\)

![Chemical Structure of 1-(Bromomethylvinyl) Dimethylphenylsilane (44)](image)

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\(_3\)) \(\delta\) 7.54 (2H, m, \text{m-H-Ph}), 7.39 (3H, m, \text{o/p-H-Ph}), 6.04 (1H, dt, \text{J=2.0, 1.6, C=CH}_2), 5.58 (1H, dt, \text{J=2.0, 0.8, C=CH}_2), 4.10 (2H, dd, \text{J=1.6, 0.8, CH}_2\text{Br}), 0.49 (6H, s, Si(CH\(_3\))\(_2\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 146.3 (Cq), 131.7 (CH), 130.1 (CH), 128.6 (CH), 38.2 (CH\(_2\)Br), -2.0 (Si(CH\(_3\))\(_2\)).
N-(tert-Butoxycarbonyl)-L-Serine β-lactone (60)\textsuperscript{15}

\[
\text{\begin{tikzpicture}
  \node at (0,0) {\text{N-(tert-Butoxycarbonyl)-L-Serine β-lactone}};
  \draw[thick] (-0.5,0) -- (0.5,0) node[right] {\text{60}};
  \draw[thick] (0,-0.5) -- (0,0.5) node[above] {\text{O}};
  \draw[thick] (-0.5,-0.5) -- (0,-0.5) node[below] {\text{Boc}};
  \draw[thick] (0,-0.5) -- (0.5,-0.5) node[right] {\text{N}};
  \draw[thick] (0.5,-0.5) -- (0.5,0) node[right] {\text{O}};
  \end{tikzpicture}}
\]

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.\textsuperscript{15} 72%); m.p. 115 °C (Lit.\textsuperscript{15} m.p. 120 °C); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.23 (1H, brs, NH), 5.12 (1H, m, NCH\(\textsubscript{2}\)), 4.44 (2H, m, NCHCH\(\textsubscript{2}\)O), 1.46 (9H, s, C(CH\(\textsubscript{3}\))\(_3\)); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 169.5 (C\(=\)O-lactone), 154.6 (C\(=\)O-Boc), 81.4 (OC(CH\(\textsubscript{3}\))\(_3\)), 66.6 (CH\(\textsubscript{2}\)O), 59.5 (NCH), 28.2 (OC(CH\(\textsubscript{3}\))\(_3\)).

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

\[
\text{\begin{tikzpicture}
  \node at (0,0) {\text{2-(2-Dimethylphenylsilanyl)allylamino-3-hydroxy propionic methyl ester}};
  \draw[thick] (0,0) -- (1,0) node[right] {\text{73}};
  \draw[thick] (0,0) -- (0,1) node[above] {\text{SiMe\textsubscript{2}Ph}};
  \draw[thick] (0,0) -- (0,-1) node[below] {\text{HN}};
  \draw[thick] (0,0) -- (-1,0) node[left] {\text{CO\textsubscript{2}Me}};
  \end{tikzpicture}}
\]

A suspension of K\(_2\)CO\(_3\) (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\(_2\)O (35 mL) and saturated aq. NaHCO\(_3\) solution (35 mL). The two phases were separated and the aqueous was extracted with Et\(_2\)O (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); [α]D^20 -34.5 (c 3.7, CH₂Cl₂); IR νmax (solution in CHCl₃) 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, CDCl₃) δ 7.52 (2H, m, m-H-Ph), 7.37 (3H, m, o/p-H-Ph), 5.88 (1H, m, C=CH₂), 5.53 (1H, m, C=CH₂), 3.72 (3H, s, OCH₃), 3.65 (1H, dd, J=10.8, 4.4, CHCH₂OH), 3.49 (1H, dd, J=10.8, 6.4, CHCH₂OH), 3.42 (1H, dt, J=14.0, 1.2, NCH₂), 3.29 (1H, dd, J=6.4, 4.4, NCH(CO₂Me)CH₂), 3.23 (1H, dt, J=14.0, 1.6, NCH₂) 2.4-1.7 (2H, brs, NH/OH) 0.41 (6H, d, J=2.0, Si(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) 173.4 (C=O), 148.0 (Cq), 138.0 (Cq), 133.8 (m-CH), 129.1 (p-CH), 128.0 (o-CH), 127.2 (CH₂), 62.3 (CH₂OH), 61.9 (NCHCO₂Me), 53.3 (NCH₂), 52.1 (OCH₃), -2.96 (Si(CH₃)₂); m/z (ES⁺) 294 (100%, MH⁺); HRMS C₁₅H₂₄NO₃Si calcd. 294.1520, found 294.1532 Anal. calcd. for C₁₅H₂₃NO₃Si 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](image)

To a magnetically stirred mixture of 73 (2.96 g, 10.1 mmol, 1.00 equiv) and Boc₂O (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 Et₂O (25 mL) and washed with saturated aq. NaHCO₃ solution (3 x 25 mL) and brine (3 x 20 mL). The organic phase was dried (MgSO₄), 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); [α]D²¹ -13.6 (c 4.0, CH₂Cl₂); IR νmax (solution in CHCl₃) 3690, 3567, 3011 (CH), 2981(CH), 1812, 1732 (C=O-ester), 1685 (C=O-Boc), 1428, 1409, 1369, 1334, 1252, 1161, 1120, 1076, 1043, 932, 837 cm⁻¹; ¹H NMR (270 MHz, d⁶-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=CH₂), 5.46 (1H, d, J=1.9, C=CH₂), 4.55 (1H, t, J=5.4, NCH(CO₂Me)CH₂OH), 4.32-4.16 (1H, brs, OH), 4.10 (1H, d, J=17.3, NCH₂), 3.96 (1H, d, J=17.5, NCH₂), 3.83 (1H, dd, J=11.1, 5.4, CHCH₂OH), 3.72 (1H, dd, J=11.1, 5.2, CHCH₃OH), 3.64 (3H, s, OCH₃), 1.37 (9H, s, C(CH₃)₃), 0.40 (6H, s, Si(CH₃)₂); C¹³ NMR (100 Hz, CDCl₃) δ 171.1 (CO₂Me), 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=CH₂), 80.9 (OC(CH₃)₃), 62.0 (NCH(CO₂Me)CH₂), 61.7 (CH₂OH), 53.0 (NCH₂), 52.2 (OCH₃), 28.2 (C(CH₃)₃), -3.3 (SiCH₃)₂; m/z (ES⁺) 416 (100%, MNa⁺); HRMS C₂₀H₃₁NNaO₅Si calcd. 416.1864, found 416.1862
2-{tert-butoxycarbonyl-[2-(Dimethylphenylsilanyl)-allyl]-amino}-3-hydroxy propionic acid (75)

![Structure of 75](image_url)

To a solution of 74 (2.29 g, 5.82 mmol, 1.00 equiv) in MeOH/H$_2$O/THF (100 mL, 1:1:2) was added LiOH.H$_2$O (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%); [α]$_D^{20}$ -2.03 (c 2.9, CH$_2$Cl$_2$); IR $\nu_{\text{max}}$ (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$^{-1}$; $^1$H 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$_2$(CO$_2$H)CH$_2$OH), 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$_2$CH$_3$), 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$_2$(CO$_2$Me)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$_3$)$_3$); m/z (ES$^+$) 402 (100%, MNa$^+$); HRMS C$_{19}$H$_{29}$NNaO$_5$Si calcd. 402.1707, found 402.1702
[2-(Dimethylphenylsilanyl)-allyl]-(2-oxo-oxetan-3-yl)carbamic acid (59)

To a solution of Ph₃P (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) [α]D²¹ -2.69 (c 4.2, CH₂Cl₂): IR ν_max (solution in CHCl₃) 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, d⁶-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=CH₂), 5.51 (1H, q, J=1.6, C=CH₂), 4.95 (1H, t, J=5.8, NCH₂O), 4.31 (2H, d, J=5.8, NCH₂O), 3.99 (2H, t, J=1.6, NCH₂), 1.41 (9H, s, C(CH₃)₃), 0.42 (6H, d, J=2.2, Si(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) 169.2 (C=O-lactone), 145.6 (Cq), 133.8 (m-CH), 129.4 (p-CH), 128.0 (o-CH), 127.4 (C=CH₂), 80.0 (OC(CH₃)₃) 65.7 (NCH₂O), 64.7 (NCH₂O), 53.2 (NCH₂), 28.1 (OC(CH₃)₃), -3.2 (Si(CH₃)₂), -3.7 (Si(CH₃)₂); m/z (ES⁺) 384 (100%, MNa⁺); HRMS C₁₉H₂₇NNaO₄Si calcd. 384.1602, found 384.1597.
2-(tert-Butoxycarbonyl-[2-(Dimethylphenylsilanyl)allyl]-amino)-acrylic acid (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 NH₄Cl solution (2.4 mL). The reaction was extracted with Et₂O (3 x 3 mL). The organic phase was combined, washed with brine (2 x 8 mL), dried (MgSO₄), 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 CHCl₃) 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, CDCl₃) 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, NCH₂C=CH₂), 5.73 (1H, s, NC(CO₂H)=CH₂), 5.53 (1H, d, J=1.6, NCH₂C=CH₂), 5.26 (1H, s, NC(CO₂H)=CH₂), 4.16 (2H, s, NCH₃C), 1.41 (9H, s, OC(CH₃)₃), 0.39 (6H, s, Si(CH₃)₂); m/z (ES⁺) 384 (100%, MNa⁺); HRMS C₁₉H₂₇NNaO₄Si calcd. 384.1607, found 384.1602.
[2-(Dimethylphenylsilyl)allyl]isopropenyl-carbamic acid tert-butyl ester (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 \(^{1}\)Pr\(_{2}\)NH (0.12 ml, 0.83 mmol, 1.50 equiv) and \(^{2}\)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\(_{4}\)Cl solution (2 mL) and the two layers were separated. The aqueous layer was extracted with Et\(_{2}\)O (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 \(\nu_{\text{max}}\) (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\(_{3}\)) \(\delta\) 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\(_{2}\)C=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\(_{2}\)C=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\(_{3}\)) \(\delta\) 154.0 (C=O), 145.8
(NCH₂C=CH₂), 145.5 (NC(CH₃)=CH₂), 137.4 (C), 133.9 (m-CH), 129.2 (p-CH), 127.9 (o-CH), 124.5 (NCH₂C=CH₂), 106.4 (NC(CH₃)=CH₂), 80.0 (OC(CH₃)₃), 54.1 (NCH₂C), 28.3 (OC(CH₃)₃), 21.8 (NC(CH₃)=CH₂), -3.2 (Si(CH₃)₂); m/z (ES⁺) 354 (100%, MNa⁺); HRMS C₁₉H₂₉NNaO₂Si calcd. 354.1860, found 354.1848.

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

To a solution of Ph₃P (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 Na₂S₂O₃ solution (20 mL). The two phases were separated and the aqueous was extracted with Et₂O (3 x 20 mL). The organic phases were combined, washed with brine (3 x 20 mL), dried (MgSO₄) and solvent removed in vacuo to obtain 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); [α]D²² -46.8 (c 4.1, CH₂Cl₂); IR νₘₚₙ (solution in CHCl₃) 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\textsubscript{3}) \(\delta\) 7.54-7.51 (2H, m, \textit{m}-H-Ph), 7.40-7.36 (3H, m, \textit{o/p-H}-Ph), 5.78 (1H, m, C=CH\textsubscript{2}), 5.67 (1H, m, C=CH\textsubscript{2}), 4.56 (1H, dt, \textit{J}=14.8, 1.4, NCH\textsubscript{2}), 3.99 (1H, dd, \textit{J}=8.8, 3.6, NCH(CO\textsubscript{2}Me)CH\textsubscript{2}O), 3.72 (3H, s, OCH\textsubscript{3}), 3.69 (1H, dd, \textit{J}=9.6, 3.6, NCH(CO\textsubscript{2}Me)CH\textsubscript{2}O), 3.62 (1H, d, \textit{J}=14.8, NCH\textsubscript{2}), 3.37 (1H, dd, \textit{J}=9.2, 8.8, NCH(CO\textsubscript{2}Me)CH\textsubscript{2}O), 0.50 (3H, s, Si(CH\textsubscript{3})\textsubscript{2}), 0.42 (3H, s, Si(CH\textsubscript{3})\textsubscript{2}); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 170.2 (C\textsubscript{O}2Me), 156.9 (N(C=O)O), 144.6 (Cq), 137.3 (Cq), 133.6 (\textit{m}-CH), 130.3 (C=CH\textsubscript{2}), 129.4 (p-CH), 128.1 (\textit{o}-CH), 63.9 (NCH(CO\textsubscript{2}Me)CH\textsubscript{2}O), 55.6 (NCH(CO\textsubscript{2}Me)CH\textsubscript{2}O), 52.7 (OCH\textsubscript{3}), 48.8 (NCH\textsubscript{2}C), -3.3 (Si(CH\textsubscript{3})\textsubscript{2}), -4.4 (Si(CH\textsubscript{3})\textsubscript{2}); m/z (ES\textsuperscript{+}) 342 (48%, MNa\textsuperscript{+}); HRMS C\textsubscript{16}H\textsubscript{21}NNaO\textsubscript{4}Si calcd. 342.1132, found 342.1121; Anal. calcd. for C\textsubscript{16}H\textsubscript{21}NO\textsubscript{4}Si C 60.16, H 6.63, N 4.38, found C 59.90, H 6.63, N 4.26%.

**Dimethyl(iodomethyl)phenyl silane (103)**\textsuperscript{28}

PhMe\textsubscript{2}SiCH\textsubscript{2}Cl (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.\textsuperscript{28} 99%); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.55 (2H, m, \textit{m}-H-Ph), 7.45-7.35 (3H, m, \textit{o/p-H}-Ph), 2.20 (2H, s, SiCH\textsubscript{2}I), 0.46 (6H, s, Si(CH\textsubscript{3})\textsubscript{2}); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 136.8 (\textit{i}-C), 133.7 (CH), 129.6 (CH), 128.0 (CH), -2.9 (Si(CH\textsubscript{3})\textsubscript{2}), -13.6 (SiCH\textsubscript{2}I).
**Ethyl-2-acetamido-2-cyano-3-(Dimethylphenylsilyl) propionate (105)**

![Chemical Structure](image)

Ethyl acetamidocyanooacetate (5.03 g, 29.5 mmol, 1.20 equiv) and PhMe₂SiCH₂I 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); ¹H NMR (400 MHz, CDCl₃) 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, OCH₃CH₂), 4.07 (1H, dq, J=10.8, 7.2, OCH₂CH₃), 1.94 (1H, d, J=14.8, SiCH₂C), 1.65 (1H, d, J=14.8, SiCH₃C), 1.63 (3H, s, (CO)CH₃), 1.30 (3H, t, J=7.2, OCH₂CH₃), 0.55 (3H, s, SiCH₃), 0.41 (3H, s, SiCH₃); ¹³C NMR (100 Hz, CDCl₃) δ 169.2 (N(CO)CH₃), 167.2 (CO₂Et), 136.4 (Cq), 133.9 (m-C), 130.3 (p-CN), 128.6 (o-CN), 117.4 (C=NC₃), 63.6 (OCH₂CH₃), 54.4 (Cq), 25.0 (SiCH₂C), 22.1 (COCH₃), 13.8 (OCH₂CH₃), -2.6 (SiCH₃), -3.0 (SiCH₃).

**2-Amino-3-(dimethylphenylsilyl)-propionic acid (106)**

![Chemical Structure](image)

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); ¹H NMR (400 MHz, d⁶-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(CO₂H)CH₂), 1.16 (1H, dd, J=14.0, 11.2, SiCH₃CH), 1.00 (1H, dd, J=14.0, 4.8, SiCH₂CH), 0.35 (3H, s, SiCH₃), 0.30 (3H, s, SiCH₃); ¹³C NMR (100 MHz, d⁶-DMSO) δ 170.9 (C=O), 140.5 (Cq), 133.9 (m-CH), 129.1 (p-...
2-Amino-3-(dimethylphenylsilanyl)-propionic acid methyl ester hydrochloride (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 Et₂O (20 mL). The two phases were separated and the aqueous phase was extracted with Et₂O (2 x 20 mL). The organic phases were combined and washed with H₂O (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 CHCl₃) 3692, 3600, 3050 (CH), 2961 (CH), 1752 (C=O), 1602, 1511, 1442, 1428, 1253, 1188, 1115, 925, 838 cm⁻¹; ¹H NMR (400 MHz, d⁶-DMSO) δ 8.5-8.2 (3H, brs, NH₃⁺), 7.50 (2H, m, m-H-Ph), 7.38 (3H, m, o/p-H-Ph), 3.90 (1H, m, NCH(CO₂Me)CH₂), 3.42 (3H, s, OCH₃), 1.35 (2H, m, CHCH₃Si), 0.35 (3H, s, SiCH₃), 0.29 (3H, s, SiCH₃); ¹³C NMR (100 MHz, d⁶-DMSO) δ 170.6 (C=O), 137.7 (C), 133.8 (m-CH), 129.8 (p-CH), 128.4 (o-CH), 52.7 (OCH₃), 50.6 (NCH(CO₂Me)CH₂), 18.8 (SiCH₂CH), -1.9
(SiCH₃), -2.8 (SiCH₃); m/z (ES⁺) 221 (100% M-HCl-CH₃) 260 (74%, MNa⁺-HCl); HRMS C₁₂H₁₉NNaO₂Si calcd. 260.1077, found 260.1075.

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

A suspension of 107 (362 mg, 1.32 mmol, 1.00 equiv), 44 (506 mg, 1.98 mmol, 1.50 equiv) and K₂CO₃ (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 Et₂O (20 mL) and saturated aq. NaHCO₃ solution (10 mL). The two phases were separated and the aqueous was extracted with Et₂O (2 x 10 mL). The organic phases were combined, dried (MgSO₄), 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 CHCl₃) 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, CDCl₃) δ 7.50 (4H, m, m-H-Ph), 7.35 (6H, m, o/p-H-Ph), 5.81 (1H, m, C=CH₂), 5.44 (1H, m, C=CH₂), 3.49 (3H, s, OCH₃), 3.23 (1H, d, J=14.4, NCH₂), 3.20 (1H, t, J=8.0, NCH₂(CO₂Me)CH₂), 3.03 (1H, d, J=14.0, NCH₂), 1.17 (1H, dd, J=14.4, 7.6, CHCH₂Si), 1.10 (1H, dd, J=14.4, 7.6, CHCH₂Si), 0.37 (6H, d, J=1.2, CH₂=CSi(CH₃)₂), 0.30 (6H, d, J=8.0, CH₂Si(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) 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=CH₂), 58.0 (NCH(CO₂Me)CH₂), 52.5 (NCH₂C), 51.3 (OCH₃), 21.2 (CHCH₂Si), -2.1 (Si(CH₃)₂), -2.8 (SiCH₃), -3.0 (SiCH₃); m/z (ES⁺) 412 (100%, MH⁺); HRMS C₂₃H₄₄NO₂Si calcd. 412.2123, found 412.2104.

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

To 108 (300 mg, 0.73 mmol, 1.00 equiv) and Boc₂O (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 Et₂O (15 mL) and washed with saturated aq. NaHCO₃ solution containing sodium sulfite (3 x 10 mL) and brine (2 x 10 mL). The organic phase was dried (MgSO₄), filtered and solvent removed under vacuum to obtain a yellow oil. Excess Boc₂O was removed by stirring the crude reaction product in ⁹PrNH₂ in Et₂O (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 νmax (solution in CHCl₃) 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, d⁶-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=CH₂), 5.40 (1H, q,
J=2.5, C=CH\textsubscript{2}), 4.40-4.28 (1H, m, NCH\textsubscript{2}), 3.89 (1H, dt, J=17.4, 1.6, NCH\textsubscript{2}C), 3.70 (1H, J=17.5, 1.6, NCH\textsubscript{2}C), 3.50 (3H, s, OCH\textsubscript{3}), 1.45 (1H, dd, J=14.7, 9.6, NCHCH\textsubscript{2}Si), 1.36 (9H, s, C(CH\textsubscript{3})\textsubscript{3}), 1.11 (1H, dd, J=14.7, 5.6, NCHCH\textsubscript{2}Si), 0.37 (6H, d, J=1.2, Si(CH\textsubscript{3})\textsubscript{2}), 0.28 (6H, d, J=2.6, Si(CH\textsubscript{3})\textsubscript{2}); \textsuperscript{13}C NMR (67.9 MHz, d\textsubscript{6}-DMSO at 90 °C) \(\delta\) 172.3 (CO\textsubscript{2}Me), 154.9 (O(C=O)N), 146.3 (C=CH\textsubscript{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=CH\textsubscript{2}), 79.9 (OC(CH\textsubscript{3})\textsubscript{3}), 56.3 (NCH), 51.9 (NCH\textsubscript{2}), 49.8 (OCH\textsubscript{3}), 28.5 (C(CH\textsubscript{3})\textsubscript{3}), 17.8 (SiCH\textsubscript{2}), -2.0 (Si(CH\textsubscript{3})\textsubscript{2}), -2.8 (Si(CH\textsubscript{3})\textsubscript{2}); m/z (ES\textsuperscript{+}) 534 (100%, M\textsuperscript{Na}\textsuperscript{+}); HRMS C\textsubscript{28}H\textsubscript{41}NO\textsubscript{4}Si 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-phenylsilanyl)-methyl]-pent-4-enoic (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\textsubscript{4}Cl solution (2 mL) and extracted with Et\textsubscript{2}O (3 x 5 mL). The organic phases were combined, washed with brine (2 x 10 mL), dried (MgSO\textsubscript{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 $\nu_{\text{max}}$ (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$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.60-7.50 (2H, m, Ph-H), 4.00-3.90 (0.6H, m, NCH$_2$), 3.78-3.70 (0.4H, m, NCH$_2$), 3.70-3.62 (3H, m, OCH$_3$), 3.17-3.05 (1H, m, NCH$_2$), 2.10-1.55 (5H, m, Alk-CH), 1.50-1.40 (9H, m, OC(CH$_3$)$_3$), 0.30-0.10 (12H, m, SiCH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 175.2 (C=O$_2$Me), 153.6 (O(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 (OC(CH$_3$)$_3$), 68.6 (Cq), 55.1 (NCH$_2$), 52.3 (OCH$_3$), 50.7, 28.6 (OC(CH$_3$)$_3$), 23.0 (CH$_2$SiMe$_3$Ph), -0.37 (SiCH$_3$), -0.66 (SiCH$_3$), -0.99 (SiCH$_3$), -1.45 (SiCH$_3$), -4.3 (SiCH$_3$), -4.4 (SiCH$_3$); m/z (ES$^+$) 534 (100%, MNa$^+$), 512 (20%, MH$^+$); HRMS C$_{28}$H$_{41}$NNaO$_4$Si$_2$ calcd. 534.2466, found 534.2463.

Data for 111; Rf 0.59 (10% EtOAc/hexanes); IR $\nu_{\text{max}}$ (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$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48 -7.41 (4H, m, m-H-Ph), 7.35-7.29 (6H, m, o/p-H-Ph), 5.70 (1H, brs, C=CH$_2$), 5.58 (1H, brs, NH), 5.46 (1H, brs, C=CH$_2$), 3.31 (1H, d, J=15.2, CCH$_2$C(SiMe$_3$Ph)=CH$_2$), 3.19 (3H, s, OCH$_3$), 2.55 (1H, d, J=15.2, CCH$_2$C(SiMe$_3$Ph)=CH$_2$), 2.24 (1H, d, J=14.8, CCH$_2$Si), 1.42 (9H, s, OC(CH$_3$)$_3$), 1.35 (1H, d, J=14.8, CCH$_2$Si), 0.32 (6H, brs, Si(CH$_3$)$_2$), 0.23 (6H, d, J=6.8, Si(CH$_3$)$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.1 (CO$_2$Me), 153.7 (O(C=O)N), 145.6 (C=CH$_2$), 138.6 (Cq), 138.3 (Cq), 134.0 (m-CH), 133.8 (m-CH),...
CH), 130.5 (C=CH₂), 128.9 (CH), 127.7 (CH), 79.1 (O(CH₃)₃), 61.9 (BocHNC), 51.9 (O(CH₃)), 43.6 (NCCH₂C(SiMe₂Ph)=CH₂), 28.5 (O(CH₃)₃), 26.0 (NCCH₂SiMe₂Ph), -1.8 (Si(CH₃)), -2.6 (Si(CH₃)), -2.7 (Si(CH₃)), -3.0 (Si(CH₃)); m/z (ES⁺) 534 (100%, Mn⁺); HRMS C₂₈H₄₁NNaO₄Si₂ calcd. 534.2466, found 534.2469.

4-(Dimethylphenylsilanyl)-2-[(dimethylphenylsilanyl)-methyl]-pyrrolidine-2-carboxylic acid methyl ester (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. NaHCO₃ 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 (MgSO₄), and solvent removed in vacuo to obtain 112 as a yellow oil (21 mg, 86%); IR νₘₐₓ (solution in CHCl₃) 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; ¹H NMR (400 MHz, CDCl₃) δ 7.55-7.40 (4H, m, m-H-Ph), 7.40-7.30 (6H, m, o/p-H-Ph), 3.43 (3H, s, OCH₃), 3.12 (1H, dd, J=10.0, 8.8, NCH₂), 2.81 (1H, t, J=10.0, NCH₂), 2.60-2.30 (1H, brs, NH), 2.32 (1H, dd, J=12.0, 6.8, NCCH₂), 1.50-1.25 (4H, m, alk-CH), 0.28 (6H, s, SiCH₃), 0.25 (3H, s, SiCH₃), 0.24 (3H, s, SiCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 177.6 (CO₂Me), 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 (OC\textsubscript{3}H\textsubscript{3}), 48.3 (CH\textsubscript{2}), 42.0 (CH\textsubscript{2}), 28.4 (Si\textsubscript{2}CH\textsubscript{2}), 25.9 (SiCH), -1.68 (Si\textsubscript{3}CH\textsubscript{3}), -2.0 (Si\textsubscript{3}CH\textsubscript{3}) -4.4 (Si\textsubscript{3}CH\textsubscript{3}), -4.6 (Si\textsubscript{3}CH\textsubscript{3}); m/z (ES\textsuperscript{+}) 412 (100%, MH\textsuperscript{+}); HRMS C\textsubscript{23}H\textsubscript{34}NO\textsubscript{2}Si\textsubscript{2} calcd. 412.2123, found 412.2132.
Chapter 5: References


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16 Literature investigation found no examples of the free amine of β-lactone.


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