Development of a Pummerer–type cyclisation for an approach to ecteinascidin 597

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Abstract

A connective Pummerer-type cyclisation has been developed for an approach to the synthesis of ecteinascidin 597.

Several electron rich glyoxamide substrates have been prepared and conditions for the connective Pummerer-type cyclisation have been developed successfully. In addition, the connective Pummerer-type cyclisation has been used with simple aldehyde substrates for the first time.

The tetrahydroisoquinoline AB system of ecteinascidin 597 has been prepared successfully using the connective Pummerer-type cyclisation. The H ring has also been built. Several approaches for the synthesis of ecteinascidin 597 from the AB and ABH ring systems have been investigated.

Ecteinascidin 597
Declaration

I hereby swear that no portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Part of this work has been published in peer reviewed journal:
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List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>Azobisisobutyronitrile</td>
</tr>
<tr>
<td>Alloc</td>
<td>Allyloxycarbonyl</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxycarbonyl</td>
</tr>
<tr>
<td>BOP</td>
<td>bis(2-Oxo-3-oxazolidinyl)phosphinic</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>Calcd</td>
<td>Calculated</td>
</tr>
<tr>
<td>CIP</td>
<td>2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate</td>
</tr>
<tr>
<td>CSA</td>
<td>Camphor sulfonic acid</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-Chloroperoxycbenzoic acid</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DIAD</td>
<td>Diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>Diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-Diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMB</td>
<td>2,4-Dimethoxybenzyl</td>
</tr>
<tr>
<td>DMDO</td>
<td>Dimethyl dioxirane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>Diastereoisomeric ratio</td>
</tr>
<tr>
<td>EDCI</td>
<td>1-ethyl-3-(3-N,N-dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>Et.</td>
<td>Ecteinascidin</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>ESI</td>
<td>Electrospray ionisation</td>
</tr>
<tr>
<td>Fmoc</td>
<td>9-Fluorenlymethyloxycarbonyl</td>
</tr>
</tbody>
</table>
HOAt 1-hydroxy-7-azabenzotriazole  
HOBt hydroxybenzotriazole  
Hz Hertz  
LAH Lithium aluminium hydride  
Me Methyl  
MNBA 2-Methyl-6-nitrobenzoic anhydride  
MOM methoxymethyl  
Ms Methanesulfonyl  
NBS N-Bromosuccinimide  
NMO 4-Methylmorpholine N-oxide  
Ph Phenyl  
PMB p-Methoxybenzyl  
Pr Propyl  
Red-Al⁰ Sodium bis(2-methoxyethoxy)aluminumhydride  
RT Room temperature  
TBAI Tetra-n-butylammonium iodide  
TBAF Tetra-n-butylammonium fluoride  
TBDPS tert-Butyldiphenylsilyl  
TBS tert-Butyldimethylsilyl  
TFA Trifluoroacetic acid  
TFAA Trifluoroacetic anhydride  
THF Tetrahydrofuran  
TIPS Triisopropylsilyl  
TMS Trimethylsilyl  
TMT 4,4′,4″-Trimethoxytrityl  
Tf Trifluoromethanesulfonyl  
TFE Tetrafluoroethylene  
Troc 2,2,2-Trichloroethoxycarbonyl  
Ts Tosyl
Chapter 1 Ecteinascidin 597

1.1 Introduction to the ecteinascidins

The ecteinascidins are a family of tetrahydroisoquinoline alkaloids isolated from the Caribbean tunicate *Ecteinascidia turbinata*.\(^1\)-\(^2\) Four kinds of ecteinascidin are shown in Figure 1. The common structure of the ecteinascidins consists of a tetrahydroisoquinoline ring system (AB ring), a ten-membered ring macrolactone system (H) and CDE ring system.

![Figure 1](image)

1, \(R = CH_3\), ecteinascidin 597  
2, \(R = H\), ecteinascidin 583  
3, \(R = CH_3\), ecteinascidin 743  
4, \(R = H\), ecteinascidin 729

The ecteinascidins have received much attention from chemists due to their antitumor and antimicrobial activities.\(^3\)-\(^5\) For instance, ecteinascidin 743 (Figure 1) inhibits reproduction in the cell lines of several tumours, such as P388 leukemia, L1210 leukemia, A549 lung cancer, HT29 colon cancer etc.\(^6\)-\(^8\) In addition, ecteinascidin 743 has been waiting for FDA approval for the treatment of ovarian and other forms of cancer due to its nanomolar cytotoxicity towards ovarian cancers.\(^9\) With the highly promising biological activities of these compounds, many synthetic approaches have been published for the preparation of members of this family, however, there still remains a demand for more efficient methodologies which can be used to produce more analogues.
of this family for biological evaluation. My studies have concentrated on the synthesis of analogues of ecteinascidin 597 (Figure 1).

1.2 Previous synthetic approaches to the ecteinascidins

1.2.1 Ecteinascidin 597 (Et. 597)

In 2006, Zhu and co-workers published an asymmetric synthesis of ecteinascidins 597 and 583.\textsuperscript{10} Zhu’s retrosynthesis of ecteinascidin 597 and 583 is depicted in Scheme 1. It was planned that phenol 9 would first be alkylated with tetrahydroisoquinoline 8. Then, the entire ABCDE pentacycle was to be formed by a Pictet-Spengler cyclisation\textsuperscript{11} and an intramolecular Strecker cyclisation.\textsuperscript{12} Finally, the ten-membered ring lactone (H ring) containing a carbon-sulfur bond was to be formed to produce ecteinascidin 597 and 583 (Scheme 1).

Alchemy = allyloxycarbonyl, P = Boc = t-butoxycarbonyl

\textbf{Scheme 1}. Retrosynthetic analysis of ecteinascidins 597 and 583
The phenol 9 was prepared from 3-methoxy-4-hydroxybenzaldehyde as illustrated in Scheme 2. TBS protection of phenol 10 then the Dakin-West oxidation of aldehyde produced a labile formate ester and subsequent hydrolysis under basic conditions formed phenol 11. The OH group of the phenol was then protected using methyl chloromethyl ether (MOMCl). Regioselective lithiation of 12 at C-2 and addition of methyl iodide gave compound 13. In this case, both the aromatic ring and the TBS protecting group were methylated. Lastly, MOM deprotection using TMSBr gave the desired phenol 9.

Scheme 2. Reagents and conditions (a) TBSCI, imidazole, DMF, RT, 98%; (b) m-CPBA, CHCl₃, 45 °C; then Na₂CO₃, MeOH, RT, 85%; (c) MOMCl, DIPEA, CH₂Cl₂, 0 °C to reflux, 96%; (d) n-BuLi, THF, −10 °C; then Mel, −78 °C to RT, 92%; (e) TMSBr, CH₂Cl₂, −20 to 0 °C, 90%.

The synthetic route to pentacyclic compound 6 is depicted in Scheme 3. The selective hydrolysis of the oxazolidine ring of compound 14 afforded primary alcohol 15, which was then oxidised using Swern conditions to produce aldehyde 16. Phenol 9 (Scheme 2) was converted into its magnesium phenolate by reaction with a Grignard reagent, then condensed stereoselectively with aldehyde 16 to give the syn aminoalcohol 17. In the next three steps, compound
17 was converted to compound 18 in good yield. Firstly, the two free OH groups were protected by MOMCl. Secondly, treatment with TMSOTf under basic conditions deprotected the BOC group, and then KF removed the silyl ether protecting group. Thirdly, the acetate was hydrolysed under basic conditions (Scheme 3).

**Scheme 3.** Reagents and conditions (a) CeCl₃·7H₂O, oxalic acid, acetonitrile, RT, 91%; (b) (COCl)₂, DMSO, CH₂Cl₂, −60 °C, then Et₃N; (c) MeMgCl, THF, 9; then 16, CH₂Cl₂, RT, 74%; (d) MOMCl, DIPEA, CHCl₃, 0 °C to reflux, 88%; (e) TBSOTf, 2,6-lutidine, CH₂Cl₂, −78 °C to RT; then KF, MeOH, RT, 86%; (f) K₂CO₃, MeOH, RT, 94%; (g) AcOH, TrocOCH₂CHO, 3 Å MS, CH₂Cl₂, RT, 90%; (h) (COCl)₂, DMSO, CH₂Cl₂, −60 °C; then TMSCN, ZnCl₂, CH₂Cl₂, RT, 87%.
In order to form the AB tetrahydroisoquinoline ring, the Pictet-Spengler reaction\textsuperscript{11} between compound 18 and TrocOCH\textsubscript{2}CHO was carried out. Interestingly, compound 19 was formed as a single diastereomer in 90% yield. This result could be rationalised by invoking trans configured intermediate iminium ion 20 as illustrated in Figure 2. In the final step of this process, the primary OH group in 19 was oxidised using Swern conditions\textsuperscript{14} and a Lewis acid-catalysed intramolecular Streecker cyclisation\textsuperscript{12} produced the ABCDE pentacyclic compound 6 as a single diastereomer.

![Figure 2](image)

The final steps of the synthesis of ecteinascidin 597 were carried out as depicted in Scheme 4. Deprotection of the Troc group on the primary alcohol of compound 6 under reductive conditions and allylation of the phenol group produced compound 21. In the next step, the protected thiol containing branch was coupled with compound 21 to give the corresponding ester 22 in high yield. In order to form the ten-membered macrolactone, the protecting group on the sulfur atom of compound 22 was first unmasked then trimethylsilyl bromide was used to cleave both MOM groups and trigger H-ring formation. After that, reaction of acetic anhydride with the OH group on the A-ring produced compound 25 in moderate yield. N-Alloc and O-Allyl deprotection was achieved simultaneously using Pd(PPh\textsubscript{3})\textsubscript{4} and n-Bu\textsubscript{3}SnH to afford compound 26. Reductive amination\textsuperscript{15} of compound 26 with HCHO and NaBH\textsubscript{3}CN installed the methyl group on the secondary amine of the D-E tetrahydroisoquinoline ring system. Finally, removal of the N-Troc group under reductive conditions and substitution of the cyano group with a hydroxyl group produced ecteinascidin 597.
Scheme 4. Reagents and conditions (a) Zn, AcOH, Et₂O, RT, 90%; (b) allyl bromide, K₂CO₃, MeCN, RT, 94%; (c) EDCI, DMAP, (R)-N-Troc-S-4,4’,4”-trimethoxytrityl cysteine, CH₂Cl₂, RT, 93%; (d) Et₃SiH, TFA, CH₂Cl₂, RT, 87%; (e) TMSBr, CH₂Cl₂, −20 °C to 10 °C; (f) Ac₂O, pyridine, DMAP, CH₂Cl₂, RT, 60%; (g) [Pd(PPh₃)₄], n-Bu₃SnH, AcOH, CH₂Cl₂, RT, 85%; (h) HCHO, NaBH₃CN, AcOH, MeCN/MeOH, RT, 95%; (i) Zn, AcOH, Et₂O, RT, 89%; (j) AgNO₃, MeCN/H₂O, RT, 92%.
1.2.2 Pentacyclic core of the Ecteinascidins

In this section, various approaches to the ABCDE ring system at the core of the ecteinascidins will be discussed.

Corey’s and Williams’ method

Scheme 5. Retrosynthesis of the pentacyclic core of Et. 743

The strategy to build the ABCDE core ring (Scheme 5) was first published by Corey and co-workers in 1996,16 with further modifications published in 2000.17
Firstly, the AB ring system 30 was constructed via a Pictet-Spengler-type cyclisation. Secondly, the right hand part 29 was attached using a Strecker reaction with an aldehyde or by coupling with the corresponding acid. Finally, both the C and D rings were formed using a Pictet-Spengler-type cyclisation to finish the pentacyclic ring system. The main difference between this and Williams’ method published later (2008),\textsuperscript{18} is that the AB ring formation was achieved by way of a radical ring closure reaction. The stereochemistry of the product 32 was explained by the chair transition structure 33 in which substituents adopt pseudoequatorial dispositions (Scheme 5).

Scheme 6. Reagents and conditions (a) BF\textsubscript{3}•OEt\textsubscript{2}, H\textsubscript{2}O; (b) BF\textsubscript{3}•OEt\textsubscript{2}, 4 Å molecular sieves, 73 % (2 steps); (c) H\textsubscript{2}, Pd/C, 100 %; (d) AcOH, KCN, 61 %; (e) Allyl bromide, Cs\textsubscript{2}CO\textsubscript{3}, 87 %; (f) DIBAL-H; (g) KF; (h) CH\textsubscript{3}SO\textsubscript{3}H, 4 Å molecular sieves, 55 % (3 steps).
The details of Corey’s method from 1996 are shown in Scheme 6. Acetal deprotection in 36 was carried out smoothly under aqueous Lewis acidic conditions, imine formation and cyclisation then formed the AB ring product. Hydrogenation with Pd/C catalyst\textsuperscript{19} removed both the benzyl and benzyl carbamate protecting groups to produce compound 37. The resulting product was condensed with 38 under Strecker conditions to produce 39 as a single diastereoisomer. In the next three steps, 39 was converted to 40\textsuperscript{20} which was then treated with acid to produce the ABCDE core system 41.

In 2000, Corey et al. developed another approach to synthesise a key pentacyclic intermediate en route to Et. 743 from intermediate 41 (Scheme 7).\textsuperscript{17} The purpose of this approach lies on improvement of total yield of 41. Instead of using a Strecker reaction to attach 37 and 38 (Scheme 6), Corey coupled amine 42 with acid 43 then homologated the amide carbonyl to introduce amino nitrile 41 (Scheme 7). In detail, coupling of secondary amine 42 with acid 43 using 1-hydroxy-7-azabenzo-triazole (HOAt) and 2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate (CIP) produced 44.\textsuperscript{21} Amide 44 was then converted to 45 in 3 steps.\textsuperscript{22} Under acidic conditions (triflic acid, H\textsubscript{2}O/CF\textsubscript{3}CH\textsubscript{2}OH), the lactol ring was opened which generated in-situ the corresponding aldehyde which then cyclised with the protected amine and aromatic ring to form the pentacyclic product 46. The lactam functional group could then be converted to an amino nitrile group using LiAlH\textsubscript{2}(OEt)\textsubscript{2}, followed by quenching with KCN (Scheme 7).\textsuperscript{23}
Using a similar strategy to that of Corey, Liu and co-workers also synthesised the pentacyclic core of the ecteinascidins (Scheme 8).\(^2\) Firstly, the AB ring was formed using a Pictet-Spengler reaction between L-DOPA derivative\(^2\) 47 and BnOCH\(_2\)CHO. Ester 48 was then converted to 49 in 2 steps. Next, 49 was coupled with acid 50 and the alcohol was then oxidised to give a mixture of aldehyde 52 and hemiaminal 53. Acid triggered Boc cleavage, concomitant imine formation and cyclisation with the D ring then gave the product 54.\(^2\) This route was successfully used by Liu and co-workers in the total synthesis of (−)-saframycin A, a naturally occurring anti-tumour agent.\(^2\)
Scheme 8. Reagents and conditions (a) BnOCH$_2$CHO, AcONa/AcOH; (b) Ac$_2$O/HCOOH then H$_2$O/MeOH, 87 % (2 steps); (c) Me$_2$SO$_4$, K$_2$CO$_3$, 90 %; (d) HCl, MeOH, 85 %; (e) LiAlH$_4$, 83 %; (f) BOP-Cl, Et$_3$N, 80 %; (g) (COCl)$_2$, DMSO, Et$_3$N, 85 %; (h) TFA, 67 %.

In 2008, Williams and co-workers synthesised the pentacyclic core of Et. 743 as demonstrated in Scheme 9.\textsuperscript{18} Firstly, stereoselective alkylation of 55 with Garner’s aldehyde 56\textsuperscript{28} using Casiraghi’s method\textsuperscript{29} produced 57. Diol 57 was then converted to 58 in 5 steps. Radical ring closure of 58 using AIBN and Bu$_3$SnH gave the AB ring product 60 as a single diasteoisomer. Transition state 59\textsuperscript{30-31} was suggested to explain for the stereoselectivity of the reaction. Ester 60 was then converted to 61 then coupled with acid chloride 62 under basic conditions. After exchanging the Fmoc protecting group to Boc protecting group, acetonide cleavage using an acidic cationic resin gave the methoxy substitution product 63 (dr 1:1). TBS deprotection, then oxidation of the primary alcohol triggered cyclisation to form the ABC ring product 64. Finally, Boc deprotection resulted in a Pictet-Spengler-type cyclisation to form the desired product 66 (Scheme 9).
**Scheme 9.** Reagents and conditions (a) Ti(O-i-Pr)$_4$; (b) AllylBr, Cs$_2$CO$_3$, 65 % (2 steps); (c) TsOH; (d) TsOH, 2,2-dimethoxypropane, 84 % (2 steps); (e) TBSOTf, 2,6-dimethylpyridine, 76 %; (f) ethyl glyoxalate; (g) Bu$_3$SnH, AIBN, 58 % (2 steps); (h) LiAlH$_4$; (i) NaH, BnBr, 77 % (2 steps); (j) 2,6-dimethylpyridine, 70 %; (k) Et$_3$NH then Boc$_2$O, 90 %; (l) Dowex 50W-X8, MeOH, 90 %; (m) TBAF, 95 %; (n) (COCl)$_2$, DMSO, Et$_3$N, 99 %; (o) TFA, anisole, 72 %.
Danishefsky’s approach

The sequence for formation of the pentacyclic core is similar to that used by Corey. The approach adopted by Danishefsky for the construction of the AB ring system 70 using a Pomeranz-Fritsch-Bobbitt cyclisation reaction. Acid 69 was then coupled with the AB ring system. Finally, a vinylogous Pictet-Spengler cyclisation was carried out to build both the C and D ring (Scheme 10).

Scheme 10

Danishefsky and co-workers’ strategy for the synthesis of the ABCDE ring system of the ecteinascidins is set out in Scheme 11. Firstly, the AB ring product 72 was formed using a Pomeranz-Fritsch-Bobbitt cyclisation reaction then the resulting product was coupled with 73. Amide 74 was then converted to 75 in 4 steps. Deprotection of the Boc group, followed by condensation of the free nitrogen and the aldehyde gave the corresponding iminium ion intermediate. This was then cyclised with the AB ring vinylogous system (75) to form the key pentacyclic system of the ecteinascidins. Interestingly, the double bond on the
B ring can be functionalised via epoxidation and reductive ring opening using NaBH$_3$CN to give product 79.

**Scheme 11.** Reagents and conditions (a) HCl, 90 %; (b) BOPCl, Et$_3$N, 85 %; (c) DDQ, 90 %; (d) Cu(OTf)$_2$, 61 %; (e) DMP, 94 %; (f) [(PPh$_3$)$_2$PdCl$_2$], Bu$_3$SnH, AcOH, 93 %; (g) CHF$_2$COOH, MgSO$_4$, 58 %; (h) TBSOTf, Et$_3$N, 100 %; (i) TrocCl, TBAI, 92 %; (j) TBAF; (k) MOMCl, (i-Pr)$_2$NEt, 79 % (2 steps); (l) DMDO; (m) NaBH$_3$CN, 78 % (2 steps)
Fukuyama’s method

Scheme 12

Fukuyama developed two methods to build a pentacyclic ring system as demonstrated in Scheme 12. The first method begins with Ugi’s 4-component reaction to combine the two important building blocks along with acetaldehyde and . The C ring was then formed using a lactamisation reaction and the D ring was built using a Heck coupling reaction. Finally, the B ring was formed via an acylation reaction with the aldehyde . The second method concentrates on the synthesis of an important intermediate in his previous approach. The difference in the approaches is shown by the green disconnection in Scheme 12. The D ring was first built via Pictet-Spengler
reaction. The A ring system was then connected with the DE ring system via a Friedel-Crafts type addition to the iminolactone 90. The C ring was next formed by addition of the secondary amine to the aldehyde revealed upon deprotection of the acetal (Scheme 12).

The first method for the synthesis of Et. 743 by Fukuyama\(^{34}\) begins with Ugi’s 4-component reaction\(^{36}\) and produced 96 in excellent yield. In the next 6 steps, 96 was converted to lactam 97 which was then selectively reduced to the hemiaminal\(^{37}\) and final dehydration using CSA formed 98. A Heck coupling reaction\(^{38}\) was then carried out to form the CDE ring product 99 (Scheme 13).

![Scheme 13](image)

**Scheme 13.** Reagents and conditions (a) MeOH, 90 %; (b) TBAF, 89 %; (c) Ac\(_2\)O, pyridine, DMAP; (d) TFA, anisole; (e) EtOAc, reflux, 87 % (2 steps); (f) MsCl, pyridine, 91 %; (g) Boc\(_2\)O, DMAP, 97 %; (h) NaBH\(_4\), H\(_2\)SO\(_4\), EtOH/CH\(_2\)Cl\(_2\); (i) CSA, quinoline, 88 % (2 steps); (j) Pd\(_2\)(dba)\(_3\) (5 % mol), P(o-tol)\(_3\) (20 % mol), Et\(_3\)N, 83 %
The following steps shown in Scheme 14 illustrate the construction of the central core of Et. 743. Firstly, compound 99 was converted to 100 as a mixture of two diastereoisomer in 5 steps\(^{39-40}\). Reduction of the iminium ion which was generated via elimination of methanol under the acidic conditions, occurred on the least hindered face to afford the expected alcohol 101. In the next 8 steps, alcohol 101 was converted to aldehyde 103. Cleavage of both benzyl protecting groups by hydrogenation triggered the cyclisation to form the pentacyclic core product 104 (Scheme 14).

**Scheme 14.** Reagents and conditions (a) KOH, MeOH/H\(_2\)O, reflux; (b) Ac\(_2\)O, pyridine, DMAP, 93 % (2 steps); (c) TFA; (d) TrocCl, NaHCO\(_3\), 74 % (2 steps), (e) dimethyldioxirane, MeOH/acetone then CSA, 90 %; (f) NaBH\(_3\)CN, TFA, 94 %; (g) TBSCl, imidazole, 92 %; (h) guanidinium nitrate, NaOMe, MeOH, 85 %; (i) BnBr, K\(_2\)CO\(_3\), 91 %; (j) Red-Al, 82 %; (k) TMSCN, BF\(_3\)•OEt\(_2\), 73 %; (l) Ac\(_2\)O, pyridine, DMAP, 92 %; (m) HF, 100 %; (n) Dess-Martin periodinane, 92 %; (o) H\(_2\), Pd/C, 94 %.
Recently, Fukuyama and co-workers developed another method to synthesise intermediate 102 during the total synthesis of Et. 743 (Scheme 15).\textsuperscript{35} Firstly, 106 was prepared from 105 in 10 steps. The absolute stereochemistry in 106 was established using two reactions; a Horner–Wadsworth–Emmons reaction\textsuperscript{41} and an asymmetric hydrogenation.\textsuperscript{42} The D ring was then formed with using a Pictet-Spengler reaction of 106 with aldehyde 107. The reaction proceeded stereoselectively with \textit{cis}-selectivity to produce amine 108 which was then converted to iminolactone 110 in 5 steps. Following this, arylation of phenol 111 with iminolactone 110 resulted in formation of 112.\textsuperscript{43-45} The stereochemical outcome of the reaction was assumed to result from attack of the benzene on the least hindered face of the iminolactone ring. Four steps were required to convert 112 to 113, which was then treated with Lewis acid to bring about cyclisation to form the C ring. The next 4 steps converted the resulting product to intermediate 102 (Scheme 15).
Scheme 15. Reagents and conditions (a) HCOOH, Na$_2$SO$_4$, 83 %; (b) BnBr, K$_2$CO$_3$, 99 %; (c) ClCH$_2$CH$_2$OCOCl, pyridine, 90 %; (d) DBU, 2-mercaptoethanol, 84 %; (e) BrCH$_2$COOPh, i-Pr$_2$NEt, 90 %; (f) NBS, Et$_3$N, 89 %; (g) TFA, 81 %; (h) Tf$_2$O, pyridine, 80 %; (i) Et$_3$N, MeOH; (j) TBSCl, imidazole, 90 % (2 steps); (q) NaBH$_4$, LiCl, 89 %; (k) BF$_3$OEt$_2$, 73 %; (l) MeZnCl, [PdCl$_2$(dpff)], 76 %; (m) NaI, 96 %; (n) Zn, AcOH; (o) TrocCl, pyridine, 44 % (2 steps).
Zhu’s method

In Zhu’s approach (Scheme 16), the D ring was first built using a Pictet-Spengler reaction. Next a substitution was carried out to connect the A ring system and the DE ring systems. The C ring was then constructed using a Strecker reaction. Finally, arylation of the aldehyde produced the pentacyclic ring system (Scheme 16).

Scheme 16

Zhu’s method involves connection of the two building blocks 120 and 121 using a Pictet-Spengler reaction to produce DE ring product 122 (Scheme 17). Amine 122 was then converted into 123 in 4 steps. Subsequently, alkylation with racemate 124 afforded 125 as a single diastereoisomer. Interestingly, the substitution reaction occurs stereoselectively via an ortho-quinone methide intermediate. TBS protection of the primary alcohol, hydrolysis of the acetate group, and oxidation of the resulting alcohol were then carried out to produce the corresponding aldehyde which was cyclised with secondary amine to form the C ring in 126. Compound 126 was then converted to 127 in 4 steps. The
resulting product 127 was finally treated with TFA to form the pentacyclic product 128 (Scheme 17).

\[ \text{Scheme 17. Reagents and conditions (a) AcOH, CF}_3\text{CH}_2\text{OH, 4 Å molecular sieves, 84 %; (b) AllocCl, NaHCO}_3, 88 %; (c) AllylBr, Cs}_2\text{CO}_3, 86 %; (d) Ac}_2\text{O, pyridine, DMAP, 92 %; (e) TFA, 72 %; (f) Et}_3\text{N, 68 %; (g) TBSi, imidazole, 97 %; (h) K}_2\text{CO}_3, 94 %; (i) Dess-Martin reagent then TMSCN, ZnCl}_2, 78 %; (j) LiBH}_4, 80 %; (k) Ac}_2\text{O, pyridine, DMAP, 92 %; (l) HF, 91 %; (m) Dess-Martin reagent, 93 %; (n) TFA, 95 %} \]
1.2.3 Macrolactone H ring formation

The macrolactone H ring was typically formed using two main strategies (Scheme 18) from the pentacyclic ring systems (see section 1.2.2).\textsuperscript{16,34,46} Firstly, the thio-acid was esterified using a primary alcohol. Secondly, the H ring was formed by addition of a sulfur nucleophile to extended quinine methide (130) or substitution of the leaving group in the benzylic position (133).

\begin{equation}
\text{Scheme 18}
\end{equation}

Scheme 19 shows one example of the formation of the macrolactone H in more detail using the first strategy (red disconnection).\textsuperscript{16} Alcohol 41 was converted to 135 in 6 steps. Oxidation of phenol 135 using (PhSeO)\textsubscript{2}O, followed by TBDPS deprotection and esterification of the resulting product with the corresponding cysteine derivative gave 136. The macrolactone H ring was then built in a one-pot reaction using the following steps. Firstly, tertiary alcohol 136 reacted with the Swern reagent formed in-situ from DMSO and Tf\textsubscript{2}O, and subsequent elimination formed the quinone methide. Next, t-BuOH was added to destroy the remaining Swern reagent. Finally, an excess of (Me\textsubscript{2}N)\textsubscript{2}C=N-t-Bu was added.
to convert the thioether to thiolate ion which promoted cyclisation to form the macrolactone H ring. Ac₂O was added to esterify the resulting phenol (Scheme 19).

Scheme 19. Reagents and conditions (a) Tf₂NPh, Et₃N, DMAP, 72 %; (b) TBDPSCI, DMAP, 89 %; (c) MOMBr, i-Pr₂NET, 92 %; (d) PdCl₂(PPh₃)₂, Bu₃SnH, AcOH, 100 %; (e) HCHO, NaBH₃CN, AcOH, 95 %; (f) PdCl₂(PPh₃)₂, SnMe₄, LiCl, 83 %; (g) (PhSeO)₂O, 82 %; (h) TBAF, 91 %; (i) Alloc-Cys(CH₂Fl)-OH, EDC-HCl, DMAP, 91 %; (j) DMSO, Tf₂O, –40 °C then i-Pr₂NET, 0 °C then t-BuOH, 0 °C then (Me₂N)₂C=N-t-Bu, then Ac₂O, 79 %.

Scheme 20 illustrates the second method for building the macrolactone ring (blue disconnection) used by Fukuyama et al. Selective protection of the phenol group on the E ring, subsequent hydrolysis of the acetate group then coupling with the L-cysteine derivative, produced 139. Deprotection of the thioether gave the corresponding thiol. The formation of H ring was finally
brought about via a nucleophilic substitution reaction of the secondary alcohol under acidic conditions (Scheme 20).

![Chemical structure](image)

**Scheme 20.** Reagents and conditions (a) Allyl bromide, i-Pr₂NEt, 89 %; (b) K₂CO₃, MeOH, 99 %; (c) EDC·HCl, DMAP, 94 %; (d) NH₂NH₂, 98 %; (e) TFA, CF₃CH₂OH; (f) Ac₂O, pyridine, DMAP, 71 % (2 steps).

Similarly, Zhu and co-workers successfully synthesised the macrolactone H ring as demonstrated in Scheme 21. The product resulting from deprotection of the primary alcohol was coupled with L-cysteine derivative 142. The thioether protecting group was then removed under acidic conditions, and subsequently cyclisation to form the macrolactone H ring occurred (Scheme 21).
Scheme 21. Reagents and conditions (a) $K_2CO_3$, 96 %; (b) EDCI, DMAP, L-cysteine derivative 142, 95 %; (c) TFA, TFE then Ac$_2$O, pyridine, DMAP, 77 %.
Chapter 2 Pummerer reactions

The Pummerer reaction, first reported in 1909 by R. Pummerer, is a reaction of sulfoxides with acid anhydrides involving four main steps (Scheme 22). A thionium ion is generated by treating a sulfoxide bearing an α-hydrogen with acetic anhydride. This thionium ion can then be attacked by a nucleophile (acetate ion) to form Pummerer product (Scheme 22).

Scheme 22

In most cases, the sulfoxide is activated by trifluoroacetic anhydride (TFAA), trifluoromethanesulfonic anhydride (Tf₂O), or a silyl chloride. It was recognised that Lewis acids such as BF₃•OEt₂ may assist intramolecular Pummerer reactions involving carbon π-nucleophiles. The example in Scheme 23 shows that treatment with BF₃•OEt₂ after TFAA triggers Pummerer cyclisation to form the the tetrahydroisoquinoline (Scheme 23).

Scheme 23
A large number of applications of the Pummerer reaction in organic synthesis have been published. The next section in this thesis, will focus on a new type of Pummerer reaction, the connective Pummerer-type reaction recently developed within the Procter group.

2.1 Pummerer-type reactions with thionium ion formation from sulfoxides

2.1.1 Additive Pummerer-type reactions

In the additive Pummerer-type reaction, a vinyl sulfoxide is first activated (for example with TFAA) then a nucleophile attacks the $\beta$-carbon atom to generate a thionium ion 158 which is then reacted with a second nucleophile to form the product 159 (Scheme 24). Reactions in Scheme 25 and results in Table 1 show some example of additive Pummerer-type reaction of isomerically pure substrate 160. The diastereoselectivity of reaction of the E-substrates reversed with those of the Z-substrates. It was suggested that the reason lied on the difference rate between traping of the thionium intermediate by trifluoroacetate and C$_{\alpha}$–C$_{\beta}$ bond rotation.

![Scheme 24](image-url)
2.1.2 Vinylogous Pummerer reactions

Vinyl sulfoxides 162 can also be activated to form extended thionium ions 163. 1,4 or 1,2 Addition of nucleophiles to these extended thionium ions produces 164 or 165 respectively. For example, Padwa successfully synthesised 3-substituted oxindole 169 by activating the sulfoxide 166 with TFAA to presumably give intermediate 167 which then undergoes cyclisation. The organosulfanyl group in the product can be easily removed using Raney nickel to produce 3-phenyl oxindole 169 (Scheme 27).

Scheme 25

<table>
<thead>
<tr>
<th>R</th>
<th>E:Z ratio of 160</th>
<th>Time (mins)</th>
<th>Yield (%)</th>
<th>dr of 161</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Hex</td>
<td>1:0</td>
<td>25</td>
<td>95</td>
<td>1.7:1</td>
</tr>
<tr>
<td>n-Hex</td>
<td>0:1</td>
<td>25</td>
<td>93</td>
<td>1:3.5</td>
</tr>
<tr>
<td>t-Bu</td>
<td>1:0</td>
<td>90</td>
<td>93</td>
<td>1.8:1</td>
</tr>
<tr>
<td>t-Bu</td>
<td>0:1</td>
<td>90</td>
<td>93</td>
<td>1:1.6</td>
</tr>
<tr>
<td>Ph</td>
<td>1:0</td>
<td>60</td>
<td>97</td>
<td>6.3:1</td>
</tr>
<tr>
<td>Ph</td>
<td>0:1</td>
<td>25</td>
<td>96</td>
<td>1:4</td>
</tr>
</tbody>
</table>

Table 1

Scheme 26
2.1.3 Interrupted Pummerer reactions

In the interrupted Pummerer-type reaction, the activated sulfoxide reacts with the nucleophile at sulfur, followed by loss of an alkyl from sulfur group to form the product 173 (Scheme 28). For example, refluxing sulfoxide 175 in toluene in the presence of TFAA produced tricycle 176 in 76% yield (Scheme 29).
2.2 Pummerer-type reactions with thionium ion using alternative methods

Recently, the Procter group successfully developed a new variant of the Pummerer reaction, called the connective Pummerer-type reaction. In this reaction thionium ions (181) are generated by activation of hemithioacetalts (179) that are formed in-situ from the corresponding aldehydes and thiols (Scheme 30).\textsuperscript{69-70} The connective Pummerer-type reaction has some important advantages. For example, the thiol and aldehyde starting materials are widely commercially available and the sometimes difficult preparation of sulfoxides/sulfoxides is not necessary as activated sulfides are essentially prepared \textit{in situ}. Further more, this reaction is very useful in convergent synthesis.

Scheme 30

2.2.1 5-Membered heterocycle formation

A popular application of the connective Pummerer-type reaction is in the formation of oxindole rings. The reaction has been used to produce products 185 by treating glyoxamides 183 with fluorous thiol (C\textsubscript{8}F\textsubscript{17}CH\textsubscript{2}CH\textsubscript{2}SH) then TFAA and BF\textsubscript{3}•OEt\textsubscript{2} (Scheme 31).\textsuperscript{70} Using a thiol bearing a fluorous tag results in a cyclative-capture strategy (phase tag introduction/heterocycle formation). Importantly, the presence of the fluorous tag in the products allows them to be purified efficiently using fluorous silica gel.\textsuperscript{71}
To confirm that the connective Pummerer-type cyclisation reaction proceeds via hemithioacetal formation, a cross-over experiment was carried out as shown in Scheme 32. Hemithioacetals 193 and 196 were prepared separately then mixed for 2.5 hours then treated with TFAA then BF₃·OEt₂ to complete the cyclisation. As a result, oxindoles 194 (68 %) and 197 (80 %) were isolated and no cross-over products were recognised. This reaction confirms that hemithioacetal are the most probable intermediates in the cyclisations and that equilibria between glyoxamides and hemithioacetal lies greatly towards the hemithioacetals. Furthermore, it rules out alternative mechanism involving the cyclisation of glyoxamides followed by thiol addition post cyclisation.
The fluorous-tagged heterocyclic products formed via the connective Pummerer-type cyclisation can be modified in many ways.\textsuperscript{55,71,73-74} For example, Procter and co-workers were successful in preparation analogues of spirotryprostatin A which is an anti-cancer natural product (Scheme 33).\textsuperscript{75} Oxindole 199 was formed from the corresponding glyoxamide 198 subsequently alkylated with 1,4-dichlorobut-2-ene then treated with \(\text{SmI}_2\) triggering tag expulsion and cyclisation to form spirooxindole 200. Pyrrolidinyl-spirooxindole 205 was formed using the \(\text{Sm}(\text{III})\) waste product from the reductive stage of the sequence and imine 203. Pyrrolidinyl-spirooxindole 205 was then converted to 206 subsequently resolution using Troc-(S)-proline. Troc deprotection using Zn and \(\text{NH}_4\text{Cl}\) and subsequently lactamisation produced analogues of spirotryprostatins A (Scheme 33).\textsuperscript{75}
Recently, Procter et al. developed a new synthesis of benzo[b]carbazoles which can be used to produce end-capped oligothiophenes for evaluation as organic semiconductors (Scheme 34). First of all, oxindole 210 was prepared in two steps via the connective Pummerer-type cyclisation, then oxidised to the sulfone and alkylated with 211. Treating 212 with SmI$_2$ triggered tag cleavage and cyclisation followed by aromatisation with $p$-benzoquinone to produce benzo[b]carbazole 213. Pd-catalysed coupling of 213 with several thienyl...
tributyltin coupling partners gave the desired products 214 (Scheme 34). Figure 3 show some examples of organic semiconductor prepared using this scope.
Procter et al. were also successful in improving the scope of the connective Pummerer-type cyclisation using more complex functionalised thiols and glyoxamides.\textsuperscript{77} Similarly, the expected oxindoles were obtained when treating glyoxamides with functionalised thiols (Scheme 35). In addition, the connective Pummerer-type cyclisation could also be carried out in a two-directional manner. This scope can also be applied to prepare alternating copolymers for optical and electrical properties evaluation (Scheme 36).\textsuperscript{78-80}
Scheme 35

Scheme 36
In 2008, the connective Pummerer-type cyclisation was applied to the synthesis of azaspirocyclic cyclohexadienones by Procter et al. (Scheme 37). With symmetrical aryl glyoxamides 230, the cyclisation of the corresponding thionium ions onto the aromatic ring at the ipso-position caused dearomatisation and gave spirocycles 231A – 231E. Further trials with unsymmetric glyoxamides 232 produced the desired products as a mixture of two diastereomers with the anti products 233 predominating (Scheme 38).

Scheme 37

2.2.2 6,7-Membered heterocycle formation

In 2005, Procter et al. reported the synthesis of tetrahydroisoquinoline systems using the connective Pummerer-type reaction (Scheme 39). The glyoxamides
were treated with fluorous thiol then activated by TFAA then BF$_3$OEt$_2$ to yield tetrahydroisoquinolines. However, not many examples of tetrahydroisoquinolines were published using this method and the reaction was far less efficient than the corresponding reaction to form 5-membered rings.

$$\text{R}^1\text{R}^2\text{R}_3\text{R}_4\text{N} - \text{O} \rightarrow 1. \text{RFSH}, \text{CH}_2\text{Cl}_2, \text{RT} \rightarrow 2. \text{TFAA then BF}_3\text{OEt}_2, \text{CH}_2\text{Cl}_2, 0 \degree \text{C to RT} \rightarrow \text{R}^1\text{R}^2\text{R}_3\text{R}_4\text{N} - \text{O}$$

Scheme 39

With the glyoxamide substrates shown in Scheme 40, the connective Pummerer-type cyclisation produced tetrahydrobenzazepinones 243A and 243B in high yield.

$$\text{R}_1\text{R}_2\text{N} - \text{O} \rightarrow 1. \text{RFSH} \rightarrow 2. \text{TFAA then BF}_3\text{OEt}_2 \rightarrow \text{R}^1\text{R}^2\text{N} - \text{O}$$

243A, $R^1 = \text{OMe}, R^2 = H, R^3 = \text{n-Pr}, 76\%$

243B, $R^1 = R^2 = \text{OMe}, R^3 = \text{n-pentyl}, 98\%$

Scheme 40

2.3 Aims and objectives

As previous studies in the group had shown that tetrahydroisoquinolinone formation using the connective Pummerer-type cyclisation could be carried out with the methoxy electron donor groups on the benzyl ring of the
glyoxamides. In this section, we planned to synthesise some substrates (Figure 4) for the following aims:

- Firstly, hydroxyamide 244 and 245 bearing nitrogen electron donor groups were prepared for the connective Pummerer-type cyclisation study. These results show an ability to synthesise analogues of Et. 597 containing nitrogen on the A ring system for biological testing.

- Secondly, an investigation of the connective Pummerer-type cyclisation with the substrates bearing substitution similar to that in the A ring of Et. 597 (246-247) were carried out.

- Thirdly, because the connective Pummerer-type cyclisation could proceed with the hydrate form of the glyoxamides, a protected glyoxamide substrate 248 was therefore prepared for cyclisation study.

- Finally, we also planned to try the connective Pummerer-type cyclisation with simple aldehydes derived from substrates 249 and 250. This type of substrate may vary the methods for the approach to the synthesis of Et. 597 and its analogues.

![Figure 4](image-url)


2.4 Results and discussion

2.4.1 Hydroxyamide synthesis

Our synthetic route to the hydroxyamide 244 is illustrated in Scheme 41. The commercially available starting material, 2-hydroxy-5-methoxybenzaldehyde, was nitrated using nitric acid in acetic acid to produce product 252 in which the nitro group was selectively incorporated at position three of the aromatic ring.\(^8^4\) Compound 252 was converted via reductive amination using \(n\)-propylamine to produce secondary amine 253 in 81% yield over two steps. The acetoxyacetyl branch was attached to the nitrogen atom of secondary amine 253 using acetoxyacetic acid in the presence of hydroxybenzotriazole (HOBt) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI). The acetate group was then hydrolyzed using potassium carbonate in aqueous methanol. The nitro group on hydroxyamide 254 was then reduced with hydrogen gas and Pd/C in 70% yield.\(^8^5\) Dimethylation of the resulting amine group was carried out by reductive amination with formaldehyde and sodium cyanoborohydride.\(^8^6\) Finally, the O-methylation of the hydroxyl group on the aromatic ring was achieved with methyl iodide and sodium carbonate, producing the desired hydroxyamide 244 in 58% yield over two steps.\(^8^7\)
Scheme 41. Reagents and conditions (a) Concentrated HNO$_3$, CH$_3$COOH, 0-15 °C, 80%; (b) n-propylamine, CH$_3$OH, reflux; (c) NaBH$_4$, CH$_3$OH, RT, 81% over two steps; (d) Acetoxyacetic acid, HOBt, EDCI, CH$_2$Cl$_2$, RT; (e) K$_2$CO$_3$, CH$_3$OH:H$_2$O (2:1), RT, 86% over two steps; (f) H$_2$, Pd/C, THF, RT, 70%; (g) HCHO, NaBH$_3$CN, MeCN; (h) MeI, Na$_2$CO$_3$, acetone, reflux, 58% over two steps.

We synthesized the hydroxyamide 245 from the commercially available acid 256 using the pathway depicted in Scheme 42. Esterification of acid 256 with methanol in the presence of sulfuric acid produced the corresponding ester 257 in 82% yield. Then, the two amino groups on the aromatic ring were methylated by reductive amination with formaldehyde. Hydrolysis of ester 258 under basic conditions and then acidification produced acid 259 in 68% yield. This acid was next coupled with n-propylamine in the presence of HOBt and EDCI to give amide 260 which was reduced to the corresponding amine 261 using lithium aluminium hydride. Finally, acetoxyacetic acid was coupled to amine 261 using EDCI and HOBt. Hydrolysis of the acetate group under mild basic conditions produced the desired hydroxyamide 245 (Scheme 42).
Scheme 42. Reagents and conditions (a) CH$_3$OH, concentrated H$_2$SO$_4$, reflux, 82%; (b) HCHO, NaBH$_3$CN, CH$_3$CN, 71%; (c) KOH, C$_2$H$_5$OH then H$_3$O$^+$, 68%; (d) CH$_3$CH$_2$CH$_2$NH$_2$, HOBt, EDCI, CH$_2$Cl$_2$. 96%; (e) LiAlH$_4$, THF; (f) acetoxyacetic acid, HOBt, EDCI, CH$_2$Cl$_2$; (g) K$_2$CO$_3$, CH$_3$OH:H$_2$O (2:1), 70% over three steps.

Hydroxyamide 246, bearing substitution similar to that in the A-ring of Et. 597 was also synthesised for our preliminary investigations (Scheme 43). Methylation of the benzyl alcohol 262 using methanol and catalytic p-TSA gave ether 263 which was then methylated at C-3 of the aromatic ring using n-BuLi and CH$_3$I. Oxidative cleavage of the benzylic methoxy group by DDQ in the presence of water afforded aldehyde 265. In the next step, bromination at C-5 using Br$_2$ produced aldehyde 266. This aldehyde was then methylated using (CH$_3$)$_2$SO$_4$. Phenol 268 was then prepared from aldehyde 267 by Baeyer-Villiger oxidation then hydrolysis of an intermediate ester using K$_2$CO$_3$ in methanol/water. Benzyl protection of the phenol group using benzyl bromide and K$_2$CO$_3$, then treatment with n-BuLi and quenching with DMF produced
aldehyde,\textsuperscript{92} which upon reductive amination with \textit{n}-propylamine then coupling with acetoxyacetyl chloride and hydrolysis of the acetate group gave model hydroxyamide \textbf{246} for our connective Pummerer cyclisation studies (Scheme 43).

\textbf{Scheme 43.} Reagents and conditions (a) MeOH, \textit{p}-TSA, RT, 98%; (b) \textit{n}-BuLi, CH\textsubscript{3}I, -15 °C, 90%; (c) DDQ, H\textsubscript{2}O, RT, 36%; (d) Br\textsubscript{2}, CH\textsubscript{3}COONa, RT, 53%; (e) (CH\textsubscript{3})\textsubscript{2}SO\textsubscript{4}, K\textsubscript{2}CO\textsubscript{3}, RT, 90%; (f) \textit{m}-CPBA, \textit{p}-TSA, 0 °C – RT; (g) K\textsubscript{2}CO\textsubscript{3}, MeOH, H\textsubscript{2}O, RT, 77% (2 steps); (h) C\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}Br, K\textsubscript{2}CO\textsubscript{3}, acetone, reflux; (i) a) \textit{n}-BuLi, −78 °C, b) DMF (j) \textit{n}-propylamine, MeOH, reflux; (k) NaBH\textsubscript{4}, RT, 60% (4 steps); (l) acetoxyacetyl chloride, Et\textsubscript{3}N, RT; (m) K\textsubscript{2}CO\textsubscript{3}, MeOH, H\textsubscript{2}O, RT, 99%.

The hydroxyamide \textbf{247} bearing the PMB protecting group on nitrogen was synthesized from \textbf{270} as illustrated in Scheme 44. Friedel-Crafts acetylation of \textbf{270} produced the corresponding ketone \textbf{271}, which was then treated with \textit{m}-CPBA to provide an intermediate phenyl ester. This ester was hydrolysed by K\textsubscript{2}CO\textsubscript{3} in methanol-water to obtain phenol \textbf{272} in high yield.\textsuperscript{93} Bromination of
272 using bromine under basic conditions (K₂CO₃) proceeded with complete regiocontrol⁹⁴ and methylation using Me₂SO₄ then gave 273.⁸⁴ Aldehyde 274 was prepared by treating 273 with n-BuLi followed by quenching with DMF.⁹² Reductive amination between aldehyde 274 and 4-methoxybenzylamine produced 275 in quantitative yield. This product was finally coupled with acetoxycetyl chloride then methanolysis by K₂CO₃ in methanol-water gave the desired hydroxyamide 247 for evaluation in the Pummerer cyclisation (Scheme 44).

Scheme 44. Reagents and conditions (a) AcCl, TiCl₄, 100 %; (b) m-CPBA, KHCO₃; (c) K₂CO₃, MeOH-H₂O (V/V 1:1), 77 % (2 steps); (d) Br₂, K₂CO₃; (e) Me₂SO₄, K₂CO₃, 61 % (2 steps); (f) a) n-BuLi, −78 °C, b) DMF, 60 %; (g) MeOC₆H₄CH₂NH₂; (h) NaBH₄, 100 % (2 steps); (i) AcOCH₂COCl, Et₃N; (j) K₂CO₃, MeOH-H₂O (V/V 1:1), 96 % (2 steps).
2.4.2 Synthesis of acetal protected glyoxamides

In our group, the acetal protected glyoxamide 248 was prepared from a coupling reaction between the corresponding amine 261 and 2,2-diethoxyacetic acid in the presence of EDCI and HOBT. This acid was synthesised from commercial 2,2-dichloroacetic acid via a substitution reaction with sodium ethoxide in ethanol assisted by microwave irradiation. Amine 261 was prepared as stated in 2.4.1 (Scheme 45).

\[
\begin{align*}
\text{N} & \quad \text{H} \\
\text{261} & \quad \text{EtO} \quad \text{COOH} \\
\text{277} & \quad \text{a} \\
\text{Cl} & \quad \text{COOH} \\
\text{276} & \quad \text{b}
\end{align*}
\]

Scheme 45. Reagents and conditions (a) EDCI, HOBT, CH₂Cl₂, 94%; (b) EtONa, EtOH, MW, 1 h, 90 °C, 91%.

2.4.3 Hydroxyamine substrate synthesis

Alcohol 249 was made from aldehyde 278 as depicted in Scheme 46. Reductive amination between aldehyde 278 and 2-aminoethanol, followed by reductive amination with 4-methoxybenzaldehyde produced the desired product 249 in 40 % overall yield.

\[
\begin{align*}
\text{OMe} & \quad \text{MeO} \\
\text{278} & \quad \text{CHO} \\
\text{249}
\end{align*}
\]

Scheme 46. Reagents and conditions (a) HOCH₂CH₂NH₂, MeOH then NaBH₄; (b) NaBH₃CN, AcOH, 4-methoxybenzaldehyde, MeCN, 40 % (2 steps).
A route was also designed to access the more complex amino alcohol 250. The approach started with esterification of racemic serine under acidic conditions\(^97\), then reductive amination with 3,5-dimethoxybenzaldehyde provided hydroxy amine 280. Secondary amine 280 was then reacted with 4-methoxybenzaldehyde to yield the desired tertiary amine. Protection of the hydroxyl group then reduction of the ester group using LiBH\(_4\) gave alcohol 250 in moderate yield.

Scheme 47. Reagents and conditions (a) SOCl\(_2\), MeOH; (b) 3,5-dimethoxybenzaldehyde, Et\(_3\)N, MeOH then NaBH\(_3\)CN; (c) 4-methoxybenzaldehyde, NaBH\(_3\)CN, AcOH, MeCN; (d) TBDPSCl, imidazole, CH\(_2\)Cl\(_2\); (e) LiBH\(_4\), Et\(_2\)O, MeOH, 41 % (5 steps).

2.4.4 Tetrahydroisoquinoline ring formation using the connective Pummerer-type cyclisation

Cyclisations of glyoxamides

In order to prepare glyoxamides for a study of the connective Pummerer cyclisation reaction, the hydroxyamides were oxidised to produce the glyoxamides which were then used directly in the connective Pummerer
cyclisation without purification. The first trial cyclisation was carried out with glyoxamide 283 as illustrated in Scheme 48.

Scheme 48. Reagents and conditions (a) (COCl)$_2$, DMSO, Et$_3$N, –78 ºC – RT; (b) methyl-3-mercaptopropionate, Lewis acid (ZnCl$_2$ or Sc(OTf)$_3$), CH$_2$Cl$_2$.

In this case, the connective Pummerer cyclisation was carried out with scandium(III) trifluoromethanesulfonate at room temperature. As we expected, the desired Pummerer cyclisation product was formed, albeit in 5% isolated yield over two steps. A trial connective Pummerer cyclisation with zinc chloride as the Lewis acid occurred with a more promising yield of 16%. At that time, we decided to pursue the use of zinc chloride. The results of our optimisation studies are summarized in Table 2. Leaving the reaction for two days at room temperature increased the yield of 284 very slightly from 16% to 21%. This suggested that the rate of this reaction was quite slow. Therefore, we attempted to carry out the reaction at higher temperature by heating at reflux in dichloromethane. Pleasingly, the yield doubled to 40%. An increase in the quantity of thiol used had no impact on yield while increasing the amount of Lewis acid gave higher yields of product (49%). Interestingly, $^1$H NMR spectroscopic analysis of the crude product showed that some glyoxamide still remained. To push the reaction to completion, the temperature of reaction was increased to 60 ºC by heating at reflux in chloroform. Under these conditions, the yield reached 62% (for 2 steps) when 1.5 equivalents of zinc chloride were used. Under these conditions, almost all the glyoxamide starting material was consumed.
<table>
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<td>1.5</td>
<td>16</td>
<td>60 °C</td>
<td>62</td>
</tr>
</tbody>
</table>

Table 2. Optimisation study of step b in Scheme 48

The optimised conditions for the connective Pummerer cyclisation were then applied to cyclisation reactions with alternative thiols as depicted in Scheme 49. The yield obtained over two steps (Swern oxidation and cyclisation) was quite good, 49% yield with a fluorous thiol (C₈F₁₇CH₂CH₂SH) and 57% with cyclohexyl thiol.

Scheme 49. Reagents and conditions (a) (COCl)₂, DMSO, Et₃N, −78 °C; (b) C₈F₁₇CH₂CH₂SH, ZnCl₂ (1.5 eq.), CHCl₃, 60 °C, 49% over 2 steps; (c) cyclohexyl mercaptan, CHCl₃, 60 °C, 57% over 2 steps.
The Pummerer cyclisation with substrate 244 was also carried out with N-Troc L-cysteine methyl ester. A good yield of 50% Pummerer product 287 was obtained. No diastereoselectivity was seen and a 1:1 mixture of diastereoisomeric products was obtained (Scheme 50).

Scheme 50. Reagents and conditions (a) (COCl)$_2$, DMSO, Et$_3$N, $-78$ °C to RT; (b) N-Troc L-cysteine methyl ester, ZnCl$_2$ (1.5 equivalents), 60 °C, 16 h, 50 %.

First trial oxidation of hydroxyamide 245 using Swern reagents produced products in which the aromatic ring was chlorinated. To eliminate this problem, Parikh-Doering oxidation$^{98}$ was applied on hydroxyamide 245, then the resulting glyoxamide reacted with thiol, catalysed by Lewis acid to produce product 289 (Scheme 51). The best result (41 % over two steps) was obtained when the oxidation step was carried out twice before the cyclisation step. With these results, it was shown for the first time that the connective Pummerer-type cyclisation can be carried out with dimethylated amino groups on the benzene ring.

Scheme 51. Reagents and conditions (a) SO$_3$-Py, DMSO, Et$_3$N, CH$_2$Cl$_2$; (b) ZnCl$_2$, HSCH$_2$CH$_2$COOCH$_3$, 60 °C, 41 % (2 steps).
The Pummerer reaction was also investigated using substrates bearing a benzene ring resembling the A ring of Et. 597. Firstly, the hydroxyamide was oxidized using ether Parikh-Doering or Swern oxidation conditions to produce the corresponding glyoxamide. The glyoxamide was treated with a suitable thiol and Lewis acid, triggering the connective Pummerer cyclisation to form a model AB ring system. Scheme 52 shows one example of tetrahydroisoquinoline 291 formation from hydroxyamide 246. The glyoxamide 290, as a mixture of aldehyde and the corresponding hydrate, was used directly in the next step without any purification. Two Lewis acids (ZnCl$_2$ and Sc(OTf)$_3$) were trialled for use in the connective Pummerer cyclisation of this substrate. The results showed that ZnCl$_2$ did not promote the reaction while Sc(OTf)$_3$ triggered cyclisation to produce 291A (R = H) in 23 – 28 % yield with traces of 291B (R = Bn) also obtained. We proposed that the yield of this reaction is related to the amount of the hydrate form of the glyoxamide: hemithiolacetal formation may be more difficult from the hydrate form of the glyoxamide. Drying the glyoxamide 290 by heating under high vacuum resulted in dehydration to give aldehyde form which was characterised by $^1$H NMR spectroscopy (Appendix 1). We found that drying the glyoxamide at 75 °C under high vacuum, then cyclisation with thiol in the presence of Sc(OTf)$_3$ gave 291A and 291B in 35 % and 20 % yields respectively. The presence of Lewis acid and thiol may cause the removal of the benzyl group in this case (Scheme 52).

![Scheme 52](image)

**Scheme 52.** Reagents and conditions (a) SO$_3$-Py, DMSO, Et$_3$N, CH$_2$Cl$_2$ or (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, –78 °C, then dried under high vacuum at 75 °C, 5 h; (b) HSCH$_2$CH$_2$COOCH$_3$, Lewis acid, 60 °C, MeCN
To simplify the study, the cyclisation was attempted with substrate 247 bearing a methyl rather than benzyl ether. The conditions developed for the cyclisation of 290 were applied in this case. However, in this case the highest yields were obtained when the glyoxamide was dried at quite high temperature (90 °C) before treatment with thiol and Lewis acid (Scheme 53).

Scheme 53. Reagents and conditions (a) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, −78 °C then dried at 90 °C for 2 hours under high vacuum; (b) thiol, Sc(OTf)$_3$, CH$_2$Cl$_2$, 60 °C, 60% (R = H, 14 hours), 53% (R = NHTroc, 17 h).

Cyclisations using an acetal-protected glyoxamide

Our previous studies section (0.0.0) showed that the connective Pummerer-type cyclisation can be performed with the hydrate form of the glyoxamide. Therefore, we planned to attempt Pummerer cyclisations using acetal-protected glyoxamides. The reaction was carried out as depicted in Scheme 54. The first trial of this reaction with zinc chloride as the Lewis acid gave none of the desired product 294. However, Sc(OTf)$_3$ (1 eq.) mediated the reaction and the desired product was obtained in 37 % yield. Unfortunately, attempt to optimise the process led to no improvement in yield.
Scheme 54. Reagents and conditions (a) HSCH$_2$CH$_2$COOCH$_3$, Lewis acid, CH$_3$CN, 80 °C, 37 %.

Cyclisation of simple aldehydes

In our group, the connective Pummerer cyclisation has only ever been carried out on glyoxamide substrates. However, to improve the scope of this reaction, it was desirable to try the cyclisation with simple aldehydes. The first trial was carried out with the model substrate 249 illustrated in Scheme 55. The amino alcohol 249 was first oxidised smoothly under standard Swern conditions to produce the corresponding aldehyde 295 which was then treated with thiol, TFAA and Lewis acid (BF$_3$•OEt$_2$) to produce the desired product 297 in 67 % yield.

Scheme 55. Reagents and conditions (a) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, −78 °C; (b) HSCH$_2$CH$_2$COOCH$_3$, CH$_2$Cl$_2$, RT; (c) TFAA, CH$_2$Cl$_2$, 0 °C to RT then BF$_3$•OEt$_2$, 0 °C to RT, 67 % (over 3 steps).
The connective Pummerer cyclisation was then attempted with an \(\alpha\)-substituted aldehyde \(298\) as illustrated in Scheme 56. The Swern oxidation of amino alcohol \(250\) was carried out smoothly to give \(298\). The aldehyde \(298\) was then reacted with thiol to form the hemithioacetal \textit{in situ} to which was then added TFAA, and then BF\(_3\)•OEt\(_2\) to yield the desired product \(299\) in 56% yield, as a mixture of diastereoisomers (dr \(\sim 2:1\)).

\[
\text{OMe OH} \quad \text{OTBDPS} \quad \text{a}\]
\[
\begin{array}{c}
\text{MeO} \\
\text{Me} \\
\text{N-PMB (rac-250)}
\end{array}
\begin{array}{c}
\text{OMe} \\
\text{Me} \\
\text{N-PMB (298)}
\end{array}
\begin{array}{c}
\text{MeO} \\
\text{Me} \\
\text{S-COMe} \\
\text{N-OTBDPS (299)}
\end{array}
\]

\textbf{Scheme 56.} Reagents and conditions (a) \((\text{COCl})_2, \text{DMSO, Et}_3\text{N, CH}_2\text{Cl}_2, -78\degree\text{C to RT}}; (b) HS\text{CH}_2\text{CH}_2\text{COOMe, CH}_2\text{Cl}_2, \text{RT}}; (c) TFAA, \text{CH}_2\text{Cl}_2, 0\degree\text{C – RT, 3 hours then BF}_3\cdot\text{OEt}_2, 0\degree\text{C – RT, 3 hours, CH}_2\text{Cl}_2, 56\%, \text{dr }\sim 2:1 \text{ (over 3 steps).}

In conclusion, the connective Pummerer-type cyclisation has been successfully carried out with both glyoxamide and simple aldehyde substrates (Figure 5). Conditions used for the connective Pummerer-type cyclisation were different with glyoxamide and aldehyde substrates. In the case of simple aldehyde substrates, the cyclisation required the conditions of previous thiol substrates, TFAA and BF\(_3\)•OEt\(_2\) to get a good yield. However, with glyoxamide substrates, only a Lewis acid (ZnCl\(_2\) or Sc(OTf)\(_3\)) and a thiol were needed for the cyclisation. It was recognised that substrates with two dimethylated nitrogen groups on aromatic rings had lower yields of cyclisation than the others.
Figure 5. Summary of products formed by the connective Pummerer-type cyclisation from corresponding glyoxamides and simple aldehydes
Chapter 3 Our first generation approach to Et. 597

3.1 Retrosynthetic analysis

Our strategy for the synthesis of Et. 597 is demonstrated in Scheme 57. The disconnection of two bonds in rings C and D gives a substrate 300 containing aldehyde and secondary amine groups. Further disconnection of the amide
bond produces two components, an ABH ring aldehyde system 302 and an acid component 301. The aldehyde group can be formed from the corresponding ABH ring system 303 by homologation of the amide carbonyl. We envisaged that ring H could be then formed via macrolactonisation of the corresponding hydroxy acid 304. Finally, we aimed to form the AB ring system from the glyoxamide 306 and thiol 305, using a connective Pummerer-type cyclisation.

3.2 AB ring system formation

In our group, a model AB ring system of Et. 597 has been shown to be accessible from the corresponding hydroxyamide 314, which was synthesised as depicted in Scheme 58. Styrene 308 was first prepared from the corresponding aldehyde 307 by Wittig reaction in good yield. In the following step, the Sharpless aminohydroxylation reaction was carried out to convert this styrene to aminoalcohol 309 in moderate yield (97 % ee). Boc deprotection using TFA produced hydroxyamine 310 in excellent yield. Next, TBS protection was carried out on the free OH group followed by reductive amination of silyloxyamine 311 with 4-methoxy-benzaldehyde in the presence of sodium cyanoborohydride to give protected hydroxyamine 312. Finally, acetoxyacetic acid was coupled with this amine, followed by hydrolysis of the acetate ester under mildly basic conditions, to produce hydroxyamide 314.
Scheme 58. Reagents and conditions (a) Methyltriphenylphosphonium bromide, t-BuOK, 92 %; (b) t-BuOCl, K₂OsO₂(OH)₄, (DHQD)₂PHAL, BocNH₂, 67 %, 97 % ee; (c) TFA, 91 %; (d) TBSCI, DMAP, Et₃N, 50 %; (e) 4-methoxybenzaldehyde, NaBH₃CN, CH₃COOH, 80 %, (f) Acetoxyacetic acid, EDCI, HOBt; (g) K₂CO₃, 87 % over 2 steps.

Glyoxamide 315 was prepared by Swern oxidation of the corresponding hydroxyamide 314 and was used immediately in the connective Pummerer cyclisation. ¹H NMR analysis of the crude product showed formation of the desired Pummerer product. Purification by column chromatography gave the desired product 316 (dr ~ 8:1) in 18 % yield and by-product 317 (dr ~ 2.5:1) in 38 % yield. In this case, the diastereomeric ratio was based on the isolated yield of products because the crude ¹H NMR was very complex. However, an attempt to confirm the stereochemistry of the major diastereoisomer of these products by NOE spectroscopy was unsuccessful.
Scheme 59. Reagents and conditions (a) (COCl)$_2$, DMSO, Et$_3$N, $-78\, ^\circ$C to RT; (b) $N$-Troc L-cysteine methyl ester, ZnCl$_2$ (1.0 eq.), CH$_2$Cl$_2$, RT.

It was believed that the by-product 317 was formed due to the Swern oxidation step. The mechanism of formation of the by-product 317 was proposed as depicted in Scheme 60. The sulfide 318 which was a by product of the Swern oxidation reacted with glyoxamide 315 to produce hemithioacetal 319 which could react with nucleophile (such as Cl$^-$) to form hemithioacetal 320. Finally, intramolecular cyclisation of thionium 321 produced compound 317 (Scheme 60).

Scheme 60
In order to eliminate the by-product 317 that may result from dimethylsulfide contamination after the Swern oxidation, Parikh-Doering oxidation conditions were used to prepare the glyoxamide 315 which was then cyclised with N-Troc L-cysteine methyl ester to form the desired product 316 (Scheme 61). The $^1$H NMR spectroscopic analysis of crude product showed a mixture of 2 diastereomers with dr 1.3:1. The isolated yield of product 316 was greatly improved (57% over 2 steps).

Scheme 61. Reagents and conditions (a) SO$_3$-Py, DMSO, Et$_3$N, CH$_2$Cl$_2$, 0 °C – RT, 20 hours; (b) N-Troc L-cysteine methyl ester, ZnCl$_2$ (1 equiv.), CHCl$_3$, RT, 17 hours.

In order to improve the yield and reproducibility of the key step for the synthesis of larger quantities of enantiomERICALLY enriched 323, another approach was investigated as shown in Scheme 62. Dihydroxylation of the styrene, then protection of the primary alcohol, followed by Misunobu reaction was carried out. The enantiomerically enriched hydroxyamide 325A was then prepared using a similar method as that described above.
Scheme 62. Reagents and conditions (a) AD-mix-α, t-BuOH, H₂O; (b) TIPSCI, imidazole, CH₂Cl₂, 83 % (2 steps); (c) (Ph)₃P, DEAD, phthalimide, THF, 57 %; (d) (NH₂)₂, EtOH, 86 % (85 % ee); (e) 4-methoxy-benzaldehyde, MeOH; (f) NaBH₄, MeOH, 86 % (2 steps); (g) AcOCH₂COCl, Et₃N, CH₂Cl₂; (h) K₂CO₃, MeOH, H₂O, 99 % (2 steps).

Our previous work on the simple substrate showed that the connective Pummerer cyclisation worked better with dried glyoxamide. Therefore, this method was applied to the substrate 325A illustrated in Scheme 63. The results showed that drying the glyoxamide 326A before the cyclisation step produced product 327A (dr 1:1) in 65 % yield after reaction with HSCH₂CH₂COOMe. However, a trial reaction with complex thiol 328 gave the desired product 329 (dr 1.4:1) along with the unwanted product 330, which could be formed from background intramolecular cyclisation of the glyoxamide, catalysed by Lewis acid.
Scheme 63. Reagents and conditions (a) \( \text{SO}_3^{-}\text{pyridine}, \text{DMSO}, \text{Et}_3\text{N}, \text{CH}_2\text{Cl}_2, 0 ^\circ\text{C}\) to RT, 20 hours, then dried at 90 \( ^\circ\text{C}\) for 3 hours; (b) \( \text{HSCH}_2\text{CH}_2\text{COOMe} \) (1 eq.), \( \text{ZnCl}_2 \) (1 eq.), \( \text{CH}_2\text{Cl}_2 \), RT, 18 hours; (c) \( \text{ZnCl}_2 \) (1 eq.), \( \text{CH}_2\text{Cl}_2 \), RT, 17 hours.

The connective Pummerer-type cyclisation was also evaluated with a substrate containing a different protecting group on nitrogen (a DMB group) as shown in Scheme 64. The hydroxyamide 325B was prepared using a similar route to that described above. Oxidation of the hydroxyamide produced the corresponding glyoxamide, which was then dried under high vacuum at 50 \( ^\circ\text{C}\) then trapped with \( \text{HSCH}_2\text{CH}_2\text{COOMe} \). Pleasingly, \( \text{ZnCl}_2 \) catalysed the cyclisation, giving the desired product 327B (dr 1.3:1) in moderate yield (51\% for 3 steps).
Scheme 64. Reagents and conditions (a) 2,4-dimethoxybenzaldehyde, MeOH, reflux, 10 hours, then NaBH₄, 0 °C – RT, 1 hour, 89 %; (b) acetoxyacetyl chloride, Et₃N, CH₂Cl₂, 0 °C – RT, 5 hours; (c) K₂CO₃, MeOH, H₂O, RT, 14 hours, 70 % (2 steps); (d) SO₃-Py, DMSO, Et₃N, CH₂Cl₂, 0 °C to RT, 16 hours, then dried at 50 °C for 1 hour; (e) HSCH₂CH₂COOMe, CH₂Cl₂, RT, 16 hours; (f) ZnCl₂, CH₂Cl₂, RT, 20 hours, 51 % (3 steps).

We then tried to synthesise the AB ring of Et. 597. Firstly, the enantiomerically enriched hydroxyamide 334 was prepared. Styrene 331 was synthesised from aldehyde 274 by Wittig reaction with excellent yield.¹⁰⁴ The stereocentre was introduced by asymmetric dihydroxylation of the styrene, then the primary alcohol was selectively protected using either TIPSCI or TBDPSCI (Scheme 65).¹⁰⁵-¹⁰⁶ Conversion of secondary alcohol to amine 332 was carried out by Mitsunobu reaction with diphenylphosphoryl azide, gave an intermediate azide which was then reduced by triphenylphosphine¹⁰⁷ to give amine 332 with good yield and excellent enantiomeric excess (94 – 95 % ee).¹⁰⁸ This amine was protected by reductive amination with PMB-aldehyde then coupled with acetoxyacetyl chloride, followed by hydrolysis under basic conditions to produce hydroxyamide 334 (Scheme 66).
Scheme 65. Reagents and conditions (a) CH$_3$P(Ph)$_3$Br, t-BuOK, 96 %; (b) AD-mix-$\alpha$, t-BuOH, H$_2$O; (c) TIPSCI (or TBDPSCI), imidazole; (c) PPh$_3$, DIAD, DPPA, THF; (d) (Ph)$_3$P, THF, H$_2$O, 61 % (4 steps, P = TIPS, 95 % ee), 50 % (4 steps, P = TBDPS, 94 % ee).

Scheme 66. Reagents and conditions (a) MeOC$_6$H$_4$CHO, MeOH then NaBH$_4$, 86 % (P = TIPS), 100 % (P = TBDPS); (b) AcOCH$_2$COCl, Et$_3$N, CH$_2$Cl$_2$; (c) K$_2$CO$_3$, MeOH-H$_2$O, 91 % (P = TIPS), 92 % (P = TBDPS).

In order to determine the enantiomeric excess of amine 332, racemic amine 332 was prepared as illustrated in Scheme 67.$^{109-110}$ Styrene 331 was first dihydroxylated$^{109}$ then selective protection of the primary alcohol and Mitsunobu reaction gave the desired amines rac-332A and rac-332B. The enantiomeric purity of amines prepared by asymmetric dihydroxylation was determined by chiral-HPLC analysis of the enantiomerically enriched amines and racemic amines.
Scheme 67. Reagents and conditions (a) NaIO₄, LiBr, AcOH; (b) K₂CO₃, MeOH, H₂O; (c) Imidazole, TIPSCl, 55 % (3 steps); (d) Ph₃P, phthalimide, DIAD; (e) hydrazine, 28 % (2 steps); (f) Imidazole, TBDPSCI, 54 % (3 steps); (g) Ph₃P, DIAD, DPPA; (h) Ph₃P, H₂O, 60 °C, 56 % (2 steps).

The Pummerer cyclisation was attempted with the A-ring substrate 334A illustrated in Scheme 68. The cyclisation reaction was attempted at room temperature and at 60 °C. At 60 °C, 4 % of the desired product 335B was produced, accompanied by 38 % of the product 335A (dr 1:1) without a protecting group on the alcohol, while at room temperature, the yield was much lower (trace of desired product 335B and 6 % of deprotected product 335A). Presumably, the TIPS group was removed due to the acidic conditions of the Pummerer reaction. Therefore, we decided to try the reaction with another protecting group (TBDPS), which is considered as having increased acid tolerance¹⁰⁰ (Scheme 69). Table 3 shows the results of reactions at different temperatures. Pleasingly, the amount of deprotected product 335A decreased significantly and the desired product 335C (dr 1:1) was obtained in moderate yield. In addition, at room temperature, the majority of the product was hemithioacetal while at high temperature, only the Pummerer cyclisation product was obtained.
Scheme 68. Reagents and conditions (a) \( \text{SO}_3 \)-pyridine, DMSO, \( \text{Et}_3\text{N} \), \( \text{CH}_2\text{Cl}_2 \), 0 °C to RT, then dried at 60 °C; (b) \( \text{HSCH}_2\text{CH}_2\text{COOMe} \), \( \text{Sc(OTf)}_3 \), \( \text{CH}_2\text{Cl}_2 \).

Scheme 69. Reagents and conditions (a) \( \text{SO}_3 \)-pyridine, DMSO, \( \text{Et}_3\text{N} \), \( \text{CH}_2\text{Cl}_2 \), 0 °C to RT then dried at about 35 °C under high vacuum; (b) \( \text{HSCH}_2\text{CH}_2\text{COOMe} \), \( \text{Sc(OTf)}_3 \), \( \text{CH}_2\text{Cl}_2 \).

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<thead>
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Table 3. Conditions and results of the reaction in Scheme 69

In addition, the formation of the by-product 330 (Scheme 63) suggested that the Pummerer product 329 might partly arised from a substitution of intermediate 330 with thiol 328, catalysed by Lewis acid. Therefore, to ensure that the Pummerer cyclisation occurs completely via hemithioacetal formation, the Pummerer cyclisation process starting from the corresponding hydroxyamide was carried out in 3 discrete steps: oxidation, hemithioacetal formation, then Pummerer cyclisation.
The first trial Pummerer cyclisations were carried out with the substrate illustrated in Scheme 70, and the results and conditions are summarized in Table 4. In all cases, some degree of TIPS deprotection was observed to afford a free OH group, which cyclised with the glyoxamide to produce by-product 336. This side reaction was considered as the reason for the low yields of Pummerer cyclisation products (335A and 335B). An additional trial in which the amount of Lewis acid was reduced gave similar results. Therefore, it was necessary to carry out the reaction with the more stable protecting group (TBDPS) as illustrated in Scheme 71. Under optimum conditions, the glyoxamides were dried under mild conditions (~ 35 °C under high vacuum) until the aldehyde peak appears with the desired intensity (by 1H NMR spectroscopy; see Appendix 1). Pleasingly, the yield of Pummerer products 338 and 335C increased to 84 % and 71 %, respectively.

Scheme 70. Reagents and conditions (a) SO3-pyridine, DMSO, Et3N, CH2Cl2, 0 °C to RT then dried at 60 °C under high vacuum (~ 2 hours); (b) HSCH2CH2COOMe, CH2Cl2, RT; (c) Lewis acid.
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<td></td>
<td></td>
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Table 4. Conditions and results of the reaction (c) shown in Scheme 70

Scheme 71. Reagents and conditions (a) SO₃-pyridine, DMSO, Et₃N, 0 °C to RT then dried at about 35 °C under high vacuum; (b) HSCH₂CH₂COOMe, CH₂Cl₂, 16 hours, RT; (c) Sc(OTf)₃, CHCl₃, 60 °C, 18 hours, 71 % (3 steps); (d) thiol 328, CH₂Cl₂, 16 hours, RT; (e) Sc(OTf)₃, CH₂Cl₂, 40 °C, 17 hours, 84 % (3 steps).

3.3 ABH ring formation

Our strategy for the synthesis of the ABH ring system involves the formation of the H ring from the corresponding AB ring system using a macrolactonisation reaction. To do this, the silicon protecting group was removed, then the ester group on the thioether branch was hydrolysed under basic conditions as shown
in Scheme 72. Starting material 327 used in this scheme was a mixture of 2 diastereomers. Epimerisation occurred during silyl ether deprotection and ester hydrolysis to give a stable cis diastereoisomer 340 (Figure 7), the structure of 340A was confirmed by X-ray crystallography.\textsuperscript{82} Pleasingly, treating this product with 2-methyl-6-nitrobenzoic anhydride (MNBA) and 4-(dimethyl-amino)-pyridine (DMAP)\textsuperscript{111} afforded the desired H ring system 341 in good yield.

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme72.png}
\caption{Reagents and conditions (a) TBAF, RT, THF, 66 %; (b) K\textsubscript{2}CO\textsubscript{3}, MeOH/H\textsubscript{2}O, RT, 100 %; (c) MNBA, DMAP, CH\textsubscript{2}Cl\textsubscript{2}, RT.}
\end{scheme}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{fig6.png}
\caption{X-ray structure of compound 340A.}
\end{figure}
Figure 7

The ABH-ring system of Et. 597 was next introduced as illustrated in Scheme 73. The TBDPS deprotection reaction was performed on the starting material existing as a mixture of 2 diastereomers. The first trial, using TBAF, gave a low yield of product. The best yield was obtained when a mixture of HF and pyridine was used. Analysis of the products by $^1$H NMR showed that there was only one diastereomer produced. Pleasingly, hydrolysis of the methyl ester group, followed by macrolactonisation produced the desired ABH ring products in good yield.

Scheme 73. Reagents and conditions (a) HF, pyridine, MeCN, 0 °C to RT, 61 %; (b) K$_2$CO$_3$, MeOH, H$_2$O, RT, 73 %; (c) MNBA, DMAP, CH$_2$Cl$_2$, RT, 72 %.
3.4 Towards the synthesis of Et. 597

With the ABH ring system successfully synthesised, we next proposed to reduce the amide carbonyl, then homologate the hemiaminal using addition of TMSCN, followed by selective reduction of the cyanide group to the aldehyde (Scheme 74)

Scheme 74

We made many attempts to reduce the amide carbonyl of the ABH ring systems (Scheme 75), using DIBAL-H and super hydride reagents. However, varying the concentration of reagents and the temperature of the reactions gave no desired product.

Scheme 75
We believed that the difficulty experienced with the reduction of the amide carbonyl was caused by the lack of an electron withdrawing group on nitrogen. Therefore, a substrate with an electron withdrawing group on nitrogen was prepared as depicted in Scheme 76 and Scheme 77.

Scheme 76. Reagents and conditions (a) HF (aq.), MeCN, 0 °C – RT; (b) PhCHO, CH$_2$Cl$_2$, reflux; (c) acryloyl chloride, Et$_3$N, CH$_2$Cl$_2$, 0 °C to RT, 56 % (unknown major diastereoisomer, 3 steps); (d) OsO$_4$, NMO, H$_2$O, acetone; (e) NaIO$_4$, H$_2$O, THF, reflux then dried at 70 °C for 2 hours; (f) HSCH$_2$CH$_2$COOMe, CH$_2$Cl$_2$, RT; (g) TFAA, CH$_2$Cl$_2$ then BF$_3$·OEt$_2$, 0 °C – RT, 50 % (358), 17 % (359).

Deprotection of silyl ether 332A then protection of both alcohol and amine groups by oxazolidine ring formation with benzaldehyde gave 354 which was then coupled with acryloyl chloride to produce alkene 355 (dr 7:1). The glyoxamide 357 was formed successfully after dihydroxylation of the alkene 355 then oxidative cleavage of the diol. The cyclisation substrate was then dried at 70 °C for 2 hours under high vacuum before treatment with the corresponding
thiol, to generate the hemithioacetal. The Pummerer cyclisation was attempted using the previously developed conditions (Sc(OTf)$_3$ and ZnCl$_2$), but unfortunately gave the desired product 358 in low yield. Pleasingly, the cyclisation using an alternative set of conditions used elsewhere in the Procter group (activation by TFAA then triggering cyclisation with BF$_3$•OEt$_2$) produced the desired product 358 in 50 % yield (dr 1:1). In addition, by-product 359 was also obtained in 17 % yield due to oxazolidine ring opening by corresponding thiol. It was observed that oxazolidine ring deprotection of a single diastereoisomer 358 proceeded readily under acidic conditions (TFA). Silyl ether protection of the resulting alcohol, then protection of the nitrogen with CBzCl was carried out to produce the desired substrate 362 (Scheme 77).

\[ \text{Scheme 77. Reagents and conditions (a) TFA, CH}_{2}\text{Cl}_2, \text{RT, 80 %; (b) TBSCl, imidazole, CH}_{2}\text{Cl}_2, \text{RT, 58 %; (c) } n-\text{BuLi, THF, } -78 \, ^\circ\text{C then CBzCl, } -78 \, ^\circ\text{C to RT, 75 %.} \]

Attempts to reduce the activated amide carbonyl of substrate 362 were made using DIBAL-H and superhydride reagents (Scheme 78). However, the reduction of the carbamate carbonyl was observed rather than the amide carbonyl (70 – 80 % yield).
In conclusion, the model and actual AB ring systems of Et. 597 were successfully formed using connective Pummerer-type cyclisations from corresponding glyoxamides in good yield (∼ 50 – 80 %). Pleasingly, hydrolysis of the esters produced the hydroxyacids with cis configuration. The H ring was then formed nicely from these hydroxyacids in 58 – 72 % yield. However, attempts to reduce the amide carbonyl of the ABH ring systems in both the model and actual systems failed. Efforts to reduce the amide carbonyl when containing a electron withdrawing group on nitrogen gave similar results.

Scheme 78
Chapter 4 Alternative approaches to Et. 597

With the problem of homologation of the amide carbonyl in our first approach to Et. 597, we decided to investigate some alternative approaches for the synthesis of Et. 597.

4.1 Second approach

4.1.1 Retrosynthetic analysis

Scheme 79
Similar to the first approach, Et. 597 was disconnected to the ABH ring system (Scheme 79). Disconnections show that the H ring can be formed via macrolactonisation of the corresponding hydroxy acid of 366. The big difference in this case lies in the key step of our synthesis to form the AB ring system. It is proposed that the AB ring system can be formed from the reaction of aldehyde 367 with thiol to form a hemithioacetal which is then activated for cyclisation. Please note, to date our studies on connective Pummerer-type cyclisations have always involved glyoxamides bearing activated aldehydes. Our proposed studies therefore represent the first attempts to use a “simple” aldehyde in the cyclisation. The R group in 367 would be a group that can be converted to the required aldehyde.

4.1.2 Results and discussion

The synthesis of product 374 began with starting material 323 as shown in Scheme 80. Reductive amination with ketone 369 - which was made from (S)-1,3,4-trihydroxybutan-2-one\(^{112}\) - produced alcohol 370 as a separable 1:1 mixture of two diastereoisomers. A single diastereoisomer 370 was oxidised by Swern reaction to produce the corresponding aldehyde 371 as a single diastereoisomer. Pleasingly, the connective Pummerer cyclisation was then carried out efficiently to produce the AB ring product 372 as a mixture of 2 diastereoisomers with dr 3:1 at the newly-formed benzylic stereocentre.

Compound 373 was prepared from the commercially available, (S)-2-amino-3-(3,4-dihydroxy-phenyl) propanoic acid (L-DOPA) (Scheme 81). Firstly, Boc protection of the primary amine was carried out with Boc\(^2\)O, then the acid and phenol moieties were methylated using Me\(_2\)SO\(_4\) under basic condition.\(^{113}\) Methylation on nitrogen was then carried out by using NaH and Mel,\(^{114}\) followed by hydrolysis of the ester group to produce 373. Acid 373 was then finally coupled with a single diastereomer 372 to give product 374 in moderate yield.
Scheme 80. Reagents and conditions (a) NaBH₃CN, MgSO₄, MeOH, RT, 53 %; (b) separation of diastereoisomers by chromatography, (COCl)₂, DMSO, Et₃N, CH₂Cl₂, −78 °C to RT; (c) HSCH₂CH₂COOME, CH₂Cl₂, RT, 1 h then TFAA, RT, 1 h then BF₃•OEt₂, 58 % (2 steps); (d) separation of diastereoisomers by chromatography, EDCI, HOBT, 373, CH₂Cl₂, 52 %.
Scheme 81. Reagents and conditions (a) Boc₂O, Et₃N, dioxane/H₂O, 0 °C – RT; (b) Me₂SO₄, K₂CO₃, acetone, reflux, 98 % (2 steps); (c) NaH, MeI, DMF, RT; (d) K₂CO₃, MeOH/H₂O, RT, 97 % (2 steps).

Oxidative cleavage of diol 374 to give the required aldehyde was attempted as depicted in Scheme 82. Two sets of reagents, NaIO₄ and Pb(OAc)₄ were trialled.¹¹⁵-¹¹⁶ In the case of NaIO₄, the reaction was carried out at 0 °C to room temperature. TLC and ¹H NMR analysis of the crude product mixture showed starting material remaining, with a trace of aldehyde and impurities also present. Leaving the reaction longer and heating the reaction increased the amount of impurities. The next trial of the oxidative cleavage reaction with Pb(OAc)₄ showed no improvement. At low temperature (−30 °C to 0 °C), TLC and ¹H NMR analysis of the crude product mixture showed starting material remaining plus traces of aldehyde and impurities. Leaving the reaction to warm to room temperature caused decomposition of all starting material.
We believed that the oxidation of alcohol 386 (Scheme 87) would produce the corresponding aldehyde for a Pictet Spengler cyclisation. Therefore, the reductive amination between the symmetric ketone (1,3-dihydroxypropan-2-one) and amine 323 was carried out to produce amine 379 in 69 % yield (Scheme 83). Oxazolidine ring formation to protect the hydroxyl group and secondary amine group gave only two diastereomers 380A and 380B. Interestingly, we found that epimerisation occurred to give a 1:1 mixture of 380A and 380B when stirring any single diastereomer in CHCl₃ overnight. To investigate whether the two diastereomers 380A and 380B were formed by reaction of the same hydroxyl group in oxazolidine ring formation, the diastereomers 380A and 380B were separated by column chromatography. The hydroxyl group of each diastereomer was then protected using TIPSCI and the oxazolidine ring was opened to produce the corresponding alcohols 382A as demonstrated in Scheme 84 and 382B in Scheme 85. Full characterisation of 382A and 382B showed them to be different suggested the diastereoisomeric mixture of oxazolidine 380A and 380B arises from the participation of different diastereotopic hydroxyl groups in the oxazolidine formation. The stereochemistry of 380B was decided via products in 4.2.2.

Scheme 83. Reagents and conditions (a) 1,3-dihydroxypropan-2-one, NaBH₃CN, MgSO₄, MeOH, RT, 69 %; (b) PhCHO, MgSO₄, toluene, reflux, 64 %.
Scheme 84. Reagents and conditions (a) TIPSCI, imidazole, CH\textsubscript{2}Cl\textsubscript{2}, RT, 63 %; (b) TFA, CH\textsubscript{2}Cl\textsubscript{2}, RT, 80 %.

Scheme 85. Reagents and conditions (a) TIPSCI, imidazole, CH\textsubscript{2}Cl\textsubscript{2}, RT, 58 %; (b) TFA, CH\textsubscript{2}Cl\textsubscript{2}, RT, 75 %.

The single diastereomer 380A was oxidised to the aldehyde 383A. This intermediate was then treated with HSCH\textsubscript{2}CH\textsubscript{2}COOMe, to form the hemithioacetal, TFAA was added, followed by BF\textsubscript{3}-OEt\textsubscript{2} to trigger the connective Pummerer-type cyclisation. Product 384 (dr 5:1) was formed in which the oxazolidine ring had been cleaved under the Pummerer reaction conditions.
Coupling with compound 385\textsuperscript{117-118} was carried out with EDCI and HOBt to produce the expected product 386 in moderate yield (Scheme 87).

Scheme 86. Reagents and conditions (a) COCl\textsubscript{2}, DMSO, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, −78 °C to RT; (b) CH\textsubscript{2}Cl\textsubscript{2}, HSCH\textsubscript{2}CH\textsubscript{2}COOMe, RT then TFAA, 0 °C to RT then BF\textsubscript{3}•OEt\textsubscript{2}, RT, 61 %.

Scheme 87. Reagents and conditions (a) TBSCI, DBU, MeCN, RT, 55 %; (b) EDCI, HOBt, 384 (single diastereoisomer), CH\textsubscript{2}Cl\textsubscript{2}, 50 %.

In conclusion, the model AB ring systems of Et. 597 were successfully prepared by using the connective Pummerer-type cyclisation from the simple aldehyde substrates. The AB ring system was then coupled nicely with the E ring system (compound 373 and 385) to produce the desired product. However, it was
difficult to carry out an oxidative cleavage of diol 374 for C and D ring formation. Therefore, the alcohol 386 was prepared successfully for future oxidation.

4.2 Third approach

4.2.1 Retrosynthetic analysis

Scheme 88

An modified approach to synthesis of Et. 597 was evaluated as a picture illustrated in Scheme 88. First, disconnection at macrolactone ring H gave a pentacyclic system 387. The B ring was proposed to form via the connective Pummerer-type cyclisation from compound 388. The next disconnection was
carried out at the amide bond to give compound 389. Finally, the D ring could be formed by a Pictet-Spengler reaction between aldehyde 390 and compound 391.

### 4.2.2 Results and discussion

![Scheme 89](image-url)  
Scheme 89. Reagents and conditions (a) COCl₂, DMSO, Et₃N, CH₂Cl₂, −78 °C to RT; (b) 392, Et₃N, MgSO₄₆, MeOH, 100 % (2 steps).
The synthesis was trialled with a simple substrate 380B as shown in Scheme 89. A single diastereomer 380B was first oxidised to the aldehyde 383B. The D ring could then be formed using a Pictet-Spengler reaction between aldehyde 383B and L-DOPA ester 392. The results showed that the D ring was formed efficiently in excellent yield. The stereochemistry of 2 major diastereomers (393 and 394) was confirmed by X-ray crystallography. A regioisomer 395 was isolated as a single diastereoisomer of unknown stereochemistry at the newly formed benzylic stereocentre.

Figure 8. X-ray structure of compound 393 and 394.
Methylation of the secondary amine and phenol groups in minor diastereoisomer 394 using Me₂SO₄ and K₂CO₃ also resulted in the hydrolysis of the methyl ester group. Esterification using TMS diazomethane then produced substrate 397 (Scheme 90).

Scheme 90. Reagents and conditions (a) MeI, K₂CO₃, acetone, RT, 70 %; (b) trimethylsilyl diazomethane, MeOH, 0 °C to RT, 100 %.

In conclusion, the D ring was successfully formed using Pictet-Spengler reaction in excellent yield. It was quite easy to convert compound 394 to compound 397 which may be used to continue the next steps to prepare analogues of Et. 597 (see more detail in the next chapter).
Chapter 5 Summary and future work

The scope of the connective Pummerer-type reaction has been explored for the synthesis of isoquinolones by preparing hydroxyamide substrates containing amino groups and developing a set of conditions for their successful cyclisation. Moderate to good yields of the desired cyclised products were obtained (Scheme 91).

**Scheme 91**

I have also synthesised substrates possessing the substitution found in the A-ring of Et. 597 and have explored the cyclisation of such substrates (Scheme 92).

**Scheme 92**
Additionally, I demonstrated that the connective Pummerer-type cyclisation reaction can also be carried out with acetal-protected glyoxamides; however, poor yields were obtained (Scheme 93).

Scheme 93

The connective Pummerer-type cyclisation can be carried out with a ‘simple’ aldehyde substrate rather than the commonly used glyoxamides (Scheme 94).

Scheme 94

A model of the AB ring system of Et. 597 was prepared successfully. The benzylic stereocenter on the B ring was built by Sharpless aminohydroxylation\textsuperscript{120} of the corresponding styrene or a two step procedure involving Sharpless dihydroxylation\textsuperscript{121} of the corresponding styrene, followed by a Mitsunobu reaction.\textsuperscript{122} The B ring was formed by applying the connective Pummerer-type cyclisation reaction conditions to an enantiomerically-pure glyoxamide (Scheme 95).
Moving on from our successful synthesis of AB ring model systems, we focussed our efforts on the construction of the actual AB ring system of Et.597 (Scheme 96).

The H ring was successfully synthesized using a macrolactonisation reaction utilising Shiina’s reagent\(^{111}\) (Scheme 97).
Due to problems with the reduction of the lactam carbonyl in the B ring, we instead focussed on an alternative retrosynthetic pathway based on the connective Pummerer-type cyclisation of a ‘simple’ aldehyde substrate instead of the corresponding glyoxamide (Scheme 98). However, the oxidative cleavage of diol 374 was unsuccessful. A related approach in which the aldehyde would be generated by an oxidation reaction instead of the oxidative cleavage was also investigated (Scheme 99). We believed that the oxidation reaction will produce the corresponding aldehyde which will cyclise upon Boc and TBS deprotection (Scheme 100).
In the final approach, the D ring was first formed using a Pictet-Spengler-type reaction (Scheme 101). We believed that oxazolidine ring opening then lactamisation with the ester would form the C ring. Next, the B ring would be formed using a connective Pummerer-type cyclisation. Finally, the macrolactone H ring will be formed en route to analogues of Et. 597 (Scheme 102).
Scheme 101

Scheme 102

Analogues of Et. 597
Chapter 6 Experimental

6.1 General experimental

All experiments were performed under an atmosphere of nitrogen using anhydrous solvents, unless stated otherwise. Glassware for inert atmosphere reactions was oven-dried and cooled under a flow of nitrogen. THF was distilled from sodium/benzophenone, CH₂Cl₂ and Et₃N were freshly distilled from CaH₂. Petroleum ether refers to the fraction of petroleum ether boiling in the range 40–60 °C. All other solvents and reagents were purchased from commercial sources and used as supplied.

¹H NMR (300 or 400 or 500 MHz) and ¹³C NMR (75 or 100 or 125 MHz) (spectra were recorded on a 300 MHz, 400 MHz or 500 MHz spectrometer, with chemical shift values being reported in parts per million (ppm) relative to residual CHCl₃ (δ_H = 7.27) and CDCl₃ (δ_C = 77.0) as internal standards unless otherwise stated. All coupling constants (J) are reported in Hertz (Hz). NMR assignments were made with the aid of COSY, HMQC, DEPT 135 experiments.

Low resolution and high resolution mass spectra were obtained using positive or negative electrospray ionization (ES). Infrared spectra were recorded using an FTIR spectrometer as evaporated films or neat using sodium chloride windows. Melting points are uncorrected.

Routine TLC analysis was carried out on aluminium sheets coated with silica gel 60 F254, 0.2 mm thickness. Plates were visualised by UV (254 nm) and/or by staining with aqueous potassium permanganate, ethanolic p-anisaldehyde or ethanolic phosphomolybdic acid. Column chromatography was carried out using 35-70μ, 60A silica gel.
6.2 Connective Pummerer-type reactions

6.2.1 Substrate syntheses

2-Hydroxy-5-methoxy-3-nitrobenzaldehyde (252)\textsuperscript{84}

A solution of 70 % aqueous nitric acid in glacial acetic acid (3.5 mL) was added dropwise to a solution of 2-hydroxy-5-methoxybenzaldehyde (1.52 g, 10.0 mmol) in glacial acetic acid (7.7 mL) at 10 °C. The reaction was stirred for 3 hours then H\textsubscript{2}O (11.7 mL) was added. The solid product was filtered and recrystallized in acetic acid to give 252 (1.37 g, 6.95 mmol, 69 %) as yellow needles. Spectroscopic data are identical to the data previously published in the literature.\textsuperscript{84}

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 3.88 (3H, s, OCH\textsubscript{3}), 7.72 (1H, d, J = 3.2 Hz, ArH), 7.86 (1H, d, J = 3.2 Hz, ArH), 10.45 (1H, s, CHO), 10.89 (1H, s, ArOH).

\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 56.3 (OCH\textsubscript{3}), 115.1 (ArCH), 122.9 (ArCH), 123.7 (ArC), 126.1 (ArC), 151.1 (ArC), 152.0 (ArC), 188.1 (CHO).

4-Methoxy-2-nitro-6-[(propylamino)methyl]phenol (253)

Aldehyde 252 (1.36 g, 6.90 mmol) was dissolved in anhydrous MeOH (100 mL) under N\textsubscript{2}. n-Propylamine (0.79 mL, 9.60 mmol) was then added. The reaction
mixture was heated at reflux for 2 hours before the reaction was allowed to cool to room temperature and NaBH₄ (0.36 g, 9.59 mmol) was added. The reaction mixture was stirred for 1 hour then the solvent was evaporated. The residue was dissolved in a 1M aqueous solution of HCl (100 mL) and the resulting mixture was extracted with EtOAc (3 × 100 mL). The aqueous phase was basified with a saturated aqueous solution of Na₂CO₃. The solid was filtered and dried under high vacuum to give 253 (1.39 g, 5.79 mmol, 83%) as a yellow solid which was used without further purification. Mp. 195–198 °C.

¹H NMR (400 MHz, CDCl₃) δ 0.98 (3H, t, J = 7.6 Hz, CH₃), 1.82 – 1.95 (2H, m, CH₂) 2.88 (2H, t, J = 7.6 Hz, NCH₂), 3.83 (3H, s, OCH₃), 4.25 (2H, s, CH₂N) 7.59 (1H, d, J = 3.2 Hz, ArCH), 7.85 (1H, d, J = 3.2 Hz, ArCH).

¹³C NMR (100 MHz, CDCl₃) δ 11.2 (CH₃), 19.5 (CH₂), 43.8 (CH₂N), 48.3 (NCH₂), 56.3 (OCH₃), 109.1 (ArCH), 122.4 (ArC), 128.3 (ArCH), 133.6 (ArC), 148.0 (ArC), 152.1 (ArC).


IR (thin film) νmax (cm⁻¹) 3297 (m, NH), 2651, 2390, 1552, 1495, 1456, 1425, 1320, 1230, 1145, 1058.

2-Hydroxy-N-(2-hydroxy-5-methoxy-3-nitrobenzyl)-N-propylacetamide (254)

Amine 253 (0.64 g, 2.66 mmol) was dissolved in anhydrous CH₂Cl₂ (20 mL) under N₂. Acetoxyacetic acid (0.55 g, 4.68 mmol), HOBt.H₂O (0.14 g, 1.02 mmol) and EDCI (0.90 g, 4.68 mmol) were also added. The solution was stirred at room
temperature for 20 hours, then washed with 1M aqueous solution of HCl, and then dried (Na$_2$SO$_4$). The solvent was evaporated and the residue was dissolved in MeOH (10 mL). K$_2$CO$_3$ (1.66 g, 12 mmol) in H$_2$O (5 mL) was added. The reaction was stirred at room temperature for 20 hours, then the solvent was evaporated and the residue was diluted with H$_2$O and neutralised by 1M aqueous solution of HCl to pH = 7–8. The solid was filtered and the filtrate was extracted with EtOAc (3 × 20 mL). The organic phases were combined and washed with brine then dried (MgSO$_4$). Evaporation of the solvent and combination of the solid gave 254 (0.69 g, 2.31 mmol, 86%) as a red solid which was used without further purification. Mp. 98–103 °C.

$^1$H NMR (500 MHz, CDCl$_3$) δ 0.89 – 0.95 (3H, m, CH$_3$ of two rotamers), 1.59 – 1.66 (2H, m, CH$_2$ of two rotamers), 3.13 (2H, t, J = 7.5 Hz, NCH$_2$ of one rotamer) 3.39 (2H, t, J = 7.5 Hz, NCH$_2$ of other rotamer), 3.80 (3H, s, OCH$_3$ of one rotamer), 3.82 (3H, s, OCH$_3$ of other rotamer), 4.18 (2H, s, CH$_2$N of one rotamer), 4.26 (2H, s, CH$_2$N of other rotamer), 4.42 (2H, s, CH$_2$OH of one rotamer), 4.70 (2H, s, CH$_2$OH of other rotamer), 7.00 (1H, d, J = 3.1 Hz, ArCH of one rotamer), 7.19 (1H, d, J = 3.1 Hz, ArCH of other rotamer), 7.44 (1H, d, J = 3.1 Hz, ArCH of one rotamer), 7.47 (1H, d, J = 3.1 Hz, ArCH of other rotamer), 10.7 (1H, br, OH of two rotamers).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 11.0 (CH$_3$ of one rotamer), 11.1 (CH$_3$ of other rotamer), 20.5 (CH$_2$ of one rotamer), 21.5 (CH$_2$ of other rotamer), 43.2 (NCH$_2$ of one rotamer), 44.1 (NCH$_2$ of other rotamer), 47.8 (CH$_2$N of one rotamer), 48.2 (CH$_2$N of other rotamer), 55.8 (OCH$_3$ of one rotamer), 55.9 (OCH$_3$ of other rotamer), 59.7 (CH$_2$OH of one rotamer), 59.8 (CH$_2$OH of other rotamer), 104.7 (ArCH of one rotamer), 105.0 (ArCH of other rotamer), 124.3 (ArCH of one rotamer), 126.7 (ArCH of other rotamer), 128.0 (ArC of one rotamer), 128.9 (ArC of other rotamer), 133.1 (ArC of one rotamer), 133.2 (ArC of other rotamer), 147.6 (ArC of one rotamer), 148.1 (ArC of other rotamer), 152.0 (ArC of one
rotamer), 152.2 (ArC of other rotamer), 169.2 (C=O of one rotamer), 172.1 (C=O of other rotamer).


IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 3444 (br, OH), 2973, 1637 (C=O), 1532, 1435, 1368, 1256, 1221, 1098, 1048.

$N$-(3-Amino-2-hydroxy-5-methoxybenzyl)-2-hydroxy-$N$-propylacetamide (255)

Nitrobenzene 254 (0.78 g, 2.62 mmol) was dissolved in anhydrous THF (50 mL) under N$_2$. Pd-C (60.0 mg) was added and the reaction was stirred under an atmosphere of hydrogen at room temperature. When most of the starting material was consumed (by TLC analysis), the reaction mixture was filtered through Celite then the filtrate was evaporated. The residue was dissolved in a 1M aqueous solution of HCl and washed with CH$_2$Cl$_2$. The aqueous layer was basified by Na$_2$CO$_3$ and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The organic extracts were washed with brine then dried (MgSO$_4$) and evaporated to give 255 (0.60 g, 2.24 mmol, 85%) as a light yellow oil which was used without further purification.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.94 (3H, t, $J = 7.8$ Hz, CH$_3$), 1.63 – 1.71 (2H, m, CH$_2$) 3.13 (2H, t, $J = 7.8$, NCH$_2$), 3.70 (3H, s, OCH$_3$), 4.20 (2H, s, CH$_2$N), 4.40 (2H, s, CH$_2$OH), 6.06 (1H, d, $J = 2.5$ Hz, ArCH), 6.31 (1H, d, $J = 2.5$ Hz, ArCH), 8.81 (1H, br. s, OH).
\begin{align*}
\delta & 11.1 \text{ (CH}_3\text{)}, 20.9 \text{ (CH}_2\text{)}, 46.4 \text{ (NCH}_2\text{)}, 47.6 \text{ (CH}_2\text{N)}, 55.5 \text{ (OCH}_3\text{)}, 59.7 \text{ (CH}_2\text{OH)}, 101.6 \text{ (ArCH)}, 105.1 \text{ (ArCH)}, 121.6 \text{ (ArC)}, 137.1 \text{ (ArC)}, 137.4 \text{ (ArC)}, 152.9 \text{ (ArC)} 173.1 \text{ (C=O)}.
\end{align*}

MS (ES+): m/z: 291 ([M + Na]⁺). HRMS (ES+): m/z: calcd for C_{13}H_{21}N_{2}O_{4}: 269.1496 ([M + H]⁺); found: 269.1497

IR (thin film) \( \nu_{\text{max}} \text{ (cm}^{-1}) \) 3361 (m, NH, OH), 1602 (C=O), 1497, 1442, 1398, 1350, 1224, 1195, 1157, 1079, 1050, 1033.

\begin{align*}
N\text{-}[3\text{-}(\text{Dimethylamino})\text{-}2,5\text{-dimethoxybenzyl}\text{-}2\text{-hydroxy}\text{-N-propylacetamide} \text{ (244)}
\end{align*}

Amine 255 (0.13 g, 0.49 mmol) was dissolved in MeCN (10 mL) and cooled in an ice bath. 34 % Formaldehyde in water (0.44 mL, 4.80 mmol) was added, then NaBH\_3CN (0.11 g, 1.68 mmol) and AcOH (0.2 mL) were added. After 5 minutes, the ice bath was removed and the reaction was stirred at room temperature for 1 hour. AcOH (0.2 mL) was added and the reaction was stirred for 3 hours at room temperature. The reaction was diluted with Et\text{2}O then an aqueous solution of Na\text{2}CO\text{3}. The phases were separated and the aqueous phase was extracted with EtOAc (3 \times 15 mL). The organic phases were combined and dried (MgSO\text{4}). Evaporation of the solvent gave crude phenol (0.14 g, 0.47 mmol, 96%) as a pale oil.

A mixture of crude phenol (0.14 g, 0.47 mmol) and K\text{2}CO\text{3} (0.64 g, 4.80 mmol) in anhydrous acetone (50 mL) was stirred at room temperature under N\text{2} for 2 hours. MeI (0.09 mL, 1.44 mmol) was then added. The reaction was heated at reflux for 20 hours. The resulting suspension was filtered and the filtrate was
evaporated. The residue was dissolved in water and extracted with CH$_2$Cl$_2$ (3 × 20 mL). The organic layer was dried (MgSO$_4$) then evaporated to give the crude product. Purification by column chromatography eluting with 50% EtOAc in petroleum ether gave 244 (0.087 g, 0.28 mmol, 59%) as a colourless pale oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 0.87 – 0.91 (3H, m, CH$_3$ of 2 rotamers), 1.55 – 1.62 (2H, m, CH$_2$ of 2 rotamers), 2.81 (6H, s, N(CH$_3$)$_2$ of 2 rotamers), 3.02 (2H, t, $J = 7.6$ Hz, NCH$_2$ of one rotamer), 3.37 (2H, t, $J = 7.6$ Hz, NCH$_2$ of other rotamer), 3.71 (3H, s, OCH$_3$ of one rotamer), 3.72 (3H, s, OCH$_3$ of other rotamer), 3.73 (3H, s, OCH$_3$ of one rotamer), 3.74 (3H, s, OCH$_3$ of other rotamer), 4.24 (2H, s, CH$_2$OH of one rotamer), 4.32 (2H, s, CH$_2$N of one rotamer), 4.34 (2H, s, CH$_2$OH of other rotamer), 4.68 (2H, s, CH$_2$N of other rotamer), 6.13 (1H, d, $J = 2.5$, ArH of one rotamer), 6.29 (1H, d, $J = 2.5$ Hz, ArH of other rotamer), 6.39 (1H, d, $J = 2.5$ Hz, ArH of one rotamer), 6.41 (1H, d, $J = 2.5$ Hz, ArH of other rotamer).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 11.1 (CH$_3$ of one rotamer), 11.3 (CH$_3$ of other rotamer), 20.5 (CH$_2$ of one rotamer), 21.2 (CH$_2$ of other rotamer), 42.0 (N(CH$_3$)$_2$ of one rotamer), 42.1 (N(CH$_3$)$_2$ of other rotamer), 43.3 (CH$_2$N of one rotamer), 44.9 (CH$_2$N of other rotamer), 46.7 (NCH$_2$CH$_2$ of one rotamer), 47.9 (NCH$_2$CH$_2$ of other rotamer), 48.7 (CH$_2$OH of one rotamer), 55.4 (OCH$_3$ of one rotamer), 58.1 (OCH$_3$ of other rotamer), 58.7 (OCH$_3$ of one rotamer), 59.8 (OCH$_3$ of other rotamer), 59.9 (CH$_2$OH of other rotamer), 103.4 (ArCH of one rotamer), 104.2 (ArCH of other rotamer), 104.8 (ArC of one rotamer), 118.0 (ArC of other rotamer), 129.4 (ArCH of one rotamer), 130.4 (ArCH of other rotamer), 143.5 (ArC of one rotamer), 144.2 (ArC of other rotamer), 146.5 (ArC of one rotamer), 146.7 (ArC of other rotamer), 155.9 (ArC of one rotamer), 156.1 (ArC of other rotamer), 171.6 (C=O of one rotamer), 171.9 (C=O of other rotamer).

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 3412 (br, OH), 2941, 1644 (C=O), 1590, 1461, 1398, 1348, 1236, 1211, 1137, 1055, 1002.

**Methyl 3,5-diaminobenzoate (257)**

![Methyl 3,5-diaminobenzoate (257)](image)

3,5-Diaminobenzoic acid (2.58 g, 16.9 mmol) was dissolved in anhydrous MeOH (42 mL) under N$_2$. Concentrated sulfuric acid (5.2 mL) was added slowly at room temperature. The reaction mixture was heated at reflux for 16 hours then cooled to room temperature. The solvent was evaporated and to the resulting mixture was added H$_2$O (50 mL), followed by a concentrated aqueous solution of Na$_2$CO$_3$ until pH = 7 – 8. The resulting mixture was extracted with EtOAc (5 × 100 mL). The organic layers were combined and dried (MgSO$_4$) and evaporated to give the product 257 (2.33 g, 14.0 mmol, 83 %) as a brown solid. This product was used without further purification. Mp. 139 – 143 °C. Spectroscopic data were identical to the data previously published in the literature.

$^1$H NMR (400 MHz, CDCl$_3$) δ 3.68 (4H, br. s, 2 × NH$_2$) 3.87 (3H, s, OCH$_3$), 6.20 (1H, t, $J = 2.0$ Hz, ArH), 6.79 (2H, d, $J = 2.0$ Hz, ArH).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 52.0 (OCH$_3$), 105.6 (ArCH), 106.9 (ArCH), 132.1 (ArC), 147.5 (ArC), 167.4 (C=O).

**Methyl 3,5-bis(dimethylamino)benzoate (258)**

![Methyl 3,5-bis(dimethylamino)benzoate (258)](image)
Amine 257 (1.60 g, 9.63 mmol) was dissolved in MeCN (100 mL). A 34 % aqueous solution of HCHO (17.6 mL, 200 mmol) was then added. The reaction mixture was cooled to between 0 °C and 5 °C. NaBH₃CN (4.40 g, 70 mmol) was added, followed by AcOH (2.0 mL). The reaction was stirred at 0 °C – 5 °C for five minutes, then at room temperature for 1 hour. AcOH (2.0 mL) was added and the reaction was stirred for 3 hours. The reaction mixture was diluted with Et₂O and basified by adding a saturated aqueous solution of NaHCO₃. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 25 mL). The organic phases were combined, dried (MgSO₄) and evaporated to give crude product. Purification by column chromatography eluting with 15% EtOAc in petroleum ether gave 258 (1.62 g, 7.29 mmol, 76 %) as white solid. Mp. 88 – 92 °C. Spectroscopic data were identical to the data previously published in the literature.¹²⁴

¹H NMR (300 MHz, CDCl₃) δ 2.99 (12H, s, 2 × N(CH₃)₂), 3.90 (3H, s, OCH₃), 6.24 (1H, t, J = 2.3 Hz, ArH), 6.87 (2H, d, J = 2.3 Hz, ArH).

¹³C NMR (75 MHz, CDCl₃) δ 40.7 (2 × N(CH₃)₂), 51.9 (OCH₃), 101.2 (ArCH), 103.2 (ArCH), 131.2 (ArC), 151.5 (ArC), 168.2 (C=O).

3,5-bis(Dimethylamino)benzoic acid (259)

Ester 258 (1.11 g, 5.00 mmol) was dissolved in a 1M solution of KOH in ethanol (50 mL). The reaction mixture was stirred at 40 °C for 4 hours then the solvent was evaporated. The residue was acidified by addition of a 1M aqueous solution of HCl to pH = 6. The resulting mixture was extracted with CH₂Cl₂ (3 × 25 mL). The organic layers were combined, dried (MgSO₄) and evaporated to give 259
(0.707 g, 3.39 mmol, 68 %) as a yellow solid. Mp. 202 – 206 °C. This product was used in the next step without purification.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.0 (12H, s, 2 × N(CH$_3$)$_2$), 6.29 (1H, t, $J = 1.6$ Hz, ArH), 6.94 (2H, d, $J = 1.6$ Hz, ArH).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 40.8 (N(CH$_3$)$_2$), 102.0 (ArCH), 103.8 (ArCH), 130.3 (ArC), 151.5 (ArC), 172.9 (C=O).

MS (ES+): $m/z$: 209([M + H]$^+$). HRMS (ES+): $m/z$: calcd for C$_{11}$H$_{17}$N$_2$O$_2$: 209.1285 ([M + H]$^+$); found: 209.1288.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2939 (br, OH), 1678 (C=O), 1595, 1491, 1283, 1055, 1033.

$N,N,N',N'$-Tetramethyl-5-[(propylamino)methyl]benzene-1,3-diamine (261)

Acid 259 (0.95 g, 4.54 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (40 mL) under N$_2$. n-Propylamine (0.37 mL, 4.53 mmol), 1-ethyl-3-(3-dimethylamino-propyl) carbodiimide (1.35 g, 7.07 mmol) and hydroxybenzotriazole (0.21 g, 1.54 mmol) were added. The mixture was stirred at room temperature for 24 hours. The solvent was evaporated and the residue was dissolved in a 1M aqueous solution of HCl and the resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 15 mL). The aqueous layer was basified by addition of a saturated aqueous solution of NaHCO$_3$ and then extracted 3 times with CH$_2$Cl$_2$ (3 × 20 mL). The organic phases were combined and dried (MgSO$_4$) and evaporated to give 260 (1.09 g, 4.37 mmol, 96 %) as a pale oil. The product was used for the next step without further purification.
Amide 260 (0.83 g, 3.33 mmol) was dissolved in anhydrous THF (40 mL) under N₂. The mixture was cooled to between 0° and 5°C and LiAlH₄ (0.28 g, 7.38 mmol) was added portionwise. The reaction was then heated at reflux for 16 hours. The reaction was cooled to room temperature and quenched sequentially with H₂O then 10% aqueous solution of NaOH, then H₂O. The resulting mixture was stirred for 30 minutes. The solid was filtered and washed with CH₂Cl₂. The filtrate was evaporated and H₂O (10 mL) was added to the residue which was then extracted with CH₂Cl₂ (3 x 20 mL). The organic phases were combined, and dried (MgSO₄) and evaporated to give 261 (0.69 g, 2.93 mmol, 88 %) as a pale oil. This product was used for the next step without further purification.

¹H NMR (400 MHz, CDCl₃) δ 0.93 (3H, t, J = 7.3 Hz, CH₃), 1.51 – 1.60 (2H, m, CH₂), 2.63 (2H, t, J = 7.1 Hz, NCH₂), 2.95 (12H, s, 2 x N(CH₃)₂), 3.73 (2H, s, CH₂N), 6.01 (1H, t, J = 2.3 Hz, ArH), 6.18 (2H, d, J = 2.3 Hz, 2 x ArH).

¹³C NMR (100 MHz, CDCl₃) δ 11.8 (CH₃), 23.1 (CH₂), 40.9 (4 x N(CH₃)₂), 51.3 (NCH₂), 55.0 (CH₂N), 96.5 (ArCH), 102.5 (ArCH), 141.7 (ArC), 151.8 (ArC).


IR (thin film) νmax (cm⁻¹) 3350 (m, NH), 2873, 1586, 1487, 1435, 1375, 1305, 1232, 1156, 1125, 1026.

\[ \text{N-[3,5-bis(Dimethylamino)benzyl]-2-hydroxy-N-propylacetamide (245)} \]
Amine 261 (1.09 g, 4.63 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (60 mL) under N$_2$. Acetoxyacetic acid (0.85 g, 7.17 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (1.37 g, 7.17 mmol) and hydroxyl-benzotriazole (0.21 g, 1.56 mmol) were added. The reaction was stirred at room temperature for 30 hours. The reaction mixture was washed with 1M aqueous solution of HCl (3 × 60 mL). The aqueous phases were combined and basified to pH = 6 then extracted with CH$_2$Cl$_2$ (3 × 100 mL). The organic layers were combined and dried (MgSO$_4$) and evaporated. The residue was dissolved in methanol (14 mL) and a solution of K$_2$CO$_3$ (2.54 g, 18.4 mmol) in H$_2$O (7 mL) was added. The solution was stirred at room temperature for 24 hours. The volatiles were removed and the residue was diluted with H$_2$O and extracted with CH$_2$Cl$_2$ (3 × 20 mL). Evaporation of the solvent gave 245 (0.95 g, 3.24 mmol, 70 %) as a light yellow pale oil. This product was used in the next step without further purification.

$^1$H NMR (500 MHz, CDCl$_3$) δ 0.88 – 0.92 (3H, m, CH$_3$ of 2 rotamers), 1.57 – 1.66 (2H, m, CH$_2$ of 2 rotamers), 2.94 (12H, s, 2 × N(CH$_3$)$_2$ of 2 rotamers), 3.01 (2H, t, J = 7.6 Hz, NCH$_2$ of one rotamer), 3.42 (2H, t, J = 7.6 Hz, NCH$_2$ of other rotamer), 3.69 (1H, br. s, OH of one rotamer), 3.78 (1H, br. s, OH of other rotamer), 4.23 (2H, br. s, CH$_2$OH of 2 rotamers), 4.27 (2H, s, CH$_2$N of one rotamer), 4.58 (2H, s, CH$_2$N of other rotamer), 5.89 (2H, s, ArH of one rotamer), 5.97 (1H, s, ArH of one rotamer), 6.00 (1H, s, ArH of other rotamer), 6.04 (2H, s, ArH of other rotamer).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 11.2 (CH$_3$ of one rotamer), 11.3 (CH$_3$ of other rotamer), 20.6 (CH$_2$CH$_3$ of one rotamer), 21.1 (CH$_2$CH$_3$ of other rotamer), 40.7 (2 × N(CH$_3$)$_2$ of one rotamer), 40.8 (2 × N(CH$_3$)$_2$ of other rotamer), 46.1 (NCH$_2$CH$_2$ of one rotamer), 48.2 (NCH$_2$CH$_2$ of other rotamer), 49.1 (CH$_3$N of one rotamer), 49.8 (CH$_3$N of other rotamer), 59.8 (CH$_2$OH of one rotamer), 59.9 (CH$_2$OH of other rotamer), 96.2 (ArCH of one rotamer), 96.6 (ArCH of other rotamer), 99.6 (2 × ArCH of one rotamer), 102.2 (2 × ArCH of other rotamer), 137.1 (ArC of one
rotamer), 137.9 (ArC of other rotamer), 151.9 (2 × ArC of one rotamer), 152.1 (2 × ArC of other rotamer), 171.5 (C=O of one rotamer), 172.0 (C=O of other rotamer).

**MS (ES+):** 
\[ m/z \] (%): 294 ([M + H]^+), 316 (100, [M + Na]^+), HRMS (ES+): \[ m/z \]: calcd for \( C_{16}H_{28}N_3O_2 \): 294.2176 ([M + H]^+); found: 294.2182.

**IR (thin film)** \( \nu_{\text{max}} \) (cm\(^{-1}\)) 3412 (br, OH), 2922, 1642 (C=O), 1584, 1488, 1436, 1378, 1308, 1233, 1158, 1126, 1079, 1032.

**2-Methoxy-4-(methoxymethyl)phenol (263)**

4-(Hydroxymethyl)-2-methoxyphenol (3.08 g, 20.0 mmol) was dissolved in anhydrous MeOH (30 mL) under N\(_2\). p-Toluenesulfonic acid (0.19 g, 1.00 mmol) was added and the reaction was stirred at room temperature for 6 hours. NaHCO\(_3\) (0.10 g) was added and the reaction mixture was stirred at room temperature for a further 15 minutes. The solvent was evaporated and EtOAc (10 mL) was added. The mixture was filtered through a silica plug column eluting with ethyl acetate. The filtrate was evaporated to give 263 (3.30 g, 19.6 mmol, 98%) as a pale oil. Spectroscopic data was identical to the data previously published in the literature.\(^{91}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 3.38 (3H, s, OCH\(_3\)), 3.91 (3H, s, OCH\(_3\)), 4.39 (2H, s, CH\(_2\)), 5.65 (1H, d, \( J = 1.8 \) Hz, OH), 6.82 (1H, dd, \( J = 8.1, 1.8 \) Hz, ArH), 6.88 – 6.90 (2H, m, 2 × ArH).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 55.9 (OCH\(_3\)), 57.8 (OCH\(_3\)), 74.8 (CH\(_2\)), 110.5 (ArCH), 114.1 (ArCH), 121.1 (ArCH), 130.1 (ArC), 145.3 (ArC), 146.6 (ArC).
2-Methoxy-4-(methoxymethyl)-3-methylphenol (264)

Phenol 263 (3.28 g, 19.5 mmol) was dissolved in anhydrous THF (30 mL) under N₂ and the mixture was cooled to –15 °C. A 2.3M solution of n-BuLi (25.4 mL) in hexane was added slowly and the temperature was kept below 0 °C. Subsequently, the reaction was stirred at between 0 and 5 °C for 2.5 hours. The reaction was then recooled to –15 °C and MeI (4.25 mL, 68.3 mmol) was added. The reaction was quenched by addition of H₂O (6 mL) and the solvent was evaporated. The residue was diluted with H₂O and acidified by addition of a 1M aqueous solution of HCl to pH = 6. The resulting mixture was extracted with CH₂Cl₂ (3 × 20 mL). The organic phases were combined and dried (MgSO₄) and evaporated to give 264 (3.20 g, 17.6 mmol, 90%) as a pale oil. Spectroscopic data was identical to the data previously published in the literature.

¹H NMR (400 MHz, CDCl₃) δ 2.29 (3H, s, CH₃), 3.38 (3H, s, OCH₃), 3.78 (3H, s, OCH₃), 4.37 (2H, s, CH₂), 5.74 (1H, br. s, OH), 6.78 (1H, d, J = 8.3 Hz, ArH), 6.97 (1H, d, J = 8.3 Hz, ArH).

¹³C NMR (100 MHz, CDCl₃) δ 11.6 (CH₃), 57.9 (OCH₃), 60.8 (OCH₃), 73.2 (CH₂), 112.2 (ArCH), 126.0 (ArCH), 128.9 (ArC), 130.4 (ArC), 145.6 (ArC), 148.6 (ArC).

4-Hydroxy-3-methoxy-2-methylbenzaldehyde (265)

Ether 264 (2.00 g, 11.0 mmol) was dissolved in CH₂Cl₂ (200 mL) then H₂O (10 mL) was added. The mixture was stirred vigorously and DDQ (2.50 g, 11.0 mmol) was
added slowly over 5 minutes. The reaction mixture was stirred at room temperature for 2 hours then filtered through celite and the solvent evaporated to give the crude product. Purification by column chromatography eluting with 20–25% of Et$_2$O in $n$-hexane gave 265 (0.65 g, 3.91 mmol, 36%) as a white solid. Spectroscopic data were identical to the data previously published in the literature.$^{91}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 2.62 (3H, s, CH$_3$), 3.81 (3H, s, OCH$_3$), 6.35 (1H, br. s, OH), 6.96 (1H, d, $J$ = 8.3 Hz, ArH), 7.55 (1H, d, $J$ = 8.3 Hz, ArH), 10.06 (1H, s, CHO).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 12.0 (CH$_3$), 61.2 (OCH$_3$), 113.1 (ArCH), 128.3 (ArC), 131.2 (ArCH), 134.2 (ArC), 145.8 (ArC), 153.9 (ArC), 191.5 (C=O).

5-Bromo-4-hydroxy-3-methoxy-2-methylbenzaldehyde (266)$^{91}$

[Chemical structure]

Aldehyde 265 (0.81 g, 4.87 mmol) was dissolved in acetic acid (14 mL). CH$_3$COONa (0.48 g, 5.84 mmol) was added followed by Br$_2$ (0.30 mL, 5.84 mmol). The reaction was stirred at room temperature in the dark for 16 hours. The reaction mixture was then added to cold water (60 mL). The precipitate was filtered and dried under high vaccum to give 266 (0.64 g, 53%) as a brown solid. Spectroscopic data were identical to the data previously published in the literature.$^{91}$

$^1$H NMR (400 MHz, CDCl$_3$) δ 2.58 (3H, s, CH$_3$), 3.85 (3H, s, OCH$_3$), 6.46 (1H, br. s, OH), 7.77 (1H, s, ArH), 10.04 (1H, s, CHO).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 11.7 (CH$_3$), 61.2 (OCH$_3$), 106.9 (ArC), 128.7 (ArC), 132.8 (ArCH), 133.7 (ArC), 146.3 (ArC), 151.3 (ArC), 190.1 (C=O).
5-Bromo-3,4-dimethoxy-2-methylbenzaldehyde (267)\textsuperscript{125}

Phenol 266 (0.44 g, 1.80 mmol) was dissolved in anhydrous DMF (3.0 mL) under N\textsubscript{2} and K\textsubscript{2}CO\textsubscript{3} (0.50 g, 3.60 mmol) and Me\textsubscript{2}SO\textsubscript{4} (0.52 mL, 5.40 mmol) were added. The reaction mixture was stirred at room temperature for 17 hours. Subsequently, additional Me\textsubscript{2}SO\textsubscript{4} (0.26 mL, 2.70 mmol) was also added. The reaction was then stirred at room temperature for 5 hours. The reaction mixture was diluted with H\textsubscript{2}O (20 mL) and the resulting mixture was extracted with EtOAc (3 × 20 mL). The organic layers were combined and washed with brine, dried (MgSO\textsubscript{4}) and evaporated to give 267 (0.42 g, 1.62 mmol, 90%) as a pale oil. Spectroscopic data were identical to the data previously published in the literature.\textsuperscript{125}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 2.54 (3H, s, CH\textsubscript{3}), 3.84 (3H, s, OCH\textsubscript{3}), 3.97 (3H, s, OCH\textsubscript{3}), 7.79 (1H, s, ArH), 10.13 (1H, s, CHO).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 11.0 (CH\textsubscript{3}), 60.6 (OCH\textsubscript{3}), 60.8 (OCH\textsubscript{3}), 115.1 (ArC), 131.4 (ArC), 131.5 (ArCH), 135.1 (ArC), 152.7 (ArC), 155.1 (ArC), 190.3 (C=O).

5-Bromo-3,4-dimethoxy-2-methylphenol (268)\textsuperscript{125}

Aldehyde 267 (0.57 g, 2.20 mmol) was dissolved in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (24 mL) and cooled to 0 °C under N\textsubscript{2}. \textupit{p}-Toluenesulfonic acid (10.0 mg) and \textupit{m}-CPBA (77%) (1.28 g, 5.72 mmol) were then added and the reaction was stirred at 0 °C for 1 hour and then at room temperature for 4 hours. The reaction mixture was
washed with a saturated aqueous solution of NaHCO₃ (3 × 20 mL) and a saturated aqueous solution of Na₂CO₃ (3 × 20 mL). The organic layer was then dried (MgSO₄) and evaporated. The residue was dissolved in MeOH (13.0 mL) and a suspension of K₂CO₃ (1.81 g, 13.1 mmol) in H₂O (6.5 mL) was added. The reaction was stirred at room temperature for 16 hours. The solvent was evaporated and the residue was basified with 1M aqueous solution of HCl to pH = 6 and extracted with CH₂Cl₂ (3 × 20 mL). The organic phases were combined and dried (MgSO₄) and evaporated to give 268 (0.42 g, 1.70 mmol, 77%) as a pale oil. Spectroscopic data were identical to the data previously published in the literature.¹²⁵

¹H NMR (400 MHz, CDCl₃) δ 2.11 (3H, s, CH₃), 3.82 (3H, s, OCH₃), 3.85 (3H, s, OCH₃), 6.77 (1H, s, ArH).

¹³C NMR (100 MHz, CDCl₃) δ 8.9 (CH₃), 60.7 (OCH₃), 60.8 (OCH₃), 113.7 (ArC), 114.1 (ArCH), 118.5 (ArC), 144.4 (ArC), 150.8 (ArC), 152.7 (ArC).

N-(5-(Benzyloxy)-2,3-dimethoxy-4-methylbenzyl)propan-1-amine (269)

Bromide 268 (0.42 g, 1.68 mmol) was dissolved in acetone (16 mL) under N₂ and K₂CO₃ (0.46 g, 3.36 mmol) and benzylbromide (0.24 mL, 2.02 mmol) were added. The reaction was then heated at reflux for 3 hours. The solvent was evaporated and the residue was diluted with H₂O (15 mL) and the resulting mixture was extracted with CH₂Cl₂ (3 × 15 mL). The organic phases were combined and washed with brine, dried (MgSO₄) and evaporated. Purification by column chromatography eluting with 5% Et₂O in n-hexane gave the crude product (0.45 g) as light yellow pale oil.
The crude product (0.45 g, 1.33 mmol) was dissolved in anhydrous Et₂O (55 mL) under N₂. The mixture was cooled to −78 °C. A 1.6 M solution of n-BuLi (2.10 mL, 3.30 mmol) in hexane was added slowly. The reaction was stirred at −78 °C for 15 minutes. DMF (1.10 mL, 13.9 mmol) was then added and the reaction was allowed to warm to −10 °C and a saturated aqueous solution of NH₄Cl (0.66 mL) was added. The reaction was stirred at room temperature for 20 minutes before H₂O (20 mL) was added and the resulting mixture was separated. The aqueous phase was extracted with EtOAc (3 × 20 mL) then the organic phases were combined washed with brine (50 mL) then dried (MgSO₄) and evaporated. Purification by column chromatography eluting with 15% Et₂O in n-hexane gave crude product as a white solid (0.30 g).

The crude product (0.30 g, 1.03 mmol) was dissolved in MeOH (20 mL) under N₂. n-Propylamine (0.10 mL, 1.24 mmol) was added. The reaction was heated at reflux for 2 hours then allowed to cool to room temperature. NaBH₄ (0.08 g, 2.06 mmol) was added and the reaction was stirred at room temperature for 1 hour then the solvent was evaporated. The residue was dissolved in a 1 M aqueous solution of HCl (15 mL) then the resulting mixture was extracted with CH₂Cl₂ (3 × 15 mL). The organic phases were combined and washed with a saturated aqueous solution of NaHCO₃ and dried (MgSO₄) then evaporated to give 269 (0.33 g, 1.00 mmol, 60%) as a colourless pale oil which was used for the next step without further purification.

**¹H NMR (400 MHz, CDCl₃) δ 0.93 (3H, t, J = 7.3 Hz, CH₃), 1.49 – 1.58 (2H, m, CH₂CH₃), 2.20 (3H, s, ArCH₃), 2.58 (2H, t, J = 7.3 Hz, NCH₂CH₂), 3.77 (2H, s, CH₂N), 3.83 (3H, s, OCH₃), 3.84 (3H, s, OCH₃), 5.05 (2H, s, OCH₂), 6.67 (1H, s, ArH), 7.31 – 7.47 (5H, m, 5 × ArH).**

**¹³C NMR (100 MHz, CDCl₃) δ 9.0 (ArCH₃), 11.8 (CH₃), 23.2 (CH₂CH₃), 48.8 (CH₂N), 51.3 (NCH₂CH₂), 60.3 (OCH₃), 60.8 (OCH₃), 70.4 (OCH₂), 107.9 (ArCH), 120.0
($ArC$), 127.2 ($ArCH$), 127.7 ($ArCH$), 128.4 ($ArCH$), 130.9 ($ArC$), 137.5 ($ArC$), 145.4 ($ArC$), 151.8 ($ArC$), 153.1 ($ArC$).


IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 3490 (m, NH), 2931, 1586, 1510, 1458, 1462, 1427, 1404, 1361, 1300, 1246, 1180, 1032

$N$-$\{(5$-(Benzyloxy)$-2,3$-dimethoxy$-4$-methylbenzyl)$-2$-hydroxy$-N$-propyl$\}$acetamide (246)

Amine 269 (329 mg, 1.00 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (15 mL) and the mixture was cooled to 0 °C. Acetoxyacetyl chloride (0.13 mL, 1.20 mmol) and Et$_3$N (0.17 mL, 1.20 mmol) were added and the reaction was allowed to warm to room temperature and stirred for 4 hours. The solvent was evaporated and the residue was dissolved in MeOH (8.6 mL) and K$_2$CO$_3$ (1.38 g, 10.0 mmol) in H$_2$O (4.3 mL) was added and the reaction was stirred at room temperature for 17 hours. The solvent was evaporated and H$_2$O (10 mL) was added to the residue before extraction with CH$_2$Cl$_2$ (3 × 15 mL). The organic phases were combined and dried (MgSO$_4$) and evaporated to give 246 (383 mg, 0.99 mmol, 99%) as a pale oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.83 – 0.88 (3H, m, CH$_3$ of 2 rotamers), 1.44 – 1.57 (2H, m, CH$_2$CH$_3$ of 2 rotamers), 2.19 (3H, s, ArCH$_3$ of one rotamer), 2.20 (3H, s, ArCH$_3$ of other rotamer), 2.88 (2H, t, $J = 7.6$ Hz, NCH$_2$CH$_2$ of one rotamer), 3.28 (2H, t, $J = 7.6$ Hz, NCH$_2$CH$_2$ of other rotamer), 3.67 (1H, t, $J = 3.8$ Hz, OH of one rotamer), 3.73 (1H, t, $J = 3.8$ Hz, OH of other rotamer), 3.79 (3H, s, OCH$_3$ of one
rotamer), 3.80 (3H, s, OCH$_3$ of one rotamer), 3.81 (3H, s, OCH$_3$ of one rotamer), 3.82 (3H, s, OCH$_3$ of another rotamer), 4.15 (2H, d, $J = 3.8$ Hz, CH$_2$OH of one rotamer), 4.19 (2H, d, $J = 3.8$ Hz, CH$_2$OH of another rotamer), 4.28 (2H, s, CH$_2$N of one rotamer), 4.65 (2H, s, CH$_2$N of another rotamer), 5.01 (2H, s, CH$_2$O of one rotamer), 5.02 (2H, s, CH$_2$O of another rotamer), 4.19 (2H, d, $J = 3.8$ Hz, CH$_2$OH of another rotamer), 4.65 (2H, s, CH$_2$N of another rotamer), 5.01 (2H, s, CH$_2$O of another rotamer), 5.02 (2H, s, CH$_2$O of another rotamer), 6.28 (1H, s, ArH of one rotamer), 6.49 (1H, s, ArH of another rotamer), 7.30 – 7.41 (5H, m, 5 × ArH of 2 rotamers).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 9.1 (ArCH$_3$ of 2 rotamers), 11.2 (CH$_3$ of one rotamer), 11.3 (CH$_3$ of another rotamer), 20.5 (CH$_2$CH$_3$ of one rotamer), 21.2 (CH$_2$CH$_3$ of another rotamer), 42.8 (CH$_2$N of one rotamer), 44.5 (CH$_2$N of another rotamer), 46.6 (NCH$_2$CH$_2$ of one rotamer), 47.7 (NCH$_2$CH$_2$ of another rotamer), 59.7 (CH$_2$OH of one rotamer), 59.8 (CH$_2$OH of another rotamer), 60.2 (OCH$_3$ of one rotamer), 60.3 (OCH$_3$ of another rotamer), 60.4 (OCH$_3$ of another rotamer), 60.9 (OCH$_3$ of another rotamer), 70.3 (CH$_2$O of one rotamer), 70.5 (CH$_2$O of another rotamer), 105.8 (ArCH of one rotamer), 107.6 (ArCH of another rotamer), 121.0 (ArC of another rotamer), 121.5 (ArC of another rotamer), 125.7 (ArC of another rotamer), 126.9 (ArC of another rotamer), 127.0 (ArCH of one rotamer), 127.1 (ArC of another rotamer), 127.7 (ArCH of one rotamer), 127.9 (ArCH of another rotamer), 128.5 (ArCH of another rotamer), 128.6 (ArCH of another rotamer), 137.0 (ArC of another rotamer), 137.4 (ArC of another rotamer), 145.0 (ArC of another rotamer), 145.5 (ArC of another rotamer), 151.7 (ArC of another rotamer), 152.1 (ArC of another rotamer), 153.2 (ArC of another rotamer), 153.4 (ArC of another rotamer), 171.7 (C=O of one rotamer), 171.9 (C=O of another rotamer).


IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 3330 (br, OH), 2935, 2835, 1736 (C=O), 1610, 1585, 1511, 1484, 1461, 1300, 1247, 1173, 1127, 1079, 1032.
AcCl (2.15 mL, 30.0 mmol) was added to a 1M solution of TiCl$_4$ in CH$_2$Cl$_2$ (30 mL, 30 mmol) at −10 °C under N$_2$. The temperature was maintained below 0 °C and a solution of 1,3-dimethoxy-2-methylbenzene (2.28 g, 15.0 mmol) in CH$_2$Cl$_2$ (7 mL) was added over 10 minutes with vigorous stirring. The reaction was stirred at 0 °C and stirred for 30 minutes. The reaction mixture was poured into a cooled 1M aqueous solution of HCl (70 mL) and the phases were separated. The aqueous phase was extracted with CH$_2$Cl$_2$ (2 × 50 mL). The organic phases were combined and washed with 1M aqueous solution of HCl (2 × 100 mL), saturated aqueous solution of NaHCO$_3$ (100 mL) then brine (100 mL), dried (MgSO$_4$) and evaporated in vacuo. The residue was dissolved in CH$_2$Cl$_2$ (25 mL) then KHCO$_3$ (2.59 g, 30.8 mmol) was added and the resulting mixture was cooled to 0 °C. A solution of m-CPBA 70% (7.59 g, 30.8 mmol) in CH$_2$Cl$_2$ (50 mL) was added dropwise in 30 minutes at 0 °C. The reaction mixture was stirred at room temperature for 17 hours. A 10 % aqueous solution of Na$_2$CO$_3$ (80 mL) and saturated Na$_2$SO$_3$ (20 mL) were added. The phases were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The organic phases were combined and washed with a 10 % aqueous solution of Na$_2$CO$_3$ (2 × 150 mL), H$_2$O (150 mL), brine (150 mL) then dried (MgSO$_4$) and concentrated in vacuo. The residue was dissolved in MeOH (155 mL) and a suspension of K$_2$CO$_3$ (21.5 g, 154 mmol) in H$_2$O (77.5 mL) was added. The reaction mixture was stirred at room temperature for 16 hours then the solvent was evaporated. The residue was diluted with H$_2$O (100 mL) and extracted with CH$_2$Cl$_2$ (3 × 100 mL). The organic phases were combined and dried (MgSO$_4$) then evaporated to give 272
(1.95 g, 11.5 mmol, 77 %) as a yellow oil. Spectroscopic data are identical to the data previously published in the literature.\textsuperscript{93}

$^1$H NMR (300 MHz, CDCl\textsubscript{3}) $\delta$ 2.18 (3H, s, CH\textsubscript{3}), 3.79 (6H, s, 2 $\times$ OCH\textsubscript{3}), 5.26 (1H, br. s, OH), 6.55 (1H, d, $J$ = 8.9 Hz, ArH), 6.76 (1H, d, $J$ = 8.9 Hz, ArH).

$^{13}$C NMR (75 MHz, CDCl\textsubscript{3}) $\delta$ 9.3 (CH\textsubscript{3}), 56.1 (OCH\textsubscript{3}), 60.9 (OCH\textsubscript{3}), 106.7 (ArCH), 111.6 (ArCH), 119.9 (ArC), 142.9 (ArC), 145.9 (ArC), 151.9 (ArC).

1-Bromo-2,3,5-trimethoxy-4-methylbenzene (273)\textsuperscript{94,126}

Phenol 272 (1.77 g, 10.5 mmol) was dissolved in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (20 mL) and K\textsubscript{2}CO\textsubscript{3} (2.32 g, 16.8 mmol) was added. The mixture was cooled to −78 °C. A solution of Br\textsubscript{2} (0.60 mL, 11.6 mmol) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (5 mL) was added over 2 hours. The reaction mixture was added to a 10 % aqueous solution of Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} and NaHCO\textsubscript{3} (1:1, 100 mL). The phases were separated and the aqueous phase was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 $\times$ 70 mL). The organic phases were combined and washed with a 10 % aqueous solution of Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} and NaHCO\textsubscript{3} (2 $\times$ 150 mL) then brine (100 mL) and dried (MgSO\textsubscript{4}) and concentrated \textit{in vacuo}. The residue was dissolved in anhydrous DMF (29 mL). K\textsubscript{2}CO\textsubscript{3} (2.90 g, 21.0 mmol) and Me\textsubscript{2}SO\textsubscript{4} (2.05 mL, 21.6 mmol) were added. The reaction was stirred at room temperature for 17 hours. Further Me\textsubscript{2}SO\textsubscript{4} (1.03 mL, 10.8 mmol) was added and the reaction was stirred at room temperature for a further 16 hours. The reaction mixture was diluted with H\textsubscript{2}O and extracted with EtOAc (3 $\times$ 100 mL). The organic phases were combined and washed with brine (100 mL) then dried (MgSO\textsubscript{4}) and evaporated. Purification by column chromatography eluting with 10 % Et\textsubscript{2}O in petroleum ether gave 273 (1.66 g, 6.36 mmol, 61 %) as a colourless
oil. Spectroscopic data are identical to the data previously published in the literature.\textsuperscript{94,126}

\[
\begin{align*}
^1\text{H NMR} & (400 \text{ MHz, CDCl}_3) \ \delta \ 2.08 & (3\text{H, s, CH}_3), & 3.79 & (3\text{H, s, OCH}_3), & 3.83 & (3\text{H, s, OCH}_3), & 3.84 & (3\text{H, s, OCH}_3), & 6.77 & (1\text{H, s, ArH}) \\
^1\text{C NMR} & (100 \text{ MHz, CDCl}_3) \ \delta \ 8.9 & (\text{CH}_3), & 55.9 & (\text{OCH}_3), & 60.6 & (\text{OCH}_3), & 109.7 & (\text{ArCH}), & 113.6 & (\text{ArC}), & 120.6 & (\text{ArC}), & 144.6 & (\text{ArC}), & 152.6 & (\text{ArC}), & 154.6 & (\text{ArC})
\end{align*}
\]

\textbf{2,3,5-Trimethoxy-4-methylbenzaldehyde (274)}\textsuperscript{92,127}

Bromide 273 (2.08 g, 7.97 mmol) was dissolved in anhydrous THF (130 mL) under N\textsubscript{2}. The mixture was cooled to $-78$ °C. A solution of n-\text{BuLi} (2.2 M in hexane, 9.0 mL, 19.9 mmol) was added slowly. The reaction was stirred at $-78$ °C for 15 minutes. DMF (6.48 mL, 83.7 mmol) was added and the reaction was allowed to warm to $-10$ °C then a saturated aqueous solution of NH\textsubscript{4}Cl (5 mL) was added. The reaction was stirred at room temperature for 20 minutes. H\textsubscript{2}O (50 mL) was added and the phases separated. The aqueous phase was extracted with EtOAc ($3 \times 50$ mL) and the combined organic phases were washed with brine (50 mL). The organic phase was dried (MgSO\textsubscript{4}) and evaporated to give the crude product. Purification by column chromatography eluting with 10% Et\textsubscript{2}O in \textit{n}-hexane gave 274 (1.00 g, 4.76 mmol, 60 %) as a colorless oil. Spectroscopic data are identical to the data previously published in the literature.\textsuperscript{92,127}

\[
\begin{align*}
^1\text{H NMR} & (400 \text{ MHz, CDCl}_3) \ \delta \ 2.19 & (3\text{H, s, ArCH}_3), & 3.83 & (3\text{H, s, OCH}_3), & 3.85 & (3\text{H, s, OCH}_3), & 3.94 & (3\text{H, s, OCH}_3), & 7.02 & (1\text{H, s, ArH}), & 10.33 & (1\text{H, s, CHO})
\end{align*}
\]
\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 9.7 (CH\(_3\)), 55.8 (OCH\(_3\)), 60.4 (OCH\(_3\)), 62.5 (OCH\(_3\)), 102 (ArCH), 127.0 (ArC), 129.7 (ArC), 151.3 (ArC), 152.0 (ArC), 154.5 (ArC), 189.4 (C=O).

\(N\)-(4-Methoxybenzyl)-1-(2,3,5-trimethoxy-4-methylphenyl)methanamine (\(275\))

![Structure](image)

Aldehyde \(274\) (0.11 g, 0.50 mmol) was dissolved in anhydrous MeOH (10 mL). 4-Methoxy-benzylamine (0.08 mL, 0.60 mmol) was added and the reaction was heated at reflux for 3 hours then cooled to 5 \(^\circ\)C. NaBH\(_4\) (0.04 g, 1.00 mmol) was added and the reaction was then stirred at room temperature for 2 hours. The solvent was evaporated and the residue was dissolved in a 1M aqueous solution of HCl (15 mL) and extracted with CH\(_2\)Cl\(_2\) (3 \(\times\) 15 mL). The organic phases were combined and dried (MgSO\(_4\)) and evaporated to give the product \(275\) (0.17 g, 0.50 mmol, 100%) as a colourless oil that was used without further purification.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.13 (3H, s, CH\(_3\)), 3.76 (2H, s, CH\(_2\)N), 3.78 (2H, s, CH\(_2\)N), 3.79 (3H, s, OCH\(_3\)), 3.80 (3H, s, OCH\(_3\)), 3.81 (3H, s, OCH\(_3\)), 3.82 (3H, s, OCH\(_3\)), 6.58 (1H, s, ArH), 6.88 (2H, d, \(J = 8.6\) Hz, 2 \(\times\) ArH), 7.28 (2H, d, \(J = 8.6\) Hz, 2 \(\times\) ArH).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 8.9 (CH\(_3\)), 48.3 (CH\(_2\)N), 52.6 (CH\(_2\)N), 55.3 (OCH\(_3\)), 55.8 (OCH\(_3\)), 60.3 (OCH\(_3\)), 60.8 (OCH\(_3\)), 106.5 (ArCH), 113.7 (ArCH), 119.6 (ArC), 129.4 (ArCH), 130.6 (ArC), 132.4 (ArC), 145.3 (ArC), 151.8 (ArC), 154.0 (ArC), 158.6 (ArC).

MS (ES\(+\)): \(m/z\): 332 ([\(M + H\]^+]), 354 ([\(M + Na\]^+]), HRMS (ES\(+\)): \(m/z\): calcd for C\(_{19}\)H\(_{26}\)NO\(_4\): 332.1856 ([\(M + H\]^+]); found: 332.1859.
IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 3293 (m, NH), 2835, 1612, 1585, 1515, 1463, 1406, 1251, 1126, 1031, 835.

2-Hydroxy-$N$-(4-methoxybenzyl)-$N$-(2,3,5-trimethoxy-4-methylbenzyl)-acetamide (247)

Amine 275 (0.17 g, 0.50 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (7 mL) at 0 °C and acetoxyacetyl chloride (0.07 mL, 0.62 mmol) and Et$_3$N (0.09 mL, 0.62 mmol) were added at 0 °C. The reaction was stirred at room temperature for 16 hours then the solvent was evaporated and the residue was dissolved in MeOH (5 mL) and a solution of K$_2$CO$_3$ (0.72 g, 5.20 mmol) in water (2.5 mL) was added. The reaction was stirred for 18 hours. After concentration in vacuo, the residue was diluted with water (10 mL) and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The organic extracts were combined and dried (MgSO$_4$) and evaporated to give 247 (0.19 g, 0.48 mmol, 96 %) as a colourless pale oil which was used without further purification.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.12 (3H, s, CH$_3$ of one rotamer), 2.13 (3H, s, CH$_3$ of the other rotamer), 3.71 (3H, s, OCH$_3$ of one rotamer), 3.73 (3H, s, OCH$_3$ of the other rotamer), 3.74 (3H, s, OCH$_3$ of one rotamer), 3.76 (3H, s, OCH$_3$ of the other rotamer), 3.80 (3H, s, OCH$_3$ of 2 rotamers), 3.81 (3H, s, OCH$_3$ of one rotamer), 3.82 (3H, s, OCH$_3$ of the other rotamer), 4.24 (2H, s, NCH$_2$ of one rotamer), 4.26 – 4.27 (4H, m, CH$_2$OH and NCH$_2$ of one rotamer), 4.33 (2H, d, $J$ = 4.3 Hz, CH$_2$OH of the other rotamer), 4.58 (2H, s, NCH$_2$ of the other rotamer), 4.63 (2H, s, NCH$_2$ of the other rotamer), 6.20 (1H, s, ArH of one rotamer), 6.54 (1H, s, ArH of the other rotamer), 6.86 (2H, d, $J$ = 8.6 Hz, 2 × ArH of one rotamer), 6.89 (2H, d, $J$ =
8.6 Hz, ArH of the other rotamer), 7.08 (2H, d, J = 8.6 Hz, ArH of one rotamer),
7.18 (2H, d, J = 8.6 Hz, ArH of the other rotamer).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 8.8 (CH\(_3\)), 43.6 (NCH\(_2\) of one rotamer), 43.9 (NCH\(_2\) of other rotamer), 47.8 (NCH\(_2\) of one rotamer), 47.9 (NCH\(_2\) of other rotamer), 55.2 (OCH\(_3\) of one rotamer), 55.3 (OCH\(_3\) of other rotamer), 55.8 (OCH\(_3\) of one rotamer), 55.9 (OCH\(_3\) of other rotamer), 60.1 (CH\(_2\)OH of 2 rotamers), 60.1 (OCH\(_3\) of one rotamer), 60.2 (OCH\(_3\) of other rotamer), 60.4 (OCH\(_3\) of one rotamer), 60.8 (OCH\(_3\) of other rotamer), 104.6 (ArCH of one rotamer), 106.8 (ArCH of other rotamer), 114.0 (ArCH of one rotamer), 114.3 (ArCH of other rotamer), 120.8 (ArC of one rotamer), 121.1 (ArC of other rotamer), 125.3 (ArC of one rotamer), 126.7 (ArC of other rotamer), 127.4 (ArC of one rotamer), 127.9 (ArCH of one rotamer), 128.5 (ArC of other rotamer), 129.7 (ArCH of other rotamer), 145.2 (ArC of one rotamer), 145.6 (ArC of other rotamer), 151.8 (ArC of one rotamer), 152.1 (ArC of other rotamer), 154.2 (ArC of one rotamer), 154.3 (ArC of other rotamer), 159.1 (ArC of one rotamer), 159.2 (ArC of other rotamer), 172.1 (C=O of one rotamer), 172.3 (C=O of other rotamer).

MS (ES+): \(m/z\): 390 ([M + H]^+)\), 412 ([M + Na]^+), HRMS (ES+): \(m/z\): calcd for C\(_{21}\)H\(_{28}\)NO\(_6\): 390.1912 ([M + H]^+); found: 390.1907.

IR (thin film) \(\nu_{max}\) (cm\(^{-1}\)) 3303 (br, OH), 2937, 1650 (C=O), 1611, 1513, 1463, 1403, 1248, 1128, 1083, 1030.

\(N-(3,5\text{-bis(Dimethylamino)benzyl})-2,2\text{-diethoxy-}N\text{-propylacetamide (248)}\)

\[
\begin{align*}
\text{N} & \equiv \text{EtO} \quad \text{OEt} \\
\text{N} & \equiv \text{EtO} \quad \text{OEt}
\end{align*}
\]

Amine 261 (0.05 g, 0.24 mmol) was dissolved in anhydrous CH\(_2\)Cl\(_2\) (4 mL) and acid 277 (0.07 g, 0.47 mmol), EDCI (0.07 g, 0.36 mmol) and HOBT (13.0 mg, 0.10
mmol) were added. The reaction was stirred at room temperature for 18 hours. The reaction mixture was then diluted with CH$_2$Cl$_2$ (5 mL) and washed with 1M aqueous solution of HCl (3 × 10 mL). The aqueous layers were combined, basified and extracted with CH$_2$Cl$_2$ (3 × 20 mL). The organic layers were then combined, dried (MgSO$_4$) and evaporated to give **248** (0.08 g, 0.22 mmol, 91%) as a pale oil which was used without further purification.

$^1$H NMR (500 MHz, CDCl$_3$) δ 0.84 – 0.87 (3H, m, CH$_3$ of 2 rotamers), 1.21 – 1.26 (6H, m, 2 × OCH$_2$CH$_3$ of 2 rotamers), 1.55 – 1.63 (2H, m, CH$_2$ of 2 rotamers), 2.92 (12H, s, 2 × N(CH$_3$)$_2$ of one rotamer), 2.93 (12H, s, 2 × N(CH$_3$)$_2$ of other rotamer), 3.27 (2H, t, $J = 7.6$ Hz, NCH$_2$CH$_2$ of one rotamer), 3.37 (2H, t, $J = 7.6$ Hz, NCH$_2$CH$_2$ of other rotamer), 3.58 – 3.77 (4H, m, 2 × OCH$_2$ of 2 rotamers), 4.54 (2H, s, CH$_2$N of one rotamer), 4.64 (2H, s, CH$_2$N of other rotamer), 5.04 (1H, s, CHOEt of one rotamer), 5.08 (1H, s, CHOEt of other rotamer), 5.98 – 6.06 (3H, m, 3 × ArH of 2 rotamers).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 11.1 (CH$_3$ of one rotamer), 11.3 (CH$_3$ of other rotamer), 15.1 (2 × OCH$_2$CH$_3$ of 2 rotamers), 20.1 (CH$_2$ of one rotamer), 21.4 (CH$_2$ of other rotamer), 40.7 (2 × N(CH$_3$)$_2$ of 2 rotamers), 46.9 (NCH$_2$CH$_2$ of one rotamer) 47.0 (NCH$_2$CH$_2$ of other rotamer), 48.1 (CH$_2$N of one rotamer), 50.5 (CH$_2$N of other rotamer), 62.8 (2 × OCH$_2$ of 2 rotamers), 96.2 (ArCH of one rotamer), 96.4 (ArCH of other rotamer), 100.1 (CHOEt of one rotamer), 100.5 (CHOEt of other rotamer), 100.9 (ArCH of one rotamer), 102.0 (ArCH of other rotamer), 138.5 (ArC of one rotamer), 138.6 (ArC of other rotamer), 151.7 (ArC of one rotamer), 151.8 (ArC of other rotamer), 167.4 (C=O of one rotamer), 167.5 (C=O of other rotamer).

IR (thin film) \( \nu_{\text{max}} \) (cm\(^{-1}\)) 2944, 1723 (C=O), 1568, 1527, 1487, 1432, 1398, 1387, 1365, 1289, 1253, 1211, 1196, 1039.

2,2-Diethoxyacetic acid (277)\(^{128}\)

To a solution of EtONa in EtOH (21%) 2,2-dichloroacetic acid (0.04 mL, 0.50 mmol) was added and the reaction was treated by microwave at 90 °C for 90 minutes. The solvent was evaporated and acidified with aqueous 1M HCl (15 mL) then extracted with CH\(_2\)Cl\(_2\) (3 \(\times\) 15 mL). The organic layers were combined and dried (MgSO\(_4\)) and evaporated to give acid 277 (0.07 g, 0.47 mmol, 94%) as a pale yellow oil which was used without further purification. Spectroscopic data were identical to the data previously published in the literature.\(^{128}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.27 (6H, t, \( J = 7.1 \) Hz, 2 \( \times \) CH\(_3\)), 3.65 – 3.75 (4H, m, 2 \( \times \) CH\(_2\)), 4.96 (1H, s, CH), 7.69 (1H, br. s, OH).

\(^13\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 14.9 (2 \( \times \) CH\(_3\)), 62.8 (2 \( \times \) CH\(_2\)), 96.9 (CH), 170.8 (C=O).

2-((3,5-Dimethoxybenzyl)(4-methoxybenzyl)amino)ethanol (249)

Benzaldehyde 278 (0.50 g, 3.01 mmol) was dissolved in anhydrous MeOH (15 mL) at room temperature. 2-Aminoethanol (0.20 mL, 3.30 mmol) was added then the reaction was heated at reflux for 3 hours. The reaction mixture was then cooled to 0 °C and NaBH\(_4\) (0.23 g, 6.00 mmol) was added quickly then the reaction mixture was allowed to warm to room temperature. After 14 hours, the solvent was removed then aqueous 1M HCl (15 mL) was added and the
resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 15 mL). The aqueous layer was basified to pH = 8 – 9 then the resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 15 mL). The organic layers were combined then washed with water (20 mL) and brine (20 mL), then dried (MgSO$_4$) and evaporated to give the intermediate product (0.44 g, 2.08 mmol).

The intermediate product (0.44 g, 2.08 mmol) and 4-methoxybenzaldehyde (0.38 mL, 3.12 mmol) were dissolved in MeCN (20 mL). The reaction mixture was cooled to 0 °C and NaBH$_3$CN (0.22 g, 3.54 mmol) was added quickly then AcOH (0.2 mL) was also added. The reaction was stirred for 5 minutes then the ice bath was removed and the reaction was stirred for 1 hour. AcOH (0.2 mL) was then added and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted by Et$_2$O (30 mL) and water (20 mL) and basified with concentrated aqueous Na$_2$CO$_3$. The aqueous phase was extracted with EtOAc (3 × 20 mL) then the organic phases were combined and washed with brine (50 mL), dried (MgSO$_4$), and evaporated. Purification by column chromatography eluting with 30 – 50 % EtOAc in petroleum ether gave 249 (0.40 g, 1.21 mmol, 40 % overall) as light yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.67 (2H, t, $J = 5.4$ Hz, NCH$_2$CH$_2$O), 3.56 (2H, s, NCH$_2$), 3.58 – 3.60 (4H, m, NCH$_2$, CH$_2$O), 3.79 (6H, s, 2 × OCH$_3$), 3.81 (3H, s, OCH$_3$), 6.37 (1H, t, $J = 2.3$ Hz, ArH), 6.49 (2H, d, $J = 2.3$ Hz, ArH), 6.87 (2H, d, $J = 8.5$ Hz, ArH), 7.23 (2H, d, $J = 8.5$ Hz, ArH).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 54.7 (NCH$_2$CH$_2$O), 55.2 (OCH$_3$), 55.3 (2 × OCH$_3$), 57.5 (NCH$_2$), 58.2 (NCH$_2$), 58.5 (CH$_2$O), 98.9 (ArCH), 106.8 (ArCH), 113.8 (ArCH), 130.2 (ArCH), 130.5 (ArC), 141.4 (ArC), 158.8 (ArC), 160.8 (ArC).

MS (ES+): $m/z$: 332 ([M + H]$^+$), HRMS (ES+): $m/z$: calcd for C$_{19}$H$_{26}$NO$_4$: 332.1857 ([M + H]$^+$); found: 332.1852.
IR (thin film) \( \nu_{\text{max}} (\text{cm}^{-1}) \): 2937 (br, OH), 2835, 1594, 1457, 1428, 1363, 1342, 1316, 1296, 1242, 1202, 1150, 1104, 1056, 1032.

**rac-3-((tert-Butyldiphenylsilyl)oxy)-2-((3,5-dimethoxybenzyl)(4-methoxybenzyl)amino)propan-1-ol (250)**

![Chemical Structure](image)

To anhydrous MeOH (45 mL) at 0 °C was added SOCl\(_2\) (3.75 mL, 51.4 mmol) dropwise and the reaction stirred for 30 minutes. DL-Serine (5.00 g, 47.6 mmol) was then added and the reaction was stirred at room temperature for 20 hours. The solvent was removed and the residue was triturated with petroleum ether many times to give HCl•DL-Ser•OMe (7.03 g, 45.2 mmol, 95%).

HCl•DL-Ser•OMe (0.78 g, 5.01 mmol) was dissolved in anhydrous MeOH (10 mL) then cooled to 0 °C before Et\(_3\)N (0.70 mL, 5.01 mmol) was added and the reaction was stirred for 15 minutes. 3,5-Dimethoxybenzaldehyde (0.83 g, 5.01 mmol) in anhydrous MeOH (5 mL) was then added and the reaction mixture was stirred at room temperature for 2 hours. NaBH\(_3\)CN (0.47 g, 7.50 mmol) was then added and the reaction was stirred at room temperature for 14 hours. Aqueous saturated NaHCO\(_3\) (20 mL) was added and the resulting mixture was extracted with EtOAc (3 × 20 mL). The organic layers were combined and washed with brine (50 mL), dried (MgSO\(_4\)) and evaporated. Purification by column chromatography eluting with 50 – 70 % EtOAc in petroleum ether gave 280 (0.78 g, 2.89 mmol, 57%) as colourless oil.

Amine 280 (0.78 g, 2.89 mmol) and 4-methoxybenzaldehyde were dissolved in MeCN (27 mL) and cooled to 0 °C. NaBH\(_3\)CN (0.31 g, 4.91 mmol) was added then AcOH (0.27 mL) was also added. After 15 minutes, the ice bath was removed and the reaction mixture was stirred at room temperature for 1 hour. AcOH (0.27 mL) was added and the reaction was stirred at room temperature for 14
hours. The reaction mixture was diluted with Et₂O (30 mL), water (30 mL) and basified by aqueous saturated Na₂CO₃ (5 mL). The aqueous phase was extracted with EtOAc (2 × 30 mL) and the organic phases were combined and washed with brine (100 mL), dried (MgSO₄) and evaporated. Purification by column chromatography eluting with 20 % EtOAc in petroleum ether gave 281 (0.94 g, 2.41 mmol, 83 %) as colourless oil.

Alcohol 281 (0.87 g, 2.24 mmol) was dissolved in anhydrous CH₂Cl₂ (15 mL) and imidazole (0.31 g, 4.48 mmol) and TBDPSCI (0.64 mL, 2.46 mmol) were added. The reaction mixture was stirred at room temperature for 14 hours and a aqueous saturated NH₄Cl (20 mL) was added. The aqueous phase was extracted with CH₂Cl₂ (2 × 20 mL) and the organic phases were washed with brine (40 mL), dried (MgSO₄) then evaporated. Purification by column chromatography eluting with 5 – 10 % EtOAc in petroleum ether gave 282 (1.40 g, 2.24 mmol, 100 %)

Ester 282 (1.56 g, 2.48 mmol) was dissolved in anhydrous Et₂O (20 mL) and cooled to 0 °C. LiBH₄ (0.27 g, 12.4 mmol) and anhydrous MeOH (0.35 mL) were added and the reaction mixture was heated at reflux for 19 hours. Aqueous saturated NaHCO₃ (20 mL) was added and the aqueous phase was extracted with EtOAc (3 × 20 mL). The organic phases were washed with brine (50 mL), dried (MgSO₄) and evaporated. Purification by column chromatography eluting with 10 – 15 % EtOAc in petroleum ether gave 250 (1.36 g, 2.26 mmol, 91 %) as colourless pale oil.

¹H NMR (400 MHz, CDCl₃) δ 1.10 (9H, s, SiC(CH₃)₃), 2.89 (1H, br. s., OH), 3.13 (1H, dd, J = 5.8, 8.9 Hz, CH₃H₈O), 3.53 – 3.60 (4H, m, CH₃H₈O, NCH, NCH₂), 3.75 (1H, dd, J = 6.1, 10.6 Hz, CH₃H₈O), 3.77 (6H, s, 2 × OCH₃), 3.81 (3H, s, OCH₃), 3.82 (1H, d, J = 5.2 Hz, NCH₃H₈O), 3.86 (1H, d, J = 5.2, NCH₃H₈O), 3.89 (1H, dd, J = 6.1, 10.6 Hz, CH₃H₈O), 6.36 (1H, t, J = 2.3 Hz, ArCH), 6.43 (2H, d, J = 2.3 Hz, 2 × ArH), 6.86 (2H, d, J = 8.8 Hz, 2 × ArH), 7.18 (2H, d, J = 8.6 Hz, 2 × ArCH), 7.41 – 7.50 (6H, m, 6 × ArH), 7.68 – 7.71 (4H, m, 4 × ArH).
$^{13}$C NMR (100 MHz, CDCl$_3$) δ 19.1 (SiC), 26.8 (SiC(CH$_3$)$_3$), 53.4 (NCH$_2$), 54.0 (NCH$_2$), 55.2 (NCH), 55.3 (2 × OCH$_3$), 59.5 (CH$_2$O), 60.0 (OCH$_3$), 61.4 (CH$_2$O), 98.9 (ArCH), 106.7 (ArCH), 113.8 (ArCH), 127.8 (ArCH), 129.8 (ArCH), 130.1 (ArCH), 131.4 (ArC), 133.0 (ArC), 135.5 (ArCH), 135.6 (ArCH), 142.3 (ArC), 158.7 (ArC), 160.8 (ArC).

MS (ES$^+$): $m/z$: 600 ([M + H]$^+$), HRMS (ES$^+$): $m/z$: calcd for C$_{36}$H$_{46}$NO$_5$Si: 600.3140 ([M + H]$^+$); found: 600.3137.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 3464 (br, OH), 3070, 2931, 1607, 1595, 1510, 1461, 1427, 1390, 1360, 1317, 1297, 1245, 1203, 1151, 1106, 1063.

6.2.2 Tetrahydroisoquinoline ring formation

**Methyl 3-(7-(dimethylamino)-5,8-dimethoxy-oxo-2-propyl-1,2,3,4-tetrahydroisoquinolin-4-ylthio)propanoate (284)**

![Structure](image.png)

Oxalyl chloride (0.06 mL, 0.70 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (3.0 mL) under N$_2$. The solution was cooled to −78 °C. Dimethyl sulfoxide (0.09 mL, 1.28 mmol) was added and the solution was stirred for 5 minutes at −78 °C. **244** (0.20 g, 0.64 mmol) in anhydrous CH$_2$Cl$_2$ (2.0 mL) was added slowly. The reaction was stirred at −78 °C for 30 minutes. Et$_3$N (0.45 mL, 3.20 mmol) was added and the reaction was allowed to warm to room temperature. The reaction was stirred for 3 hours at room temperature. The reaction mixture was diluted with CH$_2$Cl$_2$ (5 mL) and washed with aqueous saturated sodium hydrogencarbonate.
solution (3 × 5 mL). The organic layer was dried (MgSO₄) and evaporated to give 283 which was used directly in the next step without further purification.

The product 283 from the previous step was divided into 3 equal portions. One portion (0.07 g, 0.22 mmol) was dissolved in anhydrous CHCl₃ (3.5 mL) under N₂. Methyl-3-mercaptopropionate (0.04 mL, 0.32 mmol) and ZnCl₂ (44.0 mg, 0.32 mmol) were added. The reaction was heated at reflux for 16 hours. Subsequently, the reaction mixture was diluted with CHCl₃ (5 mL) and washed with H₂O (5 mL) and brine (5 mL). The organic layer was dried (MgSO₄) and evaporated to give the crude product. Purification by column chromatography eluting with 20 % of EtOAc in n-hexane containing 1% Et₃N gave 284 (0.06 g, 0.14 mmol, 63%) as a light yellow pale oil.

1H NMR (500 MHz, CDCl₃) δ 0.94 (3H, t, J = 7.6 Hz, CH₃), 1.62 - 1.70 (2H, m, CH₂), 2.74 – 2.81 (2H, m, CH₂C=O), 2.82 (6H, s, N(CH₃)₂), 2.88 – 2.94 (1H, m, SCH₂H₈), 3.09 – 3.15 (1H, m, SCH₂H₈), 3.31 – 3.36 (1H, m, NCH₂H₈), 3.59 – 3.66 (1H, m, NCH₂H₈), 3.68 (3H, s, OCH₃), 3.71 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 4.44 (1H, d, J = 16.1 Hz, CH₃H₈N), 4.54 (1H, d, J = 16.1 Hz, CH₃H₈N), 4.78 (1H, s, CHS), 6.36 (1H, s, ArH).

13C NMR (125 MHz, CDCl₃) δ 11.1 (CH₃), 20.6 (CH₂), 27.2 (SCH₂), 34.4 (CH₂C=O), 40.9 (CHS), 42.1 (N(CH₃)₂), 45.1 (CH₂N), 48.8 (NCH₂), 51.6 (OCH₃), 55.9 (OCH₃), 58.6 (OCH₃), 100.5 (ArCH), 113.4 (ArC), 127.8 (ArC), 140.6 (ArC), 145.3 (ArC), 152.2 (ArC), 168.1 (C=O), 172.4 (C=O).


IR (thin film) νmax (cm⁻¹) 2939, 1736 (C=O), 1646 (C=O), 1496, 1436, 1355, 1233, 1073, 1010.
7-(Dimethylamino)-4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-heptadecafluorodecylthio)-5,8-dimethoxy-2-propyl-1,2-dihydroisoquinolin-3(4H)-one (285)

Crude glyoxamide 283 (0.22 mmol) was dissolved in anhydrous CHCl₃ (3.5 mL) under N₂. C₈F₁₇CH₂CH₂SH (0.09 mL, 0.32 mmol) and ZnCl₂ (44.0 mg, 0.32 mmol) were also added. The reaction was heated at reflux for 18 hours. The reaction mixture was diluted with CHCl₃ (5 mL) and washed with water (5 mL) and brine (5 mL). The organic layer was dried (MgSO₄) and evaporated to give the crude product. Purification by column chromatography eluting with 10 % of EtOAc in n-hexane containing 1% Et₃N gave 285 (81.2 mg, 0.11 mmol, 50%) as a light yellow pale oil.

¹H NMR (500 MHz, CDCl₃) δ 0.95 (3H, t, J = 7.3 Hz, CH₃), 1.62 – 1.71 (2H, m, CH₂CH₃), 2.49 – 2.61 (2H, m, CH₂C₈F₁₇), 2.82 – 2.90 (1H, m, NCH₃H₈), 2.85 (6H, s, N(CH₃)$_₂$), 3.04 – 3.11 (1H, m, NCH₃H₈), 3.32 – 3.39 (1H, m, SCH₃H₈), 3.60 – 3.68 (1H, m, SCH₃H₈), 3.73 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 4.47 (1H, d, J = 16.1 Hz, ArCH₃H₈N), 4.55 (1H, d, J = 16.1 Hz, ArCH₃H₈N), 4.82 (1H, s, CHS), 6.38 (1H, s, ArH).

¹³C NMR (125 MHz, CDCl₃) δ 11.1 (CH₃), 20.6 (CH₂CH₃), 23.0 (NCH₃), 31.9 (CH₂C₈F₁₇), 41.2 (CHS), 42.1 (N(CH₃)$_₂$), 45.2 (CH₂N), 48.9 (SCH₂), 55.8 (OCH₃), 58.6 (OCH₃), 100.4 (ArCH), 112.9 (ArC), 127.8 (ArC), 140.7 (ArC), 145.5 (ArC), 152.3 (ArC), 167.8 (C=O).

MS (ES+): m/z: 793 ([M + Na]$^+$), HRMS (ES+): m/z: calcd for C$_{26}$H$_{27}$N$_2$O$_3$F$_{17}$NaS: 793.1363 ([M + Na]$^+$); found: 793.1367.
IR (thin film) \( \nu_{\text{max}} \) (cm\(^{-1}\)) 2796, 1653 (C=O), 1606, 1498, 1359, 1236, 1148, 1013.

**4-(Cyclohexylthio)-7-(dimethylamino)-5,8-dimethoxy-2-propyl-1,2-dihydriisoquinolin-3(4H)-one (286)**

![Chemical Structure](image)

Crude glyoxamide 283 (0.22 mmol) was dissolved in anhydrous CHCl\(_3\) (3.5 mL). Cyclohexyl mercaptan (0.04 mL, 0.32 mmol) and ZnCl\(_2\) (44.0 mg, 0.32 mmol) were then added and the reaction was heated at reflux for 16 hours. The reaction mixture was diluted with CHCl\(_3\) (5 mL) and washed with H\(_2\)O (5 mL) and brine (5 mL). The organic layer was dried (MgSO\(_4\)) and evaporated to give the crude product. Purification by column chromatography eluting with 15 % of EtOAc in n-hexane containing 1% Et\(_3\)N gave 286 (51.0 mg, 0.13 mmol, 58%) as a colourless pale oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 0.95 (3H, t, \( J = 7.3 \) Hz, CH\(_3\)), 1.23 – 1.80 (10H, m, 4 \times CH\(_2\) of cyclohexyl ring and CH\(_2\) of n-propyl), 1.90 – 1.92 (1H, m, CH\(_A\)H\(_B\)), 2.31 – 2.33 (1H, m, CH\(_A\)H\(_B\)), 2.83 (6H, s, N(CH\(_3\))\(_2\)), 3.09 – 3.15 (1H, m, SCH(CH\(_2\))\(_2\)), 3.32 – 3.39 (1H, m, NCH\(_A\)H\(_B\)), 3.59 – 3.64 (1H, m, NCH\(_A\)H\(_B\)), 3.72 (3H, s, OCH\(_3\)), 3.84 (3H, s, OCH\(_3\)), 4.44 (1H, d, \( J = 16.1 \) Hz, CH\(_A\)H\(_B\)H\(_N\)), 4.57 (1H, d, \( J = 16.1 \) Hz, CH\(_A\)H\(_B\)H\(_N\)), 4.87 (1H, s, CHS), 6.37 (1H, s, ArH).

\(^13\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 11.1 (CH\(_3\)), 20.6 (CH\(_2\)), 25.9 (CH\(_2\)), 32.9 (CH\(_2\)), 33.6 (CH\(_2\)), 39.6 (CHS), 42.2 (N(CH\(_3\))\(_2\)), 43.8 (SCH(CH\(_2\))\(_2\)), 45.1 (CH\(_2\)N), 48.8 (NCH\(_2\)), 56.0 (OCH\(_3\)), 58.7 (OCH\(_3\)), 100.7 (ArCH), 114.5 (ArC), 128.0 (ArC), 140.8 (ArC), 145.0 (ArC), 152.0 (ArC), 168.9 (C=O).

IR (thin film) ν_max (cm⁻¹) 2928, 2851, 1645 (C=O), 1605, 1496, 1444, 1356, 1232, 1073, 1010.

(R)-Methyl 3-(7-(dimethylamino)-5,8-dimethoxy-3-oxo-2-propyl-1,2,3,4-tetrahydroisoquinolin-4-thio)-2-((2,2,2-trichloroethoxy)carbonylamino)-propanoate (287)

Oxalyl chloride (0.06 mL, 0.70 mmol) was dissolved in anhydrous CH₂Cl₂ (3.0 mL) and the solution was cooled to −78 °C. Dimethyl sulfoxide (0.09 mL, 1.28 mmol) was added and the solution was stirred for 5 minutes at −78 °C. Alcohol 244 (0.20 g, 0.64 mmol) in anhydrous CH₂Cl₂ (2.0 mL) was then added slowly and the reaction was stirred at −78 °C for 30 minutes before Et₃N (0.45 mL, 3.20 mmol) was added and the reaction was allowed to warm to room temperature. The reaction was stirred for 3 hours at room temperature. The reaction mixture was then diluted with CH₂Cl₂ (5 mL) and washed with a saturated aqueous solution of NaHCO₃ (3 × 5 mL). The organic layer was dried (MgSO₄) and evaporated to give 283 which was used directly in the next step without further purification.

The product from the previous step was divided into 3 equal portions. One portion (0.07 g, 0.22 mmol) was dissolved in anhydrous CHCl₃ (3.5 mL). N-Troc-L-cysteine methyl ester (freshly prepared) (0.10 g, 0.32 mmol) and ZnCl₂ (44.0 mg, 0.32 mmol) were added and the reaction was heated at reflux for 16 hours. The reaction mixture was diluted with chloroform (5 mL) and washed with water (5 mL) and brine (5 mL). The organic layer was dried (MgSO₄) and evaporated to
give the crude product. Purification by column chromatography eluting with 20% of ethyl acetate in n-hexane containing 0.5% triethylamine gave 287 (64.1 mg, 0.11 mmol, 50%) as a light yellow pale oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.95 (3H, t, $J = 7.3$ Hz, CH$_3$), 1.62 – 1.71 (2H, m, CH$_2$), 2.84 (6H, s, N(CH$_3$)$_2$), 3.10 – 3.18 (1H, m, CHN), 3.34 – 3.46 (2H, m, NCH$_A$H$_B$CH$_2$ and SCH$_A$H$_B$), 3.53 – 3.66 (2H, m, NCH$_A$H$_B$CH$_2$ and SCH$_A$H$_B$), 3.71(3H, s, OCH$_3$ of one diastereomer), 3.72 (3H, s, OCH$_3$ of other diastereomer), 3.74 (3H, s, OCH$_3$ of one diastereomer), 3.78 (3H, s, OCH$_3$ of other diastereomer), 3.84 (3H, s, OCH$_3$ of one diastereomer), 3.95 (3H, s, OCH$_3$ of other diastereomer), 4.47 (2H, s, CH$_2$CCl$_3$ of one diastereomer), 4.48 (2H, s, CH$_2$CCl$_3$ of one diastereomer), 4.50 – 4.86 (2H, m, CH$_2$N), 4.78 (1H, s, CHS of one diastereomer), 4.92 (1H, s, CHS of other diastereomer), 6.37 (1H, s, ArH of one diastereomer), 6.40 (1H, s, ArH of other diastereomer), 6.76 (1H, d, $J = 8.6$ Hz, NH of one diastereomer), 7.28 (1H, d, $J = 8.0$ Hz, NH of other diastereomer).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 11.1 (CH$_3$), 20.4 (CH$_2$ of one diastereomer), 20.5 (CH$_2$ of other diastereomer), 33.7 (NCH$_2$CH$_2$ of one diastereomer), 34.0 (NCH$_2$CH$_2$ of other diastereomer), 40.9 (CHS of one diastereomer), 41.4 (CHS of other diastereomer), 42.0 (N(CH$_3$)$_2$), 45.2 (CH$_2$CCl$_3$), 48.8 (SCH$_2$ of one diastereomer), 49.0 (SCH$_2$ of other diastereomer), 52.5 (OCH$_3$ of one diastereomer), 52.9 (OCH$_3$ of other diastereomer), 55.0 (OCH$_3$ of one diastereomer), 55.7 (OCH$_3$ of other diastereomer), 55.9 (OCH$_3$ of one diastereomer), 58.5 (OCH$_3$ of other diastereomer), 74.5 (CH$_2$N of one diastereomer), 74.8 (CH$_2$N of other diastereomer), 95.4 (ArC of one diastereomer), 95.6 (ArC of other diastereomer), 100.5 (ArCH), 112.3 (ArC of one diastereomer), 112.5 (ArC of other diastereomer), 127.1 (ArC of one diastereomer), 127.3 (ArC of other diastereomer), 140.5 (ArC of one diastereomer), 145.5 (ArC of other diastereomer), 152.3 (ArC of one
diastereomer), 154.5 (ArC of other diastereomer), 168.1 (C=O), 168.3 (C=O), 170.6 (C=O of one diastereomer), 170.9 (C=O of other diastereomer).

MS (ES+): \( m/z \): 622 ([\( M + Na \)]\(^+ \)), HRMS (ES+): \( m/z \): calcd for \( C_{23}H_{32}O_7N_3^{35}Cl_3NaS: 622.0919 ([\( M + Na \)]\(^+ \)); found: 622.0910.

IR (thin film) \( \nu_{\text{max}} \) (cm\(^{-1}\)) 2955, 1737 (C=O), 1636 (C=O), 1605, 1497, 1436, 1235, 1074, 1011.

**Methyl 3-(5,7-bis(dimethylamino)-3-oxo-2-propyl-1,2,3,4-tetrahydroisoquinolin-4-ylthio)propanoate (289)**

![Methyl 3-(5,7-bis(dimethylamino)-3-oxo-2-propyl-1,2,3,4-tetrahydroisoquinolin-4-ylthio)propanoate](image)

Method A:
Sulfur trioxide pyridine complex (76.0 mg, 0.48 mmol) was dissolved in anhydrous CH\(_2\)Cl\(_2\) (2.0 mL). The mixture was cooled to –8 to –5 °C and DMSO (46.0 \( \mu \)L, 0.64 mmol) was added. The mixture was stirred at –8 to –5 °C for 15 minutes. Et\(_3\)N (0.34 mL, 2.40 mmol) was added and followed by 245 (47.0 mg, 0.16 mmol) in CH\(_2\)Cl\(_2\) (0.5 mL). The reaction was stirred at –8 to –5 °C for 5 hours. The reaction mixture was washed with a saturated aqueous solution of NaHCO\(_3\) and dried (MgSO\(_4\)) and evaporated to give the crude product.

Sulfur trioxide pyridine complex (127 mg, 0.80 mmol) was dissolved in anhydrous CH\(_2\)Cl\(_2\) (2.0 mL). The mixture was cooled to 0 °C and DMSO (69.0 \( \mu \)L, 0.96 mmol) was added. The mixture was stirred at 0 °C for 15 minutes. Et\(_3\)N (0.34 mL, 2.40 mmol) was added and followed by crude product in CH\(_2\)Cl\(_2\) (0.5 mL). The reaction was stirred at 0 – 5 °C for 5 hours. The reaction mixture was washed with aqueous saturated NaHCO\(_3\) and dried (MgSO\(_4\)) and evaporated to give 288 (48.0 mg).
Glyoxamide 288 (48.0 mg) was dissolved in anhydrous CHCl₃ (3.5 mL). HSCH₂CH₂COOCH₃ (29.0 µL, 0.24 mmol) and ZnCl₂ (33.0 mg, 0.24 mmol) were added. The reaction was heated at reflux for 20 hours. The reaction mixture was diluted with CHCl₃ (5 mL) and washed with H₂O (5 mL) and brine (5 mL). The organic layer was dried (MgSO₄) and evaporated to give the crude product. Purification by column chromatography eluting with 30 % of ethyl acetate in n-hexane containing 0.5% Et₃N gave 289 (25.8 mg, 0.07 mmol, 41%) as a light yellow pale oil.

Method B:
Glyoxamide 288 (30 mg, 0.08 mmol) was dissolved in anhydrous MeCN under N₂. HSCH₂CH₂COOMe (14 µL, 0.12 mmol) and Sc(OTf)₃ (40 mg, 0.08 mmol) were also added. The reaction was heated at reflux for 16 hours. The reaction mixture was diluted with aqueous saturated NaHCO₃ (10 mL). The resulting mixture was extracted with EtOAc (3 × 15 mL). The organic layers were combined and washed with brine (20 mL) then dried (MgSO₄) and evaporated to give crude product. Purification by column chromatography eluting with with 30 % of ethyl acetate in n-hexane containing 0.5% Et₃N gave 289 (12 mg, 0.03 mmol, 37%) as a light yellow pale oil.

¹H NMR (500 MHz, CDCl₃) δ 0.95 (3H, t, J = 7.6 Hz, CH₃), 1.60 – 1.67 (2H, m, CH₂), 2.77 (6H, s, N(CH₃)₂), 2.77 – 2.83 (2H, m, SCH₂CH₂), 2.88 – 2.95 (1H, m, NCH₃H₈CH₂), 2.95 (6H, s, N(CH₃)₂), 3.09 – 3.14 (1H, m, NCH₃H₈CH₂), 3.21 – 3.27 (1H, m, SCHₐH₈), 3.64 – 3.69 (1H, m, SCHₐH₈), 3.68 (3H, s, OCH₃), 3.97 (1H, d, J = 14.8 Hz, CHₐH₈N), 4.88 (1H, d, J = 14.8 Hz, CHₐH₈N), 4.89 (1H, s, CHS), 6.24 (1H, br. s., ArH), 6.37 (1H, br. s., ArH).

¹³C NMR (125 MHz, CDCl₃) δ 11.2 (CH₃), 20.8 (CH₂CH₃), 27.1 (NCH₂CH₂), 34.3 (SCH₂CH₂), 40.4 (N(CH₃)₂), 43.4 (CHS), 45.2 (N(CH₃)₂), 48.6 (SCH₂), 51.0 (CH₂N),
140.6 (OCH₃), 103.2 (ArCH), 104.5 (ArCH), 115.2 (ArC), 136.1 (ArC), 150.6 (ArC), 153.3 (ArC), 168.8 (C=O), 172.5 (C=O).


IR (thin film) ν max (cm⁻¹) 2936, 1734 (C=O), 1645 (C=O), 1603, 1504, 1476, 1345, 1371, 1293, 1242, 1196, 1116, 1015.

Methyl 3-((5-hydroxy-7,8-dimethoxy-6-methyl-3-oxo-2-propyl-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate (291A)

Methyl 3-((5-(benzyloxyl)-7,8-dimethoxy-6-methyl-3-oxo-2-propyl-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate (291B)

Method A:
Sulfur trioxide pyridine complex (80.0 mg, 0.50 mmol) was dissolved in anhydrous CH₂Cl₂ (2.0 mL) and the mixture was cooled to 0 °C and DMSO (50.0 μL, 0.60 mmol) was added. The mixture was stirred at 0 °C for 15 minutes. Triethylamine (0.21 mL, 1.50 mmol) was added followed by 246 (40.0 mg, 0.10 mmol) in CH₂Cl₂ (1 mL) and the reaction was stirred at room temperature for 16 hours. The reaction mixture was diluted with CH₂Cl₂ and washed with a
saturated aqueous solution of NaHCO₃, dried (MgSO₄) and evaporated to give the crude glyoxamide 290.

The crude glyoxamide 290 (40.0 mg, 0.10 mmol) was dissolved in MeCN (3 mL), and methyl-3-mercaptopropionate (18.0 µL, 0.15 mmol) and Sc(OTf)₃ (98.4 mg, 0.20 mmol) were added. The reaction was heated at 60 °C for 17 hours, then the solvent was evaporated. Brine (10 mL) was added to the residue and the resulting mixture was extracted with CH₂Cl₂ (3 × 10 mL). The organic phases were combined, dried (MgSO₄) and evaporated to give the crude product. Purification by column chromatography eluting with 25% EtOAc in petroleum ether produced 291A (11.4 mg, 0.03 mmol, 29%) as a light yellow pale oil.

Method B:

Oxalyl chloride (0.05 mL, 0.60 mmol) was dissolved in anhydrous CH₂Cl₂ (3.0 mL) and the solution was cooled to −78 °C. A solution of dimethyl sulfoxide (0.08 mL, 1.08 mmol) in anhydrous CH₂Cl₂ (2.0 mL) was added and the solution was stirred for 5 minutes at −78 °C. A solution of 246 (0.21 g, 0.54 mmol) in anhydrous CH₂Cl₂ (2.0 mL) was added slowly, and then the reaction was stirred at −78 °C for 1 hour. Triethylamine (0.38 mL, 2.70 mmol) was added and the reaction was allowed to warm to room temperature and stirred for 3 hours. The reaction mixture was diluted with CH₂Cl₂ (5 mL) and washed with a saturated aqueous solution of NaHCO₃ solution (3 × 5 mL). The organic layer was dried (MgSO₄) and evaporated to give 290, which was used directly in the next step without further purification.

Glyoxamide 290 (50.0 mg, 0.13 mmol) was dried under high vacuum at 75 °C for 5 hours then dissolved in anhydrous MeCN (4.0 mL). Methyl-3-mercaptopropionate (0.05 mL, 0.39 mmol) and Sc(OTf)₃ (0.13 g, 0.26 mmol) were added. The reaction was heated at 60 °C for 13 hours. Subsequently, the solvent was evaporated, then a saturated aqueous solution of NaHCO₃ solution
(10 mL) was added, and the resulting mixture extracted with CH$_2$Cl$_2$ (3 × 10 mL). The organic phases were combined and dried (MgSO$_4$) and evaporated to give the crude product. Purification by column chromatography eluting with 30 % EtOAc in petroleum ether gave 291A (18.0 mg, 45.3 µmol, 35 %) as a light yellow oil and 291B (16.0 mg, 32.8 µmol, 20 %) as a colourless oil.

For 291A:

$^1$H NMR (400 MHz, CDCl$_3$) δ 0.97 (3H, t, $J = 7.3$ Hz, CH$_3$), 1.66 – 1.72 (2H, m, CH$_2$), 2.19 (3H, s, ArCH$_3$), 2.76 – 2.82 (1H, m, SCH$_A$H$_B$), 2.84 – 2.90 (1H, m, SCH$_2$CH$_A$H$_B$), 2.93 – 2.98 (1H, m, SCH$_A$H$_B$), 3.31 – 3.42 (2H, m, SCH$_2$CH$_A$H$_B$ and NCH$_A$H$_B$CH$_2$), 3.57 – 3.65 (1H, m, NCH$_A$H$_B$CH$_2$), 3.76 (3H, s, OCH$_3$), 3.81 (3H, s, OCH$_3$), 3.82 (3H, s, OCH$_3$), 4.45 (1H, d, $J = 16.1$ Hz, CH$_A$H$_B$N), 4.51 (1H, d, $J = 16.1$ Hz, CH$_A$H$_B$N), 4.77 (1H, s, CHS), 6.22 (1H, br. s, OH).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 9.1 (ArCH$_3$), 11.1 (CH$_3$), 20.4 (CH$_2$), 27.4 (SCH$_2$CH$_2$), 33.9 (SCH$_2$), 40.4 (CHS), 45.1 (CH$_2$N), 48.9 (NCH$_2$CH$_2$), 52.2 (OCH$_3$), 60.3 (OCH$_3$), 60.7 (OCH$_3$), 113.9 (ArC), 119.4 (ArC), 123.2 (ArC), 142.1 (ArC), 147.9 (ArC), 151.2 (ArC), 167.4 (C=O), 173.4 (C=O).

MS (ES–): $m/z$: 396 ([M – H]$^+$), HRMS (ES–): $m/z$: calcd for C$_{19}$H$_{26}$N$_1$O$_6$S$_1$: 396.1486 ([M – H]$^+$); found: 396.1474.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2956, 1737 (C=O), 1646 (C=O), 1462, 1437, 1346, 1239, 1128, 1086, 1061.

For 291B:

$^1$H NMR (400 MHz, CDCl$_3$) δ 0.96 (3H, t, $J = 7.3$ Hz, CH$_3$), 1.62 – 1.71 (2H, m, CH$_2$CH$_3$), 2.22 (3H, s, ArCH$_3$), 2.57 – 2.65 (1H, m, SCH$_2$CH$_A$H$_B$), 2.68 – 2.76 (1H, m, SCH$_2$CH$_A$H$_B$), 2.87 – 2.94 (1H, m, SCH$_A$H$_B$), 3.04 – 3.11 (1H, m, SCH$_A$H$_B$), 3.27 – 3.24 (1H, m, NCH$_A$H$_B$), 3.62 (3H, s, OCH$_3$), 3.64 – 3.69 (1H, m, NCH$_A$H$_B$), 3.84 (3H,
s, OCH₃), 3.86 (3H, s, OCH₃), 4.43 (1H, d, \( J = 15.9 \) Hz, CH₂AH₂N), 4.58 (1H, d, \( J = 15.9 \) Hz, CH₂AH₂N), 4.81 (1H, s, CHS), 4.85 (1H, d, \( J = 11.4 \) Hz, OCH₂AH₃), 5.12 (1H, d, \( J = 11.4 \) Hz, OCH₂AH₃), 7.35 – 7.51 (5H, ArH).

\(^{13}\)C NMR (100 MHz, CDCl₃) \( \delta \) 9.9 (ArCH₃), 11.2 (CH₃), 20.7 (CH₂CH₃), 27.3 (SCH₂), 34.2 (SCH₂CH₂), 41.8 (CHS), 44.6 (CH₂N), 48.9 (CH₂CH₂), 51.6 (OCH₃), 60.2 (OCH₃), 60.7 (OCH₃), 75.7 (OCH₂), 122.3 (ArC), 125.3 (ArC), 125.7 (ArC), 127.5 (ArCH), 128.1 (ArCH), 128.6 (ArCH), 137.2 (ArC), 145.1 (ArC), 150.5 (ArC), 151.2 (ArC), 167.6 (C=O), 172.3 (C=O).

IR (thin film) \( \nu_{\text{max}} \) (cm\(^{-1}\)) 1738 (C=O), 1652 (C=O), 1465, 1350, 1295, 1119.

MS (ES+): \( m/z \): 510 ([M + Na]⁺), HRMS (ES+): \( m/z \): calcd for C\(_{26}\)H\(_{34}\)O\(_6\)NS: 488.2101 ([M + H]⁺); found: 488.2106.

Methyl 3-((5,7,8-trimethoxy-2-(4-methoxybenzyl)-6-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate (293A)

Oxalyl chloride (0.05 mL, 0.60 mmol) was dissolved in anhydrous CH₂Cl₂ (3 mL) under N\(_2\). The solution was cooled to –78 °C. A solution of dimethyl sulfoxide (0.07 mL, 0.96 mmol) in anhydrous CH₂Cl₂ (2.0 mL) was added and the resulting mixture was stirred for 5 minutes at –78 °C. 247 (186 mg, 0.48 mmol) in anhydrous CH₂Cl₂ (2 mL) was added slowly. The reaction was stirred at –78 °C for 1 hour. Triethylamine (0.33 mL, 2.40 mmol) was added and the reaction was allowed to warm to room temperature. The reaction was stirred for 3 hours at room temperature. The reaction mixture was diluted with CH₂Cl₂ (5 mL) and washed with a saturated aqueous solution of NaHCO₃ (3 × 5 mL). The organic
layer was dried (MgSO₄) and evaporated to give 292, which was used directly in the next step without further purification.

Glyoxamide 292 (50.0 mg, 0.13 mmol) was dried under high vacuum at 90 °C for 2 hours, then 95 °C for 1 hour, then dissolved in anhydrous MeCN (4.0 mL) under N₂. Methyl-3-mercaptopropionate (24.0 μL, 0.20 mmol) and Sc(OTf)₃ (98.0 mg, 0.20 mmol) were added. The reaction was heated at 60 °C for 14 hours. After that, the solvent was evaporated, then a saturated aqueous solution of NaHCO₃ (10 mL) was added, and the resulting mixture was extracted with CH₂Cl₂ (3 × 10 mL). The organic layers were combined and dried (MgSO₄) and evaporated to give the crude product. Purification by column chromatography eluting with 25 % of EtOAc in petroleum ether gave 293A (38.0 mg, 77.6 μmol, 60 %) as a light yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 2.19 (3H, s, ArCH₃), 2.78 – 2.83 (2H, m, CH₂C=O), 2.95 – 3.03 (1H, m, SCH₂H₈), 3.19 – 3.26 (1H, m, SCH₂H₈), 3.65 (3H, s, OCH₃), 3.70 (3H, s, OCH₃), 3.78 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 3.84 (3H, s, OCH₃), 4.35 (1H, d, J = 15.9 Hz, CH₃N), 4.41 (1H, d, J = 15.9 Hz, CH₂N), 4.58 (1H, d, J = 14.6 Hz, NCH₂H₈(PMB)), 4.76 (1H, d, J = 14.6 Hz, NCH₂H₈(PMB)), 4.85 (1H, s, CHS), 6.87 (2H, d, J = 8.6 Hz, ArH), 7.23 (2H, d, J = 8.6 Hz, ArH).

¹³C NMR (100 MHz, CDCl₃) δ 9.6 (CH₃), 27.3 (CH₂C=O), 34.3 (SCH₂), 41.4 (CHS), 44.0 (CH₂N), 49.6 (NCH₂ of PMB), 51.7 (OCH₃), 55.2 (OCH₃), 60.1 (OCH₃), 60.5 (OCH₃), 61.6 (OCH₃), 114.0 (ArCH), 121.7 (ArC), 124.9 (ArC), 125.3 (ArC), 128.7 (ArC), 129.2 (ArCH), 144.9 (ArC), 151.2 (ArC), 151.6 (ArC), 159.0 (ArC), 167.8 (C=O), 172.3 (C=O).

MS (ES+): m/z: 512 ([M + Na]⁺), HRMS (ES+): m/z: calcd for C₂₅H₃₂NO₇S: 490.1894 ([M + H]⁺); found: 490.1890.
IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 1737 (C=O), 1650 (C=O), 1611, 1512, 1464, 1408, 1347, 1298, 1174, 1115, 1032.

(2R)-Methyl 2-(((2,2,2-trichloroethoxy)carbonyl)amino)-3-((5,7,8-trimethoxy-2-(4-methoxybenzyl)-6-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)-propanoate (293B)

Oxalyl chloride (0.05 mL, 0.60 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (3.0 mL) under N$_2$. The solution was cooled to $-78 \, ^\circ$C. A solution of dimethyl sulfoxide (0.07 mL, 0.96 mmol) in anhydrous CH$_2$Cl$_2$ (2.0 mL) was added at $-78 \, ^\circ$C and the solution was stirred for 5 minutes at $-78 \, ^\circ$C. A solution of hydroxyamide 247 (186 mg, 0.48 mmol) in anhydrous CH$_2$Cl$_2$ (2.0 mL) was added slowly. The reaction was stirred at $-78 \, ^\circ$C for 1 hour. Triethylamine (0.33 mL, 2.40 mmol) was added and the reaction was allowed to warm to room temperature. The reaction was stirred for 3 hours at room temperature. The reaction mixture was diluted with CH$_2$Cl$_2$ (5 mL) and washed with a saturated aqueous solution of NaHCO$_3$ (3 x 5 mL). The organic layer was dried (MgSO$_4$) and evaporated to give 292, which was used directly in the next step without further purification.

Glyoxamide 292 (46.0 mg, 0.12 mmol) was dried under high vacuum at 95 $^\circ$C for 3 hours then dissolved in anhydrous MeCN (4 mL). N-Troc-L-cysteine methyl ester (56.0 mg, 0.18 mmol) and Sc(OTf)$_3$ (89.0 mg, 0.20 mmol) were added. The reaction was heated at 60 $^\circ$C for 17 hours. After that, the solvent was evaporated then a saturated aqueous solution of NaHCO$_3$ (10 mL) was added. The resulting mixture was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The organic layers were combined and dried (MgSO$_4$) and evaporated to give the crude product.
Purification by column chromatography eluting with 30% of EtOAc in petroleum ether gave **293B** (43.0 mg, 63.2 \( \mu \text{mol} \), 53%) as a light yellow foam. M.p. 49 – 53 °C.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 2.19 (3H, s, ArCH\(_3\) of one diastereomer), 2.20 (3H, s, ArCH\(_3\) of other diastereomer), 3.15 (1H, dd, \( J = 14.4, 7.1 \, \text{Hz} \), SCH\(_A\)H\(_B\) of one diastereomer), 3.18 (1H, dd, \( J = 14.4, 4.0 \, \text{Hz} \), SCH\(_A\)H\(_B\) of other diastereomer), 3.40 (1H, dd, \( J = 14.4, 7.1 \, \text{Hz} \), SCH\(_A\)H\(_B\) of one diastereomer), 3.53 (1H, dd, \( J = 14.4, 4.0 \, \text{Hz} \), SCH\(_A\)H\(_B\) of other diastereomer), 3.65 (3H, s, OCH\(_3\)), 3.77 (3H, s, OCH\(_3\)), 3.79 (3H, s, OCH\(_3\)), 3.80 (3H, s, OCH\(_3\)), 3.82 (3H, s, OCH\(_3\)) 4.37 (2H, s, NCH\(_2\)(PMB)), 4.61 – 4.80 (5H, m, CH\(_2\)N, CH\(_2\)CCl\(_3\), CHN), 4.89 (1H, s, CHS of one diastereomer), 4.99 (1H, s, CHS of other diastereomer), 6.61 (1H, d, \( J = 7.8 \, \text{Hz} \), NH of one diastereomer), 6.87 (2H, d, \( J = 8.6 \, \text{Hz} \), ArH), 7.00 (1H, d, \( J = 8.1 \, \text{Hz} \), NH of other diastereomer), 7.23 (2H, d, \( J = 8.6 \, \text{Hz} \), ArH).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 9.7 (ArCH\(_3\)), 33.8 (SCH\(_2\) of one diastereomer), 34.0 (SCH\(_2\) of other diastereomer), 41.6 (CHS of one diastereomer), 42.2 (CHS of other diastereomer), 44.0 (NCH\(_2\) (PMB)), 49.7 (CH\(_2\)N of one diastereomer), 49.8 (CH\(_2\)N of other diastereomer), 52.7 (OCH\(_3\)), 54.7 (CHN of one diastereomer), 55.3 (CHN of other diastereomer), 55.6 (OCH\(_3\)), 60.1 (OCH\(_3\)), 60.4 (OCH\(_3\)), 61.8 (OCH\(_3\)), 74.6 (CH\(_2\)CCl\(_3\) of one diastereomer), 74.7 (CH\(_2\)CCl\(_3\) of other diastereomer), 95.4 (CCl\(_3\)), 114.1 (ArCH), 120.7 (ArC of one diastereomer), 121.0 (ArC of other diastereomer), 124.5 (ArC), 125.5 (ArC), 128.4 (ArC of one diastereomer), 128.5 (ArC of other diastereomer), 129.3 (ArCH), 144.9 (ArC), 151.5 (ArC of one diastereomer), 151.9 (ArC of other diastereomer), 154.5 (ArC), 159.1 (ArC), 167.9 (C=O), 170.7 (C=O), 170.8 (C=O).

MS (ES+): \( m/z \): 701 ([M + Na]+), HRMS (ES+): \( m/z \): calcd for C\(_{28}\)H\(_{34}\)N\(_2\)O\(_9\)S\(_{35}\)Cl\(_3\): 679.1046 ([M + H]+); found: 679.1038.
IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 1737 (C=O), 1639 (C=O), 1512, 1465, 1408, 1347, 1300, 1243, 1175, 1088, 1003.

6.2.3 Cyclisation of simple aldehydes

**Methyl 3-((5,7-dimethoxy-2-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate (297)**

(COCl)$_2$ (0.03 mL, 0.33 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (5 mL). The reaction mixture was cooled to $-78 \, ^{\circ}\text{C}$ then DMSO (0.04 mL, 0.60 mmol) was added slowly and the reaction mixture was stirred for 5 minutes. 249 (100 mg, 0.30 mmol) in anhydrous CH$_2$Cl$_2$ (1 mL) was added and the reaction was stirred at $-78 \, ^{\circ}\text{C}$ for 1.5 hours. Et$_3$N (0.21 mL, 1.51 mmol) was added and the reaction was allowed to warm to room temperature and stirred for a further 3.5 hours. Saturated aqueous solution of NaHCO$_3$ (15 mL) was added and the aqueous layer extracted with CH$_2$Cl$_2$ (3 × 15 mL). The organic phases were then combined and washed with saturated solution of NaHCO$_3$ (30 mL) then dried (MgSO$_4$) and evaporated to give aldehyde 295 which was then dissolved in anhydrous CH$_2$Cl$_2$ (6 mL). Methyl-3-mercaptopropionate (0.07 mL, 0.60 mmol) was added and the reaction was stirred at room temperature for 14 hours. The reaction mixture was then divided into three portions. One portion (2 mL, 0.10 mmol) was diluted with anhydrous CH$_2$Cl$_2$ (2 mL) then TFAA (14 $\mu$L, 0.10 mmol) was added at room temperature and the reaction stirred for 3 hours. The reaction mixture was then cooled to 0 $^{\circ}\text{C}$ and BF$_3$OEt$_2$ (38 $\mu$L, 0.30 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 3 hours. Saturated aqueous anhydrous NaHCO$_3$ (10 mL) was added and the aqueous
phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The organic phases were combined and dried (MgSO$_4$) then evaporated. Purification by column chromatography eluting with 20 – 30 % EtOAc in petroleum ether gave 297 (29 mg, 0.07 mmol, 70 %) as a yellow pale oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.58 (2H, t, $J = 7.6$ Hz, SCH$_2$C$_6$H$_5$), 2.62 (1H, dd, $J = 2.7$, 11.6 Hz, CH$_3$N$_2$H$_5$CH$_5$), 2.88 (2H, t, $J = 7.8$ Hz, SCH$_2$), 3.20 (1H, br. d, $J = 11.8$, CH$_3$N$_2$H$_5$CH$_5$), 3.29 (1H, d, $J = 15.2$ Hz, NCH$_3$H$_5$H$_5$), 3.63 (1H, d, $J = 13.0$ Hz, NCH$_3$H$_5$H$_5$ (PMB)), 3.67 (3H, s, OCH$_3$), 3.71 (1H, d, $J = 13.0$ Hz, NCH$_3$H$_5$H$_5$ (PMB)), 3.75 (3H, s, OCH$_3$), 3.82 (3H, s, OCH$_3$), 3.84 (3H, s, OCH$_3$), 3.89 (1H, d, $J = 15.2$ Hz, NCH$_3$H$_5$H$_5$), 4.04 (1H, br. dd, $J = 2.0$, 2.7 Hz, CHS), 6.12 (1H, d, $J = 2.3$ Hz, ArH), 6.30 (1H, d, $J = 2.3$ Hz, ArH), 6.88 (2H, d, $J = 8.7$ Hz, ArH), 7.37 (2H, d, $J = 8.7$ Hz, ArH).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 27.4 (SCH$_2$), 35.2 (SCH$_3$CH$_2$), 39.6 (CHS), 51.6 (OCH$_3$), 55.2 (OCH$_3$), 55.3 (OCH$_3$), 55.4 (OCH$_3$), 55.7 (NCH$_3$), 57.1 (NCH$_2$CH$_2$), 61.9 (NCH$_2$ (PMB)), 96.9 (ArCH), 101.7 (ArCH), 113.6 (ArCH), 116.7 (ArC), 130.0 (ArCH), 130.1 (ArC), 136.8 (ArC), 157.9 (ArC), 158.7 (ArC), 159.5 (ArC), 172.8 (C=O).

MS (ES+): $m/z$: 432 ([M + H]$^+$); HRMS (ES+): $m/z$: calcd for C$_{23}$H$_{30}$NO$_5$S: 432.1840 ([M + H]$^+$); found: 432.1843.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 3003, 2950, 1732 (C=O), 1681, 1607, 1512, 1456, 1434, 1412, 1360, 1302, 1246, 1203, 1163, 1109, 1080, 1034.

Methyl 3-(((3-(((3-(tert-butyldiphenylsilyl)oxy)methyl)-5,7-dimethoxy-2-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate (299)
Oxalyl chloride (0.03 mL, 0.36 mmol) was dissolved in anhydrous CH₂Cl₂ (3 mL). The reaction mixture was cooled to −78 °C then DMSO (0.06 mL, 0.79 mmol) was added slowly and the reaction mixture was stirred for 10 minutes. Alcohol rac-250 (106 mg, 0.18 mmol) in anhydrous CH₂Cl₂ (1.5 mL) was added and the reaction was stirred at −78 °C for 1 hour. Et₃N (0.23 mL, 1.62 mmol) was added and the reaction was allowed to warm to room temperature and stirred for a further 1 hour. Saturated aqueous solution of NaHCO₃ (15 mL) was added and extracted with CH₂Cl₂ (3 × 15 mL). The organic phases were combined and washed with saturated solution of NaHCO₃ (30 mL) then dried (MgSO₄) and evaporated to give aldehyde 298 which was then dissolved in anhydrous CH₂Cl₂ (6 mL). Methyl-3-mercaptopropionate (0.07 mL, 0.54 mmol) was added and the reaction was stirred at room temperature for 14 hours. The reaction mixture was then divided into two portions. One portion (0.09 mmol) was diluted with anhydrous CH₂Cl₂ (3 mL) then TFAA (13 µL, 0.09 mmol) was added at room temperature and the reaction stirred for 3 hours. The reaction mixture was cooled to 0 °C then BF₃•OEt₂ (34 µL, 0.27 mmol) was added and the reaction allowed to warm to room temperature and stirred for 2 hours. Saturated aqueous NaHCO₃ (10 mL) was then added and the aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The organic phases were combined and dried (MgSO₄) then evaporated. Purification by column chromatography eluting with 10 – 15 % EtOAc in petroleum ether gave 299 (35 mg, 0.05 mmol, 56 %) as a light yellow pale oil and as a mixture of diastereoisomers (dr ~ 2:1) from which the major diastereoisomer was isolated.

For the major diastereoisomer 299:

$^1$H NMR (400 MHz, CDCl₃) δ 1.02 (9H, s, SiC(CH₃)₃), 2.68 – 2.72 (2H, m, SCH₂CH₂), 2.90 – 2.96 (2H, m, SCH₂), 3.36 – 3.48 (3H, m, NCH, CH₃CH₂O, NCH₃CH₂), 3.69 (3H, s, OCH₃), 3.72 – 3.78 (6H, m, OCH₃, NCH₃H₂, CH₃CH₂O, NCH₃H₂(PMB)), 3.81 (3H, s, OCH₃), 3.84 (3H, s, OCH₃), 3.88 (1H, d, J = 13.6 Hz, NCH₃H₂(PMB)), 4.50 (1H, s
(br.), CHS), 6.06 (1H, d, J = 2.0 Hz, ArH), 6.35 (1H, d, J = 2.0 Hz, ArH), 6.85 (2H, d, J = 8.6 Hz, ArH), 7.28 – 7.43 (8H, m, ArH), 7.49 – 7.51 (2H, m, ArH), 7.61 – 7.64 (2H, m, ArH).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 19.1 (SiC), 26.7 (SiC(CH$_3$)$_3$), 27.6 (SCH$_2$), 35.1 (SCH$_2$CH$_2$), 40.0 (CHS), 49.8 (NCH$_2$), 51.6 (OCH$_3$), 55.2 (2 × OCH$_3$), 55.3 (OCH$_3$), 59.9 (NCH$_2$ (PMB)), 60.8 (CH$_2$O), 64.9 (NCH), 96.9 (ArCH), 101.8 (ArCH), 106.4 (ArCH), 113.6 (ArCH), 115.7 (ArC), 127.6 (ArCH), 129.6 (ArCH), 131.3 (ArC), 133.2 (ArC), 135.5 (ArCH), 136.7 (ArC), 158.3 (ArC), 158.6 (ArC), 159.3 (ArC), 172.8 (C=O).

MS (ES+): m/z: 700 ([M + H]$^+$); HRMS (ES+): m/z: calcd for C$_{40}$H$_{50}$NOSSi: 700.3123 ([M + H]$^+$); found: 700.3120.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2932, 1736 (C=O), 1683, 1606, 1511, 1490, 1462, 1427, 1359, 1316, 1300, 1246, 1202, 1150, 1108.

6.3 First approach to Et. 597

6.3.1 AB ring system formation

1,3-Dimethoxy-5-vinylbenzene (308)$^{82}$

Triphenylmethylphosphonium bromide (15.5 g, 43.2 mmol) was suspended in anhydrous THF (67 mL) under N$_2$. Potassium t-butoxide (5.65 g, 50.4 mmol) was then added and the mixture was stirred at room temperature for 30 minutes, then cooled to −78 °C. Subsequently, a solution of 3,5-dimethoxybenzaldehyde (6.00 g, 36.1 mmol) in anhydrous THF (33 mL) was added dropwise at −78 °C.
then the reaction mixture was allowed to warm to room temperature. Methanol (20 mL) was added to the reaction and the solvent was evaporated. Purification by plug column chromatography eluting with 5% of ethyl acetate in petroleum ether gave 308 (5.47 g, 34.5 mmol, 95%) as a colourless oil. Spectroscopic data were identical to the data previously obtained within the Procter group.82

\[ ^1H \text{ NMR (400 MHz, CDCl}_3 \] \( \delta \) 3.82 (6H, s, 2 × OCH\(_3\)), 5.28 (1H, d, J = 10.9 Hz, ArCH=CH), 5.76 (1H, d, J = 17.4 Hz, ArCH=CH), 6.42 (1H, t, J = 2.2 Hz, ArCH), 6.60 (2H, d, J = 2.2 Hz, ArH), 6.67 (1H, dd, J = 17.4, 10.9 Hz, ArCH=CH\(_2\)).

\[ ^13C \text{ NMR (100 MHz, CDCl}_3 \] \( \delta \) 5.2 (2 × OCH\(_3\)), 100 (ArCH), 104.2 (ArCH), 114.3 (ArCH=CH\(_2\)), 136.8 (ArCH=CH\(_2\)), 139.5 (ArC), 160.8 (2 × ArC).

(R)-tert-Butyl 1-(3,5-dimethoxyphenyl)-2-hydroxyethylcarbamate (309)\(^{95,101}\)

\[
\text{MeO} \hspace{1cm} \text{OMe} \hspace{1cm} \text{NHBOc} \hspace{1cm} \text{OH}
\]

t-Butylcarbamate (3.66 g, 3.00 mmol) was dissolved in n-propanol (40 mL) in the dark. A solution of sodium hydroxide (1.22 g, 30.0 mmol) in water (80 mL) was then added followed by freshly prepared t-butyl hypochlorite\(^{129}\) (3.51 mL, 3.00 mmol). The solution was stirred at room temperature for 5 minutes then cooled to 0 °C. A solution of (DHQD)\(_2\)PHAL (0.48 g, 0.05 mmol) in n-propanol (40 mL) was added then a solution of 308 (1.65 g, 10.0 mmol) in n-propanol (70 mL) and K\(_2\)OsO\(_4\).2H\(_2\)O (0.15 g, 0.04 mmol) were added. The reaction was stirred for one hour then saturated aqueous sodium sulfite (100 mL) was added and the resulting mixture was stirred for 15 minutes. The aqueous phase was extracted with ethyl acetate (3 × 25 mL), the organic phases were combined, washed with water and brine, dried (MgSO\(_4\)), and evaporated to give crude product.
Purification by column chromatography eluting with 20 – 45 % of ethyl acetate in petroleum ether gave 309 (1.50 g, 5.04 mmol, 51%) as a white solid. Spectroscopic data were identical to the data previously obtained within the Procter group.\textsuperscript{95,101}

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.42 (9H, s, t-Bu), 2.83 (1H, br. s, OH), 3.76 (8H, br. s, 2 $\times$ OCH$_3$ and CH$_2$OH), 4.67 (1H, br. s, CHN), 5.42 (1H, br. s, NH), 6.35 (1H, t, $J$ = 2.3 Hz, ArCH), 6.43 (2H, d, $J$ = 2.3 Hz, 2 $\times$ ArCH).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 28.3 (CH$_3$), 55.2 (OCH$_3$), 56.8 (CH$_2$OH), 79.8 (C(CH$_3$)$_3$), 99.3 (ArCH), 104.6 (ArCH), 156 (ArC), 160.9 (ArC).

\textbf{(R)-2-Amino-2-(3,5-dimethoxyphenyl)ethanol (310)}\textsuperscript{95}

Carbamate 309 (0.74 g, 2.49 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (20 mL) and trifluoroacetic acid (9.5 mL) was added. The reaction was stirred at room temperature for 16 hours and the solvent was evaporated. The residue was dissolved in saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$ (3 $\times$ 15 mL). The organic phases were combined and dried (MgSO$_4$) and evaporated to give 310 (0.42 g, 2.13 mmol, 86 %) as a pale solid. This product was used for the next step without further purification. Spectroscopic data were identical to the data previously obtained within the Procter group.\textsuperscript{95}

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.54 (1H, dd, $J$ = 10.6, 8.1 Hz, CH$_A$H$_B$OH), 3.72 (1H, dd, $J$ = 10.6, 3.8 Hz, CH$_A$H$_B$OH), 3.79 (6H, s, 2 $\times$ OCH$_3$), 3.96 (1H, dd, $J$ = 10.6, 3.8 Hz, CHN), 6.37 (1H, t, $J$ = 2.3 Hz, ArH), 6.48 (1H, d, $J$ = 2.3 Hz, 2 $\times$ ArH).
13C NMR (100 MHz, CDCl3) δ 55.3 (OCH3), 57.4 (CHN), 67.8 (CH2OH), 99.1 (ArCH), 104.4 (ArCH), 139.8 (ArC), 160.9 (ArC).

(R)-2-(tert-Butyldimethylsilyloxy)-1-(3,5-dimethoxyphenyl)ethanamine (311)

Alcohol 310 (0.20 g, 1.01 mmol) was dissolved in anhydrous dichloromethane (15 mL) and tert-butyl(dimethyl)silyl chloride (0.17 g, 1.13 mmol), Et3N (2.8 mL) and DMAP (36.0 mg, 0.3 mmol) were added. The reaction was stirred for 24 hours at room temperature. A saturated aqueous solution of NaHCO3 (20 mL) was added and the aqueous phase was extracted with CH2Cl2 (2 × 20 mL). The organic phases were combined and dried (MgSO4) and evaporated to give the crude product. Purification by column chromatography eluting with 50% ethyl acetate in petroleum ether gave 311 (0.15 g, 0.48 mmol, 48%) as a pale oil. Spectroscopic data were identical to the data previously obtained within the Procter group.

1H NMR (400 MHz, CDCl3) δ 0.05 (6H, s, 2 × SiCH3), 0.09 (9H, s, C(CH3)3), 3.51 (1H, dd, J = 9.8, 8.6 Hz, CHA-H2O), 3.72 (1H, dd, J = 9.8, 3.8 Hz, CHA-H2O), 3.79 (6H, s, 2 × OCH3), 4.03 (1H, dd, J = 8.6, 3.8 Hz, CHN), 6.37 (1H, t, J = 2.3 Hz, ArH), 6.56 (2H, d, J = 2.3 Hz, 2 × ArH).

13C NMR (100 MHz, CDCl3) δ –5.4 (SiCH3), 18.3 (C(CH3)3), 25.9 (C(CH3)3), 55.3 (OCH3), 57.8 (CHN), 69.4 (CH2O), 99.3 (ArCH), 104.8 (ArCH), 145.1 (ArC), 160.7 (ArC).
(R)-2-(tert-Butyldimethylsilyloxy)-1-(3,5-dimethoxyphenyl)-N-(4-methoxybenzyl)ethanamine (312)\textsuperscript{95}

Amine 311 (0.47 g, 1.51 mmol) was dissolved in methanol (1.5 mL) and 4-methoxybenzaldehyde (0.21 mL, 1.76 mmol), NaBH\textsubscript{3}CN (0.11 g, 1.76 mmol), and acetic acid (34 \(\mu\)L) were added. The reaction was stirred at room temperature for 2 days. A saturated aqueous solution of NaHCO\textsubscript{3} (15 mL) was added and the aqueous phase was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 \(\times\) 15 mL). The organic phases were combined and dried (MgSO\textsubscript{4}) and evaporated to give the crude product. Purification by column chromatography eluting with 15% EtOAc in petroleum ether gave 312 (0.55 g, 1.28 mmol, 85 \%) as a pale oil. Spectroscopic data were identical to the data previously obtained within the Procter group.\textsuperscript{95}

\(\textsuperscript{1}H\) NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 0.02 (3H, s, SiCH\textsubscript{3}), 0.03 (3H, s, SiCH\textsubscript{3}), 0.89 (9H, s, SiC(CH\textsubscript{3})\textsubscript{3}), 2.32 (1H, br. s. NH), 3.51 (1H, d, \(J = 13.2\) Hz, NCH\textsubscript{2}H\textsubscript{6}), 3.57 (1H, d, \(J = 9.5\) Hz, CH\textsubscript{A}H\textsubscript{6}O), 3.66 (1H, dd, \(J = 9.5, 3.8\) Hz, CH\textsubscript{A}H\textsubscript{6}O), 3.72 (1H, d, \(J = 13.2\) Hz, NCH\textsubscript{2}H\textsubscript{6}), 3.75 (1H, dd, \(J = 9.5, 3.8\) Hz, CHN), 3.81 (6H, s, 2 \(\times\) OCH\textsubscript{3}), 6.4 (1H, t, \(J = 2.2\) Hz, ArCH), 6.61 (2H, d, \(J = 2.2\) Hz, 2 \(\times\) ArCH), 6.86 (2H, d, \(J = 8.8\) Hz, 2 \(\times\) ArCH), 7.21 (2H, d, \(J = 8.8\) Hz, 2 \(\times\) ArCH).

\(\textsuperscript{13}C\) NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) −5.4 (SiCH\textsubscript{3}), −5.3 (SiCH\textsubscript{3}), 18.2 (SiC(CH\textsubscript{3})\textsubscript{3}), 25.9 (C(CH\textsubscript{3})\textsubscript{3}), 50.6 (NCH\textsubscript{2}), 55.2 and 55.3 (3 \(\times\) OCH\textsubscript{3}), 64.2 (CH\textsubscript{2}O), 68.3 (CHN), 99.4 (ArCH), 105.6 (ArCH), 113.7 (ArCH), 129.2 (ArCH), 132.7 (ArC), 143.4 (ArC), 158.5 (ArC), 160.8 (ArC).
(R)-N-(2-(tert-Butyldimethylsilyloxy)-1-(3,5-dimethoxyphenyl)ethyl)-2-hydroxy-N-(4-methoxybenzyl)acetamide (314)$^{95}$

Amine 312 (0.53 g, 1.22 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (6 mL) and acetoxyacetic acid (0.17 g, 1.46 mmol), EDCI (0.28 g, 1.46 mmol) and HOBt (0.03 g, 0.24 mmol) were added. The reaction was stirred at room temperature for 2 days. The reaction mixture was washed with 0.5 M aqueous solution of HCl (3 × 6 mL), saturated aqueous NaHCO$_3$ (6 mL) and the organic phase dried (MgSO$_4$) and evaporated. The crude amide was dissolved in methanol (5 mL) and a suspension of K$_2$CO$_3$ (0.51 g, 3.66 mmol) in water (2.5 mL) was added. The reaction was stirred at room temperature for 16 hours, then the solvent was evaporated. The residue was diluted with water and the resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The organic phases were combined, dried (MgSO$_4$) and evaporated to give the crude product. Purification by column chromatography eluting with 20 – 25 % ethyl acetate in petroleum ether gave 314 (0.45 g, 0.92 mmol, 75 %) as a pale oil. Spectroscopic data were identical to the data previously obtained within the Procter group.$^{95}$

$^1$H NMR (500 MHz, CDCl$_3$) δ −0.04 (3H, s, SiCH$_3$ of one rotamer), 0.01 (3H, s, SiCH$_3$ of other rotamer), 0.03 (3H, s, SiCH$_3$ of one rotamer), 0.04 (3H, s, SiCH$_3$ of other rotamer), 0.87 (9H, s, C(CH$_3$)$_3$ of 2 rotamers), 3.67 (1H, br. s, OH of 2 rotamers), 3.72 (6H, s, 2 × OCH$_3$ of one rotamer), 3.73 (6H, s, 2 × OCH$_3$ of other rotamer), 3.75 (3H, s, OCH$_3$ of one rotamer), 3.77 (3H, s, OCH$_3$ of other rotamer), 3.86 – 3.89 (1H, m, CH$_A$H$_B$O of one rotamer), 3.93 – 3.96 (1H, m, CH$_A$H$_B$O of one rotamer), 3.99 – 4.02 (1H, m, CH$_A$H$_B$O of other rotamer), 4.08 (2H, s, CH$_2$OH of one rotamer), 4.15 – 4.19 (1H, m, NCH$_A$H$_B$ of 2 rotamers), 4.28
(2H, s, CH$_2$OH of other rotamer), 4.35 (1H, d, $J$ = 14.8 Hz, CHN of one rotamer), 4.53 (1H, d, $J$ = 14.8 Hz, CHN of other rotamer), 4.66 – 4.69 (1H, m, NCH$_A$H$_B$ of 2 rotamers), 5.47 – 5.50 (1H, m, CH$_A$H$_B$O of other rotamer), 6.26 (2H, br. s, 2 × ArCH of one rotamer), 6.36 – 6.38 (1H, m, ArCH of 2 rotamers), 6.44 (2H, br. s, 2 × ArCH of other rotamer), 6.74 (2H, d, $J$ = 8.2 Hz, 2 × ArCH of one rotamer), 6.8 (2H, d, $J$ = 8.2 Hz, 2 × ArCH of other rotamer), 7.05 (2H, d, $J$ = 8.2 Hz, 2 × ArCH of one rotamer), 7.08 (2H, d, $J$ = 8.2 Hz, 2 × ArCH of other rotamer).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ −5.7 (SiCH$_3$), 18.0 (SiC(CH$_3$)$_3$), 25.7 (C(CH$_3$)$_3$), 45.8 (NCH$_2$ of one rotamer), 47.3 (NCH$_2$ of other rotamer), 55.1 (OCH$_3$ of 2 rotamers), 55.2 (2 × OCH$_3$ of one rotamer), 55.3 (2 × OCH$_3$ of other rotamer), 60.4 (CH$_2$OH of one rotamer), 60.5 (CHN of one rotamer), 60.7 (CH$_2$OH of other rotamer), 61.1 (CHN of other rotamer), 62.0 (CH$_2$OSi of one rotamer), 62.4 (CH$_2$OSi of other rotamer), 99.5 (ArCH of one rotamer), 99.6 (ArCH of other rotamer), 106.0 (ArCH of one rotamer), 106.5 (ArCH of other rotamer), 113.5 (ArCH of one rotamer), 114 (ArCH of other rotamer), 127.7 (ArCH of one rotamer), 128.5 (ArC of one rotamer), 129.1 (2 × ArCH of other rotamer), 130.5 (ArC of other rotamer), 138.2 (ArC of one rotamer), 139.6 (ArC of other rotamer), 158.5 (ArC of one rotamer), 158.9 (ArC of other rotamer), 160.7 (ArC of one rotamer), 161.0 (ArC of other rotamer), 173.3 (C=O of one rotamer), 173.4 (C=O of other rotamer).

(R)-Methyl 3-mercapto-2-((2,2,2-trichloroethoxy)carbonylamino)propanoate (328)$^{95}$

L-cysteine dimethyl ether hydrochloride salt (0.68 g, 2.00 mmol) was dissolved in water (20 mL) and cooled to 0 °C. NaHCO$_3$ (0.67 g, 8.00 mmol) was added and the solution was stirred for 5 minutes. TrocCl (0.83 g, 6.00 mmol) was added
portionwise and the reaction was stirred at 0 °C for 2 hours then at room temperature for 5 hours. The reaction mixture was saturated with NaCl and extracted with EtOAc (4 × 20 mL). The organic layers were combined, washed with H₂O then brine, dried (MgSO₄), and evaporated to give crude product. Purification by column chromatography eluting with 50% Et₂O in petroleum ether gave bis-N-Troc cysteine dimethyl ester 328A (1.06 g, 1.71 mmol, 86%) as a colourless pale oil. Spectroscopic data were identical to the data previously obtained within the Procter group.⁹⁵

¹H NMR (500 MHz, CDCl₃) δ 3.23 (4H, d, J = 5.4 Hz, 2 × SCH₂), 3.81 (6H, s, 2 × OCH₃), 4.68 − 4.73 (2H, m, CHN-Troc), 4.75 (2H, s, 2 × CH₂H₈CCl₃), 4.77 (2H, s, CH₂H₈CCl₃), 5.95 (2H, d, J = 7.9 Hz, 2 × NH).

¹³C NMR (125 MHz, CDCl₃) δ 41.0 (SCH₂), 53.0 (OCH₃), 53.4 (CH₂CCl₃), 75.1 (CHNHTroc), 95.2 (CCl₃), 153.9 (C=O), 170.3 (C=O).

Disulfide 328A (0.53 g, 0.86 mmol) was dissolved in anhydrous dichloromethane (15 mL). DL-Dithiothreitol (0.20 g, 1.29 mmol) and triethylamine (0.36 mL, 2.58 mmol) were added. The reaction was stirred at room temperature for 3 hours then washed with aqueous 5% (w/v) degassed citric acid solution (3 × 15 mL) and degassed water (15 mL). The organic layers were then dried (MgSO₄) and evaporated to give 328 (0.48 g, 1.55 mmol, 90%) as a pale solid which was used without further purification. Spectroscopic data were identical to the data previously obtained within the Procter group.⁹⁵

¹H NMR (500 MHz, CDCl₃) δ 1.42 (1H, t, J = 8.8 Hz, SH), 3.05 (2H, dd, J = 8.8, 4.1 Hz, SCH₂), 3.82 (3H, s, OCH₃), 4.69 (1H, dt, J = 7.9, 4.1 Hz, CHN-Troc), 4.72 − 4.79 (2H, m, CH₂CCl₃), 5.92 (1H, d, J = 7.9 Hz, NH).

¹³C NMR (125 MHz, CDCl₃) δ 26.9 (SCH₂), 53.0 (OCH₃), 55.4 (CHN-Troc), 74.7 (CH₂CCl₃), 95.2 (CCl₃), 153.9 (C=O), 170.0 (C=O).
(R)-Methyl 3-((R)-1-((tert-butyldimethylsilyloxy)methyl)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-ylthio)-2-((2,2,2-trichloroethoxy)carbonylamino)propanoate (316)

Method A

Oxalyl chloride (62.0 µL, 0.70 mmol) was dissolved in anhydrous dichloromethane (3.0 mL). The solution was cooled to −78 °C before dimethyl sulfoxide (90.0 µL, 1.28 mmol) was added and the solution stirred for 5 minutes at −78 °C. A solution of 314 (313 mg, 0.64 mmol) in anhydrous dichloromethane (2.0 mL) was added slowly. The reaction was stirred at −78 °C for 30 minutes before triethylamine (0.45 mL, 3.20 mmol) was added and the reaction was allowed to warm to room temperature. The reaction was stirred for 3 hours at room temperature. The reaction mixture was diluted with CH₂Cl₂ (5 mL) and washed with aqueous saturated sodium hydrogencarbonate solution (3 × 5 mL). The organic layer was dried (MgSO₄) and evaporated to give 315, which was used directly in the next step without further purification.

The product 315 from the previous step was divided into 3 equal portions. One portion (104 mg, 0.22 mmol) was dissolved in anhydrous CH₂Cl₂ (3.5 mL). N-Troc-L-cysteine methyl ester (328) (99.4 mg, 0.32 mmol) and zinc chloride (30.0 mg, 0.22 mmol) were added and the reaction was stirred at room temperature for 16 hours. The reaction mixture was diluted with CH₂Cl₂ (5 mL) and washed with brine (5 mL). The organic layer was dried (MgSO₄) and evaporated to give the crude product. Purification by column chromatography eluting with 15% of ethyl acetate in petroleum ether gave 316A and 316B (30.5 mg, 0.04 mmol, 18%), 317A and 317B (44.1 mg, 0.09 mmol, 38%) as pale oils.
Spectroscopic data were identical to the data previously obtained within the Procter group.  

**Method B:**
Sulfur trioxide pyridine complex (800 mg, 0.10 mmol) was dissolved in anhydrous CH₂Cl₂ (2.0 mL). The mixture was cooled to 0 °C and DMSO (50.0 µL, 0.60 mmol) was added and the mixture was then stirred at 0 °C for 15 minutes. Et₃N (0.24 mL, 1.50 mmol) was added followed by 314 (50.0 mg, 0.10 mmol) in CH₂Cl₂ (0.5 mL) and the reaction was stirred at 0 °C for 4 hours and room temperature for 16 hours. The reaction mixture was washed with aqueous saturated NaHCO₃ and the organic layers dried (MgSO₄) and evaporated to give 315 (49.0 mg, 0.10 mmol).
Glyoxamide 315 (49.0 mg, 0.10 mmol) was dissolved in CHCl₃ (3.0 mL) and N-troc-L-cysteine methyl ester (328) (47.0 mg, 0.15 mmol) and zinc chloride (14.0 mg, 0.10 mmol) were added. The reaction was stirred at room temperature for 17 hours. The reaction mixture was diluted with CHCl₃ (5 mL) and washed with brine (5 mL). The organic layer was dried (MgSO₄) and evaporated to give the crude product. Purification by column chromatography eluting with 30% ethyl acetate in petroleum ether gave 316A and 316B (44.2 mg, 0.06 mmol, 57%) as a pale oil.

Major diastereomer 316A:

\[\text{^1H NMR (500 MHz, CDCl}_3\text{) }\delta \ 0.01 \ (3H, s, SiCH}_3\text{), 0.03 \ (3H, s, SiCH}_3\text{), 0.90 \ (9H, s, SiC(CH}_3\text{)}_3\text{), 3.31 \ (1H, dd, } J = 14.8, 4.1 \ Hz, \text{SCH}_A\text{H}_8\text{), 3.64 \ (1H, dd, } J = 14.8, 5.7 \ Hz, \text{SCH}_A\text{H}_8\text{), 3.75 \ (3H, s, OCH}_3\text{), 3.77 \ (3H, s, OCH}_3\text{), 3.78 - 3.82 \ (1H, m, CH}_A\text{H}_8\text{OSi), 3.81 \ (3H, s, OCH}_3\text{), 3.88 \ (3H, s, OCH}_3\text{), 4.04 \ (1H, dd, } J = 10.4, 7.9 \ Hz, \text{CH}_A\text{H}_8\text{OSi), 4.27 \ (1H, d, } J = 14.8 \ Hz, \text{NCH}_A\text{H}_8\text{), 4.37 \ (1H, dd, } J = 7.9, 6.3 \ Hz, \text{CHN), 4.73 \ (1H, d, } J = 12.0 \ Hz, \text{CH}_A\text{H}_8\text{CCl}_3\text{), 4.80 - 4.88 \ (1H, m, CHN-Troc), 4.84 \ (1H, s, CHS), 4.87 \ (1H, d, } J = 12.0 \ Hz, \text{CH}_A\text{H}_8\text{CCl}_3\text{), 5.50 \ (1H, d, } J = 14.8 \ Hz, \text{NCH}_A\text{H}_8\text{), 6.20 \ (1H, d, } J =\]
2.2 Hz, ArH), 6.39 (1H, d, J = 2.2 Hz, ArH), 6.80 (2H, d, J = 8.5 Hz, 2 × ArH), 7.14 (2H, d, J = 8.5 Hz, 2 × ArH), 7.76 (1H, d, J = 8.5 Hz, NH).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ –5.4 (SiCH$_3$), 18.2 (SiC), 25.9 (C(CH$_3$)$_3$), 35.8 (SCH$_2$), 40.6 (SCH), 49.2 (NCH$_2$), 52.6 (OCH$_3$), 55.2 (OCH$_3$), 55.4 (OCH$_3$ and CHN-Troc), 55.8 (OCH$_3$), 61.9 (CHN), 68.7 (CH$_2$OSi), 74.5 (C(CH$_2$Cl)$_3$), 95.6 (ArCH and CCl$_3$), 98.0 (ArC), 102.9 (ArCH), 113.9 (ArCH), 129.0 (ArCH), 129.3 (ArC), 135.6 (ArC), 154.7 (ArC), 157.4 (ArC), 158.9 (ArC), 160.1 (C=O), 169.3 (C=O), 170.8 (C=O).

MS (ES+): m/z (%): 801 ([M + Na]$^+$), HRMS (ES+): m/z: calcd for C$_{33}$H$_{45}$N$_2$O$_9^{35}$Cl$_3$NaSSi: 801.1573 ([M + Na]$^+$); found: 801.1574.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2952, 1737 (C=O), 1634, 1610, 1511, 1461, 1245, 1201, 1145, 1098, 1043.

$[\alpha]_D^{23} = -0.17$ (c = 1.2, CHCl$_3$).

Minor diastereomer 316B:

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ –0.25 (3H, s, SiCH$_3$), –0.11 (3H, s, SiCH$_3$), 0.73 (9H, s, C(CH$_3$)$_3$), 3.32 (1H, dd, J = 14.9, 4.8 Hz, SCH$_A$H$_B$), 3.60 (1H, dd, J = 10.9, 1.5 Hz, CH$_A$H$_B$OSi), 3.74 (3H, s, OCH$_3$), 3.76 (3H, s, OCH$_3$), 3.80 (3H, s, OCH$_3$), 3.87 (1H, dd, J = 14.9, 4.0 Hz, SCH$_A$H$_B$), 3.99 – 4.04 (5H, m, OCH$_3$ and CH$_A$H$_B$OSi and NCH$_A$H$_B$), 4.44 (1H, br. s, CHN), 4.63 (1H, s, CHS), 4.67 (1H, d, J = 12.1 Hz, CH$_A$H$_B$CCl$_3$), 4.77 – 4.82 (1H, m, CHN-Troc), 4.87 (1H, d, J = 12.1 Hz, CH$_A$H$_B$CCl$_3$), 5.56 (1H, d, J = 15.4 Hz, NCH$_A$H$_B$), 6.18 (1H, d, J = 2.0 Hz, ArH), 6.42 (1H, d, J = 2.0 Hz, ArH), 6.88 (2H, d, J = 8.6 Hz, 2 × ArH), 7.29 (2H, d, J = 8.6 Hz, 2 × ArH).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ –5.9 (SiCH$_3$), –5.7 (SiCH$_3$), 17.9 (SiC), 25.5 (C(CH$_3$)$_3$), 35.2 (SCH$_2$), 42.2 (CHS), 46.0 (NCH$_2$), 52.6 (OCH$_3$), 55.0 (CHNTroc), 55.3 (OCH$_3$), 55.4 (OCH$_3$), 55.9 (OCH$_3$), 60.3 (CHN), 64.1 (CH$_2$OSi), 74.8 (C(CH$_2$Cl)$_3$), 95.4 (ArCH and CCl$_3$), 98.0 (ArC), 101.4 (ArC), 102.3 (ArCH), 114.1 (ArCH), 129.0 (ArCH), 160
134.4 (ArC), 154.6 (ArC), 157.4 (ArC), 158.9 (ArC), 160.4 (C=O), 171.0 (C=O), 171.3 (C=O).

MS (ES+): $m/z$ (%): 779 ([M + H]$^+$), 801 ([M + Na]$^+$), HRMS (ES+): $m/z$: calcd for C$_{33}$H$_{45}$N$_2$O$_9^{35}$Cl$_3$NaSSi: 801.1573 ([M + Na]$^+$); found: 801.1572.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2929, 2855, 1739 (C=O), 1643, 1610, 1512, 1461, 1247, 1201, 1145, 1097, 1036.

[$\alpha$]$_D^{23}$ = −0.19 (c = 0.9, CHCl$_3$).

(R)-1-((tert-Butyldimethylsilyloxy)methyl)-5,7-dimethoxy-2-(4-methoxybenzyl)-4-(methylthio)-1,2-dihydroisoquinolin-3(4H)-one (317)

For major diastereomer (317A):

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.02 (3H, s, SiCH$_3$), 0.04 (3H, s, SiCH$_3$), 0.92 (9H, s, C(CH$_3$)$_3$), 2.49 (3H, s, SCH$_3$), 3.75 (3H, s, OCH$_3$), 3.76 (3H, s, OCH$_3$), 3.87 (3H, s, OCH$_3$), 3.90 (1H, dd, $J = 10.1, 6.0$ Hz, CH$_A$H$_B$OSi), 4.26 (1H, dd, $J = 10.1, 7.6$ Hz, CH$_A$H$_B$OSi), 4.30 (1H, d, $J = 14.9$ Hz, NCH$_A$H$_B$), 4.39 (1H, dd, $J = 7.6, 6.0$ Hz, CNH), 4.67 (1H, s, CHS), 5.46 (1H, d, $J = 14.9$ Hz, NCH$_A$H$_B$), 6.23 (1H, d, $J = 2.3$ Hz, ArH), 6.39 (1H, d, $J = 2.3$ Hz, ArH), 6.80 (2H, d, $J = 8.6$ Hz, 2 $\times$ ArH), 7.15 (2H, d, $J = 8.6$ Hz, 2 $\times$ ArH).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ −5.43 (SiCH$_3$), 17.4 (SiC), 18.3 (SCH$_3$), 25.9 (C(CH$_3$)$_3$), 42.0 (CHS), 49.0 (NCH$_2$), 55.2 (OCH$_3$), 55.3 (OCH$_3$), 55.9 (OCH$_3$), 62.3 (NCH), 68.1 (CH$_2$OSi), 98.0 (ArCH), 103.0 (ArCH), 113.9 (ArCH), 114.1 (ArC), 129.2 (ArCH), 129.4 (ArC), 136.0 (ArC), 157.4 (ArC), 158.8 (ArC), 160.0 (ArC), 168.7 (C=O).
MS (ES+): m/z (%): 540 (100, [M + Na]^+), HRMS (ES+): m/z: calcd for C_{27}H_{40}N_{1}O_{5}S_{1}Si_{1}: 518.2391 ([M + H]^+); found: 518.2385.

IR (thin film) ν_max (cm⁻¹) 2930, 1644 (C=O), 1609, 1511, 1461, 1419, 1359, 1246, 1200, 1146, 1101, 1034.

[α]_D^{23} = +0.25 (c = 1.1, CHCl₃).

For minor diastereomer (317B):

¹H NMR (500 MHz, CDCl₃) δ −0.18 (3H, s, SiCH₃), −0.06 (3H, s, SiCH₃), 0.77 (9H, s, C(CH₃)₃), 2.23 (3H, s, SCH₃), 3.73 (1H, dd, J = 11.0, 1.9 Hz, CH₂H₈OSi), 3.76 (3H, s, OCH₃), 3.80 (3H, s, OCH₃), 3.87 (3H, s, OCH₃), 4.05 (1H, dd, J = 11.0, 3.2 Hz, CH₂H₈OSi), 4.07 (1H, d, J = 15.5 Hz, NCH₂H₈), 4.53 − 4.54 (1H, m, NCH), 4.62 (1H, s, CHS), 5.60 (1H, d, J = 15.5 Hz, NCH₂H₈), 6.24 (1H, d, J = 2.2 Hz, ArH), 6.39 (1H, d, J = 2.2 Hz, ArH), 6.88 (2H, d, J = 8.5 Hz, 2 × ArH), 7.28 (2H, d, J = 8.5 Hz, 2 × ArH).

¹³C NMR (125 MHz, CDCl₃) δ −5.9 (SiCH₃), −5.7 (SiCH₃), 15.8 (SiC), 17.9 (SCH₃) 25.6 (C(CH₃)₃), 42.7 (CHS), 45.8 (NCH₂), 55.2 (OCH₃), 55.3 (OCH₃), 55.9 (OCH₃), 59.6 (CHN), 63.0 (CH₂OSi), 98.0 (ArCH), 101.1 (ArCH), 114.1 (ArCH), 115.1 (ArC), 128.9 (ArCH), 129.5 (ArC), 134.9 (ArC), 157.4 (ArC), 158.8 (ArC), 160.0 (ArC), 170.1 (C=O).

MS (ES+): m/z (%): 540 (100, [M + Na]^+), HRMS (ES+): m/z: calcd for C_{27}H_{40}N_{1}O_{5}Na_{1}S_{1}Si_{1}: 540.2210 ([M + Na]^+); found: 540.2214.

IR (thin film) ν_max (cm⁻¹) 2930, 2856, 1645 (C=O), 1610, 1511, 1461, 1359, 1246, 1200, 1146, 1101, 1045.

[α]_D^{23} = −0.10 (c = 1.0, CHCl₃).
(R)-N-(1-(3,5-Dimethoxyphenyl)-2-((triisopropylsilyl)oxy)ethyl)-2-hydroxy-N-(4-methoxybenzyl)acetamide (325A)\textsuperscript{82}

AD-mix-\(\alpha\) (8.06 g) was dissolved in a mixture of water (29 mL) and \(\text{t-BuOH}\) (20 mL). The solution was cooled to 0 °C and a solution of 308 (0.96 g, 5.82 mmol) in \(\text{t-BuOH}\) (9 mL) was added. The reaction was allowed to warm to room temperature and stirred for 16 hours. A saturated aqueous solution of \(\text{Na}_2\text{SO}_3\) (15 mL) was added and the reaction was stirred for 30 minutes. The aqueous phase was then extracted with EtOAc (2 \(\times\) 20 mL). The organic phases were combined and washed with brine (50 mL) then dried (\(\text{MgSO}_4\)) and evaporated to give the crude diol product.

The crude diol product was dissolved in \(\text{CH}_2\text{Cl}_2\) (45 mL) and imidazole (0.99 g, 14.6 mmol) and TIPSCl (1.24 mL, 5.82 mmol) were added. The reaction was stirred at room temperature for 17 hours. An aqueous solution of \(\text{NH}_4\text{Cl}\) (1 M, 30 mL) was added and the aqueous phase was extracted with \(\text{CH}_2\text{Cl}_2\) (2 \(\times\) 30 mL). The organic phases were combined and washed with brine (100 mL), dried (\(\text{MgSO}_4\)) then evaporated to give crude product. Purification by column chromatography eluting with 5-10% EtOAc in petroleum ether gave 322 (1.71 g, 4.82 mmol, 83 %) as a colorless oil.

Silyl ether 322 (0.85 g, 2.41 mmol) was dissolved in THF (15 mL) and \(\text{Ph}_3\text{P}\) (0.76 g, 2.89 mmol), DEAD (0.46 mL, 2.89 mmol), and phthalimide (0.43 g, 2.89 mmol) were added sequentially at room temperature and the reaction mixture stirred for 24 hours. After concentration, the crude product was purified by flash column chromatography eluting with 10 % EtOAc in petroleum ether to give phthalimide 322A (0.67 g, 1.39 mmol, 57 %) as a colorless oil.
Phthalimide 322A (0.67 g, 1.39 mmol) was dissolved in EtOH (7.5 mL) and a 62 % aqueous solution of hydrazine (0.21 mL, 4.17 mmol) was added. The reaction was heated at reflux for 2 hours then cooled to room temperature and diluted with Et₂O (10 mL). The reaction mixture was filtered through Celite and the precipitate was washed with Et₂O. The filtrate was then evaporated to give the crude product. Purification by flash column chromatography eluting with 60 % EtOAc in petroleum ether gave amine 323 (0.42 g, 1.19 mmol, 86 %) as a pale light yellow oil.

Amine 323 (0.41 g, 1.16 mmol) was dissolved in MeOH (15 mL) and 4-methoxy-benzaldehyde (0.16 mL, 1.28 mmol) was added. The reaction was heated at reflux for 3 hours then cooled to 0 °C. NaBH₄ (0.09 g, 2.32 mmol) was added in one portion and the reaction was allowed to warm to room temperature and stirred for 1 hour. The solvent was evaporated then water (20 mL) was added, and the mixture was extracted with CH₂Cl₂ (3 × 20 mL). The organic extracts were combined and dried (MgSO₄) then evaporated. Purification by flash column chromatography eluting with 30 % EtOAc in petroleum ether gave 324A (0.47 g, 0.99 mmol, 85 %) as a pale colourless oil.

Amine 324A (0.47 g, 0.99 mmol) was dissolved in CH₂Cl₂ (12 mL) then acetoxyacetyl chloride (0.13 mL, 1.20 mmol) was added. The reaction mixture was cooled to 0 °C and Et₃N (0.17 mL, 1.20 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 5 hours. The solvent was evaporated and the residue was dissolved in MeOH (9.5 mL). A solution of K₂CO₃ (1.38 g, 10.0 mmol) in H₂O (4.7 mL) was added and the reaction was stirred at room temperature for 16 hours. After evaporation, the residue was diluted with water (20 mL) and extracted with CH₂Cl₂ (3 × 20 mL). The organic phases were combined, washed with brine (50 mL), dried (MgSO₄), then evaporated to give 325A (0.52 g, 0.98 mmol, 99 %) as a pale colourless oil. Spectroscopic data are identical to the data previously obtained within the Procter group.⁸²
$^1$H NMR (400 MHz, DMSO-d6, 120 °C) $\delta$ 0.97 – 1.09 (21H, m, SiCH and SiCH(CH$_3$)$_2$), 3.71 (6H, s, OCH$_3$), 3.73 (3H, s, OCH$_3$), 4.12 (2H, d, $J$ = 6.8 Hz, CH$_2$OH), 4.16 – 4.25 (2H, m, CH$_2$OSi), 4.33 (1H, d, $J$ = 16.2 Hz, NCH$_2$H$_8$), 4.52 (1H, d, $J$ = 16.2 Hz, NCH$_2$H$_8$), 5.13 (1H, t, $J$ = 6.3 Hz, ArCHN), 6.40 (1H, t, $J$ = 2.2 Hz, ArH), 6.48 (2H, d, $J$ = 2.2 Hz, ArH), 6.79 (2H, d, $J$ = 8.6 Hz, ArH), 7.06 (2H, d, $J$ = 8.6 Hz, ArH).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 11.7 (SiCH of one rotamer), 11.8 (SiCH of other rotamer), 17.9 (CH(CH$_3$)$_2$), 45.9 (CH$_2$Ar of one rotamer), 47.2 (CH$_2$Ar of other rotamer), 55.2 (OCH$_3$), 55.2 (OCH$_3$), 55.3 (OCH$_3$), 60.4 (CH$_2$O of one rotamer), 60.7 (CH$_2$O of other rotamer), 60.8 (ArCHN of one rotamer), 61.0 (ArCHN of other rotamer), 62.5 (CH$_2$O of one rotamer), 62.7 (CH$_2$O of other rotamer), 99.5 (ArCH of one rotamer), 99.5 (ArCH of other rotamer), 105.9 (ArCH of one rotamer), 106.5 (ArCH of other rotamer), 113.5 (ArCH of one rotamer), 114.0 (ArCH of other rotamer), 127.8 (ArCH of one rotamer), 128.5 (ArC of one rotamer), 129.1 (ArCH of other rotamer), 130.4 (ArC of other rotamer), 138.2 (ArC of one rotamer), 139.6 (ArC of other rotamer), 158.5 (ArC of one rotamer), 158.9 (ArC of other rotamer), 160.6 (ArC of one rotamer), 161.0 (ArC of other rotamer), 173.2 (C=O), 173.3 (C=O).

**General procedure for 327A, 329, 330**$^{82,95}$

Sulfur trioxide-pyridine complex (260 mg, 1.65 mmol) and DMSO (0.15 mL, 2.10 mmol) were stirred in anhydrous CH$_2$Cl$_2$ (5 mL) under N$_2$ at 0 °C for 15 minutes. Et$_3$N (0.62 mL, 4.50 mmol) was added then a solution of hydroxyamide 325A (80 mg, 0.15 mmol) in anhydrous CH$_2$Cl$_2$ (2 mL) was added. The reaction allowed to warm to room temperature and stirred for 16 – 18 hours. A saturated aqueous solution of NaHCO$_3$ (10 mL) was added and the resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The organic phases were combined and washed with
1M aqueous HCl (30 mL) then a saturated aqueous solution of NaHCO₃ (30 mL). The organic phase was dried (MgSO₄) and evaporated. The residue was dried under high vacuum at 90 °C for 3 hours then dissolved in anhydrous CH₂Cl₂ (5 mL). The thiol (0.30 mmol) and ZnCl₂ (20 mg, 0.15 mmol) were added and the reaction was stirred at room temperature for 16 – 18 hours. A saturated aqueous solution of NaHCO₃ (10 mL) was added and the resulting mixture was extracted with CH₂Cl₂ (3 × 15 mL). The organic phases were combined and dried (MgSO₄) and evaporated to give the crude product. Purification by column chromatography eluting with 30 – 50 % EtOAc in petroleum ether gave the products (327A (65 %, dr 1:1), 329 (42 %, dr 1.4:1), 330 (29 %)). Spectroscopic data are identical to the data previously obtained within the Procter group.82,95

**Methyl 3-(((1R)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate (327A)**

![Chemical Structure](image)

For one diastereomer:

\(^1\text{H NMR (400 MHz, CDCl}_3\) δ 0.87 – 0.92 (21H, m, 3 × SiCH and 3 × SiCH(CH₃)₂), 2.74 (2H, t, J = 7.6 Hz, SCH₂CH₂), 2.95 (1H, dt, J = 13.6, 7.6 Hz, SCH₃H₈), 3.29 (1H, dt, J = 13.6, 7.6 Hz, SCHA₈H₈), 3.69 (3H, s, OCH₃), 3.74 (3H, s, OCH₃), 3.77 (1H, dd, J = 10.3, 2.0 Hz, CH₃H₈OΣi), 3.81 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 3.99 (1H, d, J = 15.4 Hz, NCHA₈H₈), 4.15 (1H, dd, J = 10.3, 3.3 Hz, CH₃H₈OSi), 4.49 (1H, br. s, CHN), 4.57 (1H, s, CHS), 5.62 (1H, d, J = 15.4 Hz, NCHA₈H₈), 6.22 (1H, d, J = 2.3 Hz, ArH), 6.36 (1H, d, J = 2.3 Hz, ArH), 6.88 (2H, d, J = 8.6 Hz, ArH), 7.30 (2H, d, J = 8.6 Hz, ArH).
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 11.8 (SiCH), 17.7 (SiCH(CH$_3$)$_2$), 28.2 (SCH$_2$), 34.3 (SCH$_2$CH$_2$), 41.1 (CHS), 45.9 (NCH$_2$), 51.6 (2 × OCH$_3$), 55.3 (2 × OCH$_3$), 60.3 (CHN), 64.6 (CH$_2$OSi), 98.1 (ArCH), 101.0 (ArCH), 114.1 (ArCH), 114.8 (ArC), 129.0 (ArC), 129.1 (ArCH), 134.3 (ArC), 157.4 (ArC), 158.9 (ArC), 160.2 (ArC), 170.8 (C=O), 172.6 (C=O).

For the other diastereomer

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.03 – 1.07 (21H, m, 3 × SiCH and 3 × SiCH(CH$_3$)$_2$), 2.87 – 2.91 (2H, m, SCH$_2$CH$_2$), 3.03 – 3.10 (1H, m, SCH$_2$H$_8$), 3.34 – 3.41 (1H, m, SCH$_2$H$_8$), 3.72 (3H, s, OCH$_3$), 3.75 (3H, s, OCH$_3$), 3.76 (3H, s, OCH$_3$), 3.86 (3H, s, OCH$_3$), 3.91 (1H, dd, $J$ = 9.9, 5.7 Hz, CH$_2$H$_8$OSi), 4.26 (1H, dd, $J$ = 9.9, 7.8 Hz, CH$_2$H$_8$OSi), 4.37 – 4.42 (2H, m, CHN and NCH$_2$H$_8$), 4.72 (1H, s, CHS), 5.43 (1H, d, $J$ = 14.9 Hz, NCH$_2$H$_8$), 6.23 (1H, d, $J$ = 2.1 Hz, ArH), 6.37 (1H, d, $J$ = 2.1 Hz, ArH), 6.80 (2H, d, $J$ = 8.6 Hz, ArH), 7.14 (2H, d, $J$ = 8.6 Hz, ArH).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 11.8 (SiCH), 18.0 (SiCH(CH$_3$)$_2$), 28.5 (SCH$_2$), 34.4 (SCH$_2$CH$_2$), 39.8 (CHS), 49.1 (NCH$_2$), 51.7 (OCH$_3$), 53.4 (OCH$_3$), 55.2 (OCH$_3$), 55.7 (OCH$_3$), 62.6 (CHN), 68.9 (CH$_2$OSi), 98.0 (ArCH), 103.0 (ArCH), 113.6 (ArC), 113.9 (ArCH), 129.2 (ArCH), 129.4 (ArC), 136.2 (ArC), 157.2 (ArC), 158.8 (ArC), 160.0 (ArC), 169.1 (C=O), 172.5 (C=O).

(2R)-Methyl 3-(((1R)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)propanoate (329)$^{95}$

![Chemical Structure](image-url)
For major diastereomer 329:

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.99 – 1.08 (21H, m, SiCH and SiCH(CH$_3$)$_2$), 3.29 (1H, dd, $J$ = 14.9, 4.3 Hz, SCH$_2$H$_3$), 3.64 (1H, dd, $J$ = 14.9, 5.8 Hz, SCH$_2$H$_3$), 3.75 (3H, s, OCH$_3$), 3.77 (3H, s, OCH$_3$), 3.81 (3H, s, OCH$_3$), 3.86 (1H, m, CH$_2$H$_5$OSi), 3.88 (3H, s, OCH$_3$), 4.13 (1H, dd, $J$ = 10.0, 7.7 Hz, CH$_3$H$_5$OSi), 4.38 (2H, d, $J$ = 14.7 Hz, NCH$_2$H$_6$Ar), 4.39 (1H, dd, $J$ = 7.6, 5.8 Hz, NCH), 4.73 (1H, d, $J$ = 12.1 Hz, OCH$_2$H$_6$CCl$_3$), 4.81 – 4.84 (1H, m, CHNHTroc), 4.85 (1H, s, CHS), 4.87 (1H, d, $J$ = 12.1 Hz, OCH$_2$H$_6$CCl$_3$), 5.47 (1H, d, $J$ = 14.7 Hz, NCH$_2$H$_6$Ar), 6.22 (1H, d, $J$ = 2.2 Hz, ArH), 6.39 (1H, d, $J$ = 2.2 Hz, ArH), 6.80 (2H, d, $J$ = 8.7 Hz, ArH), 7.14 (2H, d, $J$ = 8.7 Hz, ArH), 7.72 (1H, d, $J$ = 8.6 Hz, NH).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 11.7 (SiCH), 17.9 (SiCH(CH$_3$)$_2$), 35.6 (SCH$_2$), 40.4 (CHS), 49.2 (NCH$_2$Ar), 52.6 (OCH$_3$), 55.2 (OCH$_3$), 55.4 (OCH$_3$), 55.8 (OCH$_3$), 62.3 (NCH), 69.2 (CH$_2$O), 74.6 (OCH$_2$CCl$_3$), 77.2 (CHNHTroc), 95.6 (CCl$_3$), 98.0 (ArCH), 102.9 (ArCH), 113.5 (ArC), 114.0 (ArCH), 129.1 (ArC), 129.2 (ArCH), 135.7 (ArC), 154.7 (ArC), 157.4 (ArC), 158.9 (ArC), 160.1 (C=O), 169.3 (C=O), 170.9 (C=O).

$^{1}$(1R)-4-Hydroxy-5,7-dimethoxy-2-(4-methoxybenzyl)-1-(((triisopropylsilyl)-oxy)methyl)-1,2-dihydroisoquinolin-3(4H)-one (330)$^{95}$

![Chemical structure](image)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.89 – 0.94 (21H, m, 3 × SiCH and 3 × SiCH(CH$_3$)$_2$), 3.67 (1H, dd, $J$ = 10.0, 4.2 Hz, CH$_2$H$_5$OSi), 3.76 (3H, s, OCH$_3$), 3.78 (3H, s, OCH$_3$), 3.89 (3H, s, OCH$_3$), 3.92 (1H, dd, $J$ = 10.0, 3.5 Hz, CH$_2$H$_5$OSi), 4.26 (1H, d, $J$ = 14.9 Hz, NCH$_2$H$_6$), 4.36 (1H, dd, $J$ = 4.2, 3.5 Hz, ArCHN), 5.29 (1H, s, CHOH), 5.47 (1H, d, $J$ = 14.9 Hz, NCH$_2$H$_6$), 6.16 (1H, d, $J$ = 2.4 Hz, ArH), 6.45 (1H, d, $J$ = 2.4 Hz, ArH), 6.83 (2H, d, $J$ = 8.7 Hz, ArH), 7.20 (2H, d, $J$ = 8.7 Hz, ArH).
13C NMR (100 MHz, CDCl3) δ 11.8 (SiCH), 17.7 (CH3), 48.1 (NCH2), 55.3 (OCH3), 55.4 (OCH3), 56.1 (OCH3), 61.5 (NCH), 65.2 (CHOH), 66.5 (CH2OSi), 98.7 (ArCH), 101.9 (ArCH), 114.1 (ArCH), 116.4 (ArC), 128.4 (ArC), 129.3 (ArCH), 133.9 (2 × ArC), 159.1 (ArC), 160.1 (ArC), 171.0 (C=O).

(R)-N-(2,4-Dimethoxybenzyl)-N-(1-(3,5-dimethoxyphenyl)-2-((triisopropylsilyl)oxy)ethyl)-2-hydroxyacetamide (325B)

Amine 323 (0.75 g, 2.12 mmol) was dissolved in anhydrous methanol (20 mL) under N2 then 2,4-dimethoxybenzaldehyde (0.42 g, 2.54 mmol) was added. The reaction was heated at reflux for 10 hours then cooled to 0 °C before NaBH4 (0.16 g, 4.24 mmol) was added in one portion. The reaction was allowed to warm to room temperature and stirred for 1 hour. The solvent was evaporated then water (25 mL) was added and the resulting mixture was extracted with CH2Cl2 (3 × 25 mL). The organic extracts were combined and dried (MgSO4) then evaporated. Purification by flash column chromatography eluting with 20 % EtOAc in petroleum ether gave amine 324B (0.95 g, 1.89 mmol, 89 %) as a colourless oil.

Amine 324B (0.95 g, 1.89 mmol) was dissolved in CH2Cl2 (10 mL) under N2, acetoxyacetyl chloride (0.24 mL, 2.27 mmol) was added and the reaction mixture was cooled to 0 °C and Et3N (0.32 mL, 2.27 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 5 hours. The solvent was evaporated and the residue was dissolved in MeOH (8.4 mL) and K2CO3 (1.04 g, 7.56 mmol) in water (4.2 mL) were added. The reaction was stirred at room temperature for 14 hours then methanol was evaporated and
the residue was diluted with H₂O (30 mL) and extracted with CH₂Cl₂ (3 × 30 mL).
The organic phases were combined and washed with brine (100 mL), dried (MgSO₄) then evaporated to give 325B (0.74 g, 1.32 mmol, 70 %) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 1.01 – 1.07 (42H, m, Si(CH(CH₃)₂)₃ of 2 rotamers), 3.71 – 3.78 (24H, m, 4 × OCH₃ of 2 rotamers), 4.06 – 4.08 (11H, m, CH₂O, NCH₂, CH₂OSi of one rotamer and CH₃₃H₈O, NCH₂, CH₂OSi of the other rotamer), 4.68 (1H, t, J = 6.6 Hz, NCH of one rotamer), 4.72 (1H, d, J = 15.8 Hz, CH₃₃H₈O of the other rotamer), 5.30 (1H, t, J = 6.6 Hz, NCH of the other rotamer), 6.27 – 6.40 (10H, m, ArH of 2 rotamers), 7.01 (1H, d, J = 8.5 Hz, ArH of one rotamer), 7.24 (1H, d, J = 8.5 Hz, ArH of the other rotamer).

¹³C NMR (125 MHz, CDCl₃) δ 11.8 (SiCH of one rotamer), 11.9 (SiCH of the other rotamer), 17.9 (SiCH(CH₃)₂ of 2 rotamer), 43.7 (NCH₂ of PMB), 55.1 (OCH₃ of 2 rotamer), 55.2 (2 × OCH₃ of 2 rotamers), 55.4 (OCH₃ of 2 rotamers), 60.5 (CH₂O), 61.1 (NCH of one rotamer), 61.6 (NCH of the other rotamer), 62.6 (CH₂OSi of one rotamer), 63.0 (CH₂OSi of the other rotamer), 97.9 (ArCH of one rotamer), 98.3 (ArCH of the other rotamer), 99.4 (ArCH of 2 rotamers), 103.9 (ArCH of one rotamer), 104.2 (ArCH of the other rotamer), 105.8 (ArCH of 2 rotamers), 106.3 (ArCH of 2 rotamers), 116.7 (ArC of 2 rotamers), 118.6 (ArC of 2 rotamers), 129.0 (ArCH of one rotamers), 129.7 (ArCH of the other rotamers), 138.7 (ArC of one rotamer), 140.2 (ArC of the other rotamer), 157.2 (ArC of one rotamer), 157.9 (ArC of the other rotamer), 159.8 (ArC of one rotamer), 160.5 (ArC of the other rotamer), 160.8 (ArC of 2 rotamers), 173.0 (C=O of one rotamer), 173.4 (C=O of the other rotamer).

MS (ES+): m/z: 584 ([M + Na]+); HRMS (ES+): m/z: calcd for C₃₀H₄₇NO₇SiNa: 584.3014 ([M + H]+); found: 584.3014.
IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 3294 (br, OH), 2865, 1644 (C=O), 1608, 1594, 1507, 1459, 1428, 1388, 1347, 1290, 1261, 1205, 1154, 1084, 1067, 1036, 1013

$[\alpha]_D^{23} = -0.04$ (c = 3.9, CHCl$_3$).

**Methyl 3-(((1R)-2-(2,4-dimethoxybenzyl)-5,7-dimethoxy-3-oxo-1-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate (327B)**

![Chemical Structure](image)

Sulfur trioxide pyridine complex (0.71 g, 4.45 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (15 mL) under N$_2$. The mixture was cooled to 0 °C and DMSO (0.70 mL, 8.90 mmol) was added. The mixture was stirred at 0 °C for 15 minutes then triethylamine (2.48 mL, 17.80 mmol) and 325B (0.50 g, 0.89 mmol) in CH$_2$Cl$_2$ (3 mL) were added and the reaction was stirred at room temperature for 16 hours. The reaction mixture was diluted with CH$_2$Cl$_2$ (40 mL) and washed with aqueous saturated NaHCO$_3$ (2 × 30 mL), dried (MgSO$_4$) and evaporated to give the crude glyoxamide which was then dried under high vacuum at 50 °C for 1 hour. The dried glyoxamide 326B was dissolved in anhydrous CH$_2$Cl$_2$ (10 mL) then HSCH$_2$CH$_2$COOCH$_3$ (0.21 mL, 1.78 mmol) was added. The reaction was stirred at room temperature for 16 hours. The reaction mixture was diluted with anhydrous CH$_2$Cl$_2$ (10 mL) then ZnCl$_2$ (0.18 g, 1.34 mmol) was added. The reaction mixture was stirred for a further 20 hours. A saturated aqueous solution of NaHCO$_3$ (20 mL) was added, and the resulting mixture extracted with CH$_2$Cl$_2$ (3 × 20 mL). The organic phases were combined and dried (MgSO$_4$) and evaporated to give the crude product. Purification by column chromatography eluting with 15 – 25 % EtOAc in petroleum ether gave 327B (0.29 g, 0.45 mmol, 51 %) as a colourless pale oil and as a mixture of diastereomers (dr 1.3:1) from which one diastereoisomer was isolated.
For one diastereomer:

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.02 – 1.12 (21H, m, Si(CH$_2$CH$_3$)$_2$), 2.86 – 2.92 (2H, m, SCH$_2$CH$_2$), 3.03 – 3.09 (1H, m, SCH$_2$H$_8$), 3.35 – 3.40 (1H, m, SCH$_2$H$_8$), 3.71 (3H, s, OCH$_3$), 3.75 (3H, s, OCH$_3$), 3.77 (6H, s, 2 × OCH$_3$), 3.85 (3H, s, OCH$_3$), 3.86 (3H, s, OCH$_3$), 3.87 (6H, s, 2 × OCH$_3$), 3.94 (1H, dd, $J = 9.8$, 6.3 Hz, CH$_2$OSi), 4.22 (1H, dd, $J = 9.8$, 7.3 Hz, CH$_2$OSi), 4.53 (1H, dd, $J = 7.3$, 6.3 Hz, NCH), 4.56 (1H, d, $J = 15.2$ Hz, NCH$_8$H$_8$), 4.68 (1H, s, CHS), 5.12 (1H, d, $J = 15.2$ Hz, NCH$_8$H$_8$), 6.29 (1H, d, $J = 2.3$ Hz, ArH), 6.35 (1H, dd, $J = 8.4$, 2.3 Hz, ArH), 6.38 (1H, d, $J = 2.5$ Hz, ArH), 6.41 (1H, d, $J = 2.5$ Hz, ArH), 7.02 (1H, d, $J = 8.4$ Hz, ArH).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 11.7 (SiCH), 17.9 (SiCH(CH$_3$)$_2$), 28.5 (SCH$_2$), 34.4 (SCH$_2$CH$_2$), 39.8 (CHS), 45.0 (NCH$_2$), 51.6 (OCH$_3$), 55.2 (OCH$_3$), 55.3 (2 × OCH$_3$), 55.7 (OCH$_3$), 63.5 (NCH), 68.3 (CH$_2$OSi), 97.8 (ArCH), 98.3 (ArCH), 103.2 (ArCH), 103.9 (ArCH), 113.6 (ArC), 117.8 (ArC), 129.7 (ArCH), 136.7 (ArC), 157.2 (ArC), 158.4 (ArC), 159.8 (ArC), 159.9 (ArC), 169.3 (C=O), 172.6 (C=O).

MS (ES+): $m/z$: 662 ([M + H]$^+$), 685 ([M + Na]$^+$); HRMS (ES+): $m/z$: calcd for C$_{34}$H$_{52}$NO$_8$SSi: 662.3177 ([M + H]$^+$); found: 662.3178.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2941, 2864, 1736 (C=O), 1643 (C=O), 1608, 1505, 1454, 1419, 1359, 1287, 1287, 1255, 1200, 1148, 1043.

$[\alpha]_D^{23} = +0.09$ (c = 1.6, CHCl$_3$).

1,3,4-Trimethoxy-2-methyl-5-vinylbenzene (331)

Triphenylmethylphosphonium bromide (4.29 g, 12.0 mmol) was suspended in anhydrous THF (40 mL) under N$_2$. Potassium t-butoxide (1.57 g, 14.0 mmol) was
added and the mixture was stirred at room temperature for 30 minutes before cooling to −78 °C. Subsequently, a solution of aldehyde 274 (2.10 g, 10.0 mmol) in anhydrous THF (12 mL) was added dropwise at −78 °C then the reaction mixture was allowed to warm to room temperature. The reaction was quenched by the addition of MeOH (20 mL) and the solvent was evaporated. Purification by plug column chromatography eluting with 5% of EtOAc in petroleum ether gave 331 (2.00 g, 9.62 mmol, 96%) as a colourless oil.

\[
\begin{align*}
\text{H NMR (400 MHz, CDCl}_3\text{)} & \delta 2.14 (3H, s, \text{ArCH}_3), 3.80 (3H, s, \text{OCH}_3), 3.84 (6H, s, 2 \times \text{OCH}_3), 5.28 (1H, dd, J = 11.1, 1.3 Hz, \text{C_H}_A\text{H}_B), 5.72 (1H, dd, J = 17.9, 1.3 Hz, \text{CH}_A\text{H}_B), 6.74 (1H, s, \text{ArH}), 7.02 (1H, dd, J = 17.9, 11.1 Hz, \text{C_H}=\text{CH}_2) \\
\text{C NMR (100 MHz, CDCl}_3\text{)} & \delta 9.0 (\text{CH}_3), 55.7 (\text{OCH}_3), 60.5 (\text{OCH}_3), 61.1 (\text{OCH}_3), 101.9 (\text{ArCH}), 113.9 (\text{CH}=\text{CH}_2), 120.9 (\text{ArC}), 128.5 (\text{ArC}), 131.2 (\text{CH}=\text{CH}_2), 144.9 (\text{ArC}), 152.1 (\text{ArC}), 154.2 (\text{ArC}).
\end{align*}
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MS (ES+): \(m/z\): 208 ([M\(^+\)], 209 ([M + H\(^+\)], 231 ([M + Na\(^+\)]) HRMS (ES+): \(m/z\): calcd for C\(_{12}\)H\(_{17}\)O\(_3\): 209.1173 ([M + H\(^+\)]; found: 209.1167.

IR (thin film) \(\nu_{\text{max}}\) (cm\(^{-1}\)) 2933, 1601 (C=C), 1572, 1480, 1463, 1402, 1231, 1132, 1090, 1041.

\((R)\)-2-(((Triisopropylsilyl)oxy)-1-(2,3,5-trimethoxy-4-methylphenyl)ethanamine (332A)

AD-mix-\(\alpha\) (6.10 g) was dissolved in H\(_2\)O (22 mL) and t-BuOH (10 mL) at 0 °C. A solution of 331 (0.92 g, 4.42 mmol) in t-BuOH (12 mL) was then added and the
reaction was allowed to warm to room temperature and stirred for 17 hours. A saturated aqueous solution of NaSO$_3$ (15 mL) was added and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was then extracted with CH$_2$Cl$_2$ (3 × 30 mL). The organic phases were combined and washed with brine (100 mL) then dried (MgSO$_4$) and evaporated to give the crude diol product.

The crude diol product was dissolved in CH$_2$Cl$_2$ (30 mL) and imidazole (0.75 g, 11.05 mmol) and TIPSCl (0.94 mL, 4.42 mmol) were added. The reaction was stirred at room temperature for 16 hours before H$_2$O (30 mL) was added. The aqueous phase was extracted with CH$_2$Cl$_2$ (2 × 30 mL) and the organic phases were combined and dried (MgSO$_4$) then evaporated to give crude product. Purification by column chromatography eluting with 2.5 % EtOAc in petroleum ether gave protected alcohol (1.57 g, 3.94 mmol, 89 %) as a colorless oil.

Protected alcohol (0.87 g, 2.18 mmol) and Ph$_3$P (1.43 g, 5.45 mmol) were dissolved in anhydrous THF (15 mL) and cooled to 0 °C before DIAD (1.07 mL, 5.45 mmol) was added dropwise then DPPA (1.17 mL, 5.45 mmol) was added. The reaction mixture was stirred at 0 °C for 3 hours and the solvent was evaporated. Purification by column chromatography eluting with 1 % EtOAc in petroleum ether gave the intermediate azide as a colorless oil.

The azide was dissolved in THF (10 mL) and Ph$_3$P (1.30 g, 4.95 mmol) and H$_2$O (0.30 mL, 16.5 mmol) were added. The reaction was heated at 60 °C for 3 hours then the solvent was evaporated. Purification by column chromatography eluting with 30 % EtOAc in petroleum ether gave 332A (0.60 g, 1.50 mmol, 69 %) as a colourless oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ 1.06 – 1.08 (21H, m, 3 × SiCH and 3 × SiCH(CH$_3$)$_2$), 1.74 (2H, br. s, NH$_2$), 2.12 (3H, s, ArCH$_3$), 3.58 (1H, dd, $J = 9.6$, 8.3 Hz, OCH$_3$H$_b$), 3.81 (3H, s, OCH$_3$), 3.82 (6H, s, 2 × OCH$_3$), 3.87 (1H, dd, $J = 9.6$, 3.8 Hz, OCH$_3$H$_a$), 4.44 (1H, dd, $J = 8.3$, 3.8 Hz, CHN), 6.79 (1H, s, ArH).
$^{13}$C NMR (100 MHz, CDCl$_3$) δ 8.8 (ArCH$_3$), 11.9 (SiCH), 18.0 (SiCH(CH$_3$)$_2$), 51.8 (CHN), 55.8 (OCH$_3$), 60.2 (OCH$_3$), 60.9 (OCH$_3$), 68.7 (OCH$_2$), 104.1 (ArCH), 119.5 (ArC), 132.9 (ArC), 144.6 (ArC), 151.6 (ArC), 154.1 (ArC).

MS (ES+): m/z: 398 ([M + H]$^+$) HRMS (ES+): m/z: calcd for C$_{21}$H$_{40}$NO$_4$NSi: 398.2722 ([M + H]$^+$); found: 398.2737.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 3390 (m, NH), 2864, 1482, 1463, 1404, 1349, 1231, 1126, 1090, 1067, 1033.

$[\alpha]_D^{27} = -2.87$ (c = 1.0, CHCl$_3$)

Enantiomeric excess was measured to be 95% using chiral HPLC (ChiralPak AD column, 98:2 hexane–isopropanol) and a racemic standard.

**rac-2-((Triisopropylsilyl)oxy)-1-(2,3,5-trimethoxy-4-methylphenyl)ethanamine (rac-332A)**

Styrene 331 (80 mg, 0.38 mmol) and NaIO$_4$ (24.4 mg, 0.11 mmol) and LiBr (7 mg, 0.08 mmol) were dissolved in AcOH (2.5 mL). The reaction mixture was heated at reflux for 20 hours. Water (10 mL) was then added and the mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL) and the organic extracts were washed with aqueous concentrated Na$_2$S$_2$O$_3$ (20 mL) then H$_2$O (20 mL) then a saturated aqueous solution of NaHCO$_3$ (20 mL) and dried (MgSO$_4$) before concentration in vacuo. The residue was dissolved in MeOH (3.6 mL) and a solution of K$_2$CO$_3$ (0.52 g, 3.80 mmol) in H$_2$O (1.8 mL) was added. The reaction was stirred at room temperature for 18 hours, MeOH was evaporated, water (10 mL) was added and the resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The organic
extracts were dried (MgSO$_4$) and evaporated and the residue was dissolved in CH$_2$Cl$_2$ (4 mL) and imidazole (65 mg, 0.95 mmol) and TIPSCI (0.08 mL, 0.38 mmol) were added. The reaction was stirred at room temperature for 17 hours. Aqueous saturated NH$_4$Cl (10 mL) was added and the aqueous phase extracted by CH$_2$Cl$_2$ (3 \times 10$ mL$). The organic extracts were dried (MgSO$_4$) and evaporated. Purification by column chromatography eluting with 2.5 % EtOAc in petroleum ether gave protected alcohol (85 mg, 0.21 mmol, 55 %) as a colourless oil.

The protected alcohol (73 mg, 0.18 mmol), Ph$_3$P (66 mg, 0.25 mmol) and phthalimide (37 mg, 0.25 mmol) were dissolved in THF (2 mL) at room temperature and DIAD (0.05 mL, 0.25 mmol) was added slowly. The reaction was stirred at room temperature for 18 hours. Purification by column chromatography eluting with 3 % EtOAc in petroleum ether gave the crude phthalimide, which was dissolved in EtOH (5 mL). (NH$_2$)$_2$ (0.04 mL of a 62 % solution in water, 0.54 mmol) was then added and the reaction was heated at reflux for 4 hours then solvent was evaporated. Purification by column chromatography eluting with 30 % EtOAc in petroleum ether gave amine rac-332A (20.5 mg, 0.05 mmol, 28 %) as a colorless oil.

See data for compound 332A

(R)-N-(4-Methoxybenzyl)-2-((triisopropylsilyl)oxy)-1-(2,3,5-trimethoxy-4-methylphenyl)ethanamine (333A)

Amine 332A (0.64 g, 1.61 mmol) was dissolved in MeOH (20 mL) then 4-methoxy-benzaldehyde (0.21 mL, 1.61 mmol) was added and the reaction was heated at reflux for 4 hours then cooled to 0 °C. NaBH$_4$ (0.18 g, 4.83 mmol) was added in one portion and the reaction was allowed to warm to room
temperature and stirred for 2.5 hours. The solvent was evaporated then water (20 mL) was added and the resulting mixture was extracted with CH₂Cl₂ (3 × 20 mL). The organic extracts were combined and dried (MgSO₄) then evaporated. Purification by flash column chromatography eluting with 20 % EtOAc and 1% Et₃N in petroleum ether gave 333A (0.72 g, 1.39 mmol, 86 %) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ 1.03 – 1.06 (21H, m, 3 × SiCH and 3 × SiCH(CH₃)₂), 2.14 (3H, s, ArCH₃), 3.53 – 3.58 (2H, m, OCH₃A and NCH₂B₁), 3.69 (1H, d, J = 13.1 Hz, NCH₂B₂), 3.75 (3H, s, OCH₃), 3.80 (3H, s, OCH₃), 3.82 – 3.85 (7H, m, 2 × OCH₃ and OCH₂B₂), 4.27 (1H, dd, J = 9.3, 3.8 Hz, CHN), 6.85 (2H, d, J = 8.6 Hz, ArH), 6.95 (1H, s, ArH), 7.22 (2H, d, J = 8.6 Hz, ArH).

¹³C NMR (100 MHz, CDCl₃) δ 8.9 (ArCH₃), 11.9 (SiCH), 17.9 (SiCH(CH₃)₂), 51.1 (NCH₂), 55.3 (OCH₃), 55.8 (OCH₃), 57.9 (CHN), 60.2 (OCH₃), 60.7 (OCH₃), 67.5 (OCH₂), 104.3 (ArCH), 113.7 (ArCH), 119.4 (ArC), 129.2 (ArCH), 130.8 (ArC), 133.0 (ArC), 145.6 (ArC), 151.6 (ArC), 154.3 (ArC), 158.5 (ArC).


IR (thin film) νmax (cm⁻¹) 3390 (m, NH), 1512, 1463, 1404, 1257, 1126, 1088, 1064, 1031.

[α]D²⁴ = -7.43 (c = 1.5, CHCl₃).

(R)-2-Hydroxy-N-(4-methoxybenzyl)-N-{2-{((triisopropylsilyl)oxy)-1-(2,3,5-trimethoxy-4-methylphenyl)ethyl}acetamide (334A)
Amine 333A (0.72 g, 1.39 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (20 mL), and acetoxyacetyl chloride (0.18 mL, 1.67 mmol) was added. The reaction mixture was then cooled to 0 °C and Et$_3$N (0.23 mL, 1.67 mmol) was added. The reaction was subsequently allowed to warm to room temperature and stirred for 5 hours. The solvent was evaporated and the residue was dissolved in MeOH (27 mL) before K$_2$CO$_3$ (1.92 g, 13.9 mmol) in water (13.5 mL) was added. The reaction was then stirred at room temperature for 17 hours. After evaporation, the residue was diluted with H$_2$O (30 mL) and extracted with CH$_2$Cl$_2$ (3 × 30 mL). The organic phases were combined and washed with brine (100 mL), dried (MgSO$_4$) then evaporated to give 334A (0.73 g, 1.27 mmol, 91 %) as a pale colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 1.04 – 1.09 (21H, m, 3 × SiCH and 3 × SiCH(CH$_3$)$_2$), 2.11 (3H, s, ArCH$_3$ of one rotamer), 2.14 (3H, s, ArCH$_3$ of other rotamer), 3.72 – 3.81 (13H, m, 4 × OCH$_3$ and CH$_A$H$_B$OH), 3.92 (1H, dd, $J = 10.3$, 4.8 Hz, CH$_A$H$_B$OSi), 4.03 (1H, dd, $J = 10.3$, 9.1 Hz, CH$_A$H$_B$OSi), 4.31 (1H, d, $J = 15.1$ Hz, NCH$_A$H$_B$), 4.55 – 4.69 (2H, m, NCH$_A$H$_B$ and CH$_A$H$_B$OH), 5.01 (1H, dd, $J = 9.1$, 4.8 Hz, CHN of one rotamer), 5.8 (1H, m, CHN of other rotamer), 6.35 (1H, s, ArCH of one rotamer), 6.72 (2H, d, $J = 8.6$ Hz, ArCH of one rotamer), 6.78 (2H, d, $J = 8.6$ Hz, ArCH of other rotamer), 6.86 (1H, s, ArCH of other rotamer), 7.03 (2H, d, $J = 8.6$ Hz, ArCH).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 8.8 (ArCH$_3$), 11.8 (SiCH), 17.9 (SiCH(CH$_3$)$_2$), 45.3 (NCH$_2$), 55.2 (CHN), 55.3 (OCH$_3$), 56.0 (OCH$_3$), 60.0 (OCH$_3$), 60.2 (OCH$_3$), 60.3 (CH$_2$OH), 62.8 (CH$_2$OSi), 104.7 (ArCH), 113.5 (ArCH), 114.0 (ArCH of one rotamer), 122 (ArCH of other rotamer), 126.1 (ArC of one rotamer), 127.5 (ArC of other rotamer), 129.0 (ArC of one rotamer), 130.6 (ArC of other rotamer), 145.8 (ArC), 152.0 (ArC), 154.0 (ArC), 158.5 (ArC), 173.5 (C=O)
MS (ES+): m/z (%): 576 ([M + H]⁺), 598 ([M + Na]⁺); HRMS (ES+): m/z: calcd for C₃₁H₅₀NO₇Si: 576.3351 ([M + H]⁺); found: 576.3354.

IR (thin film) νₘₐₓ (cm⁻¹) 3292 (br, OH), 2864, 1643 (C=O), 1512, 1462, 1406, 1245, 1126, 1033, 882.

[α]₀²⁴ = -13.10 (c = 1.4, CHCl₃).

(R)-2-((tert-Butyldiphenylsilyl)oxy)-1-(2,3,5-trimethoxy-4-methylphenyl)-ethanamine (332B)

AD-mix-α (4.44 g) was dissolved in water (15 mL) and t-BuOH (10 mL) at 0 °C and a solution of styrene 331 (0.67 g, 3.22 mmol) in t-BuOH (5 mL) was added. The reaction was allowed to warm to room temperature and stirred for 17 hours. A saturated aqueous solution of NaSO₃ (9 mL) was added and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was then extracted with CH₂Cl₂ (3 × 15 mL), the organic phases were combined and washed with brine (50 mL) then dried (MgSO₄) and evaporated to give the crude diol product.

The crude diol product was dissolved in CH₂Cl₂ (23 mL) and imidazole (0.44 g, 6.44 mmol) and TBDPSCI (0.84 mL, 3.22 mmol) were added. The reaction was stirred at room temperature for 2 hours. Water (20 mL) was added and the aqueous phase was extracted with CH₂Cl₂ (2 × 20 mL). The organic phases were combined and dried (MgSO₄) then evaporated to give the crude product. Purification by column chromatography eluting with 2.5 % EtOAc in petroleum ether gave protected alcohol (1.46 g, 3.03 mmol, 94 %) as colourless oil.
Protected alcohol (0.57 g, 1.19 mmol) and \( \text{Ph}_3\text{P} \) (0.78 g, 2.98 mmol) were dissolved in anhydrous THF (8 mL) and cooled to 0 °C. DIAD (0.59 mL, 2.98 mmol) was added dropwise then DPPA (0.64 mL, 2.98 mmol) was also added and the reaction mixture was stirred at 0 °C for 6 hours before the solvent was evaporated. Purification by column chromatography eluting with 1 % EtOAc in petroleum ether gave the intermediate azide.

The azide product was dissolved in THF (8 mL) and \( \text{Ph}_3\text{P} \) (0.94 g, 3.57 mmol) and \( \text{H}_2\text{O} \) (0.21 mL, 11.9 mmol) were added. The reaction was heated at 60 °C for 3 hours before the solvent was evaporated. Purification by column chromatography eluting with 30 % EtOAc in petroleum ether gave \( \text{332B} \) (0.30 g, 0.63 mmol, 53 %) as a colourless oil.

\(^1\text{H} \text{NMR} (500 \text{ MHz, CDCl}_3) \delta 1.08 (9\text{H}, \text{s, C(\text{CH}_3)_3}), 2.11 (3\text{H}, \text{s, CH}_3), 3.62 – 3.66 (4\text{H}, \text{m, OCH}_2\text{H}_8, \text{OCH}_3), 3.83 (1\text{H}, \text{dd, } J = 9.8, 4.1 \text{ Hz, OCH}_2\text{H}_8), 4.49 (1\text{H}, \text{dd, } J = 7.9, 4.1 \text{ Hz, CHN}), 6.73 (1\text{H}, \text{s, ArH}), 7.34 – 7.43 (6\text{H}, \text{m, ArH}), 7.63 – 7.69 (4\text{H}, \text{m, ArH}).

\(^{13}\text{C} \text{NMR} (125 \text{ MHz, CDCl}_3) \delta 8.8 (\text{CH}_3), 19.3 (\text{C(\text{CH}_3)_3}), 26.9 (\text{C(\text{CH}_3)_3}), 51.5 (\text{CHN}), 55.8 (\text{OCH}_3), 60.1 (\text{OCH}_3), 60.8 (\text{OCH}_3), 69.2 (\text{OCH}_2), 104.1 (\text{ArCH}), 119.5 (\text{ArC}), 127.6 (\text{ArCH}), 129.6 (\text{ArCH}), 132.8 (\text{ArC}), 133.5 (\text{ArC}), 135.6 (\text{ArCH}), 144.6 (\text{ArC}), 151.2 (\text{ArC}), 154.0 (\text{ArC}).

\( \text{MS (ES+): } m/z: 480 ([M + H]^+) \) \( \text{HRMS (ES+): } m/z: \text{calcd for C}_{28}\text{H}_{38}\text{N}_1\text{O}_4\text{Si: } 480.2565 ([M + H]^+) ; \text{found: } 480.2568. \)

\( \text{IR (thin film) } \nu_{\text{max}} (\text{cm}^{-1}) 3390 (\text{m, NH}), 2931, 1639, 1608, 1586, 1511, 1482, 1460, 1427, 1403, 1188, 1065. \)

\( [\alpha]_D^{24} = + 0.42 (c = 3.5, \text{CHCl}_3) \)

Enantiomeric excess was measured as 94% using chiral HPLC (ChiralPak AD column, 98:2 hexane–isopropanol) and a racemic standard.
**rac-2-((tert-Butyldiphenylsilyl)oxy)-1-(2,3,5-trimethoxy-4-methylphenyl)-ethanamine (rac-332B)**

![Chemical Structure](attachment:image.png)

Styrene **331** (170 mg, 0.72 mmol), NaIO$_4$ (46 mg, 0.22 mmol) and LiBr (12.5 mg, 0.15 mmol) were dissolved in AcOH (5 mL) and the reaction mixture was heated at reflux for 20 hours. Water (15 mL) was added and the solution extracted with CH$_2$Cl$_2$ (3 × 15 mL). The organic extracts were washed with saturated aqueous solution of Na$_2$S$_2$O$_3$ (30 mL) then water (30 mL) then saturated aqueous NaHCO$_3$ (30 mL) and dried (MgSO$_4$) then evaporated. The residue was dissolved in MeOH (6.8 mL) and a solution of K$_2$CO$_3$ (0.99 g, 7.2 mmol) in water (3.4 mL) was added. The reaction was stirred at room temperature for 17 hours before the MeOH was evaporated, water (10 mL) was added and the resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The organic extracts were dried (MgSO$_4$) and evaporated. The residue was dissolved in CH$_2$Cl$_2$ (5 mL), and imidazole (98 mg, 1.44 mmol), and TBDPSCl (0.19 mL, 0.72 mmol) were added. The reaction was stirred at room temperature for 2 hours before a saturated aqueous solution of NH$_4$Cl (10 mL) was added and the mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The organic extracts was dried (MgSO$_4$) and evaporated. Purification by column chromatography eluting with 5 % EtOAc in petroleum ether gave protected alcohol (0.19 g, 0.40 mmol, 63 %) as a colorless oil.

Protected alcohol (0.13 g, 0.27 mmol) and Ph$_3$P (0.18 g, 0.68 mmol) were dissolved in anhydrous THF (7 mL) and the solution cooled to 0 °C. DIAD (0.13 mL, 0.68 mmol) was added dropwise then DPPA (0.15 mL, 0.68 mmol) was added and the reaction mixture was stirred at 0 °C for 6 hours before the solvent was evaporated. Purification by column chromatography eluting with 1 % EtOAc in petroleum ether gave the intermediate azide.
The azide product was dissolved in THF (5 mL) and Ph₃P (0.21 g, 0.81 mmol) and water (0.05 mL, 2.7 mmol) were added. The reaction was heated at 60 °C for 3 hours then the solvent was evaporated. Purification by column chromatography eluting with 30 % EtOAc in petroleum ether gave rac-332B (0.07 g, 0.15 mmol, 56 %) as a colourless oil.

See data for compound 332B

(R)-2-(((tert-Butyldiphenylsilyl)oxy)-N-(4-methoxybenzyl)-1-(2,3,5-trimethoxy-4-methylphenyl)ethanamine (333B)

Amine 332B (0.24 g, 0.50 mmol) was dissolved in MeOH (10 mL) and 4-methoxy-benzaldehyde (0.08 mL, 0.60 mmol) was added. The reaction was heated at reflux for 4 hours then cooled to 0 °C before NaBH₄ (0.06 g, 1.50 mmol) was added in one portion. The reaction was allowed to warm to room temperature and stirred for 2.5 hours. The solvent was evaporated then water (20 mL) was added and the resulting mixture was extracted with CH₂Cl₂ (3 × 20 mL). The organic extracts were combined and dried (MgSO₄) then evaporated. Purification by column chromatography eluting with 20 % EtOAc and 1% Et₃N in petroleum ether gave 333B (0.30 g, 0.50 mmol, 100 %) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 1.05 (9H, s, C(CH₃)₃), 2.11 (3H, s, CH₃), 3.53 (3H, s, OCH₃), 3.57 (1H, d, J = 12.9 Hz, NCH₂H₆), 3.62 – 3.66 (1H, m, OCH₂H₆), 3.71 (1H, d, J = 12.9 Hz, NCH₂H₆), 3.76 (3H, s, OCH₃), 3.77 – 3.80 (1H, m, OCH₂H₆), 3.79 (3H, s, OCH₃), 3.82 (3H, s, OCH₃), 4.31 (1H, dd, J = 8.8, 4.1 Hz, CHN), 6.86 – 6.88 (3H, m, ArCH), 7.25 (2H, d, J = 8.5 Hz, ArCH), 7.33 – 7.44 (6H, m, ArCH), 6.61 – 7.64 (4H, m, ArCH)
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 8.8 (CH$_3$), 19.2 (C(CH$_3$)$_3$), 26.8 (C(CH$_3$)$_3$), 51.0 (NCH$_2$), 55.3 (OCH$_3$), 55.8 (OCH$_3$), 57.3 (CHN), 60.1 (OCH$_3$), 60.6 (OCH$_3$), 68.0 (OCH$_2$), 104.3 (ArCH), 113.8 (2 ArCH), 119.4 (ArC), 127.6 (ArCH), 129.3 (ArCH), 130.7 (ArC), 133.0 (ArC), 133.4 (ArC), 135.5 (ArCH), 135.6 (ArCH), 145.5 (ArC), 151.6 (ArC), 154.2 (ArC), 158.5 (ArC).

MS (ES+): $m/z$: 600 ([M + H]$^+$) HRMS (ES+): $m/z$: calcd for C$_{36}$H$_{46}$N$_1$O$_5$Si: 600.3140 ([M + H]$^+$); found: 600.3141.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 3930 (m, NH), 2856, 1638, 1610, 1510, 1461, 1427, 1404, 1375, 1344, 1299, 1244, 1111, 1032.

$[\alpha]_D^{24} = -5.47$ (c = 1.2, CHCl$_3$).

(R)-N-(2-((tert-Butyldiphenylsilyl)oxy)-1-(2,3,5-trimethoxy-4-methylphenyl)-ethyl)-2-hydroxy-N-(4-methoxybenzyl)acetamide (334B)

Amine 333B (0.30 g, 0.50 mmol) was dissolved in CH$_2$Cl$_2$ (8 mL), and acetoxyacetyl chloride (0.07 mL, 0.60 mmol) was added and the reaction mixture was cooled to 0 °C and Et$_3$N (0.08 mL, 0.60 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 5 hours before the solvent was evaporated and the residue was dissolved in MeOH (10 mL). A solution of K$_2$CO$_3$ (0.69 g, 5.00 mmol) in H$_2$O (5 mL) was added and the reaction was stirred at room temperature for 17 hours before the methanol was evaporated and the residue was diluted with H$_2$O (20 mL) and extracted with CH$_2$Cl$_2$ (3 × 20 mL). The organic phases were combined and washed with brine (50 mL) and dried (MgSO$_4$) then evaporated to give 334B (0.30 g, 0.46 mmol, 92%) as a pale colourless oil.
$^1$H NMR (400 MHz, CDCl$_3$) δ 1.02 (9H, s, C(CH$_3$)$_3$), 2.09 (3H, s, CH$_3$), 3.64 – 3.75 (12H, s, 4 × OCH$_3$), 3.83 – 4.59 (6H, m, CH$_2$OH, CH$_2$O, NCH$_2$), 5.02 (1H, dd, $J = 8.7$, 5.4 Hz, CHN of one rotamer), 5.87 – 5.90 (1H, m, CHN of other rotamer), 6.22 (1H, s, ArH of one rotamer), 6.66 (2H, d, $J = 8.6$ Hz, ArH of one rotamer), 6.70 (1H, s, ArH of other rotamer), 6.71 (2H, d, $J = 8.6$ Hz, ArH of other rotamer), 6.92 (2H, d, $J = 8.6$ Hz, ArH of one rotamer), 6.97 (2H, d, $J = 8.6$ Hz, ArH of other rotamer), 7.33 – 7.48 (6H, m, ArH), 7.52 – 7.62 (4H, m, ArH).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 8.8 (CH$_3$), 19.0 (C(CH$_3$)$_3$), 26.7 (C(CH$_3$)$_3$), 45.2 (NCH$_2$ of one rotamer), 47.3 (NCH$_2$ of other rotamer), 54.8 (CHN of one rotamer), 55.2 (OCH$_3$ of one rotamer), 55.3 (OCH$_3$ of other rotamer), 55.8 (CHN of other rotamer), 56.0 (OCH$_3$), 59.9 (OCH$_3$ of one rotamer), 60.0 (OCH$_3$ of other rotamer), 61.2 (OCH$_3$), 60.7 (OCH$_2$), 62.9 (CH$_2$OH), 104.8 (ArCH of one rotamer), 106.1 (ArCH of other rotamer), 113.4 (ArCH of one rotamer), 114.0 (ArCH of other rotamer), 121.1 (ArC of one rotamer), 121.9 (ArC of other rotamer), 125.8 (ArC of one rotamer), 127.5 (ArC of other rotamer), 127.7 (ArCH of one rotamer), 127.9 (ArCH of other rotamer), 129.0 (ArCH of one rotamer), 129.7 (ArCH of other rotamer), 130.0 (ArCH of one rotamer), 130.4 (ArCH of other rotamer), 132.6 (ArC of 2 rotamers), 135.4 (ArCH of one rotamer), 135.6 (ArCH of other rotamer), 145.8 (ArC of one rotamer), 145.9 (ArC of other rotamer), 151.8 (ArC), 153.9 (ArC), 158.4 (ArC of one rotamer), 158.8 (ArC of other rotamer), 172.8 (C=O of one rotamer), 173.4 (C=O of other rotamer).

MS (ES+): $m/z$: 658 ([M + H]$^+$), 680 ([M + Na]$^+$); HRMS (ES+): $m/z$: calcd for C$_{38}$H$_{48}$NO$_7$Si: 658.3195 ([M + H]$^+$); found: 658.3193.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 3432 (br, OH), 3071, 2932, 2857, 1642 (C=O), 1610, 1586, 1511, 1485, 1461, 1404, 1244, 1176, 1110, 1030.

$[\alpha]_D^{24} = -7.79$ (c = 3.5, CHCl$_3$).
Methyl 3-(((1R)-1-(((tert-butyldiphenylsilyl)oxy)methyl)-5,7,8-trimethoxy-2-(4-methoxybenzyl)-6-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)-propanoate (335C)

Method A

Sulfur trioxide-pyridine complex (58 mg, 365 \( \mu \text{mol} \)) and DMSO (57 \( \mu \text{L} \), 730 \( \mu \text{mol} \)) were stirred in anhydrous CH\(_2\)Cl\(_2\) (2 mL) at 0 °C for 15 minutes. Et\(_3\)N (0.20 mL, 1.46 mmol) was added, then a solution of hydroxyamide 334B (48 mg, 73 \( \mu \text{mol} \)) in anhydrous CH\(_2\)Cl\(_2\) (1 mL) was added. The reaction was allowed to warm to room temperature and stirred for 17 hours. A saturated aqueous solution of NaHCO\(_3\) (10 mL) was added and the resulting mixture was extracted with CH\(_2\)Cl\(_2\) (3 \( \times \) 10 mL). The organic phases were combined and washed with a 1M aqueous solution of HCl (30 mL) then a saturated aqueous solution of NaHCO\(_3\) (30 mL). The organic layer was dried (MgSO\(_4\)) and evaporated. The residue was dried under high vacuum at 35 °C for 4 hours then dissolved in anhydrous CHCl\(_3\) (3 mL) before HSCH\(_2\)CH\(_2\)COOMe (18 \( \mu \text{L} \), 0.15 mmol) and Sc(OTf)\(_3\) (36 mg, 73 \( \mu \text{mol} \)) were added, and the reaction was heated at reflux for 18 hours. A saturated aqueous solution of NaHCO\(_3\) (10 mL) was added and the resulting mixture was extracted with CH\(_2\)Cl\(_2\) (3 \( \times \) 15 mL). The organic phases were combined and dried (MgSO\(_4\)) and evaporated to give the crude product. Purification by column chromatography eluting with 20 – 60 % EtOAc in petroleum ether gave 335C as a mixture of 2 diastereomers (dr 1:1) (23 mg, 30 \( \mu \text{mol} \), 41 %) and 335A (without TBDPS) as a single diastereomer (4.5 mg, 8.7 \( \mu \text{mol} \), 12 %).
Method B

Sulfur trioxide-pyridine complex (0.22 g, 1.38 mmol) and DMSO (0.22 mL, 2.75 mmol) were stirred in anhydrous CH$_2$Cl$_2$ (5 mL) at 0 °C for 15 minutes before Et$_3$N (0.77 mL, 5.50 mmol) and a solution of hydroxyamide 334B (0.18 g, 0.28 mmol) in anhydrous CH$_2$Cl$_2$ (2 mL) were added. The reaction was allowed to warm to room temperature and stirred for 18 hours. A saturated aqueous solution of NaHCO$_3$ (15 mL) was added and the resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 15 mL). The organic phases were combined and washed with a 1M aqueous solution of HCl (40 mL) then a saturated aqueous solution of NaHCO$_3$ (40 mL). The organic phase was dried (MgSO$_4$) and evaporated. The residue was dried under high vacuum at 35 °C for 4 – 5 hours then dissolved in anhydrous CH$_2$Cl$_2$ (5 mL) and HSCH$_2$CH$_2$COOMe (0.07 mL, 0.55 mmol) was added, and the reaction was stirred at room temperature for 16 hours. The solvent was evaporated, then the residue was dissolved in anhydrous CHCl$_3$ (8 mL) and Sc(OTf)$_3$ (0.14 mg, 0.28 mmol) was also added. The reaction was heated at reflux for 18 hours. A saturated aqueous solution of NaHCO$_3$ (10 mL) was added and the resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 15 mL). The organic phases were combined, dried (MgSO$_4$) and evaporated to give the crude product. Purification by column chromatography eluting with 20 – 60 % EtOAc in petroleum ether gave 335C (0.15 g, 0.20 mmol, 71 %, dr 1:1) as a light yellow pale oil.

For one diastereomer:

$^1$H NMR (500 MHz, CDCl$_3$) δ 0.94 (9H, s, C(CH$_3$)$_3$), 2.27 (3H, s, CH$_3$), 2.59 – 2.69 (2H, m, SCH$_2$CH$_2$), 2.93 – 2.99 (1H, m, SCH$_2$CH$_2$H$_3$), 3.20 – 3.26 (1H, m, SCH$_2$CH$_2$H$_3$), 3.42 – 3.44 (1H, m, OCH$_2$CH$_2$H$_3$), 3.48 (3H, s, OCH$_3$), 3.66 (3H, s, OCH$_3$), 3.67 (3H, s, OCH$_3$), 3.73 (3H, s, OCH$_3$), 3.79 (3H, s, OCH$_3$), 3.86 (1H, d, J = 14.8 Hz, NCH$_2$CH$_2$H$_3$), 3.94 (1H, dd, J = 10.4, 2.5 Hz, OCH$_2$CH$_2$H$_3$), 4.57 (1H, s, CHS), 4.69 (1H, br. s, CHN), 186
5.54 (1H, d, J = 14.8 Hz, NCH$_2$H$_3$), 6.85 (2H, d, J = 7.7 Hz, ArH), 7.13 (2H, d, J = 7.7 Hz, ArH), 7.20 – 7.73 (10H, m, ArH).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 9.8 (CH$_3$), 19.0 (C(CH$_3$)$_3$), 26.5 (C(CH$_3$)$_3$), 28.2 (SCH$_2$CH$_2$), 34.2 (SCH$_2$CH$_2$), 42.3 (CHS), 46.6 (NCH$_2$), 51.6 (OCH$_3$), 55.2 (OCH$_3$), 57.3 (CHN), 60.0 (2 × OCH$_3$), 61.2 (OCH$_3$), 63.3 (OCH$_3$), 114.0 (ArCH), 123.1 (ArCH), 123.9 (ArCH), 125.5 (ArC), 127.4 (ArCH), 127.8 (ArCH), 128.9 (ArC), 129.5 (ArCH), 129.9 (ArCH), 132.5 (ArC), 133.0 (2 × ArC), 135.3 (ArCH), 135.6 (ArC), 144.3 (ArC), 151.0 (ArC), 152.0 (ArC), 158.9 (ArC), 170.8 (C=O), 172.5 (C=O).

MS (ES+): m/z: 758 ([M + H]$^+$), 780 ([M + Na]$^+$); HRMS (ES+): m/z: calcd for C$_{42}$H$_{52}$NO$_8$SiS: 758.3178 ([M + H]$^+$); found: 758.3177.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2997, 1738 (C=O), 1651, 1513, 1465, 1428, 1406, 1348, 1296, 1245, 1175, 1112, 1083.

$[\alpha]_D^{24} = -15.9$ (c = 0.64, CHCl$_3$).

For the other diastereomer:

$^1$H NMR (500 MHz, CDCl$_3$) δ 1.13 (9H, s, C(CH$_3$)$_3$), 2.14 (3H, s, CH$_3$), 2.85 – 2.88 (2H, m, SCH$_2$CH$_2$), 3.06 – 3.12 (1H, m, SCH$_2$CH$_2$), 3.38 – 3.41 (1H, m, SCH$_2$CH$_2$), 3.43 (3H, s, OCH$_3$), 3.70 (3H, s, OCH$_3$), 3.72 (3H, s, OCH$_3$), 3.76 (3H, s, OCH$_3$), 3.79 (1H, dd, J = 10.1, 3.3 Hz, OCH$_2$CH$_3$), 3.81 (3H, s, OCH$_3$), 4.44 (1H, dd, J = 10.1, 9.6 Hz, OCH$_2$CH$_3$), 4.62 (1H, d, J = 14.5 Hz, NCCH$_2$H$_3$), 4.74 (1H, s, CHS), 4.91 (1H, dd, J = 9.6, 3.3 Hz, CHN), 5.68 (1H, d, J = 14.5 Hz, NCCH$_2$H$_3$), 6.80 (2H, d, J = 8.5 Hz, ArH), 7.16 (2H, d, J = 8.5 Hz, ArH), 7.38 – 7.40 (6H, m, ArH), 7.69 – 7.73 (4H, m, ArH).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 9.7 (CH$_3$), 19.2 (C(CH$_3$)$_3$), 26.9 (C(CH$_3$)$_3$), 28.5 (SCH$_2$), 34.3 (SCH$_2$CH$_2$), 40.3 (CHS), 49.7 (NCH$_2$), 51.7 (OCH$_3$), 55.2 (OCH$_3$), 57.0 (CHN), 60.0 (2 × OCH$_3$), 61.5 (OCH$_3$), 69.1 (OCH$_2$), 113.9 (ArCH), 114.0 (ArCH), 122.0
(ArC), 125.3 (ArC), 125.9 (ArC), 127.7 (2 × ArCH), 129.5 (2 × ArCH), 129.6 (ArC), 129.7 (ArCH), 133.0 (ArC), 135.6 (ArCH), 144.9 (ArC), 151.1 (ArC), 151.7 (ArC), 158.8 (ArC), 168.8 (C=O), 172.4 (C=O).

MS (ES+): m/z: 758 ([M + H]+), 780 ([M + Na]+); HRMS (ES+): m/z: calcd for C_{42}H_{52}NO_{8}Si: 758.3178 ([M + H]+); found: 758.3193.

IR (thin film) ν_{max} (cm\(^{-1}\)) 2934, 1739 (C=O), 1649 (C=O), 1512, 1463, 1408, 1244, 1112, 1086.

[α]_D^{24} = -2.58 (c = 0.66, CHCl_3).

**General procedure for the preparation of 335A, 335B, 336**

Sulfur trioxide-pyridine complex (0.14 g, 0.85 mmol) and DMSO (0.13 mL, 1.70 mmol) were stirred in anhydrous CH_2Cl_2 (3 mL) at 0 °C for 15 minutes. Et_3N (0.47 mL, 3.40 mmol) and a solution of hydroxyamide 334A (0.10 g, 0.17 mmol) in anhydrous CH_2Cl_2 (1.5 mL) were then added. The reaction was allowed to warm to room temperature and stirred for 16 – 18 hours. A saturated aqueous solution of NaHCO_3 (10 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined and washed with 1M aqueous solution of HCl (30 mL) then a saturated aqueous solution of NaHCO_3 (30 mL). The organic phase was dried (MgSO_4) and evaporated. The residue was dried under high vacuum at 60 °C for 3 – 4 hours then dissolved in anhydrous CH_2Cl_2 (4 mL). HSCH_2CH_2COOMe (0.04 mL, 0.34 mmol) was then added and the reaction was stirred at room temperature for 18 hours. The solvent was evaporated and the residue was dissolved in anhydrous CHCl_3 (4 mL). Sc(OTf)_3 (0.5 – 1.5 eq.) was added and the reaction was heated at reflux for 16 – 18 hours. A saturated aqueous solution of NaHCO_3 (10 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic phases
were combined and dried (\(\text{MgSO}_4\)) and evaporated to give the crude product. Purification by column chromatography eluting with 25 – 60 % EtOAc in petroleum ether gave the products (335A (~ 6 %), 335B (16 – 18 %), 336 (31 – 43 %)).

Methyl 3-(((1R)-1-(hydroxymethyl)-5,7,8-trimethoxy-2-(4-methoxybenzyl)-6-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate (335A)

![Chemical structure of 335A]

For one diastereoisomer:

\(^1\text{H} \text{NMR (400 MHz, CDCl}_3\) \delta 2.19 (3H, s, CH\(_3\)), 2.82 – 2.93 (2H, m, SCH\(_2\text{CH}_3\)), 3.16 – 3.23 (1H, m, SCH\(_A\text{H}_B\)), 3.30 – 3.40 (1H, m, SCH\(_A\text{H}_B\)), 3.57 (3H, s, OCH\(_3\)), 3.72 (3H, s, OCH\(_3\)), 3.76 (3H, s, OCH\(_3\)), 3.79 (3H, s, OCH\(_3\)), 3.86 (3H, s, OCH\(_3\)), 3.89 – 3.93 (1H, m, CH\(_A\text{H}_B\)OH), 4.16 – 4.20 (1H, m, CH\(_A\text{H}_B\)OH), 4.35 (1H, d, \(J = 14.9 \text{ Hz, NCH}_A\text{H}_B\)), 4.75 (1H, dd, \(J = 7.1, 5.0 \text{ Hz, CHN}\)), 4.79 (1H, s, CHS), 5.43 (1H, d, \(J = 14.9 \text{ Hz, NCH}_A\text{H}_B\)), 6.82 (2H, d, \(J = 8.7 \text{ Hz, ArH}\)), 7.19 (2H, d, \(J = 8.7 \text{ Hz, ArH}\)).

\(^1\text{C} \text{NMR (100 MHz, CDCl}_3\) \delta 9.8 (CH\(_3\)), 28.6 (SCH\(_2\)), 34.3 (SCH\(_2\text{CH}_2\)), 40.6 (CHS), 49.1 (NCH\(_2\)), 51.8 (OCH\(_3\)), 55.2 (OCH\(_3\)), 57.4 (NCH), 60.1 (2 × OCH\(_3\)), 61.6 (OCH\(_3\)), 66.1 (CH\(_2\)OH), 114.0 (ArCH), 121.6 (ArC), 125.7 (ArC), 126.0 (ArC), 129.0 (ArC), 129.4 (ArCH), 144.8 (ArC), 151.4 (ArC), 152.1 (ArC), 158.9 (ArC), 168.8 (C=O), 172.5 (C=O).

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2937, 1736 (C=O), 1641 (C=O), 1612, 1511, 1460, 1406, 1345, 1295, 1244, 1175, 1116, 1067, 1005.

$[\alpha]_D^{24} = +3.17$ (c = 1.2, CHCl$_3$).

Methyl 3-(((1R)-5,7,8-trimethoxy-2-(4-methoxybenzyl)-6-methyl-3-oxo-1-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate (335B)

![Chemical structure](image)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.85 – 0.90 (21H, m, 3 × SiCH and 3 × SiCH(CH$_3$)$_2$ of one diastereomer), 1.11 – 1.13 (21H, m, 3 × SiCH and 3 × SiCH(CH$_3$)$_2$ of other diastereomer), 2.18 (3H, s, ArCH$_3$ of one diastereomer), 2.19 (3H, s, ArCH$_3$ of other diastereomer), 2.55 – 2.67 (2H, m, SCH$_2$CH$_2$ of one diastereomer), 2.88 – 2.96 (3H, m, SCH$_2$CH$_2$ of other diastereomer and SCH$_A$H$_B$ of one diastereomer), 3.08 – 3.22 (2H, m, SCH$_A$H$_B$ of other diastereomer and SCH$_A$H$_B$ of one diastereomer), 3.39 – 3.46 (1H, m, SCH$_A$H$_B$ of other diastereomer), 3.54 – 3.85 (32H, m, 5 × OCH$_3$ of 2 diastereomers and CH$_A$H$_B$OSi of one diastereomer and CH$_A$H$_B$OSi of other diastereomer), 3.91 (1H, d, J = 14.9 Hz, NCH$_A$H$_B$ of one diastereomer), 4.07 (1H, dd, J = 9.6, 2.5 Hz, CH$_A$H$_B$OSi of one diastereomer), 4.29 (1H, dd, J = 11.8, 5.3 Hz, CH$_A$H$_B$OSi of other diastereomer), 4.41 – 4.52 (2H, m, NCH$_A$H$_B$ of other diastereomer and NCH of one diastereomer), 4.65 (1H, s, CHS of one diastereomer), 4.76 (1H, s, CHS of other diastereomer), 4.80 (1H, dd, J = 9.6, 3.0 Hz, CHN of other diastereomer), 5.53 (1H, d, J = 14.9 Hz, NCH$_A$H$_B$ of one diastereomer), 5.58 (1H, d, J = 14.4 Hz, NCH$_A$H$_B$ of other diastereomer), 6.79 (2H, d, J = 8.8 Hz, 2 × ArH of one diastereomer), 6.88 (2H, d, J = 8.8 Hz, 2 × ArH
of other diastereomer), 7.16 (2H, d, \(J = 8.8\) Hz, 2 × ArH of one diastereomer),
7.33 (2H, d, \(J = 8.8\) Hz, 2 × ArH of other diastereomer).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 9.7 (ArCH\(_3\) of one diastereomer), 9.8 (ArCH\(_3\) of
other diastereomer), 11.7 (SiCH of one diastereomer), 11.8 (SiCH of other
diastereomer), 17.7 (SiCH(CH\(_3\))\(_2\) of one diastereomer), 18.0 (SiCH(CH\(_3\))\(_2\) of other
diastereomer), 28.1 (SCH\(_2\) of one diastereomer), 28.4 (SCH\(_2\) of other
diastereomer), 34.1 (SCH\(_2\)CH\(_2\) of one diastereomer), 34.3 (SCH\(_2\)CH\(_2\) of other
diastereomer), 40.4 (CHS of one diastereomer), 42.2 (CHS of other
diastereomer), 46.4 (NCH\(_2\) of one diastereomer), 49.6 (NCH\(_2\) of other
diastereomer), 51.6 (OCH\(_3\) of one diastereomer), 51.7 (OCH\(_3\) of other
diastereomer), 55.2 (OCH\(_3\) of one diastereomer), 55.3 (OCH\(_3\) of other
diastereomer), 57.2 (NCH of one diastereomer), 57.5 (NCH of other
diastereomer), 59.9 (OCH\(_3\) of one diastereomer), 60.0 (OCH\(_3\) of other
diastereomer), 60.1 (OCH\(_3\) of one diastereomer), 60.4 (OCH\(_3\) of other
diastereomer), 61.3 (OCH\(_3\) of one diastereomer), 61.5 (OCH\(_3\) of other
diastereomer), 63.0 (CH\(_2\)O of one diastereomer), 68.7 (CH\(_2\)O of other
diastereomer), 113.8 (ArCH of one diastereomer), 114.0 (ArCH of other
diastereomer), 122.1 (ArC of one diastereomer), 123.0 (ArC of other
diastereomer), 125.3 (ArC of one diastereomer), 125.5 (ArC of other
diastereomer), 125.9 (ArC of 2 diastereomers), 129.0 (ArC of one diastereomer),
129.4 (ArCH of one diastereomer), 129.5 (ArCH of other diastereomer), 129.7
(ArC of other diastereomer), 144.3 (ArC of one diastereomer), 144.9 (ArC of
other diastereomer), 151.2 (ArC of one diastereomer), 151.3 (ArC of other
diastereomer), 151.8 (ArC of one diastereomer), 152.0 (ArC of other
diastereomer), 158.7 (ArC of one diastereomer), 158.9 (ArC of other
diastereomer), 168.6 (C=O of one diastereomer), 170.5 (C=O of other
diastereomer), 172.4 (C=O of one diastereomer), 172.5 (C=O of other
diastereomer).
MS (ES+): \( m/z \): 676 ([M + H]\(^+\)), 698 ([M + Na]\(^+\)); HRMS (ES+): \( m/z \): calcd for \( \text{C}_{35}\text{H}_{54}\text{NO}_{8}\text{SSi}: 676.3334 ([M + H]\(^+\)) \); found: 676.3320.

IR (thin film) \( \nu_{\text{max}} \) (cm\(^{-1}\)) 2941, 2865, 1789 (C=O), 1648 (C=O), 1512, 1461, 1346, 1296, 1244, 1174, 1114, 1094, 1068.

\([\alpha]_D^{24} = -6.73 \) (c = 1.0, CHCl\(_3\)).

(5R)-2-Hydroxy-4-(4-methoxybenzyl)-5-(2,3,5-trimethoxy-4-methylphenyl)-morpholin-3-one (336)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 2.14 (3H, s, ArCH\(_3\) of one diastereomer), 2.15 (3H, s, ArCH\(_3\) of other diastereomer), 3.51 (1H, d, \( J = 14.6 \) Hz, NCH\(_A\)H\(_B\) of one diastereomer), 3.61 – 3.81 (14H, m, 4 \( \times \) OCH\(_3\) of 2 diastereomers, NCH\(_A\)H\(_B\) of other diastereomer and CH\(_A\)H\(_B\)O of one diastereomer), 3.89 (1H, dd, \( J = 12.1, 4.0 \) Hz, CH\(_A\)H\(_B\)O of one diastereomer), 4.20 (1H, dd, \( J = 12.2, 8.3 \) Hz, CH\(_A\)H\(_B\)O of other diastereomer), 4.44 (1H, dd, \( J = 12.2, 4.0 \) Hz, CH\(_A\)H\(_B\)O of other diastereomer), 4.69 (1H, m, CHN of one diastereomer), 4.92 (1H, m, CHN of other diastereomer), 5.30 (1H, d, \( J = 14.6 \) Hz, NCH\(_A\)H\(_B\) of one diastereomer), 5.42 (1H, d, \( J = 14.6 \) Hz, NCH\(_A\)H\(_B\) of other diastereomer), 5.47 (1H, s, CHO\(_{\text{HOH}}\) of one diastereomer), 5.49 (1H, s, CHO\(_{\text{HOH}}\) of other diastereomer), 6.35 (1H, s, ArH of one diastereomer), 6.40 (1H, s, ArH of other diastereomer), 6.80 (2H, d, \( J = 8.6 \) Hz, ArH of one diastereomer), 6.85 (2H, d, \( J = 8.6 \) Hz, ArH of other diastereomer), 7.05 (2H, d, \( J = 8.6 \) Hz, ArH of one diastereomer), 7.16 (2H, d, \( J = 8.6 \) Hz, ArH of other diastereomer).
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 8.9 (ArCH$_3$), 46.2 (NCH$_2$ of one diastereomer), 47.0 (NCH$_2$ of other diastereomer), 53.0 (CHN), 55.3 (OCH$_3$), 55.9 (OCH$_3$), 60.2 (OCH$_3$), 60.6 (OCH$_3$ of one diastereomer), 60.8 (OCH$_3$ of other diastereomer), 63.4 (CH$_2$O of one diastereomer), 63.7 (CH$_2$O of other diastereomer), 90.5 (CHOH of one diastereomer), 91.2 (CHOH of other diastereomer), 103.9 (ArCH of one diastereomer), 104.3 (ArCH of other diastereomer), 113.9 (ArCH of one diastereomer), 114.1 (ArCH of other diastereomer), 121.3 (ArC of one diastereomer), 121.6 (ArC of other diastereomer), 125.7 (ArC of one diastereomer), 127.4 (ArC of other diastereomer), 127.9 (ArC of one diastereomer), 128.0 (ArC of other diastereomer), 129.9 (ArCH), 144.7 (ArC of one diastereomer), 145.2 (ArC of other diastereomer), 152.0 (ArC), 154.3 (ArC of one diastereomer), 154.5 (ArC of other diastereomer), 159.1 (ArC of one diastereomer), 159.3 (ArC of other diastereomer), 167.7 (C=O of one diastereomer), 168.1 (C=O of other diastereomer).

MS (ES+): $m/z$: 418 ([M + H]$^+$), 440 ([M + Na]$^+$); HRMS (ES+): $m/z$: calcd for C$_{22}$H$_{28}$NO$_7$: 418.1861 ([M + H]$^+$); found: 418.1841.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 3300 (br, OH), 2934, 1639 (C=O), 1611, 1585, 1511, 1482, 1459, 1403, 1341, 1300, 1244, 1176, 1121, 1060, 1029.

$[\alpha]_D^{24}$ = + 4.69 (c = 0.4, CHCl$_3$).
(2R)-Methyl 3-(((1R)-1-((((tert-butyldiphenylsilyl)oxy)methyl)-5,7,8-trimethoxy-2-(4-methoxybenzyl)-6-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)propanoate (338)

Sulfur trioxide-pyridine complex (0.29 g, 1.82 mmol) and DMSO (0.29 mL, 3.71 mmol) were stirred in anhydrous CH$_2$Cl$_2$ (7 mL) under N$_2$ at 0 °C for 15 minutes. Et$_3$N (1.02 mL, 7.33 mmol) and a solution of hydroxyamide 334B (0.24 mg, 0.36 mmol) in anhydrous CH$_2$Cl$_2$ (4 mL) were then added and the reaction was allowed to warm to room temperature and stirred for 16 hours. A saturated aqueous solution of NaHCO$_3$ (15 mL) was then added and the resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 15 mL). The organic phases were combined and washed with 1 M aqueous HCl (30 mL) then saturated aqueous NaHCO$_3$ (30 mL) and the organic phase was dried (MgSO$_4$) and evaporated. The residue was dried under high vacuum at 35 °C for 4 – 5 hours then dissolved in anhydrous CH$_2$Cl$_2$ (10 mL) and thiol 328 (0.22 g, 0.72 mmol) was added, and the reaction was stirred at room temperature for 16 hours. Sc(OTf)$_3$ (0.18 g, 0.36 mmol) was next added and the reaction was heated at reflux for 17 hours. A saturated aqueous solution of NaHCO$_3$ (10 mL) was added and the resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The organic phases were combined and dried (MgSO$_4$) and evaporated to give the crude product. Purification by column chromatography eluting with 20 – 60 % EtOAc in petroleum ether gave 338 (0.29 g, 0.30 mmol, 84 %, dr 1:1) as a pale oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 0.99 (9H, s, C(CH$_3$)$_3$ of one diastereomer), 1.12 (9H, s, C(CH$_3$)$_3$ of other diastereomer), 2.14 (3H, s, CH$_3$ of one diastereomer), 2.24
(3H, s, CH$_3$ of other diastereomer), 3.19 – 3.25 (2H, m, SCH$_A$H$_B$ of 2 diastereomers), 3.40 (3H, s, OCH$_3$ of one diastereomer), 3.43 (3H, s, OCH$_3$ of other diastereomer), 3.52 – 3.62 (2H, m, SCH$_A$H$_B$ of 2 diastereomers), 3.70 – 3.84 (27H, m, 4 × OCH$_3$ of 2 diastereomers, OCH$_A$H$_B$ of 2 diastereomers, NCH of one diastereomer), 4.29 (1H, dd, $J = 10.3$, 10.3 Hz, OCH$_A$H$_B$ of one diastereomer), 4.37 (1H, d, $J = 14.6$ Hz, NCH$_A$H$_B$ of one diastereomer), 4.59 – 4.63 (2H, m, NCH$_A$H$_B$ of other diastereomer, CHS of one diastereomer), 4.75 – 4.84 (6H, m, CH$_2$CCl$_3$ of 2 diastereomers, CHNH of 2 diastereomers), 4.89 – 4.92 (2H, m, CHS of other diastereomer, CHN of other diastereomer), 5.30 – 5.39 (2H, m, OCH$_A$H$_B$ of other diastereomer, NCH$_A$H$_B$ of one diastereomer), 5.70 (1H, d, $J = 14.6$ Hz, NCH$_A$H$_B$ other diastereomer), 6.80 – 6.86 (4H, m, ArH of 2 diastereomers), 7.15 – 7.20 (4H, m, ArH of 2 diastereomers), 7.29 – 7.72 (20H, m, ArH of 2 diastereomers).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 9.4 (CH$_3$ of one diastereomer), 9.8 (CH$_3$ of other diastereomer), 19.0 (C(CH$_3$)$_3$ of one diastereomer), 19.2 (C(CH$_3$)$_3$ of other diastereomer), 26.8 (C(CH$_3$)$_3$ of one diastereomer), 26.9 (C(CH$_3$)$_3$ of other diastereomer), 35.1 (SCH$_2$ of 2 diastereomers), 40.8 (CHS of 2 diastereomers), 48.8 (NCH$_2$ of one diastereomer), 49.1 (NCH$_2$ of other diastereomer), 52.7 (CHNH of one diastereomer), 55.2 (OCH$_3$ of 2 diastereomers), 55.7 (CHN of one diastereomer), 56.0 (CHN of other diastereomer), 56.8 (OCH$_3$ of 2 diastereomers), 60.0 (OCH$_3$ of 2 diastereomers), 60.8 (OCH$_3$ of 2 diastereomers), 61.4 (OCH$_3$ of 2 diastereomers), 65.5 (CH$_2$OSi of one diastereomer), 65.8 (CHNH of other diastereomer), 69.2 (CH$_2$OSi of other diastereomer), 74.6 (CH$_2$CCl$_3$ of one diastereomer), 74.7 (CH$_2$CCl$_3$ of other diastereomer), 95.5 (CCl$_3$ of 2 diastereomers), 113.9 (ArCH of one diastereomer), 114.0 (ArCH of other diastereomer), 121.7 (ArC of one diastereomer), 123.1 (ArC of other diastereomer), 124.1 (ArC of one diastereomer), 124.9 (ArCH of other diastereomer), 126.0 (ArCH of one diastereomer), 126.7 (ArC of other
diastereomer), 127.7 (ArCH of one diastereomer), 127.8 (ArCH of other
diastereomer), 128.5 (ArC of one diastereomer), 129.2 (ArC of other
diastereomer), 129.4 (ArCH of one diastereomer), 129.5 (ArCH of other
diastereomer), 129.8 (ArCH of one diastereomer), 129.9 (ArCH of other
diastereomer), 132.4 (ArC of one diastereomer), 132.6 (ArC of other
diastereomer), 132.8 (ArC of one diastereomer), 133.0 (ArC of other
diastereomer), 144.2 (ArC of one diastereomer), 144.9 (ArC of other
diastereomer), 150.7 (ArC of one diastereomer), 151.4 (ArC of other
diastereomer), 152.7 (ArC of one diastereomer), 154.7 (ArC of other
diastereomer), 158.9 (ArC of one diastereomer), 159.0 (ArC of other
diastereomer), 168.8 (C=O of 2 diastereomers), 170.9 (C=O of 2 diastereomers),
171.4 (C=O of 2 diastereomers).

MS (ES+): m/z: 947 ([M + H]+); HRMS (ES+): m/z: calcd for C_{45}H_{54}N_{2}O_{10}SSi^{35}Cl_{3}:
947.2329 ([M + H]+); found: 947.2366.

IR (thin film) ν_{max} (cm^{-1}) 2933, 1738 (C=O), 1640 (C=O), 1511, 1460, 1427, 1408,
1343, 1297, 1242, 1175, 1104, 1088, 1053, 1004.

[α]24^D = −1.56 (c = 0.3, CHCl₃).

6.3.2 ABH ring formation

3-(((1R,4R)-1-(Hydroxymethyl)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-
1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoic acid (340A)
Silyl ether 327A (0.26 g, 0.41 mmol, 2 diastereomers dr 1:1) was dissolved in THF (2 mL), cooled to 0 °C and a 1.0 M solution of TBAF in THF (0.82 mL, 0.82 mmol) was added. The reaction mixture was warmed slowly to room temperature and stirred for 5 hours. A saturated aqueous solution of NaHCO₃ (10 mL) was added and the resulting mixture was extracted with CH₂Cl₂ (3 × 10 mL). The organic extracts were combined and dried (MgSO₄) and evaporated. Purification by column chromatography eluting with 50 – 70 % EtOAc in petroleum ether gave the intermediate ester. The ester was dissolved in MeOH (5.6 mL) and a solution of K₂CO₃ (0.73 g, 5.26 mmol) in water (2.8 mL) was added and the reaction mixture was stirred at room temperature for 16 hours. The solvent was evaporated, then water (10 mL) was added and the resulting mixture was acidified to pH = ~ 5 then extracted with CH₂Cl₂ (3 × 15 mL). The organic phase was dried (MgSO₄) and evaporated to give 340A (97 mg, 0.21 mmol, 51 %, 1 diastereomer). Spectroscopic data were identical to the data previously obtained within the Procter group.⁸²

¹H NMR (400 MHz, CDCl₃) δ 2.82 – 2.98 (2H, m, SCH₂CH₂), 3.10 – 3.17 (1H, m, SCH₃H₆), 3.28 – 3.35 (1H, m, SCH₃H₆), 3.75 (3H, s, OCH₃), 3.76 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 3.91 (1H, dd, J = 11.5, 5.9 Hz, CH₃H₆OH), 4.09 (1H, dd, J = 11.5, 6.4 Hz, CH₃H₆OH), 4.30 (1H, d, J = 15.1 Hz, NCH₆H₆), 4.41 (1H, dd, J = 6.4, 5.9 Hz, CHN), 4.76 (1H, s, CHS), 5.38 (1H, d, J = 15.1 Hz, NCH₆H₆), 6.21 (1H, d, J = 2.0 Hz, ArH), 6.38 (1H, d, J = 2.0 Hz, ArH), 6.80 (2H, d, J = 8.6 Hz, ArH), 7.15 (2H, d, J = 8.6 Hz, ArH).

¹³C NMR (100 MHz, CDCl₃) δ 28.8 (SCH₂), 34.5 (SCH₂CH₂), 40.0 (CHS), 49.0 (NCH₂), 55.2 (OCH₃), 55.4 (OCH₃), 55.8 (OCH₃), 62.3 (CHN), 66.4 (CH₂OH), 98.0 (ArCH), 102.3 (ArCH), 113.4 (ArC), 114.1 (ArCH), 128.6 (ArC), 129.2 (ArCH), 135.4 (ArC), 157.4 (ArC), 158.9 (ArC), 160.3 (ArC), 170.0 (C=O), 175.7 (C=O).
(1R,8R)-10,12-Dimethoxy-13-(4-methoxybenzyl)-3,4,7,8-tetrahydro-8,1-(epiminomethano)benzo[g][1,5]oxathiecin-5,14(1H)-dione (341A)\textsuperscript{82}

MNBA (19.4 mg, 56.4 \( \mu \)mol) and DMAP (12.7 mg, 104 \( \mu \)mol) were dissolved in anhydrous CH\(_2\)Cl\(_2\) (10 mL) and a solution of 340A (20 mg, 43.4 \( \mu \)mol) in anhydrous CH\(_2\)Cl\(_2\) (10 mL) was added slowly over 12 hours at room temperature. The reaction was then stirred for 3 hours. A saturated aqueous solution of NaHCO\(_3\) (20 mL) was added and the aqueous phase was extracted with CH\(_2\)Cl\(_2\) (2 \( \times \) 20 mL). The organic phases were combined and dried (MgSO\(_4\)) and evaporated to give the crude product. Purification by column chromatography eluting with 20% EtOAc in CHCl\(_3\) gave 341A (16.8 mg, 37.9 \( \mu \)mol, 67\%) as a pale yellow foam. Spectroscopic data were identical to the data previously obtained within the Procter group.\textsuperscript{82}

\( ^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 2.40 – 2.60 (3H, m, SCH\(_A\)H\(_B\) and SCH\(_2\)CH\(_3\)), 2.89 – 2.94 (1H, m, SCH\(_A\)H\(_B\)) 3.78 (6H, s, 2 \( \times \) OCH\(_3\)), 3.87 (3H, s, OCH\(_3\)), 3.98 (1H, d, \( J = 15.4 \) Hz, NCH\(_A\)H\(_B\)), 4.28 (1H, dd, \( J = 11.3, 1.6 \) Hz, CH\(_A\)H\(_B\)O), 4.43 (1H, br. s, CHN), 4.89 (1H, dd, \( J = 11.3, 1.8 \) Hz, CH\(_A\)H\(_B\)O), 5.00 (1H, s, CHS), 5.61 (1H, d, \( J = 15.4 \) Hz, NCH\(_A\)H\(_B\)), 6.20 (1H, d, \( J = 1.8 \) Hz, ArH), 6.42 (1H, d, \( J = 1.8 \) Hz, ArH), 6.84 (2H, d, \( J = 8.3 \) Hz, ArH), 7.19 (2H, d, J = 8.3 Hz, ArH).

\( ^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 26.2 (CH\(_2\)), 38.5 (SCH\(_2\)CH\(_2\)), 41.0 (CHS), 46.9 (NCH\(_2\)), 55.3 (OCH\(_3\)), 55.4 (OCH\(_3\)), 55.8 (OCH\(_3\)), 59.5 (CHN), 63.1 (CH\(_2\)O), 97.9 (ArCH), 101.7 (ArCH), 114.2 (ArCH), 128.1 (2 \( \times \) ArC), 129.5 (ArCH), 134.3 (ArC), 157.9 (ArC), 159.1 (ArC), 160.6 (ArC), 168.6 (C=O), 170.4 (C=O).
Silyl ether 327B (0.25 g, 0.38 mmol, 2 diastereomers) was dissolved in THF (5 mL) and the solution cooled to 0 °C. A 1.0 M solution of TBAF in THF (0.76 mL, 0.76 mmol) was then added and the reaction mixture was stirred for 3 hours before a saturated aqueous solution of NaHCO₃ (10 mL) was added and the resulting mixture was extracted with CH₂Cl₂ (3 × 10 mL). The organic phases were combined and dried (MgSO₄) and evaporated. Purification by column chromatography eluting with 60 % EtOAc in petroleum ether gave 329B (0.13 g, 0.26 mmol, 68 %) as a white foam.

Ester 329B (0.08 g, 0.16 mmol) was dissolved in MeOH (4 mL) and a solution of K₂CO₃ (0.12 g, 0.87 mmol) in water (2 mL) was added and the reaction mixture was stirred at room temperature for 16 hours. The solvent was evaporated, then water (10 mL) was added and the resulting mixture was acidified to pH = ~5 then extracted with CH₂Cl₂ (3 × 15 mL). The organic phase was dried (MgSO₄) and evaporated to give hidroxy acid 340B. MNBA (0.07 mg, 0.21 mmol) and DMAP (0.05 g, 0.39 mmol) were dissolved in anhydrous CH₂Cl₂ (20 mL) and a solution of 340B in anhydrous CH₂Cl₂ (10 mL) was added slowly over 12 hours at room temperature. The reaction was then stirred for 3 hours before a saturated aqueous solution of NaHCO₃ (20 mL) was added. The aqueous phase was extracted with CH₂Cl₂ (2 × 30 mL) and the organic phases were combined, dried (MgSO₄) and evaporated to give the crude product. Purification by column chromatography eluting with 50 % EtOAc in petroleum ether gave 341B (0.07 g, 0.14 mmol, 86 %) as a light yellow foam.
$^{1}$H NMR (400 MHz, CDCl$_3$) δ 2.49 – 2.54 (3H, m, SCH$_2$H$_2$ and SCH$_4$H$_8$), 2.89 – 2.94 (1H, m, SCH$_2$H$_8$), 3.77 (3H, s, OCH$_3$), 3.80 (3H, s, OCH$_3$), 3.82 (3H, s, OCH$_3$), 3.86 (3H, s, OCH$_3$), 4.25 (1H, d, J = 14.9 Hz, NCH$_2$H$_8$), 4.33 (1H, d, J = 11.1 Hz, CH$_3$H$_3$OSi), 4.54 (1H, s, NCH), 4.93 (1H, d, J = 11.1 Hz, CH$_3$H$_3$OSi), 4.95 (1H, s, CHS), 5.29 (1H, d, J = 14.9 Hz, NCH$_2$H$_8$), 6.23 (1H, d, J = 1.8 Hz, ArH), 6.41 – 6.45 (3H, m, ArH), 7.19 (1H, d, J = 8.3 Hz, ArH).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 26.1 (SCH$_2$), 38.5 (SCH$_2$H$_2$), 41.1 (CHS), 42.0 (NCH$_2$), 55.3 (OCH$_3$), 55.4 (OCH$_3$), 55.5 (OCH$_3$), 55.8 (OCH$_3$), 60.2 (NCH), 63.6 (CH$_2$OSi), 97.7 (ArCH), 98.4 (ArCH), 101.8 (ArCH), 104.4 (ArCH), 116.8 (ArC), 129.7 (ArC), 131.1 (ArCH), 134.7 (ArC), 157.9 (ArC), 158.6 (ArC), 160.4 (ArC), 160.5 (ArC), 168.5 (C=O), 170.4 (C=O).

MS (ES+): m/z: 474 ([M + H]$^+$); HRMS (ES+): m/z: calcd for C$_{24}$H$_{27}$NO$_7$SNa: 496.1400 ([M + Na]$^+$); found: 496.1409.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2930, 2838, 1736 (C=O), 1643 (C=O), 1608, 1505, 1454, 1419, 1359, 1287, 1257, 1202, 1146, 1126, 1031, 933.

$\left[\alpha\right]_{D}^{23} = +0.16$ (c = 1.1, CHCl$_3$).

**Methyl 3-(((1R)-1-(hydroxymethyl)-5,7,8-trimethoxy-2-(4-methoxybenzyl)-6-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate (342)**

Silyl ether **335C** (1:1 dr, 40 mg, 52.8 $\mu$mol) was dissolved in MeCN (0.5 mL). Pyridine (0.2 mL) was added and the mixture was cooled to 0 °C. A 60 % aqueous solution of HF (0.05 mL) was added and the reaction was stirred at 0 °C for 2 hours then the temperature allowed to warm to room temperature and
stirred for 15 hours. A 1 M aqueous solution of HCl (10 mL) was added and the resulting mixture was extracted with CH₂Cl₂ (3 × 10 mL). The organic phases were washed with 1 M aqueous HCl (20 mL) then dried (MgSO₄) and evaporated. Purification by column chromatography eluting with 45 % EtOAc in petroleum ether gave recovered starting material (10 mg, 25 %) and 342 (22 mg, 31.0 μmol, 71 %, based on recovered starting material).

¹H NMR (400 MHz, CDCl₃) δ 2.19 (3H, s, CH₃), 2.82 – 2.93 (2H, m, SCH₂CH₂), 3.16 – 3.23 (1H, m, SCH₂H₂), 3.30 – 3.40 (1H, m, SCH₂H₂), 3.57 (3H, s, OCH₃), 3.72 (3H, s, OCH₃), 3.76 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 3.89 – 3.93 (1H, m, CH₂H₂OH), 4.16 – 4.20 (1H, m, CH₂H₂OH), 4.35 (1H, d, J = 14.9 Hz, NCH₂H₂), 4.75 (1H, dd, J = 7.1, 5.0 Hz, CHN), 4.79 (1H, s, CHS), 5.43 (1H, d, J = 14.9 Hz, NCH₂H₂), 6.82 (2H, d, J = 8.7 Hz, ArH), 7.19 (2H, d, J = 8.7 Hz, ArH).

¹³C NMR (100 MHz, CDCl₃) δ 9.8 (CH₃), 28.6 (SCH₂), 34.3 (SCH₂CH₂), 40.6 (CHS), 49.1 (NCH₂), 51.8 (OCH₃), 55.2 (OCH₃), 57.4 (NCH), 60.1 (2 × OCH₃), 61.6 (OCH₃), 66.1 (CH₂OH), 114.0 (ArCH), 121.6 (ArC), 125.7 (ArC), 126.0 (ArC), 129.0 (ArC), 129.4 (ArCH), 144.8 (ArC), 151.4 (ArC), 152.1 (ArC), 158.9 (ArC), 168.8 (C=O), 172.5 (C=O).


IR (thin film) ν_max (cm⁻¹) 3290 (br, OH), 2937, 1736 (C=O), 1641 (C=O), 1612, 1511, 1460, 1406, 1345, 1295, 1244, 1175, 1116, 1067, 1005.

[α]D²⁴ = + 3.17 (c = 1.2, CHCl₃).
3-(((1R)-1-(Hydroxymethyl)-5,7,8-trimethoxy-2-(4-methoxybenzyl)-6-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoic acid (344)

Ester 342 (80 mg, 0.15 mmol) was dissolved in MeOH (5.6 mL) and a solution of K$_2$CO$_3$ (0.39 g, 2.80 mmol) in water (2.8 mL) was added. The reaction was stirred at room temperature for 16 hours. The solvent was then evaporated and the residue was diluted with water and acidified by using 1 M HCl to pH = 5 – 6 and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The organic phases were combined and dried (MgSO$_4$) then evaporated to give 344 (55 mg, 0.11 mmol, 73 %) as a light yellow foam.

$^1$H NMR (400 MHz, CDCl$_3$) δ 2.19 (3H, s, CH$_3$), 2.81 – 2.88 (1H, m, SCH$_2$CH$_2$H$_6$), 2.94 – 3.01 (1H, m, SCH$_2$CH$_2$H$_6$), 3.17 – 3.24 (1H, m, SCH$_2$H$_6$), 3.32 – 3.39 (1H, m, SCH$_2$H$_6$), 3.56 (3H, s, OCH$_3$), 3.75 (3H, s, OCH$_3$), 3.79 (3H, s, OCH$_3$), 3.87 (3H, s, OCH$_3$), 3.88 – 3.93 (1H, m, CH$_2$CH$_2$OH), 4.16 – 4.21 (1H, m, CH$_2$CH$_2$OH), 4.35 (1H, d, J = 14.6 Hz, NCH$_2$H$_6$), 4.76 (1H, dd, J = 7.3, 4.8 Hz, CHN) 4.82 (1H, s, CHS), 5.46 (1H, d, J = 14.6 Hz, NCH$_2$H$_6$), 6.81 (2H, d, J = 8.6 Hz, ArH), 7.18 (2H, d, J = 8.6 Hz, ArH).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 9.8 (CH$_3$), 28.8 (SCH$_2$), 34.4 (SCH$_2$CH$_2$), 40.6 (CHS), 49.4 (NCH$_2$), 55.2 (OCH$_3$), 57.3 (CHN), 60.2 (2 × OCH$_3$), 61.5 (OCH$_3$), 66.1 (CH$_2$OH), 114.0 (ArCH), 121.7 (ArC), 125.4 (ArC), 126.1 (ArC), 128.7 (ArC), 129.5 (ArCH), 144.8 (ArC), 151.4 (ArC), 152.0 (ArC), 159.0 (ArC), 169.6 (C=O), 175.4 (C=O).

MS (ES−): m/z: 504 ([M − H]$^+$), 505 ([M]$^+$); HRMS (ES−): m/z: calcd for C$_{25}$H$_{30}$NO$_8$S: 504.1697 ([M − H]$^+$); found: 504.1705.
IR (thin film) $\nu_{max}$ (cm$^{-1}$) 2904 (OH), 1724 (C=O), 1613 (C=O), 1512, 1465, 1408, 1345, 1247, 1068.

$[\alpha]_0^{24} = -3.73$ (c = 1.1, CHCl$_3$).

(1R,8R)-9,10,12-Trimethoxy-13-(4-methoxybenzyl)-11-methyl-3,4,7,8-tetrahydro-8,1-(epiminomethano)benzo[g][1,5]oxathiecin-5,14(1H)-dione (346)

MNBA (41 mg, 0.12 mmol) and DMAP (27 mg, 0.22 mmol) were dissolved in anhydrous CH$_2$Cl$_2$ (10 mL) and a solution of 344 (50 mg, 0.099 mmol) in anhydrous CH$_2$Cl$_2$ (10 mL) was added slowly over 12 hours at room temperature. The reaction was then stirred for 3 hours before a saturated aqueous solution of NaHCO$_3$ (20 mL) was added and the aqueous phase was extracted with CH$_2$Cl$_2$ ($2 \times 20$ mL). The organic phases were combined and dried (MgSO$_4$) and evaporated to give the crude product. Purification by column chromatography eluting with 40% EtOAc in petroleum ether gave 346 (34.7 mg, 0.071 mmol, 72%) as a white foam.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.22 (3H, s, CH$_3$), 2.47 – 2.60 (2H, m, CH$_2$C=O), 2.64 – 2.71 (1H, m, SCH$_2$H$_8$), 2.97 – 3.02 (1H, m, SCH$_2$H$_8$), 3.69 (3H, s, OCH$_3$), 3.78 (3H, s, OCH$_3$), 3.80 (3H, s, OCH$_3$), 3.81 (3H, s, OCH$_3$), 4.01 (1H, d, $J = 15.4$ Hz, NCH$_2$H$_8$), 4.34 (1H, dd, $J = 11.3, 1.3$ Hz, OCH$_2$H$_8$), 4.68 (1H, br. s, CHN), 4.84 (1H, dd, $J = 11.3, 2.0$ Hz, OCH$_2$H$_8$), 5.01 (1H, s, CHS), 5.55 (1H, d, $J = 15.4$ Hz, NCH$_2$H$_8$), 6.85 (2H, d, $J = 8.7$ Hz, ArH), 7.22 (2H, d, $J = 8.7$ Hz, ArH).
$^{13}$C NMR (100 MHz, CDCl$_3$) δ 10.0 (CH$_3$), 26.8 (CH$_2$C=O), 38.4 (SCH$_2$), 41.2 (CHS), 47.1 (NCH$_2$), 55.1 (CHN), 55.2 (OCH$_3$), 60.0 (OCH$_3$), 60.1 (OCH$_3$), 61.0 (OCH$_3$), 61.9 (OCH$_2$), 114.1 (ArCH), 123.7 (ArC), 126.1 (ArC), 128.3 (2 × ArC), 129.5 (ArCH), 144.6 (ArC), 151.2 (ArC), 152.2 (ArC), 159.1 (ArC), 170.5 (2 × C=O).

MS (ES+): $m/z$: 488 ([M + H]$^+$), 510 ([M + Na]$^+$); HRMS (ES+): $m/z$: calcd for C$_{25}$H$_{30}$NO$_7$S: 488.1738 ([M + H]$^+$); found: 488.1759.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2937, 1743 (C=O), 1645 (C=O), 1512, 1460, 1408, 1347, 1246, 1177, 1070, 1035, 1006.

$[\alpha]_D^{24} = +14.23$ (c = 3.2, CHCl$_3$).

(2R)-Methyl 3-(((1R)-1-(hydroxymethyl)-5,7,8-trimethoxy-2-(4-methoxybenzyl)-6-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)propanoate (343)

Silyl ether 338 (65 mg, 68.5 µmol) was dissolved in MeCN (0.7 mL). Pyridine (0.4 mL) was added and the mixture was cooled to 0 °C. A 60 % aqueous solution of HF (0.1 mL) was added, and the reaction was stirred at 0 °C for 2 hours then the temperature allowed to increase gradually to room temperature and stirred for 15 hours. A 1 M aqueous solution of HCl (15 mL) was added and the resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 15 mL). The organic phases were washed with 1M aqueous solution of HCl (30 mL) then dried (MgSO$_4$) and evaporated to give the crude product. Purification by column chromatography eluting with 45
% EtOAc in petroleum ether gave 343 (31.5 mg, 44.4 μmol, 79 %) based on recovered starting material.

$^1$H NMR (400 MHz, CDCl$_3$) δ 2.19 (3H, s, CH$_3$), 3.34 – 3.40 (1H, m, SCH$_A$H$_B$), 3.54 – 3.58 (4H, m, SCH$_A$H$_B$ and OCH$_3$), 3.76 – 3.85 (13H, m, 4 × OCH$_3$ and OCH$_A$H$_B$), 4.10 – 4.16 (1H, m, OCH$_A$H$_B$), 4.40 (1H, d, $J =$ 14.9 Hz, NCH$_A$H$_B$), 4.76 – 4.78 (3H, m, CH$_2$C=O and CHN), 4.90 – 4.96 (2H, m, CHS and CHNH), 5.57 (1H, d, $J =$ 14.9 Hz, NCH$_A$H$_B$), 6.81 (2H, d, $J =$ 8.6 Hz, 2 × ArH), 6.95 (1H, d, $J =$ 8.8 Hz, NH), 7.20 (2H, d, $J =$ 8.6 Hz, 2 × ArH).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 9.9 (CH$_3$), 36.7 (SCH$_2$), 42.1 (CHS), 49.5 (NCH$_2$), 52.8 (OCH$_3$), 54.9 (CHNH), 55.2 (OCH$_3$), 57.2 (CHN), 60.1 (OCH$_3$), 60.2 (OCH$_3$), 61.6 (OCH$_3$), 66.0 (OCH$_2$), 74.7 (CH$_2$C=O), 95.3 (CCl$_3$), 114.0 (2 × ArCH), 121.1 (ArC), 125.4 (ArC), 126.1 (ArC), 128.9 (ArC), 129.6 (2 × ArCH), 144.8 (ArC), 151.7 (ArC), 152.3 (ArC), 155.1 (ArC), 158.9 (NHC=O), 169.4 (C=O), 171.2 (C=O).

MS (ES+): m/z: 731 ([M + Na]$^+$); HRMS (ES+): m/z: calcd for C$_{29}$H$_{36}$N$_2$O$_{10}$S$_3$Cl$_3$: 709.1151 ([M + H]$^+$); found: 709.1183.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 3307 (br, OH), 2951, 1736 (C=O), 1630 (C=O), 1511, 1463, 1408, 1344, 1295, 1245, 1176, 1114, 1067, 1035.

$[\alpha]_D^{24} = -2.56$ (c = 2.7, CHCl$_3$).
(2R)-3-(((1R)-1-(Hydroxymethyl)-5,7,8-trimethoxy-2-(4-methoxybenzyl)-6-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)propanoic acid (345)

Ester 343 (37 mg, 52.0 µmol) was dissolved in MeOH (1 mL) and a solution of K₂CO₃ (72 mg, 520 µmol) in H₂O (0.5 mL) was added. The reaction was stirred at room temperature for 4 hours then the solvent was evaporated. The residue was diluted with water (5 mL) and acidified with 1 M aqueous solution of HCl to pH = 5 – 6 then extracted with CH₂Cl₂ (3 × 10 mL). The organic phases were combined and dried (MgSO₄) then evaporated to give the crude product. Purification by column chromatography eluting with 50 % EtOAc in n-hexane and 0.5 % TFA gave 345 (23.2 mg, 33.3 µmol, 64 %) as a yellow foam.

¹H NMR (400 MHz, CDCl₃) δ 2.17 (3H, s, CH₃), 3.31 (1H, dd, J = 14.9, 7.8 Hz, SCH₂H₆), 3.54 (3H, s, OCH₃), 3.63 (1H, dd, J = 14.9, 2.5 Hz, SCH₂H₆), 3.74 – 3.86 (10H, m, 3 × OCH₃ and OCH₂H₄), 4.07 – 4.22 (1H, m, OCH₂H₄), 4.32 (1H, d, J = 14.8 Hz, NCH₂H₆ of one rotamer), 4.40 (1H, d, J = 14.8 Hz, NCH₂H₆ of other rotamer), 4.69 – 4.86 (4H, m, CH₂Cl₃, CHN, CHNH), 4.97 (1H, s, CHS), 5.50 (1H, d, J = 14.8 Hz, NCH₂H₆ of one rotamer), 5.60 (1H, d, J = 14.8 Hz, NCH₂H₆ of other rotamer), 6.37 (1H, d, J = 7.8 Hz, NH of one rotamer), 6.80 (2H, d, J = 8.3 Hz, ArH), 7.06 (1H, d, J = 7.8 Hz, NH of other rotamer), 7.18 (2H, d, J = 8.3 Hz, ArH).

¹³C NMR (100 MHz, CDCl₃) δ 9.6 (CH₃), 37.6 (SCH₂), 42.6 (CHS), 50.1 (NCH₂), 55.2 (NCH and OCH₃), 57.3 (CHNH), 60.1 (OCH₃), 60.2 (OCH₃), 61.5 (OCH₃), 65.9 (OCH₂), 74.8 (CH₂Cl₃), 95.2 (ClCl₃), 114.0 (ArCH of one rotamer), 114.1 (ArCH of
other rotamer), 121.1 (ArC), 124.9 (ArC), 126.2 (ArC), 128.2 (ArC), 129.5 (ArCH of one rotamer), 129.7 (ArCH of other rotamer), 144.7 (ArC), 151.7 (ArC), 152.2 (ArC), 153.3 (ArC), 159.0 (2 × C=O), 170.7 (C=O).

**MS (ES+):** \( m/z \): 695 ([M + H]^+), 717 ([M + Na]^+); **HRMS (ES+):** \( m/z \): calcd for C_{28}H_{33}N_{2}O_{10}^{35}Cl_{3}Na: 717.0814 ([M + Na]^+); found: 717.0819.

**IR (thin film)** \( \nu_{\text{max}} \) (cm\(^{-1}\)): 2927 (OH), 1728 (C=O), 1629 (C=O), 1512, 1465, 1408, 1345, 1246, 1067.

\[ [\alpha]_{D}^{24} = -8.92 \quad (c = 1.2, \text{CHCl}_3). \]

**2,2,2-Trichloroethyl ((1R,4R,8R)-9,10,12-trimethoxy-13-(4-methoxybenzyl)-11-methyl-5,14-dioxo-1,3,4,5,7,8-hexahydro-8,1-(epiminomethano)benzo[g][1,5]-oxathiecin-4-yl)carbamate (347)**

\[ \text{OMe} \]
\[ \text{MeO} \]
\[ \text{MeO} \]
\[ \text{MeO} \]
\[ \text{NHTroc} \]
\[ \text{O} \]
\[ \text{S} \]
\[ \text{O} \]
\[ \text{N} \]

MNBA (7.7 mg, 22.4 \( \mu \)mol) and DMAP (5.0 mg, 41.3 \( \mu \)mol) were dissolved in anhydrous CH\(_2\)Cl\(_2\) (5 mL). A solution of 345 (12 mg, 17.2 \( \mu \)mol) in anhydrous CH\(_2\)Cl\(_2\) (7 mL) was added over 12 hours at room temperature. The reaction was then stirred for 3 hours before a saturated aqueous solution of NaHCO\(_3\) (10 mL) was added. The aqueous phase was extracted with CH\(_2\)Cl\(_2\) (2 \( \times \) 10 mL) and the organic phases were combined and dried (MgSO\(_4\)) and evaporated to give the crude product. Purification by column chromatography eluting with 40% EtOAc in petroleum ether gave 347 (7.8 mg, 11.5 \( \mu \)mol, 67%) as a white foam.
$^1$H NMR (400 MHz, d$_6$-DMSO, 383 K) δ 1.76 (3H, s, CH$_3$), 2.35 (1H, dd, J = 15.8, 3.0 Hz, SCH$_A$H$_B$), 2.68 (1H, dd, J = 15.8, 7.6 Hz, SCH$_A$H$_B$), 3.27 (3H, s, OCH$_3$), 3.21 (3H, s, OCH$_3$), 3.37 (6H, s, 2 × OCH$_3$), 3.64 – 3.67 (2H, m, NC$_A$H$_B$ and OC$_A$H$_B$), 3.79 (1H, ddd, J = 7.6, 3.0, 3.0 Hz, C$_H$NHTroc), 4.35 – 4.39 (3H, m, CH$_2$CCl$_3$ and CHN), 4.48 (1H, s, CH$_N$), 4.77 – 4.82 (2H, m, NCH$_A$H$_B$ and OCH$_A$H$_B$), 6.45 (2H, d, J = 8.7 Hz, 2 × ArH), 6.79 (2H, d, J = 8.7 Hz, 2 × ArH), 7.01 (1H, br. s, NH).

$^{13}$C NMR (100 MHz, d$_6$-DMSO, 383 K) δ 9.1 (CH$_3$), 31.2 (SCH$_2$), 39.9 (CH$_S$), 46.0 (NCH$_2$), 54.6 (CHN), 54.7 (OCH$_3$), 55.5 (CHNH), 59.4 (OCH$_3$), 59.5 (OCH$_3$), 60.2 (OCH$_3$), 62.8 (NCH$_2$), 73.6 (CH$_2$CCl$_3$), 78.5 (CCl$_3$), 95.5 (ArC), 113.8 (ArCH), 123.3 (ArC), 124.8 (ArC), 128.2 (ArC), 128.7 (ArCH), 143.7 (ArC), 150.5 (ArC), 151.5 (ArC), 158.4 (ArC), 165.5 (C=O), 168.6 (2 × C=O).

MS (ES+): m/z: 677 ([M + H]$^+$), 699 ([M + Na]$^+$); HRMS (ES+): m/z: calcd for C$_{28}$H$_{32}$N$_2$O$_9$S$^{35}$Cl$_3$: 677.0889 ([M + H]$^+$); found: 677.0883.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2944, 1739 (C=O), 1645 (C=O), 1521, 1463, 1408, 1346, 1302, 1245, 1177, 1069.

$\left[\alpha\right]_D^{24} = +12.40$ (c = 1.0, CHCl$_3$).

6.3.3 Towards the synthesis of Et. 597

1-((4R)-2-Phenyl-4-(2,3,5-trimethoxy-4-methylphenyl)oxazolidin-3-yl)prop-2-en-1-one (355)

Silyl ether 332A (0.60 g, 1.51 mmol) was dissolved in MeCN (18 mL) and the reaction mixture was cooled to 0 °C then a 60 % aqueous solution of HF (6.0 mL) was added. The reaction was stirred at 0 °C for 1 hour then at room
temperature for 2 hours. 1 M aqueous solution of HCl (30 mL) and EtOAc (30 mL) were then added and the organic phase was washed with 1 M aqueous solution of HCl (2 × 30 mL). The combined aqueous phases were then combined and basified to pH = 8 – 9 and extracted with CH₂Cl₂ (3 × 60 mL). The organic phase was then dried (MgSO₄) and evaporated to give 354 (0.32 g, 1.33 mmol, 88 %) as white solid.

Amino alcohol 354 (0.90 g, 3.73 mmol) was dissolved in anhydrous CH₂Cl₂ (20 mL). Benzaldehyde (0.36 mL, 3.54 mmol) was added and the reaction mixture was heated at reflux for 16 hours. The reaction mixture was then cooled to 0 °C then acryloyl chloride (0.33 mL, 4.10 mmol) was added and the reaction was stirred for 1 hour then Et₃N (0.57 mL, 4.10 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 16 hours before the solvent was evaporated to give crude product. Purification by column chromatography eluting with 15 – 20 % EtOAc in petroleum ether gave 355 as an 7:1 mixture of diastereoisomers from which the major diastereoisomer 355 was isolated (0.80 g, 2.09 mmol, 56 %) and as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 2.07 (3H, s, ArCH₃), 3.36 (3H, s, OCH₃), 3.81 (3H, s, OCH₃), 3.87 (3H, s, OCH₃), 4.04 (1H, dd, J = 5.8, 7.7 Hz, CHAHB₃O), 4.59 (1H, dd, J = 7.7, 7.7 Hz, CH₃), 5.47 (1H, dd, J = 5.8, 7.7 Hz, NCH₂CH₂O), 5.66 (1H, dd, J = 1.0, 10.1 Hz, CH=CH₂), 6.23 – 6.31 (1H, m, CH=CH₂), 6.47 (1H, dd, J = 1.0, 17.0 Hz, CH=CH₂), 6.78 (1H, s, ArH), 7.37 – 7.67 (6H, m, ArH and NCHPh).

¹³C NMR (125 MHz, CDCl₃) δ 8.8 (ArCH₃), 55.4 (OCH₃), 55.2 (NCH₂CH₂O), 60.2 (OCH₃), 60.8 (OCH₃), 74.0 (CH₂O), 89.8 (NCHPh), 103.6 (ArCH), 120.5 (ArC), 126.7 (ArC), 126.9 (ArCH), 128.4 (ArCH), 128.6 (ArCH), 129.3 (ArC), 130.0 (CH=CH₂), 138.9 (CH=CH₂), 146.2 (ArC) 151.6 (ArC), 154.3 (ArC), 166.0 (C=O).

MS (ES⁺): m/z: 384 ([M + H]⁺); HRMS (ES⁺): m/z: calcd for C₂₂H₂₆NO₅: 384.1806 ([M + H]⁺); found: 384.1808.
IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2932, 1654 (C=O), 1610 (C=C), 1589, 1483, 1462, 1418, 1404, 1356, 1340, 1279, 1230, 1221, 1211, 1189, 1103.

$[\alpha]_D^{23} = + 0.23$ (c = 1.0, CHCl$_3$).

**Methyl 3-(((10bR)-7,9,10-trimethoxy-8-methyl-5-oxo-3-phenyl-3,5,6,10b-tetrahydro-1H-oxazolo[4,3-a]isoquinolin-6-yl)thio)propanoate (358)**

**Methyl 3-(((phenyl)(((1R)-5,7,8-trimethoxy-4-((3-methoxy-3-oxopropyl)thio)-6-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-1-yl)methoxy)methyl)thio)-propanoate (359)**

Alkene 355 (0.38 g, 1.00 mmol) was dissolved in acetone (24 mL) and 4-methylmorpholine N-oxide (0.33 g, 2.82 mmol) and water (4.8 mL) were added. OsO$_4$ (5.08 mg, 0.02 mmol) in t-BuOH (0.2 mL) was then added dropwise at room temperature. The reaction mixture was stirred for 16 hours then a saturated aqueous solution of Na$_2$S$_2$O$_3$ (20 mL) was added. The resulting mixture was extracted with CH$_2$Cl$_2$ (3 x 20 mL). The organic phases were combined and washed with brine (30 mL) then dried (MgSO$_4$) and evaporated to give crude product 356 which was then dissolved in THF (20 mL) and NaIO$_4$ (0.43 g, 2.00 mmol) and H$_2$O (4.1 mL) were added. The reaction mixture was heated at 40 °C for 4 hours before a saturated aqueous solution of NaHCO$_3$ (20 mL) was added. The resulting mixture was extracted with EtOAc (3 x 20 mL) and the organic phases were combined and washed with brine (30 mL) then dried (MgSO$_4$) and evaporated to give glyoxamide 357 which was dried at 70 °C for 2 hours under high vacuum. The glyoxamide 357 was then dissolved in CH$_2$Cl$_2$ (6 mL) and
HSCH₂CH₂COOMe (0.13 mL, 1.10 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours. Additional CH₂Cl₂ (14 mL) and TFAA (0.28 mL, 2.00 mmol) were then added and the reaction mixture was stirred at room temperature for 2 hours then cooled to 0 °C. BF₃•OEt₂ (0.13 mL, 1.00 mmol) was added and the reaction was allowed to warm to room temperature and stirred for 14 hours. A saturated aqueous solution of NaHCO₃ (20 mL) was added and the aqueous phase was extracted with CH₂Cl₂ (2 × 20 mL). The organic phases were combined then dried (MgSO₄) and evaporated. Purification by column chromatography eluting with 20 – 30 % EtOAc in petroleum ether gave 358 (0.25 g, 0.50 mmol, 50 %) as a mixture of 2 diastereomers (dr 1:1) (yellow oil) and 359 (0.10 g, 0.17 mmol, 17 %) as a mixture of 2 diastereoisomers (dr 1:1) yellow oil.

For 358:

¹H NMR (500 MHz, CDCl₃) δ 2.23 (3H, s, ArCH₃ of one diastereomer), 2.25 (3H, s, ArCH₃ of the other diastereomer), 2.56 – 3.24 (8H, m, SCH₂CH₂ of 2 diastereomers), 3.66 (3H, s, OCH₃ of one diastereomer), 3.69 (3H, s, OCH₃ of the other diastereomer), 3.78 – 3.83 (1H, m, CH₁H₉O of one diastereomer) 3.82 (3H, s, OCH₃ of one diastereomer), 3.83 (6H, s, 2 × OCH₃ of 2 diastereomer), 3.85 (3H, s, OCH₃ of the other diastereomer), 3.86 (3H, s, OCH₃ of one diastereomer), 3.87 (3H, s, OCH₃ of the other diastereomer), 4.08 (1H, dd, J = 9.3, 10.6 Hz, CH₁H₉O of the other diastereomer), 4.76 (1H, s, CHS of one diastereomer), 4.78 (1H, dd, J = 6.1, 9.3 Hz, CH₁H₉O of the other diastereomer), 4.86 (1H, s, CHS of the other diastereomer), 5.03 (1H, dd, J = 6.0, 8.5 Hz, CH₁H₉O of one diastereomer), 5.14 – 5.20 (2H, m, NCH₂CH₂ of 2 diastereomer), 6.29 (1H, s, NCHPh of one diastereomer), 6.36 (1H, s, NCHPh of the other diastereomer), 7.20 – 7.56 (10H, m, 5 × ArH of 2 diastereomers)
$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 9.8 (ArCH$_3$ of 2 diastereomers), 27.2 (SCH$_2$CH$_2$ of one diastereomer), 27.4 (SCH$_2$CH$_2$ of the other diastereomer), 34.1 (SCH$_2$CH$_2$ of one diastereomer), 34.2 (SCH$_2$CH$_2$ of the other diastereomer), 41.8 (CHS of 2 diastereomers), 51.6 (OCH$_3$ of one diastereomer), 51.7 (OCH$_3$ of the other diastereomer), 55.8 (NCHCH$_2$ of one diastereomer), 56.1 (NCHCH$_2$ of the other diastereomer), 60.0 (OCH$_3$ of one diastereomer), 60.1 (OCH$_3$ of the other diastereomer), 60.4 (OCH$_3$ of one diastereomer), 60.7 (OCH$_3$ of the other diastereomer), 61.7 (OCH$_3$ of one diastereomer), 61.8 (OCH$_3$ of the other diastereomer), 69.1 (NCHPh of one diastereomer), 72.5 (NCHPh of the other diastereomer), 88.5 (ArCH of one diastereomer), 89.3 (ArCH of the other diastereomer), 121.5 (ArC of one diastereomer), 122.8 (ArC of the other diastereomer), 124.8 (ArC of one diastereomer), 125.4 (ArC of the other diastereomer), 126.4 (ArCH of one diastereomer), 126.6 (ArCH of the other diastereomer), 128.4 (ArCH of one diastereomer), 128.5 (ArCH of the other diastereomer), 128.8 (ArC of one diastereomer), 129.0 (ArC of the other diastereomer), 137.8 (ArC of one diastereomer), 138.4 (ArC of the other diastereomer), 145.5 (ArC of one diastereomer), 145.7 (ArC of the other diastereomer), 151.6 (ArC of one diastereomer), 151.7 (ArC of the other diastereomer), 152.1 (ArC of one diastereomer), 152.3 (ArC of the other diastereomer), 164.9 (C=O of one diastereomer), 165.5 (C=O of the other diastereomer), 172.2 (C=O of 2 diastereomers).

MS (ES+): $m/z$: 488 ([M + H]$^+$); HRMS (ES+): $m/z$: calcd for C$_{25}$H$_{30}$NO$_7$S: 488.1738 ([M + H]$^+$); found: 488.1730.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2942, 1731 (C=O), 1698 (C=O), 1660, 1464, 1405, 1341, 1225, 1176, 1115, 1067, 1002, 960.

$[\alpha]_D^{\text{23}} = -0.21$ (c = 1.6, CHCl$_3$).
For 359 (major diastereoisomer):

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.19 (3H, s, ArCH$_3$), 2.66 – 2.71 (4H, m, 2 × SCH$_2$CH$_2$), 2.92 – 2.99 (4H, m, 2 × SCH$_2$), 3.35 (3H, s, OCH$_3$), 3.69 – 3.74 (8H, m, 2 × OCH$_3$, CH$_2$O), 3.85 (3H, s, OCH$_3$), 3.90 (3H, s, OCH$_3$), 4.45 (1H, s, CHS), 5.10 (1H, dd, $J = 1.4$, 8.3 Hz, NCH$_2$CH$_2$), 5.98 (1H, s, SCHPh), 7.15 (2H, dd, $J = 2.0$, 7.8 Hz, 2 × ArH), 7.30 – 7.33 (3H, m, 3 × ArH).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 9.8 (ArCH$_3$), 26.8 (SCH$_2$CH$_2$), 26.9 (SCH$_2$CH$_2$), 34.1 (2 × SCH$_2$), 41.7 (NCH$_2$CH$_2$), 51.9 (2 × OCH$_3$), 52.9 (CHS), 59.9 (OCH$_3$), 60.0 (OCH$_3$), 60.8 (OCH$_3$), 63.1 (CH$_2$O), 73.2 (SCHPh), 124.3 (ArC), 125.1 (ArC), 125.9 (ArC), 128.1 (ArCH), 128.2 (ArCH), 128.8 (ArCH), 140.0 (ArC), 147.5 (ArC), 150.9 (ArC), 151.2 (ArC), 166.7 (C=O), 172.0 (C=O), 172.1 (C=O).

MS (ES+): m/z: 608 ([M + H]$^+$), 630 ([M + Na]$^+$); HRMS (ES+): m/z: calcd for C$_{29}$H$_{38}$NO$_9$S$_2$: 608.1983 ([M + H]$^+$); found: 608.1985.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 3290 (m, NH), 1735 (C=O), 1655 (C=O), 1626 (C=O), 1524, 1463, 1404, 1365, 1342, 1301, 1242, 1194, 1175, 1113, 1068, 1022.

$[\alpha]_D^{23} = + 0.01$ (c = 1.2, acetone).

(1R)-Benzyl 1-(((tert-butyldimethylsilyl)oxy)methyl)-5,7,8-trimethoxy-4-((3-methoxy-3-oxopropyl)thio)-6-methyl-3-oxo-3,4-dihydroisoquinoline-2(1H)-carboxylate (362)

N,O Acetal 358 (0.17 g, 0.35 mmol, single diastereomer) was dissolved in anhydrous CH$_2$Cl$_2$ (15 mL) at room temperature. TFA (5 mL) was added and the
reaction was stirred for 62 hours. The solvent was evaporated then a saturated aqueous solution of NaHCO$_3$ (15 mL) was added. The aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 15 mL) and the organic phases were combined and dried (MgSO$_4$) then evaporated. Purification by column chromatography eluting with 30 – 40 % EtOAc in petroleum ether gave 360 (0.11 g, 0.28 mmol, 80 %) as a light yellow oil.

Amino alcohol 360 (0.13 g, 0.33 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (5 mL) at room temperature and imidazole (0.06 g, 0.82 mmol) and TBSCl (0.08 g, 0.50 mmol) were added. The reaction mixture was stirred for 4 days before saturated aqueous solution of NH$_4$Cl (10 mL) was added. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 10 mL) and the organic phases were combined and dried (MgSO$_4$) then evaporated. Purification by column chromatography eluting with 30 % EtOAc in petroleum ether gave 361 (0.10 g, 0.19 mmol, 58 %) as a colourless pale oil.

Silyl ether 361 (0.08 g, 0.16 mmol) was dissolved in anhydrous THF (7 mL). The reaction mixture was cooled to –78 °C then a 1.3 M solution of n-BuLi in hexane (0.18 mL, 0.24 mmol) was added dropwise and the reaction mixture stirred for 25 minutes. CbzCl (0.05 mL, 0.32 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred for 16 hours. A saturated aqueous NaHCO$_3$ (10 mL) was added and the aqueous layer extracted with EtOAc (3 × 15 mL). The organic phases were combined and washed with brine (30 mL) then dried (MgSO$_4$) and evaporated. Purification by column chromatography eluting with 15 – 20 % EtOAc in petroleum ether gave 362 (0.08 g, 75 %) as a colourless pale oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 0.06 (3H, s, SiCH$_3$), 0.07 (3H, s, SiCH$_3$), 0.89 (9H, s, SiC(CH$_3$)$_3$), 2.20 (3H, s, ArCH$_3$), 2.84 – 2.88 (2H, m, SCH$_2$CH$_3$), 3.08 – 3.15 (1H, m, SCH$_3$H$_6$), 3.32 – 3.38 (1H, m, SCH$_3$H$_6$), 3.70 (3H, s, OCH$_3$), 3.80 – 3.83 (4H, m, OCH$_3$ and CH$_3$H$_6$OSi), 3.84 (3H, s, OCH$_3$), 3.86 (3H, s, OCH$_3$), 4.22 (1H, t, $J = 10.1$ Hz).
Hz, \( \text{CH}_3\text{H}_8\text{OSi} \), 4.77 (1H, s, \( \text{CHS} \)), 5.31 (1H, d, \( J = 12.6 \) Hz, \( \text{OCH}_3\text{H}_8 \)), 5.36 (1H, d, \( J = 12.6 \) Hz, \( \text{OCH}_3\text{H}_8 \)), 5.91 (1H, dd, \( J = 4.5, 10.1 \) Hz, \( \text{NCH}_3\text{H}_8 \)), 7.32 – 7.39 (3H, m, 3 × ArH), 7.47 – 7.49 (2H, m, 2 × ArH).

\( ^{13}C \) NMR (100 MHz, CDCl\(_3\)) \( \delta = 5.4 \) (2 × SiCH\(_3\)), 9.8 (ArCH\(_3\)), 25.8 (SiC), 26.0 (SiC(CH\(_3\))\(_3\)), 28.6 (SCH\(_2\)CH\(_2\)), 34.0 (SCH\(_2\)), 42.7 (CHS), 51.8 (OCH\(_3\)), 57.1 (NCH\(_2\)H), 60.0 (OCH\(_3\)), 60.6 (OCH\(_3\)), 61.6 (OCH\(_3\)), 66.9 (CH\(_2\)OSi), 68.7 (CH\(_2\)O), 120.6 (ArC), 124.0 (ArC), 126.4 (ArC), 127.9 (ArCH), 128.1 (ArCH), 128.5 (ArCH), 135.4 (ArC), 145.4 (ArC), 151.6 (ArC), 151.9 (ArC), 153.9 (NC(O)O), 167.5 (C=O), 172.2 (C=O).

MS (ES\(^+\)): \( m/z: 670 ([M + Na]^+) \); HRMS (ES\(^+\)): \( m/z: \) calcd for C\(_{32}\)H\(_{46}\)NO\(_9\)SSi: 648.2658 ([M + H]\(^+\)); found: 648.2651.

IR (thin film) \( \nu_{\text{max}} \) (cm\(^{-1}\)) 2930, 2855, 1775 (C=O), 1735 (C=O), 1699 (C=O), 1466, 1390, 1376, 1346, 1298, 1249, 1216, 1113, 1077, 1004, 998.

\[ [\alpha]_{D}^{23} = + 0.02 \] (c = 1.6, CHCl\(_3\)).

6.4 Alternative approaches to Et. 597

2-\(((\text{R})-1-(3,5-\text{Dimethoxyphenyl})-2-((\text{triisopropyl}silyl)oxy)\text{ethyl})\text{amino})-2-((\text{R})-\text{2,2-dimethyl-1,3-dioxolan-4-yl})\text{ethanol} (370)

(S)-1,3,4-Trihydroxybutan-2-one (3.1 g, 21.9 mmol, 85 %) was dissolved in AcOH (2.5 mL) then toluene (5 mL) was added then removed in vacuo. The residue was then dissolved in anhydrous acetone (6 mL) and 2,2-dimethoxypropane (0.7 mL) then TsOH (0.42 g, 2.20 mmol) was added. The reaction mixture was stirred at room temperature for 1 hour. CH\(_3\)COONa (0.36 g, 4.40 mmol) was added and
then the solvent removed. Purification by column chromatography eluting with 30 % EtOAc in petroleum ether gave 369 (1.78 g, 11.1 mmol, 51 %) as a colourless pale oil.

Amine 323 (0.72 g, 2.03 mmol) and 369 (0.65 g, 4.06 mmol) were dissolved in anhydrous methanol (20 mL) and NaBH₃CN (0.25 g, 4.06 mmol) was added at room temperature followed by MgSO₄ (0.24 g, 2.03 mmol). The reaction was stirred at room temperature for 36 hours. The solvent was evaporated then a saturated aqueous solution of NaHCO₃ (20 mL) was added. The resulting mixture was extracted with CH₂Cl₂ (3 × 20 mL), the organic phases combined and dried (MgSO₄) then concentrated. Purification by column chromatography eluting with 15 % EtOAc in petroleum ether produced 370A (0.27 g, 0.54 mmol, 27 %, one diastereomer) as a light yellow pale oil and a fraction which was further purified by column chromatography eluting with 10 % EtOAc and 1 % Et₃N in petroleum ether to give 370B (0.26 g, 0.52 mmol, 26 %, the other diastereomer) as a colourless pale oil.

For 370A:

¹H NMR (400 MHz, CDCl₃) δ 1.05 − 1.07 (21H, m, Si(CH(CH₃)₂)₃), 1.34 (6H, s (br.), C(CH₃)₂), 2.51 (1H, dt (br.), J = 3.5, 7.0 Hz, NCH), 3.55 (1H, t, J = 9.3 Hz, CH₂H₂OSi), 3.71 − 3.78 (4H, m, CH₂O, CH₂H₂OSi, CH₂H₂OH), 3.79 (6H, s, 2 × OCH₃), 3.89 (1H, dd, J = 3.5, 9.3 Hz, CHCH₂OSi), 4.03 (1H, dt, J = 6.8, 14.4 Hz, CHO), 4.16 (1H, dd, J = 6.5, 8.3 Hz, CH₂H₂OH), 6.37 (1H, t, J = 2.3 Hz, ArH), 6.52 (2H, d, J = 2.3 Hz, ArH).

¹³C NMR (100 MHz, CDCl₃) δ 11.9 (Si(CH(CH₃)₂)₃), 17.9 (Si(CH(CH₃)₂)₃), 25.3 (CCH₃), 26.6 (CCH₃), 55.3 (2 × OCH₃), 57.8 (NCH), 61.0 (CH₂O), 62.2 (CHCH₂OSi), 68.6 (CH₂OH and CH₂OSi), 77.8 (CHO), 99.5 (ArCH), 105.7 (ArCH), 109.2 (OCO). 143.4 (ArC), 160.8 (ArC).
MS (ES+): m/z: 498 ([M + H]^+); HRMS (ES+): m/z: calcd for C_{26}H_{48}NO_{6}Si: 498.3246 ([M + H]^+); found: 498.3235.

IR (thin film) ν_{max} (cm\(^{-1}\)) 3490 (m, OH, NH), 2865, 1596, 1460, 1428, 1369, 1249, 1203, 1152, 1095, 1061, 1014.

[α]_D^{23} = −0.11 (c = 4.7, CHCl₃).

For 370B:

\(^1\text{H} \text{NMR} (400 \text{ MHz}, \text{CDCl}_3) \delta 1.06 − 1.08 (21H, m, \text{Si(CH(CH)}_3)_2)\), 1.35 (3H, s, CCH₃), 1.43 (3H, s, CCH₃), 2.69 (1H, dt, J = 8.0, 4.0 Hz, NCH), 3.13 (1H, dd, J = 4.0, 11.2 Hz, C\text{H}_A\text{H}_B\text{OH}), 3.24 (1H, dd, J = 4.0, 11.2 Hz, C\text{H}_A\text{H}_B\text{OH}), 3.65 − 3.73 (3H, m, C\text{H}_A\text{H}_B\text{OSi}, \text{CH}_2\text{O}), 3.79 (6H, s, 2 × OCH₃), 3.94 (1H, dt, J = 3.8, 8.6 Hz, CHO), 4.04 (1H, dd, J = 6.6, 8.1 Hz, C\text{H}_A\text{H}_B\text{OSi}), 4.21 (1H, dd, J = 6.6, 13.9 Hz, C\text{HCH}_2\text{OSi}), 6.37 (1H, t, J = 2.3 Hz, ArH), 6.54 (2H, d, J = 2.3 Hz, ArH).

\(^1\text{C} \text{NMR} (100 \text{ MHz}, \text{CDCl}_3) \delta 11.9 (\text{SiCH}), 18.0 (\text{Si(CH(CH)}_3)_2)\), 25.4 (C\text{CH}_3), 26.8 (C\text{CH}_3), 55.3 (2 × OCH₃), 61.0 (NCH), 61.2 (CH₂OH), 65.4 (CHO), 66.8 (CH₂OSi), 68.4 (CH₂O), 70.5 (C\text{HCH}_2\text{OSi}), 99.5 (ArCH), 105.4 (ArCH), 109.2 (OCO), 111.3 (ArC), 160.9 (ArC).

MS (ES+): m/z: 498 ([M + H]^+); HRMS (ES+): m/z: calcd for C_{26}H_{48}NO_{6}Si: 498.3246 ([M + H]^+); found: 498.3257.

IR (thin film) ν_{max} (cm\(^{-1}\)) 3500 (br, OH), 2939, 2865, 1595, 1460, 1429, 1369, 1294, 1246, 1204, 1152, 1051, 1014.

[α]_D^{23} = −0.10 (c = 3.0, CHCl₃).
Methyl 3-(((1R)-3-((R)-1,2-dihydroxyethyl)-5,7-dimethoxy-1-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate (372)

Oxalyl chloride (0.07 mL, 0.78 mmol) was dissolved in anhydrous CH₂Cl₂ (3.0 mL) and the solution cooled to −78 °C. Dimethyl sulfoxide (0.15 mL, 2.08 mmol) was added and the solution stirred for 5 minutes at −78 °C before a solution of 370 (0.26 g, 0.52 mmol, single diastereoisomer) in anhydrous CH₂Cl₂ (2.0 mL) was added slowly. The reaction was stirred at −78 °C for 1.5 hours then Et₃N (0.58 mL, 4.16 mmol) was added and the reaction was allowed to warm to room temperature. The reaction was then stirred for 5 hours at room temperature before addition of CH₂Cl₂ (20 mL) and washing with a saturated aqueous solution of NaHCO₃ (3 × 15 mL). The organic phase was dried (MgSO₄) and evaporated to give aldehyde 371 which was dissolved in anhydrous CH₂Cl₂ (15 mL), HSCH₂CH₂COOMe (0.12 mL, 1.04 mmol) added, and the reaction mixture stirred for 1.5 hours. The reaction mixture was then cooled to 0 °C and TFAA (0.11 mL, 0.78 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 1.5 hours before BF₃·OEt₂ (0.13 mL, 1.04 mmol) was added at 0 °C and the reaction was allowed to warm to room temperature and stirred for 14 hours. A saturated aqueous solution of NaHCO₃ (20 mL) was added and the resulting mixture was extracted with CH₂Cl₂ (3 × 20 mL). The organic phases were combined and dried (MgSO₄) then evaporated. Purification by column chromatography eluting with 3 – 6 % MeOH in CHCl₃ gave 372 (0.17 g, 0.30 mmol, 58 %, dr 3:1) as a yellow pale oil.
For minor diastereomer:

$^1$H NMR (400 MHz, CDCl$_3$) δ 1.04 – 1.07 (21H, m, Si(CH(CH$_3$)$_2$)$_3$), 2.63 – 2.80 (2H, SCH$_2$CH$_3$), 2.92 – 2.98 (1H, m, SCH$_3$H$_3$), 3.06 – 3.11 (1H, m, SCH$_3$H$_3$), 3.30 (1H, dd, J = 2.0, 9.1 Hz, CHCH$_2$OSi), 3.70 (3H, s, OCH$_3$), 3.78 (3H, s, OCH$_3$), 3.81 – 3.87 (7H, m, OCH$_3$, CH$_2$OH and CH$_2$OSi), 3.97 – 4.02 (2H, m, NCH and CHO), 4.39 (1H, d, J = 2.3 Hz, CHS), 6.20 (1H, d, J = 2.3 Hz, ArH), 6.35 (1H, d, J = 2.3 Hz, ArH).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 11.9 (SiCH), 17.9 (Si(CH(CH$_3$)$_2$)$_3$), 27.8 (SCH$_2$), 34.9 (SCH$_2$CH$_3$), 40.1 (CHS), 51.9 (OCH$_3$), 55.2 (OCH$_3$), 55.3 (OCH$_3$), 56.3 (CHCH$_2$OSi), 57.1 (NCH), 66.2 (CH$_2$OH), 66.7 (CH$_2$OSi), 70.7 (CHO), 96.9 (ArCH), 102.8 (ArCH), 119.3 (ArC), 136.2 (ArC), 157.4 (ArC), 159.2 (ArC), 173.3 (C=O).

MS (ES+): m/z: 558 ([M + H]$^+$); HRMS (ES+): m/z: calcd for C$_{27}$H$_{48}$NO$_7$SSi: 558.2916 ([M + H]$^+$); found: 558.2931.

IR (thin film) $\nu_{max}$ (cm$^{-1}$) 3400 (m, OH, NH), 2864, 1735 (C=O), 1604, 1460, 1200, 1151, 1050, 881.

$[\alpha]_D^{23} = +0.02$ (c = 3.1, CHCl$_3$).

For major diastereomer:

$^1$H NMR (400 MHz, CDCl$_3$) δ 1.01 – 1.02 (21H, m, Si(CH(CH$_3$)$_2$)$_3$), 2.59 – 2.64 (2H, m, SCH$_2$CH$_3$), 2.75 – 2.85 (2H, m, SCH$_2$), 3.14 (1H, d (br.), J = 7.3 Hz, CHCH$_2$OSi), 3.68 – 3.72 (4H, m, OCH$_3$, CH$_3$H$_8$OSi), 3.76 (3H, s, OCH$_3$), 3.84 (3H, s, OCH$_3$), 3.92 – 3.97 (2H, m, CHO, CH$_3$H$_8$OSi), 4.08 (1H, m, NCH), 4.11 – 4.14 (2H, m, CH$_2$OH), 4.24 (1H, s (br.), CHS), 6.33 (1H, d, J = 2.3 Hz, ArH), 6.37 (1H, d, J = 2.3 Hz, ArH).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 11.9 (SiCH), 17.9 (Si(CH(CH$_3$)$_2$)$_3$), 27.6 (SCH$_2$), 34.8 (SCH$_2$CH$_3$), 40.0 (CHS), 51.7 (OCH$_3$), 55.3 (2 × OCH$_3$), 58.1 (CHCH$_2$OSi), 58.9 (NCH), 63.7 (CH$_2$OSi), 66.4 (CH$_2$OH), 71.4 (CHO), 96.7 (ArCH), 101.4 (ArCH), 119.2 (ArC), 137.7 (ArC), 157.2 (ArC), 159.7 (ArC), 172.4 (C=O).
MS (ES+): m/z: 558 ([M + H]+); HRMS (ES+): m/z: calcd for C_{27}H_{48}NO_{7}SSi: 558.2916 ([M + H]⁺); found: 558.2933.

IR (thin film) ν\text{max} (cm\textsuperscript{-1}) 3333 (br, OH), 2941, 2864, 1735 (C=O), 1604, 1460, 1435, 1355, 1289, 1244, 1200, 1151, 1116, 1048, 1013.

[α]\text{D}^23 = −0.05 (c = 1.2, CHCl\textsubscript{3}).

(S)-2-((tert-Butoxycarbonyl)(methyl)amino)-3-(3,4-dimethoxyphenyl)-propanoic acid (373)

(S)-2-Amino-3-(3,4-dimethoxyphenyl)propanoic acid (1.38 g, 7.00 mmol) was dissolved in a 50 % solution of 1,4-dioxane in water (22 mL) at 0 °C and Et\textsubscript{3}N (1.17 mL, 8.40 mmol) then Boc\textsubscript{2}O (1.83 g, 8.40 mmol) were added. The reaction mixture was stirred at 0 °C for 0.5 hours then at room temperature for 14 hours. The solvent was evaporated then water (20 mL) was added and the resulting mixture was washed with EtOAc (20 mL). The aqueous phase was acidified using a 1 M aqueous solution of HCl to pH = 1 then the resulting mixture was extracted with EtOAc (3 × 30 mL). The organic phases were combined and washed with brine (50 mL) then dried (MgSO\textsubscript{4}) and evaporated to give the crude product 376 which was then dissolved in anhydrous acetone (14 mL). K\textsubscript{2}CO\textsubscript{3} (3.38 g, 24.5 mmol) and Me\textsubscript{2}SO\textsubscript{4} (2.25 mL, 23.8 mmol) were also added and the reaction was heated at reflux for 50 hours. The solvent was evaporated then water (20 mL) was added. The resulting mixture was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 20 mL) and the organic phases were combined and dried (MgSO\textsubscript{4}) then evaporated. Purification by column chromatography eluting with 30 % EtOAc in petroleum ether gave compound 377 (2.32 g, 6.84 mmol, 98 %) as a white solid.
NaH (0.19 g, 4.68 mmol, 60 %) was dissolved in anhydrous DMF (15 mL). (1.33 g, 3.90 mmol) and Mel (0.97 mL, 15.6 mmol) in anhydrous DMF (20 mL) were then added and the reaction was stirred at room temperature for 2 hours. A saturated aqueous solution of NH₄Cl (50 mL) was added slowly then the resulting mixture was extracted with Et₂O (3 × 50 mL). The organic phases were combined, washed with brine (100 mL) then dried (MgSO₄) and evaporated. Purification by column chromatography eluting with 20 % EtOAc in petroleum ether gave crude product (0.84 g, 2.37 mmol, 61 %) as a colourless pale oil.

The crude product (0.50 g, 1.40 mmol) was dissolved in methanol (6 mL) and K₂CO₃ (0.38 g, 2.80 mmol) in water (3 mL) was added then the reaction was stirred at room temperature for 16 hours. After diluting with water (20 mL), the resulting mixture was extracted with CH₂Cl₂ (3 × 20 mL) and the organic phases were combined and dried (MgSO₄) then evaporated to produce (0.46 g, 1.36 mmol, 97 %) as a light yellow pale oil.

¹H NMR (400 MHz, CDCl₃) δ 1.35 (9H, s, CCH₃ of one rotamer), 1.40 (9H, s, CCH₃ of the other rotamer), 2.70 (3H, s, NCH₃ of one rotamer), 2.76 (3H, s, NCH₃ of the other rotamer), 2.96 – 3.09 (2H, m, CH₃H₈ of 2 rotamers), 3.21 – 3.31 (2H, m, CH₃H₈ of 2 rotamers), 3.85 (6H, s, OCH₃ of 2 rotamers), 3.86 (6H, s, OCH₃ of 2 rotamers), 4.53 (1H, dd, J = 4.3, 10.9 Hz, NCH of one rotamer), 4.85 (1H, dd, J = 5.0, 10.6 Hz, NCH of the other rotamer), 6.59 – 6.81 (6H, m, ArH of 2 rotamers)

¹³C NMR (100 MHz, CDCl₃) δ 28.1 (C(CH₃) of one rotamer), 28.2 (C(CH₃) of the other rotamer), 32.8 (NCH₃ of 2 rotamers), 34.2 (CH₂ of one rotamer), 34.8 (CH₂ of the other rotamer), 55.8 (OCH₃ of 2 rotamers), 55.9 (OCH₃ of 2 rotamers), 60.4 (NCH of one rotamer), 61.7 (NCH of the other rotamer), 80.6 (C(CH₃) of 2 rotamers), 111.1 (ArCH of one rotamer), 111.2 (ArCH of the other rotamer), 111.8 (ArCH of one rotamer), 111.9 (ArCH of the other rotamer), 120.9 (ArCH of one rotamer), 121.0 (ArCH of the other rotamer), 129.5 (ArC of one rotamer), 129.9 (ArC of the other rotamer), 147.7 (ArC of one rotamer), 148.8 (ArC of the
other rotamer), 154.9 (ArC of one rotamer), 156.3 (ArC of the other rotamer), 176.1 (C=O of 2 rotamers), 176.3 (C=O of 2 rotamers).

MS (ES−): m/z: 338 ([M − H]+); HRMS (ES−): m/z: calcd for C_{17}H_{24}NO_{6}: 338.1609 ([M − H]+); found: 338.1606.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 3006 (br, OH), 2975, 1737 (C=O), 1686 (C=O), 1592, 1515, 1452, 1419, 1391, 1366, 1322, 1255, 1235, 1138, 1076.

$\alpha$D$^{23} = -0.10$ (c = 3.9, CHCl$_3$).

**Methyl 3-(((1R)-2-(((S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(3,4-dimethoxyphenyl)propanoyl)-3-((R)-1,2-dihydroxyethyl)-5,7-dimethoxy-1-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate (374)**

![Chemical Structure](image)

Amine 372 (major diastereoisomer) (0.30 g, 0.54 mmol) and acid 373 (0.29 g, 0.86 mmol), HOBt (0.03 g, 0.19 mmol) and EDCI (0.16 g, 0.86 mmol) were dissolved in anhydrous CH$_2$Cl$_2$ (25 mL) and the reaction mixture was stirred for 16 hours. A saturated aqueous solution of NaHCO$_3$ (20 mL) was added and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 20 mL). The organic phases were combined and dried (MgSO$_4$) then evaporated. Purification by column chromatography eluting with 20 % acetone in n-hexane gave 374 (0.25 g, 0.28 mmol, 52 %) as colourless pale pale oil.

$^1$H NMR (400 MHz, acetone-d6) $\delta$ 1.03 − 1.07 (21H, m, Si(CH(CH$_3$)$_3$)$_3$), 1.29 − 1.35 (9H, m, OC(CH$_3$)$_3$), 2.64 − 2.68 (2H, m, SCH$_2$CH$_2$), 2.71 − 2.74 (2H, m, SCH$_3$CH$_2$),
2.82 – 2.90 (3H, m, NCH₃), 2.96 – 3.00 (1H, m, CH₃H₆), 3.15 – 3.27 (2H, m, CH₃H₈ and CH), 3.59 – 3.62 (1H, m, CH₃H₆), 3.64 (3H, s, OCH₃), 3.75 (3H, s, OCH₃), 3.77 – 3.78 (6H, m, 2 × OCH₃), 3.84 (3H, s, OCH₃), 3.92 – 3.07 (1H, m, CH), 4.01 – 4.06 (1H, m, CH₃H₆), 4.12 – 4.17 (1H, m, CH₃H₆), 4.19 – 4.24 (1H, m, CH₃H₆), 4.46 (1H, s, CHS), 4.56 – 4.80 (2H, m, 2 × CH), 6.39 (1H, d, J = 2.3 Hz, ArH), 6.48 – 6.50 (1H, m, ArH), 6.73 (1H, d, J = 8.3 Hz, ArH), 6.81 – 6.87 (2H, m, ArH).

¹³C NMR (100 MHz, acetone-d₆) δ 13.2 (SiCH), 19.0 (Si(CH₃)₃), 28.4 (C(CH₃)₃), 29.0 (NCH₃), 33.8 (SCH₂CH₂), 34.3 (SCH₂), 35.6 (NCH₂), 39.6 (CHS), 52.2 (OCH₃), 55.1 (CH), 56.0 (OCH₃), 56.3 (OCH₃), 56.5 (OCH₃), 56.6 (OCH₃), 59.9 (CH), 62.1 (CH), 68.6 (CH₂O), 69.4 (CH), 70.0 (CH₂O), 80.5 (C(CH₃)₃ of one rotamer), 80.6 (C(CH₃)₃ of other rotamer), 98.1 (ArCH), 102.9 (ArCH), 113.3 (ArCH), 114.2 (ArCH), 117.6 (ArC), 122.5 (ArCH of one rotamer), 122.8 (ArCH of other rotamer), 131.9 (ArC), 139.5 (ArC), 149.6 (ArC), 150.7 (ArC), 156.9 (ArC), 160.0 (ArC), 161.0 (C=O), 172.4 (C=O), 173.4 (C=O).

MS (ES+): m/z: 879 ([M + H]+); HRMS (ES+): m/z: calcd for C₄₄H₇₁N₂O₁₂SSi: 879.4492 ([M + H]+); found: 879.4499.

IR (thin film) νmax (cm⁻¹) 3289 (br, OH), 2864, 1736 (C=O), 1693, 1605, 1516, 1461, 1422, 1391, 1364, 1333, 1256, 1238, 1219, 1199, 1148, 1083, 1052.

[α]D²³ = −0.06 (c = 3.3, CHCl₃).

(3-((R)-1-(3,5-Dimethoxyphenyl)-2-((triisopropylsilyl)oxy)ethyl)-2-phenyloxazolidin-4-yl)methanol (380)
Amine 323 (3.70 g, 10.46 mmol) was dissolved in anhydrous methanol (110 mL) and 1,3-dihydroxypropan-2-one (1.59 g, 17.7 mmol), NaBH₃CN (1.31 g, 20.8 mmol) and MgSO₄ (1.26 g, 10.50 mmol) were added. The reaction mixture was stirred at room temperature for 2 days then the solvent was evaporated and a saturated aqueous solution of NaHCO₃ (30 mL) was added to the residue and the resulting mixture was extracted with CH₂Cl₂ (3 × 30 mL). The organic phases were combined and dried (MgSO₄) then evaporated. Purification by column chromatography eluting with 30 – 40 % EtOAc in petroleum ether gave 379 (3.10 g, 7.24 mmol, 69 %) as a colourless pale oil.

Amino alcohol 379 (1.00 g, 2.34 mmol) was dissolved in anhydrous toluene (10 mL) and PhCHO (0.35 mL, 3.51 mmol) and MgSO₄ (0.84 g, 7.02 mmol) were added. The reaction mixture was heated at reflux for 2 days before a saturated aqueous solution of NaHCO₃ (20 mL) was added and the resulting mixture was extracted with EtOAc (3 × 20 mL). The organic phases were combined then washed with brine (30 mL), dried (MgSO₄) then evaporated. Purification by column chromatography eluting with 15 % EtOAc in petroleum ether gave 380 (0.77 g, 1.49 mmol, 64 %) as mixture of 2 diastereoisomers (dr 1.5:1) and as a light yellow pale oil.

For the major diastereomer 380A:

$^1$H NMR (400 MHz, benzene-d6) δ 0.98 (3H, s, Si(CH(CH₃)₂)₃), 0.99 (18H, s, Si(CH(CH₃)₂)₃), 2.82 (1H, s (br.), OH), 3.36 – 3.42 (8H, m, CH₂OH and 2 × OCH₃), 3.48 – 3.54 (1H, m, NCH), 3.56 (1H, dd, $J = 6.6, 8.2$ Hz, CH₅H₈O), 3.64 (1H, dd, $J = 2.5, 8.2$ Hz, CH₅H₈O), 3.86 (1H, dd, $J = 5.3, 10.6$ Hz, CH₅H₈OSi), 3.98 (1H, dd, $J = 5.3, 8.3$ Hz, CH₅H₈OSi), 4.22 (1H, dd, $J = 8.3, 10.3$ Hz, CH₅H₈OSi), 5.81 (1H, s, NCHAr), 6.48 (1H, t, $J = 2.3$ Hz, ArH), 6.65 (2H, d, $J = 2.3$ Hz, ArH), 7.15 – 7.16 (1H, m, ArH), 7.24 (2H, dd, $J = 7.1, 7.1$ Hz, ArH), 7.78 (2H, d, $J = 7.1$ Hz, ArH).
\(^{13}\)C NMR (100 MHz, benzene-d6) \(\delta\) 12.5 (SiCH), 18.5 (Si(CH(CH\(_3\))_2)_3), 55.3 (2 \times OCH\(_3\)), 61.2 (NCH), 65.3 (CH\(_2\)OH), 67.0 (CH\(_2\)OSi), 67.8 (CHCH\(_2\)OSi), 69.0 (CH\(_2\)O), 96.2 (NCHAr), 100.0 (ArCH), 107.8 (ArCH), 128.3 (ArCH), 128.9 (ArCH), 129.0 (ArCH), 142.2 (ArC), 142.3 (ArC), 162.0 (ArC).

MS (ES\(+\)): \(m/z\): 516 ([M + H]\(^+\)); HRMS (ES\(+\)): \(m/z\): calcd for C\(_{29}\)H\(_{46}\)NO\(_5\)Si: 516.3140 ([M + H]\(^+\)); found: 516.3138.

IR (thin film) \(\nu_{\text{max}}\) (cm\(^{-1}\)) 3240 (br, OH), 2864, 1595, 1458, 1428, 1344, 1312, 1292, 1203, 1152, 1093, 1064.

\([\alpha]_D^{23}\) = -0.08 (c = 3.9, acetone).

For minor diastereoisomer 380B:

\(^1\)H NMR (400 MHz, benzene-d6) \(\delta\) 1.04 (3H, s, Si(CH(CH\(_3\))_2)_3), 1.05 (18H, s, Si(CH(CH\(_3\))_2)_3), 3.30 (6H, s, 2 \times OCH\(_3\)), 3.40 – 3.42 (2H, m, CH\(_2\)O), 3.55 (1H, dd, \(J = 4.5, 8.1\) Hz, CH\(_A\)H\(_B\)OSi), 3.60 – 3.65 (1H, m, NCH), 3.82 (1H, dd, \(J = 7.1, 8.1\) Hz, CH\(_A\)H\(_B\)OSi), 3.97 – 4.05 (3H, m, CHCH\(_2\)OSi and CH\(_2\)OH), 5.64 (1H, s, OCHAr), 6.41 (1H, t, \(J = 2.3\) Hz, ArH), 6.57 (2H, d, \(J = 2.3\) Hz, ArH), 7.05 – 7.15 (3H, m, ArH), 7.64 (2H, d, \(J = 7.3\) Hz, ArH).

\(^{13}\)C NMR (100 MHz, benzene-d6) \(\delta\) 12.6 (SiCH), 18.6 (Si(CH(CH\(_3\))_2)_3), 55.2 (2 \times OCH\(_3\)), 63.5 (NCH), 64.7 (CH\(_2\)O), 67.2 (CH\(_2\)OH), 68.1 (CH\(_2\)OSi), 69.0 (CHCH\(_2\)OSi), 95.8 (OCHAr), 100.3 (ArCH), 107.5 (ArCH), 128.3 (ArCH), 128.4 (ArCH) 128.5 (ArCH), 142.8 (ArC), 142.9 (ArC), 161.7 (ArC).

MS (ES\(+\)): \(m/z\) (%): 516 ([M + H]\(^+\)); HRMS (ES\(+\)): \(m/z\): calcd for C\(_{29}\)H\(_{46}\)NO\(_5\)Si: 516.3140 ([M + H]\(^+\)); found: 516.3138.

IR (thin film) \(\nu_{\text{max}}\) (cm\(^{-1}\)) 3294 (br, OH), 2864, 1595, 1460, 1458, 1428, 1345, 1292, 1203, 1152, 1094, 1062.
\[ \alpha_d^{23} = +0.12 \ (c = 2.0, \text{acetone}) \].

3-\((R)\)-1-(3,5-Dimethoxyphenyl)-2-((triisopropylsilyl)oxy)ethyl)-2-phenyl-4-(((triisopropylsilyl)oxy)methyl)oxazolidine (381A)

Alcohol 380A (0.10 g, 0.19 mmol, minor diastereomer) was dissolved in anhydrous CH\(_2\)Cl\(_2\) (3 mL) at room temperature before imidazole (0.04 g, 0.57 mmol) and TIPSCI (0.06 mL, 0.29 mmol) were added and the reaction was stirred for 2 days. A saturated aqueous solution of NH\(_4\)Cl (10 mL) was added and the resulting mixture was extracted with CH\(_2\)Cl\(_2\) (3 × 10 mL). The organic phases were combined, dried (MgSO\(_4\)) then evaporated. Purification by column chromatography eluting with 3 – 5 % EtOAc in petroleum ether gave 381A (0.08 g, 0.12 mmol, 63 %) as a colourless pale oil.

\(^1\)H NMR (500 MHz, acetone-d6) \( \delta \) 1.03 – 1.06 (42H, m, 2 × Si(CH\(\left(\text{CH}_3\right)\)_2)\_3), 3.50 (1H, t, J = 9.5 Hz, CH\(_A\)H\(_6\)O), 3.65 – 3.69 (7H, m, 2 × OCH\(_3\) and CH\(_A\)H\(_6\)O), 3.76 – 3.81 (1H, m, CH\(_{CH2}\)OSi), 3.87 (1H, dd, J = 3.8, 8.5 Hz, CH\(_A\)H\(_8\)OSi), 3.97 (1H, t, J = 5.9 Hz, CH\(_{CH2}\)OSi), 4.01 – 4.05 (2H, m, CH\(_A\)H\(_8\)OSi and CH\(_A\)H\(_8\)OSi), 4.26 (1H, dd, J = 10.1, 5.9 Hz, CH\(_A\)H\(_8\)OSi), 5.46 (1H, s, NCHO), 6.28 (1H, t, J = 2.2 Hz, ArH), 6.47 (2H, d, J = 2.2 Hz, ArH), 7.24 – 7.29 (3H, m, ArH), 7.43 (2H, d, J = 6.3 Hz, ArH).

\(^{13}\)C NMR (125 MHz, acetone-d6) \( \delta \) 13.3 (SiCH), 19.0 (Si(CH\(\left(\text{CH}_3\right)\)_2)\_3), 56.1 (2 × OCH\(_3\)), 63.3 (CH\(_{CH2}\)OSi), 67.8 (CH\(_2\)O), 67.9 (CH\(_2\)OSi), 69.2 (CH\(_{CH2}\)OSi), 69.8 (CH\(_2\)OSi), 97.0 (NCHO), 100.7 (ArCH), 108.1 (ArCH), 129.1 (ArCH), 129.2 (ArCH), 129.3 (ArCH), 143.5 (ArC), 144.7 (ArC), 162.1 (ArC).

MS (ES\(^+\)): \textit{m/z}: 672 ([M + H]\(^+\)); HRMS (ES\(^+\)): \textit{m/z}: calcd for C\(_{38}\)H\(_{66}\)NO\(_5\)Si\(_2\): 672.4474 ([M + H]\(^+\)); found: 672.3382.
IR (thin film) \( \nu_{\text{max}} \) (cm\(^{-1}\)) 2941, 2864, 1596, 1460, 1204, 1153, 1064, 881, 803.

\[ \alpha \] \( \text{D}_{23} = +0.10 \) (c = 1.3, acetone).

2-(((\(R\))-1-(3,5-Dimethoxyphenyl)-2-((triisopropylsilyl)oxy)ethyl)amino)-3-((triisopropylsilyl)oxy)propan-1-ol (382A)

Oxazolidine **381A** (82 mg, 0.12 mmol) was dissolved in anhydrous CH\(_2\)Cl\(_2\) (3 mL) at room temperature and TFA (0.5 mL) was added, and the reaction mixture was stirred for 4 hours. A saturated aqueous solution of NaHCO\(_3\) (15 mL) was added and the resulting mixture was extracted with CH\(_2\)Cl\(_2\) (3 × 15 mL). The organic phases were combined and dried (MgSO\(_4\)) then evaporated. Purification by column chromatography eluting with 5 – 10 % EtOAc in petroleum ether gave **382A** (21 mg, 0.04 mmol, 80 % (based on recovered starting material)) as a colourless pale oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 1.06 – 1.07 (42H, m, 2 × Si(CH(CH\(_3\))\(_2\))\(_3\)), 2.66 – 2.73 (1H, m, CH\(_2\)OSi), 3.47 – 3.56 (2H, m, CH\(_2\)OH), 3.64 – 3.80 (10H, m, 2 × OCH\(_3\), CH\(_2\)OSi, CH\(_2\)OSi, CH\(_A\)H\(_8\)OSi), 3.93 – 3.98 (1H, m, CH\(_A\)H\(_8\)OSi), 6.37 (1H, t, \( J = 1.9 \) Hz, ArH), 6.55 (2H, s (br.), ArH).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 11.9 (SiCH), 18.0 (Si(CH\(_3\))\(_3\)), 55.3 (2 × OCH\(_3\)), 57.3 (CH\(_2\)OSi), 63.1 (CH\(_2\)OH), 63.5 (CHCH\(_2\)OSi), 65.8 (CH\(_2\)OSi), 68.7 (CH\(_2\)OSi), 99.5 (ArCH), 105.7 (ArCH), 143.5 (ArC), 160.9 (ArC).

MS (ES+): \( m/z \): 584 ([M + H]\(^+\)); HRMS (ES+): \( m/z \): calcd for C\(_{31}\)H\(_{62}\)NO\(_5\)Si\(_2\): 584.4161 ([M + H]\(^+\)); found: 584.4161.
IR (thin film) $\nu_{\text{max}} \text{ (cm}^{-1}\text{)}$ 3394 (m, NH, OH), 2864, 1596, 1460, 1428, 1204, 1153, 1101, 1063, 1013, 995.

$[\alpha]_D^{23} = -0.11 \text{ (c = 2.2, CHCl}_3\text{).}$

3-((R)-1-(3,5-Dimethoxyphenyl)-2-((triisopropylsilyl)oxy)ethyl)-2-phenyl-4-(((triisopropylsilyl)oxy)methyl)oxazolidine (381B)

Alcohol 380B (100 mg, 0.19 mmol, major diastereomer) was dissolved in anhydrous CH$_2$Cl$_2$ (3 mL) at room temperature and imidazole (39 mg, 0.57 mmol) and TIPSCI (0.06 mL, 0.29 mmol) were added and the reaction was stirred for 2 days. A saturated aqueous solution of NH$_4$Cl (10 mL) was added and the resulting mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The organic phases were combined, dried (MgSO$_4$) then evaporated. Purification by column chromatography eluting with 3 – 5 % EtOAc in petroleum ether gave 381B (75 mg, 0.11 mmol, 58 %) as a colourless pale oil.

$^1$H NMR (500 MHz, acetone-d$_6$) $\delta$ 0.87 – 0.96 (42H, m, 2 × Si(CH(CH$_3$)$_2$)$_3$), 3.21 – 3.26 (1H, m, CHCH$_2$OSi), 3.39 (1H, dd, $J = 9.4$, 10.4 Hz, CH$_2$H$_8$O), 3.53 (1H, dd, $J = 4.7$, 9.4 Hz, CH$_2$H$_8$O), 3.59 (1H, dd, $J = 6.8$, 9.8 Hz, CH$_2$H$_8$OSi), 3.80 (6H, s, 2 × OCH$_3$), 3.85 – 3.89 (2H, m, CH$_2$H$_8$OSi and CH$_2$H$_8$OSi), 3.92 (1H, dd, $J = 5.7$, 6.8 Hz, CHCH$_2$OSi), 3.97 (1H, dd, $J = 2.2$, 8.5 Hz, CH$_2$H$_8$OSi), 5.67 (1H, s, NCHO), 6.43 (1H, t, $J = 2.2$ Hz, ArH), 6.62 (2H, d, $J = 2.2$ Hz, ArH), 7.31 – 7.39 (3H, m, ArH), 7.65 (2H, d, $J = 6.9$ Hz, ArH).

$^{13}$C NMR (125 MHz, acetone-d$_6$) $\delta$ 13.1 (SiCH), 18.8 (Si(CH(CH$_3$)$_2$)$_3$), 56.1 (2 × OCH$_3$), 64.4 (CHCH$_2$OSi), 66.9 (CH$_2$O), 68.8 (CH$_2$OSi), 69.3 (CH$_2$OSi), 70.8
(CHCH₂OSi), 97.4 (NCHO), 100.4 (ArCH), 108.3 (ArCH), 129.1 (ArH), 129.4 (ArCH), 129.7 (ArCH), 143.4 (ArC), 145.1 (ArC), 162.4 (ArC).

MS (ES+): m/z: 672 ([M + H]⁺); HRMS (ES+): m/z: calcd for C₃₈H₆₆NO₅Si₂: 672.4474 ([M + H]⁺); found: 672.4478.

IR (thin film) ν_max (cm⁻¹) 2940, 2864, 1596, 1460, 1204, 1153, 1064, 880.

[α]_D²³ = −0.09 (c = 2.1, acetone).

2-(((R)-1-((3,5-dimethoxyphenyl)-2-((triisopropylsilyl)oxy)ethyl)amino)-3-((triisopropylsilyl)oxy)propan-1-ol (382B)

Oxazolidine 381B (75 mg, 0.11 mmol) was dissolved in anhydrous CH₂Cl₂ (3 mL) at room temperature and TFA (0.5 mL) was added and the reaction mixture was stirred for 4 hours. A saturated aqueous solution of NaHCO₃ (15 mL) was added and the resulting mixture was extracted with CH₂Cl₂ (3 × 15 mL). The organic phases were combined and dried (MgSO₄) then evaporated. Purification by column chromatography eluting with 5 – 10 % EtOAc in petroleum ether gave 382B (17 mg, 0.03 mmol, 75 % (based on starting material recovered)) as a colourless pale oil.

¹H NMR (500 MHz, CHCl₃) δ 1.01 – 1.06 (42H, m, 2 × Si(CH(CH₃)₂)₃), 2.69 – 2.75 (1H, m, CHCH₂OSi), 3.61 – 3.82 (12H, m, 2 × OCH₃, CHCH₂OSi, CH₂OSi, CH₃H₈OSi), 3.85 – 3.91 (1H, m, CH₃H₈OSi), 6.36 (1H, t, J = 2.2 Hz, ArH), 6.56 (2H, s (br.), ArH).

¹³C NMR (125 MHz, CHCl₃) δ 11.7 (SiCH), 17.9 (Si(CH(CH₃)₂)₃), 55.3 (2 × OCH₃), 56.6 (CHCH₂OSi), 62.1 (CH₂OH), 62.7 (CH₂OSi), 66.4 (CHCH₂OSi), 68.7 (CH₂OSi), 99.3 (ArCH), 105.6 (ArCH), 143.9 (ArC), 160.8 (ArC).
MS (ES+): \( m/z: 584 \ ([M + H]^+) \); HRMS (ES+): \( m/z \): calcd for C\(_{31}\)H\(_{62}\)NO\(_5\)Si\(_2\): 584.4161 ([M + H]+); found: 584.4165.

IR (thin film) \( \nu_{\text{max}} \) (cm\(^{-1}\)) 3399 (m, NH, OH), 2864, 1596, 1460, 1203, 1153, 1061.

\( [\alpha]_D^{23} = -0.03 \) (c = 1.6, CHCl\(_3\)).

**Methyl 3-(((1R)-3-(hydroxymethyl)-5,7-dimethoxy-1-(((triisopropylsilyl)-oxy)methyl)-1,2,3,4-tetrahydroisoquinolin-4-ylthio)propanoate (384)**

\[
\begin{align*}
\text{OMe} & \quad \text{S} & \quad \text{COOMe} \\
\text{MeO} & \quad \text{NH} & \quad \text{OH} \\
\text{TIPS} & \\
\end{align*}
\]

(COCl\(_2\)) (0.07 mL, 0.84 mmol) was dissolved in anhydrous CH\(_2\)Cl\(_2\) (10 mL) and the reaction mixture was cooled to \(-78^\circ\text{C}\) then DMSO (0.16 mL, 2.24 mmol) was added slowly and the reaction mixture was stirred for 5 minutes. Alcohol 380A (0.29 g, 0.56 mmol) in anhydrous CH\(_2\)Cl\(_2\) (2 mL) was then added and the reaction was stirred at \(-78^\circ\text{C}\) for 1.5 hours before Et\(_3\)N (0.62 mL, 4.48 mmol) was added and the reaction was allowed to warm to room temperature and stirred for a further 3 hours. A saturated aqueous solution of NaHCO\(_3\) (15 mL) was added and the mixture extracted with CH\(_2\)Cl\(_2\) (3 × 20 mL). The organic phases were combined and washed with a saturated aqueous solution of NaHCO\(_3\) (50 mL) then dried (MgSO\(_4\)) and evaporated to give crude aldehyde 383A which was then dissolved in anhydrous CH\(_2\)Cl\(_2\) (15 mL) and HSCH\(_2\)CH\(_2\)COOMe (0.14 mL, 1.12 mmol) was added. The reaction was stirred at room temperature for 1 hour. Then the reaction mixture was cooled to 0 \({}^\circ\text{C}\). TFAA (0.12 mL, 0.84 mmol) was added and the reaction was stirred for 1 hour, before BF\(_3\)-OEt\(_2\) (0.14 mL, 1.12 mmol) was added and the reaction was stirred for 14 hours. A saturated aqueous solution of NaHCO\(_3\) (20 mL) was added and the aqueous phase was extracted with CH\(_2\)Cl\(_2\) (3 × 20 mL). The organic phases were combined and dried.
(MgSO$_4$) then evaporated. Purification by column chromatography eluting with 35 – 50 % EtOAc in petroleum ether gave 384 (0.18 g, 0.34 mmol, 61 %) as a mixture of 2 diastereomers (dr 5:1) and as a pale yellow oil.

For the minor diastereomer:

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.09 (3H, s, Si(CH(CH$_3$)$_2$)$_3$), 1.10 (18H, s, Si(CH(CH$_3$)$_2$)$_3$), 2.60 – 2.64 (2H, m, SCH$_2$CH$_3$), 2.78 – 2.83 (2H, m, SCH$_2$), 3.31 (1H, dd, J = 8.9, 10.7 Hz, CH$_A$H$_B$OH), 3.53 (1H, ddd, J = 2.8, 4.6, 8.9 Hz, NCH), 3.65 (1H, dd, J = 4.6, 10.7 Hz, CH$_A$H$_B$OH), 3.69 (3H, s, OCH$_3$), 3.77 – 3.83 (7H, m, 2 × OCH$_3$ and CH$_A$H$_B$OSi), 4.12 – 4.17 (2H, m, CHS and CH$_A$H$_B$OSi), 4.25 (1H, dd, J = 5.6, 7.3 Hz, CH$_2$OSi), 6.38 (2H, s, ArH).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 11.9 (SiCH), 18.0 (Si(CH(CH$_3$)$_2$)$_3$), 26.8 (SCH$_2$), 34.8 (SCH$_2$CH$_3$), 37.9 (CHS), 51.7 (OCH$_3$), 54.0 (CHCH$_2$OSi), 55.3 (OCH$_3$), 55.5 (OCH$_3$), 58.4 (NCH), 64.6 (CH$_2$OH), 66.7 (CH$_2$OSi), 97.0 (ArCH), 102.0 (ArCH), 115.4 (ArC), 137.3 (ArC), 158.1 (ArC), 159.6 (ArC), 172.5 (C=O).

MS (ES+): m/z: 528 ([M + H]$^+$); HRMS (ES+): m/z: calcd for C$_{26}$H$_{46}$NO$_6$Si: 528.2810 ([M + H]$^+$); found: 528.2805.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 3310 (m, NH, OH), 2864, 1736 (C=O), 1602, 1460, 1201, 1052, 881, 832.

$[\alpha]_D^{23} = + 0.04$ (c = 2.4, CHCl$_3$).

For the major diastereomer:

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.00 (3H, s, Si(CH(CH$_3$)$_2$)$_3$), 1.01 (18H, s, Si(CH(CH$_3$)$_2$)$_3$), 2.63 – 2.78 (2H, m, SCH$_2$CH$_3$), 2.82 – 2.98 (2H, m, SCH$_2$), 3.33 (1H, ddd, J = 2.1, 5.4, 7.7 Hz, NCH), 3.70 (3H, s, OCH$_3$), 3.78 (3H, s, OCH$_3$), 3.84 – 3.89 (4H, m, OCH$_3$ and CH$_A$H$_B$OH), 3.98 (1H, dd, J = 2.1, 9.3 Hz, CH$_A$H$_B$OH), 4.13 (1H,
dd, $J = 2.5, 9.1$ Hz, $\text{CH}_2\text{H}_8\text{OSi}$, $4.21 - 4.24$ (3H, m, $\text{CH}_2\text{H}_8\text{OSi}$ and CHS and $\text{CHCH}_2\text{OSi}$), $6.34$ (1H, d, $J = 2.3$ Hz, ArH), $6.36$ (1H, d, $J = 2.3$ Hz, ArH).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 11.9 (SiCH), 17.9 (Si(CH(CH$_3$)$_3$)$_3$), 28.2 (SCH$_2$), 29.7 (SCH$_2$CH$_3$), 40.1 (CHS), 51.8 (OCH$_3$), 55.3 (OCH$_3$), 55.4 (OCH$_3$), 58.6 (CHCH$_2$OSi), 58.8 (NCH), 63.2 (CH$_2$OH), 65.8 (CH$_2$OSi), 97.2 (ArCH), 101.2 (ArCH), 118.9 (ArC), 135.9 (ArC), 157.3 (ArC), 159.9 (ArC), 172.6 (C=O).

MS (ES+): $m/z$: 528 ([M + H]$^+$); HRMS (ES+): $m/z$: calcd for C$_{26}$H$_{48}$NO$_6$SSi: 528.2810 ([M + H]$^+$); found: 528.2807.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 3341 (m, NH, OH), 2864, 1736 (C=O), 1603, 1460, 1354, 1202, 1152, 881, 883.

$\lbrack \alpha \rbrack_{D}^{23} = -0.08$ (c = 1.2, CHCl$_3$).

(5)-3-(3,4-bis((tert-Butyldimethylsilyl)oxy)phenyl)-2-((tert-butoxycarbonyl)-amino)propanoic acid (385)

Acid 376 (0.30 g, 1.00 mmol) was dissolved in anhydrous MeCN (8 mL) then TBSCl (0.33 g, 2.20 mmol) and DBU (0.33 mL, 2.20 mmol) were added. The reaction was stirred at room temperature for 36 hours. Water (20 mL) was added and the resulting mixture was acidified to pH = 4 – 5 then extracted with CH$_2$Cl$_2$ (3 x 20 mL). The organic phases were combined and dried (MgSO$_4$) then evaporated. Purification by column chromatography eluting with 2 – 4 % MeOH in CHCl$_3$ gave 385 (0.29 g, 0.55 mmol, 55 %) as a light yellow foam.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.19 (12H, s, $4 \times \text{SiCH}_3$), 0.98 (9H, s, SiC(CH$_3$)$_3$), 0.99 (9H, s, SiC(CH$_3$)$_3$), 1.43 (9H, s, O=CC(CH$_3$)$_3$), 2.97 (1H, dd, $J = 6.3, 13.9$ Hz,
CH$_2$Ar), 3.05 (1H, dd, $J = 5.0$, 13.9 Hz, CH$_2$Ar), 5.53 – 4.57 (1H, m, NCH), 4.90 (1H, d (br.), $J = 7.9$ Hz, NH), 6.63 (1H, d, $J = 8.2$ Hz, ArH), 6.66 (1H, s, ArH), 6.76 (1H, d, $J = 8.2$ Hz, ArH).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ –4.1 (SiCH$_3$), 25.6 (SiC(CH$_3$)$_3$), 25.9 (SiC(CH$_3$)$_3$), 28.3 (O=CC(CH$_3$)$_3$), 36.9 (CH$_2$), 54.2 (NCH), 80.2 (O=CC(CH$_3$)$_3$), 121.2 (ArCH), 122.2 (ArCH), 122.3 (ArCH), 128.6 (ArC), 146.0 (ArC), 146.7 (ArC), 155.4 (C=O), 176.6 (C=O).

MS (ES+): $m/z$: 548 ([M + Na]$^+$); HRMS (ES+): $m/z$: calcd for C$_{26}$H$_{47}$NO$_6$Si$_2$Na: 548.2835 ([M + Na]$^+$); found: 548.2823.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2955 (br, OH), 2930, 1716 (C=O), 1508, 1472, 1443, 1421, 1392, 1366, 1294, 1251, 1160, 1126, 1057, 1005.

$[\alpha]_D^{23} = +0.03$ (c = 3.7, CHCl$_3$).

**Methyl 3-(((1R)-2-((S)-3,4-bis((tert-butyldimethylsilyl)oxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanoyl)-3-(hydroxymethyl)-5,7-dimethoxy-1-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)thio)propanoate (386)**

Amine 385 (0.15 g, 0.28 mmol) and acid 385 (0.15 g, 0.28 mmol), HOBt (14.0 mg, 0.10 mmol) and EDCI (0.06 g, 0.45 mmol) were dissolved in anhydrous CH$_2$Cl$_2$ (15 mL) and the reaction mixture was stirred for 14 hours. A saturated aqueous solution of NaHCO$_3$ (15 mL) was added and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 15 mL). The organic phases were combined and dried.
(MgSO₄) then evaporated. Purification by column chromatography eluting with 15 – 20 % EtOAc in petroleum ether gave 386 (0.14 g, 0.14 mmol, 50 %) as light yellow pale oil.

¹H NMR (400 MHz, CDCl₃) δ 0.16 – 0.19 (12H, m, 4 × SiCH₃), 0.97 – 1.03 (39H, m, Si(CH(CH₃)₂)₃, 2 × C(CH₃)₃), 1.41 (9H, s, O=CC(CH₃)₃), 2.59 – 2.73 (2H, m, SCH₂CH₃), 2.81 – 2.95 (3H, m, SCH₂ and CHCH₂OH), 3.03 (1H, d, J = 5.3, 13.9 Hz, CH₆Ar), 3.30 (1H, br. s, CHS), 3.68 (3H, s, OCH₃), 3.78 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 3.94 – 3.97 (1H, m, CH₆Ar), 4.07 – 4.15 (3H, m, CH₆H₆Ar and CHNH and CHCH₂OSi), 4.32 – 4.46 (2H, m, CH₂OH), 4.57 (1H, dd, J = 6.1, 13.9 Hz, CH₆H₆OSi), 5.09 (1H, s (br.), NH), 6.35 (2H, s (br.), ArH), 6.57 (1H, dd, J = 2.2, 8.1 Hz, ArH), 6.63 (1H, d, J = 2.2 Hz, ArH), 6.70 (1H, d, J = 8.1 Hz, ArH).

¹³C NMR (100 MHz, CDCl₃) δ −4.1 (SiCH₃), −4.0 (SiCH₃), 11.9 (SiCH), 18.0 (Si(CH(CH₃)₂)₃), 18.4 (SiC(CH₃)₃), 25.9 (C(CH₃)₃), 28.1 (SCH₂CH₂), 28.3 (C(CH₃)₃ and SCH₂), 35.0 (CHCH₂OH), 36.6 (CH₂Ar), 37.3 (CHS), 41.1 (CHNH), 51.7 (CH₂OH), 54.3 (CHCH₂OSi), 55.1 (OCH₃), 55.2 (OCH₃), 55.3 (OCH₃), 58.5 (CH₂OSi), 79.7 (OCC(CH₃)₃), 96.7 (ArCH), 101.3 (ArCH), 119.2 (ArC), 121.0 (ArC), 122.2 (ArCH), 122.3 (ArCH), 128.9 (ArCH), 140.9 (ArC), 145.9 (ArC), 146.6 (ArC), 155.1 (ArC), 157.3 (ArC), 165.2 (C=O), 171.6 (C=O), 172.3 (C=O).

MS (ES+): m/z: 1035 ([M + H]+); HRMS (ES+): m/z: calcd for C₅₂H₉₁N₂O₁₁SSi₃: 1035.5646 ([M + H]+); found: 1035.5601.

IR (thin film) νmax (cm⁻¹) 3400 (m, OH, NH), 2862, 1739 (C=O), 1715 (C=O), 1605 (C=O), 1509, 1462, 1423, 1390, 1363, 1288, 1251, 1201, 1160, 1126, 1054, 1016.

[α]D²³ = −0.06 (c = 3.8, CHCl₃).

Methyl (S)-2-amino-3-(3,4-dihydroxyphenyl)propanoate hydrochloride (392)¹³₀

234
L-3,4-dihydroxyphenylalanin (2.00 g, 10.10 mmol) was dissolved in anhydrous methanol (70 mL) and the reaction was cooled to 0 °C then SOCl₂ (1.47 mL, 20.2 mmol) was added slowly. The reaction was then heated at reflux for 14 hours, the solvent was then removed and the resulting mixture was washed with n-hexane (5 × 20 mL) then dried to give 392 (2.47 g, 10.00 mmol, 99 %) as white solid. Spectroscopic data were identical to the data previously published in the literature.¹³⁰

¹H NMR (500 MHz, MeOH-d₄) δ 3.00 – 3.05 (1H, m, CH₂H₂Ar), 3.10 (1H, dd, J = 5.4, 14.5 Hz, CH₂H₂Ar), 3.81 (3H, s, OCH₃), 4.21 (1H, dd, J = 4.1, 5.4 Hz, NCH), 6.55 (1H, d, J = 7.9 Hz, ArH), 6.67 (1H, s (br.), ArH), 6.74 (1H, d, J = 7.9 Hz, ArH).

¹³C NMR (125 MHz, MeOH-d₄) δ 36.9 (CH₂), 53.7 (OCH₃), 55.6 (NCH), 117.0 (ArCH), 117.5 (ArCH), 122.0 (ArCH), 126.4 (ArC), 146.4 (ArC), 147.0 (ArC), 170.7 (C=O).

**Synthesis of 393, 394, and 395**
(COCl)_2 (0.10 mL, 1.20 mmol) was dissolved in anhydrous CH_2Cl_2 (16 mL) and the reaction mixture was cooled to −78 °C then DMSO (0.23 mL, 3.20 mmol) was added slowly and the reaction mixture was stirred for 5 minutes. Alcohol 380B (0.41 g, 0.80 mmol, minor diastereomer) in anhydrous CH_2Cl_2 (3 mL) was added and the reaction was stirred at −78 °C for 1.5 hours. Et_3N (0.89 mL, 6.40 mmol) was then added and the reaction was allowed to warm to room temperature and stirred for a further 3 hours. A saturated aqueous solution of NaHCO_3 (20 mL) was added and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were combined and washed with a saturated aqueous solution of NaHCO_3 (50 mL) then dried (MgSO_4) and evaporated to give aldehyde 383B which was dissolved in anhydrous methanol (15 mL) at room temperature. L-DOPA ester 392 (0.30 g, 1.20 mmol) and Et_3N (0.17 mL, 1.20 mmol) in anhydrous methanol (5 mL) and MgSO_4 (0.39 g, 3.20 mmol) were then added and the reaction was stirred at room temperature for 14 hours. A saturated aqueous solution of NaHCO_3 (30 mL) was then added and the resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic phases were combined and dried (MgSO_4) then evaporated. Purification by column chromatography eluting with 30 – 35 % EtOAc in petroleum ether gave 393 (0.08 g, 0.11 mmol, 13 %), 394 (0.45 g, 0.63 mmol, 79 %), 395 (0.04 g, 0.06 mmol, 8 %).

For 393:

^1^H NMR (500 MHz, CDCl_3) δ 1.06 – 1.08 (21H, m, Si(CH(CH_3)_2)_3), 2.76 – 2.84 (2H, m, CH_2Ar), 3.21 (1H, dd, J = 5.3, 10.3 Hz, CHCOOMe), 3.68 (6H, s, 2 OCH_3), 3.78 –
3.85 (5H, m, OCH₃, CHNH, CH₂H₆OSi), 3.95 – 3.98 (2H, m, CH₂H₆OSi and CHCH₂OSi), 4.05 (1H, dd, J = 5.6, 10.5 Hz, CH₂H₆O), 4.20 (1H, m, NCH), 4.28 (1H, dd, J = 8.0, 10.5 Hz, CH₂H₆O), 5.62 (1H, s, CHO), 6.23 (2H, d, J = 2.3 Hz, ArH), 6.25 (1H, d, J = 2.3 Hz, ArH), 6.43 (1H, s, ArH), 6.60 (1H, s, ArH), 7.35 – 7.41 (3H, m, ArH), 7.68 (2H, d, J = 6.3 Hz, ArH).

¹³C NMR (125 MHz, CDCl₃) δ 11.9 (SiCH), 18.1 (Si(CH(CH₃)₂)₃), 31.9 (CH₂Ar), 52.1 (CH₂COOMe), 55.2 (2 × OCH₃), 55.7 (OCH₃), 56.5 (CHNH), 60.0 (NCH), 61.0 (CH₂H₂OSi), 63.2 (CH₂O), 67.6 (CH₂OSi), 77.2 (CHO), 95.9 (ArCH), 99.0 (ArCH), 106.0 (ArCH), 111.3 (ArCH), 116.2 (ArCH), 126.5 (ArC), 128.2 (ArCH), 128.7 (ArCH), 129.0 (ArC), 140.1 (ArC), 142.1 (ArC), 142.2 (ArC), 143.1 (ArC), 160.3 (ArC), 173.3 (C=O).


IR (thin film) νmax (cm⁻¹) 3400 (m, OH, NH), 2863, 1737 (C=O), 1597, 1457, 1428, 1364, 1291, 1269, 1203, 1151, 1108, 1062.

[α]D²³ = −0.14 (c = 1.2, CHCl₃); Mp. 85 – 88 °C.

For 394:

¹H NMR (400 MHz, CDCl₃) δ 0.92 (3H, s, Si(CH(CH₃)₂)₃), 0.93 (18H, s, Si(CH(CH₃)₂)₃), 2.62 (1H, dd, J = 11.1, 16.0 Hz, CH₂H₆Ar), 2.79 (1H, dd, J = 4.8, 16.0 Hz, CH₂H₆Ar), 3.08 (1H, d, J = 9.5 Hz, CHNH), 3.79 (6H, s, 2 × OCH₃), 3.80 – 3.84 (4H, m, OCH₃ and CH₂H₆OSi), 3.99 – 4.09 (5H, m, CH₂H₆OSi, CH₂O, CH₂COOMe, CH₂H₂OSi), 4.41 (1H, ddd, J = 2.5, 6.6, 9.5 Hz, NCH), 5.69 (1H, s, CHO), 5.94 (1H, s, ArH), 6.20 (1H, s, ArH), 6.36 (1H, t, J = 2.2 Hz, ArH), 6.56 (2H, d, J = 2.2 Hz, ArH), 7.28 – 7.40 (3H, m, ArH), 7.55 (2H, d, J = 7.8 Hz, ArH).
\[^13\]C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 11.7 (SiCH), 17.8 (Si(CH(CH\(_3\))\(_2\))\(_3\)), 29.9 (CH\(_2\)Ar), 50.2 (CHCOOMe), 52.3 (OCH\(_3\)), 55.3 (2 \times OCH\(_3\)), 56.3 (CHNH), 63.0 (NCH), 67.6 (CH\(_2\)OSi), 67.9 (CH\(_2\)O), 69.5 (CHCH\(_2\)OSi), 77.2 (CHO), 95.7 (ArCH), 99.7 (ArCH), 106.3 (ArCH), 115.7 (ArCH), 118.3 (ArC), 124.9 (ArC), 126.1 (ArCH), 127.9 (ArCH), 128.5 (ArCH), 141.7 (ArC), 142.6 (ArC), 142.7 (ArC), 144.5 (ArC), 160.9 (ArC), 173.2 (C=O).

MS (ES+): \(m/z\): 707 ([M + H]\(^+\)); HRMS (ES+): \(m/z\): calcd for C\(_{39}\)H\(_{54}\)N\(_2\)O\(_8\)SiNa: 729.3542 ([M + Na]\(^+\)); found: 729.3543.

IR (thin film) \(\nu_{\text{max}}\) (cm\(^{-1}\)) 3490 (m, OH, NH), 2864, 1735 (C=O), 1596, 1458, 1429, 1291, 1257, 1225, 1203, 1153, 1109, 1062.

\([\alpha]_D\)\(^{23}\) = – 0.01 (c = 1.4, CHCl\(_3\)); Mp. 96 – 100 °C.

For 395:

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.79 (21H, s, Si(CH(CH\(_3\))\(_2\))\(_3\)), 2.71 (1H, dd, \(J = 11.4, 14.3\) Hz, CH\(_A\)H\(_B\)Ar), 2.97 (1H, dd, \(J = 3.0, 14.3\) Hz, CH\(_A\)H\(_B\)Ar), 3.44 (2H, m, CH\(_2\)O), 3.56 (1H, dd, \(J = 3.0, 11.3\) Hz, CHCOOMe), 3.65 – 3.70 (7H, m, 2 \times OCH\(_3\) and CHCH\(_2\)OSi), 3.78 – 3.82 (4H, m, OCH\(_3\) and NCH), 4.13 (1H, dd, \(J = 6.6, 9.8\) Hz, CH\(_A\)H\(_B\)OSi), 4.50 (1H, d, \(J = 10.1\) Hz, CHNH), 4.65 (1H, br. d, \(J = 9.0\) Hz, CH\(_A\)H\(_B\)OSi), 5.36 (1H, s, CHO), 6.33 (1H, s (br.), ArH), 6.39 (2H, s (br.), ArH), 6.60 (1H, d, \(J = 7.9\) Hz, ArH), 6.77 (1H, d, \(J = 7.9\) Hz, ArH), 7.11 (2H, d (br.), \(J = 7.0\) Hz, ArH), 7.24 – 7.27 (3H, m, ArH).

\[^13\]C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 11.5 (SiCH), 17.7 (Si(CH(CH\(_3\))\(_2\))\(_3\)), 33.0 (CH\(_2\)Ar), 52.2 (OCH\(_3\)), 54.2 (CHNH), 55.2 (2 \times OCH\(_3\)), 55.3 (CHCOOMe), 66.8 (CH\(_2\)O), 68.4 (CH\(_2\)OSi), 70.7 (NCH), 72.2 (CHCH\(_2\)OSi) 77.2 (CHO), 98.1 (ArCH), 100.4 (ArCH), 107.2 (ArCH), 113.2 (ArCH), 120.8 (ArCH), 126.8 (ArC), 127.3 (ArCH), 128.0 (ArCH), 128.5 (ArC), 138.1 (ArC), 141.2 (ArC), 141.6 (ArC), 145.0 (ArC), 160.7 (ArC), 173.5 (C=O).
MS (ES+): m/z: 707 ([M + H]+); HRMS (ES+): m/z: calcd for C_{39}H_{55}N_{2}O_{8}Si: 707.3722 ([M + H]+); found: 707.3709.

IR (thin film) \( \nu_{\text{max}} \) (cm\(^{-1}\)) 3492 (m, OH, NH), 2864, 1738 (C=O), 1597, 1455, 1430, 1349, 1286, 1203, 1151, 1109, 1063, 1013, 993.

\([\alpha]_{D}^{23} = +0.22 \ (c = 1.5, \text{CHCl}_3)\).

(3S)-Methyl 1-(3-((R)-1-(3,5-dimethoxyphenyl)-2-((triisopropylsilyl)oxy)-ethyl)-2-phenyloxazolidin-4-yl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylate (397)

Amine 394 (0.19 g, 0.27 mmol) was dissolved in anhydrous acetone (10 mL) and K\(_2\)CO\(_3\) (0.22 g, 1.59 mmol) and MeI (0.33 mL, 5.32 mmol) were added. The reaction mixture was stirred in the dark for 14 hours before the solvent was evaporated. Purification by column chromatography eluting with 15 – 20 % EtOAc in petroleum ether gave acid 396 (0.14 g, 0.19 mmol) as a yellow foam.

Acid 396 (0.11 g, 0.14 mmol) was dissolved in anhydrous methanol (3 mL) and the reaction was cooled to 0 °C then a 2 M solution of trimethylsilyl diazomethane in n-hexane (0.6 mL, 1.20 mmol) was added. The reaction was stirred at 0 °C for 1 hour then allowed to warm to room temperature and stirred for 3 hours. A further solution of 2 M trimethylsilyl diazomethane in n-hexane (0.3 mL, 0.60 mmol) was added and the reaction was stirred for a further 2 hours. The solvent was evaporated to produce 397 (0.11 g, 0.14 mmol, 100 %) as yellow pale oil.
$^1$H NMR (400 MHz, CDCl$_3$) δ 0.85 (21H, s (br.), Si(CH(CH$_3$)$_3$)$_3$), 2.28 (3H, s, NCH$_3$), 2.80 (1H, dd, $J = 2.5$, 12.6 Hz, CH$_A$H$_B$Ar), 2.94 – 3.03 (5H, m, CH$_A$H$_B$Ar, CH$_2$O, NCH, CHCOOMe), 3.60 (1H, dd, $J = 4.5$, 6.0 Hz, CH$_A$CH$_2$OSi), 3.68 (6H, s, 2 × OCH$_3$), 3.71 – 3.74 (1H, m, CH$_A$CH$_2$O) 3.76 (3H, s, OCH$_3$), 3.86 (3H, s, OCH$_3$), 3.93 (3H, s, OCH$_3$), 4.22 (1H, dd, $J = 6.0$, 8.8 Hz, CH$_A$H$_B$OSi), 4.36 (1H, dd, $J = 4.5$, 8.8 Hz, CH$_A$H$_B$OSi), 5.47 (1H, s, CHO), 6.25 (1H, t, $J = 2.2$ Hz, ArH), 6.30 (2H, d, $J = 2.2$ Hz, ArH), 6.65 (1H, s, ArH), 6.75 (1H, s, ArH), 7.23 – 7.31 (3H, m, ArH), 7.42 (2H, d, $J = 7.3$ Hz, ArH).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 11.7 (SiCH), 17.8 (Si(CH(CH$_3$)$_2$)$_3$), 31.5 (CH$_2$Ar), 46.9 (NCH$_3$), 52.0 (OCH$_3$), 55.1 (2 × OCH$_3$), 55.6 (OCH$_3$), 55.8 (OCH$_3$), 64.8 (CHCOOMe), 66.0 (NCH), 67.0 (CH$_2$O), 67.1 (CH$_A$CH$_2$O), 68.6 (CH$_2$OSi), 70.6 (CH$_A$CH$_2$OSi), 77.2 (CHO), 99.3 (ArCH), 99.2 (ArCH), 107.0 (ArCH), 110.2 (ArCH), 113.2 (ArCH), 126.0 (ArC), 127.0 (ArCH), 127.7 (ArCH), 129.6 (ArC), 142.3 (ArC), 144.0 (ArC), 146.8 (ArC), 147.7 (ArC), 160.4 (ArC), 174.5 (C=O).

MS (ES+): $m$/z: 749 ([M + H]$^+$); HRMS (ES+): $m$/z: calcd for C$_{42}$H$_{60}$N$_2$O$_8$SiNa: 771.4012 ([M + Na]$^+$); found: 771.4012.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2941, 2863, 1740 (C=O), 1508, 1460, 1430, 1343, 1290, 1251, 1226, 1202, 1152, 1117.

$[\alpha]_D^{23} = +0.34$ (c = 1.8, CHCl$_3$).
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Appendix 1

Glyoxamide before drying

Glyoxamide after drying

Chemical Shift (ppm)
Appendix 2

Column: Chiralpak AD-H
UV wavelength: 216 nm
Eluent: Hexane: IPA 98:2
Velocity: 1mL/min
Column: Chiralpak AD-H
UV wavelength: 216 nm
Eluent: Hexane: IPA 98:2
Velocity: 1mL/min
Appendix 3

X-ray structure of compound 393

Crystal data and structure refinement for s3722ma.

Identification code           s3722ma
Formula weight                2134.78
Temperature                   150(2) K
Wavelength                    1.54178 Å
Crystal system, space group   Monoclinic, C2
Unit cell dimensions          a = 19.4900(2) Å   alpha = 90 deg.
                               b = 10.85720(10) Å  beta = 92.1810(10) deg.
                               c = 55.0887(6) Å    gamma = 90 deg.
Volume                        11648.7(2) Å³
2, Calculated density         4, 1.217 Mg/m³
Absorption coefficient 0.967 mm\(^{-1}\)

F(000) 4584

Crystal size 0.20 x 0.18 x 0.04 mm

Theta range for data collection 2.41 to 66.59 deg.

Limiting indices -22<=h<=23, -12<=k<=12, -65<=l<=65

Reflections collected / unique 29057 / 16402 [R(int) = 0.0403]

Completeness to theta = 66.59 99.1 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 0.9623 and 0

Refinement method Full-matrix least-squares on F\(^2\)

Data / restraints / parameters 16402 / 27 / 1385

Goodness-of-fit on F\(^2\) 1.230

Final R indices [I>2\(\sigma(I)\)] R1 = 0.0952, wR2 = 0.2731

R indices (all data) R1 = 0.1003, wR2 = 0.2849

Absolute structure parameter 0.00(4)

Largest diff. peak and hole 0.593 and -0.391 e.A\(^{-3}\)

Atomic coordinates ( x 10\(^4\)) and equivalent isotropic displacement parameters (A\(^2\) x 10\(^3\)) for s3722ma. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

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_____________________________________________________________
X-ray structure of compound 394

Crystal data and structure refinement for s3719ma.

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Absorption coefficient: 0.971 mm\(^{-1}\)
F(000): 3112
Crystal size: 0.20 x 0.18 x 0.12 mm
Theta range for data collection: 2.1659 to 74.0826 deg.
Limiting indices: \(-12 \leq h \leq 10, -9 \leq k \leq 11, -100 \leq l \leq 99\)
Reflections collected / unique: 29530 / 7799 [R(int) = 0.0900]
Completeness to theta = 66.60: 99.8%
Absorption correction: Semi-empirical from equivalents
Max. and min. transmission: 1.00000 and 0.55271

Refinement method: Full-matrix least-squares on F\(^2\)
Data / restraints / parameters: 7799 / 62 / 561
Goodness-of-fit on F\(^2\): 1.449
Final R indices [I>2sigma(I)]: R1 = 0.1279, wR2 = 0.3207
R indices (all data): R1 = 0.1331, wR2 = 0.3251
Absolute structure parameter: 0.16(4)
Extinction coefficient: 0.00064(13)
Largest diff. peak and hole: 0.527 and -0.687 e.A\(^{-3}\)

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for s3719ma. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

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